

FDA and NBTS
Workshop on Product Development for CNS Metastases

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Page 1			Page 3		
1	WORKSHOP ON PRODUCT DEVELOPMENT FOR CNS METASTASES	PAGE	1	CONTENTS (continued)	PAGE
2			2	AGENDA ITEM	
3			3	Panel Discussion	
4			4	Derrick Queen, MD, PhD	37
5			5	Luke Walker, MD	41
6	Co-Sponsored by the FDA and		6	Victoria Ebiana, MD	43
7	National Brain Tumor Society		7	Michael Davies, MD, PhD	44
8			8	Manmeet Ahluwalia, MD	46
9			9	Session II: Key Issues for Clinical	83
10			10	Development for Brain	
11	Friday, March 22, 2019		11	Moderators - Chana Weinstock, MD	
12	8:33 a.m. to 3:57 p.m.		12	Nancy Lin, MD	
13			13	Discussant Presentations:	
14			14	Identifying Targets for Brain Mets	
15			15	Clinical Studies	
16	FDA White Oak Campus		16	Priscilla Brastianos, MD	84
17	Building 31		17	Selecting Drug Candidates for	
18	The Great Room		18	Brain Mets	
19	10903 New Hampshire Avenue		19	Nancy Lin, MD	98
20	Silver Spring, Maryland		20	Issues with Conducting Brain Mets	
21			21	Clinical Trials	
22			22	Kim Margolin, MD	117
Page 2			Page 4		
1	CONTENTS	PAGE	1	CONTENTS (continued)	PAGE
2	AGENDA ITEM		2	AGENDA ITEM	
3	Opening Remarks		3	Standardizing Brain Mets	
4	David Arons, JD	8	4	Response Assessment	
5	Richard Pazdur, MD	12	5	Ben Ellingson, MD	125
6	Presenting the Challenge		6	Panel Discussion	138
7	Patrick Wen, MD	14	7	Session Recap	
8	Joohee Sul, MD	18	8	Chana Weinstock, MD	159
9	Session I: Defining the Problem of		9	Session III: Clinical Benefit in	
10	CNS Metastases	20	10	Patients with Brain Mets	162
11	Moderators - Laleh Amiri-Kordestani, MD		11	Moderators - Carey Anders, MD	
12	Greg Riely, MD		12	Tatiana Prowell, MD	
13	Discussant Presentations:		13	Discussant Presentations:	
14	Clinical Management of CNS Metastasis		14	Regulatory Definition of "Clinical Benefit"	
15	2019: Current Strategies,		15	Paul Kluetz, MD	163
16	Investigations, and Key Challenges		16	Panel Discussion	175
17	Michael Davies, MD, PhD	20	17	Terri Armstrong, PhD	176
18			18	Shelly Engfer-Triebenbach	178
19			19	Chitkala Kalidas, PhD	181
20			20	Benjamin Levy, MD	182
21			21	Jeffrey Wefel, MD	185
22			22	Arvin Yang, MD, PhD	186

		Page 5			Page 7
1	C O N T E N T S (continued)	PAGE	1	C O N T E N T S (continued)	PAGE
2	AGENDA ITEM		2	AGENDA ITEM	
3	Panel Recap		3	Summary and Next Steps	
4	Carey Anders, MD	229	4	Patrick Wen, MD	383
5	Discussant Presentations:		5	Joohee Sul, MD	385
6	Regulatory Challengers for CNS		6	David Arons, JD	388
7	Metastases		7		
8	Shanthy Marur, MD	233	8		
9	Panel Discussion	241	9		
10	Lynda Weatherby	243	10		
11	Hussein Tawbi, MD, PhD	249	11		
12	Palavi Mishra-Kalyani, PhD	251	12		
13	Vinai Gondi, MD	252	13		
14	Patricia Keegan, MD	253	14		
15	Kim Blackwell, MD	255	15		
16	Michael Atkins, MD	257	16		
17	Panel Recap		17		
18	Tatiana Prowell, MD	314	18		
19			19		
20			20		
21			21		
22			22		
		Page 6			Page 8
1	C O N T E N T S (continued)	PAGE	1	P R O C E E D I N G S	
2	AGENDA ITEM		2	(8:31 a.m.)	
3	Session IV: Therapy Development:		3	Opening Remarks	
4	Challenges and Opportunities	316	4	MR. ARONS: Good morning, everybody.	
5	Moderators - Joohee Sul, MD		5	Welcome. Thanks for finding your seats, and we're	
6	Patrick Wen, MD		6	live.	
7	Panel Discussion		7	Welcome and thank you for being here today	
8	Peggy Zuckerman	317	8	for the CNS Metastasis Product Development	
9	Edjah Ndoum, MD	320	9	Workshop. I'm David Arons with National Brain	
10	Caroline Chung, MD	320	10	Tumor Society. As we get started, just a few	
11	Lauren Abrey, MD	320	11	logistical points.	
12	Tatiana Prowell, MD	322	12	First, number one, please mute your cell	
13	Kim Margolin, MD	326	13	phones. That would be appreciated. Second, this	
14	Nancy Lin, MD	329	14	is a public event, and thanks to the FDA, it is	
15	Overview of the American Brain Tumor		15	being livestreamed. Third, your participation is	
16	Association's Metastatic Brain Tumor		16	wanted, encouraged, and frankly expected.	
17	Initiative		17	This is a working meeting in the truest	
18	Ralph DeVito	375	18	sense of the word. At the end of the day, we hope	
19	Nicole Willmarth, PhD	377	19	that new ideas, opportunities, and recommendations	
20			20	are brought forward so that action steps can be	
21			21	identified. In fact, during the Q&A session, we	
22			22	hope that you'll take a robust role, and Wendy may	

<p>1 even call on you.</p> <p>2 Now about the disease itself we're talking</p> <p>3 about or this collection of diseases. Brain</p> <p>4 metastases are the most common type of intracranial</p> <p>5 neoplasm, with the total number diagnosed annually</p> <p>6 outnumbering all other intracranial tumors</p> <p>7 combined.</p> <p>8 They outnumber primary brain tumors by a</p> <p>9 ratio of 10 to 1 according to some studies and</p> <p>10 occur in about 25 to 45 percent of all patients</p> <p>11 with cancer. Conservative estimates suggest that</p> <p>12 100,000 to upwards of 180,000 new cases of brain</p> <p>13 metastases are diagnosed every year in the United</p> <p>14 States.</p> <p>15 As brain tumor and cancer patient advocates,</p> <p>16 we know firsthand this is a highly vulnerable</p> <p>17 population with significant unmet medical need.</p> <p>18 There are not enough therapeutic options, let alone</p> <p>19 cures, for CNS metastasis patients. Today is a</p> <p>20 very important opportunity to work together to</p> <p>21 identify ideas, opportunities, and realistic</p> <p>22 strategies, and even innovative out-of-the-box</p>	<p>Page 9</p>	<p>1 Wen.</p> <p>2 In addition, we thank the content committee</p> <p>3 members that are quite numerous, and a lot of</p> <p>4 appreciation goes to our presenters and those who</p> <p>5 volunteered many hours to prepare information,</p> <p>6 including the videos, in preparation for this that</p> <p>7 will advance our workshop's goals, and a big thanks</p> <p>8 to Wendy Selig, our project director from</p> <p>9 WSCollaborative, who led the entire planning</p> <p>10 process, and also to Sarah O'Connor from NBTS,</p> <p>11 Dianne Spillman, and Joan Todd from the FDA, who</p> <p>12 were instrumental.</p> <p>13 A very special thanks here to all the</p> <p>14 patients. This is about you, and it's about all</p> <p>15 the CNS metastasis patients worldwide. The</p> <p>16 patients traveled here today, and they have a lot</p> <p>17 they can contribute, and we really look forward to</p> <p>18 hearing your perspectives and views in this</p> <p>19 conversation. We value your experience and want to</p> <p>20 hear it.</p> <p>21 Now, it is an honor to introduce Dr. Rick</p> <p>22 Pazdur, the director of FDA's Oncology Center of</p>	<p>Page 11</p>
<p>1 thinking to advance clinical research in this area.</p> <p>2 In addition to bringing our collective expertise to</p> <p>3 bear on the subject, let us all be driven by a</p> <p>4 sense of urgency and spirit of collaboration to</p> <p>5 make positive change.</p> <p>6 A big thank you to the Food and Drug</p> <p>7 Administration for hosting this workshop and for</p> <p>8 partnering to plan the workshop. Thank you to</p> <p>9 partner organizations that formed the planning</p> <p>10 committee. They are Accelerate Brain Cancer Cure;</p> <p>11 American Brain Tumor Association; Friends of Cancer</p> <p>12 Research; Kidney Cancer Research Alliance;</p> <p>13 LUNGevity Foundation; National Brain Tumor Society;</p> <p>14 Metastatic Breast Cancer Alliance; Melanoma</p> <p>15 Research Alliance; RANO; and Society for</p> <p>16 Neuro-Oncology.</p> <p>17 Thank you to additional organizations that</p> <p>18 helped the workshop come about, including Bayer;</p> <p>19 BMS; Celgene; Edison; Elekta; Lilly; Merck;</p> <p>20 Novocure; and Seattle Genetics. We are truly</p> <p>21 grateful to the workshop steering committee,</p> <p>22 including Dr. Joohee Sul, Nancy Lin, and Patrick</p>	<p>Page 10</p>	<p>1 Excellence. We thank Dr. Pazdur for his</p> <p>2 leadership, innovation, and for also being a</p> <p>3 patient advocate himself. Thank you, Dr. Pazdur.</p> <p>4 (Applause.)</p> <p>5 DR. PAZDUR: Thank you very much. I welcome</p> <p>6 you here to the White Oak Campus at the FDA. For</p> <p>7 many of you, this has probably been an initial</p> <p>8 visit here, and it's a campus that we've been here</p> <p>9 for a little more than 10 years.</p> <p>10 I think what's special about this conference</p> <p>11 is that it brings a lot of diverse groups of people</p> <p>12 together that perhaps never have worked here before</p> <p>13 together. Generally, when we have meetings, we</p> <p>14 have meetings centering on lung cancer, colon</p> <p>15 cancer, breast cancer, myeloma, and melanoma, but</p> <p>16 we very rarely bring groups of people together to</p> <p>17 look at a site of metastatic disease or an approach</p> <p>18 to a particular problem that joins various diseases</p> <p>19 together. So this is somewhat of a unique</p> <p>20 conference, and I hope that we will have a very</p> <p>21 productive meeting.</p> <p>22 I'm very interested in this meeting. As a</p>	<p>Page 12</p>

<p style="text-align: right;">Page 13</p> <p>1 practicing oncologist years ago, one of the things 2 I dreaded most in approaching patients, especially 3 in discussing with them when they had disease 4 progression, was when they had brain metastases, 5 because I think delivering this news to patients is 6 a really devastating discussion that one has to 7 have. It's a special site of metastatic disease, 8 and I think we should consider what is unique about 9 brain metastasis versus other sites of metastatic 10 disease.</p> <p>11 This goes to how we approach this in drug 12 development, and I hope that this will be one of 13 the avenues that we will discuss here, what are 14 novel clinical trial designs to look and assess the 15 effects of therapy.</p> <p>16 What I'm hoping for is that we will have 17 some form of guidance that will come from the FDA 18 after this meeting, at least a formulation of a 19 guidance, that will direct sponsors and other 20 clinical developers in this area to have a better 21 understanding of what it would take to get a drug 22 developed in a particular indication for a brain</p>	<p style="text-align: right;">Page 15</p> <p>1 In 2014, the neuro-oncology community had a 2 couple of workshops with the FDA, and we found 3 those workshops incredibly useful and increasing 4 our understanding of what is required to develop 5 drugs, in this case for gliomas. As a result of 6 the workshop, we developed this brain tumor 7 standardized imaging protocol that was led by Ben 8 Ellingson, which has now become the imaging 9 protocol used in the vast majority of glioblastoma 10 trials.</p> <p>11 I think we all know about the significant 12 morbidity and mortality from brain metastases, and 13 it's been over two years ago that I talked to 14 Joohee about potentially having a workshop to 15 clarify what we need to do to develop more 16 effective therapies for brain metastases patients 17 and provide some clarity in terms of trial design 18 and endpoints, both in the place of brain 19 metastases in the general development of drug in 20 oncology and also specifically for developing 21 treatments for brain metastases, both local 22 therapies and systemic therapies. That hopefully</p>
<p style="text-align: right;">Page 14</p> <p>1 metastases.</p> <p>2 I again would like to thank you for being 3 here. I hope this is a productive meeting. It's 4 something that I'm very interested in. Our staff 5 is represented from all of the disease specific 6 areas here, and I really would like to thank them 7 for their efforts, those members in the FDA that 8 have worked on this, as well as the organizing 9 committee and the various organizations that have 10 already been stated, that have participated in 11 formulating this conference.</p> <p>12 I'm going to turn it over to Wendy, to 13 Joohee, and Patrick. Thank you.</p> <p>14 (Applause.)</p> <p>15 Presentation - Patrick Wen</p> <p>16 DR. WEN: On behalf of my co-chair, Joohee 17 Sul, I'd like to welcome all of you. I want to 18 echo David's thanks to the FDA, Dr. Pazdur and 19 Joohee. I want to thank the National Brain 20 Tumor Society, David Arons and Wendy Selig, and all 21 the patient organizations and sponsors that have 22 made this meeting possible.</p>	<p style="text-align: right;">Page 16</p> <p>1 will be the goal of the meeting today.</p> <p>2 There are a lot of things we can talk about 3 in brain metastasis, but the focus should be on 4 these issues. In the last couple of years, there 5 have been two important papers that have tried to 6 clarify these issues.</p> <p>7 One, the ASCO Friends of Cancer Research 8 brain metastases working group has provided some 9 guidance on how to incorporate metastases patients 10 in the general development in oncology, dividing 11 them into patients with treated or stable 12 metastases, with active metastases, and also to try 13 to incorporate those that have leptomeningeal 14 metastases.</p> <p>15 The RANO group has also published a paper 16 providing guidance on the same issue, dividing 17 brain metastases patients and drugs into three 18 categories: agents that have a high likelihood of 19 helping brain metastases; those that have a low 20 likelihood of helping brain metastases; and those 21 where we're not sure about the efficacy.</p> <p>22 In today's meeting, I hope that we will talk</p>

<p style="text-align: right;">Page 17</p> <p>1 about whether we should incorporate these guidances 2 routinely into drug development strategies, and 3 also whether we should incorporate the RANO brain 4 metastases criteria routinely into clinical trials 5 for brain metastasis, and then also to define the 6 optimal endpoints for clinical trials.</p> <p>7 I think by the end of today, our hope is 8 that we have more clarity on what trials and 9 endpoints should be performed to develop new 10 treatments for brain metastases. Just like with 11 the glioma workshops, we want to identify issues 12 that still need to be addressed. One of them will 13 be the standardized brain imaging protocols for 14 brain metastases and develop a roadmap to address 15 these issues. In addition to the FDA guidance, the 16 hope is that we will also have a paper that comes 17 out of this meeting.</p> <p>18 We look forward to a really productive day, 19 and thank you so much to all of you. I know you're 20 all incredibly busy, and we're very fortunate to 21 have all of you here today to help us find better 22 treatments for our patients, so thank you.</p>	<p>1 brain metastases. 2 Dr. Wen has nicely I think provided an 3 overview of the goals. Just one thing I think 4 would be important to keep in mind, and one thing I 5 think I've come to realize being here at the FDA, 6 is that for all these issues we're going to discuss 7 today, the context is incredibly important, that 8 these endpoints in study designs don't exist in a 9 vacuum, and although data can often be fixed, the 10 context in which they're interpreted can be very 11 variable. I think that has a huge impact on how we 12 view these types of therapies and their impact on 13 patients.</p> <p>14 The last point I'd like to make is I know it 15 can be difficult to speak up in a public setting. 16 I personally have always dreaded public speaking, 17 but I encourage everyone to please speak up and 18 present your ideas. I know that sometimes it can 19 be tough to say something that might go against the 20 crowd, but if there are dissenting opinions out 21 there, we need to bring all these aspects to light 22 so that we can have a fruitful discussion. So</p>
<p style="text-align: right;">Page 18</p> <p>1 I also wanted to mention that the Society 2 for Neuro-Oncology and the RANO group is committed 3 to continuing this effort. This is not just a 4 one-off meeting. So as a follow-on later this 5 summer, The Society for Neuro-Oncology will have 6 our inaugural brain metastases meeting to continue 7 this conversation and to push the development of 8 better treatments for brain metastases, and 9 hopefully many of you will be able to come, so 10 thank you.</p> <p>11 (Applause.)</p> <p>12 Presentation - Joohee Sul</p> <p>13 DR. SUL: Good morning. For those of you 14 who don't know me, my name is Joohee Sul, and I'm a 15 medical reviewer here at the FDA and a 16 neuro-oncologist. I'm going to be brief because I 17 know we're short on time; we're crunched on time. 18 But I just want to echo Dr. Pazdur, David Arons, 19 and Patrick Wen in thanking everyone for coming and 20 for participating, and that we're looking forward 21 to a lively discussion about some of the topics and 22 issues and challenges that we face with evaluating</p>	<p>1 thank you very much. 2 (Applause.)</p> <p>3 Session I</p> <p>4 Presentation - Michael Davies</p> <p>5 DR. DAVIES: Good morning. My name is 6 Dr. Michael Davies. Thank you very much for the 7 opportunity to talk today. As Dr. Pazdur 8 mentioned, it's really, again, a unique experience 9 today. We not only have people from multiple 10 different disease sites but actually also from 11 different therapeutic approaches. So one of the 12 things in the discussion about this meeting was to 13 actually think about starting the day off with 14 trying to give everybody a framework to understand 15 where we are in different diseases and with 16 different treatment modalities.</p> <p>17 So as has been mentioned, it was my honor to 18 participate with the other speakers you've seen 19 here and recording webinars that are available 20 through the FDA website. And again, I personally 21 have benefited tremendously from being able to 22 review these other talks. These are my</p>

Page 21	<p>1 disclosures.</p> <p>2 What, again, I would just like to reinforce,</p> <p>3 as David said, is, again, the significance of the</p> <p>4 problem of brain metastasis. Indeed, the estimates</p> <p>5 are that up to 170,000 patients are diagnosed with</p> <p>6 CNS involvement per year, and we expect that CNS</p> <p>7 involvement actually is the cause of up to 100,000</p> <p>8 deaths per year from cancer. I actually think that</p> <p>9 these rates, at least in incidence, are probably</p> <p>10 rising as we've developed therapies that are</p> <p>11 achieving better and better control of extracranial</p> <p>12 disease.</p> <p>13 What I'd like to do in the next few minutes,</p> <p>14 then, is just to again provide some of the</p> <p>15 highlights from the webinars. And again, I hope</p> <p>16 that people have had a chance to look at these</p> <p>17 webinars or have a chance to go back after the</p> <p>18 meeting, but to really talk about, again, where we</p> <p>19 stand in the management of CNS disease, both in</p> <p>20 terms of standard-of-care options and also clinical</p> <p>21 investigations for radiation therapy, systemic</p> <p>22 therapy, for breast cancer, lung cancer, and</p>
Page 22	<p>1 melanoma. And then finally to talk upon what's</p> <p>2 probably our final frontier, which is</p> <p>3 leptomeningeal disease.</p> <p>4 Just to start off with Dr Brown's talk about</p> <p>5 the role of radiotherapy in the management of brain</p> <p>6 metastasis, this again is an area where clearly</p> <p>7 we've moved from the era of whole-brain radiation</p> <p>8 therapy to stereotactic radiosurgery. This in many</p> <p>9 ways is the standard of care for patients with</p> <p>10 oligometastatic disease and very effective at</p> <p>11 achieving local control in tumors that are less</p> <p>12 than 2 centimeters.</p> <p>13 The real limitation is the fact that we know</p> <p>14 that it doesn't do a good job of controlling tumors</p> <p>15 that were not radiating, and the key question is</p> <p>16 how can we improve control throughout the brain in</p> <p>17 addition to that local control. And while we know</p> <p>18 that whole-brain radiotherapy will increase</p> <p>19 controlling the CNS, it comes at the expense of</p> <p>20 worsening neurocognitive function and quality of</p> <p>21 life without impact on overall survival.</p> <p>22 So whole-brain radiation therapy is</p>

<p style="text-align: right;">Page 25</p> <p>1 see a higher risk of brain metastasis. Again, she 2 did a very nice job of summarizing both the 3 commercially available therapies we have for each 4 of those subtypes, as well as a number of the 5 ongoing clinical trials.</p> <p>6 I don't think I'm going to try to go through 7 all of those approaches, but just really to say 8 that, again, clearly in the HER2 space it's 9 building upon a backbone of HER2 targeted 10 therapies, triple negative cancer at this point, 11 Really building upon chemotherapy, and now in the 12 realm of ER/PR positive starting to add things like 13 CDK4 inhibitors and other targeted therapies to our 14 hormonal therapies.</p> <p>15 So again, just to summarize our challenges 16 here in the HER2 positive space, multiple active 17 regimens, but these are regimens that often have 18 relatively transient benefit with progression-free 19 survival on the range of approximately 6 months. 20 Again, this is a disease that has shown that 21 chemotherapy absolutely can have a role in the 22 management of patients with CNS involvement, but</p>	<p style="text-align: right;">Page 27</p> <p>1 cancer driven by oncogenic targets, and in 2 particular EGFR mutations and out fusions that have 3 really provided new therapeutic opportunities.</p> <p>4 Actually, as we think about the management 5 of patients with stage 4 and non-small cell lung 6 cancer, we now sort of divide patients into those 7 who have these driver oncogenes that are 8 targetable, and those patients really are getting 9 treated with targeted therapy up front. For the 10 rest of the patients, what we are really moving 11 into is an era now where the standard upfront 12 therapy is immune therapy, either by itself or in 13 combination with chemotherapy.</p> <p>14 In addition to really talking about the 15 number of the key trials, I think what was really 16 sort of nice about his presentation was also 17 talking about how the lung cancer field has learned 18 and progressed over the last decade about how to 19 appropriately design and interpret these clinical 20 trials, and as he goes into in depth, a number of 21 rookie mistakes that were learned from that can 22 really inform I think our other fields where we</p>
<p style="text-align: right;">Page 26</p> <p>1 how can we do better or how can we build upon the 2 current activity; and certainly the idea that 3 there's now multiple new targets of interest, 4 including both targeted therapies and 5 immunotherapies, and increasingly bringing these 6 different types of strategies together.</p> <p>7 I'd like to just in particular highlight 8 that she discussed future directions, questions, 9 and opportunities, that one of the things that 10 we'll talk about later today is the need for better 11 preclinical models to help us develop, validate, 12 and prioritize new therapeutic strategies is I 13 think one of the other great unmet needs that we 14 have in our field.</p> <p>15 So moving on, Dr. Ross Camidge gave what he 16 called the State of the Tumor Address for patients 17 with non-small cell lung cancer and brain 18 metastasis, again, really a wonderful summary that 19 he provided. As he pointed out, really our 20 understanding of lung cancer has evolved quite 21 rapidly over the last few years such that we now 22 have multiple molecularly defined subtypes of lung</p>	<p style="text-align: right;">Page 28</p> <p>1 sometimes haven't really dealt with some of these 2 challenges yet, including not separating treated 3 versus untreated brain metastases; whether patients 4 got whole-brain or stereotactic radiosurgery.</p> <p>5 I think one that we've seen is a particular 6 challenge is the impact of variation in the 7 frequency and modality of CNS surveillance or even 8 CNS screening before patients are enrolled into 9 clinical trial and the impact that can have on the 10 difficulty of interpreting the results from some of 11 these clinical studies.</p> <p>12 In addition to those overall concepts, I 13 just wanted to highlight two key clinical trials 14 and the lessons that were learned that I think are 15 particularly impactful for thinking about this in 16 the future. This is a slide presented at ESMO 17 2018, a randomized trial of brigatinib versus 18 crizotinib in ALK-driven tumors, and what we can 19 see on the left are the outcomes in patients with 20 brain metastases; on the right, patients without 21 brain metastases.</p> <p>22 What we can see here is that very early it</p>

<p style="text-align: right;">Page 29</p> <p>1 became clear in patients with brain metastases, 2 that there was a marked difference in the efficacy 3 of these two agents that actually wasn't detectable 4 at early time points in patients without CNS 5 involvement.</p> <p>6 This again actually highlights the challenge 7 that we have clinically in managing patients with 8 brain metastasis but also highlight the opportunity 9 to learn much quicker which agents are going to be 10 effected by including patients with brain 11 metastases in these trials; that again, there's 12 particular opportunity and really a need not to 13 deny patients these types of agents that have such 14 impressive activity.</p> <p>15 Building upon that, he talked about how 16 laratinib was actually approved in November of 2018 17 for patients with ALK-driven tumors who were 18 refractory to other therapies, where interestingly, 19 this is a therapy that actually had higher response 20 rates in the brain than it actually extracranially, 21 again, reinforcing where there's actually really 22 tremendous opportunities for drug development in</p>	<p style="text-align: right;">Page 31</p> <p>1 and immune therapies approved for stage 4 patients 2 between 2011 and 2018. And I would point out that 3 all of the registration studies for those agents 4 that led to those approvals excluded patients with 5 active brain metastases. Not a single patient with 6 active brain metastasis was included in those 7 studies, and as I'll show, we have clear evidence 8 that those treatments can benefit patients with CNS 9 metastasis.</p> <p>10 Again, like lung cancer, we actually talk 11 about both targeted therapy and immune therapy are 12 driver mutations, the BRAF mutation that's present 13 in about 50 percent of patients. Our standard of 14 care for those patients in the targeted therapy era 15 is combined BRAF and MEK inhibitors. And although 16 we have three regimens that have been approved, we 17 only have data for one of them in patients with 18 brain metastases, dabrafenib and trametinib.</p> <p>19 As you can see in the waterfall plot, when 20 we treated patients with BRAF mutant brain 21 metastases, we saw disease control rates of almost 22 80 percent, very similar to what we see in</p>
<p style="text-align: right;">Page 30</p> <p>1 patients with active and progressing brain 2 metastases.</p> <p>3 Again, it was really a beautiful lecture, 4 multiple key points, and I would just highlight the 5 real take-home message is that capturing robust CNS 6 efficacy data is becoming increasingly important as 7 CNS active drugs emerge in non-small cell lung 8 cancer, and particularly, again, the question of as 9 we move into this era, the rationale for how we 10 start to do randomized trials, not just with 11 multiple targeted therapies and immunotherapies, 12 but how we incorporate radiation therapy in these 13 patients as well.</p> <p>14 Moving onto my easy topic, which is 15 melanoma, since that's what I take care of, brain 16 metastasis is always been a huge problem in this 17 disease, even before we had effective therapy. In 18 the old era in which all we had was chemotherapy, 19 the median survival for melanoma patients with 20 brain involvement was about 4 months.</p> <p>21 The treatment of melanoma has been 22 absolutely revolutionized, and we had 11 targeted</p>	<p style="text-align: right;">Page 32</p> <p>1 extracranial disease, but the duration of these 2 responses was about 7 months. That's half of what 3 we see in patients without brain metastases. And 4 in this study, 50 percent of patients progressed in 5 the brain while their extracranial disease was 6 controlled. So we're still struggling to learn why 7 this happens and, again, how to overcome that type 8 of differential activity.</p> <p>9 In parallel, we've been revolutionized by 10 the development of effective immune therapies. We 11 had initial clinical trials with single-agent 12 checkpoint inhibitors with ipilimumab and 13 pembrolizumab, which showed the proof of concept 14 that immunotherapy can achieve responses in 15 patients with brain metastases.</p> <p>16 Both achieved responses in about 20 percent 17 in patients who don't require steroids. We've 18 actually seen in patients that require steroids to 19 control cerebral edema much inferior results. But 20 what we've also seen is that when these responses 21 happen, they can be quite durable.</p> <p>22 What really revolutionized our expectations</p>

<p>1 for patients with brain metastases were two trials 2 that look to combined immunotherapy with ipilimumab 3 and nivolumab, patients, again, who did not require 4 steroids, where we saw response rates of close to 5 50 to 60 percent. And what's been so striking is 6 the fact that almost all of those responses are 7 still ongoing such that we saw a one-year overall 8 survival rate of 81 percent in the CheckMate 204 9 study.</p> <p>10 Importantly -- and I think this is something 11 that we went in looking very carefully -- these 12 studies showed no increase in adverse events or CNS 13 related toxicities in either study; that it was 14 absolutely safe to use these immunotherapies in 15 patients with brain metastases.</p> <p>16 While we're very excited about the progress 17 we've made with immunotherapy, we recognize that 18 these therapies haven't actually shown yet any data 19 that they can improve outcomes in patients who 20 require steroids, which is quite common. We still 21 have 40 percent of patients who blow right through 22 these, and aren't benefiting from them, and clearly</p>	<p>Page 33</p>	<p>1 how aggressive this is. It's also a field that's 2 very challenging because there aren't standards for 3 neurologic examination. They're still moving 4 standards in terms of imaging assessment and even 5 CSF cytological diagnosis.</p> <p>6 There is a dearth of clinical trials. All 7 of the trials that I talked about for patients with 8 brain metastasis actually excluded patients with 9 leptomeningeal disease, so it's a huge unmet need.</p> <p>10 But there are also key challenges we have as a 11 field of optimizing the design of these trials, 12 including the inclusion criteria, and actually 13 defining the endpoints for these studies is going 14 to be very important for us moving forward.</p> <p>15 Just to summarize all of this, I know it was 16 a quick and brief overview, but hopefully it 17 provides you at least a bit of a taste of what 18 those webinars actually have. Again, I encourage 19 you to go back and watch them. Some of the themes 20 are certainly this consistent underrepresentation 21 or delay for patients with CNS disease for 22 inclusion in clinical trials and early therapeutic</p>	<p>Page 35</p>
<p>1 looking for less toxic regimens.</p> <p>2 Again, our key challenge with targeted 3 therapy, how do we extend the duration of 4 responses? We actually will have our first 5 randomized trial comparing standard versus higher 6 dosing of BRAF-MEK combinations in the coming year. 7 What we're really looking at now as a field is 8 combinatorial approaches, not only combining 9 different immune therapies but immune and targeted 10 therapies, and again, the role of radiation therapy 11 as well.</p> <p>12 Finally, we have the final frontier, I would 13 call it, which is leptomeningeal disease. Again, 14 Dr. Le Rhun is really one of the world's experts in 15 this. For those of you who aren't as familiar with 16 this, this is, again, when you have disease not 17 focally in the brain but on the leptomeninges, so a 18 diffuse problem.</p> <p>19 The striking data is the median survival of 20 these patients is actually in the range of 2 to 21 3 months. I know in melanoma, we actually measure 22 our outcomes in weeks instead of months because of</p>	<p>Page 34</p>	<p>1 development. This is a particular problem for 2 brain mets, but even amongst the patients with CNS 3 involvement, and an even worse problem for patients 4 with leptomeningeal disease.</p> <p>5 That being said, we now have clear proof of 6 concept for the efficacy of systemic therapies in 7 these patients, and as we saw in lung cancer, there 8 is the potential to identify effective regimens 9 earlier or even regimens that have enhanced 10 activity in the CNS. We'll talk a little bit later 11 about what we know about the unique biology and 12 immunology of brain metastasis, which may provide 13 unique therapeutic opportunities as well.</p> <p>14 As we move forward, we still, though, today, 15 I think we'll focus a lot on our key questions and 16 challenges around trial design, including what are 17 the patient characteristics, inclusion and 18 exclusion criteria, and what are the best clinical 19 trial endpoints, and finally, moving from an era of 20 single-agent, single modalities, non-randomized 21 studies into combinatorial approaches, bringing 22 different therapeutic modalities together, and I</p>	<p>Page 36</p>

<p style="text-align: right;">Page 37</p> <p>1 hope learning from each other what we've learned in 2 different diseases to accelerate more effective 3 treatments and better trials. Thank you very much. 4 (Applause.) 5 Panel Discussion 6 DR. AMIRI-KORDESTANI: Thank you, 7 Dr. Davies. Excellent talk. 8 Now, we actually have excellent panelists we 9 have from pharma, patient, and actually also 10 academia. I wanted to actually give the 11 opportunity to each of them to introduce themselves 12 and give a few words, and then we can actually open 13 it up to questions and also take questions from the 14 audience. Thank you. 15 MR. QUEEN: Hi. Good morning. My name is 16 Derrick Queen, and I'm here to tell you about my 17 experience with brain metastases. Through my life, 18 great health was a part of my self-identity. I'd 19 always played athletics. I was captain of my 20 college hockey team, and I continued to play 21 competitive ice hockey after college. 22 I had a stressful job. I was working as a</p>	<p style="text-align: right;">Page 39</p> <p>1 that largest tumor but then had to figure out how 2 to address the rest of the cancer that had spread 3 to my body. 4 As part of that process, when the potential 5 treatments were outlined to me -- and actually as 6 part of that, just in my own research, I learned 7 that for somebody like me, the median survival rate 8 was about 4 and a half months. So I knew I had to 9 act quickly. I had two young kids. They were 12 10 and 14 years old. Besides thinking about how to 11 fight for my life, the other thought that went 12 through my head was what do I need to teach my two 13 boys before I die? 14 So there became the quest of how to beat 15 this disease. I was BRAF positive. Two drugs that 16 worked for me with incredible efficacy, I took 17 those drugs, but as Mike Davies just said, these 18 drugs for melanoma patients can last 6 months. In 19 my case, it was even shorter. It was 3 months 20 where they began to shrink my tumors, and after 21 3 months, that was it. My body became resistant to 22 them, and then new tumors appeared.</p>
<p style="text-align: right;">Page 38</p> <p>1 hedge fund portfolio manager in New York. Three 2 years ago, about exactly three years ago, I 3 experienced a very debilitating headache that was 4 unusual, that ultimately led to an MRI. At that 5 MRI, the doctors took me aside, what was a very 6 unusual experience for me because I was always used 7 to doctor's telling me you're in incredible 8 physical shape, and you're were really healthy and 9 go home. 10 But that was not what they told me. On that 11 day, they put up scans of my brain and said these 12 are the images that we just took of your brain, and 13 you've got 3 brain tumors and tumors in both lungs. 14 The tumors in your brain have progressed to a state 15 where one is so large, it's pushing everything from 16 the left side of your head over to the right side 17 of your head, and we can't let you leave the 18 hospital, and we need to operate immediately. 19 So here I was. Nobody in my family had ever 20 had cancer before, and this was the first news that 21 I had. I had to understand what this was and how 22 to cope with it, so I had brain surgery to remove</p>	<p style="text-align: right;">Page 40</p> <p>1 One of the things that was really disturbing 2 to me as a patient is that, at that time, there 3 were about 11 drugs on clinical trials for patients 4 like me, but because I had brain metastases, I was 5 not eligible for any of them. So one set of drugs 6 had done what they could, and then I had exhausted 7 that outcome. So it naturally begs the question of 8 what other drugs are there and what could they do 9 for me, and will I exhaust them also to the point 10 where I have no more options but death? 11 I consider myself incredibly lucky because 12 we tried something new, that was relatively new at 13 that time, where I got a dose of pembrolizumab 14 combined with stereotactic radiation. And again, I 15 was lucky because when I showed up to the hospital 16 that first day that I told you about, my brain mets 17 were just on the border of 2 centimeters, and that 18 was verging on becoming too big for stereotactic 19 radiation, so I got in under the wire. 20 That was in September 2016, and 3 months 21 later on Christmas Eve of 2016, I found out that 22 that treatment was actually working and my tumors</p>

Page 41	Page 43
<p>1 were responding and had shrunk by greater than 2 50 percent, and 5 months later, I was completely 3 off pembrolizumab. So my last dose was in May of 4 2017, and so I'm coming up on two years where I'm 5 back to playing competitive hockey and haven't had 6 a treatment since May of 2017.</p> <p>7 (Applause.)</p> <p>8 DR. WALKER: Hi. I'm Luke Walker. I'm with 9 Seattle Genetics and lead the tucatinib clinical 10 program there. Tucatinib is an oral anti-HER2 11 agent that we've been developing with hopes of 12 being able to treat patients with HER2 positive 13 brain metastases. From the very early-phase 1 14 trials, I've included patients with active as well 15 as treated brain metastases.</p> <p>16 I think the take-home that we have so far is 17 that it does take some extra care and attention, 18 and there are certainly extra complexities in this 19 endeavor, but it's certainly achievable. We're 20 currently in a registration trial that we expect 21 to have data on this year of 600 patients, about 22 half of whom we expect to have brain metastases.</p>	<p>1 and that requires extra care. 2 We also know that the use, for instance, of 3 MRIs of the brain for an independent blinded review 4 can be challenging, generally, but when you add in 5 that we're using brain MRIs in a non-neuro-oncology 6 trial, and the average medical oncologist is not 7 maybe as well versed in the nuances of the 8 different sequences of the MRIs, and making sure 9 that you really have good information and that 10 they're working with the radiology group at their 11 institution and so forth to get good quality data, 12 all that requires a bit of extra work.</p> <p>13 I think that in the end that extra work is 14 worth it and it's doable, and I hope that with some 15 of the actions that we're able to talk about today, 16 we can make that still easier and make these trials 17 more accessible to patients like Derrick.</p> <p>18 DR. EBIANA: I'm Victoria Ebiana, and I'm a 19 clinical director at Merck. I'm actually a 20 neuro-oncologist by training, and I don't think 21 it's an accident that I'm sitting next to Derrick. 22 I'm really incredibly touched by his story. He was</p>

Page 45	<p>1 physician scientist and run a lab that does a lot 2 of work on what really are the factors that predict 3 the development of brain metastasis, that are 4 unique to brain metastasis, and that drive 5 therapeutic resistance in brain metastasis.</p> <p>6 I would say that one of the things that 7 we've seen is that, again, we have the clear proof 8 of concept now that the agents that are safe and 9 effective extracranially are generally safe and 10 effective intracranially. There absolutely can be 11 unique challenges in thinking about what else we 12 need to do in settings where they're not as 13 effective, but I think we really need to reset the 14 expectations on therapeutic development to really 15 include these patients as early as possible.</p> <p>16 I think some of the unique challenges we do 17 run into are this is a group of patients where 18 often we really feel very uncomfortable waiting our 19 normal period that we wait to get patients started 20 on a therapy and thinking are there ways we can 21 facilitate designs to allow patients get treated 22 sooner.</p>
Page 46	<p>1 The other thing that's really exciting at 2 our institution is in January we opened our brain 3 metastasis clinic. We're now seeing patients with 4 brain metastasis from any disease, and patients 5 come into a room and actually get to meet at the 6 same time with a medical oncologist and 7 neurosurgeon and radiation oncologist to talk about 8 the multidisciplinary management of these tumors, 9 talking both about standard of care and about 10 clinical trials.</p> <p>11 We think this is a really powerful way to 12 optimize the care we can to deliver to these 13 patients and hopefully provides a really unique 14 platform for really facilitating and expediting new 15 clinical trials for these patients. So something I 16 think that is afield, hopefully is another place 17 that we can get to, to help improve their outcomes.</p> <p>18 DR. AHLUWALIA: Good morning, everyone. I'm 19 Manmeet Ahluwalia. I'm a medical neuro-oncologist, 20 and I work at Cleveland Clinic. My interests are 21 treating both primary brain tumors and brain 22 metastases with a primary interest of clinical</p> <p>1 trials, and also primarily looking at combinatorial 2 efforts with radiosurgery and some of these newer 3 agents.</p> <p>4 First of all, a great story by Derrick. I'm 5 really heartened to see a great response that 6 you've had, so I congratulate you on your success.</p> <p>7 I'm so excited because when I started doing this 10 8 years back as a medical oncologist, we had a very 9 limited role actually in the management of brain 10 metastases. It primarily was a neurosurgeon's game 11 where they would take the brain mets out, and then 12 it would be followed mostly by radiation.</p> <p>13 Most of the talk really was, would we give 14 whole-brain radiation or would we do stereotactic 15 radiosurgery? As Mike had shown work from Paul 16 Brown, I think the field has moved that at least in 17 the radiation, there are now efforts because 18 neurocognition is a big problem with these 19 patients. So the field is moving towards how can 20 you decrease the neurocognitive side effects when 21 you treat these patients. As Derrick's case 22 proves, these patients are living longer.</p>

<p style="text-align: right;">Page 49</p> <p>1 are two points, and Nancy Lin's talk also 2 highlighted that at least, which Mike Davies 3 covered, is not only do you need to look at these 4 agents and their response rates, you also need to 5 look at what's the duration of response, because as 6 in your case, these two agents work beautifully 7 before we see that, but the challenge is the 8 duration of response is not there.</p> <p>9 So we actually had recently published our 10 experience of over 150 patients where we treated 11 them with combined radiosurgery and immune 12 checkpoint blockade. A number of these patients 13 were treated actually with pembrolizumab but also 14 nivolumab.</p> <p>15 What we found was when we were able to 16 combine the stereotactic radiosurgery with the 17 immune checkpoint blockade, within 3 weeks of 18 treatment, we saw the best response, actually 19 completed responses naught of 50 percent. That's 20 higher than what we see with pembrolizumab alone, 21 which is around 30 percent in non-small cell and 20 22 percent in melanoma. Now we know the combinatorial</p>	<p style="text-align: right;">Page 51</p> <p>1 for patients with lung cancer who develop brain 2 metastases.</p> <p>3 I think we've heard a lot of interesting 4 beginning thoughts on defining the problem of CNS 5 metastases. I wanted to step back for a second. I 6 think we've really heard a lot about how we've made 7 dramatic improvements and now enrolling patients 8 with brain metastases into our clinical trials.</p> <p>9 Why didn't we do that before? What's 10 the -- and I think this is really just to educate 11 more than anything. Mike, maybe you can elaborate 12 on why patients with brain metastases were excluded 13 from trials before.</p> <p>14 DR. DAVIES: Certainly one of the issues has 15 always been concerns about whether these drugs will 16 actually penetrate the blood-brain barrier and have 17 activity. Dabrafenib was, again, a drug that is a 18 mutant selected BRAF inhibitor that was in some 19 ways selected for clinical development specifically 20 because it didn't cross an intact blood-brain 21 barrier in preclinical development, and therefore 22 it was thought this was an agent that wouldn't have</p>
<p style="text-align: right;">Page 50</p> <p>1 efforts are better, but we also need to look at one 2 with the neurotoxicities when we combine this.</p> <p>3 The other thing we like to look at is 4 whether the patient is asymptomatic or symptomatic. 5 I think that plays a critical role of which therapy 6 to do. We also at Cleveland Clinic have a 7 multidisciplinary program just like Mike Davies 8 said, because one thing I would definitely want to 9 stress on today is it takes a village to take care 10 of a patient with brain mets just like brain 11 tumors. So neurosurgeons, radiation oncologists, 12 medical neuro-oncologists, neuropsychologists, they 13 all have to work together to optimize the treatment 14 for these patients.</p> <p>15 So I'm very excited to be here and looking 16 forward to excellent talks. Thank you.</p> <p>17 DR. RIELY: I'll introduce myself as well. 18 I'm Greg Riely. I'm a medical oncologist who 19 treats primarily patients with lung cancer. As you 20 saw in Mike's presentation, patients with lung 21 cancer have the plurality of brain metastases that 22 we diagnose each year, so it's a critical problem</p>	<p style="text-align: right;">Page 52</p> <p>1 neurologic toxicities.</p> <p>2 Therefore, in the initial development, there 3 was a thought not to include patients with brain 4 metastases. And I can tell you melanoma 5 investigators around the world really harped on the 6 fact, well by the time you can see a brain 7 metastasis on an MRI, we know the blood-brain 8 barrier has been disrupted.</p> <p>9 So in the actual fact, the reason that we 10 initially saw activity in patients with brain 11 metastases is because there were clinical trials 12 that were ongoing that didn't require CNS imaging 13 in asymptomatic patients.</p> <p>14 So there were some patients who even though 15 PET scan is not the best way to actually look at 16 response to treatment in the brain, patients who 17 had PET scans had undiagnosed brain mets that 18 clearly shrunk on dabrafenib, and that really 19 changed the paradigm from saying that you couldn't 20 treat these patients to absolutely recognizing this 21 was a huge unmet need. Therefore, even though 22 dabrafenib was the second BRAF inhibitor to be</p>

<p style="text-align: right;">Page 53</p> <p>1 improved, we ended up with data for it almost two 2 years before we had data for the first FDA approved 3 BRAF inhibitor in patients in the brain. 4 Certainly, I think the other concern has 5 been historically the very poor outcomes in these 6 patients. I think sometimes people have just been 7 intimidated in thinking about how they're going to 8 talk about the efficacy of their drug if testing it 9 in patients who have had very poor outcomes. If 10 anything, I think we in the community harp on the 11 fact, well that's the population that we are most 12 desperately needing new treatments for and in fact 13 are most impressed by when we see activity. 14 I think, again, this idea that in the lung 15 cancer space, in particular this new paradigm, that 16 absolutely this may be a place where you can see 17 activity the earliest I think is a really important 18 concept and lesson that I hope drives further 19 assessment. 20 In terms of toxicities, I would say that we 21 had lots of concerns going in with immunotherapy 22 about whether we would see toxicity from increased</p>	<p style="text-align: right;">Page 55</p> <p>1 molecules. If you have a small molecule less than 2 400 dalton rate, you would probably traverse the 3 blood-brain barrier. 4 But as Mike alluded to, and we see this in 5 primary brain tumors as well as brain metastasis, 6 that actually when you're seeing brain mets, there 7 is a disruption of the blood-brain barrier. Then 8 it actually gets into the point of how potent the 9 agent is that is going to be able to traverse. 10 We also in our own practice have used 11 radiosurgery selectively to artificially disrupt 12 the blood-brain barrier. So what we know when we 13 use radiation -- at least in primary brain tumors, 14 we use a lot of that knowledge to translate it to 15 our brain metastases practices. 16 When you use radiation, there is a phenomena 17 of pseudoprogression, which is due to more further 18 disruption of the blood-brain barrier, and people 19 like Ben Ellingson can tell you better; but then 20 there's more gadolinium that actually spreads out, 21 and this basically tells you that there's a 22 disruption of the blood-brain barrier.</p>
<p style="text-align: right;">Page 54</p> <p>1 inflammation in the CNS. I have to say that hasn't 2 really been much of an issue. It's an issue that 3 we deal with anyways in routine clinical practice. 4 So I think those barriers, at least in terms 5 of concerns about efficacy and safety, I think 6 those are sort of falling away, so I really hope 7 that as we move forward, we are able to change that 8 paradigm. 9 DR. RIELY: Manmeet, Mike mentioned this 10 notion of a blood-brain barrier. I think this is 11 kind of a fundamental concept as we think about 12 treating brain tumors and treating brain 13 metastases. What's a blood-brain barrier and what 14 challenges does that -- 15 DR. AHLUWALIA: Yes, sure. Just basically, 16 blood-brain barrier is the lining around the brain 17 that exists actually. It's basically what we think 18 is so that the toxins don't get into the brain. So 19 it's the natural protection that exists in the 20 body. This has also been challenged traditionally 21 with the chemotherapies that tend to be large 22 molecules or the antibodies which tend to be large</p>	<p style="text-align: right;">Page 56</p> <p>1 So we tried to use some combinatorial 2 approaches where we are at least trying to increase 3 the blood-brain barrier penetration, and there's 4 also now interested in using ultrasounds, focused 5 ultrasounds of the brain actually, where you can 6 use high frequency or low frequency, which can 7 noninvasively disrupt the blood-brain barrier. 8 So I think this has been a major challenge 9 for the neuro-oncology community, how to get drugs 10 to get in. But a number of these small molecule 11 inhibitors, actually the good part is they have 12 good blood-brain barrier penetration, and 13 tucatinib now has excellent blood-brain barrier 14 penetration. 15 So I think companies are really picking up 16 on this, that brain metastases is a significant 17 clinical problem. A large number of patients have 18 brain metastases, especially from lung cancer, 19 melanoma, and breast cancer and a significant unmet 20 need, and they're focusing on how to develop 21 agents. 22 DR. DAVIES: If I could add just one point</p>

<p>1 to that. Again, we were really thrilled with the 2 activity we saw with these immunotherapies, which 3 again are all antibody based at this point. It's 4 actually unknown at this point whether these 5 antibodies actually have to get into the brain to 6 work or whether actually inducing a response in the 7 extracranial disease is sufficient to be able to 8 get trafficking of immune cells into the brain. 9 It's an unanswered question at this point.</p> <p>10 One of the things we do know is that when we 11 see responses in brain mets to immunotherapy, we 12 almost always see concordant responses in the 13 body as well; that it's not that those usually sort 14 of separate.</p> <p>15 That being said, we do actually see with 16 immunotherapies that we do have patients who are 17 responding in the body who progress in the brain or 18 have mixed responses. So I think there's still a 19 lot of questions around this that haven't been 20 answered to this point, but it is an open question 21 with immunotherapy; do you even have to cross the 22 blood-brain barrier with your drug or is it</p>	<p>Page 57</p>	<p>1 patients with radiologic leptomeningeal disease or 2 is this cytologic leptomeningeal disease, to ensure 3 that these patients have access as well; or if 4 there is still a differentiation, is there a way to 5 include cohorts within trials that might include 6 leptomeningeal disease that could be assessed 7 differently so that we can maintain access even if 8 the outcomes remain different.</p> <p>9 DR. DAVIES: If I could just add to that, 10 with Dr. Le Rhun not here, again, to your point, 11 it's one of the things that if you include cohorts 12 of those patients in your study, if you see 13 activity in patients with leptomeningeal disease, 14 that is something where there is such an unmet 15 need.</p> <p>16 Priscilla Brastianos is at the other end of 17 the table, and Mass General and MD Anderson, and 18 I'll let Priscilla talk about her experience. We 19 have an experience with immunotherapy for 20 leptomeningeal disease, actually intrathecal 21 immunotherapy, for a long time with IL-2, and now a 22 trial, first in-human study of intrathecal plus</p>	<p>Page 59</p>
<p>1 sufficient to stimulate a T cell to do the work for 2 you?</p> <p>3 DR. AMIRI-KORDESTANI: I wanted to go back 4 to the issue with the patients with leptomeningeal 5 disease, that still actually a majority of them are 6 being excluded from the majority of the clinical 7 trials. From your perspective, how could you 8 actually see that they could actually be enrolled 9 in the trials? Maybe you could start.</p> <p>10 DR. WALKER: That remains probably the last 11 frontier I think for these types of patients. For 12 our registrational trial, for instance, we did 13 exclude patients with leptomeningeal disease but 14 are currently exploring that, for instance, in an 15 investigator initiated trial.</p> <p>16 So I think that there probably needs to be a 17 little bit more data around the use of systemic 18 agents for leptomeningeal disease to make sure that 19 there's comfort that these patients can be enrolled 20 and also receive benefits.</p> <p>21 I certainly think that if we can get some 22 comfort there, and then define are we talking about</p>	<p>Page 58</p>	<p>1 systemic nivolumab, including patients who've 2 progressed on PD-1.</p> <p>3 One of the things that was a bit of a 4 challenge in getting the trial up and running was 5 the concern that there weren't enough patients to 6 conduct these studies. It is actually always 7 different to mine from the literature how many 8 patients there are with leptomeningeal disease. I 9 can tell you that once we opened the trial, the 10 number of patients who had leptomeningeal disease 11 who came to our front door went up probably 5 to 12 10-fold.</p> <p>13 These patients are out there. They 14 absolutely need studies. I would say also as 15 physicians, we absolutely need therapies to offer 16 to these patients. So I think this is a huge 17 untapped opportunity, and maybe Priscilla can talk 18 about her experience.</p> <p>19 DR. BRASTIANOS: Sure. Actually, thanks 20 Mike. So yes, as Mike mentioned, we're also 21 looking at immunotherapy and leptomeningeal 22 disease, and I'd like to second Mike's point.</p>	<p>Page 60</p>

<p>Page 61</p> <p>1 We added this as a separate cohort as part 2 of our immunotherapy trials. We have two trials 3 right now. We have a pembro and brain met trial, 4 but then we added an additional cohort; so to speak 5 to your point, adding additional cohorts with a 6 separate endpoint. Our endpoint is overall 7 survival for the leptomeningeal cohort, where's the 8 other brain met cohorts we have, we have RANO for 9 brain mets as the endpoint, so we added a separate 10 cohort.</p> <p>11 We filled up the leptomeningeal cohort in a 12 year and a half. For the pembro study, with 13 patients coming from all over the country, 14 actually, people fly to Boston with leptomeningeal 15 disease to get on studies because there are so few 16 leptomeningeal studies. We very quickly 17 transitioned to opening an ipi-nivo study for 18 leptomeningeal disease, again filling up really 19 quickly.</p> <p>20 Last year, we presented the result at ASCO, 21 and we're going to be submitting a manuscript very 22 soon, as we met primary endpoint for the</p>	<p>1 in the audience, and there's actually a full study, 2 which I'll be looking at ANG1005, an agent that was 3 looked at in brain metastases but showed very nice 4 activity in leptomeningeal disease. Also, 5 osimertinib is a drug that we have looked at a 6 trial ongoing right now, combining radiosurgery and 7 osimertinib. Obviously, there's a lot of active 8 data with the BLOOM study showing that 9 leptomeningeal patients actually get a response. 10 I think the different tumor types are 11 different. Sometimes you have to act very quickly 12 with patients with leptomeningeal disease. I think 13 the window of opportunity is really short in these 14 patients, but as has been expressed with prior 15 experience, if you do have cohorts, you'll see 16 patients will fly in and will come because they 17 don't have too many options.</p> <p>18 DR. BRASTIANOS: And to add to that, I think 19 it's incredibly important -- and I'll talk more 20 about this later -- to add in translational studies 21 so we can understand these patients more 22 particularly for the leptomeningeal study. I know</p>
<p>Page 62</p> <p>1 pembrolizumab and leptomeningeal cohort, which we 2 presented at ASCO last year.</p> <p>3 So just a plug for, yes, the patients are 4 out there. The patients are willing to travel to 5 come to these trials. It would be great if as a 6 community we opened up more multicenter trials. 7 And Mike and I have talked about joining forces, 8 but we'd love to join forces with more institutions 9 to allow these patients to go on study because 10 they're out there and they're in great need of 11 going on these trials.</p> <p>12 DR. AHLUWALIA: To add to that, I agree 13 completely with some of the sentiments that have 14 been echoed. I think leptomeningeal disease, as 15 has been called the last frontier, is obviously I 16 think one of the biggest challenges in the whole of 17 solid-tumor oncology, how to treat patients with 18 leptomeningeal disease.</p> <p>19 I think during our investigations of 20 patients with brain metastases, we have tried to 21 add cohorts of leptomeningeal disease in the past. 22 There's a trial -- actually Priya Kumthekar is here</p>	<p>Page 64</p> <p>1 Mike is doing this, and our group, again, joining 2 forces, but understanding responses and biomarkers 3 for the leptomeningeal cohort is especially 4 important, too.</p> <p>5 DR. DAVIES: The other thing I'll vouch for 6 as well is, just reinforcing Dr. Lin's point, 7 leptomeningeal disease is a place where we 8 absolutely need models to be developed for us to 9 help with therapeutic development, and again, an 10 area that's very difficult to get funding for at 11 this point because of the perception that it's a 12 rare entity.</p> <p>13 MS. SELIG: I wanted to take facilitator's 14 prerogative here and go back, if I could, to the 15 question -- and I see Luke's microphone 16 on -- really for our industry friends up here and 17 in the room of why haven't we been doing this 18 before. And you used the word "comfort," and I 19 would really love to hear some discussion about how 20 can we get to a place where there is more comfort, 21 especially with our industry colleagues, for 22 opening these kinds of trials. So maybe you could</p>

<p>1 start.</p> <p>2 DR. WALKER: Well, I think some of it</p> <p>3 relates to some of the comments that were made</p> <p>4 earlier about the need for these patients to have</p> <p>5 treatment very, very quickly. Sometimes in a</p> <p>6 clinical trial setting, it can take weeks for all</p> <p>7 of the necessary things to be done to get a patient</p> <p>8 on clinical trials, and some of these patients may</p> <p>9 not have that type of time.</p> <p>10 So there may need to be a different approach</p> <p>11 to these types of patients because of the nature of</p> <p>12 their disease. But I think if we can work very</p> <p>13 closely with our investigator colleagues to come up</p> <p>14 with ways to make sure that we're safely getting</p> <p>15 the patients on trial, obviously, but at the same</p> <p>16 time making it to where it's really feasible to do</p> <p>17 so and get them access to trials, that that's what</p> <p>18 really needs to be done.</p> <p>19 DR. RIELY: I think sometimes in clinical</p> <p>20 development, it's a bit of a catch-22. You have a</p> <p>21 new drug, you're not sure it's going to work in the</p> <p>22 CNS, so you don't want to put those patients on,</p>	<p>Page 65</p>	<p>1 perhaps the big concern is the patients are not</p> <p>2 going to have -- I think it's been more that these</p> <p>3 patients don't respond to systemic therapy. And I</p> <p>4 think that that's still ingrained in people's</p> <p>5 thoughts.</p> <p>6 So it's the worry about exposing these</p> <p>7 patients to potentially ineffective therapies, even</p> <p>8 though nobody's ever really tried them in a</p> <p>9 clinical trial setting. I think if we can get to</p> <p>10 the point where we have some level of clinical</p> <p>11 evidence, even if it's not a randomized trial, that</p> <p>12 some of these agents could be a beneficial.</p> <p>13 I think your point about the availability of</p> <p>14 patients is also a very important one because it is</p> <p>15 difficult to come up with a clinical trial if you</p> <p>16 think you're going to enroll one patient every</p> <p>17 6 months. But I think the reality is that these</p> <p>18 patients are actually much more available and the</p> <p>19 need is really much greater than that, and that</p> <p>20 makes the trials easier to do.</p> <p>21 DR. EBIANA: I'd just like to add to that</p> <p>22 we'd have to think about criteria that would make</p>	<p>Page 67</p>
<p>1 and then you develop an efficacy profile, and you</p> <p>2 say it looks like it's working, we're not sure how</p> <p>3 it works in the brain; let's keep those patients</p> <p>4 out and go forward.</p> <p>5 So I think from the industry perspective,</p> <p>6 it's hard from the trial design perspective to</p> <p>7 think about how we do that.</p> <p>8 One more thing I wanted to address on the</p> <p>9 trial front, and you alluded to it for</p> <p>10 leptomeningeal disease, when you're thinking about</p> <p>11 enrolling patients like that, how do you determine</p> <p>12 response and how do you identify it, that sort of</p> <p>13 thing. I think that's been a real limitation up</p> <p>14 until very recently. We now have the RANO criteria</p> <p>15 for leptomeningeal disease.</p> <p>16 I think one of your key decisions when</p> <p>17 you're developing a drug is trying to find a</p> <p>18 surrogate endpoint that will help you. Do you</p> <p>19 think that's probably the overriding issue in terms</p> <p>20 of leptomeningeal disease or is it a more of the</p> <p>21 fact that those patients are the sickest?</p> <p>22 DR. WALKER: It's both, but I think that</p>	<p>Page 66</p>	<p>1 it less likely that the patient would need to get</p> <p>2 something like radiation that would then confound</p> <p>3 our ability to really tell if the agent was</p> <p>4 working. A lot of patients with leptomeningeal</p> <p>5 disease need to get radiation to control symptoms</p> <p>6 or disease, and that would really make it extremely</p> <p>7 difficult to tell if the therapy was working and</p> <p>8 makes it almost impossible to really design a trial</p> <p>9 that we can interpret the results from.</p> <p>10 So that's another potential challenge, but</p> <p>11 again, we do have trials that examine</p> <p>12 leptomeningeal disease, mostly through our</p> <p>13 investigator-initiated program specifically for</p> <p>14 that reason. It's much easier to do that when all</p> <p>15 of the patients are being treated at a single</p> <p>16 institution and can be assessed rapidly.</p> <p>17 DR. RIELY: I think the</p> <p>18 investigator-initiated trials is a nice opportunity</p> <p>19 to get investigators who are wholly devoted to</p> <p>20 this, and I think that's an important aspect of it.</p> <p>21 I'll move to the microphone here.</p> <p>22 DR. NDOUM: Hey. How's it going? Edjah</p>	<p>Page 68</p>

<p style="text-align: right;">Page 69</p> <p>1 Ndoum. I'm a neurosurgical oncologist at the NIH. 2 Thank you for allowing me to be here. I was one of 3 the few neurosurgeons here. You knew we weren't 4 going to be silent the entire time. 5 One point I did want to make out is in 6 looking through the list of people, I don't think 7 there were any neurosurgeons on the panels or 8 speakers today, which to me is a little 9 interesting, because I know, as you mentioned, I 10 think neurosurgeons were very involved early on in 11 treatment of brain metastases, and I think we've 12 been kind of pushed to the side in a lot of cases. 13 I was talking with Dr. de Groot about the 14 clinic that you guys have at MD Anderson as you 15 mentioned earlier about having brain metastases' 16 patients seen by a neurosurgeon and an oncologist 17 and an radiation oncologist. I think that's a 18 fantastic model. I think it's something that could 19 be adopted more broadly. 20 Where this ties in is when we're talking 21 about designing trials for brain metastasis 22 patients and figuring out how the drugs work in</p>	<p style="text-align: right;">Page 71</p> <p>1 So I just wanted to put that in for the 2 discussion and see where we go from there. Thanks 3 for having me. 4 DR. BRASTIANOS: Just to add to that -- and 5 Mike mentioned this before -- absolutely, we need 6 our neurosurgical collaborators. As part of our 7 multiclinic at Mass General, we work closely. A 8 lot of these patients get shunted, both for ICP, 9 but also it allows us to collect CSF. 10 So absolutely, these brain met patients need 11 neurosurgical input, and the leptomeningeal disease 12 patients, too. And I'm sure others would 13 absolutely agree. 14 DR. DAVIES: We actually designed a trial in 15 melanoma around this question of why were brain 16 metastases not responding as durably to the BRAF 17 inhibitors. We're taking patients. We said, well, 18 this is a patient who is going to undergo surgical 19 resection. They haven't received BRAF inhibitor 20 before. Actually, what we did is we did the study 21 to treat for basically 10 to 14 days before 22 neurosurgery, and actually planned to get, when</p>
<p style="text-align: right;">Page 70</p> <p>1 brain metastasis patients, personally in the 2 glioblastoma space, my kind of mini soap box has 3 been talking about actually measuring how drugs 4 work in the tumor. The preclinical models are 5 fantastic, but we actually need to know how they 6 work in patients because the models aren't perfect. 7 So I think that insofar as particularly 8 leptomeningeal. Dr. Brastianos mentioned that 9 you're working on actually getting biomarkers with 10 that CSF or tissue that actually sees why the drugs 11 are getting there or having an effect. 12 I think that sort of model is something that 13 might be needed in small pilots that drug companies 14 can maybe consider supporting, where there is a 15 small subset of patients on a much bigger trial 16 that you're doing, where these are patients that we 17 know are going to resect the single tumor like 18 Mr. Queen, it had done for him. But you're getting 19 a dose of the drug ahead of time. We're taking the 20 tumor out, seeing what changes there might be or 21 what targets are there, and what concentrations the 22 drug has there.</p>	<p style="text-align: right;">Page 72</p> <p>1 possible, biopsies of extracranial tumors 2 essentially before the start of treatment and then 3 on the day of neurosurgery. 4 The challenge we had is in the current era, 5 it became so hard to find that patient who was 6 going to undergo surgery, who could wait for a 7 clinical trial, because often we're doing surgery 8 in patients who are highly symptomatic, and again, 9 the part about the time it takes to put patients 10 onto a trial where there wasn't a plan basically to 11 do gamma knife and where there wasn't a plan 12 basically to do systemic therapy. 13 I have to say the small number of patients 14 that we accrued, we've already had remarkable 15 insights in the difference that we've seen in the 16 brain met and the extracranial met on therapy, that 17 I think we'll reinvigorate interest in this. But 18 as we've talked about, the question is how can we 19 design those studies such that we actually can 20 successfully accrue patients, because that's a huge 21 challenge to those types of studies. But we're 22 very jealous of the GBM and the window studies;</p>

<p>1 absolutely.</p> <p>2 DR. AHLUWALIA: Just to add to that, I think 3 that's a great point. We have tried this approach 4 as well, having a strong neurosurgery program, and 5 typically these patients used to be operated on 6 much more before. Then, as the radiosurgery 7 equipment and the ability to do radiosurgery 8 changed, a lot of these patients actually ended up 9 undergoing radiosurgery rather than a resection.</p> <p>10 Also, the other thing that has changed is 11 because we do MRI screenings much more often now 12 compared to a decade back, we tend to catch these 13 lesions generally when they're smaller as compared 14 to when they used to be larger before, where they 15 absolutely needed to come out.</p> <p>16 When we have this discussion on our tumor 17 boards, whether someone who has a 1.5 centimeter or 18 a 2-centimeter lesion, the neurosurgeon says, yeah, 19 I can take it out, but at the same time I can do 20 radiosurgery and they'll be home, and you can carry 21 on the systemic treatments at the same time.</p> <p>22 I think with us learning a little bit more</p>	<p>1 brought out by Mr. Queen's story. One of the 2 issues is this whole idea of radiation and where to 3 put it in the continuum of treatment. We have this 4 therapy that we know can be quite effective for a 5 short period of time. So it can be helpful for 6 patients who need some kind of intervention, but 7 where do we fit that in with clinical trials, and 8 at what point do you allow patients to forego 9 radiation and try a clinical trial?</p> <p>10 The other topic I wanted to touch on briefly 11 was what Dr. Riely had brought up, going back to 12 the problem of CNS medicine and why have they not 13 been included. There are all the standard reasons 14 that we know about, the side effects. People are 15 afraid that their drug will result in bad outcomes, 16 so they don't want to develop it in this patient 17 population.</p> <p>18 It seems that the other reason is that we 19 haven't looked, and that's a really I think 20 important point that Dr. Ahluwalia just brought up, 21 is that we haven't done screening in the past as 22 much as we do now. It's sort of been this don't</p>
<p>1 about the biology of the disease, the fact that 2 that it's different in the brain as compared to 3 extracranially, I think there is, again, gain an 4 evolving role of the neurosurgeon, and we have seen 5 much more receptiveness on the part of the 6 neurosurgeons to take these patients to surgery. 7 Also, in this era of immunotherapy, you want the 8 mass effect to be decreased rapidly because you 9 don't like steroids, because steroids impact the 10 efficacy of most of the immunotherapies that we use 11 in our clinic.</p> <p>12 So I think the role of neurosurgeons is 13 coming back actively in terms of removing these 14 tumors, and obviously we are also in the process of 15 actually designing phase zero trials. I think we 16 have done this much more successful in the GBM 17 space, and I think in brain makes this a little bit 18 more challenging.</p> <p>19 MS. SELIG: Dr. Sul, did you have a comment 20 you wanted to make?</p> <p>21 DR. SUL: Yes. I think a lot of this 22 discussion is also highlighting a point that was</p>	<p>1 ask/don't tell. You don't want to know. You don't 2 want to go there and look. But it seems that we 3 really need to if we're going to count it along 4 with the other systemic mets. We've kind of left 5 it behind.</p> <p>6 Those are just the two points I wanted to 7 bring up.</p> <p>8 DR. DAVIES: Just to follow on to that, 9 again, Dr. Lin brought this up in talking about 10 breast cancer. One of the other things is about 11 strategies for patients that we know are at risk of 12 developing brain metastasis; how can we develop 13 trials and strategies to reduce that risk? That's 14 incredibly dependent upon coming up with 15 standardized ways that patients are surveilled for 16 brain metastasis.</p> <p>17 DR. LIN: I'll add that part of the don't 18 ask/don't tell really has to do with if you 19 diagnose a patient with a small asymptomatic brain 20 metastasis, they're now excluded from their next 21 clinical trial. It's a huge disincentive, from a 22 clinical perspective, to screen that patient.</p>

<p style="text-align: right;">Page 77</p> <p>1 In breast cancer, all of the guidelines 2 basically say don't screen patients with brain MRI 3 on a regular basis. Yael Lazer [ph] in our group 4 is the radiation oncologists is going to launch a 5 randomized trial to actually look at the question 6 of screening in breast cancer patients. But a huge 7 part of that really has to do with we're worried 8 we're going to do a patient a disservice.</p> <p>9 You find an 8-millimeter lesion and they 10 can't go on to the next trial of a HER2 TKI, which 11 may be perfectly effective against that brain met, 12 and they lose out on this next option. I think 13 these two things are linked. If we actually allow 14 more patients with brain metastases on clinical 15 trials, you're going to reduce the disincentive to 16 screen.</p> <p>17 DR. RIELY: In the limited time we have 18 left, I wanted to get to the microphone for another 19 question.</p> <p>20 AUDIENCE MEMBER: Thank you so much. My 21 name is Simon Tooma [ph], hematologist/oncologist. 22 I was at academia, so I'm currently working at</p>	<p style="text-align: right;">Page 79</p> <p>1 When is the right time to somehow say, you 2 know what, for our drug specifically, maybe it's 3 not time to put patients with brain mets because 4 chances are it's probably not going to benefit 5 them?</p> <p>6 DR. RIELY: I'll jump in first on that. I 7 think the key thing when I approach this is that 8 you don't go in with the a priori assumption that 9 drug's not going to work for people with brain 10 metastasis, so you have to have to keep your mind 11 open to that. But you also have to keep your mind 12 open to the observation that it's not working in 13 patients with brain metastases.</p> <p>14 So you begin the development with 15 inclusion/exclusion criteria, which allows safe 16 development of the drug, so you allow patients with 17 brain metastases, but they're not large brain 18 metastases, for instance; they're small ones. 19 Then, if you see that the majority of patients who 20 progress are progressing in the CNS, then you 21 realize that's not the place you want to be, and 22 then you can refine this. But I think you build</p>
<p style="text-align: right;">Page 78</p> <p>1 Lilly. I'd like to pose a question certainly to 2 the panelists today. Certainly, I'm so glad to 3 hear that there's definitely a lot of discussions 4 around getting patients with brain mets during the 5 early phases of clinical development as soon as 6 possible, but maybe if I could ask the panelists 7 for some guidance and maybe from our industry 8 colleagues here as well.</p> <p>9 It's good to certainly put patients in. 10 Many times, many of the drug companies certainly 11 have overlapping drugs specific to a specific 12 target, and we know that they have different 13 profiles going to the brain, and we don't know, a 14 priori, based on their TPU, their likelihood of 15 going to the brain.</p> <p>16 In that particular circumstance, can the 17 panel give some guidance in terms of when is it 18 time, on the other hand, to say maybe we shouldn't 19 continue to do it because as you're going through 20 dose escalation or the dose expansion stage of your 21 study, you may not be seeing activity if you allow 22 patients with brain mets.</p>	<p style="text-align: right;">Page 80</p> <p>1 that from data in the drug development experience, 2 not from just sort of an a priori assumption that 3 it ain't going to work there.</p> <p>4 DR. LIN: I can comment as well. That's 5 part of what the RANO group has tried to put 6 together, a framework for this, and Ross Camidge 7 was the first author of the trial design 8 publication. The idea is there are many ways to 9 mitigate this concern. You could have expansion 10 cohorts that are specific in the phase 1 for brain 11 metastasis patients. There are many -- if you 12 don't want a specific expansion cohort, you could 13 have a minimum number of brain met patients that 14 you're going to enroll in a more generalized 15 expansion.</p> <p>16 So I think there are ways to certainly look 17 at this a little bit better in that early-phase 18 setting. We'll have the case discussion, and the 19 afternoon will be on in the ALK story. I think 20 what it really highlights is that if you include 21 patients early on in the drug development, then you 22 actually have data on which to base a decision</p>

<p>1 whether or not to enroll such patients in your 2 registration trial. 3 If you don't generate that data, you're left 4 with this catch-22, which is where most drugs are 5 at this point, where you want to be conservative. 6 You don't want to let those patients on 7 registration trials. But then it means that 8 patients with brain mets don't have access to these 9 agents until well after drugs are developed, and 10 that's something we hope we can change. 11 MS. SELIG: I'm going to jump in here again. 12 You've heard my voice. I forgot to introduce 13 myself. I'm Wendy Selig, and I'm going to be 14 keeping the trains running here. We're about to 15 let this panel go, but there will be an opportunity 16 for you to come back with your question after the 17 next set of talks. 18 I just thought, can I take one more 19 prerogative and give Derrick a very quick last word 20 so we keep the voice of our patient as we go into 21 the next session? The next session is going to be 22 for individual talks. That's what these folks up</p>	<p>Page 81</p>	<p>1 anything else to add. I think in the interest of 2 time, we'll just keep it moving. But it's 3 fantastic to hear and see so many concerned people 4 to address this issue, which is clearly a solvable 5 problem, and I think it's in everyone's interest to 6 find a solution. Thank you. 7 MS. SELIG: Okay. So we're going to move on 8 to the next session. Our two chairs are right 9 there. If you guys want to introduce it briefly, 10 and then we'll go right into the talks. 11 Session II 12 DR. WEINSTOCK: Thank you very much. That 13 was an excellent session. I think it really helped 14 to define what we're going to be discussing in 15 Session II. 16 I'm Chana Weinstock. I'm one of the GU 17 oncology team leaders here, and I think the 18 inclusion of a GU oncologist I think brings to 19 light what Dr. Pazdur stated at the beginning of 20 this workshop, which is that we're trying to get 21 many voices involved here that maybe don't 22 traditionally think about</p>	<p>Page 83</p>
<p>1 here are doing up here. I just want to summarize 2 what I heard some people are thinking in terms of 3 themes in the problem area that we're then going to 4 be wanting to solve. 5 We heard about inclusion of patients. We 6 heard about timing of inclusion of patients. We 7 heard about how to address radiation in this 8 discussion. We need to be thinking of whether 9 we're actually looking in the right places, and 10 then we heard from Dr. Riely about our assumptions. 11 So just be thinking of those concepts as we move 12 forward. 13 Derrick, a very quick last point, and then 14 we're going to go into the next session, which is 15 for individual talks from over here. You guys can 16 use the podium or stay at your seats, as you will; 17 except for Nancy. Your microphone I think is the 18 one that's buzzing, so during the break, we'll 19 address it, but maybe you could use one of the 20 other ones. 21 Derrick? 22 MR. QUEEN: Wendy, thanks. I don't have</p>	<p>Page 82</p>	<p>1 brain metastases in drug development. So I'm very 2 interested in hearing how this evolves. 3 DR. LIN: I'm Nancy Lin. I'm a medical 4 oncologist focusing on breast cancer at Dana Farber 5 Cancer Institute and have been very involved with 6 Patrick in the RANO efforts, as well as in the ASCO 7 Friends of Cancer initiative for eligibility 8 criteria. 9 MS. SELIG: We have four talks and we're 10 going to keep on schedule. We've asked each 11 speaker to have a relatively parsimonious 12 representation of slides so we leave time for 13 discussion. 14 Presentation - Priscilla Brastianos 15 DR. BRASTIANOS: Thanks so much for the 16 invitation to speak today. As I mentioned, my name 17 is Priscilla Brastianos. I'm a physician scientist 18 at Mass General Hospital. I also lead a 19 multidisciplinary brain metastasis clinic there. 20 Just to put a plug in for what Mike said, the 21 patients are out there. With this 22 multidisciplinary clinic, we started the clinic</p>	<p>Page 84</p>

<p style="text-align: right;">Page 85</p> <p>1 four years ago, and our patient volume has exploded 2 by -- we've 5 times increased patient volume in the 3 clinic since we started this four years ago. So 4 there's a huge unmet clinical need, and it's 5 wonderful that we're all here together to try to 6 figure this out together.</p> <p>7 Today with my talk, what I hope to show is 8 how preclinical work can lead to new drug targets, 9 and I'm going to show that, again, it's an unmet 10 clinical need, and we do need more preclinical 11 models as well as more molecular studies to try to 12 understand what the therapeutic targets are for 13 brain metastases patients.</p> <p>14 These are my disclosures. Briefly, 15 molecular epidemiology of brain metastases, we've 16 already talked briefly about this earlier. About 17 30 to 40 percent of advanced HER2 positive breast 18 cancer patients will develop brain mets; 40 to 19 50 percent of metastatic triple negative patients 20 will develop brain mets; 25 to 40 percent of 21 advanced EGFR positive disease will develop brain 22 mets; and about 27 to 40 percent of ALK positive</p>	<p style="text-align: right;">Page 87</p> <p>1 decisions for systemic targeted therapies in brain 2 metastases patients. Historically, we've had a 3 limited understanding of how brain metastases 4 genetically evolved from their primary tumors. 5 There have been a few studies to try to 6 answer this question. The first study, to use 7 next-generation sequencing technology to try to 8 understand differences between brain metastases and 9 primary tumors, had one patient sample and showed 10 few de novo genetic alterations in brain 11 metastases.</p> <p>12 This very nice work by Dr. Davies group did 13 proteomic analysis in resected brain mets and 14 extracranial mets for melanoma patients and showed 15 PI3 kinase pathway activation in CNS metastases.</p> <p>16 Now we've brought together a team of 17 collaborators nationally and internationally to try 18 to understand the issues and try to understand what 19 are the targets in brain metastases, and we've now 20 collected more than 1500 matched brain metastases 21 primary tumors in normal DNA.</p> <p>22 This has been an enormous collaborative</p>
<p style="text-align: right;">Page 86</p> <p>1 patients at baseline will have brain mets; and 35 2 to about 70 percent in the second-line setting will 3 develop mets. In melanoma, about 40 to 50 percent 4 of advanced BRAF positive disease will develop 5 brain metastases. These are some of the important 6 targets we need to be thinking about.</p> <p>7 However, as Dr. Davies had said earlier, 8 patients will often develop progressive brain 9 metastases in the setting of stable extracranial 10 disease. This is an example of a 24-year-old 11 patient of mine with brain metastases with stable 12 extracranial disease and this devastating scan 13 here. We have a number of unanswered clinical 14 questions.</p> <p>15 Number one, do we see intracranial 16 progression because of incomplete drug penetration 17 or are there different genetic drivers? What are 18 the targetable mutations in brain metastases? And 19 finally, can we rely on a primary tumor biopsy to 20 make decisions for systemic targeted therapies in 21 brain metastases, which is what standardly often 22 done now as we do rely on a primary biopsy to make</p>	<p style="text-align: right;">Page 88</p> <p>1 effort and actually funded by some of the funders 2 here today, such as American Brain Tumor 3 Association and Melanoma Research Alliance. As 4 part of these efforts now, we're genomically 5 characterizing brain metastases primary tumors to 6 try to identify new therapeutic targets. As part 7 of this collaboration, we share data back to the 8 collaborators so that each of the collaborative can 9 then develop preclinical models and validate these 10 studies.</p> <p>11 Just again, how important it is and how 12 critical it is that we joined forces to try to 13 answer these questions.</p> <p>14 As part of these efforts, this is the first 15 study we published on this. We had done whole 16 exome sequencing of a hundred brain metastases 17 matched with primary and normal tissue, and this 18 included additional extracranial sites, as well as 19 temporally, regionally, and anatomically separated 20 brain metastases.</p> <p>21 For each matched brain metastasis and 22 primary tumor from the same patient, we mapped out</p>

<p style="text-align: right;">Page 89</p> <p>1 the genomic evolution to try to figure out where 2 different genetic alterations occur. Are they in 3 the brain metastasis only, depicted by the red; are 4 they in the primary tumor only, depicted by the 5 blue; or are they shared depicted, by the gray line 6 here?</p> <p>7 What we found across all the cases was this 8 pattern of divergent or branched evolution where 9 the brain metastasis and the primary tumor shared a 10 common ancestor, but there was significant genetic 11 evolution such that there were new oncogenic 12 mutations in the brain metastasis.</p> <p>13 Why is this such an important concept? 14 Well, we need to know if the therapeutic targets 15 are different in the brain compared to the 16 extracranial sites. This is the pattern we saw 17 across all our brain metastases. Charles Darwin 18 depicted this in his notebook in 1837 showing this 19 pattern of branched evolution. This is exactly the 20 pattern we're seeing in brain metastases.</p> <p>21 Take this back to the clinic. Do brain 22 metastases harbor clinically significant genetic</p>	<p style="text-align: right;">Page 91</p> <p>1 alterations in HER2 and EGFR. 2 Not surprising, many of these patients were 3 breast and lung patients. What was surprising is 4 that it was not uncommon to see ERBB2 5 amplifications or EGFR amplifications or mutations 6 in the brain metastasis and not detected in the 7 primary tumor sample.</p> <p>8 Genetic divergence between primary 9 metastatic samples, it creates a major challenge to 10 clinical decision making in oncology. What about 11 regional heterogeneity within the brain itself?</p> <p>12 How representative of both CNS disease as a single 13 brain metastasis sample? To answer that question, 14 we sequenced regionally, anatomically, and 15 temporally distinct areas of brain metastases.</p> <p>16 Here's an example of a patient with a 17 salivary gland ductal carcinoma that had a 18 cerebellar tumor taken out before whole brain, and 19 then a parietal metastasis taken out after 20 whole-brain radiation. And you can see the red are 21 the brain metastases. They were all more 22 genetically homogenous with each other and shared</p>
<p style="text-align: right;">Page 90</p> <p>1 differences compared to their primary tumors? 2 Indeed they do. This is an example of a patient 3 that had a brain metastasis from a renal cell 4 carcinoma developed synchronously with the primary 5 tumor.</p> <p>6 There's a shared common ancestor, so there 7 are shared mutations; yet the brain metastasis had 8 PIK3CA mutation and loss of CDKN2A that was not 9 detected in the primary tumor biopsy. This was the 10 case across the entire cohort. More than half the 11 cases had a clinically actionable alteration in the 12 brain metastasis that was not detected in the 13 primary tumor biopsy.</p> <p>14 Were there commonalities? So we can start 15 thinking about clinical trials for these patients 16 and that's why we're all here today. We found that 17 more than half the cases had alterations in the CDK 18 pathway. This included loss of CDKN2A and CDK46 19 amplifications. Forty-three percent of cases with 20 alterations associated with sensitivity to PI3 21 kinase inhibitors, so PIK3CA mutations, PIK3R1, 22 et cetera, and about a third of cases with</p>	<p style="text-align: right;">Page 92</p> <p>1 the same clinically actionable drivers that were 2 not detected in the primary tumor sample.</p> <p>3 What we're seeing is that CNS metastases are 4 relatively homogenous and we're validating this 5 across the larger cohort of samples. This actually 6 is another plug for why we need surgical 7 intervention, too, is because we are seeing that 8 brain metastases do harbor new mutations that are 9 not in the extracranial or in the primary tumor.</p> <p>10 However, central nervous system disease may 11 be difficult to access in many cases or 12 craniotomies are not trivial in every patient.</p> <p>13 Then we looked at extracranial sites and how well 14 do they recapitulate genetic vulnerabilities in 15 brain metastases.</p> <p>16 Here's an example of a patient with an 17 ovarian cancer. This patient had a primary tumor, 18 a lymph node, and a brain metastasis. Here we 19 showed the brain metastasis in the regional lymph 20 node sharing this common ancestor, yet the brain 21 metastasis harbors this long branch, so lots of 22 genetic divergence, and this aura kinase</p>

<p style="text-align: right;">Page 93</p> <p>1 amplification not detecting the primary tumor or 2 the regional lymph node. 3 Similarly, here's another example of a lung 4 adeno, so just as lymph nodes were not reliable 5 surrogates, nor were distal mets. Here's an 6 example of a lung cancer patient where we had the 7 brain metastasis, the primary tumor, and the bony 8 metastasis, and you can see here this genetic 9 divergence of this brain metastasis harboring these 10 alterations that are not in the primary tumor or 11 the brain metastasis. 12 This is very nice work by Mike Davies group 13 that was just published, where they actually looked 14 at melanoma brain metastases and patient matched 15 extracranial metastases and did RNA-seq analysis 16 and actually found oxidative phosphorylation being 17 enriched in melanoma brain metastases compared to 18 patient-matched extracranial metastases. So the 19 theme you're seeing here is that brain metastases 20 are evolving. They are distinct from their primary 21 tumors. 22 I just told you about this divergent</p>	<p style="text-align: right;">Page 95</p> <p>1 Will targeting those differences lead to improved 2 overall survival? 3 Actually, another plug for doing more 4 preclinical studies, our group and others are 5 creating patient derived xenograft models of brain 6 metastases, and again another place where the 7 fields can join forces. 8 This is a study that we published in the 9 last month. We developed patient-derived xenograft 10 models of breast cancer brain metastases and 11 actually looked at the efficacy of this PI3 kinase 12 inhibitor, the CNS penetrant PI3 kinase inhibitor 13 in most models, and showed that GDC-0084 does 14 inhibit tumor growth in vivo in a PIK3CA mutant 15 cell line and not in a PIK3CA wild type cell line. 16 Mike Davies' group, following up on their 17 work, they actually looked at the efficacy of an 18 OXPHOS inhibitor in a patient-derived xenograft 19 model of melanoma brain metastases. Here they 20 treated nude mice with human xenografts with either 21 an OXPHOS inhibitor or with a vehicle and showed 22 that mice treated with this inhibitor lived</p>
<p style="text-align: right;">Page 94</p> <p>1 evolution and how is this important to us? If we 2 were to exclusively sample the primary tumor or an 3 extracranial site, one may miss those potentially 4 clinically actionable drivers since our data showed 5 that clinically actual drivers occur in the brain 6 metastasis branch more than 50 percent of the time. 7 The other point I made earlier was that many 8 brain metastases patients do develop progressive 9 intracranial disease in the setting of extracranial 10 disease being stable. The question has always 11 been, is it a blood-brain barrier issue or is it an 12 oncogenic; is it a heterogeneity or genetic 13 heterogeneity issue? 14 So our data suggest that at least in part it 15 is a genetic heterogeneity issue, and there are 16 additional oncogenic alterations in the brain 17 metastasis that are contributing to this divergence 18 of therapeutic responses. 19 However, now we need to answer the question, 20 will targeting those molecular drivers in CNS 21 metastases lead to improved overall survival? We 22 just showed that there are genetic differences.</p>	<p style="text-align: right;">Page 96</p> <p>1 significantly longer. Again, we need to be 2 developing patient-derived xenograft models and 3 looking for inhibitors in these models. 4 How does this apply to patients? Now we're 5 starting a national biomarker-driven trial in brain 6 metastases, so we need to show that targeting what 7 we see in the brain leads to improved outcomes. 8 This trial just got approved from the FDA -- thank 9 you -- and a central IRB. It's set to open in 10 about a month to be activated nationally. It's 11 going to be an Alliance NCI trial, and many people 12 in this room have contributed to this trial, 13 including Carey Anders sitting in the audience and 14 Priya Kumthekar, and we're grateful. This has been 15 a massive, multidisciplinary and 16 multi-institutional effort to get this trial up and 17 running, so thank you, thank you to everyone. 18 Basically, we're going to be targeting 19 patients by what we see in the brain, and these are 20 patients that had brain metastasis tissue taken out 21 as part of clinical care and will go on to this 22 study. Actually, the primary endpoint will be a</p>

<p style="text-align: right;">Page 97</p> <p>1 response rates by RANO brain met criteria, so we 2 encourage all sites to get this trial open. The 3 idea is as we discover more therapeutic targets in 4 these patients with our genomics, we can actually 5 add additional arms. And we've partnered with 6 pharmaceutical companies to actually expand this 7 trial.</p> <p>8 In conclusion, what we're seeing is that 9 brain metastases harbor distinct clinically 10 actionable genetic alterations compared to their 11 primary tumors. Different brain metastases regions 12 are relatively homogenous. Extracranial mets are 13 not a reliable surrogate for brain metastases when 14 it comes to clinically actionable genetic drivers, 15 and alterations in the CDK pathway and PI3 kinase 16 pathways are frequent, and now work from Mike 17 Davies showing OXPHOS being enriched in brain 18 metastases and a national genomically guided trial 19 is planned.</p> <p>20 Of course, I'd like to acknowledge a number 21 of individuals who have contributed to all of this. 22 I guess we'll take some questions now or we'll do</p>	<p style="text-align: right;">Page 99</p> <p>1 brain metastases will not be good candidates for 2 clinical trials, as the competing risk of death or 3 deterioration will prevent proper evaluation of a 4 new therapeutic strategy, so we'll look at that. 5 The second historical paradigm is that 6 penetration across the intact blood-brain barrier 7 is required for activity in the CNS. So again, the 8 first assumption or corollary to that is that if a 9 drug does not show good CNS penetration across the 10 intact blood-brain barrier in animal models, it is 11 futile to study the drug for treatment of brain 12 metastases, and by extension, all those patients 13 should be excluded from all phases of drug 14 development. The reality is that is sort of the 15 paradigm that we've gone through over the last few 16 decades.</p> <p>17 The second corollary assumption to the 18 blood-brain barrier penetration is as or more 19 important than the mechanism of action or targeted 20 to the drug. So often when people are thinking 21 about whether or not to consider their drug for 22 treatment of brain metastases, the order of</p>
<p style="text-align: right;">Page 98</p> <p>1 questions later. 2 (Applause.) 3 MS. SELIG: Thank you. We are going to hold 4 the questions until the end of all the talks. 5 Dr. Lin? 6 Presentation - Nancy Lin 7 DR. LIN: Good morning, and thank you all 8 for joining. I'm going to talk for a few minutes 9 about selecting drug candidates for treatment of 10 brain metastases. These are my disclosures. What 11 I wanted to organize this talk around really is 12 around two historical paradigms, and I hope that we 13 can reexamine whether or not we should follow these 14 or not follow these in the years ahead. 15 The first historical paradigm is that 16 patients with brain metastases experience very poor 17 survival, and the corollaries to this from a drug 18 development standpoint have been, one, the 19 assumption that by the time brain metastases occur, 20 the cancer is highly refractory and unlikely to 21 respond to any systemic therapy, and the second 22 corollary or assumption has been that patients with</p>	<p style="text-align: right;">Page 100</p> <p>1 questions usually is does it penetrate the 2 blood-brain barrier, and only as a secondary, does 3 it have activity against the disease in question? 4 I am certain many of you in the audience 5 have had people come to you with drugs that they're 6 developing, and they say, "Well, we have this drug 7 that penetrates the blood-brain barrier." And you 8 ask, "Well, why do you think it might work in 9 breast cancer or lung cancer melanoma?" And then 10 the answer may be a little more sketchy. So I 11 think hopefully towards the end of this talk, we 12 can really flip that paradigm around and ask 13 perhaps the questions in a different order 14 The end results of these assumptions is that 15 patients with brain metastases have largely been 16 excluded from cancer clinical trials despite a very 17 high prevalence in some tumor types. You saw data 18 that Mike Davies presented from the breast cancer 19 literature. Only 1 percent of all phase 1 or 2 20 trials in many, many decades have specifically 21 focused on breast cancer brain metastases, and 22 similar, looking at lung cancer trials, even with</p>

<p>Page 101</p> <p>1 clinicaltrials.gov searches in the relatively 2 recent years. 3 So the question is, are these assumptions 4 true? If so, how true or how not true, and how 5 should we really be selecting drug candidates for 6 clinical trials? In terms of assumption number 1, 7 patients with brain metastases experience very poor 8 survival; how true is that? I'm showing you data 9 from breast cancer for melanoma and from lung 10 adenocarcinoma, really showing that at least for 11 some subsets of patients, survival after brain 12 metastasis diagnosis has substantially improved. 13 This is an academic collaboration led by 14 Paul Sperduto, pooling data from radiation oncology 15 databases across the United States. This focused 16 on breast cancer. What you can see is that for the 17 best prognosis group, which were patients with a 18 good performance status, HER2 positive subtype and 19 age less than 60, the median survival from a 20 diagnosis of brain metastasis was about 2 years. 21 So certainly these are patients who could 22 enter clinical trials where the endpoints would be</p>	<p>1 ALK rearrangement with a good performance status 2 and young age experience actually quite substantial 3 median survival compared to our historical 4 assumptions. 5 Finally, the poster child of this major 6 shift is melanoma. These are data from the 7 CheckPoint [sic] 204 study that you heard about 8 that was published in the New England Journal last 9 year. This is looking at overall survival in 10 patients treated with combination checkpoint 11 inhibition, and you can see that the numbers are 12 really quite astounding in comparison to what all 13 of our assumptions have been over the last decade. 14 So I think, for sure at this point, for some 15 subsets of patients, the survival after brain 16 metastasis diagnosis has substantially improved, 17 and even among those patients where it has not, I 18 would argue that these are patients who still have 19 a tremendous unmet medical need, and we don't want 20 to ignore those patients as well. 21 Now let's move into assumption number 2, 22 that penetration across the intact blood-brain</p>
<p>Page 102</p> <p>1 reached before their survival endpoint would be 2 reached. And remember, these patients were entered 3 between 1985 and 2007, so if anything, there's been 4 10 more years or 10 plus more years of progress. 5 Some have criticized this, quite rightly, as 6 being really a selected population of patients who 7 made it to an academic cancer center. Badi 8 Alazor [ph], who's a radiation oncologist in our 9 group has recently recapitulated this analysis with 10 a SEER database and in the SEER database looking at 11 patients presented with stage 4 de novo breast 12 cancer where we do have sites of disease. In fact, 13 the median survival almost completely lines up with 14 what was seen in the Sperduto analysis. 15 If we look at lung adenocarcinoma, again, 16 here the prognostic factors that came out were 17 different: age performance status, extracranial 18 disease, as well the number of brain metastasis, 19 and importantly the gene status, whether or not 20 there was an either an EGFR mutation or ALK 21 rearrangement. Again, you can see for the best 22 prognosis group, those patients with either EGFR or</p>	<p>Page 104</p> <p>1 barrier is required for CNS activity, and we'll 2 look to see how true or not true that is. The 3 first point is that penetration of the blood-brain 4 barrier is really irrelevant if the drug is 5 inactive against the target cancer. 6 I just can't stress that point enough. The 7 idea that the target is very important, as you 8 heard about from Priscilla, is so critical. These 9 are data looking at temozolomide, which obviously 10 is a very commonly used drug in neuro-oncology 11 based upon its PK characteristics, but these are 12 data looking at temozolomide for the use of 13 established active breast cancer brain metastases. 14 The first is a trial from NCIC Canada, which 15 basically was stopped for futility, no responses 16 seen in the first stage; another trial from Italy 17 looking at 51 patients with a 4 percent response 18 rate; and finally a randomized trial assessing 19 whether temozolomide may be a radio sensitizer, a 20 hundred patients enrolled in this study and no 21 difference in any of the outcomes. So again, I 22 think the target is really critical in selecting</p>

<p style="text-align: right;">Page 105</p> <p>1 the drug. 2 The second point is that it appears quite 3 clearly that lack of penetration across the intact 4 blood-brain barrier does not preclude activity 5 against established brain metastases. These are 6 data looking at whole body audio radiograph of 7 lapatinib penetration in male rats after a single 8 dose. You can see that there's almost nothing that 9 gets in. The brain plasma ratio is less than 0.13. 10 But in fact, lapatinib is quite active in 11 the brain. These were data from our very first 12 study looking at lapatinib and monotherapy. The 13 third person treated on the study, you can see 14 clearly that there's activity in the pre-baseline 15 versus the post with lapatinib monotherapy despite 16 the rat data that I showed you. And if combined 17 with chemotherapy, particularly in patients who had 18 not received previous radiation, so less heavily 19 pretreated patients, we see response rates in 20 excess of 60 percent. 21 How could this be? It's really this point 22 that came out earlier, which is that there is a</p>	<p style="text-align: right;">Page 107</p> <p>1 clear anti-CNS tumor activity. You can see this is 2 for anti-HER2 two agents, for chemotherapy, for 3 BRAF inhibitors; perhaps immune checkpoint 4 inhibitors may not need to get in to exert their 5 effect; EGFR inhibitors, and ALK inhibitors, as 6 well as VEGF inhibitors. 7 So we really I think have enough data at 8 this point to be quite convincing that blood-brain 9 barrier penetration across an intact blood-brain 10 barrier is not required for activity. 11 The question that this raises is whether 12 blood-brain barrier penetration is relevant at all. 13 So again, existing data tells us that lack of 14 penetration across an intact blood-brain barrier 15 does not preclude efficacy. And I would argue that 16 because of these data, we really should not use 17 these types of preclinical models to exclude 18 patients from clinical trials. 19 However, this still raises the question of 20 whether better blood-brain barrier penetration 21 might lead to more or more durable CNS efficacy or 22 could correlate with prevention affects. Here I</p>
<p style="text-align: right;">Page 106</p> <p>1 difference in biodistribution in normal brain 2 versus brain metastases. This was a study actually 3 using radiolabeled lapatinib as a PET tracer; 6 4 patients were recruited, 3 of these patients had 5 brain metastases. In normal brain, you can see 6 there's very little uptake, however, in brain 7 metastases there's substantially more uptake; 8 although in one of the patients, as you see, there 9 was heterogeneity between different lesions. 10 Akiko Morikawa, who is here in the audience 11 today, also led a study where rather than using a 12 PET tracer, they directly measured lapatinib 13 concentrations in a brief presurgical exposure 14 study, again, showing that lapatinib does reach 15 therapeutic levels in brain metastases, although in 16 a heterogeneous fashion, across and between 17 metastases. 18 This is a list of a few examples of drugs 19 which we know do not freely penetrate an intact 20 blood-brain barrier. In fact, some of them, 21 including for melanoma, were designed not to 22 penetrate the blood-brain barrier, but there's</p>	<p style="text-align: right;">Page 108</p> <p>1 think we don't fully know the answers, but I'm 2 going to show you some data, and we can think about 3 how convinced we are. 4 I'm going to show you data from the lung 5 cancer arena. This is data looking at crizotinib 6 versus alectinib in ALK rearranged lung cancer. 7 Crizotinib, we know very little crosses the intact 8 blood-brain barrier. There were interestingly 9 early observations of CNS-only progression leading 10 to a concern that this may be a liability of the 11 compound. And although CNS responses were seen, 12 numerically the systemic response rates were 13 higher. 14 In contrast, alectinib has excellent CNS 15 penetration, including into the CSF in preclinical 16 models, and in the early-phase studies, there were 17 high and similar response rates in a brain versus 18 extracranial sites. I will note that I'm only able 19 to make this slide because patients with active 20 brain metastases were allowed onto the early-phase 21 trials, so we had this data going into the 22 registration trial designs.</p>

Page 109	Page 111
<p>1 This shows the design of the ALEX trial, 2 which looked at ALK rearranged non-small cell lung 3 cancer. Patients were enrolled who are untreated 4 with advanced disease with a performance status 5 0 to 2, and they could have had asymptomatic brain 6 metastases or leptomeningeal disease and still be 7 eligible. Patients without brain metastases were 8 also eligible.</p> <p>9 Patients were randomized to either alectinib 10 or crizotinib, and the primary endpoint was 11 investigator assessed PFS across both compartments, 12 brain and body. Importantly, the stratification 13 factors included the presence or absence of CNS 14 disease at baseline.</p> <p>15 Notably, 40 percent of the study population 16 had brain metastasis at baseline, speaking to the 17 prevalence of this problem in patients, and also 18 notably in the protocol, there was CNS imaging at 19 baseline in every 8 weeks mandated across all 20 patients regardless of whether brain metastases 21 were present at baseline or not, so this is very 22 different than many of the trial designs that we</p>	<p>1 breast cancer medical oncologist, TDM1 is an 2 antibody drug conjugate that conjugates 3 trastuzumab, a monoclonal antibody that targets 4 HER2, along with a payload of emtansine. In the 5 metastatic setting, TDM1 is approved for treatment 6 of HER2 positive metastatic breast cancer, and 7 there was an attempt to bring it into the 8 early-stage setting.</p> <p>9 In the metastatic setting, after the 10 approval of TDM1 for treatment of general HER2 11 positive metastatic breast cancer, a number of 12 groups put together a case series to demonstrate 13 that there is activity in the CNS in the range of 14 20 to 50 percent in terms of response rate across 15 the various studies.</p> <p>16 I will point out that none of the either 17 phase 1, phase 2, or registration trials of TDM1 18 included patients with active brain metastases. 19 They were excluded from all phases of their drug 20 development, but nevertheless, we do know that it 21 has some activity in the CNS, and presumably 22 because of its size, it does not cross the intact</p>
<p>1 see. Interestingly, despite the fact that 2 crizotinib does not cross the intact blood-brain 3 barrier, 50 percent of patients achieved a CNS 4 response with crizotinib, but it was significantly 5 higher with alectinib at 81 percent.</p> <p>6 You can see in terms of their primary 7 endpoint of progression free survival that this 8 favored alectinib over crizotinib, and because of 9 the mandated CNS imaging, they were able to 10 actually create proper curves looking at the 11 cumulative incidence of CNS progression and 12 demonstrate a prevention effect of alectinib.</p> <p>13 So I think that this study is very 14 instructive. You will hear more about the ALK 15 story in a later session; but really, in terms of 16 both the study design and the inclusion, what led 17 up to the study to allow these patients to enroll, 18 to really help us learn something very important 19 about this patient population in which brain 20 metastases are so common.</p> <p>21 I'm going to contrast that with the 22 KATHERINE data. For those of you who are not</p>	<p>1 blood-brain barrier.</p> <p>2 The KATHERINE trial looked at patients who 3 were treated with curative intent with new adjuvant 4 chemotherapy, and then at the time of surgery if 5 there was residual disease, the randomization was 6 trastuzumab, which is the standard of care or 7 switch to TDM1.</p> <p>8 You can see in terms of the overall endpoint 9 of invasive disease-free survival, there was a 10 substantial advantage of TDM1 more than 10 percent 11 absolute delta and that there was also a 12 substantial decrease in the risk of distant 13 recurrence. But somewhat disappointingly, there 14 was actually no change in the incidence of CNS 15 disease as first site of relapse, raising the 16 question of whether CNS penetration is required for 17 prevention effect. I don't know that we know; we 18 don't have that many data points to look at, but 19 certainly does raise that question.</p> <p>20 The other point from this study to note is 21 that if we think about -- these are our highest 22 risk patients at this point, the patients who are</p>

<p style="text-align: right;">Page 113</p> <p>1 eligible for neoadjuvant therapy, and you can see 2 that if we were to march into the future, given 3 that about half of the distant recurrences were in 4 the brain, and of these patients where the distant 5 recurrence was not in the brain, probably somewhere 6 between 20 and 50 percent will eventually develop 7 brain metastases; that in the future as breast 8 cancer medical oncologists, we are going to 9 be -- for the HER2 positive metastatic patients, 10 they're going to be brain metastases patients, and 11 again, really stressing the point that studying 12 this patient population is so very important. 13 Finally, and Priscilla has touched on this 14 as well, is whether better preclinical models can 15 help with drug selection. I think it's very clear 16 at this point that just simply doing audio 17 radiographs studies or studies to look at 18 distribution of drug in normal animals really does 19 not help us determine which drugs will be effective 20 in the brain. I've shown you many examples of 21 that. The question is can we develop better 22 preclinical models?</p>	<p style="text-align: right;">Page 115</p> <p>1 in a mammary fat pad. They can be grown out. They 2 recapitulate the genomic and IC characteristics of 3 the original patient's tumor, and then you can run 4 mouse clinical trials, really testing a number of 5 different combinations and trying to prioritize 6 which combinations or strategies to take into the 7 clinic. 8 At this point in time, because there are a 9 relative dearth of trials in terms of breast cancer 10 or other brain metastases that have reported out, 11 relative to corresponding models, I think it's hard 12 to conclude at this point which model is going to 13 be the most predictive. But hopefully, if we 14 continue to do these experiments in parallel, then 15 in the future we'll have better ways to select 16 which drugs to prioritize for drug development. 17 In conclusion, I hope that we will take away 18 some ability to rethink our assumptions. I think 19 that that is really going to be key into changing 20 how we take care of patients with brain metastases 21 relative to clinical trials. In terms of 22 conditions for efficacy of systemic therapy against</p>
<p style="text-align: right;">Page 114</p> <p>1 There are 3 strains of preclinical models, 2 major strains. One is to take established cell 3 lines, inject them intracranially, and then test 4 the drug in those intracranial models, and that's 5 still probably the most common way that these 6 studies are done. 7 Pat Keegan at the NCI has pioneered the use 8 of these brain metastatic cell lines where she 9 takes normal breast cancer cell lines and injects 10 them intracardiac. They then spontaneously 11 metastasize to the brain, select out those brain 12 metastases, put them back intracardiac, and over 13 multiple passages have created several lines that 14 are very highly metastatic to the brain in a more 15 spontaneous fashion and does not require 16 intracranial, so that's one additional strain. 17 Finally, I think more and more we're seeing 18 people start to put together patient-derived 19 xenograft models, and this is an example of how 20 that works. A patient who is undergoing a clinical 21 resection at the time of resection can sense that 22 tumor is put in a mouse brain and also can be put</p>	<p style="text-align: right;">Page 116</p> <p>1 established brain metastases, I think, number one, 2 is there needs to be a rational target. It needs 3 to be active against the underlying disease, and 4 either achieve therapeutic levels in tumor tissue 5 or exert effects independent of penetration in 6 tumor tissue. That may be the case with checkpoint 7 inhibitors. But it's very clear that penetration 8 across an intact blood-brain barrier is not 9 required. 10 What are the conditions for prevention 11 effect? Again, you'd like a rational target, but 12 here there actually may be the opportunity to look 13 at agents that actually directly affect brain 14 metastatic potential. So there may be agents that 15 actually are not necessarily effective against 16 established metastases, but if we can identify the 17 underlying factors that allow cancer to go to the 18 brain, there may be the ability to target those 19 pathways as well. 20 I would argue that at least for right now, 21 the existing data suggests, although it does not 22 prove, that penetration across an intact</p>

<p style="text-align: right;">Page 117</p> <p>1 blood-brain barrier may be associated with a better 2 prevention, a potential at least for those drugs 3 that need to exert their action at the tumor site. 4 Finally, in terms of preclinical models, 5 again, I would argue that standard drug 6 distribution studies in normal animals is not 7 enough and really should not be used solely as an 8 exclusion for patients to enter into early-phase 9 trials. Intracranial models are probably better, 10 although which model and under what circumstance, I 11 think we still need to work out. So thank you. 12 (Applause.) 13 DR. WEINSTOCK: Thank you very much. Our 14 next talk is by Dr. Margolin about issues with 15 conducting brain metastases clinical trials. 16 Presentation - Kim Margolin 17 DR. MARGOLIN: Thank you very much. I think 18 that I was asked to really put together some 19 concepts, very briefly, that will jump start or 20 kick start a discussion for later on rather than 21 giving you the definitive answers to any questions. 22 By this time of the morning, I think you've heard</p>	<p style="text-align: right;">Page 119</p> <p>1 approval of agents that treat patients with brain 2 metastases, and it has to be put into context as I 3 just said. 4 How do we define these needs and how do we 5 define the regulatory strategies, which rather 6 complicated challenges? We know from history that 7 the gold standard for all of what we do in cancer 8 patients is of course overall survival and 9 certainly has been traditionally the standard for a 10 criterion for FDA approval of a new agent. 11 Certainly in the days when I was on ODAC, that was 12 really the be-all and end-all, and it was with 13 great trepidation that we ever talked about fuzzy 14 endpoints like progression-free survival and all of 15 the challenges to using those endpoints, but they 16 do have some pros and cons. 17 We talked already about some of the concepts 18 of looking at intracranial response rates in 19 progression-free survival. And for those of you 20 who had the time and pleasure of looking at Ross 21 Camidge's webcast, it was really quite amazing. I 22 think you'll be hearing more about that later on</p>
<p style="text-align: right;">Page 118</p> <p>1 almost all of the things that I'm going to say in 2 my slide set anyway or seen most of these slides, 3 so we'll keep it brief. 4 So why are we here? Do we really need 5 regulatory criteria for the approval of agents that 6 treat brain metastases? Actually I'm going to go 7 back for a second just to point out the fact that I 8 underlined this comment, that this is to talk about 9 issues in conducting clinical trials for patients 10 with brain metastases rather than treating brain 11 metastases. 12 I think that's really super important as we 13 talk about the two compartments and the idea of 14 competing risks of death or morbidities from 15 cancer, being the extracranial disease versus the 16 intracranial disease, including leptomeningeal 17 disease. So we have multiple challenges that are 18 all interacting with each other. 19 So back to why we're here, yes, it would 20 appear, based on the number and nature of the 21 people in this group, that we do need some 22 regulatory criteria for the development and the</p>	<p style="text-align: right;">Page 120</p> <p>1 today talking about drugs and brain metastases and 2 some interesting concepts about assessing. 3 There are other endpoints, of course, 4 neurologic quality of life. Patient reported 5 outcomes are also important and maybe harder in 6 some ways and easier in some ways to quantitate. 7 There are indirect criteria but equally important 8 such as patients coming off of steroids. 9 We've talked very little about the 10 interactions of steroids with some of the endpoints 11 and some of the therapeutic strategies, but for 12 those of us who are more in the immunotherapy 13 world, that's a really critical concept and 14 challenge that has to be addressed uniquely; 15 combination strategies with stereotactic 16 radiosurgery and with neurosurgery and other ways 17 to combine therapeutic strategies, and maybe 18 even in my world, in melanoma, some of the targeted 19 agents with immunotherapies are going to be very 20 important. 21 Then how can we define other surrogate 22 endpoints that may support accelerated approvals if</p>

<p style="text-align: right;">Page 121</p> <p>1 we're truly going to look at drug approvals that 2 are uniquely designed for patients with brain 3 metastases? What about the use of concepts like 4 when can you discontinue some of the adjunctive 5 therapies? We haven't talked about therapeutic 6 strategies like bevacizumab as well. Importantly, 7 there are currently no comparators, so we're kind 8 of forging or blazing a new trial here and using 9 approved therapies as benchmarks.</p> <p>10 I think you've really heard a lot about the 11 incidence of brain metastases in various solid 12 tumors, but I just want to point out a couple of 13 things. There are patients in whom brain 14 metastases are found at the first presentation of 15 metastatic disease, particularly in melanoma where 16 it may be as high as 20 percent of patients or even 17 more with melanoma. Then of course there is the 18 other cohort, which is at the time of progression 19 on their first or subsequent therapies for 20 metastatic disease.</p> <p>21 In melanoma, pretty routinely, every time a 22 patient has the first metastatic disease or first</p>	<p style="text-align: right;">Page 123</p> <p>1 the growth of certain clones in the brain that can 2 occur. I'm not going through all the details here, 3 but there are many opportunities for clones to 4 become prone to CNS metastases and thriving in the 5 brain.</p> <p>6 You've really heard about this. I don't 7 think we should focus heavily on this slide, and 8 you've heard about lung cancer brain metastases, 9 and you've heard about breast cancer brain 10 metastases, so I don't want to dwell on what you've 11 already heard or will be hearing about more today.</p> <p>12 What about clinical trial design today?</p> <p>13 There's a lot of retrospective literature about the 14 sequencing versus the simultaneous modalities, 15 particularly SRS and systemic therapy for various 16 tumors metastatic to the brain. But with all due 17 respect to my colleague, Dr. Ahluwalia and others, 18 it's really critical to really prospectively study 19 these sequences and these combinations. All of the 20 principles in the first slide must be considered, 21 and I won't regroup that.</p> <p>22 The challenges in the imaging are also</p>
<p style="text-align: right;">Page 122</p> <p>1 progression in need of another, we look at the 2 brain. From what I've heard this morning, I think 3 that's going to be more and more true for the two 4 other big diseases that metastasize to the brain; 5 that is lung cancers and breast cancers.</p> <p>6 Then of course the concept of looking for 7 escape metastases, how often and what type of 8 scanning should be done in patients with these 9 diseases who appear to be responding to our 10 systemic therapy for disease outside the brain 11 who've never had known disease in the brain. 12 Sometimes you get surprised.</p> <p>13 What are some of the biologies of brain 14 metastases? You heard a very elegant explanation 15 from Priscilla Brastianos and as well from my Mike 16 Davies who have really done pioneering work in the 17 field. This is one of my favorite slides from a 18 somewhat older now review by Mike Davies' group 19 where I fixed the captions a little bit, but really 20 sort of speaks to the concepts of when and where 21 some of the mutations or non-mutational changes 22 that may occur, that predispose to or facilitate</p>	<p style="text-align: right;">Page 124</p> <p>1 important, and you'll be hearing about that in the 2 next speaker's talk. So again, I won't dwell on 3 that, but timing, size, alterations and appearance, 4 peritumoral edema, hemorrhage, new lesions, 5 pseudoprogression, obviously the critical 6 importance of defining the compartments and how you 7 use those data to determine the value of a 8 particular therapeutic intervention.</p> <p>9 Then of course the whole problem of 10 radionecrosis from prior SRS and whether you 11 believe that some of our systemic therapies are 12 enhancing that and how can that be addressed and 13 how can it be identified, treated, prevented, and 14 so forth.</p> <p>15 These are some of the categories of 16 metastatic disease in the CNS and outside the CNS. 17 It looks like a complicated slide, but this is the 18 true clinical world where each patient's disease 19 really does need to be customized and thought 20 about, and it does take a village. All of these 21 categories are the underlying groups and cohorts 22 that we have to think about in terms of clinical</p>

<p style="text-align: right;">Page 125</p> <p>1 trial design, as well as in the design of some of 2 the pathways, for example, for the NCCN and ASCO, 3 and so on and so forth. So clinical trial design 4 reflects real decisions and real decisions reflect 5 the clinical trial design.</p> <p>6 This is my last slide. I told you I'd keep 7 it brief, and this is just the title and the 8 authorship of -- and the first line kind of snuck 9 in there -- for systemic agents in patients with 10 brain metastases from solid tumors, which is the 11 guideline by the -- and now I know how to pronounce 12 it -- RANO working group. It's a living dynamic 13 group of individuals that are really trying to 14 define this field in primary brain tumors and brain 15 metastases, and happy to be a member of that group 16 that meets every year at ASCO with quite an 17 important output.</p> <p>18 So I'll stop there and listen to 19 Dr. Ellingson next. Thank you.</p> <p>20 (Applause.)</p> <p>21 Presentation - Ben Ellingson</p> <p>22 DR. ELLINGSON: Thank you. My name is Ben</p>	<p style="text-align: right;">Page 127</p> <p>1 assessment, there are really two components that we 2 have to consider. The first part is image 3 acquisition. That typically requires T2 weighted 4 or T2-weighted FLAIR scan. What these measures 5 are is really water content within the brain. 6 They're used to identify brain metastases that 7 maybe don't have blood-brain barrier disruption. 8 The second set of sequences that we consider 9 our pre- and post-contrast T1-weighted images. 10 These are kind of your classic contrast enhancing 11 lesions that we typically see or define emergence 12 of these brain tumors. But really what they do, 13 what they're measuring, is disruption of the 14 blood-brain barrier and gadolinium or your contrast 15 agent leaking into the extravascular space. 16 The last set of images that are used quite 17 routinely are diffusion and perfusion MRI, and 18 these typically reflect cell density in the case of 19 diffusion and perfusion vascularity within the 20 tumor because we know these tumors tend to be 21 highly vascular. 22 Now, once we have that information, that's</p>
<p style="text-align: right;">Page 126</p> <p>1 Ellingson. I'm a professor of radiology at UCLA, 2 and I've done a lot of work in standardizing brain 3 mets response assessment, particularly 4 radiographic, and radiographic measurement, and how 5 we're going to actually judge these things. Unlike 6 tumors in other parts of the body, which you're all 7 familiar with, serial biopsies are not really 8 possible. They're safe when we talk about CNS 9 metastases. So there are really few pathologically 10 confirmed responses.</p> <p>11 We rely heavily on imaging, particularly 12 MRI, but sometimes PET imaging, for routine 13 clinical monitoring and response assessment for new 14 therapeutics. MRI has exquisite soft tissue 15 contrast, so we can see different aspects of the 16 brain biology. It doesn't use ionizing radiation, 17 unlike CT and other modalities. And really, 18 there's a variety of different flavors that we can 19 use to evaluate anatomy and physiology, so it makes 20 it particularly attractive.</p> <p>21 Now, When we talk about response assessment, 22 and again, particularly radiographic response</p>	<p style="text-align: right;">Page 128</p> <p>1 only one piece of the puzzle, the other part of the 2 puzzle really is quantifying disease burden and 3 interpreting that in terms of its clinical meaning. 4 In terms of disease quantification, we do size 5 measurements, we do quantification, maybe total 6 lesion volume; and then in response to 7 determination, this is the thresholds that we set 8 up that's really a meaningful change, and these 9 make up our critical endpoints.</p> <p>10 About a month ago, there was an article in 11 the New York Times that talked about The Joy of 12 Standards. It was an opinion article, and it 13 really talked a lot about how, although very boring 14 and not talked about enough, life is a lot easier 15 when you have standards and you can plug your 16 devices into any outlet.</p> <p>17 We really need to make these standards to 18 make meaningful progress. There are standards all 19 around us, electrical outlets and gasoline pumps. 20 Even cinderblocks that make up structures have 21 standards that they comply with. The modern 22 laptop, for example, has over 250 standards that</p>

<p>Page 129</p> <p>1 they comply with. 2 Many of these standards, the vast majority 3 of them, are really voluntary consensus 4 recommendations much like we've done or are going 5 to do in this field. So really building and 6 improving upon a set of standards, it may not be 7 the greatest set of tools we have, but building 8 upon those is really the path to tangible progress, 9 so having a concrete baseline in which to build is 10 critical. 11 Our first attempt at standardizing brain 12 tumor imaging protocol came in 2015, and it was 13 really the result of a workshop much like this. 14 This was designed for primary brain tumor clinical 15 trials, primarily high-grade gliomas like 16 glioblastoma. It was designed after a lot of 17 meetings, a lot of phone calls, and a lot of people 18 invested a lot of time in this. 19 It was designed to be synergistic and used 20 in cooperative group settings and allowed for use 21 in community and academic medical centers, so 22 there's a lot of flexibility. It was supposed to</p>	<p>Page 131</p> <p>1 other aspect of these consensus protocols was 2 really requiring diffusion MRI to be acquired in 3 addition to these anatomic scans. That was for a 4 variety of reasons, one being to rule out stroke, 5 and the other to look at cell density and what's 6 going on within the tumor. 7 There are unique challenges associated with 8 brain mets that are not necessarily true for 9 high-grade gliomas. Thin 3D images are absolutely 10 critical to accurately quantify the extent of 11 disease. So unlike high-grade gliomas that may 12 have one or even a few target lesions, there can be 13 many target lesions or many small lesions 14 throughout the brain in patients with brain mets. 15 So there's a requirement for high resolution 3D 16 imaging of the brain and spine if we're looking at 17 leptomeningeal spread. 18 There's also a need for better contrast to 19 noise, and some anecdotal evidence or some evidence 20 from the literature suggests that in order to 21 detect really small lesions, we may want to move 22 from our traditional standardized gradient echo to</p>
<p>Page 130</p> <p>1 be compatible with most clinical MRI protocols, so 2 it wasn't burdensome to the different institutions 3 and the different medical facilities that are going 4 to be conducting these trials. 5 I already touched upon this, but really the 6 minimum standards that we came up with were pre- 7 and post-contrast, T1-weighted images to look at 8 contrast enhancing lesions, and we wanted these to 9 be volumetric. Typically, we acquire in the brain 10 prior to this thick slices, 2-dimensional axial 11 slices, and then we try to make some measurements 12 on those. 13 What we required is 1 to 1 and a half 14 millimeter isotropic, meaning equal in all sizes, 15 resolution so we can really accurately measure 16 these lesions. The second aspect was 2-dimensional 17 T2 or FLAIR imaging. I mentioned this before. 18 This is to look at non-enhancing disease or 19 cerebral edema. 20 We were pushing the limits of the 21 manufacturer saying we want thinner slices so we 22 can really see the true extent of the disease. The</p>	<p>Page 132</p> <p>1 a more spin echo based approach, which again is not 2 standardized across vendors, so it could be 3 particularly challenging in a multicenter, 4 multisite study, but there seems to be evidence 5 that that might provide additional value. Again, 6 this can be extra cost to the institutions to get 7 these types of sequences; it's not standardized. 8 And there's a big difference between high field and 9 low-field scanners. 10 In general, 3D turbo spin echo seems to be 11 the best to delineate these lesions followed by 3D 12 gradient echo, which is part of the standardized 13 brain tumor protocol to date, followed by 14 2-dimensional turbo spin echo, which is the 15 previous standard of care acquisition. 16 In building upon the standards that we 17 already established a few years back, Tim Kauffman 18 at the Mayo Clinic, and in myself playing a small 19 part, were leading this effort to try to build upon 20 that protocol and integrate some of the 21 recommendations for the RANO brain met 22 recommendations in order to be compliant with those</p>

<p style="text-align: right;">Page 133</p> <p>1 standards as well.</p> <p>2 Really, the two main pieces -- and again,</p> <p>3 this is still a work in progress and we're setting</p> <p>4 up meetings to try to hammer this out, but the two</p> <p>5 pieces that are added to this are dynamic</p> <p>6 susceptibility contrast perfusion MRI, so look at</p> <p>7 vasculature within these lesions.</p> <p>8 This is particularly important when we look</p> <p>9 at SRS and other things that we've alluded to</p> <p>10 before that may disrupt the blood-brain barrier as</p> <p>11 a result of damaging the vasculature, as well a</p> <p>12 delayed contrast-enhanced T1-weighted scan using</p> <p>13 the turbo spin echo to see the added value of this</p> <p>14 additional sequence; again, building upon what we</p> <p>15 have previously done.</p> <p>16 The second part of response assessment or</p> <p>17 radiographic response assessment is the</p> <p>18 interpretation. Now that you have these</p> <p>19 measurements or you have these images, what do you</p> <p>20 do with them? At about the same time, in 2015,</p> <p>21 Nancy Lin and a variety of others in the RANO group</p> <p>22 came up with a RANO criteria for brain mets,</p>	<p style="text-align: right;">Page 135</p> <p>1 steroids, and clinically they're either</p> <p>2 neurologically stable or they're actually improved.</p> <p>3 Partial response is a little bit lower bar,</p> <p>4 so that's more than 30 percent decrease in the sum</p> <p>5 of those longest diameter measurements. They may</p> <p>6 have stable or improved non-target lesions, and,</p> <p>7 again, with corticosteroids, they have to be stable</p> <p>8 or decreasing, and the same thing with neurological</p> <p>9 status.</p> <p>10 Progressive disease is defined as more than</p> <p>11 20 percent increase in those lesions or any of</p> <p>12 these things that are on the list here. You may</p> <p>13 have unequivocal progressive disease in non-target</p> <p>14 lesions. You may see new lesions become present or</p> <p>15 they may have declining neurological status, which</p> <p>16 isn't realizable on radiographic scans.</p> <p>17 There are some special considerations, and I</p> <p>18 mentioned a couple of those before.</p> <p>19 Immunotherapies and SRS, there's a need to verify</p> <p>20 progressive disease. So just because the lesion</p> <p>21 gets bigger doesn't necessarily mean the drug isn't</p> <p>22 working. There are a couple of ways to mitigate,</p>
<p style="text-align: right;">Page 134</p> <p>1 specifically for brain mets.</p> <p>2 This really focuses only on parenchymal mets</p> <p>3 only, so not leptomeningeal spread or anything like</p> <p>4 that. It was based on RECIST 1.1. It looks at the</p> <p>5 longest single diameter of contrast-enhancing</p> <p>6 lesions. They have to be measurable disease, which</p> <p>7 again is a criteria of traditional RANO and other</p> <p>8 response assessment criteria as well, greater than</p> <p>9 1 centimeter with relatively thin slices. You're</p> <p>10 not supposed to include the cystic, or any</p> <p>11 resection cavity, or any tumor that's taken out.</p> <p>12 The idea is to sum up 5 target lesions if there's</p> <p>13 more than that, then you only look at the 5 largest</p> <p>14 lesions, and you add them up as a sum total lesion</p> <p>15 burden.</p> <p>16 You then use this rubric. And I'm not going</p> <p>17 to go into a lot of detail, but the idea is very</p> <p>18 similar. If you're familiar with RECIST or you're</p> <p>19 familiar with RANO. A complete response is</p> <p>20 complete elimination of all target lesions or</p> <p>21 shrinkage to the point they disappear. Non-target</p> <p>22 lesions are gone. The patients aren't on any</p>	<p style="text-align: right;">Page 136</p> <p>1 but, again, this is still a work in progress.</p> <p>2 There's the iRANO criteria that focuses mostly on</p> <p>3 high-grade gliomas, mostly in the upfront setting.</p> <p>4 But the idea behind that is to give approximately a</p> <p>5 6-month window or allow for evaluation period in</p> <p>6 order to see what's going on with the lesion. If</p> <p>7 it's getting bigger and the patient is stable,</p> <p>8 let's just keep watching and see what happens.</p> <p>9 There's another strategy that kind of builds</p> <p>10 on the iRANO and the RANO criteria that we've</p> <p>11 developed with Patrick and Tim Cloughesy that we</p> <p>12 call the modified RANO. The idea there is very</p> <p>13 similar to iRECIST, where you want confirmed</p> <p>14 sequential progressive disease events and then go</p> <p>15 back and back date when that first progressive</p> <p>16 disease event happened. That way we can mitigate</p> <p>17 and actually define pseudoprogression and</p> <p>18 radionecrosis.</p> <p>19 Lastly, I just want to touch on some</p> <p>20 advanced imaging and promises of the near future.</p> <p>21 I've only talked really about anatomic imaging and</p> <p>22 to some degree perfusion imaging, but there are a</p>

<p style="text-align: right;">Page 137</p> <p>1 lot of things on the horizon that can add different 2 aspects to what's going on with an individual 3 patient disease.</p> <p>4 There seems to be some evidence that a DSC 5 perfusion imaging provides additional value, so 6 again looking at the vascular components of the 7 enhancing lesion. MR spectroscopy allows you to 8 look at other metabolites within the tumor, and 9 that might be important to understand whether or 10 not the tumor is proliferating rapidly and whether 11 or not the cells are breaking down.</p> <p>12 Lastly, PET imaging, there's a wide variety 13 of radionuclerized available, but the most common 14 being FDG PET systemically used, as well as in the 15 brain, we find a lot of value in amino acid PET, so 16 looking at methionine, and phenylalanine, and other 17 neutral amino acids.</p> <p>18 Again, there is still this need for 19 standardization and large multicenter data sets to 20 really determine feasibility and the value of both 21 RANO BM and a standardized brain tumor protocol, 22 but there are a lot of efforts ongoing to kind of</p>	<p style="text-align: right;">Page 139</p> <p>1 that hope plays in all of this. It gives the 2 patient a will to live, to fight, to find the best 3 doctors, to seek out the best cures.</p> <p>4 As a patient, I know from my personal 5 experience, as I said, there was a stable of drugs 6 that were out there that I did not have access to. 7 And what does that do? It completely extinguishes 8 that hope in a patient, and I think it's really 9 important that we keep that in mind as we want to 10 make the latest technology available to the sickest 11 patient pool.</p> <p>12 (Applause.)</p> <p>13 DR. WEINSTOCK: I think there have been some 14 very interesting and thought provoking questions 15 raised. I'm going to start by touching on the 16 intact blood-brain barrier and how important that 17 is in thinking about drug development in the 18 metastatic space, whether the data that we have so 19 far is convincing enough to maybe think about 20 targets first and then blood-brain barrier 21 penetration next; so wondering if any of our 22 panelists had some thoughts in that regard.</p>
<p style="text-align: right;">Page 138</p> <p>1 set those in place so we have a standard to move 2 forward to evaluate new drugs in CNS mets. Thank 3 you.</p> <p>4 (Applause.)</p> <p>5 Panel Discussion</p> <p>6 DR. WEINSTOCK: Thank you very much to our 7 presenters for those excellent talks to help frame 8 the discussion. I'm going to turn it over to our 9 patient rep for comment.</p> <p>10 MR. QUEEN: Well, thanks. It's clear that 11 there's a lot of talented people working on this 12 problem, and I think, as I said earlier, it's 13 solvable. I think I'd be remiss, though, as a 14 patient not to reiterate one point that hasn't 15 really been touched upon. I touched upon it 16 initially in my initial comments.</p> <p>17 That is, from the patient perspective, I'm a 18 firm believer in modern medicine on all the things 19 that we're talking about here, but there's another 20 element of being a patient that we've not talked 21 about, and that's an element of hope and what 22 important role</p>	<p style="text-align: right;">Page 140</p> <p>1 DR. AHLUWALIA: Clearly, I think that's a 2 perennial question that we all struggle with, at 3 least in primary glioblastoma or glioma patients. 4 Some of the efforts that we have done, which 5 definitely we can learn from, is that we have 6 paid -- this is not directly related to brain mets, 7 but to put it in perspective is that we have 8 patients who have an enhancing component of the 9 disease, and we have patients who have a 10 non-enhancing component.</p> <p>11 What we have done through the American Brain 12 Tumor Consortium are multiple trials actually 13 looking at the drug penetration in the enhancing 14 component, but also looking at what's the drug 15 concentration in the non-enhancing component. 16 Certainly, if there are drugs which would have a 17 target that can be looked at both in gliomas or in 18 brain mets, I think that would be an easy thing. 19 We do phase zero trials all the time, so I think 20 that would be something to piggy back in learning 21 about the drugs. Obviously, as related to other 22 people on the panel and some stellar docs earlier</p>

Page 141	Page 143
<p>1 on, there are not good mouse models, so I think 2 utilizing some of the patients. 3 In brain mets, the challenge, it's very 4 difficult to do the same because if someone has 5 brain mets, they have a blood-brain barrier that's 6 broken. So if you're going to resect, you resect 7 that. But to the neurosurgeon and the team, how 8 comfortable they are intersecting a small part of 9 the brain, which may not have an eloquent 10 component, which is next to where the enhancing 11 component is. I think it's easier done in the 12 glioma world than in the brain mets world. 13 DR. DAVIES: I wanted to follow up on a 14 concept that 15 Dr. Lin had talked about in terms of some of the 16 subtleties of looking at the clinical data. Again, 17 I've talked about the dabrafenib data, the proof of 18 concept that a drug that couldn't cross the intact 19 blood-brain barrier had activity in patients with 20 established brain metastases. At the same time, we 21 know the most common site of progression in 22 patients who are receiving a dabrafenib is the</p>	<p>1 show efficacy in preventing the development of 2 brain metastasis. 3 So the concept of blood-brain barrier, as 4 you said, may be very important in prevention of 5 brain mets, but I don't think excludes the 6 possibility of activity in established brain mets 7 where the blood-brain barrier has been disrupted. 8 DR. LIN: Just speaking to our advocate's 9 point -- patient's point, I think the slide that I 10 showed with all the drugs that we know don't go 11 into the brain and there is activity that has been 12 reported, that activity by and large has been 13 reported in either ISTs [ph], or case series, or 14 some sort of little experience that was published 15 after the drug got an indication for the underlying 16 metastatic disease. 17 Speaking from the patient perspective, 18 that's like incredibly hard to see. There's no 19 data for brain metastasis until the drug's already 20 been through every hoop that there is and managed 21 to get through phase 3 and get an FDA label. I 22 think we just really have to change that. That</p>
Page 142	Page 144
<p>1 development of new brain metastasis. 2 I think that the idea is that for patients 3 with established brain metastases, even for drugs 4 that don't cross the blood-brain barrier, we may 5 get the proof of concept that a pathway is 6 important in brain metastases with the activity we 7 see, that doesn't exclude the possibility as you 8 discussed, that we might get even better results 9 with drugs that penetrate the blood-brain barrier 10 to a greater degree, or -- and this is one of the 11 things we're going to test in an upcoming 12 trial -- by pushing drugs to higher doses than 13 what's the FDA-approved dose. There's actually a 14 significant experience with this with EGFR 15 inhibitors. 16 So again, I really do agree with that 17 concept -- not being overly discouraged -- of this 18 idea that you can see CNS escape doesn't mean the 19 drugs can't be effective there. And in the same 20 way, it's also the disappointing fact that some of 21 these drugs that show activity in patients with 22 established brain mets on the other hand didn't</p>	<p>1 timing is just not acceptable timing. 2 DR. BRASTIANOS: Just to add, for our 3 pharmaceutical collaborators who are here, I think 4 focusing on the target is important, but we 5 shouldn't forget focusing on CNS penetrant 6 compounds also. We certainly see -- Pat Keegan has 7 done some beautiful work where she's shown 8 heterogeneous uptake and established mouse models 9 with multiple brain metastases. 10 Certainly, we do see response in the brain 11 for agents that we didn't expect responses in the 12 brain, as Dr. Davies and Dr. Lin mentioned, but 13 certainly with an IATA [ph] we should 14 also -- looking at the already established 15 inhibitors in brain metastases patients, we should 16 in parallel be developing agents that do have CNS 17 penetration, too, while we're focusing on the right 18 targets. 19 DR. MARGOLIN: Yes, I think that's really 20 important because I think even when you talk about 21 this concept where there's tumor, if it's over a 22 certain size or micro size, the integrity of the</p>

<p style="text-align: right;">Page 145</p> <p>1 blood-brain barrier's loss, there's probably areas 2 of minimal residual disease that are still not 3 getting the drug, and I would think that could be a 4 focus for escape.</p> <p>5 DR. WEINSTOCK: So we're going to go to our 6 audience.</p> <p>7 DR. ANDREWS: Hi. It's a great discussion, 8 and my tribute to the panel. My name is David 9 Andrews. I'm a career academic neurosurgeon in 10 Philadelphia, and I'm joining my landsman from 11 building 10, Dr. Nuwam [ph] here, to represent 12 neurosurgery. Our forum includes the public and 13 courageous patients like Derrick Queen.</p> <p>14 I would frame this disease this way. Brain 15 metastases are the most threatening phase of any 16 cancer and therefore are the highest priority for 17 treatment, either because of potential increased 18 intracranial pressure or actual increased 19 intracranial pressure. We also know that when we 20 treat patients with brain mets, it bifurcates into 21 two separate teams because of the unique physiology 22 and danger of brain mets. So it's usually a</p>	<p style="text-align: right;">Page 147</p> <p>1 think that's very strongly supported. 2 What about a cerebellar metastasis? They're 3 unique in one sense. They're more of a challenge. 4 The posterior fossa is more constrained. I think 5 we have a lower threshold for operating because of 6 concerns of obstruction of the fourth ventricle. 7 But Ray Sawaya, actually at MD Anderson, was the 8 first to point out that when you take out a 9 cerebellar met, you can actually spread the 10 disease, particularly if you do a piecemeal 11 resection. 12 So that's raised the issue that particularly 13 we have to be more multidisciplinary to consider 14 neoadjuvant radiosurgery first to sterilize tumor 15 cells at resection to minimize the chance of 16 peeled [ph] spread or leptomeningeal spread. 17 The final couple of issues are the number of 18 metastases and the size of metastases. So again, 19 we're getting into the realm of radiosurgery. Most 20 of us as neurosurgeons practicing radiosurgery are 21 comfortable with radiosurgery for up to 22 4 metastases. As kind of a quaint vignette, one of</p>
<p style="text-align: right;">Page 146</p> <p>1 neurologic team that deals with the mets and then 2 the systemic team, who are the medical oncologists 3 that manage the systemic disease. So immediately 4 for patients, often they're dealing with two 5 separate teams.</p> <p>6 The third and very obvious thing is we're 7 dealing with a disease in which, still, systemic 8 cancer is treated with radiation, surgery, and 9 chemotherapy, so as a neurosurgeon, I'm going to 10 frame the surgical side of this.</p> <p>11 Single mets were sort of immortalized as a 12 surgical operation by Roy Patchell's landmark paper 13 in 1990 where you remove a single met with an 14 improved overall survival. That's carried forward 15 to date, although there's now question when the 16 systemic cancer is now known, we can simply radiate 17 that metastasis.</p> <p>18 So what about all oligometastasis? 19 Certainly, if there's one symptomatic met, we as 20 neurosurgeons will take it out; otherwise 21 stereotactic radiosurgery I think is now more the 22 standard of care than whole-brain radiation. I</p>	<p style="text-align: right;">Page 148</p> <p>1 our early international meetings at ISRS in Madrid 2 in 1997 included a Japanese neurosurgeon by the 3 name of Doctor Yamamoto. Back then, the gamma 4 knife was the way to treat brain mets as the mode 5 for radiosurgery. 6 Well, he would put a frame on, and he would 7 treat up to 30 brain metastases over about two 8 days, which was sort of outlandish. But he was 9 sort of laughed off the podium, but 25 years later, 10 he actually had a prospective randomized trial that 11 actually showed noninferiority of treatment of up 12 to 5 to 10 metastases compared to oligometastases 13 for overall survival in these patients, so that was 14 an important advance. 15 The latest evolution in radiosurgery is one 16 of single isocenter treatment of multiple 17 metastases within an hour, and quite precisely. So 18 the radiosurgery aspect of management of metastases 19 has become a very important part of our 20 armamentarium. 21 I'll conclude by actually what Dr. Margolin 22 has stated so well, and all of you have, that this</p>

<p style="text-align: right;">Page 149</p> <p>1 is a multidisciplinary effort, and I think 2 multidisciplinary clinics should include the 3 neurosurgeon, the radiation oncologist, the 4 neuro-oncologist, the neuropathologist, and the 5 neuroradiologist. It's only together that 6 collectively our wisdom can carry these patients 7 forward. Thank you.</p> <p>8 DR. WEN: I wanted to follow up on Ben's 9 talk. When the RANO BM criteria was proposed, the 10 hope was that it would become the standardized 11 response criteria in the field. I wanted to see 12 what the feeling of the panel and the FDA is. 13 Should we use RANO BM for all trials going forward 14 or are there issues that we need to address? 15 Another issue that you may want to comment on is 16 the size, whether the 1 centimeter is required for 17 the trials or whether we can go down to half a 18 centimeter. Thank you.</p> <p>19 DR. ELLINGSON: I think the two questions 20 that Patrick asked first was maybe for the FDA, but 21 I can answer it, my opinion, but should RANO BM be 22 used as the response criteria for trials moving</p>	<p style="text-align: right;">Page 151</p> <p>1 the systemic response criteria is and kind of 2 integrate into that would be important. 3 I think with the second question, it all 4 depends on the acquisition and the timing that you 5 get with respect to the size of the lesions. 6 Traditionally, we've made those lesions the minimum 7 size being 1 centimeter because we relied on 8 suboptimal imaging and what we could reliably 9 measure over and over and over again. So I think 10 it's a valid question, what's the minimum size to 11 get into these studies and whether or not -- 12 MS. SELIG: We have a few people here 13 [inaudible - off mic].</p> <p>14 AUDIENCE MEMBER: My name is 15 [indiscernible], biopharma, clinical stage and 16 [indiscernible] and Duke, Mayo Clinic. My father 17 died of a brain metastasis at age 65. My question 18 is actually to Nancy. You show two ALK tyrosine 19 kinase inhibitor difference. Is that simply due to 20 a dose difference with no [indiscernible], and the 21 dose of 600 milligram BID with 250 milligram?</p> <p>22 DR. LIN: Greg might actually be the right</p>
<p style="text-align: right;">Page 150</p> <p>1 forward and brain mets? The second question was 2 should the size requirements be as large as they 3 are? I think that were your questions. I think 4 Luke brought this up as well.</p> <p>5 One of the challenges I think when you have 6 large trials that include mets and systemic disease 7 is the expertise in the person doing the 8 measurements. If you don't have not even 9 diagnostic radiologists but oncology trained 10 neuro-oncology radiologists to do those 11 measurements, at least in gliomas, you can run into 12 pitfalls, and I think that that's something to 13 consider.</p> <p>14 One of the things I like about the RANO BM 15 criteria is it piggybacks on RECIST, which people 16 may have, at least in these trials, more experience 17 with. I think if we flop back and forth between 18 two different criteria, one that's a bidirectional 19 measurement, one that's unidirectional, and have 20 different criteria, there's at least a possibility 21 of some competing things. I think maybe something 22 that would allow that to synergize with whatever</p>	<p style="text-align: right;">Page 152</p> <p>1 person to answer the question since I will go on a 2 limb and talk about lung cancer. It's a little bit 3 of comparing not exactly apples to apples because 4 alectinib even extracranially a better drug than 5 crizotinib, yet we see that effect both in the 6 brain and in the body.</p> <p>7 How much of the additional effect that we 8 see in the brain is related to its better 9 blood-brain barrier penetration effects and how 10 much is just that it's a better drug I think the 11 trial can't really sort out. I don't really think 12 it's necessarily a dosing issue, personally. I 13 think it's just in more general terms a better 14 drug.</p> <p>15 I do think that the prevention data that I 16 showed you was, to me, one of the more striking 17 data points from that study, really showing that we 18 actually can prevent brain metastases. I think 19 that that to me was one of the most striking 20 findings, that we don't have to be satisfied with 21 simply treating established brain metastases.</p> <p>22 MS. SELIG: Great. Go ahead.</p>

<p>Page 153</p> <p>1 AUDIENCE MEMBER: Eric Yonas [ph], MD 2 Anderson. Fantastic speakers and incredible 3 presentations. 4 MS. SELIG: Can you get a little closer to 5 the microphone? 6 AUDIENCE MEMBER: Yes. Two questions. One 7 is really looking at the molecular determinants of 8 metastatic progression across diseases versus what 9 the definitions of lethality are within diseases, 10 how much commonality is really across these 11 diseases? If you did an unsupervised clustering, 12 what's actually brain metastasis specific and 13 what's actually disease specific? 14 The question's important from a standpoint 15 of therapy development. Are we developing a 16 pan-metastasis treatment or are we improving 17 treatments for diseases? 18 My second question is just a comment from 19 the group on the immune microenvironment. The 20 brain immune microenvironment from a standpoint of 21 its basal state, what do brain metastases do and 22 how should we change our immunotherapy approaches</p>	<p>1 work is important. 2 If you want to comment on your work and the 3 immune -- 4 DR. DAVIES: I think what's relevant for 5 both the molecular biology of brain mets and the 6 immunology of brain mets, it's actually clear that 7 the tumor microenvironment impacts these tumors 8 differently than what we see in other sites in the 9 body. 10 An actual fact, the differences that we saw 11 in melanoma, we actually recapitulate in animal 12 models just by injecting tumors into the brain 13 versus subQ; not a clonal selection, not 14 genetically driven, but epigenetically driven. And 15 there's no reason to think that that is actually 16 specific to melanoma, and we have work going on 17 across other diseases that preliminarily supports 18 that. 19 MS. SELIG: Great. Last two comments over 20 here. 21 AUDIENCE MEMBER: Hi. This is an excellent 22 presentation. My name is Jill Mancuso. I'm a</p>
<p>Page 154</p> <p>1 for these metastases? 2 MS. SELIG: So we'll take one quick response 3 and two quick comments, and then give our 4 moderators a chance. We'll have time later to get 5 back to some of these questions; otherwise you're 6 going to get no break. 7 DR. BRASTIANOS: Do you want me to answer 8 the question? 9 MS. SELIG: One quick answer. 10 DR. BRASTIANOS: I'll do it first, and then, 11 Mike, you can take the second question. First 12 question, in our work right now, we're looking 13 across diseases, what are the commonalities? In 14 the initial data set of a hundred brain mets across 15 all histologies, CDK pathway seems to be important 16 and PI3 kinase pathway seems to be important. 17 Many of these could be important drivers of 18 progression in general, but we are seeing that they 19 are very common in brain metastases across the 20 histologies. With our larger data set, we'll be 21 able to answer that more fully, but certainly 22 CDK/PI3 kinase in both our work and Mike Davies'</p>	<p>Page 155</p> <p>1 patient advocate and also an individual member of 2 the Metastatic Breast Cancer Alliance. Just 3 briefly, I was diagnosed with advanced breast 4 cancer in 2007 -- and not de novo -- in the lung, 5 then in the brain in 2008. The lung was treated 6 with VATS and then RFA when it recurred, and the 7 brain was treated with craniotomy and IMRT. I 8 haven't had any sign of the disease since then. 9 My question is, when I got the report, the 10 MRI report, on the brain metastasis, it said that 11 it was a cystic metastasis. I believe that was the 12 word, and I didn't really understand that. I knew 13 what a cyst was, but I didn't understand. I asked 14 the surgeon, and she said that it was -- well, it 15 wasn't a solid. 16 That was basically the first and the last 17 time I've ever really heard about this. So I'm 18 wondering is any work or anything ever done in the 19 lab to understand what drives either getting a 20 cystic brain metastasis or a solid brain 21 metastases, which I know can occur sometimes in the 22 different cancers that go to the brain; that it</p>

<p style="text-align: right;">Page 157</p> <p>1 could be maybe 50/50 or maybe it occurs more in one 2 than the other. But I don't know whether there's 3 any work done in the lab to understand what drives 4 this that could eventually lead to maybe 5 differentiating the types of drugs people should 6 get, depending, and also lead to maybe controlling 7 it in the body.</p> <p>8 MS. SELIG: I don't know if we can have a 9 quick answer to that or we can just pose that. Is 10 that a quick answer?</p> <p>11 DR. DAVIES: I don't think anybody knows the 12 answer to your question.</p> <p>13 MS. SELIG: That's what I was afraid of. 14 It's a good point to come back to further 15 subtyping.</p> <p>16 Last comment?</p> <p>17 MS. COLLYAR: Hi. Deborah Collyar with 18 Patient Advocates and Research, and I really 19 appreciate everyone's comments. It's been good 20 presentations. I wanted to reiterate the important 21 points I think that Kim Margolin brought out about 22 study endpoints, and PFS really is not a good one</p>	<p style="text-align: right;">Page 159</p> <p>1 Session Recap - Chana Weinstock 2 DR. WEINSTOCK: Thank you. I think some of 3 the thoughts that occurred to me over the first two 4 sessions, I would encapsulate them as if you design 5 these trials, they will enroll since patients with 6 brain metastases are out there and have previously 7 faced many barriers to trial enrollment, and from 8 the patient perspective, this is vitally important. 9 If you study CNS disease early on, it will inform 10 our ability to select drugs and develop them 11 appropriately.</p> <p>12 Then to the last comment, if you collect 13 trial data thoughtfully and via standardized 14 assessment with endpoints that are clinically 15 meaningful and take the patient's perspective into 16 account, then that will help inform our reporting 17 of study results and future patient care.</p> <p>18 So I think we heard a lot of very good 19 discussion on some interesting data about genetic 20 divergence of brain metastases, from the primary 21 and how that's been shown by us in really good 22 rapid autopsy studies that have demonstrated this</p>
<p style="text-align: right;">Page 158</p> <p>1 for patients in lots of ways. So there are ways I 2 think that we do need to have discussions together 3 about how to get better endpoints.</p> <p>4 One point that did not come out that may 5 this afternoon is the design of the clinical trials 6 is actually very important to the patient 7 communities as well. I'll just bring one example, 8 and that's in phase 1's. We want to try to get 9 away from 3 plus 3's if at all possible and 10 consider intra-patient dosing as well, so that's 11 just one example.</p> <p>12 MS. SELIG: Hold those thoughts. We have a 13 panel coming up on endpoints and a panel coming up 14 on trial designs after the break. To our 15 moderator, I just want to say we have about 16 115 people listening and following along on the 17 webcast. This is terrific, the full room here and 18 a lot of people paying attention.</p> <p>19 Dr. Weinstock, do you want to have the last 20 couple of thoughts about what you heard, and then 21 we'll go into about a 10-minute break, and we'll 22 start again at 11:15.</p>	<p style="text-align: right;">Page 160</p> <p>1 quite elegantly. Then we talked a little bit about 2 rethinking our assumptions about how to choose 3 drugs in the best way possible to develop in this 4 space and whether blood-brain barrier penetration 5 needs to be the primary means by which we select 6 these drugs.</p> <p>7 We talked about moving away from overall 8 survival as possibly the only gold standard 9 endpoint in this setting, and we're going to really 10 touch on that in the afternoon. But as a 11 regulator, endpoints and how we define them is a 12 very important conversation to have, so I think 13 we'll get into that in the afternoon.</p> <p>14 Then we talked about standardizing 15 radiographic endpoints to look at how to develop 16 these endpoints thoughtfully and how efforts 17 towards this have started with the RANO assessment 18 criteria. So I think that's very important, and 19 using that going forward will be important as well.</p> <p>20 Then just the role of hope in thinking about 21 patients and how we develop these trials with the 22 patients in mind. Like I said, I'm a GU</p>

<p style="text-align: right;">Page 161</p> <p>1 oncologist. I think if a patient came to me with 2 brain metastases and wanted to know what to expect 3 from some of the approved drugs, I think that would 4 be a difficult conversation to have. But if we 5 design these trials going forward so that there is 6 more data, the conversation could be better 7 informed and hopefully the results are better. I 8 think the melanoma data is astonishing, just that 9 overall survival of 80 percent plus 12 months can 10 give everyone a lot of hope, and hopefully we'll 11 take that going forward.</p> <p>12 Thank you. I think it's break time.</p> <p>13 MS. SELIG: We will come back at 11:20 to 14 get started right away. Thank you so much to 15 everybody here for an amazing job. This was a 16 terrific first two panels. Thank you.</p> <p>17 (Whereupon, at 11:08 a.m., a recess was 18 taken.)</p> <p>19 MS. SELIG: Okay. If everyone could take 20 their seats please. I know that was a short break, 21 but you'll all thank me at the end of the day when 22 it's Friday, late afternoon, and you can get where</p>	<p style="text-align: right;">Page 163</p> <p>1 Dr. Kluetz talk about regulatory definition of 2 clinical benefit, and we'll follow that with a 3 panel presentation.</p> <p>4 Presentation - Paul Kluetz</p> <p>5 DR. KLUETZ: Thank you very much. My name 6 is Paul Kluetz. I'm a medical oncologist within 7 the Oncology Center of Excellence and also a 8 genital urinary specialist. So it's interesting, 9 again, to span the histologic diseases for this 10 brain metastasis symposium. Today I'm going to 11 talk a little bit about clinical benefit and how we 12 look at clinical benefit, and the fact that it 13 isn't just the primary efficacy endpoint; that it's 14 a constellation of things, and there's multiple 15 facets of this concept.</p> <p>16 I think everyone knows that in the United 17 States, in order to market a drug, you need to have 18 the drug approved through one of two pathways. 19 There's a traditional approval pathway and an 20 accelerated approval pathway. I think probably in 21 the clinical trial design section of today, it will 22 really talk about how it comes down to the primary</p>
<p style="text-align: right;">Page 162</p> <p>1 you need to go. We're going to start now with 2 Session III. The morning was really an opportunity 3 to set the table, and we're now tasking our next 4 set of panels and moderators with really aiming at 5 now what do we do and concrete suggestions for how 6 we move forward as a community on brain mets.</p> <p>7 Just the format here, Session III has two 8 parts. The first part happens before lunch. The 9 second part happens after lunch. Each part is 10 kicked off by a very brief 10-minute talk from an 11 FDA colleagues who's going to set the stage for 12 that panel, and each panel, again, is moderated by 13 a clinician and an FDA colleague.</p> <p>14 So with that, I'm going to turn it over to 15 Dr. Anders and Dr. Prowell, and to Dr. Kluetz for 16 the first talk.</p> <p>17 Session III</p> <p>18 DR. PROWELL: Good morning. It's such a 19 pleasure to be here this morning. We've already 20 had such a rich conversation. The title of our 21 session is Clinical Benefit in Patients with Brain 22 Metastases, and we're going to start by hearing</p>	<p style="text-align: right;">Page 164</p> <p>1 endpoint of the clinical trial. What are you able 2 to show in an adequate well-controlled trial, that 3 you either prolong life, you create a better life 4 for the patient, or you have an established 5 surrogate endpoint effect that's large enough to 6 predict a downstream direct clinical benefit.</p> <p>7 An accelerated approval, we use surrogate 8 endpoints that are, quote, "reasonably likely to 9 predict clinical benefit." So these are endpoints 10 that aren't directly measuring clinical benefits 11 themselves, but they intend to predict a downstream 12 benefit in how patients feel or function, and 13 because there's some residual uncertainty regarding 14 this endpoint, postmarketing clinical trials are 15 typically done to verify that benefit. And in 16 oncology, that's typically been response rate, 17 durable response rate in single-arm trials.</p> <p>18 When I think about an efficacy endpoint, I 19 think about it in three buckets. I think about 20 what is being measured, I think about how 21 accurately is it being measured, and I think about 22 how much of an effect has been demonstrated in a</p>

<p style="text-align: right;">Page 165</p> <p>1 trial. What is being measured is actually the 2 primary endpoint or the efficacy endpoint; what are 3 you actually measuring? Again, direct benefit 4 measures survival or how someone feels or 5 functions.</p> <p>6 Symptom or functional benefits are 7 considered more meaningful, however, how accurately 8 is something being measured also needs to be taken 9 into consideration. What is the accuracy of the 10 assay that you're using? How susceptible is this 11 endpoint to bias? How accurate is the timing of 12 the event if it's a time-to-event endpoint?</p> <p>13 Finally, if there's a very large magnitude 14 of benefit, that can overcome some of the 15 limitations of an endpoint. Conversely, if there's 16 a very small benefit, even in survival, you may 17 wonder whether that risk-benefit is reasonable.</p> <p>18 To demonstrate this idea of how something's 19 measured and how important it is to understand the 20 measurement characteristics, we'll use survival all 21 the way through presenting more of the procedures 22 as an idea of when you have more interpretation or</p>	<p style="text-align: right;">Page 167</p> <p>1 Finally, this idea of preventing morbid 2 procedures or preventing or delaying the supportive 3 care medications, again, germane to what you do 4 with steroids, this is an important endpoint. 5 Clinically, it's pretty meaningful, but there's a 6 lot of subjectivity in the decision of a physician 7 whether or not to undergo a procedure or whether or 8 not to give a supportive care med. 9 I guess what I'm trying to say is there's no 10 free lunch, obviously, with an endpoint. There are 11 pluses and there are minuses for each of these 12 types of endpoints, and we just need to understand 13 what the strengths and limitations are. 14 With overall survival, it's a direct measure 15 of clinical benefit. It's a strong clinical 16 outcome. As I mentioned, it has the lowest 17 potential for bias, but there are feasibility 18 problems with overall survival. As we all know, 19 there's crossover in trials. If it's a very rare 20 disease, it's hard to get a randomized set of 21 patients, et cetera. 22 Tumor endpoints are interesting because</p>
<p style="text-align: right;">Page 166</p> <p>1 subjectivity in your assay or in your endpoint, it 2 can lead to more variability in the measure, and it 3 can actually increase your risk for bias. So 4 survival has the lowest potential for bias. Why? 5 Because there really is no interpretation required. 6 We know the event time to the day, and therefore 7 it's a very strong endpoint.</p> <p>8 Progression-free survival in measurable 9 tumors, standard RECIST type of progression-free 10 survival is also pretty objective and relatively 11 easy to measure. As a prostate cancer doc, we have 12 a challenge with progression-free survival, and I 13 think it's very similar to the challenge that you 14 have within this community, which is that this is 15 not a very easy to measure lesion. Ninety percent 16 of prostate cancer metastases are to the bone, and 17 if anyone's read a bone scan, they know that it's 18 not quite as easy to interpret as a CT scan.</p> <p>19 So now we have two additional lesions that a 20 nuclear medicine doc needs to understand is this 21 progression or not, so a lot more interpretation 22 there.</p>	<p style="text-align: right;">Page 168</p> <p>1 there's a little bit of controversy. Is this a 2 direct clinical benefit or is it a surrogate 3 endpoint? We've gone back and forth about this. 4 If you look at our most recent clinical benefit 5 guidance, we call it clinical benefit as well as a 6 surrogate because it is a little bit of both. 7 While it's not a direct measure of clinical 8 benefit, it is a direct measure of the disease. 9 You're directly looking at the tumor. So it's a 10 challenging one. There's a little bit of a plus or 11 minus there. 12 It does have a relatively low risk for bias, 13 it's an objective measure, and it's imminently 14 feasible, so this is an endpoint that we use very 15 commonly in oncology, not surprisingly. 16 Clinical outcomes, patient-reported 17 outcomes, are one type, but there's also now 18 potentially wearable devices and other digital 19 health types of applications and are directly 20 measuring how someone feels or functions, so their 21 symptom or functional outcome measures. They are 22 pretty feasible, although there can be some</p>

<p style="text-align: right;">Page 169</p> <p>1 operational challenges for those in industry that 2 there are well aware of and making sure their 3 completion rate is high for patient-reported 4 outcomes, et cetera.</p> <p>5 Again, with the risk for bias, it's a little 6 bit of a plus minus. Minus, there is subjectivity, 7 and there's going to be some variability in these 8 PRO instruments. But then again, there's no other 9 assay currently that can measure how you are 10 feeling, so it's kind of what we have.</p> <p>11 Finally, this idea of clinical outcomes as 12 health care utilization, reducing health care 13 utilization or preventing something like a 14 cystectomy in bladder cancer, which is a very 15 morbid procedure, has a very big clinical outcome 16 component to it. It is feasible as a measure, 17 however, there is this issue of bias with respect 18 to what is the trigger to undergo this procedure.</p> <p>19 So I really want to bring home the fact that 20 when we look at clinical benefit, that was 21 efficacy. But clinical benefit, whether we approve 22 a drug or not, efficacy is only one component. It</p>	<p style="text-align: right;">Page 171</p> <p>1 a response rate with the idea that there's such a 2 high likelihood of obviously cosmetic improvement 3 and potentially symptomatic improvement. Now, 4 would we like sponsors to directly measure those 5 symptoms and other kinds of improvements? Yes, and 6 we are seeing that more often.</p> <p>7 To give you an example of this totality of 8 data approach and that we shouldn't rely on one 9 endpoint, especially where there's some uncertainty 10 surrounding its measure, for instance, response in 11 the brain tumor, COUGAR 302 was a trial done that 12 was the second approved indication for abiraterone 13 in prostate cancer.</p> <p>14 As I said, prostate cancer's measure for 15 tumor measures, progression free survival, there's 16 a lot of uncertainty in that because it was two new 17 bone lesions. It was a very kind of complicated 18 algorithm for the assay. It wasn't our typical 19 PFS, so it was really considered kind of an 20 unestablished surrogate endpoint at the time.</p> <p>21 The trial showed a statistically significant 22 improvement in the delay in this radiographic</p>
<p style="text-align: right;">Page 170</p> <p>1 has to be done in an acceptable safety profile, and 2 then there's the clinical context. The clinical 3 context has to do with the rarity of the disease. 4 The clinical context has to do with the unmet need, 5 the available therapies, and many different things.</p> <p>6 I'm going to end with the idea of response 7 rate, not being response rate, not being response 8 rate. If there's a 30 percent response rate, it 9 can be mean very different things in two different 10 kinds of tumors.</p> <p>11 Here's a cross-sectional CT scan of the 12 pelvis, and you can see that a 2.2 centimeter 13 pelvic lymph node has been reduced by more than 50 14 percent. That's a RECIST response, but it is quite 15 uncertain whether or not this would lead to 16 downstream benefit.</p> <p>17 Conversely, where the tumors are located is 18 obviously very important. Here we have two areas 19 of skin disease that are quite disfiguring and 20 likely to be quite symptomatic. You have basal 21 Cell carcinoma and CTCL, cutaneous T-cell lymphoma.</p> <p>22 Both of these drugs were granted approval based on</p>	<p style="text-align: right;">Page 172</p> <p>1 progression with a nonsignificant trend for OS. So 2 we had one primary endpoint, which was a kind of an 3 unestablished surrogate, and if they had not 4 measured anything else, they may have gotten an 5 accelerated approval rather than a regular 6 approval.</p> <p>7 But look how they designed this trial. 8 There was a delay in the time to first opiate use. 9 There was a delay in the time to cytotoxic 10 chemotherapy, which had a more safety profile in 11 that agent. Time to patient-reported pain was 12 delayed. Time to ECOG performance status was 13 delayed, performance decline, and there was a very 14 favorable safety profile.</p> <p>15 So in the totality of data, this was given a 16 regular approval. And I just want to leave you 17 with the fact that you should make sure that you 18 paint a picture of your therapy that you're trying 19 to show is clinically beneficial to patients using 20 more than one endpoint.</p> <p>21 What does this mean for what we're doing 22 today? I think brain metastases has some</p>

<p style="text-align: right;">Page 173</p> <p>1 similarities I guess to this prostate cancer 2 example. The tumor location is obviously very 3 important in this particular situation. We've 4 already heard, and we will continue to hear, that 5 the functional and symptomatic declines that you 6 can see in these either primary brain tumors or 7 metastases are large.</p> <p>8 So location, depth of response, duration of 9 response are taken into account. I think there's 10 plenty of clinical outcomes that can be measured in 11 this disease: survival, obviously cognitive and 12 physical function, pain, ability to carry out 13 activities, walking, et cetera. And then this idea 14 of events, treatment related events or delaying 15 healthcare utilization or preventing healthcare 16 utilization that has its own morbidity is 17 important.</p> <p>18 We talked about steroids. Could you delay 19 or prevent cranial radiation; could you delay or 20 prevent pain meds like opiates; and of course 21 seizures are a big problem, and can you delay or 22 prevent those.</p>	<p style="text-align: right;">Page 175</p> <p>1 some common terminology that I won't go over, but 2 we have our own language, and if we can all stick 3 to similar language in our clinical trial design 4 and our publications, it would do a service to 5 everyone. So thank you for your attention. 6 (Applause.)</p> <p>7 Panel Discussion</p> <p>8 DR. ANDERS: Excellent. Well, thank you for 9 that fantastic framework as we move into the panel 10 discussion today. We had a fascinating exchange 11 and call as we were preparing for our session today 12 amongst the members, and I'm looking forward to 13 what each of the members has to say based on the 14 varying backgrounds and complementary expertise. 15 Our charge was to discuss the design of 16 endpoint framework for CNS metastasis, and as we 17 considered this, we realized before we discussed 18 endpoints, we really needed to go back to what our 19 individual goals were for the many different 20 scenarios for trials designed for CNS metastasis 21 studies, the phase of the study, whether or not it 22 was early phase, phase 1, or registrational</p>
<p style="text-align: right;">Page 174</p> <p>1 So my take-home message should be, I think 2 for all you to take home, is that there's no 3 perfect efficacy endpoint. It's always going to be 4 a balance between meaningfulness and risk for bias 5 and feasibility. I think all available data should 6 be used, and you should be thinking about that up 7 front in your trial design because we need to 8 determine clinical benefit based on a totality 9 approach, especially in diseases that are hard to 10 quantify.</p> <p>11 Radiographic response rate is not the same 12 across diseases. We have approved drugs based on 13 the endpoint because the location was so important, 14 and I think that is consistent with where these 15 tumors are located in the brain tumor situation.</p> <p>16 I think technology is really improving our 17 ability to do a better job with functional and 18 symptom measurements, whether that's electronically 19 captured patient-reported outcomes, whether that's 20 wearable devices, or whether that's an iPad type of 21 cognitive function assay.</p> <p>22 I've left you with a slide also that it has</p>	<p style="text-align: right;">Page 176</p> <p>1 phase 3; whether or not the intervention was local 2 or systemic or a neurocognitive protectant, just to 3 name a few.</p> <p>4 I think I'll start with Terri Armstrong here 5 at the NCI, just introductions and thoughts.</p> <p>6 DR. ARMSTRONG: Well, thanks so much. I 7 appreciate the opportunity to be here. I head up 8 the outcome section in the neuro-oncology branch, 9 and I've learned a lot since being here. I think a 10 couple of things that have framed my thoughts from 11 earlier, this idea of maintaining hope and this 12 idea of access that we don't want to lose track of 13 as we talk about the nitty-gritty of the outcomes 14 that are key messages that, Mr. Queen shared with 15 us.</p> <p>16 I think also, importantly, we heard from 17 Dr. Brastianos on the differences in the metastasis 18 in terms of what the mutational burden and load is, 19 and those compared to other parts of the body and 20 the significance of that as we start to plan 21 trials; and from Dr. Margolin about understanding 22 that patients come to this from different places;</p>

<p style="text-align: right;">Page 177</p> <p>1 20 percent of the time, a diagnosis, if it's at the 2 end stage of disease and this idea of escape 3 metastasis and how do we monitor for that. I think 4 typically we find those when patients are 5 symptomatic, and then how does that then impact the 6 outcome of patients if we're waiting for that. 7 My personal thoughts are to remember that 8 the brain is not disassociated from the body, at 9 least for most of us, and most of these patients 10 are going to have disease in their brain and their 11 bodies, so we don't want to lose sight of the 12 importance of those two. And the work that we know 13 from people like Ethan Basch, that if we can 14 improve symptoms, we can improve survival and that 15 we need to understand that, and focus on that, and 16 measure that in our trials. 17 These ideas may influence our ideas about 18 clinical outcomes assessment going forward, but I 19 think rationally we have to identify a small subset 20 of things that we can measure, including how the 21 patient functions that I think will be integral to 22 understanding the benefit of therapy going forward</p>	<p style="text-align: right;">Page 179</p> <p>1 my brain mets were found when I was asymptomatic 2 because I more or less demanded a brain scan after 3 6 months, lo and behold, I had 7 brain mets. 4 During this time, alectinib and brigatinib 5 both were on a clinical trial, so after talking to 6 Dr. Camidge and Dr. Shah [ph] about options and 7 availabilities, I decided to go on brigatinib and 8 was on it for 28 months, and it was wonderful. It 9 did not have an exclusion, obviously, for brain 10 mets because I came into it with 7, so I know not 11 of what my esteemed patient advocate before me 12 spoke. I was fortunate that they accepted patients 13 with brain metastases. 14 I had a great run on that 28 months. I 15 wasn't disease-free all the time, but it started 16 developing the last 6 months. We were slowly 17 watching it grow, and if that isn't something, 18 sitting by and waiting until your next scan to see, 19 oh, how much has it grown this time, and what will 20 we do, and different things like that. 21 The next option that I went to was a 22 clinical trial specifically designed for brain</p>
<p style="text-align: right;">Page 178</p> <p>1 and introducing those early in trial. Thank you. 2 MS. ENGFER-TRIEBENBACH: Good morning. My 3 name is Shelly Engfer-Triebenbach, and I have a 4 little bit of laryngitis, so bear with me. I'm 5 coming to you as a patient advocate from Minnesota. 6 I was so excited to see rain yesterday as opposed 7 to snow, that we've seen in the last six months. 8 (Laughter.) 9 MS. ENGFER-TRIEBENBACH: I am a stage 4 lung 10 cancer survivor, activist, patient advocate, 11 whatever you want to call me. My experience with 12 brain mets started after 9 months on crizotinib. I 13 knew as a patient that it did not cross the 14 blood-brain barrier, and that information was given 15 to me by other patients who had been on this drug 16 prior to me. So that patient-to-patient 17 communication is so important and should be a part 18 of any type of clinical trial. 19 I have asked and tried to get this going, 20 but so far it has not happened because I know the 21 HIPAA and blah, blah, blah. 22 But anyway, patients do talk, and because of that,</p>	<p style="text-align: right;">Page 180</p> <p>1 mets. In fact, you had to have brain mets to get 2 into this trial. I now am seeing Dr. Shah [ph] at 3 Mass General. Even the lorlatinib drug has been 4 approved, my arm of the trial still continues, as 5 they want to get more information about this 6 particular drug and its ability to control brain 7 mets. 8 There is one pesky brain met that, 9 unfortunately, it has not controlled in my brain. 10 I had SRS last May and so far so good. Everything 11 has been stable to this point, but I continue on in 12 the lorlatinib trial. That goes without saying 13 about the different types of side effects you can 14 have from the lorlatinib drug, but I am fortunately 15 not one of those patients that experiences that. 16 I notice on my bio -- I forgot to mention my 17 wonderfully supportive family. I have a great 18 husband and two children, and they were 10 years 19 old and 7 years old when I was diagnosed, so 20 they've been through the gamut with me with scans 21 and ups and downs, and they love to meet the 22 doctors and oncologists that I encounter and get to</p>

<p>1 see.</p> <p>2 Talking about what you were saying about</p> <p>3 hope, seeing all these people coming together from</p> <p>4 such different entities, that's what gives patients</p> <p>5 hope because you guys care about this, and it's</p> <p>6 important to you as well, so thank you.</p> <p>7 (Applause.)</p> <p>8 DR. KALIDAS: Hello. I'm Chitkala Kalidas.</p> <p>9 I lead the global regulatory affairs organization</p> <p>10 for oncology and in vitro diagnostics at Bayer.</p> <p>11 First off, I'd like to thank the FDA as well as the</p> <p>12 National Brain Tumor Society for bringing so many</p> <p>13 multiple stakeholders together today to address</p> <p>14 this very important issue in oncology, so thank you</p> <p>15 very much.</p> <p>16 Being in drug development and in regulatory</p> <p>17 affairs in particular, I'm used to the drug</p> <p>18 development process allowing for the study of</p> <p>19 special populations and vulnerable populations.</p> <p>20 Examples would be the pediatric population and also</p> <p>21 understanding how a drug works in patients with</p> <p>22 renal insufficiency or hepatic insufficiency.</p>	<p>Page 181</p>	<p>1 patients and how we create endpoints specifically</p> <p>2 for patients with brain metastases.</p> <p>3 I can give you my comments through the prism</p> <p>4 of being a lung cancer doctor for the past 10 to 15</p> <p>5 years. There's a lot of complexity with therapies</p> <p>6 that we give with our patients in lung cancer. We</p> <p>7 have patients like Shelly who received drugs that</p> <p>8 have a very high chance of getting into the brain</p> <p>9 and eliciting responses in the brain, and it's</p> <p>10 really changed the way that we think about treating</p> <p>11 the brain.</p> <p>12 These genotype directed therapies like</p> <p>13 alectinib, or brigatinib, or osimertinib, there's a</p> <p>14 high chance that they can get in, and it has,</p> <p>15 again, altered the way that we think about treating</p> <p>16 these patients. Then we have, of course, other</p> <p>17 drugs like immunotherapy, which have created these</p> <p>18 fascinating tales of the curve, but we still remain</p> <p>19 unclear about what chances these drugs really have</p> <p>20 of getting into the brain and eliciting responses</p> <p>21 in the brain.</p> <p>22 So we have such divergent therapies within</p>	<p>Page 183</p>
<p>1 So this enables a drug to be used in a safe</p> <p>2 manner so that the patients that this drug is</p> <p>3 targeted for can derive benefit from the drug. I</p> <p>4 see the discussion today as a natural progression</p> <p>5 of that. Oncology is all about an unmet medical</p> <p>6 need, and the patient population that we are</p> <p>7 talking about has a very high unmet medical need.</p> <p>8 Today's discussion, in conjunction with the</p> <p>9 draft guidance that the FDA has just very recently</p> <p>10 issued on the cancer clinical trial eligibility</p> <p>11 criteria for CNS mets, I think is very helpful,</p> <p>12 especially for sponsors to have a very thoughtful</p> <p>13 and informed discussion with the FDA on early</p> <p>14 clinical trials as well as registrational trials.</p> <p>15 So I'm really looking forward to this discussion on</p> <p>16 the endpoints and how to bring this forward.</p> <p>17 DR. LEVY: I'm Ben Levy. I'm a thoracic</p> <p>18 medical oncologist from Johns Hopkins primarily</p> <p>19 based out of Sibley Memorial Hospital. I'm humbled</p> <p>20 to be on this esteemed faculty and panel, and</p> <p>21 perhaps more humbled by the complexity of the topic</p> <p>22 of really trying to tease out how we manage</p>	<p>Page 182</p>	<p>1 lung cancer, and I think that really leads to the</p> <p>2 discussion of how do we create endpoints for</p> <p>3 trials. This has been pitched forth by RANO and</p> <p>4 published recently, is that perhaps endpoints have</p> <p>5 to be designed based on how likely we think the</p> <p>6 drugs are going to get into the brain, and that can</p> <p>7 be challenging because oftentimes we don't have a</p> <p>8 lot of data on this.</p> <p>9 The last thing I'll say is just in terms of</p> <p>10 quality of life, which I think we all know is so</p> <p>11 important for our patients, I'm all for looking at</p> <p>12 not only overall survival, as was discussed in the</p> <p>13 nice talk at the beginning, but putting that in the</p> <p>14 context of tolerability of the drug but also</p> <p>15 quality of life.</p> <p>16 I'll say as a clinician, as much as we're in</p> <p>17 favor of this, it's extremely hard to capture at</p> <p>18 times. And how to tease out quality of life</p> <p>19 related to neurocognitive problems versus quality</p> <p>20 of life overall for their cancer is exceptionally</p> <p>21 challenging, and it's something that I think we'll</p> <p>22 have to think through as we begin to have more of a</p>	<p>Page 184</p>

<p style="text-align: right;">Page 185</p> <p>1 discussion about this.</p> <p>2 DR. WEFEL: Hello. My name is Jeff Wefel.</p> <p>3 I'm a neuropsychologist at MD Anderson Cancer</p> <p>4 Center, and I have focused a lot of time and effort</p> <p>5 on trying to make cognitive endpoints in clinical</p> <p>6 trials feasible and accessible to multinational</p> <p>7 clinical trial settings and have been fortunate to</p> <p>8 work with a lot of really motivated and intelligent</p> <p>9 investigators to share this aspect of clinical</p> <p>10 trials with them.</p> <p>11 To the benefit of patients, I think we've</p> <p>12 changed standard of care a couple of times and that</p> <p>13 we hope to do that a couple more times, of course,</p> <p>14 in the space of cognition as it contributes to the</p> <p>15 disease experience that patients have.</p> <p>16 So I think this is a really compelling and</p> <p>17 exciting session that maybe we can hammer out some</p> <p>18 standardization around clinical outcome assessments</p> <p>19 for this space as well, as we tried to do in the</p> <p>20 glioma space just a couple of years ago through</p> <p>21 these same sort of meetings and mechanisms. So I'm</p> <p>22 looking forward to this, and I appreciate the</p>	<p style="text-align: right;">Page 187</p> <p>1 patients that are being impacted specifically by</p> <p>2 the intracranial disease.</p> <p>3 So I think actually the focus hopefully</p> <p>4 today will be about a framework because from a</p> <p>5 development perspective, at least my personal lens,</p> <p>6 how can we establish what's the most clinically</p> <p>7 meaningful endpoint in such a way that we can meet</p> <p>8 the needs of different stakeholders, first and</p> <p>9 foremost being obviously the patient?</p> <p>10 So what's most meaningful to the patient,</p> <p>11 but then you have additional stakeholders at hand,</p> <p>12 including regulators, including payers, and</p> <p>13 otherwise, that have perhaps potentially different</p> <p>14 thresholds in relationship to understanding what</p> <p>15 would be an acceptable endpoint for them.</p> <p>16 At a minimum, if we can understand actually</p> <p>17 how to establish that framework, to establish that</p> <p>18 the surrogate is acceptable as an endpoint that</p> <p>19 could lead to ultimately approval and access to the</p> <p>20 patients, I think that will be a critical landmark</p> <p>21 that we could potentially try to achieve today.</p> <p>22 Two things, actually, just as an aside that</p>
<p style="text-align: right;">Page 186</p> <p>1 invitation to be here.</p> <p>2 DR. YANG: Hi. My name's Arvin Yang. I'm</p> <p>3 the development lead for our melanoma and are</p> <p>4 genital urinary cancers at BMS. I'm actually</p> <p>5 representing BMS on behalf of our broad development</p> <p>6 program that we have across multiple tumor types,</p> <p>7 including actually those that are primary within</p> <p>8 CNS, including GBMs and so forth.</p> <p>9 From the standpoint of -- actually I wanted</p> <p>10 to make probably a couple of different points.</p> <p>11 First, I'm privileged actually for the opportunity</p> <p>12 to see the union of all these different groups that</p> <p>13 are coming together.</p> <p>14 I think it's been highlighted earlier, but</p> <p>15 it highlights the unmet need and the urgency in</p> <p>16 regards to what's actually becoming probably more</p> <p>17 of an urgency or an emergency in relationship to</p> <p>18 this disease area, because as we control this</p> <p>19 disease more extracranially, you'll see -- I think</p> <p>20 melanoma was highlighted as one example -- that</p> <p>21 this will become more and more of a higher</p> <p>22 percentile or frequency in relationship to those</p>	<p style="text-align: right;">Page 188</p> <p>1 through the morning discussion for me has emerged</p> <p>2 as actually quite impactful, are some of the points</p> <p>3 mentioned earlier in regards to that even in the</p> <p>4 screening of patients, there's a tendency not to</p> <p>5 screen them in order to preserve options.</p> <p>6 I think that's actually a critical element</p> <p>7 that we have to think carefully about, but it's in</p> <p>8 the context of the full extent of drug development</p> <p>9 whereby there are elements in regards to the</p> <p>10 benefit-risk, and the safety, and the tolerability</p> <p>11 that come into play, but we need to probably think</p> <p>12 more carefully about how can we effectively do that</p> <p>13 and have patients actually capable or able to</p> <p>14 access these experimental regimens, but in a way</p> <p>15 that doesn't limit then the potential to uncover</p> <p>16 the true activity of those regimens.</p> <p>17 The other actually novel point I'll just</p> <p>18 mention, we've probably not directly pointed out is</p> <p>19 there something biologically distinct in regards to</p> <p>20 the CNS mets in a way that perhaps we could then</p> <p>21 identify tumor-specific or region-specific</p> <p>22 endpoints that may then be a novel endpoint by</p>

<p style="text-align: right;">Page 189</p> <p>1 which we could then move forward in a more rapid 2 fashion, because we have to think about it 3 potentially from a positive perspective, that if 4 the intracranial disease is so unique, is there 5 some way that we can actually provide some 6 incentive, or otherwise, for development in that 7 sphere and potentially through some type of 8 surrogate? So let me stop there.</p> <p>9 DR. ANDERS: Excellent. I appreciate 10 everybody's comments from the different viewpoints. 11 As I'm sitting here thinking about all the 12 different things we've heard, there are a lot of 13 topics to cover. But I thought we could start by 14 really thinking about endpoints more from an 15 early-phase development perspective and then a 16 later phase development perspective.</p> <p>17 This comment that you brought up, Arvin, the 18 concept of a surrogate, which I almost hesitate to 19 say because I don't know that we have a great or 20 perfect surrogate, but I'd be curious to hear what 21 the panel members have to say about how we should 22 be approaching endpoints in the early phase, first</p>	<p style="text-align: right;">Page 191</p> <p>1 I'll give you a history lesson in 2 relationship to even Yervoy and Opdivo development. 3 The initial Yervoy phase 3 trials, they did not 4 include patients that incorporated brain mets, even 5 those that were treated, because there was the 6 potential for questions in relationship to the 7 safety aspects. But also as you choose patients or 8 put criteria in order to reveal the potential 9 benefits, you don't potentially want a scenario 10 where there could be factors that blunt that 11 ability to detect that activity.</p> <p>12 So there's that balance in relationship to 13 as you do the early drug development, is there a 14 scenario whereby you have risk in relationship to 15 not determining the signal because of the poor 16 prognosis and so forth.</p> <p>17 The history lesson is this, though. As we 18 then developed Opdivo, we did actually incorporate 19 patients that had previously treated brain mets. 20 We moved from not including them at all to then 21 actually including those that had stable brain mets 22 in a way because we understood then that there were</p>
<p style="text-align: right;">Page 190</p> <p>1 in man, first in human, as opposed to a later stage 2 when we're really thinking about registrational 3 strategies; and this concept we heard of earlier 4 and when we believe there is a signal that is 5 appropriate to move forward and when we believe the 6 signal is not appropriate to move forward.</p> <p>7 Anyone want to take that? Anyone from the 8 audience?</p> <p>9 DR. YANG: I guess I can probably start the 10 conversation.</p> <p>11 DR. ANDERS: Sure.</p> <p>12 DR. YANG: Hopefully there will be more to 13 be added. Obviously, naturally within early 14 development in regards to a drug, it's always a 15 question of understanding the signal or proof of 16 concept related also to this toxicity and safety 17 profile. Just by way of example -- and this may be 18 more of a late-stage example, but I think it's 19 relevant -- is from the standpoint, even before the 20 guidance came out recently, in relationship to the 21 type of patients that could be incorporated into 22 clinical trials.</p>	<p style="text-align: right;">Page 192</p> <p>1 some level of activity. We could then reveal the 2 activity of the agent itself without 3 potentially -- including a broader population. 4 So there was a natural evolution I think is 5 the point that I'm trying to make here. So in the 6 early space, there's probably opportunities by 7 which you can still reveal the activity of the 8 molecule itself but not jeopardizing either safety 9 or other efficacy signals that otherwise would be 10 blunted if you include a broad population.</p> <p>11 DR. PROWELL: I can make a comment on that. 12 Maybe because we don't have a statistical 13 perspective, I'm realizing here when we're looking 14 at drugs in very early development where the design 15 of the trials is likely to be a single-arm trial. 16 I think that's a place where response is going to 17 be more important because that's interpretable even 18 in the absence of a control arm.</p> <p>19 I think in later phase development, and 20 maybe particularly in more refractory patient 21 populations or settings where the prognosis of the 22 disease overall is poor, overall survival becomes</p>

<p style="text-align: right;">Page 193</p> <p>1 interpretable and also really important because, as 2 Dr. Lin highlighted earlier, the prognosis of 3 patients with brain mets has changed for the better 4 a lot in the last two decades, but nonetheless, the 5 median remains about two years, which is not great, 6 and certainly not great for the very young patients 7 that we often see being diagnosed with this 8 condition.</p> <p>9 DR. KLUETZ: I know there's a lot of 10 enthusiasm about clinical outcomes and I think 11 there's rightly a lot of enthusiasm in this 12 setting, but what I would mention to echo Tatiana 13 is that especially in early-phase development, you 14 need to make an upfront decision on whether you're 15 developing a supportive care medication or are you 16 developing an anticancer drug?</p> <p>17 We need to make sure that this drug is 18 reducing the tumor. And when we do that through 19 response rate, we can then say, and in addition to 20 clinical benefit to the patient was a functional 21 improvement or a cognitive improvement. It would 22 be a very challenging regulatory action for, say, a</p>	<p style="text-align: right;">Page 195</p> <p>1 ipi trials from Medarex actually included patients 2 with treated brain metastases. It was actually the 3 observation in those patients that we didn't see 4 additional brain metastases forming. In some of 5 the patients who had some swelling around their 6 brain metastases, who then underwent surgical 7 resection, there was no viable tumor left there 8 that led to the initial trial of ipilimumab in 9 patients with active brain metastases that Kim 10 Margolin led to.</p> <p>11 I think there is value in including patients 12 with treated brain metastases in those early trials 13 once you know you have a drug that has efficacy. 14 At least from my view, if you have no efficacy in 15 the systemic situation -- I can't think of any 16 situation where something would work in the brain 17 that didn't work systemically, but once you 18 establish that the drug works, I think it's 19 reasonable to include patients with treated brain 20 metastases.</p> <p>21 Also, I think when it comes to melanoma, I 22 assume all of our patients with metastatic melanoma</p>
<p style="text-align: right;">Page 194</p> <p>1 reduction in pain alone with no evidence of 2 antitumor activity.</p> <p>3 I can't imagine what the endpoint would be 4 other than a tumor measure in early stage. The 5 question is, back to the previous panel, is it 6 RANO? As a community, you really need to figure 7 out what your response rate is because that is 8 going to drive early development.</p> <p>9 DR. LEVY: Just to piggyback that, in terms 10 of the phase 1 experience, again is it wise to have 11 a cohort specifically just of brain metastases 12 patients so you can gain further signal? If you 13 see an early signal with some of these drugs, do 14 you want to open that up and have a cohort 15 specifically for -- if we're looking at response 16 rate and we need a denominator in these early 17 stages, do we want to open it up and have a 18 specific cohort if there is an early signal?</p> <p>19 DR. ANDERS: The question at the microphone 20 or comment?</p> <p>21 DR. ATKINS: I just wanted to make a little 22 correction to Arvin's statement. The actual early</p>	<p style="text-align: right;">Page 196</p> <p>1 have brain metastases. It's just that our MRIs 2 can't show them yet. So if you're treating 3 patients with systemic disease and not seeing 4 recurrence in the brain after you see a response 5 systemically, that means you're having some effect 6 in the brain and it's certainly reasonable to take 7 patients with untreated brain metastases that are 8 asymptomatic and enroll them as well, and actually 9 see whether or not you're actually producing 10 shrinkage.</p> <p>11 To me, though, the endpoint that is most 12 relevant, in addition to seeing whether you can 13 actually see shrinkage, is to go back to Kim's 14 statement where you're actually treating patients 15 with brain metastases and not necessarily treating 16 brain metastases. I can think of situations where 17 you've controlled the systemic disease and you have 18 alternative ways of treating the brain disease, 19 where eventually that leads to a better survival 20 for those patients even if the treatment itself 21 doesn't get into the brain. But you wouldn't learn 22 that unless those patients were included on the</p>

<p style="text-align: right;">Page 197</p> <p>1 clinical trials.</p> <p>2 DR. YANG: Michael, just to clarify, you're 3 absolutely accurate, but I was referring to pivotal 4 phase 3's, not the exploratory work.</p> <p>5 DR. ATKINS: That was the one that led to 6 the FDA approval.</p> <p>7 DR. ANDERS: Thank you. Can you please 8 state your name and affiliation? You can go ahead.</p> <p>9 DR. MARGOLIN: Thanks. I didn't come up 10 here to rebut what Mike was saying or thank him. I 11 think it was Dr. Levy Who said something that 12 triggered a thought that I've been having all 13 along, and maybe Mike Davies wants to address this 14 or Priscilla Brastianos.</p> <p>15 I think not only is it important to study 16 new drug development in a new agent or strategy 17 development in patients with active brain 18 metastases, but there may be, at least in some 19 diseases and some groups, differences in the 20 biology of all disease in the patients who develop 21 brain metastases. It may be true what Mike just 22 said that everyone with melanoma is a candidate for</p>	<p style="text-align: right;">Page 199</p> <p>1 year, and when I look back at that with patients 2 with ommayas [ph] in their brains, we should be 3 getting circulating tumor cells. We should be 4 getting that peripherally in the CSF. We should be 5 getting drug bioavailability and a greater depth.</p> <p>6 This is like a lesson learned for me, just 7 looking at that phase 1/phase 2. Really, again, 8 it's not so much the number of patients always for 9 those early phases, it's the depth of info that we 10 gain.</p> <p>11 Fast forwarding that to now our phase 3 12 AngioChem study that we've been working on for 13 years now, I think the key that I've learned there 14 is early involvement of the FDA, early involvement 15 of agency -- and I can speak to my experience that 16 the first time I came on this campus was a meeting 17 for that study, and it was about three years ago. 18 And working on that special protocol agreement over 19 the past couple of years taught me that the agency 20 is very much on our side -- of course the reason 21 we're at this meeting here today -- and wants more 22 drugs developed in this area.</p>
<p style="text-align: right;">Page 198</p> <p>1 brain mets, but there might be other diseases -- we 2 certainly know in some of the subsets of breast and 3 lung cancer -- that have a predisposition based on 4 certain mutations and other biology to go to the 5 brain. So we should include patients but not lump 6 them altogether, and we should have different 7 strata and different cohorts so that we can analyze 8 them separately, I think.</p> <p>9 DR. ANDERS: Thank you. Dr. Kumthekar?</p> <p>10 DR. KUMTHEKAR: I'm Priya Kumthekar from 11 Northwestern and I have half a voice, so I'm going 12 to whisper my way through my comments. Definitely, 13 over the past 10 years had an evolution -- I'll 14 speak specifically to leptomeningeal 15 metastases -- over how we want to design our early 16 phase versus now we have a registrational phase 3 17 in the making and hopefully soon to open.</p> <p>18 So I really think moving forward when we're 19 looking at the phase 1 studies, it's important to 20 get a depth of info, even if it's a shorter breadth 21 of patients. What I mean by that is we presented 22 an intrathecal herceptin's study just this last</p>	<p style="text-align: right;">Page 200</p> <p>1 So it's really important to get them early 2 involved so that we can create special protocol 3 agreements, just like we have with that study, so 4 that these drugs are quick hopefully to hit the 5 market if we have successful studies. So looking 6 at those in two different ways with early phase and 7 late phase I think are quite important.</p> <p>8 DR. ANDERS: Priya, can you just share you 9 endpoint for your study?</p> <p>10 DR. KUMTHEKAR: Sure. With the lack of 11 validated endpoints from an imaging perspective in 12 the phase 3 study, for me it was really important 13 that overall survival was the primary endpoint for 14 exactly the reasons that were outlined in the 15 initial talk.</p> <p>16 DR. ARMSTRONG: Can I add a comment?</p> <p>17 DR. ANDERS: Absolutely.</p> <p>18 DR. ARMSTRONG: I would just add to Priya's 19 comment that in addition to things like circulating 20 DNA, that we consider those outcomes in terms of 21 how the patient is doing. Do we shrink the tumor 22 without improving the person is really important.</p>

Page 201	Page 203
<p>1 And I think related to Dr. Kluetz's comment, that 2 of course we want to see response, but in diseases 3 like LMD, we don't do a good job of measuring that. 4 So if we don't at least look at those 5 clinical outcomes at the same time, we'll never 6 know what that association is. I think although it 7 wouldn't be the reason it would be approved, I 8 think inclusion of that at that time is really 9 critical in these patient populations.</p> <p>10 DR. KUMTHEKAR: And that is a secondary 11 endpoint on our registrational study.</p> <p>12 DR. KLUETZ: A response or a clinical 13 outcome?</p> <p>14 DR. KUMTHEKAR: There are PROs as well as 15 response.</p> <p>16 DR. KLUETZ: I was going to say, just like 17 translational work that was previously brought up, 18 we need to learn as much as we can with this huge 19 phase 3 trial. If you were to do a survival 20 endpoint and not further develop a RANO type of 21 response or something, it would be really a missed 22 opportunity and really understanding your clinical</p>	<p>1 for SRS-ing one or two lesions and continue 2 patients on therapy, and see when they actually 3 progress.</p> <p>4 So having objective response rate as the 5 primary endpoints is the proximal one, but then 6 kind of adding that PFS is going to be secondary. 7 And then if they live long enough, neurocognitive 8 assessment is going to be really important for us. 9 I think in that way, we kind of address this in a 10 hierarchical way and a pragmatic way.</p> <p>11 I think one of the important issues we 12 really need to address as a group here is as much 13 as it's important to actually identify what 14 response looks like, I'm really interested in the 15 thoughts of the panel on all of our expertise here 16 and what we are going to call progression, and when 17 is that progression going to actually drive our 18 next clinical decision making. When are we going 19 to introduce SRS? And do we have to take those 20 patients off that study and move on to something 21 else or just allow them to continue moving on?</p> <p>22 DR. LEVY: I just wanted to add to that.</p>
Page 202	Page 204

<p style="text-align: right;">Page 205</p> <p>1 standard-of-care radiosurgery could be employed and 2 then maintained on the clinical trial with 3 continued systemic disease control; so kind of the 4 converse as well and really thinking these through. 5 In fact, I think earlier it was said best that 6 we're treating the patient with brain metastasis, 7 not the brain metastases themselves.</p> <p>8 Back microphone?</p> <p>9 DR. ANDREWS: David Andrews, once again, 10 from Philadelphia, Jefferson. I just want to first 11 assert that we all agree that neurologic death is 12 the accepted overall survival endpoint for brain 13 met phase 3 trials. If we all agree that's the 14 case, I may be going off the rails a little bit, 15 but I would just be asking the FDA if they would 16 consider neurologic death for primary intracranial 17 malignancies, particularly since comorbidities 18 associated with treatment or unassociated 19 comorbidities really does dilute the 20 intention-to-treat population. And I'll accept 21 going offline if you want to answer that.</p> <p>22 DR. ANDERS: Does anyone want to answer that</p>	<p style="text-align: right;">Page 207</p> <p>1 comment on this.</p> <p>2 DR. SUL: I just wanted to touch also on the 3 point about the rest of the systemic disease And 4 also going back to the question that Patrick had 5 posed at the last session about what do we think 6 about RANO. I didn't realize I was pronouncing it 7 incorrectly this entire time, but what do we think 8 about the RANO brain mets criteria.</p> <p>9 I think that they're actually very well 10 thought out, that people put a lot of thought into 11 trying to figure out how to measure and assess 12 disease. I think one of the issues, though, that 13 potentially relates to that is sort of balancing 14 this idea of how much do we compartmentalize brain 15 mets versus disease in the rest of the body.</p> <p>16 That's something that we discuss internally 17 and we struggle with as well. I've had discussions 18 with other clinical reviewers about what's the 19 significance of a small response in the brain if, 20 as Tatiana said, you've got fulminant liver disease 21 that's rapidly progressing.</p> <p>22 That also goes back to the second part of</p>
<p style="text-align: right;">Page 206</p> <p>1 one?</p> <p>2 DR. PROWELL: I think that talking about 3 primary CNS malignancies is a little outside of the 4 scope of this workshop, and interpreting neuro 5 death is complex. With most of these solid tumors 6 that we're talking about -- I'm a breast 7 oncologist. I didn't introduce myself yet, but I'm 8 Tatiana Prowell, breast oncologist at FDA and Johns 9 Hopkins.</p> <p>10 It's pretty rare scenario that we have 11 patients who have only CNS disease and that that 12 remains the case for a very long time. We do see 13 that sometimes in the HER2 positive patients who 14 are treated early stage and then have an isolated 15 CNS relapse. But it's a challenge to think about 16 how to do that outside of a primary CNS tumor 17 setting because the status of the other diseases 18 are equally important in most solid tumors. If you 19 develop fulminant hepatic failure from liver 20 metastases, your intracranial control becomes not 21 relevant.</p> <p>22 So, I don't know. Probably others want to</p>	<p style="text-align: right;">Page 208</p> <p>1 Patrick's question, which was could we actually 2 start to assess or include lesions that are even 3 smaller? I think, again, going back to the purpose 4 of this session and thinking about early versus 5 late, certainly if you're looking for activity, it 6 makes sense to include any size lesion, even a 7 non-measurable disease, if you're looking for 8 activity.</p> <p>9 If you're starting to look for what is 10 clinical benefit and what is clinically meaningful, 11 would it make sense -- and this is something I'd be 12 interested in hearing from the panel and the 13 audience about -- would it make sense to maybe try 14 and define a set of clinically meaningful brain 15 lesions?</p> <p>16 For instance, when we see patients in 17 clinic, what are the brain lesions that I know I 18 definitely want to get on? So anything that 19 happens in the posterior fossa or in the brain 20 stem, regardless of the size, that's not something 21 you necessarily want to sit around on.</p> <p>22 Leptomeningeal disease, there's a lot of debate</p>

<p style="text-align: right;">Page 209</p> <p>1 about whether or not to even treat asymptomatic 2 patients and should this just be done in a 3 palliative fashion.</p> <p>4 Then in the hemispheres, the lesions that I 5 am concerned about are the ones in eloquent cortex, 6 the ones that I know patients are symptomatic from, 7 and any lesion that I know is beyond a certain size 8 that I know I want to get right on because I know 9 that even if patients are not symptomatic now, they 10 are going to be imminently symptomatic.</p> <p>11 So is there some way that maybe we could 12 define a set of potentially "clinically 13 meaningful," quote/unquote, tumors to follow for 14 response to look for benefit?</p> <p>15 DR. LEVY: I think you just did.</p> <p>16 (Laughter.)</p> <p>17 DR. LEVY: I think you have to create broad 18 categories that are flexible. You mentioned the 19 ones that I look at when patients come in, and we 20 talk about are they symptomatic or not and what's 21 the size and location. I probably learned more 22 from you in that statement than I have from my</p>	<p style="text-align: right;">Page 211</p> <p>1 those, that's really what you're getting at and 2 acknowledging how hard it is to measure those, to 3 the point you made.</p> <p>4 DR. JUL: I'm just going to counter that 5 really quickly. Neurologists are infamous for 6 localization and for anatomy, so I think we can be 7 somewhat more precise. It's different than trying 8 to identify a specific area in the liver or the 9 lung. There's a large region that's a middle lobe 10 or a lower lobe. But I think in the brain, 11 neurologists and neuro-oncologists are very 12 specific about describing regions, so I think it's 13 possible to do that.</p> <p>14 DR. ANDERS: Another way to think about that 15 is based on the NCI guidelines that recently were 16 reported in the fall. The term was lesions that 17 are not in need of immediate therapy. And that 18 really does get at what you're saying, these very 19 worrisome posterior fossa brain stem, the motor 20 cortex lesions. So that may be another way to 21 frame that as opposed to having to think about 22 every single region of the brain.</p>
<p style="text-align: right;">Page 210</p> <p>1 radiation oncologists on whether or not they're 2 going to radiate or not. But I think it would be 3 educational to create some broad categories that 4 may set some criteria and understanding that 5 there's such heterogeneity even within those 6 categories.</p> <p>7 DR. KLUETZ: I would just mention -- first 8 of all, I think it's a really fascinating idea 9 because as I mentioned in my talk, location is so 10 important. And the reason it's important is 11 because it portends clinical benefit down the road. 12 But it is going to make it a lot more challenging, 13 and in that subjectivity category, it's going to 14 create a lot more, sort of, is that exactly in the 15 cerebellum or is that a little closer? Where is it 16 exactly?</p> <p>17 So I think there's going to be a lot more 18 radiographic complexity to bidding those as such, 19 so maybe the consideration should be more of what 20 are you actually trying to measure; cerebellar 21 walking, speech? Again, we keep getting back to 22 these clinical outcomes, and if we can measure</p>	<p style="text-align: right;">Page 212</p> <p>1 DR. KLUETZ: It's also got some precedent as 2 far as response and defining a response as the 3 number of CRs, for instance. In this case you'd 4 have, well, we have a response rate, but the 5 response rate in posterior fossa or whatever that 6 particular region is would add value to the 7 response rate itself, I guess.</p> <p>8 DR. YANG: Could I ask a question just from 9 the standpoint -- this is wonderful. From a 10 technical perspective, there may be challenges in 11 relationship to identifying essentially these 12 high-risk patients, but I'm trying to bridge this 13 back to ultimately a determination of true clinical 14 benefit.</p> <p>15 Maybe, Jeff, I'll put you on the spot, but 16 are there other mechanisms by which we could then 17 make that bridge beyond identifying that high-risk 18 population, but really then being able to establish 19 whatever results you see and actually then support 20 an established surrogate in relationship to whether 21 it be overall survival or otherwise? What are the 22 bins in a way that we could think about?</p>

<p>Page 213</p> <p>1 DR. PROWELL: I wanted to respond to 2 Dr. Sul's comment earlier. As I think about this 3 and trying to define what lesions we would put into 4 a collection of important things, these all make 5 perfect sense clinically to say posterior fossa, 6 motor cortex and whatnot. But it seems to me that 7 what you're really trying to get is measurable, and 8 that is who are the patients that we're going to 9 have to take to either another round of SRS or 10 whole-brain radiotherapy because the lesions they 11 have are problematic enough that we can't afford to 12 wait any longer to see if this drug is going to 13 work?</p> <p>14 You can just measure that. You can measure 15 time to local therapy or time to deterioration 16 requiring some sort of local intervention. I 17 wonder if it's more valuable to simply measure that 18 thing, recognizing that there's bias of course, and 19 who actually does get referred for that. But 20 nonetheless, I do think that there's a certain 21 amount of consistency in what prompts us to say to 22 our local therapy colleagues, okay, it's time. We</p>	<p>1 SRS treatment, but that was down the line several 2 years after my brain mets first appeared. So I 3 guess, yeah, that's of the utmost importance.</p> <p>4 DR. ANDERS: Excellent. Fantastic</p> <p>5 conversation. Why don't we move to Dr. Lin?</p> <p>6 DR. LIN: I have two questions. One is a 7 question actually to Paul. We've sort of toyed 8 around with this idea that if you measure let's say 9 15 symptoms at baseline and over time, you 10 potentially dilute out any signals that you see 11 because everybody has their own constellation, 12 personal constellation of symptoms.</p> <p>13 Is there a way that we could come to a 14 little bit of what other areas neurology used? For 15 example, MS you might pick a dominant symptom for 16 that patient and you follow it over time. So every 17 patient actually gets followed a different way, but 18 the endpoint is improvement. I just wonder if 19 there's some way that clinical benefit could get to 20 that point for brain mets.</p> <p>21 The second point is really just related back 22 to the issue of CNS-only progression and allowing</p>
<p>Page 214</p> <p>1 need your help.</p> <p>2 MS. SELIG: Can I just jump in for a second 3 and maybe just ask Shelly to comment on what's 4 important to you as a patient and what you think 5 should be measured about any of this, in terms of 6 how successful is a therapy.</p> <p>7 DR. ENGFER-TRIEBENBACH: Obviously, the 8 survival is key, but linked with that survival is 9 your everyday life and your quality of life, which 10 is hand in hand as far as I'm concerned. They 11 interplay with each other so much, so I don't see 12 one outweighing the other as far as a benefit to 13 patients. We want it all.</p> <p>14 MS. SELIG: What kinds of things in terms of 15 quality of life? I'm just interested. I think 16 people would like to hear.</p> <p>17 DR. ENGFER-TRIEBENBACH: Well for me, 18 avoiding whole-brain radiation is top on my list. 19 I want to be able to -- even though it's not 20 as -- how should I say this? Just from a cognitive 21 standpoint, I don't want to lose anything going 22 into any type of treatment option. I have had the</p>	<p>Page 216</p> <p>1 SRS. I think we try to be very thoughtful about 2 this in the RANO criteria really distinguishing 3 your primary endpoint determination and how you 4 manage the patient, really keeping the patient in 5 mind, the idea being that if your primary endpoint 6 is progression-free survival and you have a CNS 7 progression event, you get counted to 8 progression-free survival. It goes to the 9 endpoint. There's nothing funny about it, but then 10 you let the patient have SRS, and then you follow 11 how they do over time.</p> <p>12 We probably can learn a lot from those. In 13 the TM1 studies where that was allowed, what was 14 found is that when patients had CNS-only 15 progression and they had SRS, they were on median 16 and able to stay on TM1, the disease control, for 17 another 9 months. Remember, these are patients who 18 ordinarily in the past would all have been kicked 19 off the trial. So A, there was clinical benefit to 20 patients, and B, you actually got to document that.</p> <p>21 So I think that's a really important point.</p> <p>22 DR. ANDERS: Excellent points. Why don't we</p>

<p>Page 217</p> <p>1 go to the back of the room? 2 DR. HELLER: Thank you. I'm Kevin Heller. 3 I work at NextCure, a local biotech. I'm a 4 pediatric oncologist by training, so I will just 5 also say I think this might be a little bit out of 6 the scope but it really speaks to, Wendy, your last 7 question and, Shelly, your response about the 8 relevance of surrogate endpoints in pediatric 9 malignancies.</p> <p>10 For example, the goal perhaps ought to be 11 how long we can prolong whole-brain radiation 12 because with children, especially under the age of 13 5, you really are curtailing their development. 14 It's been written about.</p> <p>15 Tom Merchant from St. Jude, who's a 16 radiation oncologist, if we could use as an 17 endpoint -- and I'm really curious to know from our 18 FDA colleagues whether or not there's a way that we 19 could have prolongation prior to starting 20 whole-brain or even focal radiation and is that 21 even practical because that really relies on the 22 patient-reported outcomes. And then certainly if</p>	<p>1 intervention, Gleason 7, et cetera. If there's 2 some kind of objective criteria that could be used 3 that would trigger whole-brain radiation therapy 4 and you could integrate that into your decision 5 making that would provide it, that would make it a 6 stronger endpoint.</p> <p>7 DR. WEFEL: I might offer an alternative to 8 this, is to remove the surrogacy on this question. 9 You're saying you want to avoid whole-brain 10 radiation therapy because that might cause memory 11 disorder for example, so might the systemically 12 administered therapy.</p> <p>13 We see this in this concept of chemo brain, 14 so why not just follow memory? It's how we 15 function, and I think that could be a compelling 16 outcome as opposed to a surrogate that we assume 17 might have an effect on memory, which it doesn't 18 always in everybody.</p> <p>19 DR. ANDERS: A very good point.</p> <p>20 First microphone?</p> <p>21 DR. MARGOLIN: Well, I was just going to 22 make the comment that it sounds like having not</p>
<p>Page 218</p> <p>1 we get patients through the therapy, they want to 2 have their cognitive state with them.</p> <p>3 DR. KLUETZ: I was going to mention, we just 4 did a workshop -- again, there's a lot of parallels 5 in prostate cancer. But we did a workshop about 6 how do we develop drugs in local prostate cancer 7 where the median survival is decades, and the time 8 you get to metastatic disease is a long time, so it 9 was a really challenging space.</p> <p>10 What all men said was we would love to not a 11 radical prostatectomy or XRT, which portends sexual 12 dysfunction and urinary dysfunction. The 13 challenge, which was actually something we kind of 14 looked at -- and there's a sample clinical trial on 15 that site too -- was, yes, the delay or the 16 prevention of the RP or XRT was clinically 17 beneficial, but how you trigger that intervention 18 was going to need to be objectively clarified.</p> <p>19 How we went about that is there are lots of 20 active surveillance programs out there and when 21 your pathology gets to a certain point, it's just 22 sort of standard of care that that triggers your</p>	<p>Page 220</p> <p>1 only composite endpoints but multiple parallel 2 points, and then going back and studying how well 3 the endpoints function, would be really critical.</p> <p>4 After a few years on ODAC, I realize that 5 when you review the sponsor package, let's say it's 6 a new drug, you're looking for sometimes the 7 difference between drug X and Y doesn't meet, or 8 doesn't quite meet, or barely meets the original 9 discussions with the FDA, but you have several 10 other secondary endpoints. And if everything is 11 going in the same direction, then it's far more 12 compelling than if you have a split.</p> <p>13 However, having quantitative endpoints that 14 are readily and accurately saleable would be 15 critical, and I would think that memory might be 16 awfully difficult and very challenging.</p> <p>17 DR. WEFEL: So it's not.</p> <p>18 DR. MARGOLIN: Oh, good.</p> <p>19 (Laughter.)</p> <p>20 DR. WEFEL: That's a big reveal. Certainly, 21 this is something that's been done for hundreds of 22 years in the practice of psychology and</p>

<p style="text-align: right;">Page 221</p> <p>1 neuropsychology. We do have ways to do that. 2 I think the dilemma had been in the clinical 3 trials space that we don't have neuropsychologists 4 at every single site, so what we've tried to do is 5 to find ways to train healthcare providers to be 6 able to assess this in their patients, kind of like 7 the neuroradiology example where we acquire scans 8 but we may need help processing them or centrally 9 reviewing them in some way to make this 10 disseminable and accessible. It also takes a 11 little bit more time. We don't have an e-version 12 of this yet, so there's some time in the clinic 13 that's required to do this, but it's otherwise 14 tractable.</p> <p>15 DR. ANDERS: All right. We have about 10 16 more minutes before lunch. We have two folks at 17 the microphone. Why don't we start at the back.</p> <p>18 DR. ATZBERGER: My name is Alexander 19 Atzberger, and I'm a PhD student at the department 20 of neurosurgery at the Brigham and Women's Hospital 21 in Boston. I have a question about steroids in 22 brain mets trials. Steroids, dexamethasone mainly,</p>	<p style="text-align: right;">Page 223</p> <p>1 for how they're applied, and that involves telling 2 clinicians what to do, which is hard. We know this 3 as regulators. We don't regulate practice of 4 medicine, and I can tell you that whenever we do a 5 drug approval and the label is written to a T to be 6 very precise, as soon as that drugs out in the 7 community, people are like, "I don't really like 8 Taxotere; I like taxol," and people start making 9 everything up.</p> <p>10 So even within the context of a clinical 11 trial, something like these are the criteria for 12 which you can get steroids and here's which one you 13 have to use and how you have to dose it, are you 14 going to be able to get clinicians participating in 15 that clinical trial to be on board with that? I 16 don't know. And what about the patient who shows 17 up in the ER, and now they have a protocol 18 violation because they got steroids in a way that 19 wasn't allowed or prescribed in the clinical trial?</p> <p>20 I think that in order to do that, it's an 21 interesting idea, and there are compelling reasons 22 to want to do it, for the reasons you just said,</p>
<p style="text-align: right;">Page 222</p> <p>1 they're probably the most prescribed drug 2 historically for patients with brain mets. They've 3 been prescribed for about half a century, and yet 4 there's very little standardization of regimens. 5 And there's increasing evidence that these 6 drugs -- we know that they have some nasty side 7 effects, but they also have -- probably they 8 interact with immunotherapy in a negative rate. 9 And there was even a study published in Nature this 10 week that said that steroids can have inherent 11 metastasis promoting capacities in breast cancer.</p> <p>12 So my question is, do you think that steroid 13 dependency is going to be an increasingly important 14 a surrogate endpoint or study outcome in brain mets 15 trials, especially in the era of immunological 16 treatments?</p> <p>17 DR. PROWELL: This is a challenging point in 18 that it sort of is related to what Paul was talking 19 about earlier when we think about criteria for 20 referring people for radiation. I think in order 21 to be able to use these sorts of things as 22 endpoints, you really have to have some algorithm</p>	<p style="text-align: right;">Page 224</p> <p>1 but you have to be able to have clinicians who are 2 going to be on board with a protocol telling them 3 how they have to do things that typically we felt 4 were outside the scope of how directive we should 5 be in clinical trials. I don't know how likely 6 that is to work. Clinicians are pretty independent 7 minded. That's what I've discovered.</p> <p>8 DR. ATZBERGER: Thank you.</p> <p>9 DR. ANDERS: Excellent. First microphone?</p> <p>10 DR. EBIANA: Hi. I'm Victoria Ebiana from 11 Merck again. Actually, I completely agree with 12 Dr. Margolin's point, and she actually stole what I 13 was going to ask, so I'm going to turn it back 14 around to the regulators and ask you what your 15 opinion is of the idea of collecting parallel 16 pieces of data such as the radiographic data time 17 to SRS or whole-brain radiation, things like the 18 mini-mental status as an example of cognitive 19 function and just using those as parallel endpoints 20 rather than trying to use one as a surrogate for 21 the other.</p> <p>22 Would you accept that as a part of a trial</p>

<p>Page 225</p> <p>1 design and maybe as part of a packaging label, or 2 what do you think about that? 3 DR. KLUETZ: I gave an example of COUGAR 4 302, which was the prostate cancer trial that did 5 just that. So yeah, we do this all the time. The 6 question is really much more about being very, very 7 careful with your statistical hierarchy because I 8 have seen many times that someone will put survival 9 up at the very top of a hierarchical secondary 10 endpoint list where there was really no chance they 11 were going to get survival because they were 12 offering crossover, and you were like who was that 13 statistician? 14 So just be very, very careful about what 15 your hierarchy is to make sure that the thing that 16 you believe is most likely to be significant is on 17 top, and then paint the picture, just as I 18 mentioned. And I think that's absolutely how these 19 trials should be run, with many, many multiple 20 important -- both clinically beneficial as well as 21 super objective, potentially more surrogate 22 endpoints.</p>	<p>Page 227</p> <p>1 So I totally get what Tatiana says, and in 2 the ideal world, we'd only be getting big effects 3 on cognitive function or big effects on whatever 4 your functional outcome is. But I think the 5 reality is the best assays we have right now are 6 tumor measures, honestly, and then the question is, 7 is that reduction in tumor or that delay in tumor 8 portending clinical benefit through your subsequent 9 endpoints. 10 So I think you can do it either way. If you 11 have really strong activity in the early phases, 12 you could try to put your clinical benefit endpoint 13 first. But as I said before, a clinical benefit 14 endpoint in the absence of any tumor activity is a 15 supportive care medication, which has a vastly 16 different safety tolerance. 17 DR. ANDERS: We agree. 18 MS. SELIG: Dr. Anders, I wonder if you 19 could maybe let Dr. Kalidas speak last, and then we 20 can have you wrap up. If you want to hold your 21 comments for after lunch. 22 FEMALE VOICE: We don't.</p>
<p>Page 226</p> <p>1 DR. PROWELL: I would add to that. I think 2 it shouldn't be only that the thing you can win on 3 should be first. There are obvious reasons to want 4 to do that so that you can be able to look at the 5 other things and for drug developers to be able to 6 try to get your drug approved. But I think at the 7 top of the hierarchy should also be the things that 8 you actually think count as a clinician, and things 9 that, more importantly, that patients think count 10 should be at the top of your list. If you feel 11 like you can't demonstrate those things 12 statistically, then you either need a different 13 trial design or you need a different drug. 14 DR. KLUETZ: Just to counter that, the 15 things that are often most important and most 16 clinically meaningful are the things that have the 17 most variability in their measure, as I tried to 18 describe before. Therefore, sometimes we're stuck 19 to describe how you're affecting the tumor first, 20 and then you may even have non-statistically 21 significant but directionally important 22 corroborating evidence.</p>	<p>Page 228</p> <p>1 MS. SELIG: Sorry. We're running out of 2 time here, so we need to wrap up. Go ahead. 3 DR. KALIDAS: I just want to add to the 4 discussion that Tatiana and Paul just had. I think 5 the example that Paul had used from prostate 6 cancer, that would be a great example for later 7 stage development discussion with the FDA for a 8 registration trial. 9 To inform ourselves about how to come up 10 with all of those tests in the hierarchical 11 testing, we would need to have a more streamlined 12 set of tests, as Tatiana mentioned, maybe response 13 rate to something that we include in the expansion 14 cohort stage, along with the duration of response. 15 Maybe depending on what tumor type it is and 16 the prevalence of certain type of CNS mets 17 patients, we include other relevant clinical 18 measures so that we can ultimately inform what we 19 include in the registration trial, especially when 20 it comes to hierarchical testing. 21 So we do need multiple measures in the 22 late-stage trials, but perhaps in the early trials</p>

<p style="text-align: right;">Page 229</p> <p>1 we have a more streamlined approach with response 2 rate definitely included. 3 DR. ANDERS: That was actually a fantastic 4 summary. 5 AUDIENCE MEMBER: I have a very quick 6 question. When Dr. Lin talked about local control 7 and trials that do allow for brain mets and have a 8 progression in the brain, why is that specific to 9 SRS? Why doesn't it include surgery? Especially 10 because when you do surgery, you can get a 11 pathology and you can find out exactly what that 12 is. 13 FEMALE VOICE: [Inaudible - off mic]. 14 FEMALE VOICE: The comment, I know not 15 everyone could hear, was you definitely could 16 include surgery. 17 Panel Recap - Carey Anders 18 DR. ANDERS: Correct. Excellent. 19 Well, thank you to the panelists for a very 20 rich conversation. I think we've certainly, as we 21 think through the past hour and 15 minutes, have 22 defined a lot of challenges with endpoints. The</p>	<p style="text-align: right;">Page 231</p> <p>1 for some sort of a sandwich or salad. They should 2 be outside. There are all kinds of places to eat 3 out there, and we'll see you all back here. 4 (Whereupon, at 12:31 p.m., a lunch recess 5 was taken.) 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>
<p style="text-align: right;">Page 230</p> <p>1 endpoints are clearly going to differ by the stage 2 of the study and the type of intervention. These 3 can range from response rate earlier on. 4 I think we all agree overall survival is our 5 gold standard and really incorporating the totality 6 of the data to incorporate symptom burden along the 7 way. And I think, just has been thematic 8 throughout our morning, hope and access. I think 9 that's certainly being addressed by all the 10 individuals in this room. 11 I will turn it over to Wendy for, I believe, 12 lunch. 13 MS. SELIG: Great. Please thank the panel. 14 You guys did a great job. 15 (Applause.) 16 MS. SELIG: Joohee, did you have any parting 17 shots on that discussion? Patrick? Nothing? 18 (No response.) 19 MS. SELIG: Okay. Food for thought plus 20 food for everything else outside. Thirty minutes 21 for lunch. I know it's brief, but we want to start 22 right up again at 1:00. You should have signed up</p>	<p style="text-align: right;">Page 232</p> <p>1 A F T E R N O O N S E S S I O N 2 (12:59 p.m.) 3 MS. SELIG: We are going to get started. I 4 know it was a quick lunch break. Thank you all for 5 getting back and getting in your seats. If you're 6 still eating, no problem. We want to stay on time 7 here. 8 As I mentioned before, this is the second 9 part of Session III, and I'm sure we will circle 10 back around to some of the topics we were 11 discussing in the first panel. We're going to 12 start off with a brief regulatory presentation, 13 Dr. Marur, and we're also really delighted that 14 Dr. Keegan was able to join us today; welcome. You 15 two have about 10 minutes to talk about regulatory 16 challenges, and then the second panel in this 17 session is moderated by Dr. Prowell and that 18 focuses on rethinking trial designs. 19 I do want to put out there for our industry 20 colleagues in the room, we're going to want to put 21 you on the spot either as part of this discussion 22 or part of Session IV, or both. We really want to</p>

<p style="text-align: right;">Page 233</p> <p>1 hear from you about something you've heard today 2 that can incentivize and motivate you to move 3 forward in the direction of product development for 4 CNS metastasis; something you haven't heard today 5 that you need to hear in order to be able to do 6 that or something that you heard today that is 7 raising concerns that need to be addressed. 8 We have our regulatory colleagues in the 9 room. We have our clinician colleagues in the 10 room. We really need to hear from you about what 11 you're going to need in order to be able to move 12 this forward, so just putting it out there. 13 Dr. Marur and Dr. Keegan, turning it to you. 14 Thank you. 15 Presentation - Shanthi Marur 16 DR. MARUR: Good afternoon. My name is 17 Shanthi Marur. I'm a medical officer with the 18 Division of Oncology Products, and Dr. Keegan is 19 here, who is the director of the Division of 20 Oncology Products, too. Together, today we want to 21 go over what are the regulatory challenges with 22 trials that are seeking CNS efficacy claims, and</p>	<p style="text-align: right;">Page 235</p> <p>1 durability of the response, if it looks great, we 2 are open to putting this in the label. But for an 3 FDA full approval, it has based on the 4 demonstration of clinical benefit, and that is 5 improvement in survival or how the patient feels or 6 functions. ORR and duration of response does not 7 automatically translate into having an improvement 8 in survival or how the patient feels or functions. 9 Please keep that in mind. 10 The next is the demonstration of effects on 11 survival or quality of life requires randomized 12 trials. The way the current trials are designed, 13 it's not designed in a way that it shows such 14 effects. Let me elaborate on that a little bit 15 more 16 If you are coming in with the CNS efficacy 17 claim, if this is a randomized trial, often we see 18 that these trials and not stratified by presence or 19 absence of CNS mets or treated or untreated CNS 20 mets, so then when we want to analyze this data, it 21 becomes less and less interpretable. The effects 22 on the tumor in one organ site, one</p>
<p style="text-align: right;">Page 234</p> <p>1 I'm going to focus pretty much on registrational 2 trials so that we can come to a consensus today or 3 at least stimulate a discussion with these trials. 4 This is just an overview of the challenges 5 that we come across. Of these, the most 6 challenging is the efficacy endpoints, and then of 7 course all the others that are down the list, such 8 as the eligibility criteria, the CNS imaging, the 9 assessment of CNS lesions, criteria used to assess 10 the CNS response, and then the study design. They 11 all in some ways just tie in with the most burning, 12 challenging issue, which is the efficacy endpoint. 13 So what is it about the efficacy endpoint 14 that is so challenging for, especially for CNS 15 efficacy claims? The most common ones that come 16 across to us are the CNS-ORR, objective response 17 rate and the duration of response. Then of course, 18 some trials will include CNS-PFS and CNS-OS. 19 We have to remember that CNS-ORR and 20 duration of response, we will take into 21 consideration, provided the response rate 22 looks -- the magnitude of the effect and the</p>	<p style="text-align: right;">Page 236</p> <p>1 compartment -- for example, with using CNS-ORR or 2 CNS-PFS, we believe that this may not always confer 3 clinical benefit in a disease that is more systemic 4 and widespread. 5 Once you've chosen your efficacy endpoint, 6 we then look at who were included in this trial and 7 who were excluded in this trial, and we see that 8 the majority of the patients that are included in 9 the trial are asymptomatic patients, were locally 10 treated, and are stable at study entry, have known 11 neurological dysfunction, and are not on any 12 steroids or any kind of supportive medications. 13 So we have a group of patients who are 14 already good actors, and we see that patients who 15 are excluded are those who are the untreated 16 symptomatic brain mets patients. Some trials will 17 allow leptomeningeal disease, but most trials do 18 not, and we had this discussion in the sessions in 19 the morning; and not all patients have an 20 assessment of CNS involvement at study entry. Each 21 one of these can be a challenge to us when we 22 interpret the data.</p>

<p>Page 237</p> <p>1 This takes us to the CNS imaging. I'll go 2 to the first point, which is about baseline CNS 3 imaging. It's not done in all patients who get 4 enrolled into the trial. Requiring baseline CNS 5 imaging and documenting the CNS disease, it will 6 limit the patient's eligibility, so many of these 7 patients then turn out to be ineligible for at 8 least a systemic benefit. And we can understand 9 why not everyone has a baseline CNS imaging. 10 Then comes the question about the 11 on-treatment evaluations. We often see that the 12 CNS imaging assessments are not scheduled at the 13 same frequency as the extracranial disease 14 assessments, whether it's planned or unplanned. 15 Sometimes you have unplanned extracranial disease 16 assessments, and those time points, these patients 17 don't have a CNS imaging disease. 18 That leads to a high censoring rate for the 19 CNS tumor endpoints, so the patient would have 20 progressed as a result of systemic disease, or had 21 an event because of the systemic disease and comes 22 off the trial. Those patients are censored, and</p>	<p>1 is more with the CNS rather than for the systemic 2 disease. 3 Of course the assessment of intracranial 4 response, what criteria do you want to use? It's 5 different across the trials. Every trial that hits 6 our [indiscernible] it's either RECIST or it's 7 RECIST plus RANO, or RANO plus RANO LM, or 8 sometimes it's just RANO LM alone sometimes when 9 they come in for an leptomeningeal indication. 10 Then comes the study design challenges. 11 Since we're talking about registrational trials, 12 I'm going to focus only on randomized trials. The 13 randomized trials that we see, as I've mentioned 14 before, are not stratified by the presence or 15 absence of brain mets, treated versus untreated 16 brain mets, and we see that there is no 17 justification for the sample size that you want for 18 the CNS efficacy population. I'm specifically 19 talking about that population; no prespecified 20 assumptions of the treatment effects or 21 prespecified analysis plan. 22 Of course, again, I come back to this issue</p>
<p>Page 238</p> <p>1 they have not had another scan at that time point 2 of the CNS imaging. 3 Next is the assessment of the CNS lesions. 4 I'll go to the second bullet, which is basically 5 there is no agreement upon the selection of the CNS 6 lesions; that's the target lesions. What lesions 7 are you going to use as the target lesions? Have 8 these lesions been previously radiated? If they 9 have been previously radiated, how long ago was 10 there prior radiation to the study entry and was 11 their documented progression of that lesion at the 12 time of study entry? These become major challenges 13 in attributing the treatment effect to the study 14 drug. 15 I'm going to go to the first bullet, which 16 is the discordance between the investigator 17 assessment and the independent review committee, 18 specifically categorizing the measurable and the 19 non-measurable lesions. What the investigator 20 might think is non-measurable may turn out to be 21 measurable by IRC or vice versa. This high rate of 22 discrepancy in CNS-ORR between investigator an IRC</p>	<p>Page 240</p> <p>1 of high rate of censoring due to systemic 2 progression. In these patients, what is the 3 clinical benefit of intracranial objective response 4 rate in the face of systemic progression? We keep 5 forgetting that when we come in only for the CNS 6 efficacy. 7 So with this, I hope we will kick off the 8 discussion. Given that the trials must demonstrate 9 the clinical benefit of treatment, what endpoints 10 do we want to capture for clinical benefit of 11 treatment, focused on an involved site of systemic 12 disease? Who should be included in these trials to 13 seek claims for treatment of patients with CNS 14 metastases? 15 A discussion on the appropriate criteria. 16 Should it just be RECIST or RECIST plus RANO to 17 characterize the clinically important reduction in 18 intracranial metastases, and then a discussion on 19 adequately designed trials to support claims that 20 are attributable to intracranial overall response 21 rate, independent of the effects on the systemic 22 disease.</p>

Page 241	Page 243
<p>1 With this, I'm going to let the panel 2 takeover and move this discussion further. Thank 3 you.</p> <p>4 Panel Discussion</p> <p>5 DR. PROWELL: Thank you so much for those 6 introductory comment. I just want to offer one 7 minute or so of comments, and then I'm going to 8 open this up for the panel members to introduce 9 themselves and offer their initial remarks.</p> <p>10 When I have tried for a long time to 11 persuade people to include patients with brain 12 metastases in the clinical trials, before this was 13 being commonly done, the reasons that people would 14 tell me they were not going to include them were 15 things I had heard again and again, which actually 16 made no sense whatsoever, now that I've been 17 thinking about it for a longer time. They would 18 tell me we can't include these patients because 19 their prognosis is so poor; they don't live very 20 long, which really makes no sense. That's exactly 21 in whom we need to be developing drives and 22 studying.</p>	<p>1 critical to move this field forward.</p> <p>2 I would actually like to give the whole 3 panel an opportunity to introduce themselves, but 4 because I thought it was so powerful in the first 5 panel, I want to start with hearing from our 6 patient, Lynda Weatherby.</p> <p>7 MS. WEATHERBY: Hi, everybody. I'm a little 8 nervous. I wanted to start today and tell you that 9 I've been a metastatic breast cancer patient 10 advocate for about five years, and today probably 11 marks the most meaningful day on that whole half so 12 far. To be in the room with all of you is 13 really -- it inspires three emotions. It's very 14 emotional.</p> <p>15 The first is gratitude for everybody and the 16 way you're working on this. The second is fear and 17 terror at some of the things I see on these slides.</p> <p>18 And the only way I cope with that is to keep in 19 mind the words of my doctors, Julie Gralow at 20 Seattle Cancer Care Alliance and Leah Hallis [ph] 21 as my radiation oncologist at University of 22 Washington. They advise me and other friends of</p>

<p style="text-align: right;">Page 245</p> <p>1 was in kindergarten at the time, and as he was 2 graduating high school, the long silent scream in 3 my body, that was accelerating slowly and then very 4 rapidly as I approached diagnosis, revealed that I 5 had metastatic disease, which was widespread in my 6 skeleton, on my spine, pressing on my spinal cord 7 to my brain.</p> <p>8 I had a fractured rib from a met. The 9 lesions in my brain were tiny to the cerebellum, 10 but I also had, most troubling of all, a tumor on 11 my left trigeminal nerve, and my husband and I 12 laughed that I might be the only person who gets 13 breast cancer on their face, but I managed to do 14 it.</p> <p>15 I knew nothing about a trigeminal nerve 16 until this diagnosis, and I was stuck in between my 17 bone scan with my husband in Japan and him arriving 18 home on Saturday that this nerve, after a couple of 19 weeks of giving me terrible symptoms, simply locked 20 up my face, dropped me to my knees, sent me to the 21 ER. Nobody knew what was going on. I had no idea 22 that it could be breast cancer, and I thought I had</p>	<p style="text-align: right;">Page 247</p> <p>1 Tamoxifen and now an aromatase inhibitor, following 2 hysterectomy, have been working really well.</p> <p>3 Having said that, I'm in the middle of scan 4 anxiety right now because I go in on Tuesday. Last 5 year, I had to have my second gamma knife radiation 6 um, for some things that had been on watch that 7 Dr. Hallis and I agreed we should go ahead and go 8 after. And as I was in for that second gamma 9 knife, we discovered the cause of shooting pain 10 down my neck, like a stinger pain down my neck, was 11 a brand new skull metastasis. I said to my 12 husband -- it had been present -- the pain down my 13 neck had been present for about a month, and you 14 just go through thinking, what did I do? Did I 15 exercise? Every time I turned to drive, it's 16 shooting pain, and here it's a metastasis. My 17 tumor markers were normal, everything else is 18 quiet, and here it's a metastasis.</p> <p>19 It's hard to live in that space where you 20 don't want to overreact, but then it's a 21 metastasis. So fortunately, it was treated that 22 day and hopefully I won't hear any more from it</p>
<p style="text-align: right;">Page 246</p> <p>1 another problem going on that weekend before we got 2 the diagnosis of metastatic breast cancer. I was 3 rushed in for radiation to my spine. I had gamma 4 knife right away to treat the brain lesions, and 5 then this nerve.</p> <p>6 It took all summer. The trigeminal nerve 7 was so problematic for a long complicated series of 8 events. I will tell you that I ended up in a 9 neuro-oncologist office who explained to me that I 10 was really possibly facing leptomeningeal disease. 11 That was the only appointment my husband did not go 12 to with me.</p> <p>13 If you can imagine, if you're not a patient, 14 you are sitting in your chair, and then it's kind 15 of like in StarWars where the whole structure opens 16 up and you're just free falling you. That is how 17 it feels. Everything goes away and you have 18 nothing to hold on to.</p> <p>19 Fortunately, my oncologist and my radiation 20 oncologist stepped in and got me pulled back 21 together and said we're not going to go there yet, 22 and suffice it to say my first-line treatments of</p>	<p style="text-align: right;">Page 248</p> <p>1 even though there is still permanent pain going 2 down my neck.</p> <p>3 I guess I just want to say I have not done a 4 clinical trial yet. I keep an eye on it. I will 5 try to speak for the patients that I know that have 6 done them, and I am very aware of the patient 7 friends that I've lost to leptomeningeal disease 8 and brain metastases as I sit here today. So thank 9 you very much for having me.</p> <p>10 (Applause.)</p> <p>11 DR. PROWELL: Thank you so much for those 12 opening comments, and I'm struck by your saying 13 that you felt like you didn't have anything to hold 14 on to. So I think the goal of this day is for you 15 and every patient facing what you've been facing to 16 have something to hold on to at the end of this 17 day.</p> <p>18 Maybe we could just start from that end and 19 have people just introduce themselves, say their 20 name and affiliation and a brief remark.</p> <p>21 DR. WEN: I'm actually not on this panel. 22 I'm just a spectator.</p>

<p style="text-align: right;">Page 249</p> <p>1 DR. PROWELL: Please, go ahead. 2 DR. TAWBI: You were supposed to start on 3 the other end, but that's fine. My name is Hussein 4 Tawbi. I'm a melanoma medical oncologist at the 5 University of Texas MD Anderson Cancer Center. 6 I've been fortunate to actually lead trials that 7 have helped patients with brain metastases, and 8 it's really amazing to have Lynda here, and earlier 9 Derrick, and hear about your experiences. 10 I really want to actually highlight the fact 11 that Derrick started with the hope and you're 12 talking about the fear. And I really think as a 13 group here, our job is to make sure that nobody's 14 afraid of hoping, and that we can actually bring 15 these trials to patients and be able to actually 16 impact not just their survival but their daily 17 lives as well. 18 I'll just say that I started my career as a 19 phase 1 drug development person in melanoma. I 20 guess I was always the kid that drove everybody 21 nuts by asking the why question; why, why, why. It 22 was really important to me that every time I tried</p>	<p style="text-align: right;">Page 251</p> <p>1 those patients on trials. We can design trials 2 specifically for those patients and actually answer 3 the questions in an inappropriate way. 4 So I'm really looking forward to hear the 5 rest of the discussion and really to come out of 6 today with very clear guidelines so that our 7 colleagues across all diseases, not just in 8 melanoma, and obviously across oncology, to try to 9 actually demystify brain metastases and allow them 10 on trials more freely, and really allow for this 11 data to be generated. Because the answer that we 12 don't want to have is that we don't know. Thank 13 you. 14 DR. PROWELL: Thank you so much. 15 DR. MISHRA-KALYANI: Good afternoon. My 16 name is Pallavi Mishra-Kalyani, and I'm a 17 statistician at the FDA. I work in the Division of 18 Biometrics V, which is the group that supports the 19 statistical review of applications or INDs for 20 oncology and hematology products. My own 21 experience has been mostly with solid tumors and 22 review of protocols and applications for solid</p>
<p style="text-align: right;">Page 250</p> <p>1 to put a patient on a clinical trial to go through, 2 my coordinator would look at me and say, "Can't; 3 exclusion criterion," and to ask why was this 4 exclusion criteria actually in this study? Why do 5 we have to say your platelets have to be more than 6 100,000? 7 Well, that made sense for some of our 8 patients, but then you got to brain metastases. 9 You got to, again, organ dysfunction. You got to 10 just rare diseases that were not allowed. So I 11 kind of made it a mission of mine to kind of go 12 after these whys and really try to understand how 13 can we turn those around. 14 I've done some work in organ dysfunction 15 studies, but then turning to patients with brain 16 metastases, it was clear to us that those are 17 patients that are just being excluded based on 18 existing dogma rather than actual evidence, and I 19 think over time with some courageous actually 20 clinical researchers. Actually, I have to also 21 shout out for some of the companies that have been 22 involved to say, look, we can actually include</p>	<p style="text-align: right;">Page 252</p> <p>1 tumors, including lung cancer and melanoma. 2 I'm going to pause on my comments on what 3 Shanthi has presented mostly because I am in 4 agreement mostly there. I don't know if I'll add 5 anything substantial quite yet, but hopefully I can 6 help address some of the statistical concerns and 7 questions that may come up as we're discussing 8 trial designs. 9 DR. PROWELL: Thank you so much. 10 DR. GONDI: My name is Vinai Gondi. I'm a 11 radiation oncologist at Northwestern. I specialize 12 in the management of patients with brain and spine 13 tumors, both in adults and pediatrics. My focus of 14 research, my real passion has been shared earlier 15 today, and that is how do we treat tumors, and 16 specifically brain metastases, with this really 17 effective modality called radiotherapy in a safe as 18 way as possible. 19 A lot of my focus has been on 20 neuroprotective strategies and most recently 21 hippocampal sparing. So I'll weigh in on some of 22 that as it relates to drug development, but I'll</p>

<p style="text-align: right;">Page 253</p> <p>1 also weigh in on my clinical experience, as was 2 discussed before, and some of the frustrations 3 sometimes we face in clinic when we know we have 4 this really effective treatment like radiosurgery 5 or radiotherapy for someone with brain metastases, 6 but then we have to really consider 7 should we use it because then they may not be 8 eligible for a trial. We can talk about that.</p> <p>9 DR. KEEGAN: Hi. I'm Patricia Keegan. I'm 10 with the Division of Oncology Products II, and 11 we're responsible for the oversight of drug 12 development in a variety of solid tumors. The area 13 where I face this issue has primarily been with the 14 lung cancer clinical trials in drug development, 15 but I think I bring a perspective in the sense that 16 we're also responsible for consulting with other 17 parts of the agency, for instance, on trials to 18 give liver-directed therapies and other things. So 19 I think that that experience will help, and it does 20 help me inform my considerations for this specific 21 focus.</p> <p>22 I'd like to say just a little word about the</p>	<p style="text-align: right;">Page 255</p> <p>1 DR. BLACKWELL: I'm Kim Blackwell. I'm 2 currently a vice president, and at Eli Lilly, I 3 oversee the early-phase oncology and 4 immuno-oncology efforts there. I should disclose 5 some people might think I have a multiple 6 personality because I just joined Lilly a year ago, 7 after 25 years of clinical practice running both 8 the breast cancer program and ultimately founding 9 the Center for Solid Tumor Brain Mets at Duke 10 University.</p> <p>11 Prior to leaving my university appointment, 12 I actually founded a company that's focused on the 13 treatment of early solid tumor brain mets. So I 14 have academic experience, I have early life science 15 experience, and I now have big pharma experience, 16 so I'll try to say, "And now I'm speaking from this 17 role, and now I'm speaking from this role." But I 18 think I'm uniquely equipped to try to speak on the 19 pharma perspective, both big and early-life 20 science, just from an investment and how do you 21 start a company that's focused on this.</p> <p>22 I became passionate about this, in part,</p>
<p style="text-align: right;">Page 254</p> <p>1 issue of patients not being enrolled in clinical 2 trials, not just related to CNS malignancies, but 3 that I think, based on my experience with FDA, that 4 probably the single greatest limiting factor to 5 patients not getting into clinical trials based on 6 eligibility criteria is that people just recycle 7 clinical protocols, and they don't look at the 8 drugs that they're studying and make a specific 9 decision on each eligibility criteria as to why 10 this makes sense to be here or not to be there.</p> <p>11 Much of that has led to the reason that 12 we're regularly excluding patients with CNS 13 metastases or other conditions, not because they 14 need to be, but because we're not focusing on what 15 is absolutely necessary to conduct the clinical 16 trial. So I guess we should probably try and 17 refocus our energies on being a little less 18 academically lazy about clinical trial development 19 and trying to be more considerate of when we 20 developed eligibility criteria, what's the real 21 thinking behind that in light of both the disease 22 and the drugs being studied.</p>	<p style="text-align: right;">Page 256</p> <p>1 because I worked at a university that had the 2 world's largest brain tumor center, and I remember 3 Carey and I having a discussion probably 20 years 4 ago saying we have all these tools that they're 5 using for GBM. Why don't we apply them to the 6 treatment of solid tumor brain metastases in the GU 7 neurosurgery, cool radiation techniques.</p> <p>8 Treatments for breast cancer, and in 9 particular HER2 positive breast cancer, got a lot 10 better; so much so that over the past 7 to 10 years 11 of my career at Duke, I watched women not die of 12 their HER2 positive metastatic breast cancer, but 13 actually die of the consequences of the radiation 14 that was required to keep their brain mets under 15 control.</p> <p>16 So I think now's a good time to have this 17 conference. I'm honored to be here, and hopefully 18 I can contribute to some of the discussions. I 19 don't think I can represent all pharma, but I can 20 certainly give you what my experience has been in 21 the first year having joined Lilly and what we 22 worry about and what we don't worry about in</p>

<p style="text-align: right;">Page 257</p> <p>1 developing pharmaceuticals in this space. 2 DR. ATKINS: I'm Michael Atkins. I am a 3 medical oncologist and deputy director of the 4 Georgetown Lombardi Cancer Center here in the D.C. 5 area. My major interests are in melanoma 6 treatment, kidney cancer treatment, and 7 immunotherapy. 8 Being a longstanding clinical trialist, I've 9 sort of taken the general idea that industry's job 10 when they're developing drugs is to get the drugs 11 approved as fast as possible, and it's academic 12 medicine's job to figure out how to use those drugs 13 along the way, and that's including subsets of 14 patients with Comorbidities; how to develop 15 biomarkers; how to sequence them or combine them 16 with other agents; and also whether they are 17 effective in specific organs such as the CNS. 18 I do think that the experience I've had with 19 immunotherapy and melanoma suggests that you can, 20 while you're developing drugs and getting them 21 approved, potentially address some of those 22 questions along the way without delaying</p>	<p style="text-align: right;">Page 259</p> <p>1 itself perfectly to have overall survival be an 2 endpoint in randomized trials in patients with 3 brain metastases and having neurologic function be 4 the secondary endpoint. 5 Although it's nice to see tumor shrinkage 6 and may be great to see PFS being prolonged in the 7 CNS, I think you might not always see those things, 8 but you may see an impact on survival, particularly 9 in patients who otherwise would have had short 10 survival. If your drugs really work, then they 11 should work better than the standard of care in the 12 patients who are at the greatest risk. 13 DR. PROWELL: Great. Thank you for all 14 those introductions. We have about 45 minutes or 15 so, and I want to try to focus our panel discussion 16 around four main topics. I'll just outline what 17 those are briefly, and then maybe we can comment on 18 them, and of course we encourage the audience to 19 ask questions or contribute from the microphone. 20 The first is when we should include patients 21 with brain metastasis or leptomeningeal disease, 22 because I don't want to forget about those</p>
<p style="text-align: right;">Page 258</p> <p>1 development or approval of the drugs, or in some 2 points cases, even expediting the approval by 3 allowing more patients to be eligible for one's 4 trials, while at the same time getting some 5 real-world, or closer to real-world, experience. 6 I think as Hussein and Kim have proven in 7 the ipi-nivo 204 trial for patients with melanoma 8 and brain metastases, when it comes to 9 immunotherapy for patients with melanoma, there is 10 no effective blood-brain barrier. 11 I think taking that approach, I don't know 12 why that same statement wouldn't apply to every 13 other cancer where immune therapy has efficacy, and 14 certainly that would be justification for taking 15 patients with treated brain metastases or 16 asymptomatic brain metastases, as was in the 204 17 trial, and allowing them to be part of earlier 18 clinical trials in other cancers, and also, if it's 19 a poor prognostic factor, then one could stratify 20 for that. 21 Because patients with brain metastases have 22 generally had such poor outcome, I think it lends</p>	<p style="text-align: right;">Page 260</p> <p>1 patients. When should we include them, and by 2 when, I mean when in drug development, at what 3 point? How early are we comfortable including 4 them? 5 Second is I want to think about how we 6 should include them. And by how I mean do they go 7 into the overall trial population, particularly in 8 settings where brain metastases are very prevalent, 9 certain diseases where they're very prevalent, or 10 do they belong in their own separate cohort? 11 The third is how do we incorporate local 12 therapy into clinical trials? And then the fourth 13 is how do we move beyond this mind-set of letting 14 patients with brain mets be in our clinical trials 15 to actively pursuing drug development in patients 16 with brain mets or leptomeningeal disease? I think 17 it is a different question and an important kind of 18 reframing of our thought process. 19 So one of the complaints I've heard early 20 on, I was involved with a lot of people in this 21 room, Dr. Amiri, Dr. Sul, Dr. Lin, with the ASCO 22 friends' effort to modernize eligibility criteria</p>

<p style="text-align: right;">Page 261</p> <p>1 in brain mets. One of the concerns that we heard 2 when we started thinking about how we were going to 3 address that topic was people saying, well, 4 patients who have brain mets are different. They 5 have different efficacy, they have different 6 safety, and that makes it really complex to put 7 them in clinical trials. And that's why we've not 8 done it and that's why we don't want to do it. 9 One solution that came out of literally 10 years of people sitting around talking around 11 tables and on phones was the notion of including 12 these patients in separate cohorts, which addresses 13 many of the issues. There are statistical 14 considerations that this brings up, and there are 15 pragmatic considerations about trial design, and 16 analysis, and size of the trial, and so on. 17 I'd like to have the panel maybe begin by 18 thinking about that issue, responding to the idea 19 that patients with CNS involvement should be their 20 own separate cohort, and maybe we can 21 start -- whoever wants to go first. We don't 22 necessarily have to go down the whole row, but</p>	<p style="text-align: right;">Page 263</p> <p>1 statistical perspective because you can make 2 arguments on how you can look at the data together 3 or look at them separately, and there are a lot of 4 different statistical methods for doing that. 5 So really, I think the concern first needs 6 to be whether or not you can do a randomized design 7 for those patients. And if you can -- and I'm 8 assuming that we're talking, again, as Shanthi 9 mentioned, in the phase 3 randomized study setting. 10 If you can randomize them, then I don't see why you 11 couldn't include them in the overall population 12 with a stratification factor to kind of cover 13 yourself. 14 DR. GONDI: Can I take off -- oh, sorry. 15 DR. TAWBI: If you don't mind, I really do 16 want to address two very important points. I think 17 one very important point that we all kind of faced 18 throughout the morning and throughout our careers 19 so far is the dearth of knowledge in this field and 20 the fact that less than 1 percent of our patients 21 that represent, really, 30 percent of metastatic 22 disease population, less than 1 percent of them are</p>
<p style="text-align: right;">Page 262</p> <p>1 whoever wants to take that. Go ahead. 2 DR. MISHRA-KALYANI: I'll start. I can't, 3 of course, again, speak to the clinical side and 4 the safety concerns exactly, but I will mention one 5 thought about -- or a couple of thoughts about 6 having patients with brain metastases in a separate 7 cohort, and that would be a question of equipoise. 8 If you're not sure that the patients with 9 brain mets will actually benefit from the standard 10 of care because there's evidence that it won't be 11 effective therapy for them, then you may consider 12 having a separate non-randomized cohort for those 13 patients so that you can just look at the effect of 14 the experimental therapy. 15 I think separate from that, if you do feel 16 like there is effective standard-of-care therapy 17 that you can compare to, the concept of having 18 patients either in a separate cohort or in the 19 overall population with a stratification factor for 20 whether or not patients have brain metastases isn't 21 necessarily going to make too much of a difference 22 in how we interpret that data, at least from a</p>	<p style="text-align: right;">Page 264</p> <p>1 represented anywhere in a clinical trial. So my 2 answer to when is as early as possible and as often 3 as possible should be the answer. 4 Now in terms of how do you address the fact 5 that this is a different population, I actually 6 will take what Pat said about not being lazy in our 7 clinical development and clinical trials. I don't 8 think there's a blanket statement for that. 9 I think we really have to think about which 10 drug are we using, what are the targets that we're 11 considering, what do we know about its penetration 12 for the blood brain or not, and then based on that, 13 try to include those in the early phases, either 14 dose escalation's completed, to have a small cohort 15 in which you can look at this; or even have a 16 separate dose escalation. 17 As Mike Davies earlier mentioned, maybe for 18 those patients, you do need a higher dose, and 19 maybe some of the toxicities can be -- we all are 20 oncologists and treat patients with chemotherapy 21 and give them awful toxicities all the time if 22 their goal is benefit. So sometimes maybe our</p>

<p style="text-align: right;">Page 265</p> <p>1 threshold for toxicity for that population may be 2 slightly different as well. 3 Then when we go later in the development, 4 stratifying should be a must, actually. It's very 5 easy. I'll talk for melanoma. A lot of those 6 patients screen fail because of brain mets. 7 Imagine if those people that screen fail just go on 8 a study, and they're just in their own separate 9 cohort, and then you can answer the question right 10 there. You can design your trial in a way that the 11 primary endpoint isn't the cohort that's not brain 12 mets if you're worried about their poor outcomes. 13 But at the end of the study, you'll have all the 14 answers that you need. 15 DR. PROWELL: I'll let Dr. Gondi in just one 16 moment. I just want to say one thing. Part of the 17 reason that industry has historically not included 18 these patients is that we've allowed them to not 19 include these patients, despite the fact that for 20 some of these diseases, the prevalence of brain 21 mets is as high as 40 or 50 percent. 22 One thing that I want to get back to you</p>	<p style="text-align: right;">Page 267</p> <p>1 leverage that in a way that allows us to include 2 these patients on trials. For later-phase studies, 3 I agree a hundred percent, putting my biostatistics 4 hat on, it makes sense to stratify patients to 5 enable them to be treated with radiosurgery before 6 they enroll on trial, and for small asymptomatic 7 mets in non-eloquent locations, not requiring 8 corticosteroids, to not have to necessarily treat 9 those lesions and stratify and be able to watch 10 that. 11 At the end of the day, if the primary 12 endpoint is survival, one thing that we have 13 trouble showing in brain metastases management is 14 that anything we do for brain metastases actually 15 has an impact at survival. There have been a lot 16 of challenges in demonstrating that. So if we know 17 that and we all agree on that, why not just allow 18 those patients, monitor them closely with MR 19 surveillance, treat the troublesome lesions with 20 radiosurgery, safe and effective. 21 In terms of earlier phase studies -- oh 22 sorry, one more thing about that. I'm going to put</p>
<p style="text-align: right;">Page 266</p> <p>1 later in the discussion, and maybe I'll ask 2 Dr. Blackwell to comment on this from an industry 3 perspective, is what sort of incentives, in terms 4 of either being able to differentiate a product 5 from other drugs in class maybe that haven't 6 studied brain mets, or what sort of concerns or 7 potential carrot and stick, if you will -- what 8 sort of regulatory things would lead companies to 9 preferentially include these patients in their 10 clinical trials? 11 Dr. Gondi? 12 DR. GONDI: I wanted to go back to something 13 that was mentioned earlier about being practical, 14 too, with clinical trial design and development. I 15 see brain metastases different but in a positive 16 way, to some extent. Again, as one of two 17 radiation oncologists in the room, I can say that 18 we have very effective treatment for brain 19 metastases, and that's radiosurgery, and it's safe, 20 and it's effective for the timeline of most 21 clinical trials. 22 So we can leverage that. In fact, we should</p>	<p style="text-align: right;">Page 268</p> <p>1 on my radiation oncologist hat now, because I have 2 hats, too -- 3 (Laughter.) 4 DR. GONDI: -- this washout period really 5 troubles me as a radiation oncologist. I've never 6 understood it. It was in this JCO paper that you 7 asked us to read in advance of this, and in most 8 trials, it's a couple months. I think the JCO 9 paper said 1 month post-radiosurgery. 10 Radiobiologically, there is no washout period. 11 What happens in 1 month radiobiologically 12 when you treat a met? You usually get a little 13 FLAIR, it calms down with steroids, and they're 14 fine. In fact, if you scan that patient a month 15 later, which we don't normally do, that tumor's 16 probably shrunk. So why do we need a washout 17 period? Why not enroll that patient right away so 18 that we're not sitting there for a month watching 19 their disease outside of the brain continue to 20 progress? 21 As it relates to earlier phase studies, the 22 thing I struggle with the most in my clinical</p>

<p style="text-align: right;">Page 269</p> <p>1 practice is so many of the patients who do earlier 2 phase studies have failed several prior systemic 3 therapies, and usually by that point, it's not 30 4 percent of them have brain mets; it's like 60 or 70 5 percent of them have brain mets by that point. 6 I think our patient advocate earlier today 7 really echoed this and it's really important. The 8 patients who've had brain mets treated should be 9 able to go on earlier phase studies. It doesn't 10 make sense to me biologically or clinically why 11 that should not be possible. 12 I can understand why there may be some 13 concern about if they have intracranial progression 14 at that time, and how do things interact with 15 radiotherapy, which I'd like to spend some time 16 weighing in on, maybe for an earlier phase study 17 that may need to be delicately looked at. But if 18 they've already been treated for their brain mets 19 and their scan is stable, they should be able to go 20 on an earlier phase study. 21 DR. ATKINS: A couple of comments. I agree 22 with Hussein that when should be as early as</p>	<p style="text-align: right;">Page 271</p> <p>1 that's what keeps some patients off of trials, is 2 they have to get their brain met radiated, and then 3 they don't want to wait 4 weeks to actually enroll. 4 DR. PROWELL: Dr. Keegan, do you want to 5 comment on the issues from a regulatory standpoint 6 of letting people get radiation and then go right 7 into this study, in terms of our being able to 8 interpret endpoint design? 9 DR. KEEGAN: Right. And I think that's why 10 we -- when Dr. Marur led off, we talked about the 11 endpoints because what you want to show often 12 drives who gets in the trial. If all you want to 13 do is show level of activities, systemic activity, 14 and if there are treated brain lesions in there but 15 you're not necessarily focusing on that, there 16 would be no reason to wait. 17 So the reason is usually because people are 18 focused on looking at activity in the CNS as well, 19 but it's simply a matter of how you design the 20 trial and what you want to be able to include at 21 the end. There's no regulatory reason, generally 22 speaking, why you would have to have a washout as</p>
<p style="text-align: right;">Page 270</p> <p>1 possible. The only qualification I would say is 2 I'd like to see that the agent has some systemic 3 disease activity before exposing patients with CNS 4 mets, because if it doesn't work systemically, it's 5 not going to work in the brain. 6 I do agree with Dr. Gondi that -- and the 7 one objection I had to the article that you 8 distributed and asked us to read is I don't see why 9 it's necessary to wait 4 weeks after radiation of 10 brain mets before enrolling patients on trial. In 11 the national cooperative group trial that I lead, 12 we decided to completely eliminate the repeat MRI 13 in patients with treated brain metastasis for 14 melanoma and just enroll them as soon as they were 15 off steroids for getting immune therapy. 16 I don't know that if you're treating every 17 lesion in the brain, you're not going to be 18 measuring those lesions. If you go put them on 19 study right away, there shouldn't be a chance for 20 new brain disease to develop. So that's the best 21 time to treat them, and I don't know why you would 22 wait on treating their systemic disease because</p>	<p style="text-align: right;">Page 272</p> <p>1 long as you would understand that those would not 2 be lesions that could evaluate for drug activity. 3 I actually have a quick question. Maybe you 4 can answer this. Why not include patients in the 5 first in-human clinical trials if there's a 6 reason -- if there's no specific safety concern, 7 why would you want to wait until you have evidence 8 of systemic activity before you would enroll those 9 patients? 10 I would say they're taking a lot of chances 11 regardless, in the very early-phase studies 12 patients are, and they don't know if they're going 13 to respond systemically either. So with close 14 monitoring, I would challenge that perhaps those 15 patients could be enrolled in phase 1 studies as 16 well. 17 DR. PROWELL: I just want to say this is 18 regulators being more liberal than academics. 19 (Laughter.). 20 DR. PROWELL: You might never see this 21 again -- 22 (Laughter.)</p>

<p style="text-align: right;">Page 273</p> <p>1 DR. PROWELL: -- so mark this in your 2 calendar, friends.</p> <p>3 DR. ATKINS: Yes, and maybe other people are 4 going to challenge me on that statement, but I 5 don't want to compromise the initial study that 6 looks at whether or not there's efficacy in a drug. 7 If you put in your phase 1 trial, where you're 8 trying to define what the doses that you're going 9 to use, and it's compromised because patients have 10 toxicity issues or you don't see any activity 11 because a large percentage of the patients were 12 patients who couldn't respond to that agent, then 13 you may slow down the development of that drug. 14 But I'm willing to listen to comments otherwise 15 because I suppose if you saw a response in the 16 brain, nothing would speed up the development of 17 that drug any faster.</p> <p>18 DR. PROWELL: So what about if we had those 19 patients in a separate cohort even in dose 20 escalation, where it's baked into the protocol that 21 if there's excessive toxicity, if you're seeing 22 seizures, if you're seeing bleeds, you're seeing</p>	<p style="text-align: right;">Page 275</p> <p>1 a CNS progression event when they enter a trial, 2 you want to have 3 months go by because, honestly, 3 most of the time in 3 months after radiation, 4 nothing happens in those first 3 months. 5 So we really wanted to get rid of the 6 3-month threshold. We had a lot of debate about 7 what that threshold would be, ranging from no time, 8 to 7 days, to 4 weeks. We felt very strongly that 9 it couldn't be any more than 4 weeks. Ultimately, 10 the consensus was that everyone felt comfortable 11 with 4 weeks, which is why that's in the guideline, 12 but in the text, there's a note that based on the 13 situation, it could be less than 4 weeks. 14 So I don't want anyone to feel like it has 15 to be 4 weeks. The guidelines, they could be 16 really anything, but we recommend a maximum of 17 4 weeks is the way that I would think about it 18 because I entirely agree, it makes no sense the way 19 that it was written before; it really makes no 20 sense.</p> <p>21 DR. ATKINS: What about the issue, Nancy, 22 about repeat imaging? Obviously, if it's less than</p>
<p style="text-align: right;">Page 274</p> <p>1 whatever, that cohort built into the protocol is 2 going to close. You're going to stop, and that's 3 going to be the end of it, and there's no need to 4 pause, and amend, and reconsent people because that 5 was built into the protocol right from day one; 6 likewise, looking at the efficacy or even the dose 7 requirement, which, as someone alluded to earlier, 8 might be different for patients who've got 9 intracranial compartment disease.</p> <p>10 I want to ask Kim to comment on one thing in 11 a minute from a pharma perspective, and then I'll 12 get you. But Nancy Lin, who was a lead author of 13 these eligibility criteria guidelines, I want to 14 have her comment on the 4-week washout period. We 15 talked about this a lot.</p> <p>16 DR. LIN: There's a story behind it as there 17 is with many things, and I actually agree with the 18 panelists. You have to remember where we're 19 starting from, which is that almost all standard 20 templates had a 3-month washout from radiation, 21 which completely makes no sense. If you're trying 22 to include people who are less least likely to have</p>	<p style="text-align: right;">Page 276</p> <p>1 4 weeks, you're not going to repeat image.</p> <p>2 DR. LIN: I totally agree. And again, it 3 has to do with where we were trying to move the 4 needle from, which was really from this 3-month or 5 6-month kind of a time frame. I think if 6 somebody's had SRA a week ago, does it make any 7 sense to repeat it? No.</p> <p>8 DR. GONDI: I just want to clarify again, 9 it's a semantic thing, but it's what causes us to 10 think about it. There's no such thing as washout 11 after radiation. The radiation is done.</p> <p>12 DR. LIN: Agreed.</p> <p>13 DR. PROWELL: Sorry. We're using this in a 14 shorthand way to mean you got to wait a little 15 while. Yes, but thank you.</p> <p>16 I want to ask Dr. Blackwell the comment on 17 the pragmatism of this, a bunch of people who are 18 not in pharma saying, "It's really simple. Just 19 have another cohort." You're going to have 20 separate dose escalation for them, you're going to 21 have separate stopping rules for them potentially 22 for toxicity.</p>

<p style="text-align: right;">Page 277</p> <p>1 How practical is this in both early-stage 2 development where you're still on the dose-finding 3 and toxicity-gathering stage, and how practical is 4 this in late-stage development? How much does this 5 add to cost, and risk, and time to accrue, and so 6 on?</p> <p>7 DR. BLACKWELL: Well, that's a lot of 8 questions. I tend to try to break this down 9 because I think sometimes when we blur what we're 10 talking about, it's hard to find solutions. In 11 terms of inclusion of patients that have treated 12 CNS mets on a trial where the sole intent is not to 13 look at CNS activity, I think that's a very 14 different discussion than how do we design trials 15 where we're intending to look at CNS activity.</p> <p>16 So I'll address the first. In the context 17 of early drug development, I actually -- so I'm 18 going to take the contrary here. I actually think 19 we need to include patients that have worst disease 20 in our dose-finding study because if we see a 21 signal, then we're going to want to develop that 22 drug.</p>	<p style="text-align: right;">Page 279</p> <p>1 I would say that Pat brings up a good point. 2 The reason we have excluded them, both 3 pharma -- even in the trials I participated in 4 prior to joining pharma was a cut and paste 5 phenomenon, which is we didn't want to be bold 6 enough or brave enough to include those patients on 7 the trial. The 25 years of my practice, I think I 8 might've seen 7 seizures and I focused on the care 9 of women with brain metastases. It's just an urban 10 legend. It happens, don't get me wrong, but the 11 problem, as much as it's discussed, is very unusual 12 in the day-to-day clinical practice.</p> <p>13 So in terms of early phase, I see where 14 there'd be no problem, and in fact I think this is 15 where patients, and the regulatory agencies, and 16 the investigators can push and say we're not going 17 to put people on this trial unless you -- I'm 18 probably going to get in trouble back at work, but 19 we're not going to put patients on a trial if you 20 don't allow patients with stable brain metastases 21 to go on it.</p> <p>22 These patients are sacrificing a lot.</p>
<p style="text-align: right;">Page 278</p> <p>1 You put a bunch of patients on whose disease 2 was going to not progress for a year anyway, then 3 you're going to fool yourself into thinking a drug 4 has activity when it really doesn't, and you set 5 yourself up for failure as you move that on at 6 whatever dose you find.</p> <p>7 Now I think precision medicine is going to 8 help us with that, so if you know what the driving 9 mutation is and you know how that disease performs 10 in a different cohort, then you can actually say, 11 okay, these patients should do this and on our 12 drug, they actually did this, so there's a signal 13 of activity there.</p> <p>14 So I do think science is actually going to 15 help us sort this out as opposed to, gosh, if your 16 hemoglobin's okay and your platelets are okay, then 17 you're the patient we want to study a drug in. So 18 I see hope in biology and science helping us 19 understand how patients would have done had they 20 not received our drug, even in the earliest stage. 21 So I actually think that patients facing brain mets 22 should be allowed.</p>	<p style="text-align: right;">Page 280</p> <p>1 Sometimes they're the first human dose. We have 2 very few signals of what the safety is. We have it 3 in preclinical models, but in people we don't. So 4 I feel pretty strongly. And you have to realize 5 that it takes a little while to change, so we have 6 to be a community and push to allow for these 7 patients to go on the early-phase trials.</p> <p>8 I feel about the same as the phase 3 9 studies. I will say, though -- I've wrote down 10 this list of things pharma worries about, so maybe 11 I can just tell you what they are really quickly. 12 We worry about the endpoints in a phase 3 study. 13 We worry about the complexity of the patient and 14 heterogeneity. And patients who have had SRS-to-1 15 lesion is a very different patient than someone 16 that's had SRS to 5, or even whole-brain radiation 17 therapy.</p> <p>18 Just like we try to homogenize patient 19 enrollment, everyone's only had 2 lines of therapy, 20 it's very hard to control that in a setting of a 21 randomized phase 3 study. So we worry about 22 patient population, heterogeneity, lines of</p>

<p style="text-align: right;">Page 281</p> <p>1 therapy, and in particular burden of disease. 2 The biggest thing -- I have to say this 3 before I get cut off -- the lack of preclinical 4 models makes it very hard for me to argue to do 5 trials in this space, having joined a large pharma 6 a year ago. It's just the way that big pharma 7 makes decisions, which is did it work in the cell 8 lines? Did it work in the animals xenografts? Did 9 it work in this? Obviously, there's safety in the 10 preclinical models, but you can't just say it's 11 because I think it's a good idea.</p> <p>12 So I think we need to work together to 13 figure out what those preclinical models would look 14 like, and I think we're going to speak about the 15 multidisciplinary buy-in. I just have a couple of 16 points of what we don't worry about because I've 17 heard it a couple of times.</p> <p>18 We don't worry that the patients are too 19 sick. The presence or absence of brain mets in a 20 setting of 4 pages of eligibility criteria is 21 probably the least of our worries. I do think it's 22 a cut and paste phenomenon, which is that's just</p>	<p style="text-align: right;">Page 283</p> <p>1 barrier from a big pro pharma perspective, we don't 2 worry about that too much because we actually have 3 whole teams of people that have thought about that 4 outside of cancer for three decades. So probably I 5 took up more of my time but I did want to make 6 those points because I don't think they'd been made 7 earlier in the day.</p> <p>8 DR. PROWELL: Thank you. I think that's 9 very appropriate. I asked you like 12 questions. 10 You responded to me in 4 minutes or something, so 11 good job.</p> <p>12 I want to take some questions from the 13 audience. We'll just maybe go front/back.</p> <p>14 DR. ABREY: Lauren Abrey, Novartis oncology. 15 I actually wanted to make a comment, and I think 16 I'm going to build on what Kim said. You have to 17 think what are we trying to do? Are we trying to 18 include brain metastases patients or are we trying 19 to develop intentional drugs for brain metastases? 20 I think it actually gets to what do you want your 21 label to look like?</p> <p>22 Do you want your brain mets to be included</p>
<p style="text-align: right;">Page 282</p> <p>1 how our protocol writers have always written it, 2 and there's not a voice to say don't forget, and 3 I'm pushing investigators to say that.</p> <p>4 We don't worry about the size of the patient 5 population. We recognize it's a huge unmet need. 6 Even in a molecular era of precision medicine, 7 there's still a huge opportunity to make 8 improvements, and pharma actually wants to improve 9 the care of patients as well.</p> <p>10 Then the third thing we don't worry about is 11 figuring out if the drug should cross the 12 blood-brain barrier or not, and this is my last 13 point. I worked for a company that's had spent 20 14 years in the neurocognitive space, the Alzheimer's 15 space, the depression space. I've got teams of 16 hundreds of chemists that could tell you with 92 17 percent precision whether or not that drug gets 18 across the blood-brain barrier. We have imaging 19 companies and that's all they do is look to see if 20 the drug gets across the blood-brain barrier and 21 people.</p> <p>22 So as much as we talk about the blood-brain</p>	<p style="text-align: right;">Page 284</p> <p>1 as under the umbrella of metastatic disease and 2 they've been represented in the trial? Then, in my 3 view, they don't belong in a separate cohort. If 4 you want to do intentional brain met development 5 either to differentiate your product or because 6 there's something unique about the patient 7 population or the product, then you need to develop 8 it quite differently.</p> <p>9 I guess I would actually rebut a little bit 10 what Kim said in that the selection for entry into 11 human, at least at my current company and my last 12 company for oncology products, would often select 13 the drug that doesn't cross the blood-brain 14 barrier. So yes, people know, but there's often a 15 bias to, for safety reasons, pick some of the ones 16 that don't cross the blood-brain barrier to try to 17 limit the possibility that you also end up with 18 seizures or something else when you take your first 19 step into human.</p> <p>20 So I think it's something we could 21 manipulate while we sit there or try to influence; 22 maybe not manipulate. That's not such a positive</p>

<p style="text-align: right;">Page 285</p> <p>1 word. But I think that's a little bit -- maybe we 2 need to frame thinking about this because my first 3 thought when Tatiana -- was we want to allow 4 patients. I want to allow patients in trial. If 5 we want to make a difference here, we need to move 6 the needle, but then we need to be thoughtful about 7 where are we moving it and what are we doing.</p> <p>8 DR. PROWELL: This is a regulatory issue 9 that I think will be interesting to talk about 10 maybe as we go on, which is that because 11 historically we have allowed companies to exclude 12 and there's no limitation of use in the indication. 13 The indication would be for whatever line, 14 non-small cell lung cancer or something, but it 15 doesn't say for patients without brain mets, or 16 we've not specifically been granting indications 17 for treatment of patients with this and brain mets, 18 or even necessarily including a lot of that data in 19 the label.</p> <p>20 So the question is for companies that are 21 coming into this now with multiple other drugs 22 already approved in that line of therapy or in the</p>	<p style="text-align: right;">Page 287</p> <p>1 in a lot of ways, for those drugs that we think are 2 close enough to change practice for all metastatic 3 patients, that's when we need to allow patients 4 with brain metastases.</p> <p>5 However, the other aspect is that I want to 6 focus back on what are the targets we're going 7 after, what is the actual biology that we are 8 trying to modulate. We are in a place where we 9 should start thinking about what's specific about 10 the brain and what targets do we want to go after.</p> <p>11 You heard Priscilla, you heard Mike earlier today, 12 and even in immune oncology, the tumor 13 microenvironment in the brain may need completely 14 different modulators. So for those targets, for 15 those pathways, we need to develop studies that are 16 specific for that population.</p> <p>17 DR. MISHRA-KALYANI: I actually wanted to 18 address something specific you said about having a 19 different cohort. I think that there are two 20 things that I would consider there, and it goes 21 back to your discussion as to what is it that we're 22 trying to include in the label.</p>
<p style="text-align: right;">Page 286</p> <p>1 same class, how do we provide that incentive to 2 really include these patients?</p> <p>3 DR. TAWBI: I'll be more than happy to 4 address this. I really think that's a great point, 5 and we're actually talking about two separate 6 things, and you're absolutely right. If you look 7 at what we've been doing so far, is we've been 8 trying to prove the things that have already been 9 approved, that are already available to everybody 10 in the community, then prove that they have 11 activity in the brain. And obviously this has been 12 a long and arduous journey.</p> <p>13 I can tell you, having had the honor of 14 leading the CheckMate 204 trial with ipi-nivo, this 15 trial had 15 patients on when ipi-nivo got FDA 16 approved. So we actually were concerned that 17 people won't put patients on study because they 18 have access to the drugs. So it took a lot of 19 sweat and blood and a lot of investigators being 20 convinced that this is an important study to do, 21 and to actually finish it. There were 90 patients 22 and now soon 119; we changed the practice. I think</p>	<p style="text-align: right;">Page 288</p> <p>1 If you were trying to include your endpoint 2 in the label that shows that you have a clinical 3 benefit due to this treatment, if you have a lot of 4 heterogeneity in your population, you might not be 5 able to adequately size or power your analysis to 6 find a clinically meaningful benefit in your 7 population if there's a lot of difference in what 8 we would expect for the clinical benefit in 9 patients with those brain metastases versus those 10 who do not have them.</p> <p>11 So if you're getting a mixed model of what 12 you actually are finding, then what you're 13 indicating in your label is the clinical benefit 14 may not be what it truly is. So in that respect, 15 there may be some real reason for you to include a 16 separate cohort. It doesn't mean that you're 17 allowing the patients -- you're pursuing them. 18 You're just pursuing them to also characterize the 19 benefit for those patients because you're 20 recognizing that it's a prognostic factor just as 21 we might with histology, squamous versus 22 non-squamous, et cetera. There usually it's a</p>

Page 289	Page 291
<p>1 stratification factor, but it's just a reason that 2 you might want to consider, so pursuing them but 3 having them in a separate cohort for that reason. 4 The second part of that would be if you 5 wanted to specifically look at the activity in the 6 brain or in CNS metastases, then there may be a 7 reason, then, to also look at those patients 8 separately for many of the reasons that have been 9 discussed. There may be local treatments or 10 radiation, and those things may affect how well 11 you're able to characterize the clinical benefit or 12 the treatment effect, and you don't want that 13 diluting whatever you're able to find in the 14 overall population.</p> <p>15 DR. ABREY: So it could be really helpful in 16 defining some of those clinical benefit endpoints 17 from the last session.</p> <p>18 DR. PROWELL: I'm going to let Dr. Gondi 19 respond, and we'll take the question at the back 20 microphone. Thank you, all standing up, for being 21 so patient. You live longer if you don't sit so 22 much, so we're doing this for you.</p>	<p>1 included brain metastases patients is based on 2 multi-institution retrospective series, where 3 people said, okay, well let's just try this in 4 brain metastases patients, some of whom got 5 radiosurgery, some whom didn't, and see if it makes 6 a -- and that's really hard to -- there's so much 7 bias there, it's hard to really extrapolate much 8 from that. So if we can include that within those 9 later phase studies, that really gives us much more 10 data from which to build.</p> <p>11 Related to that, I think on the last session 12 we talked about patient-reported quality of life 13 and the challenges of assessing that. We actually 14 now have, and we're just going to present later 15 this year, an intervention radiotherapy related 16 that actually has shown in a randomized trial 17 better preservation of patient-reported quality of 18 life. So it is possible to look at that as an 19 endpoint.</p> <p>20 But related to CNS-directed therapy, I think 21 there's a dearth of knowledge as it relates to 22 patients whose metastases fail effective local</p>

<p style="text-align: right;">Page 293</p> <p>1 local therapy, and what are the ethical and 2 pragmatic issues of that. 3 So we're going to come to Lynda in a second, 4 but a question from the back microphone, please. 5 AUDIENCE MEMBER: Thank you. As a 6 neurosurgeon, I probably stand up more than a lot 7 of you, so I'm doing okay on that front, but I do 8 appreciate the exercise today. I'll start with a 9 kind of slight rebuttal to my radiation oncology 10 colleague in that I think there is a way to improve 11 on radiation therapy for brain metastases, which 12 would be to obviate the need by giving therapies 13 that keep them from developing brain metastasis in 14 the first place. 15 That's where I think developing therapies 16 that are specifically targeted to get into the 17 brain and treat the brain beyond the breakdown of 18 the brain blood-brain barrier within the tumor 19 itself are important. So getting to this question 20 of including brain metastasis patients in early 21 trials, again, I'm a hammer, so I sound like a 22 hammer, but everything's a nail.</p>	<p style="text-align: right;">Page 295</p> <p>1 numbers of patients whose brain metastases aren't 2 responding, and I think it's exactly because we 3 aren't designing trials that are specifically 4 designed to answer the question of what does it do 5 in the brain metastases patients. 6 So it would seem to me to suggest that in 7 those early phases beyond just separating out a 8 cohort of metastasis patients and seeing what the 9 objective response is, I think if you did have a 10 few of those patients who we know are going need a 11 resection with that solitary metastasis that is 12 symptomatic, if you did design that trial 13 where -- maybe it doesn't have to be 2 weeks, maybe 14 it's a week, which most patients can tolerate, 15 where you're giving the one dose of the drug and 16 doing a resection. 17 I would even posit myself as something I'm 18 pushing in glioblastoma community that a needle 19 biopsy, which is very low morbidity, can be done in 20 a lot of these cases, in and out, 1 percent risk of 21 hemorrhage, and get some pre-tissue and post-tissue 22 before you give the drug and then after. And then</p>
<p style="text-align: right;">Page 294</p> <p>1 I do think it's important when we're 2 thinking about these early-phase trials to think 3 about ways to bring in patients and also have 4 potential endpoints where we're looking at the 5 tissue to see what the drug is actually doing in 6 the tissue and/or the brain around it. 7 There was a comment earlier about envy of 8 the window opportunity studies that are being done 9 in glioblastoma. There's no reason for anyone in 10 this room to envy the glioblastoma field. I spent 11 a lot of time in it. We envy a lot of the response 12 rates that you see in these things. 13 You're talking about shrinkage or you're 14 talking about objective responses. We don't see a 15 lot of that, so we're starting to get creative on 16 how we're doing our trials to try and stack the 17 deck a little bit and see which drugs are going to 18 work. And that's why we're doing these window of 19 opportunity trials to understand things better. 20 In some of these brain metastases patients, 21 I think we need to do the same thing. We're seeing 22 great responses, but there are still these large</p>	<p style="text-align: right;">Page 296</p> <p>1 really have an idea of that biologic endpoint. 2 Now you've done 10 patients, and I said, 3 hey, in each of these 10 patients, it got into the 4 tumor, and in each of these 10 patients, I saw a 5 change in the endpoint that I was looking at. 6 Maybe now I want to enrich for brain metastasis 7 patients when we're going to these big registration 8 trials because I know that we're going to see some 9 effect in the tissue. 10 The last thing that I wanted to just ask 11 from the regulatory perspective -- these things 12 interest me. My wife actually works at the FDA. 13 But I saw that there's a draft guidance on 14 including metastasis patients in a lot of these 15 clinical trials going forward, and one of the 16 things you mentioned is that you let industry and 17 the investigators not include the metastasis 18 patients. 19 So is there a point at which you now start 20 getting these boilerplate protocols that don't 21 include brain metastasis patients, will you then 22 send it back and say why? You need to justify the</p>

<p>1 exclusion.</p> <p>2 DR. PROWELL: We're there, and we're doing</p> <p>3 this rather -- we've seen exclusion of men, for</p> <p>4 example, from breast cancer trials. I'm a breast</p> <p>5 oncologist, and that was something we didn't even</p> <p>6 blink at when I started here in 2006, and now</p> <p>7 anybody in this room who submitted a protocol knows</p> <p>8 that if we get an IND where they propose to exclude</p> <p>9 patients, we will always send a comment back and</p> <p>10 say you need to have a scientific rationale for why</p> <p>11 you don't think this drug is going to be effective</p> <p>12 in them or you need to include them. The fact that</p> <p>13 there aren't that many of them is not a good reason</p> <p>14 to not include them, so we're there. We're there</p> <p>15 already.</p> <p>16 AUDIENCE MEMBER: The last thing I'll say is</p> <p>17 if you're at an institution and you think there's</p> <p>18 no neurosurgeons that are interested in doing the</p> <p>19 window of opportunity study at your trial, and part</p> <p>20 of the tumor section, and the [indiscernible] INS,</p> <p>21 I assure you I can find you one.</p> <p>22 DR. PROWELL: Perfect.</p>	<p>Page 297</p> <p>1 that we should have had a neurosurgeon sitting in</p> <p>2 the front all day.</p> <p>3 (Laughter.)</p> <p>4 DR. PROWELL: So we apologize. These</p> <p>5 comments have been really terrific.</p> <p>6 Actually, did you want to respond to that?</p> <p>7 DR. MOSS: Just one tiny corollary of the</p> <p>8 same point. Nelson Moss, neurosurgeon at Memorial</p> <p>9 Sloan Kettering. I'm also happy to provide tissue.</p> <p>10 Just one more plug for more data.</p> <p>11 Why don't we consider all cancer patients,</p> <p>12 potential metastasis patients, potential brain</p> <p>13 metastasis patients, and mandate MRIs at the end,</p> <p>14 at late time points in our late-stage trials? We</p> <p>15 don't have enough understanding of how these tumors</p> <p>16 behave over time. We've all seen ER positive</p> <p>17 breast cancer act in a very latent fashion on</p> <p>18 hormonal therapy, and then 13 years later giving us</p> <p>19 these tiny, slow-growing mets. Why don't we</p> <p>20 collect more data? Why don't we require this of</p> <p>21 all of our trials?</p> <p>22 DR. PROWELL: I want to move to a next</p>
<p>1 AUDIENCE MEMBER: Can I just add one more</p> <p>2 point to what he said?</p> <p>3 DR. PROWELL: Sure. I do want to make sure</p> <p>4 we get to the next topic, but please.</p> <p>5 DR. YUNG: I'm Al Yung. I'm from MD</p> <p>6 Anderson. Just one more point is I totally agree</p> <p>7 with Pat Keegan and [inaudible], that there is no</p> <p>8 reason not to include brain met patients in the</p> <p>9 phase 1 trial while we are in the signal seeking</p> <p>10 stage for drug development sake. Besides, you can</p> <p>11 build in the window opportunity trial into that</p> <p>12 stage, as well as when you see failure or brain met</p> <p>13 when you have systemic response. You actually can</p> <p>14 also take that brain met by surgery and begin to</p> <p>15 study the reason why you failed.</p> <p>16 So there is really no reason in the early</p> <p>17 phase. We just need to separate the early-phase</p> <p>18 study from the later phase when we're looking at</p> <p>19 efficacy for specific indication or targeted drug</p> <p>20 you have the precision medicine endpoint also</p> <p>21 there.</p> <p>22 DR. PROWELL: It has become abundantly clear</p>	<p>Page 298</p> <p>1 topic, and I promise I will come back to you guys.</p> <p>2 I want to move to a next topic, which is it seems</p> <p>3 like there's pretty good consensus in the room that</p> <p>4 we want to be including these patients, and we want</p> <p>5 to be including them pretty actively and</p> <p>6 aggressively, and we want to include them early in</p> <p>7 the sense of early in drug development, like</p> <p>8 phase 1.</p> <p>9 But I want to ask this who question now, and</p> <p>10 the one question of how do we feel about including</p> <p>11 patients who might have either not yet treated</p> <p>12 brain metastases, meaning no local therapy, no</p> <p>13 surgery yet, or patients who've had local therapy</p> <p>14 and are progressing? I want to get your comments</p> <p>15 on that from a patient perspective.</p> <p>16 MS. WEATHERBY: Yes And yes. I know I don't</p> <p>17 understand all the complexities, but speaking for</p> <p>18 patients -- and I spent a lot of time talking to</p> <p>19 other patient advocates at a weekend long meeting</p> <p>20 last week. Yes. When you're in this situation, we</p> <p>21 don't have a lot to lose. I know that might sound</p> <p>22 crude, but we don't. Probably the harder thing is</p>

<p>1 to know that there -- I mean, I'm hearing this 2 makes no sense. This makes no sense. We need to 3 work on it, and probably the hardest thing of all 4 is to know that something's poised for change but 5 it hasn't happened yet.</p> <p>6 The only other comment I wanted to make as 7 an advocate -- and I want to point out I'm with 8 metastatic breast cancer advocacy, which is way 9 different than early-stage breast cancer advocacy, 10 and I hope everybody in the room kind of gets that.</p> <p>11 The metastatic breast cancer advocacy movement has 12 really gotten a lot of momentum lately and is 13 really looking to work with the other metastatic 14 cancers to create these changes.</p> <p>15 I want to assure you that the patients are 16 ready, not every patient, but they're ready.</p> <p>17 Especially in metastatic breast cancer, from the 18 ones that I meet, they tilt young, desperately 19 young, and they are ready for anything. We are 20 organizing -- part of the Metastatic Breast Cancer 21 Alliance's work right now is to launch a patient 22 enrollment tool and database that. It's called</p>	<p>Page 301</p> <p>1 Dr. Blackwell to comment from a regulatory and an 2 industry perspective on that idea, potentially 3 enrolling patients who've got progressing brain 4 mets after stereotactic radiosurgery in lieu of 5 going on whole brain or taking patients who maybe 6 in the slightly simpler scenario just have brain 7 mets and haven't yet had any local therapy at all. 8 Your thoughts on that?</p> <p>9 DR. KEEGAN: So my thought is that, yes, 10 there is an ethical consideration and argument to 11 be made, and there are ways to mitigate that. Some 12 of those mitigations are adequate informed consent. 13 By and large, we should be trying not to take the 14 judgment out of the hands of the patient and their 15 physician from making a decision under adequate 16 informed consent.</p> <p>17 So I do believe that it would be possible to 18 allow a patient, adequately counseled, to make that 19 judgment. I would like to try this therapy knowing 20 that there are other therapies available and that 21 the trial should have certain safeguards built into 22 it for adequate monitoring to take patients off at</p>
<p>1 MBC Connect, which we're enrolling now. And 2 shortly in another 4 to 6 weeks, we're going to 3 roll out the 2.0 version, which is actively going 4 to match them to clinical trials based on the data 5 that they enter.</p> <p>6 So our whole purpose is to bring the 7 clinical trial information to the patients so they 8 don't have to struggle so hard to find out about 9 clinical trials. Once this momentum builds and 10 builds and spreads across cancers, can you imagine 11 how it would feel as a patient to be able to find 12 the trials and then still see that maybe these 13 blockades are in place? So yes and yes.</p> <p>14 DR. PROWELL: Thank you. I actually want to 15 ask Dr. Keegan to comment on that, and then I'm 16 going to ask Dr. Blackwell to comment on that. One 17 of the things that we struggle with as regulators 18 is when investigators or companies want to have 19 patients potentially forego known effective therapy 20 to get an investigational agent. There are real 21 ethical concerns with that.</p> <p>22 Maybe I'll ask Dr. Keegan and then</p>	<p>Page 302</p> <p>1 the earliest opportunity. But with those kinds of 2 conditions in mind, I don't see any reason why one 3 could not have a trial like that and consider it to 4 be ethical.</p> <p>5 DR. MISHRA-KALYANI: Could I add to that, to 6 Dr. Keegan's comment? And I know she's going to 7 agree with me.</p> <p>8 (Laughter.)</p> <p>9 DR. MISHRA-KALYANI: There are also 10 statistical trial design considerations that you 11 could include in those cases like adaptive design, 12 and early stopping rules, and things like that, so 13 that you can not only have informed consent for 14 patients and investigators, but you can also very 15 closely monitor your trial to make sure it doesn't 16 go too far without having a good idea of what 17 benefit the patients are getting.</p> <p>18 DR. PROWELL: Right, Dr. Keegan?</p> <p>19 DR. KEEGAN: Yes.</p> <p>20 DR. PROWELL: Thank you.</p> <p>21 Dr. Blackwell, do you want to comment from 22 an industry perspective on this?</p>

<p style="text-align: right;">Page 305</p> <p>1 DR. BLACKWELL: Yes. I agree with both. In 2 the setting of adequate consent, knowing and 3 stating that there's an appropriate standard of 4 care in the consent makes it at least acceptable to 5 me. And I can't speak for all of Lilly. 6 I do want to say something that's in -- and 7 I'm not going to go off on my list again. But it's 8 very interesting, this dynamic that I'm seeing. 9 And now I'm speaking from my history as a 10 practicing clinician, which is most doctors do what 11 they do because they think it helps people. 12 The way that patients with newly diagnosed 13 brain mets get into the system typically is they 14 have a problem. They know they have cancer. They 15 go to the emergency room. And honestly, their 16 treatment is dictated by who they see in the 17 emergency room if it's truly an emergency. So if 18 they see a radiation oncologist because, 19 unfortunately, there's not a neurosurgeon on call 20 and they need emergent therapy, then they'll get 21 radiation. 22 DR. PROWELL: No offense to radiation</p>	<p style="text-align: right;">Page 307</p> <p>1 think might help you or you can have radiation, 2 which we know will help you. And in fact, that's a 3 tough decision and it's a tough place to put 4 patients. 5 I actually thought -- some of the randomized 6 studies that reported out in 2016-17, which really 7 demonstrated that at least for whole brain compared 8 to best and supportive care, with all the caveats 9 of the trial design, it might help in this 10 discussion, Which is although we can do this, it's 11 not been shown -- and I'm talking about whole brain 12 now -- it's not been shown to improve survival, so 13 I as your practitioner am willing to say let's try 14 this; you can always have this. 15 So I just think we need to be aware -- and 16 now I'm speaking from an industry standpoint -- of 17 where that dynamic is, which is patients get 18 treated by the doctors they see, by the modality 19 that those doctors use. So I think that is 20 something we're going to have to address, and 21 educate the ER physicians, and the 22 neurosurgeons -- not all neurosurgeons but</p>
<p style="text-align: right;">Page 306</p> <p>1 oncology intended or taken. 2 DR. BLACKWELL: Yes, no offense, or 3 neurosurgery. I think the point is that what 4 happens -- and now I'm speaking from industry and 5 clinician -- is you have a patient that's facing a 6 new brain met, perhaps asymptomatic, although, 7 again, frequently they're symptomatic. That's how 8 you pick them up. I've always struggled with the 9 term "asymptomatic." 10 So you have a symptomatic brain met. The 11 patient comes in. They maybe see me as a medical 12 oncologist first. I say I have this great trial. 13 You can go on drug X. I know you're afraid of 14 getting more SRS or you're afraid of radiation in 15 general. And we sign them up, and it's, again, 16 industry speaking, too, which is it costs money to 17 just screen patients for trials. Then in the 18 criteria it says "doesn't require radiation," or 19 you feel as a clinician you have to refer them to a 20 radiation oncologist. 21 So here's the choice the patient has to 22 make, which is you can go on this trial that we</p>	<p style="text-align: right;">Page 308</p> <p>1 radiation oncologists, and even the medical 2 oncologists. 3 I frequently had discussions conducting 4 trials of patients that had new brain mets, where 5 the radiation oncologist actually said -- and this 6 is the truth, "You're going to feel bad if the 7 patient goes home and has a seizure and you didn't 8 give them radiation." That's a true story. 9 So these are the forces that -- and I'm sure 10 there are other stories here, but we just need to 11 be very practical about how patients get referred 12 to these trials and enrolled on the trials. 13 DR. PROWELL: Dr. Tawbi, respond, and then 14 the person at the back microphone who is the single 15 most patient human I've ever known -- 16 (Laughter.) 17 DR. PROWELL: -- and then I'm going to 18 invite you to respond. 19 DR. TAWBI: And happens to be my patient, so 20 I apologize, Christina. 21 I really just want to address the issue of 22 who sees the patients and at what point. Actually,</p>

<p style="text-align: right;">Page 309</p> <p>1 I think that's where the value of multidisciplinary 2 care is so important. I co-direct the brain 3 metastases clinic at MD Anderson, and that's 4 exactly the point; that we all see the patient 5 together at the same time, and we really look in 6 each other's faces about how comfortable we are 7 about waiting for SRS to happen.</p> <p>8 The way we built our clinical trials is 9 actually if we have a trial that's for patients 10 with untreated brain metastases, I actually include 11 in it that they have to be evaluated by the 12 radiation oncologist that can tell me that they can 13 do it. And actually Dr. Chung is sitting right in 14 the audience and has herself overruled me on some 15 of those patients, and said, "This cannot wait; 16 let's do it," versus now you can do systemic 17 therapy.</p> <p>18 What we've included in those studies was 19 very early imaging assessments, as early as 3 weeks 20 or 6 weeks, depending on the specific regimen, so 21 that we can -- as I said in my earlier comment, we 22 have days to manage these patients; we don't have a</p>	<p style="text-align: right;">Page 311</p> <p>1 wanted to ask, is there a potential trial designed 2 to break it down into genetic mutation? Certain of 3 these clinical trial drugs could be made available 4 to NRAS patients or different genetic mutation 5 tumor of patients, that could be a way to further 6 the ball.</p> <p>7 How does that kind of comes together in 8 trial design?</p> <p>9 DR. PROWELL: Do you want to come up? We're 10 going to have Dr. Brastianos address this question 11 probably related to the Alliance trial I'm 12 guessing.</p> <p>13 MS. SELIG: Dr. Prowell, I'm just going to 14 say maybe take the last two comments after this, 15 and then if you could summarize. Then those of you 16 who are on Session IV panel, we're going to do a 17 quick reset without anybody in the audience getting 18 up and leaving the room, and see if we can do that.</p> <p>19 DR. BRASTIANOS: That's a great question. 20 Actually, we're starting an Alliance trial and 21 actually --</p> <p>22 DR. PROWELL: Can you speak into the mic?</p>
<p style="text-align: right;">Page 310</p> <p>1 lot of time -- so that we can act on it relatively 2 quickly.</p> <p>3 DR. PROWELL: Would you like to acknowledge 4 your patient by name and invite her --</p> <p>5 DR. TAWBI: Christine Baum, one of the most 6 patient patients, as you said, but the most bright 7 as well and very well represented on social media, 8 I should say.</p> <p>9 MS. BAUM: Thank you. As my oncologist, 10 Dr. Tawbi said, I'm having my third recurrence of 11 melanoma, second metastatic, first brain met. I'm 12 an active clinical trial right now. This is my 13 second clinical trial. I'm one of nivolumab and 14 cyberknife radiation.</p> <p>15 My question has more to do with NRAS, the 16 NRAS genetic mutation of brain mets. I'm an NRAS 17 patient, which is separate than BRAF, as most of 18 you know. I know FDA has done some work with NRAS 19 mutation tumors specifically. Just to double down 20 a little bit of what my friend Derrick said this 21 morning on just making more clinical trials 22 available to brain mets patients -- but I also</p>	<p style="text-align: right;">Page 312</p> <p>1 You can turn around if you want.</p> <p>2 DR. BRASTIANOS: We're starting a national 3 trial, precision medicine trial, with that design 4 that will allow all histologies. And if you have a 5 CDK path filtration, you'll get a CDK inhibitor 6 regardless of pathology, and the same with PI3 7 kinase pathway.</p> <p>8 That's the design, and it's a 9 biomarker-driven trial for brain metastases based 10 on the science, showing that these are markers that 11 do seem to be common in brain metastases. So 12 that's a trial that is coming in a month.</p> <p>13 AUDIENCE MEMBER: Thank you. And just let 14 the record show, to all the neurosurgeons, I win 15 the standing contest today.</p> <p>16 (Laughter.)</p> <p>17 DR. PROWELL: Absolutely.</p> <p>18 (Applause.)</p> <p>19 DR. BRASTIANOS: Kim just wanted me to 20 mention also that we're looking for mutations in 21 the brain metastases themselves, so we are hoping 22 that it will target the patients with the brain</p>

<p style="text-align: right;">Page 313</p> <p>1 metastases.</p> <p>2 DR. PROWELL: Thank you. And we'll take the</p> <p>3 question on the mic.</p> <p>4 AUDIENCE MEMBER: This may be a combination</p> <p>5 comment and question brought up by, really, the</p> <p>6 first real reference to informed consent and the</p> <p>7 patient landing in the ER and those combinations.</p> <p>8 The informed consent, et cetera or the patient</p> <p>9 landing in the ER carries with it the question of</p> <p>10 whether the patient's options offered them, whether</p> <p>11 ER or in the trial, are really given to a patient</p> <p>12 who can make consent, because very often there's</p> <p>13 that emergent need, and in the clinical trial</p> <p>14 there's a lack of information on the total</p> <p>15 perspective of the options that are available.</p> <p>16 This is an issue that hits every patient.</p> <p>17 I'm seeing this kind of doctor. I'm directed into</p> <p>18 this treatment whether in the ER or in a clinic.</p> <p>19 The informed consent is usually quite narrow; "Yes,</p> <p>20 I want to be fixed tonight in the ER," or "Yes, I</p> <p>21 want to be treated in this category of response."</p> <p>22 So I'm going to always be pushing that the</p>	<p style="text-align: right;">Page 315</p> <p>1 all the sectors is that there's really enthusiasm</p> <p>2 for including patients broadly who have CNS</p> <p>3 involvement in clinical trials and that we'd like</p> <p>4 to see that happening not only robustly, but</p> <p>5 earlier in the drug development process in the</p> <p>6 sense of kind of phase 1, 2, 3, but also earlier</p> <p>7 potentially even including patients who may not</p> <p>8 necessarily have had definitive local therapy.</p> <p>9 We feel that there are ways that this can be</p> <p>10 accomplished both safely and without</p> <p>11 compromising -- either compromising patient safety</p> <p>12 or posing excessive risk to the companies</p> <p>13 developing these drugs in terms of having patients</p> <p>14 in separate cohorts that that may enable us to look</p> <p>15 at their efficacy and safety, and even their dosing</p> <p>16 requirements distinct from the main group, and</p> <p>17 hopefully without too much disruption to the</p> <p>18 overall trial if we do in fact discover that it's</p> <p>19 not safe or it's not effective to develop these</p> <p>20 drugs in patients with brain mets.</p> <p>21 I think that we had hoped to get to -- but</p> <p>22 it actually really leads into Session IV well, how</p>
<p style="text-align: right;">Page 314</p> <p>1 patient not just have informed consent but to be</p> <p>2 able to make an educated choice with the full range</p> <p>3 of options available. And that is something that</p> <p>4 is beyond this specific brain met issue but hits</p> <p>5 every patient and every trial in complex diseases,</p> <p>6 and every patient going into treatment where he or</p> <p>7 she has perhaps been diagnosed and sent in one</p> <p>8 direction when there were 10 or a lack of clarity</p> <p>9 from that initial doctor, so educated options.</p> <p>10 DR. PROWELL: Thank you. Absolutely, a</p> <p>11 terrific comment.</p> <p>12 I'll just maybe spend 30 seconds summarizing</p> <p>13 this panel's discussion. And I believe you</p> <p>14 actually want the panels to switch -- is that</p> <p>15 right -- while I'm talking?</p> <p>16 MS. SELIG: That's okay. You can talk</p> <p>17 first, and then we're going to take 60 seconds and</p> <p>18 switch.</p> <p>19 Panel Recap - Tatiana Prowell</p> <p>20 DR. PROWELL: Okay, great.</p> <p>21 Just to summarize this really terrific</p> <p>22 discussion, I think what we've heard from across</p>	<p style="text-align: right;">Page 316</p> <p>1 do we provide the incentive to really include these</p> <p>2 patients; what's in it for patients to go on these</p> <p>3 trials; and what's in it for an industry to include</p> <p>4 these patients in their trials? I think that</p> <p>5 that'll be a big focus in Session IV.</p> <p>6 So I'd like to thank all the panelists and</p> <p>7 thank the audience for being so engaged.</p> <p>8 (Applause.)</p> <p>9 MS. SELIG: Please if you're sitting in the</p> <p>10 room, just take a moment to check your phone or</p> <p>11 whatever you need to do, but don't leave. And if</p> <p>12 you are on Session IV and you're not already up</p> <p>13 there, please make your way, and we'll move</p> <p>14 everybody closer together.</p> <p>15 Joohee?</p> <p>16 DR. SUL: I also wanted to add that we felt</p> <p>17 so terrible for Edjah having to stand for so long</p> <p>18 that we actually invited him up to join panel 4, so</p> <p>19 he'll be joining to represent the neurosurgeon's</p> <p>20 perspective.</p> <p>21 Session IV</p> <p>22 DR. WEN: I think we'll get started on the</p>

<p style="text-align: right;">Page 317</p> <p>1 final session. We've had a lot of great discussion 2 today. This final session, I think what we hope 3 will come out of this are concrete steps that we 4 can take forward on how to include brain metastasis 5 patients.</p> <p>6 I guess the tradition is we started 7 excluding brain metastases patients, and now we're 8 slowly letting them in. Maybe the flip is that 9 everybody should be allowed in, and this is a good 10 reason that they shouldn't be in the trial, and how 11 can we get to that stage. I think in this final 12 session we want to be concrete. We want to come 13 out of this with clarity, both in terms of who's 14 eligible, what are the trials, and what are the 15 endpoints.</p> <p>16 Before we get going, though, maybe I'll have 17 the new people who joined the panel introduce 18 themselves. The first one, Peggy's Zuckerman.</p> <p>19 MS. ZUCKERMAN: I'm a kidney cancer patient, 20 or at least I like to say I used to be a kidney 21 cancer patient. I am 15 years, nearly to the day, 22 from having had a radical nephrectomy because I had</p>	<p>1 about this the moment I heard of this workshop, 2 that I would not have been allowed to go into that 3 treatment had I any brain metastases. So the 4 moment I got the call that said "it's clear," I 5 knew it's clear meant my brain was clear of any 6 mets, and it was clear that I was heading into the 7 first thing that gave me any hope that I would see 8 that boy graduate.</p> <p>9 I obviously responded. I quit asking why 10 me? Why did I get kidney cancer? Then I could 11 finally ask, why me? Why did I respond? Why are 12 there not more like me? Why was I so lucky to be 13 just dropped into a place where they would grant me 14 that one hopeful treatment? And that has pushed me 15 to where I am today, lucky to be here, in the most 16 essential terms, to be here on this good earth and 17 here hoping that I can add some insight into the 18 patient's role, and what options can be brought to 19 patients, and how to bring those two patients.</p> <p>20 So thank you, and I always have more to say, 21 so somebody close.</p> <p>22 (Applause.)</p>
<p style="text-align: right;">Page 318</p> <p>1 a 10-centimeter tumor that also included metastases 2 throughout my lungs, and I was clearly a goner, I 3 think is the technical term, and all I wanted to 4 do, with so many other patients, was live long 5 enough to see, in my case, my son graduate, my 6 youngest graduate from high school. That was all I 7 thought I could begin to hope for.</p> <p>8 I was one of those miracle responders to 9 high-dose interleukin. All of you will know more 10 about it, of course, than I; except that I would 11 have in many cases been precluded from even 12 considering it because it wasn't a 13 medication -- though it was the only agent, which 14 was FDA approved at the time, it wasn't one which 15 had much support in the clinic.</p> <p>16 Certainly, had I not gone to an academic 17 center, would not have even heard of it, period. 18 Obviously, it was very easy for me to make the 19 choice to enter into that treatment, and with other 20 patients very often enter into a clinical trial 21 because that is the only version of a treatment.</p> <p>22 I do remember very clearly, and thought</p>	<p>1 DR. WEN: Thanks so much. Dr. Ndoum?</p> <p>2 DR. NDOUM: Edjah Ndoum. I'm a 3 neurosurgical oncologist at the NIH and happy to be 4 here. I came here to learn and listen, actually, 5 and not to talk.</p> <p>6 DR. WEN: Caroline?</p> <p>7 DR. CHUNG: I'm Caroline Chung. I'm from MD 8 Anderson. I'm a radiation oncologist, cross 9 appointed to diagnostic radiology. I'm the 10 director of imaging technology and innovation, and 11 I'm hoping to contribute to this great discussion.</p> <p>12 It clearly shows how complicated brain metastasis 13 can be, as well as how strong a mission we have to 14 actually make things better. I think that, 15 hopefully, we can start to wrap up with some key 16 action items as we move forward. Thank you.</p> <p>17 DR. ABREY: I'm Lauren Abrey. I currently 18 work at Novartis oncology, where I lead the solid 19 tumor group and medical affairs. Previous to that, 20 I think I can say I started my career making some 21 of those working mistakes that someone brought up 22 in the first session. I think I did a bunch of</p>

<p style="text-align: right;">Page 321</p> <p>1 Temozol studies in brain met patients, and I think 2 it's been true ever since then. Brain met patients 3 are out there and participate, but I do think we 4 have to be mindful that sometimes what we ask for 5 in trials are a pretty selected group of patients 6 if we look at it that way.</p> <p>7 I really want us to start to think how does 8 what we're talking about connect to all the brain 9 met patients who are treated in the community 10 because we've got a lot of specialized centers 11 here, and not everybody has access to these 12 multidisciplinary clinics, and we really need to 13 think how they're getting treatment when they're 14 out there in the real world.</p> <p>15 DR. WEN: Thank so much.</p> <p>16 Maybe what we'll do is divide this into 17 trial design and eligibility, and then we'll talk 18 about endpoints. In the first spot, in terms of 19 trying to allow all or as many as possible brain 20 metastasis patients into general oncology 21 development, maybe, Dr. Prowell, if you could give 22 us your thoughts on this, and also whether we</p>	<p style="text-align: right;">Page 323</p> <p>1 all, knows that the reason that we put clinical 2 trials on hold is because of deficiencies, and 3 those tend to be safety issues.</p> <p>4 So I would actually say that maybe this 5 requires recharacterizing how we think about 6 exclusion of brain mets patients to be a safety 7 issue, because the reality is these patients will 8 be treated with these drugs, and the experiment 9 will occur, and the only question is will it occur 10 on a clinical trial where safety data are being 11 rigorously collected and patient safety as being 12 rigorously monitored by a specialized team, or is 13 it going to occur in someone's outpatient practice.</p> <p>14 The experiment's going to happen, so maybe 15 that's the issue, is we need to recharacterize 16 failing to include brain mets patients as a safety 17 issue and as a deficiency, and not just a comment, 18 "Hey, you need to think about including these 19 people."</p> <p>20 DR. CHUNG: I'd just like to add a comment 21 to that. I completely agree with you, and I think 22 that one of the things that we do have to think</p>
<p style="text-align: right;">Page 322</p> <p>1 should try to get the ASCO Friends of Cancer 2 guidelines and the RANO guidelines uniformly 3 adopted as a recommendation and earlier thoughts on 4 this.</p> <p>5 DR. PROWELL: Sure. I think there's been 6 movement in that direction already. We've seen NCI 7 come out with standardized templates a few months 8 ago that were based upon BM [ph], ASCO Friends 9 eligibility criteria. Although there's templated 10 language available in these manuscripts, I'm not 11 sure that that's been -- in fact, I'm sure that has 12 not been uniformly adopted by industry, but I would 13 like to see it done.</p> <p>14 As a clinician, it's hard for me to 15 understand why we actually allowed this to happen 16 for so long. Why did we allow these patients to be 17 excluded when they represent, in some cases, half 18 or more than half of the intended-use population? 19 It doesn't make a lot of sense to me.</p> <p>20 So I feel like we should be compelling these 21 patients to be included. Anybody here who's an 22 industry, or anybody here who's an investigator at</p>	<p style="text-align: right;">Page 324</p> <p>1 about is when we think about when we started 2 excluding brain metastases patients and the era in 3 which we were imaging these patients, and when you 4 compare someone who doesn't have brain metastases 5 on a brain CT versus an MRI, I'm pretty sure a good 6 proportion of those patients actually did have 7 brain metastases.</p> <p>8 So we were including patients with brain 9 metastases from the start. For some reason, we 10 continue to keep that exclusion criteria, but our 11 imaging got better, and I think that there's a 12 continued improvement in that image quality. So if 13 you find a 1-millimeter spot in the brain today, is 14 that the same thing as someone who has a sizeable 15 brain metastasis that we were finding on older 16 imaging? So I think that we do have to be 17 thoughtful about what we're saying when we're 18 saying we're excluding these patients.</p> <p>19 DR. SUL: Yes, I absolutely agree with that 20 statement. There's a big difference between 21 excluding someone based on information you don't 22 know versus information you do. I would bet my</p>

<p style="text-align: right;">Page 325</p> <p>1 house and my car that all these trials, some of the 2 industry reps have said, well, we excluded patients 3 with lepto. I can guarantee that there were 4 patients with lepto on that study, because if you 5 didn't look, it doesn't mean that it's not there. 6 So we are doing these studies; we're just 7 kind of I think fooling ourselves, and in that 8 process, we're not getting the data. 9 This goes back to I think one of the 10 questions I had asked earlier about screening and 11 looking, are we just not looking enough? I 12 understand the reasons why we don't. Sometimes we 13 say, okay, if you're not symptomatic, we're not 14 even going to go there and look, and I know that's 15 standard for patients with breast cancer, but 16 should we actually start looking more? When we do 17 all these staging screening exams, it stops right 18 at the neck with CTs and PETs, and we're not 19 including the brain as part of the entire body. 20 DR. CHUNG: Just to add to that, I think as 21 Hussein had mentioned earlier, the patients who are 22 in the studies where there seems to be a good</p>	<p style="text-align: right;">Page 327</p> <p>1 because of the bad news that melanoma has such a 2 high brain met 2 case rate, that all along I think 3 we've -- and immunotherapy has been important, and 4 steroids. 5 So we've been in this mind-set of for many 6 years of looking for brain metastases basically 7 anytime there's a first recurrence metastatic 8 disease. Some of the surgeons I work with are even 9 scanning people's brains as soon as they have a 10 sentinel node metastasis, which we could quibble 11 about that, but that's not what we're here for. 12 But the idea of not lulling yourself, just 13 like you were saying about assuming that patient's 14 don't have brain mets and including them when they 15 may, these patients who were in remission who 16 didn't have visible brain metastases at the 17 beginning of whatever their current therapy is, and 18 they're doing well on it. 19 extracranially, you can't forget the importance of 20 occasionally looking at their brain. I don't know 21 that we can legislate that. 22 But I wanted to make a couple of other</p>
<p style="text-align: right;">Page 326</p> <p>1 efficacy signal, where we're probably going to say 2 this is going to become a mainstream drug, 3 similarly, even in the upfront setting when 4 patients may have metastatic disease but don't have 5 known brain metastases, if we don't continue to 6 follow them -- or if we do continue to follow them 7 and the pharma companies are willing to fund these 8 trials, and we can continue to follow them with 9 brain imaging, that will help answer our 10 preventative questions without designing a whole 11 new trial. 12 Kim had mentioned the whole cost of 13 screening patients, and we have patients who we're 14 following who have been screened, who are on this 15 trial. And by following them, we are getting a 16 secondary endpoint that's clinically very 17 meaningful in terms of brain mets prevention. 18 DR. SUL: Kim? 19 DR. MARGOLIN: I agree with that, and I 20 think I even mentioned it earlier. It's been nice 21 for my career, Hussein, et cetera, that we've been 22 in -- melanoma has sort of been the vanguard</p>	<p style="text-align: right;">Page 328</p> <p>1 points if you'll permit. These are more global and 2 little bit off this topic, so you may choose to 3 ignore it or come back to it. I'd like to propose 4 that there are really two purposes here. 5 One is that if we're looking at the concept 6 of approving drugs with a specific idea that 7 they're going to be for patients with a given 8 disease and brain metastasis, then we have to show, 9 as so elegantly gone over in the Camidge video and 10 earlier talks this morning -- I think it was 11 Mike -- that they really should demonstrate an 12 improvement in patients with brain metastases over 13 the available options in patients with brain 14 metastases. 15 So all these amazing mutations in lung 16 cancer are the area where that's already started to 17 be shown, because otherwise the drug doesn't have 18 an advantage in those patients, and that's an FDA 19 issue. 20 What's not an FDA issue that I think is more 21 of a market penetration if you're talking from the 22 industry point of view, or a usage, and maybe even</p>

<p style="text-align: right;">Page 329</p> <p>1 a safety issue, is the idea that available drugs 2 being used more in patients with brain metastases 3 are safe and may be synergistically effective with 4 other modalities such as stereotactic radiosurgery, 5 or certain sequences are ideal, and so on and so 6 forth. That I don't think is for the FDA to have 7 to legislate.</p> <p>8 DR. LIN: The two points that I would add 9 are I would distinguish two kinds of trials, the 10 trials where the patient's CNS disease has been 11 treated, and then you enter them, and your primary 12 purpose is to control the extracranial disease. I 13 think the argument there is, really, unless there's 14 a very good safety reason, those patients should 15 just be allowed on all phases of all trials just as 16 a blanket statement.</p> <p>17 I think right now that's still not -- I mean 18 it's happening more, but it's still not happening 19 enough. We would never allow a trial for 20 metastatic breast cancer to exclude liver 21 metastasis patients. That's a completely 22 ridiculous concept, but we routinely allow trials</p>	<p style="text-align: right;">Page 331</p> <p>1 out of a standard template, what's probably not cut 2 and paste. There's just a template for phase 3 3 trials in solid tumors, and then you adapt what you 4 need, and that exclusion lives in there.</p> <p>5 I think it was the same when I was at Sloan 6 Kettering, and I cut and paste from my last 7 protocol, sometimes horribly, even to the 8 statistics section just to provoke the 9 statisticians to give me what I needed. So I think 10 some of it is just breaking old bad habits, and 11 unfortunately that's a little bit more the stick 12 than the carrot I think probably.</p> <p>13 I do think the other side, though -- and I 14 think the alectinib, brigatinib stories, 15 osimertinib start to really say why would industry 16 care about developing drugs that have unique 17 efficacy in the brain, and it's because it helps 18 you differentiate your product from the other 19 products on the market. And that's not hard for my 20 scientists to understand or my commercial team to 21 understand.</p> <p>22 So I think those stories and those examples</p>
<p style="text-align: right;">Page 330</p> <p>1 to exclude brain metastases patients even if 2 they've been treated.</p> <p>3 So I would like to see that just completely 4 go away. I still think we need specific -- whether 5 it's an individual trial, or a cohort in a trial, 6 or subset in a trial, these patients do have to be 7 looked at separately in some way because you're 8 going to be potentially looking at different 9 secondary endpoints. You might have different ways 10 that you're going to assess their CNS.</p> <p>11 So I think it's so important to do those 12 trials, but I would kind of distinguish between 13 these two types of trials. I personally think for 14 a patient who has treated brain mets that any 15 exclusions should really go away unless you really 16 know that there's a safety issue.</p> <p>17 DR. ABREY: If I could follow up on that, if 18 you're interested in thinking how do you 19 incentivize industry to want to do two very 20 different things there, I think one is breaking an 21 old habit, and whether you take Pat Keegan's 22 comment that a lot of what we do in industry comes</p>	<p style="text-align: right;">Page 332</p> <p>1 are really terrific and thinking how we can build 2 on whether it's specifically the alectinib story or 3 another to say how do we do that in other disease 4 areas and other specific mutations in a similar 5 fashion, and how much of that was intentional, and 6 how much of that was a little bit luck. I think 7 maybe some of the early alectinib was observing 8 early luck, and I think maybe some of the 9 brigatinib, lorlatinib story was a little bit more 10 intentional as the follow-on. So I think we've got 11 opportunities on both.</p> <p>12 DR. BRASTIANOS: Just a quick comment, just 13 to add to it, I completely agree, there are two 14 issues. One is we should be running brain 15 metastases trials because we are seeing that brain 16 metastases do differ from their primary and 17 extracranial sites, so that's really important, and 18 then the other issue of including the primary 19 tumors. But I think we can't forget that brain 20 metastases are genetically distinct, and we should 21 be considering brain metastases trials, and just a 22 comment to add to what you're saying.</p>

<p style="text-align: right;">Page 333</p> <p>1 DR. ABREY: I think that's something 2 even -- there was a third thing, Priscilla. I 3 think we really need to be intentional about the 4 drug development for brain tumors, including brain 5 metastasis because we suffer from the same problem 6 in the primary brain tumor, that we try to 7 piggyback on other oncology drugs and make them 8 good enough. Good enough isn't good enough 9 for this disease.</p> <p>10 DR. RIELY: I think one thing to really bear 11 in mind, and as a lung cancer doc, I think about 12 the ALK story as something that taught us a lot. I 13 think one way it helps to teach us is we look at 14 ALK and we say it was really a great story about 15 developing drugs in patients with brain metastases. 16 A big part of that is because brain metastases are 17 very common in ALK-positive lung cancer. So it's 18 inherently about treating this disease as you're 19 treating people with brain metastases, a 20 significant number of people with brain metastases. 21 So maybe that's how we can figure out 22 whether this is merely having an arm, a cohort, for</p>	<p style="text-align: right;">Page 335</p> <p>1 we can tailor an MRI screening exam so we're not 2 doing 6 or 8 different sequences and making it too 3 expensive to add to a clinical trial design. 4 So perhaps just do a volume 3DT1 pre-imposed 5 contrast and 1 T2-weighted image, like a FLAIR 6 image, and really cut the cost down of that, and it 7 could be more amenable to entering all these 8 patients in clinical studies, obviously to enroll 9 them and screen them before, as well as following 10 them during the study to see if they respond or 11 not. So we can tailor the protocol down. 12 The second thing I'd like to bring up is 13 that I'm currently working for the Focused 14 Ultrasound Foundation, and a few people have 15 brought up the new technology called focused 16 ultrasound. And what it can do is temporarily 17 reversibly and safely now open the blood-brain 18 barrier. This allows big pharma to start 19 considering either drugs that don't cross the 20 blood-brain barrier that may work for CNS mets, so 21 now we can get those drugs into the brain in 22 localized fashion, or even taking drugs that may</p>
<p style="text-align: right;">Page 334</p> <p>1 brain metastases patients or trying to include them 2 in every step of the drug development process, and 3 basically how frequent is it, and is that number 4 10 percent, is that number 20 percent? I'm not 5 sure where the cut-point is, but that's kind of how 6 I'm beginning to think about it.</p> <p>7 DR. LeBLANG: Hi. My name is Suzanne 8 LeBlang, and I'm a neuroradiologist, one of few in 9 the room here, so I've been eagerly listening to 10 the discussions all day, and I have a few thoughts 11 that I'd like to share.</p> <p>12 First of all, I do believe that doing more 13 screening, MRI scans in patients that are at these 14 high-risk levels of disease is mandatory, and I 15 think the problem lies on both sides, on the 16 clinician side not wanting to prescribe or order 17 the MRI scan because you don't know -- you won't 18 have to deal with the results, and the clinical 19 trial enrollment is an issue. And on the other 20 hand, radiologists have some blame in this as well.</p> <p>21 I think sometimes we do limited protocols 22 for orbis [ph] and not a whole brain, and I think</p>	<p style="text-align: right;">Page 336</p> <p>1 get in there to elevate their concentrations. 2 So I wanted to know your thoughts on 3 actually even opening the blood-brain barrier more 4 with this focus ultrasound and how that will enable 5 a more systemic therapy to possibly play a role in 6 between radiation oncologists, neurosurgeons, and 7 what we have today. So any thoughts on opening the 8 blood-brain barrier directly to allow these drugs 9 to enter?</p> <p>10 DR. ABREY: I'm from New York originally. I 11 live in Switzerland now, sometimes I start from 12 skepticism. I feel like trying to open the 13 blood-brain barrier has been a long conversation, 14 so we've tried to disrupt it with various osmotic 15 agent. We've done other things where we've given 16 intra-arterial, including catheters threaded right 17 to the site of the tumor and infusing. I think to 18 date, it hasn't consistently shown us benefit, 19 although individual patients clearly have derived 20 massive benefit from it, but it's more stories than 21 data.</p> <p>22 I don't want to write it off, but I think</p>

Page 337	<p>1 it's still kind of an area that needs to be 2 considered experimental, and I guess I'm still 3 worried that we need better drugs to give the 4 patients more than we need to open the blood-brain 5 barrier, but others might disagree with me.</p> <p>6 DR. NDOUM: I was just going to say, when I 7 was looking at -- I was talking to somebody earlier 8 about Visualase as well. That's another thing that 9 hasn't really been discussed a lot, but I know it's 10 very frequently discussed in neurosurgical 11 literature. So there are better local therapies or 12 alternative local therapies, and we have some local 13 therapies that seem pretty effective.</p> <p>14 So focused ultrasound would fall into the 15 category of another local option. Maybe if 16 radiosurgery had failed or something like that, and 17 you're looking for an option, you know that there's 18 a systemic drug that's very promising, but we know 19 it doesn't cross the blood-brain barrier.</p> <p>20 So maybe with the focused ultrasound, we 21 could get the contrast enhancing lesion plus a 22 slight margin around it in a different local way.</p>
Page 338	<p>1 So I think there may be a role. I think as we're 2 talking broadly about metastases, it wouldn't be 3 the first thing that I'd focus on, but I think it'd 4 be something that could be adjunctive and helpful.</p> <p>5 DR. WEN: Mike?</p> <p>6 DR. DAVIES: Mike Davies, MD Anderson. I 7 was just thinking, as we talked before, about the 8 concept of do we need separate cohorts versus just 9 stratifying. I do think the one argument that I 10 would argue for the cohorts, as we talked about, 11 there are actually endpoints that are unique to the 12 brain metastasis patients, so making sure that we 13 designed the trial so we capture those, whether 14 it's the neurocognitive dysfunction or whether it's 15 the incidence of radiation necrosis.</p> <p>16 I just wonder if we'd be able to efficiently 17 or effectively capture those if we just go to 18 stratification where we're using the same endpoints 19 on everybody and miss those sort of CNS specific 20 endpoints. So I think that could be an argument 21 for why it might make sense to use cohorts 22 specifically.</p> <p>1 The other argument, just coming back to it, 2 not argument, but about the phase 1 question of how 3 early to go in. Again, as we talked about, we all 4 know that if these drugs get approved, even if it 5 doesn't specifically say brain mets, they're going 6 to get used in patients with brain mets. So 7 getting a safety signal in brain mets in phase 1 is 8 absolutely a straightforward justification for 9 doing that.</p> <p>10 MS. ZUCKERMAN: I'd like to comment to that 11 because we focused quite a bit on the breast, on 12 lung cancer, and little on the other solid tumors, 13 and of course my favorite being kidney cancer. We 14 are finding out that there are probably far more 15 brain mets in that group than anticipated, and 16 historically.</p> <p>17 Again, because we have better reasons 18 perhaps to go in and look, suddenly it's not just a 19 small percentage, but an increasingly large 20 percentage. As the technology improves, we'll find 21 more. And if we don't know the impact of the 22 medications, all of them on brain mets and the</p>

<p>Page 341</p> <p>1 DR. ABREY: This could be a whole study in 2 human psychology. 3 (Laughter.) 4 DR. ABREY: Just a disclaimer, I spent half 5 of my career or more in academic medicine, so I 6 might not answer very straight. No, I think the 7 incentive to me would be the possibility to 8 differentiate around an enhanced labeling claim 9 because I think that's how you stand out from the 10 background. Having to either have a limitation of 11 use or some sort of restrictive comment in your 12 label is something that puts you on the defensive, 13 and nobody likes to be in that position. We want 14 to be better or competitive. I think we're all 15 competitive, before, in those rooms, so sorry. 16 DR. SUL: I think given the audience here 17 today, it's no surprise that we're all in agreement 18 that more patients should be enrolling in clinical 19 trials and that there should be more access 20 allowed, and we've talked a little bit about 21 incentives for industry, and wanted to know if we 22 could hear from Peggy a little bit about the</p>	<p>1 So access to trials starts with that doctor 2 in that office and what I will call a complete 3 diagnosis, and that includes not just where the 4 tumor landed, where else it is, and I'm going to 5 start with the brain on down. And then to find 6 what those options are for you, and then a 7 meaningful way to find all the clinical trials that 8 might be available. 9 You and your doctor may not even properly 10 characterize your disease to be able to search on 11 clinicaltrials.gov or any of the other helpful 12 sites. So that alone, just knowing that what 13 you've got, where you can go, what your disease is 14 really called, how it's characterized in the 15 literature, all these are barriers; not even to 16 understand what a clinical trial means, which is 17 one of the pushes that every patient forum and 18 every disease group wants to work with. 19 But that is why we don't get the numbers of 20 patients into trials that we need, and then to be 21 really desperate because your head's at risk, it's 22 far more concerning that I would have had brain</p>
<p>Page 342</p> <p>1 patient perspective on incentives and barriers to 2 enrolling in clinical trials. 3 MS. ZUCKERBERG: Well, first, there's 4 endless barriers, and a lot of it is simply that 5 we're not properly diagnosed as a group. I know 6 I'm speaking always from a kidney cancer 7 perspective, but I've got a feeling that most other 8 cancers are very much the same. 9 You're suddenly told you have cancer. 10 You're desperate to get it out or get it treated, 11 whatever that cancer is, and rarely do you hear 12 from your doctor that I can't do this or I won't do 13 this, you better go onto a clinical trial. If 14 you've got that far in your conversation to 15 understand that you might need a clinical trial, 16 unless you're from one of the many lovely centers 17 that have just been mentioned today, and within 100 18 miles or maybe 20 miles or so, chances are, you're 19 in a community setting, where your family is, where 20 your support system is, and where you're unlikely 21 to leave comfortably in this new stunning, 22 terrifying situation you found yourself.</p>	<p>Page 344</p> <p>1 mets than my liver was going to give me grief. And 2 I was living quite nicely with my lung mets all 3 over the place, but to think that your brain is 4 going to go, is going to be chewed up by this 5 cancer, is so frightening, so stunning, it is the 6 game changer. 7 Then to find out you've got a limited number 8 of choices in a trial, and you're now excluded 9 because of the thing that's most threatening to 10 your essential self is a betrayal of the medical 11 system and the clinical trial system to the 12 patient, in my thinking. 13 You've already been betrayed perhaps by your 14 own body, perhaps by the doctor who misdiagnosed 15 you, perhaps by the limitations of where you live 16 and what you can afford, and now the clinical trial 17 world that's supposed to be the foundation for the 18 new and improved care won't let you in because you 19 have brain mets, that's unethical, and it adds to 20 the terrible distrust we have in our society for 21 the medical world, which includes everybody from 22 patient advocates, to doctors, and to the pharmas</p>

<p>Page 345</p> <p>1 who really suffer from that. 2 I think I have probably said enough, but 3 that's enough of the barriers, and just not to 4 understand what a clinical trial is. 5 DR. WEN: Thank you. A question at the 6 back? 7 MS. SELIG: Can I pose a question on behalf 8 of a colleague who was here, but I think she had to 9 leave, and represents the lung cancer community, a 10 thought that came up -- and maybe this would be 11 something good for the regulators and the 12 clinicians to respond to. 13 She was listening to the discussion of, 14 well, we should measure this, and we should measure 15 that, and we should know these things, and we 16 should do all these tests. The flip side of that 17 is the burden on the patient that's actually in the 18 trial to go through all these tests. 19 So back to what Joohee was saying earlier, 20 could we identify those things that we all agree 21 are most important that we'd be measuring versus 22 study everything, put the patient through a zillion</p>	<p>1 So I think whatever we can do when we design 2 trials to minimize travel, to me that 3 feels -- that's what I hear from patients, is that 4 makes the biggest difference in their ability to go 5 on a trial. So if you have day 1, day 4, day 8, 6 day 11, day 16 blood draws, do they have to be done 7 at the site? Can they be done at a local lab? 8 Those very practical issues are I think really 9 important in allowing better access to trials. 10 DR. PROWELL: I'll just comment on one 11 thing. We hear you and we've heard this from 12 patients as well. This is actually a huge topic of 13 interest, not only in oncology but we've heard a 14 lot about this from the neurodegenerative diseases 15 community who have even more challenges and 16 difficulty traveling that are metastatic cancer 17 patients in many cases. 18 Just to make people aware, there actually is 19 a decentralized clinical trials working group at 20 FDA that's in the process of finalizing a draft 21 guidance that we expect to come out late summer, 22 and we're also going to have one of our two plenary</p>
<p>Page 346</p> <p>1 tests to gather all this information? Is there 2 some way to balance the need to know more and to 3 evaluate these therapies in the brain with the 4 burden on the patient of actually participating in 5 these trials? 6 DR. MARGOLIN: Wendy, I'm not going to try 7 to answer this, but I want a part B to that. Just 8 as Tatiana's question, you can't ask one person to 9 represent the whole drug company industry, there 10 are patients who want to be scanned every 11 5 minutes, who want to know. There are patients 12 who don't ever want to know. So I'm not even sure 13 that this kind of a question can be applied here; 14 just saying. 15 DR. LIN: I'll add one point to that also. 16 Patrick has been thinking about this a lot as part 17 of this snow physician paper on barriers to trial 18 enrollment. I think that more so -- I'm speaking 19 for patients now, and there are patients here who 20 can tell me what they think. I think more so than, 21 okay, there's an MRI, there's a CAT scan, there's a 22 blood test, travel is a big issue.</p>	<p>Page 348</p> <p>1 sessions at the AAADV workshop that's sponsored by 2 FDA, Duke, ASCO, ACR in Bethesda on May 9th. The 3 middle day of that workshop, we're actually having 4 a plenary session on decentralized trials that Rich 5 Schelsky from ASCO and I will be co-chairing, and 6 we'll be talking about this issue. 7 DR. RIELY: That's a great effort to be part 8 of because I think the question gets at the patient 9 experience, and that's critical. But I think we 10 need to get together and figure out what the best 11 tests to do are, because if you ask all the 12 investigators up here, we can tell you about 10 13 things that we do all the time that are dumb, and 14 getting an MRI brain is not one of them. That's 15 smart. The day 4 PK test, that's probably dumb. 16 But we all have to agree on what's important, and I 17 think that's hard. 18 DR. WEN: I'm going to take the two 19 questions really quickly, and then I want to switch 20 and talk about trials specifically for brain 21 metastases, and then talk about endpoints. We have 22 20 minutes left, so I think we want to get to</p>

<p style="text-align: right;">Page 349</p> <p>1 those. The person in the back, you've been waiting 2 a long time.</p> <p>3 AUDIENCE MEMBER: Thank you. My name is 4 [indiscernible]. I have been running for office 5 for many times, [indiscernible] to U.S. Congress 6 and U.S. Senate, plus Maryland state comptroller. 7 As a patient myself before, I think as a mother, as 8 a consumer, as a government employee, I have seen a 9 lot of problems in our health care area, including 10 the [indiscernible] data set. All the research is 11 meaningless and this data should have 12 accountability.</p> <p>13 So many times I just say if the researcher 14 wants to collect the data, first thing first. You 15 have to have independent accountability to have 16 good, accurate data. So I hope you can put this in 17 mind, first of all. To do that, you've got to be 18 independent sponsors, so you can see all those 19 sites. Those are sponsors, and some of those I can 20 testify they don't have independent or best 21 interest of the general public.</p> <p>22 DR. WEN: Thank you.</p>	<p style="text-align: right;">Page 351</p> <p>1 endpoint, sort of avoidance of whole-brain 2 radiation type of endpoint and how that might fit 3 into a regulatory framework in a bit of a different 4 way than the other kind of surrogate endpoints that 5 you might think about traditionally.</p> <p>6 The way we define an endpoint that's used in 7 a regulatory framework for regular approval, there 8 has to be demonstration of direct clinical benefit. 9 In the prostate cancer setting, we were trying to 10 wrap our heads around how to define an avoidance of 11 harm endpoint and direct clinical benefit endpoint 12 into maybe an earlier clinical endpoint that could 13 possibly, when designed appropriately -- and I 14 think we're not there quite yet -- could possibly 15 even lead to a regular approval based on avoidance 16 of harm or direct clinical benefit.</p> <p>17 I think that could be presented to sponsors 18 as a possible incentive because if you look at a 19 brain specific endpoint like this, it's sort of a 20 different way of looking at the endpoint, rather 21 than looking at a surrogate, which would need to 22 lead to an accelerated approval, this may be a</p>
<p style="text-align: right;">Page 350</p> <p>1 AUDIENCE MEMBER: The second is I would like 2 to let you know after you have a drug, it's not 3 necessary [indiscernible] best and efficient. 4 These costs to the patients. I think now our 5 health care is in trouble because all pharmacy and 6 industry, even mergers, are a revolving door and 7 don't have accountability for the best interest of 8 our general public. Certainly, it's less 9 affordable, and pharmacy, or hospital, or rehab 10 center to get patient care.</p> <p>11 DR. WEN: Thank you. Thank you very much 12 for that comment.</p> <p>13 AUDIENCE MEMBER: Pay attention to health 14 care to consumers that complain. All this 15 information -- put a consumer group up front rather 16 than putting a pharmaceutical up front. Thank you.</p> <p>17 DR. WEN: Thank you. Dr. Weinstock?</p> <p>18 DR. WEINSTOCK: Thank you. I wanted to 19 touch on a topic that came up in terms of endpoints 20 in Session III, and I want to circle back to how 21 that might apply to something that we were talking 22 about in this session. And that's the use of an</p>	<p style="text-align: right;">Page 352</p> <p>1 regular approval endpoint that weeds out earlier 2 than more conventional measures of direct clinical 3 benefit.</p> <p>4 I'm not sure if I'm getting my point across 5 because this is a very regulatory framework, but 6 I'm just saying that this could be used as an 7 incentive to enroll these trials.</p> <p>8 DR. MARGOLIN: But you still have to have 9 really good control comparator.</p> <p>10 DR. WEINSTOCK: This would have to be in 11 a -- certainly in the prostate setting, this is in 12 the context of a randomized controlled trial, but 13 my point is that it's a much earlier readout than 14 you necessarily have with the more conventional 15 measures of clinical benefit.</p> <p>16 DR. LIN: We thought about this a lot. Yael 17 Lazer [ph], who's a radiation oncologist in our 18 group, is launching a screening brain MRI trial for 19 patients with metastatic breast cancer, and we 20 thought a lot about the right endpoint. We tossed 21 around time to radiation, time to whole-brain 22 radiation, time to SRS, time to symptom</p>

<p style="text-align: right;">Page 353</p> <p>1 deterioration.</p> <p>2 One of the problems, practically speaking, 3 with the time to whole-brain radiation endpoint is 4 that people are doing now SRS to more and more 5 lesions, so it's kind of subjective when somebody 6 gets whole-brain radiation in a way. I mean, if 7 somebody has 30 lesions, not so subjective.</p> <p>8 So ultimately, we actually came around to 9 Jeff Wefel's conclusion, which is that we just 10 really have to look at neurocognitive endpoints. 11 So that's actually what the study is powered to, 12 because I think it is. I think this time to 13 whole-brain radiation is tricky because of the 14 availability of SRS and multiple lesions, 15 especially now that we can do this with single 16 ICE [ph] center and do this with many, many lesions 17 in one session.</p> <p>18 DR. ABREY: Thank you. And also for the 19 sponsor's point of view, be limiting the trial to a 20 very U.S. focus in that situation, so just thinking 21 about where whole-brain radiation is still used. 22 And also I want to put a little bit of caution</p>	<p style="text-align: right;">Page 355</p> <p>1 others in the room if they think that that's 2 something that you could even get people to rally 3 around and say we recognize that we all do this 4 differently in our own clinic, but from the 5 standpoint of this clinical trial, here are 6 criteria that we can all agree upon, which might 7 enable us to use certain endpoints like time to 8 whole-brain radiation, for example.</p> <p>9 DR. WEN: Just a quick comment from 10 Dr. Gondi and Dr. Chung, and I really want to move 11 on to the other two topics that we need to discuss.</p> <p>12 DR. GONDI: Two comments I'd say for the 13 time to whole-brain radiotherapy, but I just want 14 to make it also clear that it actually nicely 15 presented with Doctor Brown's online session. I 16 agree that whole-brain radiotherapy does have some 17 cognitive issues, but we've come a long ways in 18 preventing those cognitive issues. We didn't 19 really spend a lot of time talking about this 20 today, but hippocampal sparing, which is coming out 21 and been submitted to ASCO and prophylactic 22 [indiscernible], we're seeing fairly significant</p>
<p style="text-align: right;">Page 354</p> <p>1 here.</p> <p>2 It's still a very effective therapy and I 3 don't think we should make all patients so terribly 4 afraid of it that when you need to use it, it's 5 somehow the worst thing that could ever happen to 6 them. But I think the extreme use of radiosurgery 7 is not seen across the world, and then you'd be 8 focusing on a very limited potential market, which 9 drives a lot of the choices in pharma right now but 10 not great for patients necessarily.</p> <p>11 DR. PROWELL: We were talking during the 12 break about what is the real possibility of 13 persuading investigators in a large randomized 14 trial, or particularly in a global trial, of coming 15 up with a uniform algorithm to how they would 16 administer steroids and to which patients would 17 receive radiation, recognizing that you really are 18 dictating practice of medicine and is that even 19 something that's possible. And the 20 neuro-oncologists all said impossible; there's no 21 way you can get them to all agree on this.</p> <p>22 But I'd be curious to hear perspectives of</p>	<p style="text-align: right;">Page 356</p> <p>1 cognitive benefits with these interventions. So I 2 think to Dr. Abrey's point, sometimes the 3 metastatic disease is really what drives the 4 cognition as we try to involve safer radiotherapy 5 approaches.</p> <p>6 Secondly, as a question to the panel, as we 7 talk about all these endpoints and challenges of 8 these trials, some of the best brain met trials 9 have actually been run by the NCI, and I wonder 10 what type of opportunities we have in collaborating 11 with the NCI and industry to run basket trials in 12 the area of brain metastases.</p> <p>13 Dr. Brastianos' trial is a great example of 14 moving in that direction; did a great job with the 15 MATCH trial, which did not include brain 16 metastases. But how do we allow various industries 17 to work together in basket trials to address all 18 these other endpoints that may not have enough 19 resources to address.</p> <p>20 DR. WEN: Thank you. Let's talk briefly 21 about trials specifically for brain mets. Maybe 22 Nancy and Kim, if we could have your thoughts.</p>

<p style="text-align: right;">Page 357</p> <p>1 What does a trial look like and what are the 2 endpoints, if we had this magic drug X that's going 3 to be great for brain mets?</p> <p>4 DR. MARGOLIN: I'll take a shot first 5 because I want Nancy to be the finisher and the one 6 who says the final words of wisdom, because I wrote 7 down a couple notes, and I actually wanted to say 8 that I agree with something Mike Atkins said 9 earlier and would like to expand on that just a 10 little, which is the concept that for many, not all 11 necessarily, patients with brain metastases from 12 most of the tumors we're talking about, lung, 13 breast and melanoma, the presence of brain 14 metastases, at least when they're symptomatic and 15 of a substantial size requiring steroids, 16 et Cetera, is not always but often going to be 17 considered the overall lifespan limiting factor in 18 that patient's natural history.</p> <p>19 So the use of a survival endpoint, at least 20 as one of the endpoints, but really maybe the 21 primary endpoint in many of the trials, I really 22 think is a good idea, even though I was arguing for</p>	<p style="text-align: right;">Page 359</p> <p>1 which is patients with brain metastases, included 2 in their early-phase trials, seeing CNS responses, 3 and then those patients included actively in the 4 phase 3 registration strategies, and they were 5 enrolled with the purpose of treating both their 6 CNS and their extracranial disease.</p> <p>7 So there, if they're going to be included as 8 part of the overall set, you'll have a certain type 9 of endpoint that you need to pick that will be 10 relevant to all patients entering on a trial, and 11 then you may have secondary endpoints that are 12 important for the brain metastasis subset. So 13 that's kind of one type of study I think of.</p> <p>14 The other type of study is the study that 15 really only exclusively enrolls patients with 16 active brain metastases, where the goal is to treat 17 their brain metastasis. I think there, you can 18 obviously choose more CNS-directed endpoints. You 19 could always choose overall survival because these 20 are patients where you are probably more likely to 21 see an overall survival advantage given the dearth 22 of other therapies that the patients can receive.</p>
<p style="text-align: right;">Page 358</p> <p>1 many composite and parallel endpoints as long as 2 they go the same direction, and I don't think those 3 two things are incompatible depending on the kinds 4 of patients.</p> <p>5 Also, we often talk about the fact that you 6 can't use survival as an endpoint in randomized 7 trials because of the high likelihood that patients 8 who are assigned to one treatment will end up 9 crossing over, whether it's on study, or outside of 10 a study, to the other arm or something like it, and 11 thus that sort of blurs the ability to dissect out 12 survival as an endpoint.</p> <p>13 But I think there are times when that's not 14 altogether true, if you think about the idea that 15 the first therapy that you give somebody may be the 16 most definitive one, and that may be the one that 17 alters or defines the survival benefit. Even if 18 you could get that drug later, it may not catch up. 19 I'm going to turn the rest over to Nancy.</p> <p>20 DR. LIN: Here, I would think of two kinds 21 of studies, and I think the considerations are 22 different. I think there's the ALK kind of story,</p>	<p style="text-align: right;">Page 360</p> <p>1 But here I think, from a practical 2 standpoint, in addition to the endpoint challenges, 3 it's really the control arm because speaking for 4 breast cancer, there's no obvious control arm. You 5 could have a control arm of radiation, I guess, but 6 then you have all these considerations of what's 7 the right endpoint.</p> <p>8 I think that that's a challenge, and I'm 9 interested from a regulatory perspective under what 10 circumstances, for example, a single-arm experience 11 might have to gain regulatory approval; what sort 12 of endpoint would be sufficient understanding it's 13 a non-randomized experience, so survival is a 14 little hard unless you hit it out of the park. I 15 think the considerations are different depending on 16 whether you're including the patient or you are 17 doing a brain met specific study.</p> <p>18 DR. SUL: I think some of this goes back to 19 what we started out with in thinking about context. 20 I think that's probably one of the most common 21 questions we get asked, is can I use an objective 22 response rate to get approval? I think it's more</p>

<p style="text-align: right;">Page 361</p> <p>1 helpful to think about it in terms of in which 2 situations does looking at objective response rate 3 make the most sense to look at benefits. 4 For instance, if you're looking at a drug 5 that has no track record and you have no idea that 6 the mechanism of action ties in with the effect of 7 the drug, it's harder to look at these single-arm 8 studies. I think if you are looking at a drug that 9 has a well-proven track record in other 10 malignancies, your response rate is -- Paul was 11 saying sometimes the robustness of the data or the 12 effect can help overcome some of the uncertainties, 13 so you have a really robust response rate. You're 14 seeing CRs, which we don't see in patients with 15 brain mets, then I think those kinds of aspects are 16 helpful in helping us interpret. 17 It's not so much is it endpoint; it's the 18 data that comes from it and how we interpret it. 19 That's one of those questions I always struggle 20 with, is can I use PFS? Can I use ORR? And the 21 answer's always, well, it depends, and the 22 circumstances really are what shape the outcome,</p>	<p style="text-align: right;">Page 363</p> <p>1 think it really depends a lot on the magnitude, the 2 patient population. 3 I'm not sure how many different ways to put 4 it, but we have to take the totality of the 5 information into account when we evaluate the 6 effects of the drugs. And I know it's not the most 7 satisfying answer, but you can do it, and we'd have 8 to sit and interpret the data. 9 DR. NDOUM: Translating, she said it would 10 work. 11 DR. ANDERS: Carey Anders from Duke. I just 12 wanted to follow up on what Nancy brought up as the 13 second part of her conversation, and that's the 14 control arm. I think many of us have designed 15 single-arm, stage 2 studies with response rate or a 16 PFS compared to historical control, but many times 17 our historical control is very difficult to 18 interpret. So whether or not you actually have a 19 signal is hard to know. 20 In thinking about this, particularly in 21 breast cancer not having a gold standard, the 22 thought process around physician's best choice or</p>
<p style="text-align: right;">Page 362</p> <p>1 and nobody likes that answer. 2 DR. NDOUM: Can I -- sorry. 3 DR. PROWELL: I was going to say, you can 4 always measure it. The question is can we 5 interpret it when you submit it to us? 6 DR. NDOUM: So back to being a hammer. If 7 such a single-arm submission was backed up with 8 biological data -- say you had preclinical data 9 that every time you use drug X, you get this 10 biological response Y within the tumor, and then 11 you had an actual window of opportunity study in 12 this single-arm setting where you gave the drug and 13 you saw the exact same biological response, and 14 then you were additionally seeing these objective 15 responses in these patients in this single arm, 16 would that help support a potential filing for 17 metastatic drug-specific indication? 18 DR. SUL: I think specifically for 19 preclinical data, that's always helpful. 20 Regardless of whether you're talking about 21 interpreting the endpoint or designing the study, I 22 think that's absolutely important. But again, I</p>	<p style="text-align: right;">Page 364</p> <p>1 MD discretion and what that would look like, I 2 recognize from a patient perspective and talking to 3 my own patients about that, that's not the most 4 attractive trial design unless there is a way to 5 crossover and still allow patients access to 6 hopefully promising investigational agents. 7 So I just wanted to open up conversation 8 around control arms and how we should be thinking 9 about this as we're designing our own studies. 10 DR. WEN: Dr. Tawbi? Did anybody want to 11 comment? 12 DR. ANDERS: I'm kind of following up on the 13 EMBRACE data in breast cancer. That's always been 14 very striking to me. For those who don't do breast 15 cancer every day, eribulin was FDA approved based 16 on a survival advantage compared to physician's 17 best choice. I use that every week in my practice 18 to select eribulin when I'm stuck with that. 19 So I'm just curious if that could be 20 something we could be thinking about, also 21 recognizing that the studies are going to be 22 larger. It's a comparative design, so to have</p>

<p style="text-align: right;">Page 365</p> <p>1 appropriate power, we'd need larger studies. 2 DR. PROWELL: I think part of what made that 3 trial successful was the fact that they were going 4 in very refractory patients, so those were people 5 who had had I think at least 3 lines of therapy, 6 but the median was 5. So these were patients who 7 really had a very poor prognosis for metastatic 8 breast cancer, and overall survival was the 9 endpoint.</p> <p>10 I think that was a very pragmatic clinical 11 trial where you said, look, this is what's going to 12 happen, is you're going to give them either 13 capecitabine, or this, or this, or this, or 14 whatever the whole list of drugs that were in the 15 menu that one could choose from for treatment of 16 physician's choice.</p> <p>17 One thing that we've considered when we look 18 at trials using treatment of physician's choice as 19 a control arm is that you have to choose the 20 treatment of physician's choice before the 21 randomization. That may introduce some complexity 22 when you're talking about a brain mets trial that</p>	<p style="text-align: right;">Page 367</p> <p>1 Nancy's points about which kind of buckets of 2 clinical trials we have and which endpoints we 3 choose. I really think, even within brain 4 metastases specific clinical trials, we actually 5 should allow for different endpoints in case you 6 have IO versus non-IO. Even thinking about being 7 pragmatic and combining with SRS, SRS plus IO may 8 actually modulate the response, and you may have 9 longer term outcomes just because you added SRS 10 6 months later or even 3 months later.</p> <p>11 So we do need to kind of think about the 12 quality of the response to the immunotherapy and 13 use as compared to a targeted therapy.</p> <p>14 DR. MARGOLIN: I think sometimes the more 15 brilliant and the more creative at trial is the 16 less practical it's going to be for an approval 17 endpoint, but it's still a great comment.</p> <p>18 DR. TAWBI: Sort of a constant debate --</p> <p>19 DR. WEN: One final comment from Caroline.</p> <p>20 DR. CHUNG: I just want to make a comment 21 that we've mentioned a number of times that 22 composite endpoints would be really helpful in</p>
<p style="text-align: right;">Page 366</p> <p>1 isn't present necessarily in a conventional 2 metastatic breast cancer trial. We can maybe talk 3 about that.</p> <p>4 I'm not a neuro-oncologist, though I'm 5 sitting up here half the day. But the 6 neuro-oncologists would be the better ones to 7 really comment on that issue of the feasibility of 8 selecting that standard therapy before 9 randomization.</p> <p>10 DR. SUL: I think that also kind of goes 11 back to your earlier question about how much can we 12 dictate what goes on in a clinical trial. I think 13 the more options you have -- A, the more difficult 14 it is for physician's best choice, the more 15 difficult it is potentially to interpret that data. 16 It's also harder to design the trial to say you 17 have to choose from these two or three. But I 18 think that those are definitely things to consider, 19 that could be considered as potential control arms.</p> <p>20 DR. WEN: Dr. Tawbi?</p> <p>21 DR. TAWBI: Hussein Tawbi, MD Anderson. I 22 actually just wanted to follow up on Kim and</p>	<p style="text-align: right;">Page 368</p> <p>1 developing a surrogate that is a composite that 2 reflects both patient function as well as the 3 imaging response, et Cetera. I think the one thing 4 that I would propose that we could potentially 5 agree to do today is I think most of us would know 6 which of those endpoints that we would want to 7 include in most brain metastases trials.</p> <p>8 I think, to sort of echo Ben's message 9 around standardization, if we can actually 10 standardize which key endpoints we will include in 11 every brain metastasis trial, we can 12 actually -- we're in the modern era, as Paul 13 mentioned, using technology to our benefit, and I 14 think that we're in the modern era where we can use 15 computational oncology. We can use big data 16 approaches. We have electronic health records that 17 will allow us to bring this data together from 18 multiple trials.</p> <p>19 So it's not necessarily a retrospective 20 meta-analysis, but if we're actually collecting 21 standardized structured data across these trials, 22 we can actually start to not necessarily create</p>

<p style="text-align: right;">Page 369</p> <p>1 definitive conclusions, but we will actually 2 develop meaningful data-driven hypotheses about 3 surrogate endpoints that we can validate in future 4 trials. 5 Until we actually come to that consensus of 6 which of those structured endpoints we're going to 7 include in every brain mets trials, that just 8 wouldn't happen. But I think that would be a 9 meaningful conclusion, or meaningful product from 10 this meeting because I think we're all very 11 motivated to do it. There's going to be many 12 different trials that are going to come down the 13 pipeline, but if we can actually collaborate and 14 actually cohesively come up with a list of specific 15 endpoints we want to include, we could go a lot 16 further along in the long run. 17 DR. LIN: I totally agree, and just as an 18 example, even just for imaging, which we think is 19 very simple, or maybe not so simple, RECIST and 20 RANO are in a collaboration to actually -- and 21 EORTC is funding the data center to pull in 22 actually radiology imaging across multiple brain</p>	<p style="text-align: right;">Page 371</p> <p>1 Some collected 10. Some collected volume only. 2 Some collected linear dimension only. 3 I mean, the data itself is a mess, and then 4 you can't actually combine any data sets. You 5 actually have to start from scratch, go to the 6 original imaging, and do it all over again. So I 7 think if we maybe learn from that and do it better, 8 we can do better in the future. 9 DR. CHUNG: I think we can do it over and 10 over again more easily because we now have 11 automated methods of reanalyzing the data. So if 12 we build the algorithms, we can evaluate across 13 studies to see whether these measurements that 14 we've done manually versus in an automated way 15 fashion really agree. 16 DR. WEN: Thank you. 17 DR. AMIRI-KORDESTANI: Thank you. I just 18 wanted to actually make a clarifying comment. I'm 19 sorry. I forgot to introduce myself earlier. My 20 name is Laleh Amir. I'm a hematologist/oncologist 21 at the Division of Oncology Products I. 22 We have two pathways for approval. And as</p>
<p style="text-align: right;">Page 370</p> <p>1 metastasis trials. We're finalizing the legal 2 language of the request letters, and many of you in 3 the audience may start getting these letters asking 4 for your trial data to be able to answer some of 5 these questions. 6 The reason that we actually have to pull in 7 all the primary imaging data is that 8 unbeknownst -- I didn't realize this, but when the 9 RECIST criteria were developed, nobody pulled in 10 scans, they just pulled in the case report forms, 11 because everybody basically around world collected 12 the target lesions the same way. They measured 13 them the same way. They did them all on CT scans. 14 So no one ever had to do primary image analysis. 15 They just took the data, and they rerun it a bunch 16 of different ways, and that's why we look at 2 17 target lesions and not 5 target lesions, et cetera. 18 You can't even do that with just the imaging 19 of brain metastasis trials because everybody 20 collected a different way. They did different 21 scans. Some of them did MRIs; some of them CTs. 22 Some collected 5-target lesions. Some collected 2.</p>	<p style="text-align: right;">Page 372</p> <p>1 you know, the accelerated approval pathway 2 basically relies on an endpoint that is not really 3 a validated endpoint, and it doesn't need to show a 4 direct clinical benefit. So basically, it doesn't 5 really need to have a surrogate endpoint that is 6 already validated. As long as you come in and 7 basically discuss it with the FDA and the endpoint 8 is appropriate for that patient population, We 9 actually accept that for an accelerated approval 10 pathway. 11 That goes back also to the other comment 12 that was about in a single-arm trial like a 13 response rate be acceptable? Yes. We have 14 actually approved many drugs only based on a 15 response rate, even as a regular approval more 16 recently. So yes, it could be accepted. It really 17 depends on -- we look at, for example, duration of 18 response. We also look at what is available 19 therapy for that patient population. In a totally 20 refractory patient population that has nothing 21 available, it sounds like it should be acceptable. 22 So I really encourage, actually, that if you</p>

<p style="text-align: right;">Page 373</p> <p>1 see some encouraging results, like even an 2 intracranial response rate when the drug is 3 actually controlling the disease also outside, you 4 just come in and actually bring the results in 5 because, really, we like to see those studies 6 happen, and it may actually be adequate for an 7 accelerated approval, and then we can strategize 8 and design it more like a confirmatory study so 9 that actually the benefit could be later on proven 10 in a more randomized fashion if it is necessary.</p> <p>11 Sometimes actually, more recently, because 12 of some scenarios that you couldn't even do 13 randomized trials, we may actually not even require 14 that. So it really depends on the context, as was 15 mentioned by many of the colleagues here. That's 16 basically what I was adding.</p> <p>17 DR. WEN: Thanks so much.</p> <p>18 I want to thank the panel for the excellent 19 discussion.</p> <p>20 DR. AMIRI-KORDESTANI: Did you want to ask 21 me a question?</p> <p>22 DR. WEN: I think we're going to have to</p>	<p style="text-align: right;">Page 375</p> <p>1 They have been doing some excellent work that's 2 very complementary to all of this discussion, so 3 we're going to take a few minutes -- just a few 4 minutes, you guys -- to talk about it.</p> <p>5 Presentation - Ralph DeVito</p> <p>6 MR. DeVITO: Everything's running very 7 smoothly. Thank you, Wendy. Thanks to David, the 8 National Brain Tumor Society, for the FDA for 9 convening this group. Great conversation; just 10 absolutely wonderful.</p> <p>11 I am Ralph DeVito, CEO of the American Brain 12 Tumor Association. Nicole Willmarth is our chief 13 mission officer. We'll take just a few minutes 14 with a few slides to tell you about some work that 15 really began before I started. I've been on the 16 board about a year with ABTA, and they had 17 envisioned a real in-depth, survey-based analysis 18 of the brain mets issue.</p> <p>19 So there is a brain metastasis issue at 20 ABTA, in coordination with others, that has been in 21 effect for a while. So we just wanted to quickly 22 highlight it. I'll give an overview, and then</p>
<p style="text-align: right;">Page 374</p> <p>1 move on.</p> <p>2 MS. SELIG: I'm going to propose the 3 following. We are coming to the end. Patrick and 4 Joohee are going to have some comments also at the 5 end. I wanted to give you both a chance on this 6 panel to make any kind of final comments about this 7 discussion. Then we have a 10-minute brief 8 presentation from the American Brain Tumor 9 Association, one of the sponsoring organizations, 10 and then some closing comments.</p> <p>11 Would all of you just stay there so that we 12 just can keep going, if you don't mind, and then 13 you don't get to leave early. You have to stay and 14 listen to the ending comments, too.</p> <p>15 Joohee, Patrick, did you want to make any 16 comments now or do you want to --</p> <p>17 DR. WEN: Maybe in the interest of time, 18 we'll do it --</p> <p>19 MS. SELIG: Contemplate them. Okay.</p> <p>20 We now have Ralph DeVito and Nicole 21 Willmarth from the American Brain Tumor 22 Association, one of the sponsoring organizations.</p>	<p style="text-align: right;">Page 376</p> <p>1 Nicole will talk a little bit about some 2 preliminary high-level findings and then some next 3 steps. I also want to put a plug in for the SNO 4 brain mets conference in New York this August. 5 This should be a pretty exciting session, and it's 6 wonderful to see this issue being given great 7 in-depth focus.</p> <p>8 Let me go to the first slide. Let me just, 9 in the interest of time, skip ahead to show you our 10 collaborators, our science, our clinicians, our 11 patient advocate that's helped us with the survey 12 development. We have a third-party vendor that's 13 been working with us. Nicole and her team have 14 been working hard, and we have moved through a lot 15 of our work.</p> <p>16 We're going to do three panels of surveys. 17 We have already surveyed over 200 patients, we have 18 surveyed over 200 caregivers, and our next step is 19 to survey over 200 oncologists. With that data, 20 we're going to be developing new programs and new 21 services. And I do want to say that currently the 22 ABTA is providing high-risk, innovative research</p>

Page 377	Page 379
<p>1 that we're doing in this area, and we're also 2 offering currently to patients brochures and 3 information, webinars, and other information today. 4 With these findings, there's so much more that we 5 and you can do to serve patients far more.</p> <p>6 Nicole?</p> <p>7 Presentation - Nicole Willmarth</p> <p>8 DR. WILLMARTH: Thank you, Ralph. And I 9 also want to second his thank you to the FDA and 10 for the National Brain Tumor Society bringing 11 everybody together. I think bringing all these 12 perspectives in one room today to have these 13 discussions is so important. I feel humbled 14 listening to the conversations that we've had 15 today. I've learned so much and really appreciate 16 everybody being here.</p> <p>17 I think we've been noticing a lot of themes 18 today, one of which is hope and making sure that we 19 keep that in the back of our minds for the patient 20 perspective. But then also I think there's a theme 21 of considering that we're treating a patient with 22 brain metastases and not just treating the brain</p>	<p>1 To summarize just high level, the patient 2 survey, this again won't come as any surprise 3 probably to most people here, but a diagnosis of 4 brain metastases was a surprise to 9 in 10 of the 5 patients that we surveyed. Their top concerns upon 6 learning of their diagnosis was the impact on their 7 quality of life as well as the likelihood of 8 treatment success. I think this goes hand in hand 9 with what was discussed today, is you can't really 10 separate the importance of those to a patient.</p> <p>11 Those are really both top priorities.</p> <p>12 Also, what came out of the survey was that 13 fewer than half sought a second opinion, and they 14 really felt that -- actually most said that they 15 felt that they received enough information from 16 their oncologist, and 81 percent actually were 17 diagnosed with brain mets from the same doctor who 18 diagnosed their primary.</p> <p>19 So what this suggests is that they didn't 20 really seek out a second opinion as to what type of 21 treatment to pursue for the brain metastases, so I 22 think there's a lot we could learn there.</p>

<p style="text-align: right;">Page 381</p> <p>1 profile -- had a personal relationship with the 2 patient. The patient was in most cases their 3 parent. Caregivers expressed many of the same 4 reactions to learning of the diagnosis as the 5 patient's did. Many expressed shock and 6 depression.</p> <p>7 Over 6 in 10 said they were familiar with 8 brain metastases before becoming caregivers, 9 however, that means about 40 percent were not 10 familiar with brain metastases.</p> <p>11 Caregivers were most concerned about the 12 effect on the quality of life of the person under 13 their care and the likely success of treatments, 14 which mirrors what the patient perspective was as 15 well. And nearly 9 in 10 caregivers said that 16 there was an emotional impact on them as a result 17 of caring for a brain metastasis patient.</p> <p>18 So quickly to wrap up, because I know I've 19 already gone over, for the next steps, as Ralph 20 mentioned, we would like to also do an oncologist 21 survey, so we're currently developing a survey to 22 understand from the doctors who treat these brain</p>	<p style="text-align: right;">Page 383</p> <p>1 Summary and Next Steps 2 DR. WEN: I wanted to thank everybody for 3 coming today. It's been a really great discussion. 4 We're so lucky to have all of you here. I think 5 today we heard hopefully things that will move us 6 closer to significantly increasing the 7 participation of brain metastases patients both in 8 all oncology trials and also the development of 9 more trials specifically for brain metastases.</p> <p>10 I think Nancy gave a really nice talk 11 earlier about perhaps the limited importance of 12 blood-brain barrier penetration for a therapeutic 13 effect. Perhaps it's more important for 14 prevention, but that's something that should lower 15 the barrier of drugs being evaluated for brain 16 mets.</p> <p>17 I think ideally, all patients with brain 18 metastasis should be considered eligible for 19 oncology clinical trials, whether they should have 20 treated lesions or whether we would include 21 patients with small asymptomatic lesions where they 22 could be on drug for a month or two and closely</p>
<p style="text-align: right;">Page 382</p> <p>1 metastases patients, from their point of view, what 2 the journey is like when treating these patients. 3 That way we can understand better if there's 4 agreement or disagreement and the knowledge or 5 perception from the patient perspective and the 6 oncologist perspective.</p> <p>7 Once all the survey results have been 8 compiled and analyzed, we hope to present the data 9 at the Society for Neuro-Oncology meeting in 10 November, so stay tuned for that. That's it.</p> <p>11 (Applause.)</p> <p>12 MS. SELIG: Thank you so much. It's really, 13 really important to understand the patient 14 perspective and the patient experience, so thank 15 you guys.</p> <p>16 We're going to ask Joohee and Patrick, our 17 fearless co-chairs, to make some wrap-up closing 18 comments and in particular what you heard that you 19 think is actionable, and then the final uh, 20 next-steps discussion will come from David Arons, 21 and then we will conclude and get everybody on 22 their way. Thanks for sticking it out.</p>	<p style="text-align: right;">Page 384</p> <p>1 monitored, and taken off it if there's progression. 2 I think we need to also think about whether 3 we should recommend routine adoption of the Friends 4 of Cancer Research recommendations and the RANO 5 recommendations for eligibility into trials. I 6 think there needs to be guidance on eligibility to 7 reduce the restrictions, including time from 8 radiation and a number of other factors. 9 In terms of the trials specifically for 10 brain metastases, I think we heard that potentially 11 in some situations, objective response rate might 12 be a path to approval, and if we use that, is the 13 RANO BM criteria the one that we should use instead 14 of all these variations that are still being 15 considered in different trials. There was also 16 discussion on the need for randomization for the 17 more definitive trials and the challenges of the 18 control arm. 19 Going forward, there are some things that 20 clearly we need to do. We need a standardized 21 brain metastases imaging protocol that will be 22 similar to the one that's been used for</p>

<p style="text-align: right;">Page 385</p> <p>1 glioblastoma but with some minor differences. 2 Hopefully, that would be used for all brain 3 metastases studies so that there's less 4 variability. 5 I think we need guidance on eligibility 6 criteria for these trials on the optimal endpoints, 7 as Carolyn discussed. I think we need to 8 continue -- this is an audience that 9 really cares about this issue, but there's a whole 10 world out there that is still thinking several 11 years back where brain metastases patients should 12 just be excluded from all these trials, and we need 13 to educate them and spread the message. 14 So going forward, I think SNO and RANO are 15 definitely committed to doing this and partnering 16 with all with you, and our conference in August is 17 one step in this direction. So thank you all so 18 much for coming today. It's been a really 19 important step forward, and we're grateful to all 20 of you. 21 DR. SUL: Thank you, Patrick. 22 I'm going to actually start with my thank</p>	<p style="text-align: right;">Page 387</p> <p>1 standardization really makes interpretation of 2 information much easier, and it's essential to get 3 a clear picture of what's going on; so that's one 4 thing. 5 The second is these different baskets of 6 trials, trying to separate out the populations. We 7 sort of touched on that, but we didn't get to 8 really delve into how we would do that. So how do 9 you separate out the untreated versus the treated 10 patients? When do we decide that SRS should be the 11 point at which patients are not included on trials? 12 What's the, quote/unquote "washout period"? I know 13 that Dr. Gondi doesn't like that term, but we're 14 just going to use it because it's familiar. 15 Timing of therapy sort of ties in with that 16 as well because there are therapies like radiation 17 therapy, which are not really regulated in the same 18 way by FDA but are still considered standard of 19 care. So we need to figure out how to smartly 20 include those as well. 21 One comment I did want to make, because it 22 came up a couple of times, is it seems that people</p>
<p style="text-align: right;">Page 386</p> <p>1 yous first because I know I'll run out of time and 2 then I'll forget to thank people. I want to thank 3 everybody who participated in the planning and also 4 in the development of the workshop. I also want to 5 thank all the patients and the patient advocates 6 and representatives who came here today to give a 7 voice to all the patients who enroll on these 8 studies that we review but we don't actually get to 9 meet the patients face to face. 10 I also want to thank my FDA colleagues for 11 participating and helping, and also for having 12 discussions with me about a lot of these issues, 13 sometimes heated, sometimes controversial, and 14 really being interested in this topic, so I want to 15 start with that. 16 I think a couple of the common or recurring 17 themes that I've heard today, one of them is 18 standardization, whether or not that's an approach 19 to how we use steroids, or decide on radiation, or 20 what studies should be included, or whether it's an 21 imaging protocol. I want to go back to what Ben 22 Ellingson said it at the very beginning, that</p>	<p style="text-align: right;">Page 388</p> <p>1 are really afraid of seizures because people kept 2 saying, well, somebody had a seizure. This is 3 going to circle back to having a multidisciplinary 4 approach. 5 Neurologists in general are not afraid of 6 seizures. I mean, we see patients have seizures. 7 Status epilepticus, that's a different story. And 8 not to say that it's not serious, but it shouldn't 9 be the reason why you don't want to develop a drug 10 because guess what? We have great treatments for 11 seizures. We don't have great treatments for brain 12 metastases. So don't let that be the reason why 13 you don't want to move forward with development, 14 and ask the neurologist and the neuro-oncologist to 15 collaborate with you on these studies to make it 16 safe to include these patients and to evaluate 17 them. 18 DR. WEN: Thank you. 19 MR. ARONS: Thanks Patrick and Joohee. 20 Wendy told me to come here so that's what I'm 21 doing. I generally do what I'm told. 22 Thank you all for being here today. Thank</p>

<p style="text-align: right;">Page 389</p> <p>1 you so much to the FDA and to all the partners and 2 experts that came together. I'll have a few more 3 thank yous, but just a few points that I wrote down 4 in my notes from a patient advocacy perspective. 5 We started out the day with a theme of hope, 6 and Mr. Queen brought that. And I really want to 7 thank him for starting us out with the perfect 8 theme of the day and his story. But as we know, 9 hope is not a strategy, but what hope can do is 10 bring a sense of determination to create one. And 11 we certainly started to build the ingredients for a 12 realistic strategy to move forward against this 13 disease today in this room. 14 We recognize this is a very vulnerable 15 population, a population at great risk, but yet 16 it's very numerous. So what we began to do today 17 was to take a situation that's really a problem, 18 and try to figure out how can we use this 19 population and use what we know as assets to flip 20 this on its head and say, what can we do that can 21 work. 22 We talked about some really big points from</p>	<p style="text-align: right;">Page 391</p> <p>1 to see in new medicines, new therapies, new devices 2 for that matter. 3 So we should try to drive a truck through 4 this opportunity and come up with new medicines, 5 new therapies that both extend survival but really 6 reflect the kinds of domains and general concepts 7 that that patients wants, like what was said by a 8 patient earlier. She wanted to retain her brain's 9 functioning, period, end. She wanted to keep her 10 cognition. That would be really awesome if we 11 could see more therapies do that. 12 There's great traction to move forward in 13 this era of precision medicine with basket trials 14 and even adaptive trial design that is very patient 15 focused, and that could be done in this disease. 16 I'm agreeing with all the action items and ideas 17 that Patrick and Joohee mentioned but just wanted 18 to add those. 19 I'm hopeful that the group of nonprofit 20 organizations listed up there will all stay 21 together now kind of as a loose coalition to see 22 this through the next phase, which is getting the</p>
<p style="text-align: right;">Page 390</p> <p>1 a patient advocacy perspective; include patients in 2 trials, period end. Let's just start including the 3 patients in the trials. No more excuses, no more 4 barriers, let's move forward and begin to do that. 5 And if there's a reason against it scientifically 6 or medically, figure that out, but the default 7 status should be include patients in trials. 8 Dr. Brastianos brought up a very important 9 point scientifically, and that is, is there 10 biological considerations that make this disease 11 different from the systemic disease, that 12 ultimately not really -- her point was not 13 harmonized throughout the day, so there seems like 14 there's going to be more work to figure out when is 15 this disease uniquely different, warranting a 16 different kind of trial, different issues than say 17 the regular disease outside of the brain. 18 The FDA opened up a tremendous opportunity 19 for science today, and Paul Kluetz and others 20 talked about it, is the opportunity to develop 21 patient-focused endpoints and clinical outcomes 22 assessments that really reflect what patients want</p>	<p style="text-align: right;">Page 392</p> <p>1 summary together, working collaboratively with the 2 FDA on a guidance document. If the FDA wants any 3 help from all of us as a team, we're happy to do 4 it. And then to try to take this forward as a 5 scientific and product development agenda into the 6 future. 7 To the companies in the room, really, thank 8 you for being here today. That's huge, and we're 9 really grateful for your expertise. And as you 10 think about product development as a company and 11 the investigators thinking about product 12 development in investigator-driven trials, I think 13 all the nonprofits and patient advocacy groups here 14 would like to be of assistance to you to discuss 15 how to do this together and to reduce the barriers 16 to making new therapies possible. 17 Finally, I get to echo what Joohee said. 18 Thank you to the patients who have been here today 19 who have spoken up and who are adding so much to 20 this discussion. So thank you again, really 21 appreciate everybody who was here today and 22 everybody who patched in by the webcast for that.</p>

Page 393

1 Thank you to all those who helped make the
2 technology possible. Thanks again. Appreciate
3 your time.

4 (Applause.)

5 (Whereupon, at 3:57 p.m., the meeting was
6 concluded.)

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[60:14,15;64:8;71:5, 10,13;73:1,15;131:9; 197:3;200:17;225:18; 254:15;286:6;312:17; 314:10;324:19;339:8; 362:22;375:10	accurate (3) 165:11;197:3; 349:16 accurately (5) 130:15;131:10; 164:21;165:7;220:14 achievable (1) 41:19 achieve (3) 32:14;116:4;187:21 achieved (2) 32:16;110:3 achieving (2) 21:11;22:11 acid (1) 137:15 acids (1) 137:17 academics (1) 272:18 Accelerate (2) 10:10;37:2 accelerated (8) 120:22;163:20; 164:7;172:5;351:22; 372:1,9;373:7 accelerating (1) 245:3 accept (3) 205:20;224:22; 372:9 acceptable (7) 144:1;170:1; 187:15;18;305:4; 372:13,21 accepted (3) 179:12;205:12; 372:16 access (16) 59:3,7;65:17;81:8; 92:11;139:6;176:12; 187:19;188:14;230:8; 286:18;321:11; 341:19;343:1;347:9; 364:5 accessible (3) 43:17;185:6;221:10 accident (1) 43:21 accomplished (1) 315:10 according (1) 9:9 account (3) 159:16;173:9;363:5 accountability (3) 349:12,15;350:7 accrue (2) 72:20;277:5 accrued (1) 72:14 accuracy (1) 165:9	actively (7) 48:14;74:13;244:5; 260:15;300:5;302:3; 359:3 activist (1) 178:10 activities (2) 173:13;271:13 activity (50) 26:2;29:14;32:8; 36:10;51:17;52:10; 53:13,17;57:2;59:13; 63:4;78:21;99:7; 100:3;104:1;105:4,14; 107:1,10;111:13,21; 141:19;142:6,21; 143:6,11,12;188:16; 191:11;192:1,2,7; 194:2;208:5,8;227:11, 14;270:3;271:13,18; 272:2,8;273:10; 277:13,15;278:4,13; 286:11;289:5;340:17 actors (1) 236:14 actual (9) 24:5;52:9;94:5; 145:18;155:10; 194:22;250:18;287:7; 362:11 actually (258) 20:10,13;21:7,8; 24:7,10;27:4;29:3,6, 16,19,20,21;31:10; 32:18;33:18;34:4,20, 21;35:8,12,18;37:8,9, 10,12;39:5;40:22; 43:19;46:5;47:9; 48:17;49:9,13,18; 51:16;52:15;54:17; 55:6,8,20;56:5,11; 57:4,5,6,15;58:5,8,8; 59:20;60:6,19;61:14; 62:22;63:1,9;67:18; 70:3,5,9,10;71:14,20, 22;72:19;73:8;74:15; 77:5,13;80:22;82:9; 88:1;92:5;93:13,16; 95:3,11,17;96:22; 97:4,6;103:2;106:2; 110:10;112:14; 116:12,13,15;118:6; 126:5;135:2;136:17; 140:12;142:13;147:7, 9;148:10,11,21; 151:18,22;152:18; 153:12,13;155:6,11, 15;158:6;165:1,3; 166:3;186:4,7,9,11, 16;187:3,16,22;188:2, 10:2;11:2;17:15;	6,13,17;189:5;191:18, 21;195:1,2;196:8,9, 13,14;202:11,21; 203:2,13,17;207:9; 208:1;210:20;212:19; 213:19;215:7,17; 216:20;218:13; 224:11,12;226:8; 229:3;241:15;243:2; 248:21;249:6,10,14, 15;250:4,19,20,22; 251:2,9;255:12; 256:13;262:9;264:5; 265:4;267:14;271:3; 272:3;274:17;277:17, 18;278:10,12,14,21; 282:8;283:2,15,20; 284:9;286:5,16,21; 287:17;288:12; 291:13,16;292:10; 294:5;296:12;298:13; 299:6;302:14;307:5; 308:5,22;309:9,10,13; 311:20,21;314:14; 315:22;316:18;320:4, 14;322:15;323:4; 324:6;325:16;336:3; 338:11;340:12; 345:17;346:4;347:12, 18;348:3;353:8,11; 355:14;356:9;357:7; 363:18;366:22;367:4, 8;368:9,12,20,22; 369:1,5,13,14,20,22; 370:6;371:4,5,18; 372:9,14,22;373:3,4,6, 9,11,13;379:14,16; 385:22;386:8 adapt (1) 331:3 adaptive (2) 304:11;391:14 add (37) 25:12;43:4;56:22; 59:9;62:12,21;63:18, 20;67:21;71:4;73:2; 76:17;83:1;97:5; 134:14;137:1;144:2; 200:16,18;203:22; 212:6;226:1;228:3; 252:4;277:5;298:1; 304:5;316:16;319:17; 323:20;325:20;329:8; 332:13,22;335:3; 346:15;391:18 added (7) 61:1,4,9;133:5,13; 190:13;367:9 adding (4) 61:5;203:6;373:16; 392:19 addition (11) 10:2;11:2;17:15;
---	---	---	---	--

22:17;27:14;28:12; 131:3;193:19;196:12; 200:19;360:2	109:4;136:20;156:3 advantage (4) 112:10;328:18; 359:21;364:16	136:1;137:6,18; 141:16;142:16; 147:18;151:9;158:22; 162:12;163:9;165:3;	345:20;348:16; 354:21;355:6,16; 357:8;368:5;369:17; 371:15	301:21 allow (37) 44:13,15,16;45:21; 62:9;75:8;77:13;
additional (14) 10:17;61:4,5;88:18; 94:16;97:5;114:16; 132:5;133:14;137:5; 152:7;166:19;187:11; 195:4	adverse (1) 33:12	167:3;169:5,8;183:15; 194:10;199:7;204:1;	agreed (2) 247:7;276:12	78:21;79:16;110:17; 116:17;136:5;150:22;
additionally (1) 362:14	advise (1) 243:22	205:9;208:3;210:21; 218:4;224:11;230:22;	agreeing (1) 391:16	202:22;203:21; 204:12;229:7;236:17;
address (26) 17:14;26:16;39:2; 66:8;82:7;19;83:4; 149:14;181:13; 197:13;202:12;203:9, 12;252:6;257:21; 261:3;263:16;264:4; 277:16;286:4;287:18; 307:20;308:21; 311:10;356:17,19	advocacy (7) 301:8,9,11;378:19; 389:4;390:1;392:13	239:22;241:15,15; 242:6;250:9;262:3; 263:8;266:16;272:21; 276:2,8;293:21;305:7;	agreement (5) 199:18;238:5; 252:4;341:17;382:4	251:9,10;267:17; 279:20;280:6;285:3,4;
addressed (5) 17:12;120:14; 124:12;230:9;233:7	advocate (9) 12:3;156:1;178:5, 10;179:11;243:10; 269:6;301:7;376:11	306:7,15;339:3,17; 362:22;371:6,10; 379:2;392:20;393:2	agreements (1) 200:3	287:3;303:18;312:4; 321:19;322:16;
addresses (1) 261:12	advocates (5) 9:15;157:18; 300:19;344:22;386:5	307:19;77:11;100:3; 104:5;105:5;115:22;	agrees (1) 242:12	329:19,22;336:8;
adds (1) 344:19	advocate's (1) 143:8	116:3,15;389:12; 390:5	ahead (9)	356:16;364:5;367:5;
adeno (1) 93:4	affairs (3) 181:9,17;320:19	390:5	368:17	368:17
adenocarcinoma (2) 101:10;102:15	affect (2) 116:13;289:10	391:19;102:17; 103:2;151:17;217:12	allowed (13)	370:19;98:14;
adequate (6) 164:2;303:12,15,22; 305:2;373:6	affecting (1) 226:19	279:15	152:22;197:8;228:2;	216:13;223:19;
adequately (3) 240:19;288:5; 303:18	affects (1) 107:22	279:15	247:7;249:1;262:1;	250:10;265:18;
adjunctive (2) 121:4;338:4	affiliation (2) 197:8;248:20	199:15,19;253:17	376:9	278:22;285:11;317:9;
adjust (1) 202:21	afford (2) 213:11;344:16	agenda (1)	AHLUWALIA (8)	319:2;322:15;329:15;
adjuvant (1) 112:3	affordable (1) 350:9	392:5	46:18;19;54:15; 62:12;73:2;75:20;	341:20
administer (1) 354:16	afIELD (1) 46:16	agent (15)	123:17;140:1	allowing (8)
administered (1) 219:12	afraid (8) 75:15;157:13; 249:14;306:13,14; 354:4;388:1,5	41:11;51:22;55:9; 63:2;68:3;119:10;	aiming (1)	69:2;181:18;
Administration (1) 10:7	afternoon (7) 80:19;158:5; 160:10,13;161:22; 233:16;251:15	127:15;172:11;192:2; 197:16;270:2;273:12;	162:4	215:22;258:3,17;
administrator (1) 244:20	again (117) 14:2;20:8,20;21:2,3, 14,15,18;22:6;23:5, 21;24:10,16,19;25:1, 8,15,20;26:18;29:6, 11,21;30:3,8;31:10;	302:20;318:13;336:15	ain't (1)	288:17;290:19;347:9
adopted (3) 69:19;322:3,12	ago (15) 32:7;33:3;34:2,10,13, 16;35:18;40:14;	agents (28)	Akiko (1)	allows (6)
adoption (1) 384:3	44:20;45:7;48:5; 51:17;53:14;57:1,3; 59:10;61:18;64:1,9; 68:11;72:8;74:3;76:9;	108:6,14;109:9; 110:5,8,12;152:4;	106:10	71:9;79:15;137:7;
adults (1) 252:13	81:11;85:9;88:11; 95:6;96:1;99:7;	179:4;183:13;331:14;	Al (1)	267:1;290:20;335:18
advance (4) 10:1;11:7;148:14; 268:7	102:15,21;104:21; 106:14;107:13;	332:2,7	298:5	alluded (5)
advanced (6) 85:17,21;86:4;	113:11;116:11;117:5; 124:2;126:22;132:1,5; 133:2,14;134:7;135:7;	ALEX (1)	Alazor (1)	48:20;55:4;66:9;
		109:1	102:8	133:9;274:7
		aggressive (1)	alexander (1)	almost (11)
		35:1	221:18	24:11;31:21;33:6;
		aggressively (1)	algorithm (3)	53:1;57:12;68:8;
		300:6	171:18;222:22;	102:13;105:8;118:1;
		ago (15)	354:15	189:18;274:19
		13:1;15:13;38:2,2;	algorithms (1)	alone (5)
		85:1,3;128:10;185:20;	371:12	9:18;49:20;194:1;
		199:17;238:9;255:6;	ALK (12)	239:8;343:12
		256:4;276:6;281:6;	80:19;85:22;	along (11)
		322:8	102:20;103:1;107:5;	76:3;111:4;158:16;
		agree (31)	108:6;109:2;110:14;	197:13;228:14;230:6;
		62:12;71:13;	151:18;333:12,14;	257:13,22;327:2;
		142:16;205:11,13;	358:22	369:16;380:1
		224:11;227:17;230:4;	ALK-driven (2)	alteration (1)
		267:3,17;269:21;	28:18;29:17	90:11
		270:6;274:17;275:18;	ALK-positive (1)	alterations (10)
		276:2;298:6;304:7;	333:17	87:10;89:2;90:17;
		305:1;323:21;324:19;	Alliance (9)	20:91:1;93:10;94:16;
		326:19;332:13;	10:12,14,15;88:3;	97:10,15;124:3
			96:11;156:2;243:20;	altered (1)
			311:11,20	183:15
			Alliance's (1)	alternative (3)
				196:18;219:7;
				337:12
				alters (1)
				358:17
				although (16)
				19:9;31:15;106:8;
				15:10;8:11;116:21;
				117:10;128:13;
				146:15;168:22;201:6;

259:5;306:6;307:10; 322:9;336:19	294:6 Anders (27) 96:13;162:15; 175:8;189:9;190:11; 194:19;197:7;198:9; 200:8,17;202:9; 204:20;205:22; 211:14;215:4;216:22; 219:19;221:15;224:9; 227:17,18;229:3,17, 18;363:11,11;364:12	105:2 Applause (20) 12:4;14:14;18:11; 20:2;37:4;41:7;98:2; 117:12;125:20;138:4; 139:12;175:6;181:7; 230:15;248:10; 312:18;316:8;319:22; 382:11;393:4	approve (1) 169:21 approved (24) 24:4;29:16;31:1,16; 53:2;96:8;111:5; 121:9;161:3;163:18; 171:12;174:12;180:4; 201:7;226:6;257:11, 21;285:22;286:9,16; 318:14;339:4;364:15; 372:14	259:16;261:10,10; 294:6;312:1;337:22; 341:8;351:10;352:21; 353:8;355:3;363:22; 364:8;368:9;370:11
altogether (2) 198:6;358:14			arriving (1) 245:17	
always (30) 19:16;30:16;37:19; 38:6;51:15;57:12; 60:6;94:10;174:3; 190:14;199:8;219:18; 236:2;244:21;249:20; 259:7;282:1;297:9; 306:8;307:14;313:22; 319:20;342:6;357:16; 359:19;361:19,21; 362:4;19;364:13			article (3) 128:10,12;270:7	
Alzheimer's (1) 282:14			artificially (1) 55:11	
amazing (4) 119:21;161:15; 249:8;328:15			Arvin (2) 186:2;189:17	
amenable (1) 335:7			Arvin's (1) 194:22	
amend (1) 274:4			ASCO (12) 16:7;61:20;62:2; 84:6;125:2,16;260:21; 322:1,8;348:2,5; 355:21	
American (6) 10:11;88:2;140:11; 374:8,21;375:11			aside (2) 38:5;187:22	
amino (2) 137:15,17			ask/don't (2) 76:1,18	
Amir (1) 371:20			aspect (6) 68:20;130:16; 131:1;148:18;185:9; 287:5	
Amiri (1) 260:21			aspects (5) 19:21;126:15; 137:2;191:7;361:15	
AMIRI-KORDESTANI (4) 37:6;58:3;371:17; 373:20			assay (5) 165:10;166:1; 169:9;171:18;174:21	
among (1) 103:17			assays (1) 227:5	
amongst (2) 36:2;175:12			assert (1) 205:11	
amount (1) 213:21			assess (6) 13:14;207:11; 208:2;221:6;234:9; 330:10	
amplification (1) 93:1			assessed (3) 59:6;68:16;109:11	
amplifications (3) 90:19;91:5,5			assessing (3) 104:18;120:2; 291:13	
analysis (9) 87:13;93:15;102:9, 14;239:21;261:16; 288:5;370:14;375:17			assessment (19) 35:4;42:19;53:19; 126:3,13,21;127:1; 133:16,17;134:8; 159:14;160:17; 177:18;203:8;234:9; 236:20;238:3,17; 239:3	
analyze (2) 198:7;235:20			Armstrong (4) 176:4,6;200:16,18	
analyzed (1) 382:8			aromatase (1) 247:1	
anatomic (2) 131:3;136:21			ARONS (6) 8:4,9;14:20;18:18; 382:20;388:19	
anatomically (2) 88:19;91:14			around (36) 36:16;42:4,4;49:21; 52:5;54:16;57:19;	
anatomy (2) 126:19;211:6			58:17;71:15;78:4; 98:11,12;100:12;	
ancestor (3) 89:10;90:6;92:20			128:19;185:18;195:5; 208:21;215:8;224:14; 232:10;250:13;	
and/or (1)			assessments (6) 185:18;237:12,14, 16;309:19;390:22	

392:14	aura (1) 92:22	168:3;175:18;194:5; 196:13;199:1;205:8; 207:4,22;208:3; 210:21;212:13; 215:21;217:1;220:2; 221:17;224:13;231:3; 232:5,10;239:22; 246:20;265:22; 266:12;279:18;287:6, 21;289:19;292:17,18; 293:4;296:22;297:9; 300:1;308:14;325:9; 328:3;339:1;345:6,19; 349:1;350:20;360:18; 362:6;366:11;372:11; 377:19;378:16; 385:11;386:21;388:3	390:4;392:15 barrier's (1) 145:1 basal (2) 153:21;170:20 Basch (1) 177:13 base (1) 80:22 based (29) 57:3;78:14;104:11; 118:20;132:1;134:4; 170:22;174:8,12; 175:13;182:19;184:5; 198:3;202:3;211:15; 235:3;250:17;254:3,5; 264:12;275:12;291:1; 302:4;312:9;322:8; 324:21;351:15; 364:15;372:14 baseline (10) 86:1;109:14,16,19, 21;129:9;215:9;237:2, 4,9 basically (18) 54:15,17;55:21; 71:21;72:10,12;77:2; 96:18;104:15;156:16; 238:4;327:6;334:3; 370:11;372:2,4,7; 373:16 basis (1) 77:3 basket (3) 356:11,17;391:13 baskets (1) 387:5 Baum (2) 310:5,9 Bayer (2) 10:18;181:10 be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)	30:6;40:18;186:16; 381:8 began (3) 39:20;375:15; 389:16 begin (7) 79:14;184:22; 242:11;261:17; 298:14;318:7;390:4 beginning (6) 51:4;83:19;184:13; 327:17;334:6;386:22 begs (1) 40:7 behalf (3) 14:16;186:5;345:7 behave (1) 299:16 behavior (1) 340:22 behind (4) 76:5;136:4;254:21; 274:16 behold (1) 179:3 believer (1) 138:18 belong (2) 260:10;284:3 Ben (6) 15:7;55:19;125:21, 22;182:17;386:21 benchmarks (1) 121:9 beneficial (4) 67:12;172:19; 218:17;225:20 benefit (65) 25:18;31:8;79:4; 162:21;163:2,11,12; 164:6,9,12,15;165:3, 14,16;167:15;168:2,4, 5,8;169:20,21;170:16; 174:8;177:22;182:3; 185:11;193:20; 208:10;209:14; 210:11;212:14; 214:12;215:19; 216:19;227:8,12,13; 235:4;236:3;237:8; 240:3,9,10;262:9; 264:22;288:3,6,8,13, 19;289:11,16;290:17; 304:17;336:18,20; 351:8,11,16;352:3,15; 358:17;368:13;372:4; 373:9 benefited (1) 20:21 benefiting (1) 33:22 benefit-risk (1) 188:10
athletics (1) 37:19	avenues (1) 13:13	bad (4) 75:15;308:6;327:1; 331:10	balance (3) 174:4;191:12;346:2	basket (3) 356:11,17;391:13
ATKINS (8) 194:21;197:5; 257:2,2;269:21;273:3; 275:21;357:8	average (1) 43:6	badi (1) 102:7	balancing (1) 207:13	baskets (1) 387:5
attempt (2) 111:7;129:11	avoid (2) 219:9;340:19	baked (1) 273:20	ball (1) 311:6	Baum (2) 310:5,9
attention (5) 41:17;158:18; 175:5;244:8;350:13	avoidance (3) 351:1,10,15	balance (3) 174:4;191:12;346:2	bar (1) 135:3	Bayer (2) 10:18;181:10
attractive (2) 126:20;364:4	avoiding (2) 214:18;340:21	barely (1) 220:8	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
attributable (1) 240:20	awesome (1) 391:10	baked (1) 273:20	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
attributing (1) 238:13	awful (1) 264:21	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
ATZBERGER (3) 221:18,19;224:8	awfully (1) 220:16	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
audience (30) 37:14;63:1;77:20; 96:13;100:4;106:10; 145:6;151:14;153:1,6; 155:21;190:8;208:13; 229:5;259:18;283:13; 293:5;297:16;298:1; 309:14;311:17; 312:13;313:4;316:7; 341:16;349:3;350:1, 13;370:3;385:8	axial (1) 130:10	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
audio (2) 105:6;113:16	back (76) 21:17;35:19;41:5; 47:8;48:1;51:5;58:3; 64:14;73:12;74:13; 75:11;81:16;88:7;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)
August (2) 376:4;385:16	back (76) 21:17;35:19;41:5; 47:8;48:1;51:5;58:3; 64:14;73:12;74:13; 75:11;81:16;88:7;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	barrier (68) 51:16,21;52:8; 54:10,13,16;55:3,7,12, 18,22;56:3,7,12,13; 57:22;94:11;99:6,10, 18;100:2,7;104:1,4; 105:4;106:20,22; 107:9,10,12,14,20; 108:8;110:3;112:1; 116:8;117:1;127:7,14; 133:10;139:16,20; 141:5,19;142:4,9; 143:3,7;152:9;160:4; 178:14;258:10;	be-all (1) 119:12 bear (3) 10:3;178:4;333:10 beat (1) 39:14 beautiful (2) 30:3;144:7 beautifully (1) 49:6 became (5) 29:1;39:14;21;72:5; 255:22 become (9) 15:8;123:4;135:14; 148:19;149:10; 186:21;238:12; 298:22;326:2 becomes (4) 48:7;192:22; 206:20;235:21 becoming (4)

benefits (6) 58:20;164:10; 165:6;191:9;356:1; 361:3	47:18;48:7;67:1; 122:4;132:8;169:15; 173:21;220:20;227:2, 3:255:15,19;281:6; 283:1;296:7;316:5; 324:20;333:16; 335:18;346:22; 368:15;389:22	341:20,22;351:3; 353:22;376:1;380:22 BLACKWELL (10) 255:1,1;266:2; 276:16;277:7;302:16; 303:1;304:21;305:1; 306:2	358:11 BM (7) 137:21;149:9,13,21; 150:14;322:8;384:13	34:6 Brain (669) 8:9;9:3,8,12,15; 10:10,11,13;13:4,9, 22:14;19;15:6,12,16, 18,21;16:3,8,17,19,20; 17:3,5,10,13,14;18:6, 8;19:1;21:4;22:5,16; 23:2;24:1,5,8,14,18; 25:1;26:17;28:3,20, 21:29;1,8,10,20;30:1, 15,20;31:5,6,18,20; 32:3,5,15;33:1,15; 34:17;35:8;36:2,12; 37:17;38:11,12,13,14, 22:40:4,16;41:13,15, 22:42:8,17,18;43:3,5; 44:7,14;45:3,4,5,46:2, 4,21,21;47:9,11; 48:14,19,22;50:10,10, 21:51:1,8,12;52:3,6, 10,16,17;53:3;54:12, 12,16,18;55:5,5,6,13, 15:56:5,16,18;57:5,8, 11,17;61:3,8,9;62:20; 63:3;66:3;69:11,15, 21:70:1;71:10,15; 72:16;74:2,17;76:12, 16,19;77:2,11,14; 78:4,13,15,22;79:3,9, 13,17,17;80:10,13; 81:8;84:1,19;85:13, 15,18,20,21;86:1,5,8, 11,18,21;87:1,3,8,10, 13,19,20;88:2,5,16,20, 21:89:3,9,12,15,17,20, 21:90:3,7,12,91:6,11, 13,15,18,21;92:8,15, 18,19,20;93:7,9,11,14, 17,19;94:5,8,16;95:5, 10,19;96:5,7,19,20; 97:1,9,11,13,17;98:10, 16,19;99:1,11,22; 100:15,21;101:7,11, 20:102:18;103:15; 104:13;105:5,9,11; 106:1,2,5,5,6,15; 108:17,20;109:5,7,12, 16,20;110:19;111:18; 113:4,5,7,10,20;114:8, 11,11,14,22;115:10, 20:116:1,13,18; 117:15;118:6,10,10; 119:1;120:1;121:2,11, 13;122:2,4,10,11,13; 123:1,5,8,9,16;125:10, 14,14;126:2,16;127:5, 6,12;129:11,14;130:9; 131:8,14,14,16; 132:13,21;133:22; 134:1;137:15,21; 140:6,11,18;141:3,5,9, 12,20;142:1,3,6,22;
Ben's (2) 149:8;368:8	283:1;296:7;316:5; 324:20;333:16;	276:16;277:7;302:16; 303:1;304:21;305:1;	BMS (3) 10:19;186:4,5	
berry (1) 56:12	335:18;346:22;	306:2	board (3) 223:15;224:2; 375:16	
Besides (2) 39:10;298:10	368:15;389:22		boards (1) 73:17	
best (22) 23:13;36:18;49:18; 52:15;101:17;102:21; 132:11;139:2,3;160:3; 205:5;227:5;270:20; 307:8;348:10;349:20; 350:3,7;356:8;363:22; 364:17;366:14			bodies (1) 177:11	
bet (1) 324:22			body (18) 39:3,21;54:20; 57:13,17;105:6;	
Bethesda (1) 348:2			109:12;126:6;152:6; 155:9;157:7;176:19;	
betrayal (1) 344:10			177:8;207:15;244:9; 245:3;325:19;344:14	
betrayed (1) 344:13				boilerplate (1) 296:20
better (46) 13:20;17:21;18:8; 21:11,11;26:1,10; 37:3;50:1;55:19; 80:17;107:20;113:14, 21:115:15;117:1,9; 131:18;142:8;152:4,8, 10,13;158:3;161:6,7; 164:3;174:17;193:3; 196:19;256:10; 259:11;291:17; 294:19;320:14; 324:11;337:3,11; 339:17;341:14; 342:13;347:9;366:6; 371:7,8;382:3			bold (1) 279:5	
bevacizumab (1) 121:6			bone (4) 166:16,17;171:17; 245:17	
beyond (6) 209:7;212:17; 260:13;293:17;295:7; 314:4			bony (1) 93:7	
bias (11) 165:11;166:3,4; 167:17;168:12;169:5, 17;174:4;213:18; 284:15;291:7			border (1) 40:17	
BID (1) 151:21			boring (1) 128:13	
bidding (1) 210:18			Boston (2) 61:14;221:21	
bidirectional (1) 150:18			both (42) 15:18;21:21;19; 25:2;26:4;31:11;	
bifurcates (1) 145:20			32:16;38:13;46:9,21; 66:22;71:8;91:12;	
big (25) 10:6;11:7;40:18;			109:11;110:16; 137:20;140:17;152:5; 154:22;155:5;168:6; 170:22;179:5;225:20;	
			232:22;252:13; 254:21;255:7,19;	
			277:1;279:2;305:1;	
			315:10;317:13;	
			332:11;334:15;359:5; 368:2;374:5;379:11;	
			383:7;391:5	
				box (1) 70:2
				boy (1) 319:8
				boys (1) 39:13
				BRAF (12) 31:12,15,20;39:15;
				51:18;52:22;53:3;
				71:16,19;86:4;107:3;
				310:17
				BRAF-MEK (1)

143:2,5,6,11,19;144:9,10,12,15;145:14,20,22;148:4,7;150:1;151:17;152:6,8,18,21;153:12,20,21;154:14,19;155:5,6,12;156:5,7,10,20,20,22;159:6,20;161:2;162:6,21;163:10;171:11;172:22;173:6;174:15;177:8,10;178:12;179:1,2,3,9,13,22;180:1,6,8,9;181:12;183:2,8,9,11,20,21;184:6;191:4,19,21;193:3;194:11;195:2,4,6,9,12,16,19;196:1,4,6,7,15,16,18,21;197:17,21;198:1,5;204:4,6,16;205:6,7,12;207:8,14,19;208:14,17,19;211:10,19,22;215:2,20;219:13;221:22;222:2,14;229:7,8;236:16;239:15,16;241:11;242:4,10,14,15;245:7,9;246:4;248:8;249:7;250:8,15;251:9;252:12,16;253:5;255:9,13;256:2,6,14;258:8,15,16,21;259:3,21;260:8,14,16;261:1,4;262:6,9,20;264:12;265:6,11,20;266:6,15,18;267:13,14;268:19;269:4,5,8,18;270:5,10,13,17,20;271:2,14;273:16;278:21;279:9,20;281:19;283:18,19,22;284:4;285:15,17;286:11;287:4,10,13;288:9;289:6;290:12;291:1,4;292:1;293:11,13,17,17,18,20;294:6,20;295:1,5;296:6,21;298:8,12,14;299:12;300:12;303:3,5,6;305:13;306:6,10;307:7,11;308:4;309:2,10;310:11,16,22;312:9,11,21,22;314:4;315:20;317:4,7;319:3,5;320:12;321:1,2,8,19;323:6,16;324:2,4,5,7,8,13,15;325:19;326:5,9,17;327:2,6,14,16,20;328:8,12,13;329:2;330:1,14;331:17;332:14,15,19,21;333:4,4,6,15,16,19,20;334:1,22;335:21;338:12;339:5,6,7,15,	22:340:4,10,17,18;343:5,22;344:3,19;346:3;348:14,20;351:19;352:18;356:8,12,15,21;357:3,11,13;359:1,12,16,17;360:17;361:15;365:22;367:3;368:7,11;369:7,22;370:19;374:8,21;375:8,11,18,19;376:4;377:10,22;22;378:13,15;379:4,17,21;380:8,11,19;381:8,10,17,22;383:7,9,15,17;384:10,21;385:2,11;388:11;390:17	22:246:2;255:8;256:8,9,12;297:4,4;299:17;301:8,9,11,17,20;325:15;329:20;339:11;352:19;357:13;360:4;363:21;364:13,14;365:8;366:2	47:16	320:4;345:10;350:19;353:8;379:12;386:6;387:22;389:2
brains (2)	bridge (2)	brief (10)	build (10)	Campus (3)
22:12;17	21:12,17	18:16;35:16;106:13;118:3;125:7;162:10;230:21;232:12;248:20;374:7	26:1;79:22;129:9;132:19;283:16;291:10;298:11;332:1;371:12;389:11	12:6,8;199:16
brain's (1)	briefly (8)	building (8)	can (312)	8:20;11;17;16:2;19:9,10,15,18,22;22:16;25:21;26:1,1;27:21;28:9,18,22;31:8,19;32:14,21;33:19;37:12;39:18;43:4,16;45:10,20;46:12,17;47:19;48:9,12;51:11;52:4,6;53:16;55:19;56:5,6;57:12;58:19,21;59:7;60:9,17;63:21;64:20;65:6,12;67:9;68:9,16;70:14;72:18,19;73:19,19,20;75:4,5;76:12;78:16;79:22;80:4;81:10,18;82:15;85:8;86:19;88:8;90:14;91:20;93:8;95:7;97:4;98:13;100:12;101:16;102:21;103:11;105:8;13:106:5;107:1;108:2;110:6;112:8;113:1,14,21;114:21;22:115:1,3;116:16;120:21;121:4;123:1;124:12,13;126:15,18;128:15;130:15,22;131:12;132:6;136:16;137:1;140:5,17;142:18;146:16;147:9;149:6,17,21;150:11;152:18;153:4;154:11;156:21;157:8,9;161:9,22;165:14;166:2,3;168:22;169:9;170:9,12;173:6,10,21;175:2;177:13,14,20;180:13;182:3;183:3,14;184:6;185:17;187:6,7,16;188:12;189:5;190:9;192:7,11;193:19;194:12;196:12,16;197:7,8;198:7;199:15;200:2,8,16;201:18;204:3,12,15;210:22;211:6;213:14,14;214:2;216:12;217:11;222:10;223:4,12;226:2,4;227:10,20;228:18;229:10,11;230:3;233:2;234:2;
branched (2)	Brigham (1)	bring (16)	burden (7)	calendar (1)
89:8,19	22:1:20	12:16;19;21;76:7;111:7;158:7;169:19;182:16;249:14;253:15;294:3;302:6;319:19;335:12;368:17;373:4;389:10	128:2;134:15;176:18;230:6;281:1;345:17;346:4	273:2
brand (1)	bringing (7)	brings (4)	call (10)	call (10)
247:11	10:2;26:5;36:21;181:12;377:10,11;378:2	12:11;83:18;261:14;279:1	9:1;34:13;136:12;168:5;175:11;178:11;203:16;305:19;319:4;343:2	9:1;34:13;136:12;168:5;175:11;178:11;203:16;305:19;319:4;343:2
Brastianos (20)	bracket (1)	broader (4)	called (6)	26:16;62:15;252:17;301:22;335:15;343:14
59:16;60:19;63:18;70:8;71:4;84:14,15,17;122:15;144:2;154:7;10;176:17;197:14;311:10,19;312:2;19;332:12;390:8	12:16;19;21;76:7;111:7;158:7;169:19;182:16;249:14;253:15;294:3;302:6;319:19;335:12;368:17;373:4;389:10	186:5;192:10;209:17;210:3	26:16;62:15;252:17;301:22;335:15;343:14	273:2
Brastianos' (1)	bringing (7)	broader (4)	calls (1)	273:2
356:13	10:2;26:5;36:21;181:12;377:10,11;378:2	186:5;192:10;209:17;210:3	129:17	129:17
brave (1)	brings (4)	broader (4)	calms (1)	129:17
279:6	12:11;83:18;261:14;279:1	186:5;192:10;209:17;210:3	268:13	129:17
breadth (1)	broken (1)	broader (4)	came (19)	129:17
198:20	141:6	186:5;192:10;209:17;210:3	60:11;102:16;105:22;129:12;130:6;132:22;161:1;179:10;190:20;199:16;261:9	129:17
break (10)	brought (17)	broken (1)	came (19)	129:17
82:18;154:6;158:14,21;161:12,20;232:4;277:8;311:2;354:12	8:20;75:1,11,20;76:9;87:16;150:4;157:21;189:17;201:17;313:5;319:18;320:21;335:15;363:12;389:6;390:8	141:6	60:11;102:16;105:22;129:12;130:6;132:22;161:1;179:10;190:20;199:16;261:9	129:17
breakdown (1)	brought (17)	broken (1)	came (19)	129:17
293:17	8:20;75:1,11,20;76:9;87:16;150:4;157:21;189:17;201:17;313:5;319:18;320:21;335:15;363:12;389:6;390:8	141:6	60:11;102:16;105:22;129:12;130:6;132:22;161:1;179:10;190:20;199:16;261:9	129:17
breaking (3)	brought (17)	broken (1)	came (19)	129:17
137:11;330:20;331:10	8:20;75:1,11,20;76:9;87:16;150:4;157:21;189:17;201:17;313:5;319:18;320:21;335:15;363:12;389:6;390:8	141:6	60:11;102:16;105:22;129:12;130:6;132:22;161:1;179:10;190:20;199:16;261:9	129:17
Breast (67)	brought (17)	broken (1)	came (19)	129:17
10:14;12:15;21:22;23:22;24:5,12,13,19,21,22;56:19;76:10;77:1,6;84:4;85:17;91:3;95:10;100:9,18,21;101:9;16;102:11;104:13;111:1,6,11;113:7;114:9;115:9;122:5;123:9;156:2,3;198:2;206:6,8;222:11;243:9;244:11;245:13	8:20;75:1,11,20;76:9;87:16;150:4;157:21;189:17;201:17;313:5;319:18;320:21;335:15;363:12;389:6;390:8	141:6	60:11;102:16;105:22;129:12;130:6;132:22;161:1;179:10;190:20;199:16;261:9	129:17

236:21;237:8;246:13; 249:14;250:13,22; 251:1;252:5;253:8; 256:18,19,19;257:19; 259:17;261:20; 262:13,17;263:1,2,6,7, 10,14;264:15,19; 265:9,10;266:17,22; 269:12;272:4;278:10; 279:16;280:11; 286:13;291:8;295:14, 19;297:21;298:1,10, 13;302:10;304:13,14; 306:13,22;307:1,10, 14;309:12,12,16,21; 310:1;311:18,22; 312:1;313:12;314:16; 315:9;317:4,11; 319:17,18;320:13,15, 20;325:3;326:8; 327:21;332:1;333:21; 335:1,11,16,21; 340:11;343:13; 344:16;345:7;346:13, 20;347:1,7;348:12; 349:16,18,19;353:15; 354:21;355:6;359:17, 22;360:21;361:12,20, 20;362:2,3,4;363:7; 366:2,11;368:9,11,14, 15,22;369:3,13;371:8, 9,12;373:7;374:12; 377:5;378:6;382:3; 389:9,18,20,20	246:2;249:5;252:1; 253:14;255:8;256:8,9, 12;257:4,6;258:13; 283:4;285:14;297:4; 299:11,17;301:8,9,11, 17,20;305:14;317:19, 21;319:10,322:1; 325:15;328:16; 329:20;333:11,17; 339:12,13;342:6,9,11; 344:5;345:9;347:16; 351:9;352:19;360:4; 363:21;364:13,15; 365:8;366:2;378:12, 15;380:8,12;384:4	256:11;320:20; 326:21;341:5	21:7;219:10;247:9	210:15;245:9
caners (8)	careers (1)	causes (1)	cerebral (2)	
122:5,5;156:22; 186:4;258:18;301:14; 302:10;342:8	263:18	276:9	32:19;130:19	
cancer's (1)	careful (3)	caution (1)	certain (15)	
171:14	202:20;225:7,14	353:22	44:14;100:4;123:1; 144:22;198:4;209:7; 213:20;218:21; 228:16;260:9;303:21; 311:2;329:5;355:7; 359:8	
candidate (1)	carefully (3)	caveats (1)	certainly (36)	
197:22	33:11;188:7,12	307:8	26:2;35:20;41:18, 19;51:14;53:4;58:21; 78:1,2,9,10;80:16; 101:21;112:19;119:9, 11;140:16;144:6,10, 13;146:19;154:21; 193:6;196:6;198:2; 208:5;217:22;220:20; 229:20;230:9;256:20; 258:14;318:16;350:8; 352:11;389:11	
capable (1)	caregiver (1)	cavity (1)	cetera (11)	
188:13	378:10	134:11	90:22;167:21; 169:4;173:13;219:1; 288:22;313:8;326:21; 357:16;368:3;370:17	
capacities (1)	caregivers (8)	CDK (5)	chair (1)	
222:11	376:18;378:15; 380:21,22;381:3,8,11, 15	90:17;97:15; 154:15;312:5,5	246:14	
capecitabine (1)	cares (1)	CDK/PI3 (1)	chairs (3)	
365:13	385:9	154:22	83:8;290:2,3	
captain (1)	Carey (4)	CDK4 (1)	challenge (22)	
37:19	96:13;229:17; 256:3;363:11	25:13	28:6;29:6;34:2; 49:7;56:8;60:4;68:10;	
captions (1)	caring (1)	carried (1)	72:4,21;91:9;120:14; 141:3;147:3;166:12, 13;206:15;218:13; 236:21;272:14;273:4; 290:7;360:8	
122:19	381:17	carries (1)	challenged (1)	
capture (4)	Caroline (3)	313:9	54:20	
184:17;240:10; 338:13,17	320:6,7;367:19	carrot (2)	challenges (30)	
captured (1)	Carolyn (1)	266:7;331:12	18:22;25:15;28:2; 35:10;36:16;42:1;	
174:19	385:7	carry (3)	45:11,16;54:14;62:16;	
capturing (1)	carried (1)	73:20;149:6;173:12	118:17;119:6,15;	
30:5	cases (17)	case (17)	123:22;131:7;150:5;	
car (1)	9:12;69:12;89:7; 90:11,17,19,22;92:11; 258:2;295:20;304:11;	15:5;39:19;47:21; 49:6;80:18;90:10;	169:1;212:10;229:22;	
325:1	318:11;322:17; 347:17;381:2	111:12;116:6;127:18; 143:13;205:14;	232:16;233:21;234:4;	
carcinoma (3)	CAT (1)	206:12;212:3;318:5; 327:2;367:5;370:10	238:12;239:10;	
90:4;91:17;170:21	346:21	catch (2)	267:16;291:13;	
care (42)	149:16,18;151:7;	73:12;358:18	347:15;356:7;360:2;	
22:9;30:15;31:14; 41:17;43:1;46:9,12;	170:12	catch-22 (2)	384:17	
50:9;96:21;112:6; 115:20;132:15;	centimeter (6)	22:12;40:17	challenging (15)	
146:22;159:17;167:3;	73:17;134:9;	central (2)	35:2;43:4;74:18;	
8:169:12;12;181:5;	149:16,18;151:7;	92:10;96:9	132:3;168:10;184:7;	
185:12;193:15;	170:12	centrally (1)	21:193:22;210:12;	
218:22;227:15;	centimeters (2)	221:8	218:9;220:16;222:17;	
243:20;244:8,21;	22:12;40:17	century (1)	234:6,12,14	
259:11;262:10;279:8;	category (3)	222:3	Chana (2)	
282:9;290:18;305:4;	210:13;313:21;	CEO (1)	83:16;159:1	
307:8;309:2;331:16;	337:15	375:11	chance (9)	
344:18;349:9;350:5;	catheters (1)	91:18;147:2,9;	21:16;17;147:15;	
10,14;381:13;387:19;	336:16	210:20		
career (6)	cause (3)	cerebellum (2)		
145:9;249:18;				

154:4;183:8,14; 225:10;270:19;374:5	choice (9) 306:21;314:2; 318:19;363:22; 364:17;365:16,18,20; 366:14	52:18;83:4;105:3,14; 140:1;230:1;318:2,22; 320:12;336:19;384:20	Cleveland (2) 46:20;50:6	335:3,8;341:18;342:2, 13,15;343:7,16; 344:11,16;345:4; 347:19;351:8,11,12, 16;352:2,15;355:5; 365:10;366:12;367:2, 4;372:4;380:2,4,7,10, 18;383:19;390:21	144:5,16;159:9; 175:16,20;182:11; 186:8;188:20;206:3, 11,15,16;216:6; 228:16;233:4,22; 234:8,9,10,14;235:16, 19,19;236:20;237:1,2, 4,5,9,12,17,19;238:2, 3,5;239:1,18;240:5, 13;254:2,12;257:17; 259:7;261:19;270:3; 271:18;275:1;277:12, 13,15;289:6;290:6; 315:2;329:10;330:10; 335:20;338:19;359:2, 6
change (11) 10:5;54:7;81:10; 112:14;128:8;143:22; 153:22;280:5;287:2; 296:5;301:4	choices (2) 344:8;354:9	choose (9) 160:2;191:7;328:2; 359:18,19;365:15,19; 366:17;367:3	chosen (1) 236:5	clinically (24) 29:7;89:22;90:11; 92:1;94:4,5;97:9,14; 135:1;159:14;167:5; 172:19;187:6;208:10, 14;209:12;213:5; 218:16;225:20; 226:16;240:17; 269:10;288:6;326:16	CNS-directed (4) 290:9;291:20; 292:11;359:18
changed (7) 52:19;73:8,10; 183:10;185:12;193:3; 286:22		Christina (1) 308:20	Christine (1) 310:5	clinical (220) 10:1;13:14;20:17:4, 6;21:20;24:16;25:5; 27:19;28:9,11,13;	CNS-only (3) 108:9;215:22; 216:14
changer (1) 344:6		Christmas (1) 40:21		32:11;35:6;22;36:18; 40:3;41:9;42:4,9;	CNS-ORR (4) 234:16,19;236:1; 238:22
changes (4) 42:8;70:20;122:21; 301:14		Chung (8) 309:13;320:7,7; 323:20;325:20; 355:10;367:20;371:9		43:19;46:10,15,22; 51:8,19;52:11;54:3; 56:17;58:6;65:6,8,19; 67:9,10,15;72:7;75:7, 9;76:21;22;77:14;	CNS-OS (1) 234:18
changing (1) 115:19		cinderblocks (1) 128:20		78:5;85:4,10;86:13; 90:15;91:10;96:21;	CNS-PFS (2) 234:18;236:2
characteristics (4) 36:17;104:11; 115:2;165:20		circle (4) 232:9;350:20; 378:2;388:3		99:2;100:16;101:6,22; 107:18;114:20;115:4,	coalition (1) 391:21
characterize (4) 240:17;288:18; 289:11;343:10		circulating (2) 199:3;200:19		21:117:15;118:9;	co-chair (1) 14:16
characterized (1) 343:14		circumstance (2) 78:16;117:10		123:12;124:18,22;	co-chairing (1) 348:5
characterizing (1) 88:5		circumstances (2) 360:10;361:22		125:3,5;126:13;128:3;	co-chairs (1) 382:17
charge (1) 175:15		claim (3) 235:17;340:17; 341:8		129:14;130:1;141:16;	co-direct (1) 309:2
Charles (1) 89:17		claims (4) 233:22;234:15; 240:13,19		151:15;158:5;162:21;	cognition (3) 185:14;356:4; 391:10
check (1) 316:10		clarified (1) 218:18		163:2,11,12,21;164:1,	cognitive (11) 173:11;174:21; 185:5;193:21;214:20; 218:2;224:18;227:3; 355:17,18;356:1
CheckMate (2) 33:8;286:14		clarify (4) 15:15;16:6;197:2; 276:8		6,9,10,14;167:15,15;	cohesively (1) 369:14
checkpoint (7) 32:12;49:12,17; 103:7,10;107:3;116:6		clarifying (1) 371:18		168:2,4,5,7,16;169:11, 15,20,21;170:2,2,4;	cohort (34) 61:1,4,7,10,11;62:1; 64:3;80:12;90:10;
chemists (1) 282:16		clarity (4) 15:17;17:8;314:8; 317:13		173:10;174:8;175:3;	92:5;121:18;194:11, 14,18;228:14;260:10;
chemo (2) 219:13;244:17		class (2) 266:5;286:1		177:18;178:18;179:5, 22;182:10,14;185:5,7,	261:20;262:7,12,18;
chemotherapies (1) 54:21		classic (1) 127:10		9,18;190:22;193:10, 20;197:1;201:5,12,22;	264:14;265:9,11;
chemotherapy (10) 25:11,21;27:13; 30:18;105:17;107:2; 112:4;146:9;172:10; 264:20		clear (18) 29:1;31:7;36:5; 45:7;107:1;113:15;		202:3;203:18;204:21;	273:19;274:1;276:19;
chewed (1) 344:4		child (1) 116:7;138:10;155:6;		205:2;207:18;208:10;	278:10;284:3;287:19;
chief (1) 375:12		children (2) 180:18;217:12		210:11,22;212:13;	288:16;289:3;295:8;
child (1) 103:5		clearly (14) 387:3		215:19;216:19;	330:5;333:22
cohorts (14) 59:5,11;61:5,8; 62:21;63:15;80:10;				218:14;221:2;223:10,	cohorts (14) 59:5,11;61:5,8; 62:21;63:15;80:10;

124:21;198:7;261:12; 315:14;338:8,10,21	comfort (4) 58:19,22;64:18,20	360:20;386:16 commonalities (2) 90:14;154:13	competitive (4) 37:21;41:5;341:14, 15	concentrations (3) 70:21;106:13;336:1
collaborate (2) 369:13;388:15	comfortable (5) 141:8;147:21; 260:3;275:10;309:6	commonality (1) 153:10	compiled (1) 382:8	concept (24) 32:13;36:6;45:8; 53:18;54:11;89:13;
collaborating (1) 356:10	comfortably (1) 342:21	commonly (3) 104:10;168:15; 241:13	complain (1) 350:14	120:13;122:6;141:14; 18:142:5,17;143:3;
collaboration (4) 10:4;88:7;101:13; 369:20	comfy (1) 290:3	communication (1) 178:17	complaints (1) 260:19	144:21;163:15; 189:18;190:3,16;
collaborative (2) 87:22;88:8	coming (21) 18:19;34:6;41:4; 61:13;74:13;76:14;	communities (1) 158:7	complementary (2) 175:14;375:2	219:13;262:17;328:5; 329:22;338:8;357:10
collaboratively (1) 392:1	120:8;158:13,13; 178:5;181:3;186:13;	community (16) 15:1;53:10;56:9; 62:6;129:21;162:6;	complete (4) 134:19,20;340:9; 343:2	concepts (8) 28:12;82:11; 117:19;119:17;120:2;
collaborators (5) 71:6;87:17;88:8; 144:3;376:10	235:16;285:21; 312:12;339:1;354:14; 355:20;374:3;383:3;	166:14;194:6;223:7; 280:6;286:10;295:18;	completed (2) 49:19;264:14	121:3;122:20;391:6
colleague (4) 123:17;162:13; 293:10;345:8	385:18	321:9;342:19;345:9; 347:15	completely (12) 41:2;62:13;102:13; 139:7;224:11;270:12;	concern (7) 53:4;60:5;80:9; 108:10;263:5;269:13;
colleagues (12) 64:21;65:13;78:8; 162:11;213:22; 217:18;232:20;233:8; 9:251:7;373:15; 386:10	comment (58) 74:19;80:4;118:8; 138:9;149:15;153:18; 155:2;157:16;159:12;	comorbidities (3) 205:17,19;257:14	274:21;287:13; 323:21;329:21;330:3; 332:13	272:6
collect (4) 71:9;159:12; 299:20;349:14	189:17;192:11; 194:20;200:16,19; 201:1;204:4;207:1;	companies (14) 56:15;70:13;78:10;	completion (1) 169:3	concerned (5) 83:3;209:5;214:10; 286:16;381:11
collected (9) 87:20;323:11; 370:11,20,22,22; 371:1,1,2	213:2;214:3;219:22; 229:14;241:6;259:17; 266:2;271:5;274:10;	97:6;250:21;266:8; 282:19;285:11,20; 302:18;315:12;326:7;	complex (5) 42:16,20;206:5; 261:6;314:5	concerning (1) 343:22
collecting (2) 224:15;368:20	14:276:16;283:15; 294:7;297:9;301:6;	340:15;392:7	complexities (2) 41:18;300:17	concerns (12) 51:15;53:21;54:5; 67:1;147:6;233:7;
collection (2) 9:3;213:4	302:15,16;303:1;	company (8) 255:12,21;282:13;	complexity (5) 182:21;183:5; 210:18;280:13;365:21	252:6;261:1;262:4; 266:6;302:21;379:5
collective (1) 10:2	304:6;21;309:21;	284:11,12;340:14;	compliant (1) 132:22	conclude (3) 115:12;148:21; 382:21
collectively (1) 149:6	313:5;314:11;323:17;	346:9;392:10	complicated (5) 119:6;124:17;	concluded (1) 393:6
college (2) 37:20,21	20,330:22;332:12,22;	comparative (1) 364:22	171:17;246:7;320:12	conclusion (4) 97:8;115:17;353:9;
COLLYAR (2) 157:17,17	339:10;341:11;	comparator (1) 352:9	comply (2) 128:21;129:1	369:9
colon (1) 12:14	347:10;350:12;355:9;	comparators (1) 121:7	component (8) 140:8,10,14,15;	conclusions (1) 369:1
combination (4) 27:13;103:10; 120:15;313:4	364:11;366:7;367:17;	compare (2) 262:17;324:4	141:10,11;169:16,22	concordant (1) 57:12
combinations (6) 23:10;34:6;115:5,6; 123:19;313:7	19,20;371:18;372:11;	compared (14) 73:12,13;74:2;	components (2) 127:1;137:6	concrete (4) 129:9;162:5;317:3,
combinatorial (5) 34:8;36:21;47:1; 49:22;56:1	387:21	89:15;90:1;93:17;	composite (4) 220:1;358:1;	12
combine (5) 49:16;50:2;120:17; 257:15;371:4	comments (25) 65:3;138:16;154:3;	97:10;103:3;148:12;	comparing (2) 34:5;152:3	condition (1) 193:8
combined (6) 9:7;31:15;33:2; 40:14;49:11;105:16	155:19;157:19;183:3;	176:19;307:7;363:16;	comparison (1) 103:12	conditions (4) 115:22;116:10;
combining (3) 34:8;63:6;367:7	189:10;198:12;	364:16;367:13	compartment (2) 236:1;274:9	254:13;304:2
	227:21;241:7;248:12;	comparing (2) 34:5;152:3	compartmentalize (1) 207:14	conduct (2) 60:6;254:15
	252:2;269:21;273:14;	comparison (1) 103:12	compromise (1) 273:5	conducted (1) 378:16
	299:5;300:14;311:14;	compartment (2) 236:1;274:9	compromised (1) 273:9	conducting (4) 117:15;118:9;
	355:12;374:4,6,10,14;	compartmentalize (1) 207:14	compromising (2) 315:11,11	130:4;308:3
	16;380:13;382:18	compatible (1) 130:1	comptroller (1) 349:6	confer (1) 236:2
	commercial (1) 331:20	compelling (5) 185:16;219:15;	computational (1) 368:15	conference (6) 12:10,20;14:11;
	commercially (1) 25:3	220:12;223:21;322:20	concentration (1) 140:15	256:17;376:4;385:16
	committed (2) 18:2;385:15	compatible (1) 130:1		confirmatory (1) 373:8
	committee (5) 10:10,21;11:2;14:9;	compelling (5) 185:16;219:15;		
	238:17	220:12;223:21;322:20		
	common (16) 9:4;33:20;89:10;	competing (3) 99:2;118:14;150:21		
	90:6;92:20;110:20;			
	114:5;137:13;141:21;			
	154:19;175:1;234:15;			
	312:11;333:17;			

confirmed (2) 126:10;136:13	332:21;335:19; 377:21;378:2,8,22	259:19;320:11 contributed (2) 96:12;97:21	299:7 correction (1) 194:22	create (11) 110:10;164:3; 183:1;184:2;200:2; 209:17;210:3,14; 301:14;368:22;389:10
conflicting (1) 244:16	213:21	contributes (1) 185:14	correlate (1) 107:22	created (2) 114:13;183:17
conform (1) 42:9	35:20;174:14	contributing (1) 94:17	corresponding (1) 115:11	creates (1) 91:9
confound (1) 68:2	336:18	control (30) 21:11;22:11,16,17; 31:21;32:19;68:5; 180:6;186:18;192:18; 204:6,16;205:3;	corroborating (1) 226:22	creating (1) 95:5
congratulate (1) 47:6	140:12	206:20;216:16;229:6; 256:15;280:20;	cortex (3) 209:5;211:20;213:6	creative (2) 294:15;367:15
congratulations (1) 48:5	367:18	329:12;352:9;360:3,4, 5;363:14,16,17;364:8; 365:19;366:19;384:18	corticosteroids (2) 135:7;267:8	criteria (52) 17:4;35:12;36:18; 44:14;66:14;67:22;
Congress (1) 349:5	163:14;215:11,12	controlled (5) 32:6;42:13;180:9; 196:17;352:12	79:15;84:8;97:1; 118:5,22;120:7;	79:15;84:8;97:1; 118:5,22;120:7;
conjugate (1) 111:2	constrained (1) 147:4	controlling (4) 22:14,19;157:6; 373:3	costs (2) 132:6;277:5; 326:12;335:6	133:22;134:7,8;136:2, 10;149:9,11,22;
conjugates (1) 111:2	constraints (1) 378:22	controversial (1) 386:13	COUGAR (2) 171:11;225:3	150:15,18,20;151:1;
conjunction (1) 182:8	consulting (1) 253:16	controversy (1) 168:1	counseled (1) 303:18	160:18;182:11;191:8; 207:8;210:4;216:2;
Connect (2) 302:1;321:8	consumer (2) 349:8;350:15	convening (1) 375:9	couple (3) 216:7	219:2;222:19;223:11;
cons (1) 119:16	consumers (1) 350:14	conventional (3) 352:2,14;366:1	counter (2) 211:4;226:14	234:8,9;239:4;240:15;
consensus (6) 129:3;131:1;234:2; 275:10;300:3;369:5	Contemplate (1) 374:19	conversation (14) 11:19;18:7;160:12; 161:4,6;162:20;	country (1) 61:13	242:22;250:4;254:6,9, 20;260:22;274:13;
consent (10) 303:12,16;304:13; 305:2,4;313:6,8,12, 19;314:1	content (2) 11:2;127:5	190:10;215:5;229:20; 336:13;342:14; 363:13;364:7;375:9	couple (24) 15:2;16:4;24:1; 121:12;135:18,22;	281:20;306:18;322:9;
consequence (1) 340:20	contest (1) 312:15	conversations (1) 377:14	147:17;158:20; 176:10;185:12,13,20;	324:10;355:6;370:9;
consequences (1) 256:13	context (14) 19:7,10;119:2; 170:2,3,4;184:14;	converse (2) 204:21;205:4	186:10;199:19; 245:18;262:5;268:8;	384:13;385:6
Conservative (2) 9:11;81:5	continue (14) 18:6;78:19;115:14; 173:4;180:11;203:1;	Conversely (2) 165:15;170:17	269:21;281:15,17; 327:22;357:7;386:16;	criterion (2) 119:10;250:3
consider (19) 13:8;40:11;70:14; 99:21;127:2,8;147:13; 150:13;158:10; 200:20;205:16;253:6; 262:11;287:20;289:2; 292:10;299:11;304:3; 366:18	continued (3) 37:20;205:3;324:12	continued (3) 37:20;205:3;324:12	387:22	critical (18) 50:5,22;88:12;
considerate (1) 254:19	continues (1) 180:4	continuing (1) 18:3	courageous (2) 145:13;250:19	104:8,22;120:13;
consideration (4) 165:9;210:19; 234:21;303:10	continuum (1) 75:3	contrary (1) 277:18	course (21) 97:20;119:8;120:3;	123:18;124:5;128:9;
considerations (9) 135:17;253:20; 261:14,15;304:10; 358:21;360:6,15; 390:10	contrast (10) 108:14;110:21; 126:15;127:10,14;	contrast (10) 129:20;270:11	convincing (2) 107:8;139:19	129:10;131:10;
considered (12) 123:20;165:7; 171:19;175:17; 290:18;337:2;357:17; 365:17;366:19; 383:18;384:15;387:18	130:8;131:18;133:6; 335:5;337:21	coordination (1) 375:20	cool (1) 256:7	187:20;188:6;201:9;
considering (8) 264:11;318:12;	contrast-enhanced (1) 133:12	coordinator (1) 250:2	cooperative (2) 129:20;270:11	220:3,15;243:1;348:9
	contrast-enhancing (1) 134:5	cope (2) 38:22;243:18	coordination (1) 375:20	criticized (1) 102:5
	contribute (4) 11:17;256:18;	cord (1) 245:6	coordinator (1) 250:2	crizotinib (9) 28:18;108:5,7;
		corollaries (1) 98:17	cope (2) 189:13;263:12	109:10;110:2,4,8;
		corollary (4) 98:22;99:8,17;	covered (1) 49:3	152:5;178:12
			cranial (1) 173:19	cross (13) 51:20;57:21;110:2;
			craniotomies (1) 92:12	111:22;141:18;142:4;
			craniotomy (1) 156:7	178:13;282:11;
				284:13,16;320:8;
				335:19;337:19
				crosses (1) 108:7
				crossing (1) 358:9
				crossover (3) 167:19;225:12;
				364:5
				cross-sectional (1) 170:11
				crowd (2) 19:20;242:9
				CRs (2)

212:3;361:14		39:17;44:20,21;49:2; 50:7;51:14;56:22; 59:9;64:5;71:14;76:8; 86:7;87:12;93:12; 97:17;100:18;122:16; 141:13;144:12;155:4; 157:11;197:13; 264:17;338:6,6	decentralized (2) 347:19;348:4	358:16;369:1;384:17
crude (1)	D	decide (2)	degree (2)	
300:22		386:19;387:10	136:22;142:10	
crunched (1)	dabrafenib (6)	decided (2)	delay (9)	
18:17	31:18;51:17;52:18, 22:141:17,22	179:7;270:12	35:21;171:22; 172:8,9;173:18,19,21; 218:15;227:7	
CSF (5)	daily (1)	decision (9)	delayed (3)	
35:5;70:10;71:9; 108:15;199:4	249:16	80:22;91:10;167:6; 193:14;203:18;219:4; 254:9;303:15;307:3	133:12;172:12,13	
CT (5)	dalton (1)	decisions (6)	delaying (3)	
126:17;166:18; 170:11;324:5;370:13	55:2	66:16;86:20;87:1; 125:4,4;281:7	167:2;173:14; 257:22	
CTCL (1)	damaging (1)	deck (1)	delicately (1)	
170:21	133:11	294:17	269:17	
CTs (2)	Dana (1)	decline (1)	delighted (1)	
325:18;370:21	84:4	172:13	232:13	
cumulative (1)	danger (1)	declines (1)	delineate (1)	
110:11	145:22	173:5	132:11	
curative (1)	Darwin (1)	declining (1)	deliver (1)	
112:3	89:17	135:15	46:12	
Cure (1)	data (94)	decrease (4)	delivering (1)	
10:10	19:9;30:6;31:17; 33:18;34:19;41:21; 43:11;53:1,2;58:17; 63:8;80:1,22;81:3; 88:7;94:4,14;100:17; 101:8,14;103:6;104:9, 12:105:6,11,16;107:7, 13:16;108:2,4,5,21; 110:22;112:18; 116:21;124:7;137:19; 139:18;141:16,17; 143:19;152:15,17; 154:14,20;159:13,19; 161:6,8;171:8;172:15; 174:5;184:8;224:16, 16:230:6;235:20; 236:22;251:11;	47:20;48:9;112:12; 135:4	delta (1)	
cures (2)	262:22;263:2;285:18; 291:10;299:10,20; 302:4;323:10;325:8; 336:21;349:10,11,14, 16;361:11,18;362:8,8, 19;363:8;364:13;	decreased (1)	112:11	
9:19;139:3	366:15;368:15,17,21; 369:21;370:4,7,15; 371:3,4,11;376:19; 382:8	day-to-day (1)	delve (1)	
curious (5)	database (3)	279:12	387:8	
189:20;217:17; 340:13;354:22;364:19	102:10,10;301:22	decreasing (1)	demanded (1)	
current (6)	databases (1)	135:8	179:2	
23:22;26:2;72:4; 235:12;284:11;327:17	101:15	default (1)	demonstrate (6)	
currently (12)	data-driven (1)	390:6	110:12;111:12; 165:18;226:11;240:8; 328:11	
24:3;41:20;58:14; 77:22;121:7;169:9; 255:2;320:17;335:13; 376:21;377:2;381:21	369:2	defensive (1)	demonstrated (3)	
curtailing (1)	date (4)	341:12	159:22;164:22; 307:7	
217:13	132:1	deficiencies (1)	demonstrating (1)	
curve (2)	69:13;87:10; 102:11;156:4	323:2	267:16	
183:18;244:2	deal (2)	deficiency (1)	demonstration (3)	
curves (1)	54:3;334:18	323:17	235:4,10;351:8	
110:10	dealing (2)	deficits (1)	demystify (1)	
customized (1)	146:4,7	24:9	251:9	
124:19	deals (1)	define (16)	denied (3)	
cut (6)	146:1	17:5;58:22;83:14; 119:4,5;120:21; 125:14;127:11;	380:3,6,10	
279:4;281:3,22; 331:1,6;335:6	dealt (1)	136:17;160:11; 208:14;209:12;213:3; 273:8;351:6,10	denominator (1)	
cutaneous (1)	28:1	defined (3)	194:16	
170:21	dearth (5)	26:22;135:10; 229:22	density (2)	
cut-point (1)	35:6;115:9;263:19; 291:21;359:21	defines (1)	127:18;131:5	
334:5	death (6)	358:17	deny (1)	
cyberknife (1)	40:10;99:2;118:14; 205:11,16;206:5	defining (5)	29:13	
310:14	deaths (1)	35:13;51:4;124:6; 212:2;289:16	department (1)	
cyst (1)	21:8	definitely (9)	221:19	
156:13	debate (3)	50:8;78:3;140:5; 198:12;208:18;229:2, 15:366:18;385:15	dependency (1)	
cystectomy (1)	208:22;275:6;	definition (1)	222:13	
169:14	367:18	163:1	dependent (1)	
cystic (3)	debilitating (1)	definitions (1)	76:14	
134:10;156:11,20	38:3	153:9	depending (5)	
cytologic (1)	Deborah (1)	definitive (5)	157:6;228:15;	
59:2	157:17	117:21;315:8;	309:20;358:3;360:15	
cytological (1)	decade (4)		depends (6)	
35:5	27:18;48:1;73:12;		42:19;151:4;	
cytotoxic (1)	103:13		361:21;363:1;372:17;	
172:9	decades (5)		373:14	
	99:16;100:20;		depicted (4)	
	193:4;218:7;283:4			

89:3,4,5,18	despite (5) 100:16;105:15; 110:1;244:1;265:19	36:1;45:3,14;51:19, 21:52:2;64:9;65:20; 78:5;79:14,16;80:1, 21:84:1;98:18;99:14; 111:20;115:16;	230:1;332:16	127:17,19;131:2
depression (2) 282:15;381:6	detail (1) 134:17	118:22;139:17;142:1; 143:1;153:15;181:16, 18:186:3,5;187:5; 188:8;189:6,15,16;	difference (13) 29:2;72:15;104:21; 106:1;132:8;151:19, 20:220:7;262:21;	digital (1) 168:18
depth (5) 27:20;173:8; 198:20;199:5,9	details (2) 42:4;123:2	192:14,19;193:13; 194:8;197:16,17; 217:13;228:7;233:3;	285:5;288:7;324:20; 347:4	dilemma (1) 221:2
deputy (1) 257:3	detect (2) 131:21;191:11	242:13;249:19; 252:22;253:12,14;	differences (9) 87:8;90:1;94:22; 95:1;155:10;176:17;	dilute (2) 205:19;215:10
derive (1) 182:3	detectable (1) 29:3	254:18;258:1;260:2, 15:264:7;265:3;	197:19;242:13;385:1	diluting (1) 289:13
derived (2) 95:5;336:19	detected (4) 90:9,12;91:6;92:2	266:14;273:13,16; 277:2,4,17;284:4;	different (97) 20:10,11,15,16; 23:14;24:20;26:6;	dimension (1) 371:2
Derrick (12) 37:16;43:17,21; 44:17;47:4;81:19; 82:13,21;145:13; 249:9,11;310:20	detecting (1) 93:1	298:10;300:7;315:5; 321:21;333:4;334:2;	34:9;36:22;37:2;	direct (12) 13:19;164:6;165:3;
Derrick's (1) 47:21	deterioration (4) 99:3;202:5;213:15; 353:1	376:12;383:8;386:4; 388:13;392:5,10,12	42:22;43:8;59:8;60:7;	167:14;168:2,7,8;
design (52) 15:17;27:19;35:11; 36:16;66:6;68:8; 72:19;80:7;109:1; 110:16;123:12;125:1, 1,3,5;158:5;159:4; 161:5;163:21;174:7; 175:3,15;192:14; 198:15;225:1;226:13; 234:10;239:10; 242:21;251:1;261:15; 263:6;265:10;266:14; 271:8,19;277:14; 295:12;304:10,11; 307:9;311:8;312:3,8; 321:17;335:3;347:1; 364:4,22;366:16; 373:8;391:14	determinants (1) 153:7	devices (4) 128:16;168:18; 174:20;391:1	63:10,11;65:10;74:2;	351:8,11,16;352:2;
designed (20) 24:13;71:14; 106:21;121:2;129:14, 16,19;172:7;175:20; 179:22;184:5;204:12; 235:12,13;240:19; 295:4;311:1;338:13; 351:13;363:14	determining (1) 191:15	DeVito (4) 374:20;375:5,6,11	78:12;86:17;89:2,15;	372:4
designing (7) 69:21;74:15; 290:15;295:3;326:10; 362:21;364:9	devastating (2) 13:6;86:12	devoted (1) 68:19	97:11;100:13;102:17;	directed (3) 183:12;290:6;
designs (8) 13:14;19:8;45:21; 108:22;109:22; 158:14;232:18;252:8	develop (38) 15:4,15;17:9,14; 26:11;51:1;56:20; 66:1;75:16;76:12; 85:18,20,21;86:3,4,8; 88:9;94:8;113:6,21; 159:10;160:3,15,21; 197:20;201:20; 206:19;218:6;257:14; 270:20;277:21; 283:19;284:7;287:15; 315:19;369:2;388:9; 390:20	dexamethasone (1) 221:22	106:9;109:22;115:5;	313:17
desire (1) 340:19	developed (12) 13:22;15:6;21:10; 64:8;81:9;90:4;95:9; 136:11;191:18; 199:22;254:20;370:9	diagnose (2) 50:22;76:19	126:15,18;130:2,3;	direction (7) 220:11;233:3;
desperate (2) 342:10;343:21	developers (2) 13:20;226:5	diagnosed (13) 9:5,13;21:5;156:3; 180:19;193:7;242:16; 244:13;305:12;314:7; 342:5;379:17,18	137:1;150:18,20;	314:8;322:6;356:14;
desperately (2) 53:12;301:18	developing (24) 15:20;24:8;41:11; 66:17;76:12;96:2;	diagnosis (12) 35:5;101:12,20; 103:16;177:1;245:4, 16:246:2;343:3;379:3, 6;381:4	156:22;170:5,9,9;	358:2;385:17
	100:6;144:16;153:15; 179:16;193:15,16; 241:21;257:1,10,20; 293:13,15;315:13; 331:16;333:15;368:1; 376:20;381:21	diagnostic (2) 150:9;320:9	175:19;176:22;	directionally (1) 226:21
	Development (84) 8:8;13:12;15:19; 16:10;17:2;18:7; 23:17;29:22;32:10;	diagnostics (1) 181:10	179:20;180:13;181:4;	directions (1) 26:8
		diameter (2) 134:5;135:5	186:10,12;187:8,13;	directive (1) 224:4
		Dianne (1) 11:11	189:10,12;198:6,7;	directly (9) 106:12;116:13;
		dictate (1) 366:12	200:6;211:7;215:17;	140:6;164:10;168:9,
		dictated (1) 305:16	226:12,13;227:16;	19:171:4;188:18;
		dictating (1) 354:18	239:5;260:17;261:4,5, 5;263:4;264:5;265:2;	336:8
		die (3) 39:13;256:11,13	266:15;274:8;277:14;	director (6) 11:8,22;43:19;
		died (1) 151:17	278:10;280:15;	233:19;257:3;320:10
		differ (2)	287:14,19;301:9;	disagree (1) 337:5
			311:4;330:8,9,20;	disagreement (1) 382:4
			335:2;337:22;351:3;	disappear (1) 134:21
			20:358:22;360:15;	disappointing (1) 142:20
			363:3;367:5;369:12;	disappointingly (1) 112:13
			370:16,20,20;384:15;	disassociated (1) 177:8
			387:5;388:7;390:11, 15,16,16	disciplines (1) 42:21
			differential (1) 32:8	disclaimer (1) 34:1:4
			differentiate (4) 266:4;284:5;	disclose (1) 255:4
			331:18;341:8	disclosures (3) 21:1;85:14;98:10
			differentiating (1) 157:5	discontinue (1) 121:4
			differentiation (1) 59:4	discordance (1) 238:16
			differently (4) 59:7;155:8;284:8;	discouraged (1) 142:17
			355:4	
			difficult (11) 19:15;64:10;67:15;	
			68:7;92:11;141:4;	
			161:4;220:16;363:17;	
			366:13,15	
			difficulty (2) 28:10;347:16	
			diffuse (2) 23:2;34:18	
			diffusion (3)	

discover (2) 97:3;315:18	130:18,22;131:11; 134:6;135:10,13,20;	disservice (1) 77:8	dogma (1) 250:18	63:18;64:5,6;65:2,19; 66:22;67:21;68:17,22;
discovered (2) 224:7;247:9	136:14,16;137:3; 140:9;143:16;145:2;	distal (1) 93:5	domains (1) 391:6	69:13;70:8;71:4,14; 73:2;74:19,21;75:11;
discrepancy (1) 238:22	14:146:3,7;147:10; 150:6;153:13;156:8;	distant (3) 112:12;113:3,4	dominant (1) 215:15	20:76:8,9,17;77:17; 79:6;80:4;82:10;
discretion (1) 364:1	159:9;167:20;168:8; 170:3,19;173:11; 177:2,10;185:15;	distinct (6) 91:15;93:20;97:9; 188:19;315:16;332:20	done (45) 23:19;40:6;65:7,18; 70:18;74:16;75:21;	83:12,19;84:3,15; 86:7;87:12;98:5,7;
discuss (7) 13:13;19:6;175:15; 207:16;355:11;372:7; 392:14	186:18,19;187:2; 189:4;192:22;196:3; 17,18;197:20;202:8;	distinguish (2) 329:9;330:12	distinguishing (1) 133:15;140:4,11; 141:11;144:7;156:18;	117:13,14,17;123:17; 125:19,22;138:6;
discussed (12) 26:8;142:8;175:17; 184:12;253:2;279:11; 289:9;337:9,10;378:8; 379:9;385:7	204:5,15;205:3; 206:11;207:3,12,15, 20;208:7,22;216:16;	distinguishing (1) 216:2	distrust (1) 13:15;17,20,21;239:2;	139:13;140:1;141:13, 15;143:8;144:2,12,12,
discussing (4) 13:3;83:14;232:11; 252:7	218:8;236:3,17;237:5, 13,15,17,20,21;239:2; 240:12,22;242:5,19;	distrust (1) 344:20	disturbing (1) 40:1	19;145:5,7,11;148:21;
discussion (56) 13:6;18:21;19:22; 20:12;37:5;64:19; 71:2;73:16;74:22; 80:18;82:8;84:13; 117:20;138:5,8;145:7; 159:19;175:7,10; 182:4,8,13,15;184:2; 185:1;188:1;228:4,7; 230:17;232:21;234:3; 236:18;240:8,15,18; 241:2,4;251:5;256:3; 259:15;266:1;277:14; 287:21;307:10; 314:13,22;317:1; 320:11;345:13; 373:19;374:7;375:2; 382:20;383:3;384:16; 392:20	254:21;259:21; 260:16;263:22; 268:19;270:3,20,22; 274:9;277:19;278:1,9; 281:1;284:1;326:4; 327:8;328:8;329:10, 12;332:3;333:9,18; 334:14;343:10,13,18; 356:3;359:6;373:3; 389:13;390:10,11,15, 17;391:15	divergence (5) 91:8;92:22;93:9; 94:17;159:20	door (2) 60:11;350:6	19:149:8,19;151:22;
discussions (9) 78:3;158:2;207:17; 220:9;256:18;308:3; 334:10;377:13;386:12	disease-free (2) 112:9;179:15	divergent (3) 89:8;93:22;183:22	dose (20) 40:13;41:3;70:19; 78:20;20:105:8;	154:7,10;155:4;
disease (184) 9:2;12:17;13:3,7, 10:14;5:20;10:21;12, 19:22;3,10;25:20; 30:17;31:21;32:1,5; 34:13,16;35:9,21; 36:4;39:15;42:14; 46:4;57:7;58:5,13,18; 59:1,2,6,13,20;60:8, 10,22;61:15,18;62:14, 18,21;63:4,12;64:7; 65:12;66:10,15,20; 68:5,6,12;71:11;74:1; 85:21;86:4,10,12; 91:12;92:10;94:9,10; 100:3;102:12,18; 109:4,6,14;112:5,15; 116:3;118:15,16,17; 121:15,20,22;122:10, 11;124:16,18;128:2,4;	diseases (25) 9:3;12:18;20:15; 37:2;122:4,9;153:8,9, 11,17;154:13;155:17; 163:9;174:9,12; 197:19;198:1;201:2; 206:17;250:10;251:7; 260:9;265:20;314:5; 347:14	diverse (1) 12:11	diverse (1) 40:13;41:3;70:19; 78:20;20:105:8;	157:11;158:19;159:2;
disfiguring (1) 170:19	divide (2) 27:6;321:16	dividing (2) 16:10,16	dividing (2) 277:2,20	162:15,15,15,18;
disheartening (1) 380:14	divided (1) 24:19	Division (5) 233:18,19;251:17; 253:10;371:21	dose-finding (2) 142:12;273:8	163:1;179:6,6;180:2;
disincentive (2) 76:21;77:15	disrupt (4) 55:11;56:7;133:10; 336:14	DNA (2) 87:21;200:20	doses (2) 142:12;273:8	181:8;182:17;185:2;
disorder (1) 219:11	disrupted (2) 52:8;143:7	doable (1) 43:14	dose-finding (2) 277:2,20	186:2;189:9;190:9,11;
disrupt (4) 55:11;56:7;133:10; 336:14	disruption (6) 55:7,18,22;127:7, 13;315:17	doc (3) 166:11,20;333:11	door (2) 60:11;350:6	12;192:11;193:2,9;
doctor's (1) 38:7	docs (1) 140:22	docs (1) 140:22	dose (20) 40:13;41:3;70:19; 78:20;20:105:8;	194:9,19;21;197:2,5,7;
dissect (1) 358:11	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	docs (1) 140:22	9,11;198:9,9,10;
disseminable (1) 221:10	disrupt (4) 55:11;56:7;133:10; 336:14	doctors (10) 38:5;139:3;180:22; 243:19;244:7;305:10; 307:18,19;344:22; 381:22	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	200:8,10,16,17,18;
dissenting (1) 238:11	disruption (6) 55:7,18,22;127:7, 13;315:17	document (2) 216:20;392:2	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	201:1,10,12,14,16;
documented (1) 223:11	dissect (1) 358:11	documented (1) 238:11	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	202:6,9,10;203:22;
documenting (1) 231:11	dissenting (1) 19:20	documenting (1) 237:5	Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	204:20;205:9,22;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	206:2;207:2;209:15;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	17;210:7;211:4,14;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	212:1,8;213:1,2;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	214:7,17;215:4,5,6;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	216:22;217:2;218:3;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	219:7,19,21;220:17,
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	18,20;221:15,18;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	222:17;224:8,9,10,12;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	225:3;226:1,14;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	227:17,18,19;228:3;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	229:3,6,18;232:13,14,
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	17;233:13,13,16,18;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	241:5;247:7;248:11;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	21;249:1,2;251:14,15;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	252:9,10;253:9;255:1;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	257:2;259:13;260:21;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	21,21;262:2;263:14;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	15;265:15,15;266:2;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	11,12;268:4;269:21;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	270:6;271:4,4,9,10;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	272:17,20;273:1,3,18;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	274:16;275:21;276:2;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	8,12,13,16;277:7;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	283:8,14;285:8;286:3;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	287:17;289:15,18,18;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	290:2,6;292:16;297:2;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	22;298:3,5,22;299:4;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	7,22;302:14,15,16,22;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	303:1,9;304:5,6,9,18;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	18,19,20,21;305:1,22;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	306:2;308:13,13,17;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	19;309:13;310:3,5,10;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	311:9,10,13,19,22;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	312:2,17,19;313:2;
			Doctor (11) 148:3;183:4; 313:17;314:9;340:6; 342:12;343:1,9; 344:14;355:15;379:17	314:10,20;316:16,22;

320:1,1,2,6,7,17; 321:15,21;322:5; 323:20;324:19; 325:20;326:18,19; 329:8;330:17;332:12; 333:1,10;334:7; 336:10;337:6;338:5,6; 340:11,12;341:1,4,16; 345:5;346:6,15; 347:10;348:7,18; 349:22;350:11,17,17, 18;352:8,10,16; 353:18;354:11;355:9, 10,10,12;356:2,13,20; 357:4;358:20;360:18; 362:2,3,6,18;363:9, 11;364:10,10,12; 365:2;366:10,20,20, 21;367:14,18,19,20; 369:17;371:9,16,17; 373:17,20,22;374:17; 377:8;383:2;385:21; 387:13;388:18;390:8	101:5;104:4,10;105:1; 111:2,19;113:15,18; 114:4;115:16;117:5; 121:1;135:21;139:17; 140:13,14;141:18; 143:15;145:3;152:4, 10,14;163:17,18; 169:22;178:15;180:3, 6,14;181:16,17,21; 182:1,2,3;184:14; 188:8;190:14;191:13; 193:16,17;195:13,18; 197:16;199:5;213:12; 220:6,7;222:1;223:5; 226:5,6,13;238:14; 242:13;249:19; 252:22;253:11,14; 260:2,15;264:10; 272:2;273:6,13,17; 277:17,22;278:3,12, 17,20;282:11,17,20; 284:13;294:5;295:15, 22;297:11;298:10,19; 300:7;306:13;315:5; 326:2;328:17;333:4; 334:2;337:18;346:9; 350:2;357:2;358:18; 361:4,7,8;362:9,12; 373:2;383:22;388:9	due (5) 55:17;123:16; 151:19;240:1;288:3 Duke (5) 151:16;255:9; 256:11;348:2;363:11 dumb (2) 348:13,15 durability (1) 235:1 durable (3) 32:21;107:21; 164:17 durably (1) 71:16 duration (10) 32:1;34:3;49:5,8; 173:8;228:14;234:17, 20;235:6;372:17 during (7) 8:21;62:19;78:4; 82:18;179:4;335:10; 354:11 dwell (2) 123:10;124:2 dynamic (4) 125:12;133:5; 305:8;307:17 dysfunction (6) 218:12,12;236:11; 250:9,14;338:14	182:13;189:22; 190:13;191:13;192:6, 14;194:4,8,13,16,18, 22;195:12;198:15; 199:9,14,14;200:1,6; 206:14;208:4;227:11; 228:22;255:13,14; 260:3,19;264:2,13; 269:22;277:17; 279:13;293:20;295:7; 298:16;300:6,7; 304:12;309:19,19; 332:7,8;339:3;374:13
draft (3) 182:9;296:13; 347:20		early/late (1) 290:16	educated (2) 314:2,9 educational (1) 210:3 effect (22) 70:11;74:8;107:5; 110:12;112:17; 116:11;152:5,7;164:5, 22;196:5;219:17; 234:22;238:13; 262:13;289:12;296:9; 361:6,12;375:21; 381:12;383:13
dramatic (1) 51:7		early-life (1) 255:19	effected (1) 29:10
draws (1) 347:6		early-phase (13) 41:13;80:17; 108:16,20;117:8; 189:15;193:13;255:3; 272:11;280:7;294:2; 298:17;359:2	effective (32) 15:16;22:10;23:7; 30:17;32:10;36:8; 37:2;45:9,10,13;75:4; 77:11;113:19;116:15; 142:19;252:17;253:4; 257:17;258:10; 262:11,16;266:18,20; 267:20;290:11; 291:22;297:11; 302:19;315:19;329:3; 337:13;354:2
dreaded (2) 13:2;19:16		early-stage (4) 111:8;244:12; 277:1;301:9	effectively (3) 48:19;188:12; 338:17
drive (5) 45:4;194:8;203:17; 247:15;391:3		earth (1) 319:16	effects (16) 13:15;47:20;48:16; 75:14;116:5;152:9; 180:13;222:7;227:2,3; 235:10,14,21;239:20; 240:21;363:6
driven (4) 10:3;27:1;155:14, 14		easier (7) 43:16;67:20;68:14; 120:6;128:14;141:11; 387:2	efficacy (41) 16:21;29:2;30:6; 36:6;39:16;53:8;54:5; 66:1;74:10;95:11,17; 107:15,21;115:22; 143:1;163:13;164:18; 165:2;169:21,22; 174:3;192:9;195:13; 14:233:22;234:6,12, 13,15;235:16;236:5; 239:18;240:6;258:13; 261:5;273:6;274:6; 298:19;315:15;326:1; 331:17
driver (2) 27:7;31:12		eat (1) 231:2	efficient (1) 350:3
drivers (7) 86:17;92:1;94:4,5, 20;97:14;154:17		eating (1) 232:6	efficiently (1) 338:16
drives (8) 53:18;156:19; 157:3;241:21;271:12; 340:21;354:9;356:3		Ebiana (5) 43:18,18;67:21; 224:10,10	effort (8) 18:3;88:1;96:16; 132:19;149:1;185:4; 260:22;348:7
driving (1) 278:8		echo (11) 14:18;18:18; 131:22;132:1,10,12, 14:133:13;193:12; 368:8;392:17	efforts (14) 14:7;47:2,17;48:8, 11,17;50:1;84:6;88:4; 14:137:22;140:4; 160:16;255:4
dropped (2) 245:20;319:13		echoed (2) 62:14;269:7	
drove (1) 249:20		ECOG (1) 172:12	
Drug (135) 10:6;13:11,21; 15:19;17:2;29:22; 44:3;51:17;53:8; 57:22;63:5;65:21; 66:17;70:13,19,22; 75:15;78:10;79:2,16; 80:1,21;84:1;85:8; 86:16;98:9,17;99:9, 11,13,20,21;100:6;		edema (3) 32:19;124:4;130:19	
drug's (2) 79:9;143:19		Edison (1) 10:19	
drug-specific (1) 362:17		Edjah (3) 68:22;316:17;320:2	
DSC (1) 137:4		educate (3) 51:10;307:21; 385:13	
ductal (1) 91:17			

EGFR (8) 27:2;85:21;91:1,5; 102:20,22;107:5; 142:14	247:17;284:18; 340:12;343:4	61:6,6,9,22;66:18; 96:22;102:1;109:10; EMBRACE (1) 364:13	124:12;127:10; 130:8;137:7;140:8,13; 141:10;337:21	375:17
either (30) 27:12;33:13;95:20; 102:20,22;109:9; 111:16;116:4;135:1; 143:13;145:17; 156:19;164:3;173:6; 192:8;213:9;226:12; 227:10;232:21;239:6; 262:18;264:13;266:4; 272:13;284:5;300:11; 315:11;335:19; 341:10;365:12	emerge (1) 30:7	163:13;164:1,5,14,18; 165:2,2,11,12,15; 166:1,7;167:4,10; emerged (1) 188:1	envy (3) 294:7,10,11	
	emerged (1) 188:1	168:3,14;171:9,20; emergence (1) 127:11	EORTC (1) 369:21	
		175:16;187:7,15,18; emergency (4) 186:17;305:15,17, 17	epidemiology (1) 85:15	
		188:22;194:3;196:11; emergent (2) 305:20;313:13	epigenetically (1) 155:14	
		200:9,13;201:11,20; 202:18;205:12; 215:18;216:3,5,9; 217:17;219:6;222:14;	epilepticus (1) 388:7	
		225:10;227:12,14; 234:12,13;236:5; 259:2,4;265:11; emotionally (2) 380:5,16	equal (1) 130:14	
		267:12;271:8;288:1; 291:19;296:1,5; emotions (1) 243:13	equally (2) 120:7;206:18	
		298:20;326:16;351:1, 2,6,11,11,12,19,20; employed (1) 205:1	equipment (1) 73:7	
		352:1,20;353:3; 357:19,21;358:6,12; employee (1) 349:8	equipoise (1) 262:7	
		359:9;360:2,7,12; 361:17;362:21;365:9; 367:17;372:2,3,5,7	equipped (1) 255:18	
		endpoints (85) 15:18;17:6,9;19:8; 23:13;35:13;36:19; 42:5;101:22;119:14, enables (1) 182:1	ER (9) 223:17;245:21; 299:16;307:21;313:7, 9,11,18,20	
		15:120:3,10,22;128:9; 157:22;158:3,13; 159:14;160:11,15,16; 164:8,9;167:12,22;	ER/PR (1) 25:12	
		175:18;182:16;183:1; 184:2,4;185:5;188:22; encourage (5) 19:17;35:18;97:2;	era (16) 22:7;23:7,12;27:11; 30:9,18;31:14;36:19;	
		259:18;372:22	72:4;74:7;222:15; 282:6;324:2;368:12, 14;391:13	
		encouraged (1) 8:16	ERBB2 (1) 91:4	
		encouraging (1) 373:1	eribulin (2) 364:15,18	
		end (25) 8:18;17:7;43:13; 59:16;98:4;100:11,14;	Eric (1) 153:1	
		161:21;170:6;177:2; 248:16,18;249:3; 265:13;267:11;	escalation (4) 78:20;264:16; 273:20;276:20	
		271:21;274:3;284:17; 299:13;358:8;374:3,5; 378:16;390:2;391:9	escalation's (1) 264:14	
		end-all (1) 119:12	escape (4) 122:7;142:18; 145:4;177:2	
		endeavor (1) 41:19	ESMO (1) 28:16	
		ended (3) 53:1;73:8;246:8	especially (18) 13:2;42:13;44:9,11;	
		ending (1) 374:14	56:18;64:3,21;171:9;	
		endless (1) 342:4	174:9;182:12;193:13;	
Ellingson (8) 15:8;55:19;125:19, 21,22;126:1;149:19; 386:22	endpoint (97)	energies (1) 254:17	217:12;222:15;	
eloquent (2) 141:9;209:5		engaged (1) 316:7	228:19;229:9;234:14;	
else (9) 45:11;83:1;172:4; 203:21;230:20;		ENGFER-TRIEBENBACH (5) 178:2,3,9;214:7,17	301:17;353:15	
		England (1) 103:8	essential (3) 319:16;344:10;	
		enhanced (2) 36:9;341:8	387:2	
		enhancing (8)	essentially (2) 72:2;212:11	
			establish (5) 187:6,17,17;195:18;	

212:18	350:6;351:15;354:18; 355:2;357:22;358:17; 367:3,6,10;369:18; 370:18;372:15;373:1, 12,13;391:14	exam (1) 335:1 examination (1) 35:3 examine (1) 68:11 example (31) 86:10;90:2;91:16; 92:16;93:3,6;114:19; 125:2;128:22;158:7, 11;171:7;173:2; 186:20;190:17,18; 215:15;217:10; 219:11;221:7;224:18; 225:3;228:5,6;236:1; 297:4;355:8;356:13; 360:10;369:18;372:17	36:18;117:8;179:9; 250:3,4;297:1,3; 323:6;324:10;331:4; 380:2	180:15;249:9 experiment (1) 323:8 experimental (3) 188:14;262:14; 337:2
esteemed (2) 179:11;182:20	event (7) 8:14;136:16; 165:12;166:6;216:7; 237:21;275:1	exclusions (1) 330:15	exclusively (2) 94:2;359:15	experiments (1) 115:14 experiment's (1) 323:14
estimates (2) 9:11;21:4	events (5) 33:12;136:14; 173:14,14;246:8	excuses (1) 390:3	exercise (2) 247:15;293:8	expertise (5) 10:2;150:7;175:14; 203:15;392:9
et (11) 90:22;167:21; 169:4;173:13;219:1; 288:22;313:8;326:21; 357:16;368:3;370:17	eventually (4) 113:6;157:4; 196:19;292:4	exert (3) 107:4;116:5;117:3	experts (2) 34:14;389:2	explained (2) 24:21;246:9
Ethan (1) 177:13	e-version (1) 221:11	exhaust (1) 40:9	exhausted (1) 40:6	explanation (1) 122:14
ethical (4) 293:1;302:21; 303:10;304:4	everybody (24) 8:4;20:14;161:15; 215:11;219:18;243:7, 15;249:20;286:9;	exist (1) 19:8	exploded (1) 85:1	exploratory (1) 197:4
evaluate (8) 23:14;126:19; 138:2;272:2;346:3; 363:5;371:12;388:16	301:10;316:14;317:9; 321:11;338:19; 344:21;370:11,19; 377:11,16;382:21;	existing (3) 325:17	exploring (1) 58:14	exposing (2) 67:6;270:3
evaluated (2) 309:11;383:15	383:2;386:3;392:21, 22	Excellent (2) 12:1;163:7	exposure (1) 106:13;116:21; 250:18	exposure (1) 106:13
evaluating (2) 18:22;23:18	everybody's (1) 189:10	Excellent (16) 37:7,8;50:16;56:13; 83:13;108:14;138:7; 155:21;175:8;189:9; 215:4;216:22;224:9; 229:18;373:18;375:1	exome (1) 54:17,19	expressed (3) 63:14;381:3,5
evaluation (2) 99:3;136:5	everyday (1) 214:9	except (2) 82:17;318:10	expect (1) 88:16	exquisite (1) 126:14
evaluations (1) 237:11	everyone (13) 18:19;19:17;46:18; 96:17;161:10,19; 163:16;175:5;197:22; 229:15;237:9;242:11; 275:10	exceptionally (1) 184:20	expect (7) 21:6;41:20,22; 144:11;161:2;288:8; 347:21	extend (2) 34:3;391:5
even (100) 9:1,22;28:7;30:17; 35:4;36:2,3,9;39:19; 52:14,21;57:21;59:7; 67:7,11;100:22; 103:17;120:18; 121:16;128:20; 131:12;142:3,8; 144:20;150:8;152:4; 165:16;180:3;188:3; 190:19;191:2,4; 192:17;196:20; 198:20;204:17;208:2, 6;209:1,9;210:5; 214:19;217:20,21; 222:9;223:10;226:20; 242:11,18;248:1; 258:2;264:15;273:19; 274:6;278:20;279:3; 280:16;282:6;285:18; 287:12;295:17;297:5; 308:1;315:7,15; 318:11,17;325:14; 326:3,20;327:8; 328:22;330:1;331:7; 333:2;335:22;336:3; 339:4;340:3;18;343:9, 15;346:12;347:15;	excess (1) 105:20	expectations (2) 32:22;45:14	extension (1) 99:12	
everyone's (3) 83:5;157:19;280:19	everything's (2) 293:22;375:6	excessive (2) 273:21;315:12	expected (1) 8:16	extent (5) 130:22;131:10; 188:8;266:16;290:8
evidence (12) 31:7;67:11;131:19, 19;132:4;137:4;	evidence (12) 31:7;67:11;131:19, 19;132:4;137:4;	exchange (1) 175:10	expediting (2) 46:14;258:2	extinguishes (1) 139:7
194:1;222:5;226:22; 250:18;262:10;272:7	194:1;222:5;226:22; 250:18;262:10;272:7	excited (5) 33:16;44:18;47:7; 50:15;178:6	expense (1) 22:19	extra (6) 41:17,18;43:1,12, 13;132:6
evolution (8) 89:1,8,11,19;94:1; 148:15;192:4;198:13	evolved (2) 26:20;87:4	exciting (4) 46:1;48:21;185:17; 376:5	expensive (1) 335:3	extracranial (28) 21:11;32:1,5;42:13; 57:7;72:1,16;86:9,12; 87:14;88:18;89:16; 92:9,13;93:15,18; 94:3,9;97:12;102:17; 108:18;118:15; 237:13,15;242:5; 329:12;332:17;359:6
evolves (1) 84:2	evolving (2) 74:4;93:20	exclude (7) 58:13;107:17; 142:7;285:11;297:8; 329:20;330:1	experience (38) 11:19;20:8;37:17; 38:6;49:10;59:18,19; 60:18;63:15;80:1;	extracranially (6) 29:20;45:9;74:3; 152:4;186:19;327:19
exact (1) 362:13	exact (1) 362:13	excluded (17) 31:4;35:8;51:12; 58:6;76:20;99:13;	98:16;101:7;103:2; 139:5;142:14;143:14;	extrapolate (1) 291:7
exactly (13) 38:2;42:10;89:19;	38:2;42:10;89:19; 152:3;200:14;210:14, 16;229:11;241:20; 242:15;262:4;295:2; 309:4	100:16;111:19;236:7, 15;250:17;279:2; 322:17;325:2;344:8; 380:18;385:12	150:16;178:11; 185:15;194:10; 199:15;251:21;253:1;	extravascular (1) 127:15
excludes (1) 143:5	excluding (5) 254:12;317:7; 324:2,18,21	excludes (1) 143:5	19:254:3;255:14,15, 15;256:20;257:18; 258:5;292:1;348:9;	extreme (1) 354:6
exclusion (11)		exclusion (11)	360:10,13;380:4,17; 382:14	

extremely (2) 68:6;184:17	fall (2) 211:16;337:14	347:20;348:2;364:15; 372:7;375:8;377:9;	39:1;85:6;89:1; 194:6;202:16;207:11;	162:8;16;172:8; 181:11;186:11;187:8;
eye (1) 248:4	falling (2) 54:6;246:16	386:10;387:18;389:1; 390:18;392:2,2	257:12;281:13; 333:21;348:10;	189:22;190:1;199:16; 205:10;210:7;215:2;
F	familiar (7) 34:15;126:7; 134:18,19;381:7,10; 387:14	FDA-approved (1) 142:13	387:19;389:18;390:6, 14	219:20;224:9;226:3; 19;227:13;232:11;
face (9) 18:22;240:4; 245:13,20;253:3,13; 290:7;386:9,9	family (3) 38:19;180:17; 342:19	FDA's (1) 11:22	figuring (2) 69:22;282:11	237:2;238:15;243:4; 15;256:21;259:20;
faced (2) 159:7;263:17	fantastic (7) 69:18;70:5;83:3; 153:2;175:9;215:4; 229:3	FDG (1) 137:14	filling (1) 362:16	261:21;263:5;272:5; 275:4;277:16;280:1;
faces (1) 309:6	far (18) 41:16;139:19; 178:20;180:10;212:2; 214:10,12;220:11; 243:12;244:7,9; 263:19;286:7;304:16; 339:14;342:14; 343:22;377:5	fear (4) 243:16;244:5; 249:12;340:19	filled (1) 61:11	284:18;285:2;293:14; 306:12;310:11;313:6;
facets (1) 163:15	far (18) 41:16;139:19; 178:20;180:10;212:2; 214:10,12;220:11; 243:12;244:7,9; 263:19;286:7;304:16; 339:14;342:14; 343:22;377:5	fearless (1) 382:17	filling (1) 61:18	314:17;317:18;319:7; 320:22;321:18;327:7;
facilitate (2) 45:21;122:22	Farber (1) 84:4	feasibility (4) 137:20;167:17; 174:5;366:7	filtration (1) 312:5	334:12;338:3;342:3; 349:14,14,17;357:4;
facilitating (1) 46:14	fascinating (3) 175:10;183:18; 210:8	feasible (5) 65:16;168:14,22; 169:16;185:6	final (10) 22:2;34:12;147:17; 317:1,2,11;357:6;	358:15;376:8;386:1
facilitator's (1) 64:13	fashion (9) 106:16;114:15; 189:2;209:3;299:17; 332:5;335:22;371:15; 373:10	feel (15) 45:18;164:12; 226:10;262:15; 275:14;280:4,8;	firsthand (1) 9:16	
facilities (1) 130:3	Fast (2) 199:11;257:11	feeling (3) 149:12;169:10; 342:7	first-line (1) 246:22	
facing (5) 246:10;248:15,15; 278:21;306:5	faster (1) 273:17	feels (6) 165:4;168:20; 235:5,8;246:17;347:3	fit (2) 75:7;351:2	
fact (36) 8:21;22:13;24:2,5; 33:6;52:6,9;53:11,12; 66:21;74:1;102:12; 105:10;106:20;110:1; 118:7;142:20;155:10; 163:12;169:19; 172:17;180:1;205:5; 249:10;263:20;264:4; 265:19;266:22; 268:14;279:14; 297:12;307:2;315:18; 322:11;358:5;365:3	fat (1) 115:1	felt (7) 224:3;248:13; 275:8,10;316:16;	five (1) 243:10	
factor (7) 254:4;258:19; 262:19;263:12; 288:20;289:1;357:17	father (1) 151:16	379:14,15	fixed (3) 19:9;122:19;313:20	
factors (6) 45:2;102:16; 109:13;116:17; 191:10;384:8	favor (1) 184:17	FEMALE (3) 227:22;229:13,14	FLAIR (4) 127:4;130:17; 268:13;335:5	
faculty (1) 182:20	favorable (1) 172:14	few (29) 8:10;21:13;26:21; 37:12;61:15;69:3;	flavors (1) 126:18	
fail (3) 265:6,7;291:22	favored (1) 110:8	87:5,10;98:8;99:15; 106:18;126:9;131:12;	flexibility (1) 129:22	
failed (5) 269:2;292:13; 298:15;337:16;340:2	favorite (2) 122:17;339:13	132:17;151:12;176:3; 220:4;280:2;295:10;	flexible (1) 209:18	
failling (1) 323:16	FDA (52)	322:7;334:8,10; 335:14;375:3,3,13,14;	flip (4) 100:12;317:8; 345:16;389:19	
failure (3) 206:19;278:5; 298:12		389:2,3	flop (1) 150:17	
fairly (1) 355:22		fewer (1) 379:13	fly (2) 61:14;63:16	
		field (16) 23:12;26:14;27:17;	focal (1) 217:20	
		34:7;35:1,11;47:16, 19:122:17;125:14;	focally (1) 34:17	
		129:5;132:8;149:11; 243:1;263:19;294:10	focus (18) 16:3;36:15;123:7;	
		27:22;95:7	firm (1) 138:18	
		27:22;95:7	First (88) 8:12;34:4;38:20;	
		27:22;95:7	40:16;47:4;53:2;	
		27:22;95:7	59:22;79:6;80:7;87:6;	
		27:22;95:7	88:14;98:15;99:8;	
		27:22;95:7	104:3,14,16;105:11;	
		27:22;95:7	112:15;121:14,19,22;	
		27:22;95:7	22:123:20;125:8;	
		27:22;95:7	127:2;129:11;136:15;	
		27:22;95:7	139:20;147:8,14;	
		27:22;95:7	149:20;154:10,11;	
		27:22;95:7	156:16;159:3;161:16;	
		27:22;95:7	134:2;136:2;232:18	

focusing (8) 56:20;84:4;144:4,5; 17:254:14;271:15; 354:8	184:3;186:8;191:16; 329:6	free (4) 110:7;167:10; 171:15;246:16	funded (1) 88:1	391:6
folks (2) 81:22;221:16	fortunate (4) 17:20;179:12; 185:7;249:6	freely (2) 106:19;251:10	funders (1) 88:1	generalized (1) 80:14
follow (17) 76:8;98:13,14; 141:13;149:8;163:2; 204:15;209:13; 215:16;216:10; 219:14;326:6,6,8; 330:17;363:12;366:22	fortunately (3) 180:14;246:19; 247:21	frequency (5) 28:7;56:6,6;186:22; 237:13	funding (2) 64:10;369:21	Generally (7) 12:13;43:4;45:9; 73:13;258:22;271:21; 388:21
followed (4) 47:12;132:11,13; 215:17	Forty-three (1) 90:19	frequent (2) 97:16;334:3	funny (1) 216:9	generate (1) 81:3
following (8) 95:16;158:16; 247:1;326:14,15; 335:9;364:12;374:3	forum (2) 145:12;343:17	frequently (3) 306:7;308:3;337:10	further (8) 53:18;55:17; 157:14;194:12; 201:20;241:2;311:5; 369:16	generated (1) 251:11
follow-on (2) 18:4;332:10	forward (45) 8:20;11:17;17:18; 18:20;35:14;36:14; 42:10;50:16;54:7; 66:4;82:12;138:2; 146:14;149:7,13; 150:1;160:19;161:5; 11:162:6;175:12; 177:18,22;182:15,16; 185:22;189:1;190:5,6; 198:18;233:3,12; 243:1;251:4;296:15; 317:4;320:16;384:19; 385:14,19;388:13; 389:12;390:4;391:12; 392:4	Friday (1) 161:22	fusions (1) 27:2	genetic (18) 86:17;87:10;89:2; 10,22;91:8;92:14,22; 93:8;94:12,15,22; 97:10,14;159:19; 310:16;311:2,4
Food (3) 10:6;230:19,20	friend (1) 310:20	Friends (10) 10:11;16:7;64:16; 84:7;243:22;248:7; 273:2;322:1,8;384:3	futile (1) 99:11	genetically (3) 87:4;155:14;332:20
fool (1) 278:3	friends' (1) 260:22	futility (1) 104:15	future (10) 26:8;28:16;113:2,7; 115:15;136:20; 159:17;369:3;371:8; 392:6	Genetics (2) 10:20;41:9
fooling (1) 325:7	frightening (1) 344:5	fuzzy (1) 119:13	genital (2) 163:8;186:4	genomic (2) 89:1;115:2
forces (6) 62:7,8;64:2;88:12; 95:7;308:9	forwarding (1) 199:11		genomically (3) 88:4;91:22;97:18	genomics (1) 97:4
forego (2) 75:8;302:19	fossa (5) 147:4;208:19; 211:19;212:5;213:5	front (9) 27:9;60:11;66:9; 174:7;202:9;293:7; 299:2;350:15,16	gadolinium (2) 55:20;127:14	genotype (1) 183:12
foremost (1) 187:9	found (11) 15:2;40:21;48:3; 49:15;89:7;90:16; 93:16;121:14;179:1; 216:14;342:22	front/back (1) 283:13	gain (4) 74:3;194:12; 199:10;360:11	Georgetown (1) 257:4
forget (6) 144:5;259:22; 282:2;327:19;332:19; 386:2	Foundation (3) 10:13;335:14; 344:17	frustrations (1) 253:2	game (2) 47:10;344:6	germane (1) 167:3
forgetting (1) 240:5	founded (1) 255:12	full (6) 63:1;158:17;188:8; 235:3;314:2;378:2	gamma (5) 72:11;148:3;246:3; 247:5,8	gets (13) 55:8;105:9;135:21; 215:17;218:21;
forging (1) 121:8	founding (1) 255:8	fully (2) 108:1;154:21	gamut (1) 180:20	245:12;271:12; 282:17,20;283:20;
forgot (3) 81:12;180:16; 371:19	four (4) 84:9;85:1,3;259:16	fulminant (2) 206:19;207:20	gasoline (1) 128:19	301:10;348:8;353:6
form (3) 13:17;380:8,12	fourth (2) 147:6;260:12	function (11) 22:20;23:19; 164:12;173:12; 174:21;219:15;220:3; 224:19;227:3;259:3; 368:2	gather (1) 346:1	given (10) 113:2;172:15;
format (1) 162:7	fractured (1) 245:8	functional (6) 165:6;168:21; 173:5;174:17;193:20; 227:4	gave (5) 26:15;225:3;319:7; 362:12;383:10	178:14;240:8;313:11;
formed (1) 10:9	frame (7) 138:7;145:14; 146:10;148:6;211:21; 276:5;285:2	functioning (1) 391:9	GBM (3) 72:22;74:16;256:5	328:7;336:15;341:16;
forming (1) 195:4	framed (1) 176:10	functions (5) 165:5;168:20; 177:21;235:6,8	GBMs (1) 186:8	359:21;376:6
forms (2) 292:13;370:10	framework (9) 20:14;80:6;175:9; 16:187:4,17;351:3,7; 352:5	fund (2) 38:1;326:7	GDC-0084 (1) 95:13	gives (3) 139:1;181:4;291:9
formulating (1) 14:11	frankly (1) 8:16	fundamental (1) 54:11	glad (1) 78:2	giving (6) 117:21;204:1;
formulation (1) 13:18			gland (1) 91:17	245:19;293:12;
forth (9) 43:11;124:14; 125:3;150:17;168:3;			Gleason (1) 219:1	295:15;299:18
			glioblastoma (8) 15:9;70:2;129:16;	
				140:3;294:9,10;
				295:18;385:1
			glioma (4)	

17:11;140:3; 141:12;185:20	granted (1) 170:22	292:4 growth (2) 95:14;123:1	322:15;323:14;354:5; 365:12;369:8;373:6	349:9;350:5,13; 368:16
gliomas (7) 15:5;129:15;131:9, 11;136:3;140:17; 150:11	granting (1) 285:16	GU (4) 83:16,18;160:22; 256:6	happened (3) 136:16;178:20; 301:5	healthcare (5) 173:15,15;221:5; 244:20,20
global (3) 181:9;328:1;354:14	grateful (5) 10:21;44:3;96:14; 385:19;392:9	guarantee (1) 325:3	happening (3) 315:4;329:18,18	healthy (2) 38:8;244:21
goal (5) 16:1;217:10; 248:14;264:22;359:16	gratitude (1) 243:15	guess (14) 97:22;167:9;173:1; 190:9;212:7;215:3;	happens (11) 32:7;136:8;162:8,9; 202:20;208:19;	hear (23) 11:20;24:16;42:2; 44:4;64:19;78:3;83:3;
goals (3) 11:7;19:3;175:19	gray (1) 89:5	248:3;249:20;254:16; 284:9;317:6;337:2; 360:5;388:10	268:11;275:4;279:10; 306:4;308:19	110:14;173:4;189:20; 214:16;229:15;233:1, 5,10;247:22;249:9;
goes (17) 11:4;13:11;27:20; 180:12;207:22;216:8; 244:9;246:17;287:20; 308:7;325:9;360:18; 366:10,12;372:11; 379:8;380:1	great (43) 26:13;37:18;47:4,5; 62:5,10;73:3;119:13; 145:7;152:22;155:19; 179:14;180:17; 189:19;193:5,6;228:6;	guessing (1) 311:12	happy (6) 125:15;242:8; 286:3;299:9;320:3; 392:3	251:4;341:22;342:11; 347:3,11;354:22
gold (4) 119:7;160:8;230:5; 363:21	230:13,14;235:1; 259:6,13;286:4; 294:22;306:12; 311:19;314:20;317:1; 320:11;333:14;348:7;	guidance (15) 13:17,19;16:9,16; 17:15;78:7;17;168:5;	harbor (3) 89:22;92:8;97:9	heard (43) 51:3,6;81:12;82:2,5, 6,7,10;103:7;104:8;
Gondi (15) 252:10,10;263:14; 265:15;266:11,12; 268:4;270:6;276:8; 289:18;290:2,6; 355:10,12;387:13	354:10;356:13,14; 357:3;367:17;375:9; 376:6;383:3;388:10, 11;389:15;391:12	182:9;190:20;296:13; 347:21;384:6;385:5; 392:2	harboring (1) 93:9	117:22;121:10;122:2, 14;123:6,8,9,11;
goner (1) 318:2	greater (5) 41:1;67:19;134:8; 142:10;199:5	guidances (1) 17:1	harbors (1) 92:21	156:17;158:20;
Good (53) 8:4;18:13;20:5; 22:14;37:15;43:9,11; 44:20;46:18;56:11,12; 78:9;98:7;99:1,9; 101:18;103:1;141:1; 157:14,19;22;159:18, 21;162:18;178:2; 180:10;201:3;204:5; 19:219:19;220:18; 233:16;236:14; 251:15;256:16;279:1; 281:11;283:11; 297:13;300:3;304:16; 317:9;319:16;324:5; 325:22;329:14;333:8, 8,8;345:11;349:16; 352:9;357:22	greatest (3) 129:7;254:4;259:12	guided (1) 97:18	hard (24) 66:6;72:5;115:11; 143:18;167:20;174:9;	159:18;173:4;176:16; 189:12;190:3;233:1,4, 6;241:15;260:19;
gosh (1) 278:15	Greg (2) 50:18;151:22	guideline (2) 125:11;275:11	184:17;211:2;223:2; 247:19;277:10;	261:1;281:17;287:11, 11;314:22;318:17;
government (1) 349:8	grief (1) 344:1	guidelines (7) 77:1;211:15;251:6; 274:13;275:15;322:2;	280:20;281:4;290:13, 16;291:6,7;302:8;	319:1;347:11,13;
gradient (2) 131:22;132:12	Groot (1) 69:13	guys (8) 69:14;82:15;83:9; 181:5;230:14;300:1; 375:4;382:15	322:14;331:19; 348:17;360:14; 363:19;376:14	382:18;383:5;384:10; 386:17
graduate (3) 318:5,6;319:8	group (39) 16:8,15;18:2;43:10; 45:17;64:1;77:3;80:5; 87:12;93:12;95:4,16; 101:17;102:9,22;	H	hearing (10) 11:18;44:6;84:2;	
graduating (1) 245:2	118:21;122:18; 125:12,13,15;129:20; 133:21;153:19; 203:12;236:13;	habit (1) 330:21	119:22;123:11;124:1;	
Gralow (1) 243:19	249:13;251:18; 270:11;315:16; 320:19;321:5;339:15; 342:5;343:18;347:19;	habits (1) 331:10	162:22;208:12;243:5;	
grant (1) 319:13	350:15;352:18;375:9; 391:19	half (18) 32:2;39:8;41:22; 48:4;61:12;90:10,17;	301:1	
	groups (7) 12:11,16;111:12; 124:21;186:12; 197:19;392:13	113:3;130:13;149:17; 198:11;222:3;243:11;	heartened (1) 47:5	
	grow (1) 179:17	322:17;18;341:4; 366:5;379:13	heated (1) 386:13	
	growing (1) 48:14	Hallis (2) 243:20;247:7	heavily (3) 105:18;123:7;	
	grown (2) 115:1;179:19	hammer (5) 133:4;185:17; 293:21,22;362:6	126:11	
	grows (1)	hand (8) 78:18;142:22; 187:11;214:10,10;	hedge (1) 38:1	
		334:20;379:8,8	Heller (2) 217:2,2	
		hands (1) 303:14	Hello (2) 181:8;185:2	
		happen (8) 32:21;309:7;	help (25) 17:21;26:11;46:17;	
			48:12;64:9;66:18;	
			110:18;113:15,19;	
			138:7;159:16;214:1;	
			221:8;252:6;253:19;	
			20;278:8,15;307:1,2;	
			9;326:9;361:12;	
			362:16;392:3	
			helped (5) 10:18;83:13;249:7;	
			376:11;393:1	
			helpful (9) 75:5;182:11;	
			289:15;338:4;343:11;	
			361:1,16;362:19;	

367:22	higher (10)	227:20;246:18; 248:13,16;323:2	10:7	ideal (2)
helping (5)	25:1;29:19;34:5; 49:20;108:13;110:5; 142:12;186:21; 264:18;292:12	home (7)	hour (2)	227:2;329:5
helps (3)	112:21;145:16	38:9;73:20;169:19; 174:2;245:18;292:15; 308:7	hours (1)	ideally (1)
305:11;331:17; 333:13	highest (2)	homogenize (1)	11:5	383:17
hematologist/oncologist (2)	129:15;131:9,11; 136:3	280:18	house (1)	ideas (6)
77:21;371:20	high-grade (4)	homogenous (3)	325:1	8:19;9:21;19:18; 177:17,17;391:16
hematology (1)	129:15;131:9,11; 136:3	91:22;92:4;97:12	How's (1)	identified (3)
251:20	high-level (2)	227:6;275:2;305:15	68:22	8:21;24:12;124:13
hemispheres (1)	376:2;378:5	honor (3)	huge (14)	9:21;17:11;36:8;
209:4	highlight (7)	11:21;20:17;286:13	19:11;30:16;35:9; 52:21;60:16;72:20;	66:12;88:6;116:16;
hemoglobin's (1)	24:1;26:7;28:13; 29:8;30:4;249:10; 375:22	honored (1)	76:21;77:6;85:4; 201:18;282:5,7; 347:12;392:8	127:6;177:19;188:21; 203:13;211:8;345:20
278:16	highlighted (4)	256:17	human (7)	identifying (2)
hemorrhage (2)	49:2;186:14,20; 193:2	hoop (1)	95:20;190:1;280:1; 284:11,19;308:15;	212:11,17
124:4;295:21	highlighting (1)	143:20	341:2	ignore (2)
hepatic (2)	74:22	hope (45)	humbled (3)	103:20;328:3
181:22;206:19	highlights (5)	8:18;22;12:20; 13:12;14:3;16:22;	182:19,21;377:13	II (3)
HER2 (16)	21:15;29:6;80:20; 186:15;380:21	17:7,16;21:15;37:1; 43:14;53:18;54:6; 81:10;85:7;98:12;	hundred (4)	83:11,15;253:10
24:21;25:8,9,16; 41:12;77:10;85:17; 91:1;101:18;111:4,6, 10:113:9;206:13; 256:9,12	highly (5)	115:17;138:21;139:1, 8:149:10;160:20; 161:10;176:11;181:3, 5:185:13;202:2,6;	162:2,7,17;232:9; 350:20	III (5)
herceptin's (1)	9:16;72:8;98:20; 114:14;127:21	230:8;240:7;242:20; 244:4;249:11;278:18;	hundreds (2)	IL-2 (1)
198:22	high-risk (4)	301:10;317:2;318:7; 319:7;349:16;377:18; 382:8;389:5,9,9	220:21;282:16	59:21
Here's (8)	212:12,17;334:14; 376:22	hoped (1)	husband (5)	image (6)
91:16;92:16;93:3,5; 170:11;223:12; 306:21;340:17	himself (1)	315:21	180:18;245:11,17; 246:11;247:12	127:2;276:1;
herself (1)	12:3	hopeful (2)	Hussein (7)	324:12;335:5,6;
309:14	HIPAA (1)	319:14;391:19	202:10;249:3; 258:6;269:22;325:21;	370:14
hesitate (1)	178:21	hopefully (21)	326:21;366:21	images (6)
189:18	hippocampal (2)	15:22;18:9;35:16; 46:13,16;100:11;	hypotheses (1)	38:12;127:9,16;
heterogeneity (9)	252:21;355:20	115:13;161:7,10; 187:3;190:12;198:17;	369:2	130:7;131:9;133:19
91:11;94:12,13,15; 106:9;210:5;280:14; 22:288:4	hippocampus (1)	200:4;247:22;252:5;	hysterectomy (1)	imagine (4)
heterogeneous (2)	48:11	256:17;315:17;	247:2	194:3;246:13;
106:16;144:8	histologic (1)	320:15;364:6;383:5;	I	265:7;302:10
Hey (3)	163:9	385:2	IATA (1)	imaging (44)
68:22;296:3;323:18	histologies (3)	hopes (1)	144:13	15:7,8;17:13;35:4;
Hi (10)	154:15,20;312:4	41:11	IC (1)	52:12;109:18;110:9;
37:15;41:8;145:7; 155:21;157:17;186:2; 224:10;243:7;253:9; 334:7	histology (1)	hoping (5)	115:2	123:22;126:11,12;
hierarchical (4)	288:21	13:16;249:14; 312:21;319:17;320:11	ice (2)	129:12;130:17;
203:10;225:9; 228:10,20	historical (6)	Hopkins (2)	37:21;353:16	131:16;136:20,21,22;
hierarchy (3)	98:12,15;99:5; 103:3;363:16,17	182:18;206:9	ICP (1)	137:5,12;151:8;
225:7,15;226:7	historically (6)	horizon (1)	71:8	200:11;234:8;237:1,3,
high (21)	53:5;87:2;222:2; 265:17;285:11;339:16	137:1	idea (42)	5,9,12,17;238:2;
16:18;56:6;100:17; 108:17;121:16; 131:15;132:8;169:3; 171:2;182:7;183:8,14; 237:18;238:21;240:1; 245:2;265:21;318:6; 327:2;358:7;379:1	histories (1)	hoping (5)	26:2;53:14;75:2;	275:22;282:18;
high-dose (1)	42:16	13:16;249:14; 312:21;319:17;320:11	80:8;97:3;104:7;	309:19;320:10;324:3,
318:9	history (6)	Hopkins (2)	118:13;134:12,17;	11,16;326:9;368:3;
	42:20;119:6;191:1, 17:305:9;357:18	182:18;206:9	136:4,12;142:2,18;	369:18,22;370:7,18;
	hit (2)	horizon (1)	165:18,22;167:1;	371:6;384:21;386:21
	200:4;360:14	137:1	immediate (1)	immediately (2)
	hits (3)	hormonal (2)	211:17	38:18;146:3
	239:5;313:16;314:4	25:14;299:18	imminently (2)	168:13;209:10
	hockey (3)	horribly (1)	146:11	immortalized (1)
	37:20,21;41:5	331:7	146:11	146:11
	hold (7)	hospital (6)	immune (16)	27:12;31:1,11;
	98:3;158:12;	38:18;40:15;84:18; 182:19;221:20;350:9	32:10;34:9,9;49:11;	
		hosting (1)	17:57:8;107:3;153:19;	
			20:155:3;258:13;	
			270:15;287:12	

immunological (1) 222:15	309:2;327:3;330:11; 332:17;345:21;347:9;	250:22;259:20;260:1, 6;263:11;264:13;	increase (5) 22:18;33:12;56:2; 135:11;166:3	industry's (1) 257:9
immunology (2) 36:12;155:6	348:16;359:12; 362:22;377:13;	265:19;266:9;267:1; 271:20;272:4;274:22;	increased (4) 53:22;85:2;145:17, 18	ineffective (1) 67:7
immuno-oncology (1) 255:4	382:13;383:13; 385:19;390:8	277:19;279:6;283:18; 286:2;287:22;288:1,	increasing (3) 15:3;222:5;383:6	ineligible (1) 237:7
immunotherapies (8) 26:5;30:11;33:14; 57:2,16;74:10;120:19; 135:19	Importantly (6) 33:10;102:19; 109:12;121:6;176:16; 226:9	15:291:8;296:17,21; 297:12,14;298:8; 300:6;304:11;309:10;	increasingly (5) 26:5;30:6;204:21; 222:13;339:19	infamous (1) 211:5
immunotherapy (23) 32:14;33:2,17; 44:11,16,16;53:21; 57:11,21;59:19,21; 60:21;61:2;74:7; 120:12;153:22; 183:17;222:8;257:7, 19:258:9;327:3; 367:12	impossible (2) 68:8;354:20	316:1,3;317:4;323:16; 334:1;356:15;368:7; 10:369:7,15;383:20;	incredible (3) 38:7;39:16;153:2	inferior (1) 32:19
impact (13) 19:11,12;22:21; 28:6,9;74:9;177:5; 249:16;259:8;267:15; 339:21;379:6;381:16	impressed (1) 53:13	387:20;388:16;390:1, 7	incredibly (8) 15:3;17:20;19:7; 40:11;43:22;63:19; 76:14;143:18	inflammation (1) 54:1
impacted (1) 187:1	impressive (1) 29:14	included (26) 31:6;41:14;75:13; 88:18;90:18;109:13;	IND (1) 297:8	influence (2) 177:17;284:21
impactful (2) 28:15;188:2	improve (9) 22:16;33:19;46:17; 177:14,14;282:8; 290:13;293:10;307:12	111:18;148:2;195:1; 196:22;229:2;236:6,8; 240:12;242:14;	Indeed (2) 21:4;90:2	info (2) 198:20;199:9
impacts (1) 155:7	improved (10) 53:1;94:21;95:1; 96:7;101:12;103:16; 135:2,6;146:14; 344:18	265:17;283:22;291:1; 309:18;318:1;322:21;	independent (8) 43:3;116:5;224:6; 238:17;240:21;	inform (6) 27:22;159:9,16; 228:9,18;253:20
importance (7) 23:18;124:6; 177:12;215:3;327:19; 379:10;383:11	improvement (10) 171:2,3,22;193:21, 21:215:18;235:5,7; 324:12;328:12	359:1,3,7;386:20; 387:11	includes (3) 145:12;343:3; 344:21	information (16) 11:5;43:9;127:22; 178:14;180:5;302:7;
important (106) 9:20;16:5;19:4,7; 30:6;35:14;53:17; 63:19;64:4;67:14; 68:20;75:20;86:5; 88:11;89:13;94:1; 99:19;104:7;110:18; 113:12;118:12;120:5, 7,20;124:1;125:17; 133:8;137:9;138:22; 139:9,16;142:6;143:4; 144:4,20;148:14,19; 151:2;153:14;154:15, 16,17;155:1;157:20; 158:6;159:8;160:12, 18,19;165:19;167:4; 170:18;173:3,17; 174:13;178:17;181:6, 14;184:11;192:17; 193:1;197:15;198:19; 200:1,7,12,22;202:13; 203:8,11,13;206:18; 210:10,10;213:4; 214:4;216:21;222:13; 225:20;226:15,21; 240:17;249:22; 260:17;263:16,17; 269:7;286:20;290:14, 20;293:19;294:1;	improves (1) 339:20	including (46) 10:18;22;11:6;26:4; 28:2;29:10;35:12;	in-depth (2) 375:17;376:7	313:14;324:21,22; 346:1;350:15;363:5; 377:3,3;379:15;387:2
improving (4) 129:6;153:16; 174:16;200:22	improvements (3) 51:7;71:15;282:8	36:16;60:1;96:13; 106:21;108:15;	indicating (1) 288:13	informed (9) 161:7;182:13;
IMRT (1) 156:7	inactive (1) 104:5	118:16;177:20;186:7, 8;187:12,12;191:20,	indication (10) 13:22;24:4;143:15; 171:12;239:9;285:12;	303:12,16;304:13;
inappropriate (1) 251:3	inaugural (1) 18:6	21;192:3;195:11; 242:10;252:1;257:13;	indications (1) 13:22	313:6,8,19;314:1
incentive (7) 189:6;286:1;316:1;	incentivize (2) 233:2;330:19	260:3;261:11;285:18;	individual (7) 81:22;82:15;137:2;	infusing (1) 336:17
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incentives (3) 266:3;341:21;342:1	293:20;296:14;300:4, 5,10;315:2,7;323:18;	individuals (3) 97:21;125:13;	ingrained (1) 67:4
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incompatible (1) 358:3	324:8;325:19;327:14;	indirect (1) 120:7	ingredients (1) 389:11
incentivize (2) 233:2;330:19	incomplete (1) 86:16	332:18;333:4;336:16;	individual (7) 81:22;82:15;137:2;	inherent (1) 222:10
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incorporate (8) 16:9,13;17:1,3;	349:9;360:16;384:7;	indirectly (1) 333:18	inherently (1) 333:18
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incompatible (1) 358:3	390:2	inhibit (1) 95:14	inhibit (1) 95:14
incentivize (2) 233:2;330:19	inclusion (9) 35:12,22;36:17;	inclusion/exclusion (1) 201:8;277:11	inhibition (1) 103:11	inhibition (1) 103:11
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incompatible (1) 358:3	79:15	inhibitor (12) 51:18;52:22;53:3;	inhibitors (15) 25:13;31:15;32:12;
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incomplete (1) 86:16	incompatible (1) 358:3	71:19;95:12,12,18,21;	56:11;71:17;90:21;
incentivize (2) 233:2;330:19	incorporate (8) 16:9,13;17:1,3;	incomplete (1) 86:16	22:151:19;247:1;	96:3;107:3,4,5,5,6;
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incompatible (1) 358:3	incorporate (8) 16:9,13;17:1,3;	312:5	116:7;142:15;144:15
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incompatible (1) 358:3	incompatible (1) 358:3	in-human (2) 59:22;272:5	in-human (2) 59:22;272:5
incentivize (2) 233:2;330:19	incomplete (1) 86:16	incompatible (1) 358:3	initial (12) 12:7;32:11;52:2;	initial (12) 12:7;32:11;52:2;
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incorporate (8) 16:9,13;17:1,3;	incompatible (1) 358:3	incomplete (1) 86:16	138:16;154:14;191:3;
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incompatible (1) 358:3	incompatible (1) 358:3	incomplete (1) 86:16	195:8;200:15;241:9;
incentivize (2) 233:2;330:19	incompatible (1) 358:3	incompatible (1) 358:3	incomplete (1) 86:16	273:5;314:9;378:5
incidence (6) 21:9,24:7;110:11; 112:14;121:11;338:15	incompatible (1) 358:3	incompatible (1) 358:3	initially (2) 52:10;138:16	initially (2) 52:10;138:16
include (68) 44:7;45:15;52:3; 59:5,5,11;80:20;	incompatible (1) 358:3	incompatible (1) 358:3	initiated (1)	initiated (1)

58:15	164:11;244:3	interpreted (1)	45:10;114:3	126:16
initiative (1)	intended (1)	19:10	intra-patient (1)	iPad (1)
84:7	306:1	interpreting (4)	158:10	174:20
inject (1)	intended-use (1)	28:10;128:3;206:4;	intrathecal (3)	ipi (1)
114:3	322:18	362:21	59:20,22;198:22	ipilimumab (3)
injecting (1)	intending (1)	intersecting (1)	introduce (13)	32:12;33:2;195:8
155:12	277:15	141:8	11:21;37:11;50:17;	ipi-nivo (4)
injects (1)	intensification (1)	intervention (9)	81:12;83:9;203:19;	61:17;258:7;
114:9	292:12	75:6;92:7;124:8;	206:7;241:8;243:3;	286:14,15
innovation (2)	intent (2)	176:1;213:16;218:17;	248:19;317:17;	iRANO (2)
12:2;320:10	112:3;277:12	219:1;230:2;291:15	365:21;371:19	136:2,10
innovative (2)	intentional (5)	interventions (1)	introducing (1)	IRB (1)
9:22;376:22	283:19;284:4;	356:1	178:1	96:9
input (1)	332:5,10;333:3	intimidated (1)	introductions (2)	IRC (2)
71:11	intention-to-treat (1)	53:7	176:5;259:14	238:21,22
INS (1)	205:20	into (106)	introductory (1)	iRECIST (1)
297:20	interact (2)	16:11,17:17;2,4;	241:6	136:13
insight (1)	222:8;269:14	23:6,12;24:20;27:6,	invasive (1)	irrelevant (1)
319:17	interacting (1)	11,20;28:8;30:9;	112:9	104:4
insights (1)	118:18	36:21;45:17;46:5;	invested (1)	isocenter (1)
72:15	interactions (1)	51:8;54:18;55:8;57:5,	129:18	148:16
insofar (1)	120:10	8;81:20;82:14;83:10;	investigational (2)	isolated (1)
70:7	interest (11)	103:21;108:15,21;	302:20;364:6	206:14
inspires (1)	26:3;46:22;72:17;	111:7;113:2;115:6,19;	investigations (2)	isotropic (1)
243:13	83:1,5;296:12;347:13;	117:8;119:2;127:15;	21:21;62:19	130:14
instance (12)	349:21;350:7;374:17;	128:16;134:17;	investigator (7)	ISRS (1)
42:6,7;43:2;58:12,	376:9	143:11;145:20;	58:15;65:13;	148:1
14:79:18;171:10;	interested (12)	147:19;150:11;151:2,	109:11;238:16,19,22;	issue (42)
202:5;208:16;212:3;	12:22;14:4;56:4;	11;155:12;158:21;	322:22	16:16;54:2,2;58:4;
253:17;361:4	84:2;203:14;208:12;	159:15;160:13;165:9;	investigator-driven (1)	66:19;83:4;94:11,13;
instead (2)	214:15;297:18;	173:9;175:9;179:10;	392:12	15:147:12;149:15;
34:22;384:13	330:18;360:9;380:17;	180:2;183:8,20;184:6;	investigator-initiated (2)	152:12;169:17;
Institute (1)	386:14	188:11;190:21;	68:13,18	181:14;215:22;
84:5	interesting (10)	196:21;204:4;207:10;	investigators (12)	234:12;239:22;
institution (4)	51:3;69:9;120:2;	213:3;214:22;219:4;	52:5;68:19;185:9;	253:13;254:1;261:18;
43:11;46:2;68:16;	139:14;159:19;163:8;	234:20;235:7;237:4;	279:16;282:3;286:19;	275:21;285:8;292:19;
297:17	167:22;223:21;285:9;	242:20;244:9;254:5;	296:17;302:18;	308:21;313:16;314:4;
institutions (4)	305:8	260:7,12;271:7;	304:14;348:12;	323:7,15,17;328:19,
42:22;62:8;130:2;	interestingly (3)	273:20;274:1,5;278:3;	354:13;392:11	20:329:1;330:16;
132:6	29:18;108:8;110:1	284:10,19;285:21;	investment (1)	332:18;334:19;
instructive (1)	46:20;257:5	292:18;293:16;296:3;	255:20	346:22;348:6;366:7;
110:14	interleukin (1)	298:11;303:21;	invitation (2)	375:18,19;376:6;
instrumental (1)	318:9	305:13;311:2,22;	84:16;186:1	385:9
11:12	internally (1)	313:17;314:6;315:22;	invite (2)	issued (1)
instruments (1)	207:16	318:19,20;319:2,6,13,	308:18;310:4	182:10
169:8	international (1)	17;321:16,20;335:21;	invited (1)	issues (30)
insufficiency (2)	148:1	337:14;343:20;351:3,	316:18	16:4,6;17:11,15;
181:22,22	internationally (1)	12;363:5;380:13;	involve (1)	18:22;19:6;44:9;
intact (15)	87:17	384:5;387:8;392:5	356:4	51:14;75:2;87:18;
51:20;99:6,10;	interplay (1)	intra-arterial (1)	involved (7)	117:14;118:9;147:17;
103:22;105:3;106:19;	214:11	336:16	69:10;83:21;84:5;	149:14;203:11;
107:9,14;108:7;110:2;	interpret (12)	intracardiac (2)	200:2;240:11;250:22;	207:12;242:21;
111:22;116:8,22;	27:19;68:9;166:18;	114:10,12	involvement (13)	261:13;271:5;273:10;
139:16;141:18	236:22;262:22;271:8;	intracranial (23)	21:6,7;23:8;25:22;	292:2;293:2;323:3;
integral (1)	361:16,18;362:5;	9:4,6;86:15;94:9;	29:5;30:20;36:3;	332:14;340:7;347:8;
177:21	363:8,18;366:15	114:4,16;117:9;	199:14,14;236:20;	355:17,18;386:12;
integrate (3)	interpretable (3)	118:16;119:18;	261:19;315:3;340:9	390:16
132:20;151:2;219:4	192:17;193:1;	145:18,19;187:2;	involves (1)	ISTs (1)
144:22	235:21	189:4;204:22;205:16;	223:1	143:13
intelligent (1)	interpretation (5)	206:20;239:3;240:3;	IO (2)	Italy (1)
185:8	133:18;165:22;	18,20;269:13;274:9;	367:6,7	104:16
intend (2)	166:5,21;387:1	373:2	ionizing (1)	items (2)

320:16;391:16	303:14,19	Kidney (7) 10:12;257:6; 317:19,20;319:10; 339:13;342:6	303:19;305:2; 343:12	100:15
IV (6) 232:22;311:16; 315:22;316:5,12,21	JUL (1) 211:4	knowledge (4) 55:14;263:19; 291:21;382:4	larger (5) 73:14;92:5;154:20; 364:22;365:1	
J	Julie (1) 243:19	known (6) 122:11;146:16; 236:10;302:19; 308:15;326:5	largest (3) 39:1;134:13;256:2	
January (1) 46:2	jump (4) 79:6;81:11;117:19; 214:2	knows (4) 157:11;163:16; 297:7;323:1	laryngitis (1) 178:4	
Japan (1) 245:17	justification (3) 239:17;258:14; 339:8	Kumthekar (9) 62:22;96:14;198:9, 10,10;200:10;201:10, 14;202:6	last (42) 16:4;19:14;26:21; 27:18;39:18;41:3; 58:10;61:20;62:2,15; 81:19;82:13;95:9; 99:15;103:8,13;125:6; 127:16;155:19; 156:16;157:16; 158:19;159:12;178:7; 179:16;180:10;184:9; 193:4;198:22;207:5; 217:6;227:19;247:4; 282:12;284:11; 289:17;291:11; 296:10;297:16; 300:20;311:14;331:6	
Japanese (1) 148:2	justify (1) 296:22	L	Lastly (3) 136:19;137:12; 244:4	
JCO (2) 268:6,8	K	lab (4) 45:1;156:19;157:3; 347:7	late (5) 161:22;200:7; 208:5;299:14;347:21	
jealous (1) 72:22	Kalidas (4) 181:8,8;227:19; 228:3	label (10) 143:21;223:5; 225:1;235:2;283:21; 285:19;287:22;288:2, 13;341:12	lately (1) 301:12	
Jeff (3) 185:2;212:15;353:9	KATHERINE (2) 110:22;112:2	labeling (2) 340:16;341:8	latent (1) 299:17	
Jefferson (1) 205:10	Kauffman (1) 132:17	lack (6) 105:3;107:13; 200:10;281:3;313:14; 314:8	later (30) 18:4;26:10;36:10; 40:21;41:2;44:19; 63:20;98:1;110:15; 117:20;119:22;148:9; 154:4;189:16;190:1; 192:19;228:6;244:22; 265:3;266:1;268:15; 290:7;291:9,14; 298:18;299:18; 358:18;367:10,10; 373:9	
jeopardizing (1) 192:8	Keegan (15) 114:7;144:6; 232:14;233:13,18; 253:9,9;271:4,9; 298:7;302:15,22; 303:9;304:18,19	Laleh (1) 371:20	later-phase (1) 267:2	
Jill (1) 155:22	Keegan's (2) 304:6;330:21	land (1) 343:4	latest (2) 139:10;148:15	
Joan (1) 11:11	keep (23) 19:4;66:3;79:10,11; 81:20;83:2;84:10; 118:3;125:6;136:8; 139:9;210:21;235:9; 240:4;243:18;248:4; 256:14;293:13; 324:10;374:12; 377:19;378:1;391:9	landing (2) 313:7,9	late-stage (4) 190:18;228:22; 277:4;299:14	
job (12) 22:14;25:2;37:22; 161:15;174:17;201:3; 230:14;249:13;257:9, 12;283:11;356:14	keeping (2) 81:14;216:4	landmark (2) 146:12;187:20	laughed (2) 148:9;245:12	
Johns (2) 182:18;206:8	keeps (1) 271:1	landsman (1) 145:10	Laughter (1) 299:3	
join (4) 62:8;95:7;232:14; 316:18	kept (1) 388:1	language (4) 175:2,3;322:10; 370:2	Laughter (12) 178:8;209:16; 220:19;268:3;272:19, 22;290:1,5;304:8; 308:16;312:16;341:3	
joined (5) 88:12;255:6; 256:21;281:5;317:17	Kettering (2) 299:9;331:6	lapatanib (3) 105:7;106:12,14	launch (2)	
joining (6) 62:7;64:1;98:8; 145:10;279:4;316:19	Kevin (1) 217:2	lapatinib (4) 105:10,12,15;106:3		
joins (1) 12:18	key (18) 22:15;23:5;24:2,8; 27:15;28:13;30:4; 34:2;35:10;36:15; 66:16;79:7;115:19; 176:14;199:13;214:8; 320:15;368:10	laptop (1) 128:22		
Joohee (16) 10:22;14:13,16,19; 15:14;18:12,14; 230:16;316:15; 345:19;374:4,15; 382:16;388:19; 391:17;392:17	kick (2) 117:20;240:7	laratinib (1) 29:16		
Journal (1) 103:8	kicked (2) 162:10;216:18	large (20) 38:15;54:21,22; 56:17;79:17;137:19; 143:12;150:2,6;164:5;		
journey (2) 286:12;382:2	kid (1) 249:20	knife (5) 165:13;173:7;211:9; 273:11;281:5;294:22;		
Joy (1) 128:11		knowing (3) 303:13;339:19; 340:14;354:13		
Jude (1) 217:15		largely (1)		
judge (1) 126:5				
judgment (2)				

77:4;301:21	342:21;345:9;374:13	292:13;353:5,7,14,16; 370:12,17,17,22; 383:20,21	likes (2) 341:13;362:1	320:4;374:14
launching (1) 352:18	leaving (2) 255:11;311:18	less (21) 22:11;24:15;34:1; 55:1;68:1;101:19; 105:9,18;179:2;	listening (4) 158:16;334:9; 345:13;377:14	
Lauren (2) 283:14;320:17	LeBLANG (2) 334:7,8	235:21,21;254:17; 263:20,22;274:22;	literally (1) 261:9	
layer (1) 204:13	lecture (1) 30:3	275:13,22;340:5; 350:8;367:16;385:3	literature (6) 60:7;100:19; 123:13;131:20;	
Lazer (2) 77:3;352:17	led (12) 11:9;15:7;31:4; 38:4;101:13;106:11; 110:16;195:8,10;	lesson (4) 53:18;191:1,17; 199:6	337:11;343:15	
lazy (2) 254:18;264:6	197:5;254:11;271:10	lessons (1) 28:14	LITT (1) 292:6	
Le (2) 34:14;59:10	left (9) 28:19;38:16;76:4; 77:18;81:3;174:22;	lethality (1) 153:9	little (56) 12:9;36:10;44:1; 58:17;69:8;73:22;	
lead (22) 41:9;42:8;48:17; 84:18;85:8;94:21; 95:1;107:21;157:4,6; 166:2;170:15;181:9; 186:3;187:19;249:6; 266:8;270:11;274:12; 320:18;351:15,22	195:7;245:11;348:22	letters (2) 370:2,3	74:17;80:17;100:10; 106:6;108:7;120:9;	
leaders (1) 83:17	legal (1) 370:1	letting (3) 260:13;271:6;317:8	122:19;135:3;143:14; 152:2;153:4;160:1;	
leadership (1) 12:2	legend (1) 279:10	level (4) 67:10;192:1;	163:11;168:1,6,10;	
leading (3) 108:9;132:19; 286:14	legislate (2) 327:21;329:7	271:13;379:1	169:5;178:4;194:21; 205:14;206:3;210:15;	
leads (5) 96:7;184:1;196:19; 237:18;315:22	lends (1) 258:22	levels (3) 106:15;116:4; 334:14	215:14;217:5;221:11; 222:4;235:14;243:7;	
Leah (1) 243:20	lens (1) 187:5	leverage (2) 266:22;267:1	253:22;254:17;	
leaking (1) 127:15	lepto (2) 325:3,4	LEVY (7) 182:17,17;194:9; 197:11;203:22;	268:12;276:14;280:5;	
learn (11) 29:9;32:6;110:18; 140:5;196:21;201:18; 216:12;242:7;320:4; 371:7;379:22	leptomeningeal (53) 16:13;22:3;34:13; 35:9;36:4;58:4,13,18;	209:15,17	284:9;285:1;294:17; 310:20;328:2;331:11;	
learned (10) 27:17,21;28:14; 37:1;39:6;176:9; 199:6,13;209:21; 377:15	59:1,2,6,13,20;60:8; 10,21;61:7,11,14,16; 18:62:1,14,18,21; 63:4,9,12,22;64:3,7;	liability (1) 108:10	332:6,9;339:12; 341:20,22;353:22;	
learning (5) 37:1;73:22;140:20; 379:6;381:4	66:10,15,20;68:4,12; 70:8;71:11;109:6; 118:16;131:17;134:3;	liberal (1) 272:18	357:10;360:14;376:1; 378:7;380:22	
least (33) 13:18;21:9;35:17; 47:16;49:2;54:4; 55:13;56:2;94:14; 101:10;116:20;117:2; 140:3;150:11,16,20; 177:9;187:5;195:14; 197:18;201:4;234:3; 237:8;262:22;274:22; 281:21;284:11;305:4; 307:7;317:20;357:14; 19,365:5	147:16;198:14;202:8; 208:22;236:17;239:9; 242:19;246:10;248:7; 259:21;260:16	lies (1) 334:15	live (9) 8:6;139:2;203:7;	
leave (7) 38:17;84:12; 172:16;316:11;	leptomeninges (1) 34:17	lieu (1) 303:4	241:19;247:19;	
	lesion (14) 73:18;77:9;128:6;	life (20) 22:21;37:17;39:11; 120:4;128:14;164:3,3;	289:21;318:4;336:11;	
	134:14;135:20;136:6; 137:7;166:15;208:6;	184:10,15,18,20; 214:9,9,15;235:11;	344:15	
	209:7;238:11;270:17;	255:14;291:12,18; 379:7;381:12		
	280:15;337:21	lifespan (1) 357:17		
	lesions (61) 42:19;73:13;106:9;	lifestyle (1) 244:22		
	124:4;127:11;130:8;	light (3) 19:21;83:19;254:21		
	16:13:1;12,13,13,21;	16:18,20;78:14;		
	132:11;133:7;134:6;	171:2;358:7;379:7		
	12,14,20,22;135:6,11;	likely (10) 68:1;164:8;170:20;		
	14,14;151:5,6;166:19;	184:5;192:15;224:5;		
	171:17;203:1;208:2;	225:16;274:22;		
	15,17;209:4;211:16;	359:20;381:13		
	20:213:3,10;234:9;	listed (1) 391:20		
	238:3,6,6,6,7,8,19;	listen (4) 125:18;273:14;		
	245:9;246:4;267:9,19;			
	270:18;271:14;272:2;			

local (26) 15:21;22:11,17; 176:1;213:15,16,22; 217:3;218:6;229:6; 260:11;289:9;291:22; 292:13,20;293:1; 300:12,13,303:7; 315:8;337:11,12,12, 15,22;347:7	315:14;321:6;325:5, 14;333:13;339:18; 351:18;353:10;357:1; 361:3,7;364:1;365:11, 17;370:16;372:17,18	9,11;207:10;208:22; 210:12,14,17;216:12; 218:4;229:22;242:12, 20;252:19;256:9; 260:20;263:3;265:5;	101:9;102:15;108:4,6; 109:2;122:5;123:8; 152:2;156:4,5;178:9; 183:4,6;184:1;198:3; 204:9;211:9;252:1; 253:14;285:14;	male (1) 105:7
localization (1) 211:6	looked (13) 63:3,5;75:19;92:13; 93:13;95:11,17;109:2; 112:2;140:17;218:14; 269:17;330:7	274:15;275:6;277:7; 279:22;285:18; 286:18,19;287:1; 288:3,7;290:21;292:6; 293:6;294:11,11,15;	328:15;333:11,17; 339:12;344:2;345:9; 357:12	malignancies (5) 205:17;206:3; 217:9;254:2;361:10
localized (1) 335:22	looking (72) 18:20;33:11;34:1,7; 44:7;47:1;48:8,10,18; 50:15;60:21;63:2; 69:6;82:9;96:3;	295:20;296:14; 300:18,21;301:12; 310:1;317:1;321:10; 322:19;330:22; 333:12;337:9;342:4; 346:16;347:14;349:9;	328:15;333:11,17; 339:12;344:2;345:9; 357:12	mammary (1) 115:1
locally (1) 236:9	100:22;102:10;103:9; 104:9,12,17;105:6,12; 108:5;110:10;119:18, 20;122:6;131:16; 137:6,16;140:13,14;	352:16,20;354:9; 355:19;363:1;369:15; 376:14;377:17;378:7; 379:22;386:12	328:15;333:11,17; 339:12;344:2;345:9; 357:12	man (1) 190:1
located (2) 170:17;174:15	141:16;144:14;153:7; 154:12;168:9;175:12;	379:22;386:12	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manage (5) 146:3;182:22; 202:16;216:4;309:22
location (5) 173:2,8;174:13; 209:21;210:9	182:15;184:11; 185:22;192:13;	53:21;92:21;158:1; 218:19;244:18	328:15;333:11,17; 339:12;344:2;345:9; 357:12	managed (2) 143:20;245:13
locations (1) 267:7	194:15;198:19;199:7; 200:5;208:5,7;220:6; 251:4;271:18;274:6; 294:4;296:5;298:18;	62:8;64:19;180:21; 218:10	328:15;333:11,17; 339:12;344:2;345:9; 357:12	management (9) 21:19;22:5;25:22; 27:4;46:8;47:9; 148:18;252:12;267:13
locked (1) 245:19	301:13;312:20; 325:11,11,16;327:6, 20;328:5;330:8;337:7, 17;351:20,21;361:2,4, 8	342:16	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manager (1) 38:1
Lombardi (1) 257:4	looks (7) 66:2;124:17;134:4; 203:14;234:22;235:1; 273:6	6:2;19:5;6;168:12; 295:19	328:15;333:11,17; 339:12;344:2;345:9; 357:12	managing (2) 29:7;290:11
long (23) 59:21;92:21;203:7; 206:12;217:11;218:8; 238:9;241:10,20; 245:2;246:7;272:1; 286:12;300:19; 316:17;318:4;322:16; 336:13;349:2;355:17; 358:1;369:16;372:6	loose (1) 391:21	135:3;147:5; 211:10;383:14	328:15;333:11,17; 339:12;344:2;345:9; 357:12	Mancuso (1) 155:22
longer (6) 47:22;96:1;213:12; 241:17;289:21;367:9	lorlatinib (4) 180:3,12,14;332:9	166:4;167:16	328:15;333:11,17; 339:12;344:2;345:9; 357:12	mandate (1) 299:13
longest (2) 134:5;135:5	lose (5) 77:12;176:12; 177:11;214:21;300:21	16:19;56:6;168:12; 295:19	328:15;333:11,17; 339:12;344:2;345:9; 357:12	mandated (2) 109:19;110:9
longstanding (1) 257:8	loss (3) 90:8,18;145:1	20:11;319:12,15;	328:15;333:11,17; 339:12;344:2;345:9; 357:12	mandatory (1) 334:14
look (77) 11:17;12:17;13:14; 17:18;21:16;33:2; 42:12;48:22;49:3,5; 50:1,3;52:15;76:2; 77:5;80:16;99:4; 102:15;104:2;112:18; 113:17;116:12;121:1; 122:1;130:7;18;131:5; 133:6,8;134:13;137:8; 160:15;163:12;168:4; 169:20;172:7;199:1; 201:4;208:9;209:14, 19;226:4;236:6;250:2, 22;254:7;262:13; 263:2,3;264:15; 277:13,15;281:13; 282:19;283:21;286:6; 289:5,7;291:18;309:5;	lost (1) 248:7	383:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manmeet (2) 46:19;54:9
	lot (110) 11:3,16;12:11;16:2; 36:15;44:6,9;45:1;	41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manner (1) 182:2
	48:8;51:3,6;55:14; 57:19;63:7;68:4; 69:12;71:8;73:8; 74:21;78:3;121:10; 123:13;126:2;128:13, 14;129:16,17,17,18, 22;134:17;137:1,15, 22;138:11;158:18; 159:18;161:10; 166:21;167:6;171:16; 176:9;183:5;184:8; 185:4,8;189:12;193:4,	41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manually (1) 371:14
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manufacturer (1) 130:21
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manuscript (1) 61:21
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	manuscripts (1) 322:10
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	many (65) 11:5;12:7;18:9; 22:8;42:3,21;60:7; 63:17;78:10,10;80:8, 11;83:3,21;91:2; 92:11;94:7;96:11; 100:4,20;20;109:22; 112:18;113:20;123:3; 129:2;131:13,13;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	major (6) 56:8;91:9;103:5; 114:2;238:12;257:5
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	majority (6) 15:9;58:5,6;79:19; 129:2;236:8
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	makes (20) 67:20;68:8;74:17; 126:19;208:6;241:20;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	126:19;208:6;241:20; 254:10;261:6;267:4;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	274:21;275:18,19;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	281:4,7;291:5;301:2, 2,305:4;347:4;387:1
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	making (15) 43:8;65:16;91:10; 169:2;198:17;203:18;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	219:5;223:8;303:15;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	310:21;320:20;335:2;
		41:8;150:4	328:15;333:11,17; 339:12;344:2;345:9; 357:12	338:12;377:18;392:16

373:15;381:3,5 mapped (1) 88:22 march (1) 113:2 margin (1) 337:22 Margolin (16) 117:14,16,17; 144:19;148:21; 157:21;176:21; 195:10;197:9;219:21; 220:18;326:19;346:6; 352:8;357:4;367:14 Margolin's (1) 224:12 mark (1) 273:1 marked (1) 29:2 markers (2) 247:17;312:10 market (5) 163:17;200:5; 328:21;331:19;354:8 marks (1) 243:11 Marur (6) 232:13;233:13,15, 16,17;271:10 Maryland (1) 349:6 Mass (5) 59:17;71:7;74:8; 84:18;180:3 massive (2) 96:15;336:20 mastectomy (1) 244:14 match (3) 87:20;302:4;356:15 matched (3) 88:17,21;93:14 matter (2) 271:19;391:2 maximum (1) 275:16 may (96) 8:22;36:12;41:3,6; 42:9;53:16;65:8,10; 77:11;78:21;92:10; 94:3;100:10;104:19; 107:4;108:10;116:6, 12,14,18;117:1; 120:22;121:16; 122:22;129:6;131:11, 21;133:10;135:5,12, 14,15;141:9;142:4; 143:4;149:15;150:16; 158:4;165:16;172:4; 177:17;180:10; 188:22;190:17; 197:18,21;205:14;	210:4;211:20;212:10; 221:8;226:20;236:2; 238:20;252:7;253:7; 259:6,8;262:11;265:1; 269:12,17;273:13; 287:13;288:14,15; 289:6,9,10;290:7; 313:4;315:7,14;326:4; 327:15;328:2;329:3; 335:20,22;338:1; 340:1,1;343:9;348:2; 351:22;356:18; 358:15,16,18;359:11; 365:21;367:7,8;370:3; 373:6,13 maybe (85) 42:17;22;43:7; 51:11;58:9;60:17; 64:22;70:14;78:6,7, 18;79:2;82:19;83:21; 120:5,17;127:7;128:5; 139:19;149:20; 150:21;157:1,1,4,6; 185:17;192:12,20; 197:13;208:13; 209:11;210:19; 212:15;214:3;225:1; 227:19;228:12,15; 248:18;259:17; 261:17,20;264:17,19, 22;266:1,5;269:16; 272:3;273:3;280:10; 283:13;284:22;285:1, 10;295:13,13;296:6; 302:12,22;303:5; 306:11;311:14; 314:12;317:8,16; 321:16,21;323:4,14; 328:22;332:7,8; 333:21;337:15,20; 342:18;345:10; 351:12;356:21; 357:20;366:2;369:19; 371:7;374:17 Mayo (2) 132:18;151:16 MBC (1) 302:1 MD (14) 44:22;59:17;69:14; 147:7;153:1;185:3; 202:10;249:5;298:5; 309:3;320:7;338:6; 364:1;366:21 mean (20) 135:21;142:18; 170:9;172:21;198:21; 242:15,16,16,17,18; 260:2,6;276:14; 288:16;301:1;325:5; 329:17;353:6;371:3; 388:6 meaning (4)	128:3;130:14; 292:21;300:12 meaningful (18) 128:8,18;159:15; 165:7;167:5;187:7,10; 208:10,14;209:13; 226:16;243:11;288:6; 326:17;343:7;369:2,9, 9 meaningfulness (1) 174:4 meaningless (1) 349:11 means (5) 81:7;160:5;196:5; 343:16;381:9 meant (1) 319:5 measurable (5) 134:6;166:8;213:7; 238:18,21 measure (30) 34:21;130:15; 151:9;166:2,11,15; 167:14;168:7,8,13; 169:9,16;171:4,10,14; 177:16,20;194:4; 207:11;210:20,22; 211:2;213:14,14,17; 215:8;226:17;345:14, 14;362:4 measured (10) 106:12;164:20,21; 165:1,8,19;172:4; 173:10;214:5;370:12 measurement (3) 126:4;150:19; 165:20 measurements (8) 128:5;130:11; 133:19;135:5;150:8, 11;174:18;371:13 measures (10) 127:4;165:4; 168:21;171:15;202:8; 227:6;228:18,21; 352:2,15 measuring (8) 70:3;127:13; 164:10;165:3;168:20; 201:3;270:18;345:21 mechanism (2) 99:19;361:6 mechanisms (2) 185:21;212:16 med (1) 167:8 Medarex (1) 195:1 media (1) 310:7 median (10) 30:19;34:19;39:7; 30:19;34:19;39:7;	101:19;102:13;103:3; 193:5;216:15;218:7; 365:6 medical (29) 9:17;18:15;43:6; 44:21;22;46:6,19; 47:8;50:12,18;84:3; 103:19;111:1;113:8; 129:21;130:3;146:2; 163:6;182:5,7,18; 233:17;249:4;257:3; 306:11;308:1;320:19; 344:10,21 medically (1) 390:6 medication (3) 193:15;227:15; 318:13 medications (4) 167:3;236:12; 339:22;340:7 medicine (11) 75:12;138:18; 166:20;223:4;278:7; 282:6;298:20;312:3; 341:5;354:18;391:13 medicines (2) 391:1,4 medicine's (1) 257:12 meds (1) 173:20 meet (8) 44:14;46:5;180:21; 187:7;220:7,8;301:18; 386:9 meeting (19) 8:17;12:21,22; 13:18;14:3,22;16:1, 22;17:17;18:4,6; 20:12;21:18;199:16, 21;300:19;369:10; 382:9;393:5 meetings (6) 12:13,14;129:17; 133:4;148:1;185:21 meets (2) 125:16;220:8 MEK (1) 31:15 Melanoma (50) 10:14;12:15;22:1; 30:15,19,21;34:21; 39:18;44:9,21;49:22; 52:4;56:19;71:15; 86:3;87:14;88:3; 93:14,17;95:19;100:9; 101:9;103:6;106:21; 120:18;121:15,17,21; 155:11,16;161:8; 186:3,20;195:21,22; 197:22;249:4,19; 251:8;252:1;257:5,19;	258:7,9;265:5;270:14; 310:11;326:22;327:1; 357:13 MEMBER (16) 77:20;125:15; 151:14;153:1,6; 155:21;156:1;229:5; 293:5;297:16;298:1; 312:13;313:4;349:3; 350:1,13 members (6) 11:3;14:7;175:12, 13;189:21;241:8 Memorial (2) 182:19;299:8 memory (4) 219:10,14,17; 220:15 men (2) 218:10;297:3 mention (8) 18:1;180:16; 188:18;193:12;210:7; 218:3;262:4;312:20 mentioned (35) 20:8,17;54:9;60:20; 69:9,15;70:8;71:5; 84:16;130:17;135:18; 144:12;167:16;188:3; 209:18;210:9;225:18; 228:12;232:8;239:13; 263:9;264:17;266:13; 290:15;296:16; 325:21;326:12,20; 342:17;367:21; 368:13;373:15; 378:20;381:20;391:17 mentioning (1) 202:12 menu (1) 365:15 Merchant (1) 217:15 Merck (4) 10:19;43:19;44:13; 224:11 merely (1) 333:22 mergers (1) 350:6 mess (1) 371:3 message (4) 30:5;174:1;368:8; 385:13 messages (1) 176:14 met (32) 61:3,8,22;71:10; 72:16,16;77:11;80:13; 97:1;132:21;146:13, 19;147:9;180:8; 205:13;245:8;268:12;
--	---	---	--	---

271:2;284:4;298:8,12, 14;306:6,10;310:11; 314:4;321:1,2,9; 327:2;356:8;360:17	290:12;291:1,4,22; 292:2;293:11;294:20; 295:1,5;300:12;309:3, 10;312:9,11,21;313:1; 317:7;318:1;319:3; 324:2,4,7,9;326:5; 327:6,16;328:12,14; 329:2;330:1;332:15, 16,20,21;333:15,16, 19,20;334:1;338:2; 348:21;356:12,16; 357:11,14;359:1,16; 367:4;368:7;377:22; 378:1,14,16;379:4,21; 380:9,11;381:8,10; 382:1;383:7,9;384:10, 21;385:3,11;388:12	287:2;301:8,11,13,17, 20;310:11;326:4; 327:7;329:20;347:16; 352:19;356:3;362:17; 365:7;366:2	82:17;153:5;194:19; 202:9;205:8;219:20; 221:17;224:9;259:19; 289:20;292:17;293:4; 308:14	145:2
meta-analysis (1) 368:20	methionine (1) 137:16	middle (3) 211:9;247:3;348:3	mini-mental (1) 224:18	mini-mental (1)
metabolites (1) 137:8	methods (2) 263:4;371:11	might (46) 19:19;42:8,12;59:5; 70:13,20;100:8;	minimize (3) 48:18;147:15;347:2	minimize (3)
metastases (296) 9:4,13;13:4;14:1; 15:12,16,19,21;16:8,9, 12,12,14,17,19,20; 17:4,10,14;18:6,8; 19:1,24:5,14,18;28:3, 20,21;29:1,11;30:2; 31:5,18,21;32:3,15; 33:1,15;37:17;40:4; 41:13,15,22;42:17; 44:8;46:22;47:10; 50:21;51:2,5,8,12; 52:4,11;54:13;55:15; 56:16,18;62:20;63:3; 69:11;71:16;77:14; 79:13,17,18;84:1; 85:13,15;86:5,9,11,18, 21;87:2,3,8,11,15,19, 20;88:5,16,20;89:17, 20,22;91:15,21;92:3, 8,15;93:14,15,17,18, 19;94:8,21;95:6,10, 19;96:6;97:9,11,13, 18;98:10,16,19;99:1, 12,22;100:15,21; 101:7;104:13;105:5; 106:2,5,7,15,17; 108:20;109:6,7,20; 110:20;111:18;113:7, 10;114:12;115:10,20; 116:1,16;117:15; 118:6,10,11;119:2; 120:1;121:3,11,14; 122:7,14;123:4,8,10; 125:10,15;126:9; 127:6;141:20;142:3,6; 144:9,15;145:15; 147:18,18,22;148:7, 12,17,18;152:18,21; 153:21;154:1,19; 156:21;159:6,20; 161:2;162:22;166:16; 172:22;173:7;179:13; 183:2;194:11;195:2,4, 6,9,12,20;196:1,7,15, 16;197:18,21;198:15; 205:7;206:20;240:14, 18;241:12;248:8; 249:7;250:8,16;251:9; 252:16;253:5;254:13; 256:6;258:8,15,16,21; 259:3;260:8;262:6,20; 266:15,19;267:13,14; 279:9,20;283:18,19; 287:4;288:9;289:6;	minimum (5) 80:13;130:6;151:6, 10;187:16	minimum (5)		
metastases' (1) 69:15	metastasis (111) 8:8;9;19;11:15; 13:9;16:3;17:5;21:4; 22:6;23:2;24:1,8; 25:1;26:18;29:8; 30:16;31:6,9;35:8; 36:12;45:3,4,5;46:3,4; 52:7;55:5;69:21;70:1; 76:12,16,20;79:10; 80:11;84:19;88:21; 89:3,9;12;90:3,7,12; 91:6,13,19;92:18,19, 21;93:7,8,9,11;94:6, 17;96:20;101:12,20; 102:18;103:16; 109:16;142:1;143:2, 19;146:17;147:2; 151:17;153:12; 156:10,11,20;163:10; 175:16,20;176:17; 177:3;205:6;222:11; 233:4;247:11,16,18, 21;259:21;270:13; 293:13,20;295:8,11; 296:6,14,17,21; 299:12,13;317:4; 320:12;321:20; 324:15;327:10;328:8; 329:21;333:5;338:12; 359:12,17;368:11; 370:1,19;375:19; 380:19;381:17;383:18	might've (1) 279:8	Minnesota (1) 178:5	Minnesota (1)
Mike (32) 39:17;44:21;47:15; 48:20;49:2;50:7; 51:11;54:9;55:4; 60:20,20;62:7;64:1; 71:5;84:20;93:12; 95:16;97:16;100:18; 122:15,18;154:11,22; 197:10,13,21;264:17; 287:11;328:11;338:5, 6;357:8	miracle (1) 318:8	miracle (1)		
Mike's (2) 50:20;60:22	mirrors (1) 381:14	mirrors (1)		
miles (2) 342:18,18	misdiagnosed (1) 344:14	misdiagnosed (1)		
millimeter (1) 130:14	MISHRA-KALYANI (6) 251:15,16;262:2; 287:17;304:5,9	MISHRA-KALYANI (6)		
miss (2) 94:3;338:19	miss (2)	miss (2)		
missed (1) 201:21	mission (3) 250:11;320:13; 375:13	mission (3)		
mistakes (2) 27:21;320:21	mistakes (2) 27:21;320:21	mistakes (2)		
mitigate (4) 80:9;135:22; 136:16;303:11	mitigations (1) 303:12	mitigations (1)		
mix (1) 378:13	mix (1) 378:13	mix (1)		
mixed (2) 57:18;288:11	mixed (2) 57:18;288:11	mixed (2)		
modalities (6) 20:16;36:20,22; 123:14;126:17;329:4	modalities (6) 20:16;36:20,22; 123:14;126:17;329:4	modalities (6)		
modality (5) 23:4;28:7;252:17; 290:10;307:18	modality (5) 23:4;28:7;252:17; 290:10;307:18	modality (5)		
mode (1) 148:4	mode (1) 148:4	mode (1)		
model (6) 69:18;70:12;95:19; 115:12;117:10;288:11	model (6) 69:18;70:12;95:19; 115:12;117:10;288:11	model (6)		
models (29)		models (29)		

26:11;64:8;70:4,6; 85:11;88:9;95:5,10, 13:96:2,3;99:10; 107:17;108:16; 113:14,22;114:1,4,19; 115:11;117:4,9;141:1; 144:8;155:12;280:3; 281:4,10,13	268:8;275:2,3,4; 322:7;367:10,10	384:17;389:2;390:3,3, 14;391:11	299:22;300:2;316:13; 320:16;355:10;374:1; 383:5;388:13;389:12; 390:4;391:12	291:2
moderated (2) 162:12;232:17	morbid (2) 167:1;169:15	Morikawa (1) 106:10	moved (5) 22:7;23:6;47:16; 191:20;376:14	multi-institutional (1) 96:16
moderator (1) 158:15	morbidities (1) 118:14	morning (19) 8:4;18:13;20:5; 37:15;44:20;46:18; 98:7;117:22;122:2; 162:2,18,19;178:2; 188:1;230:8;236:19; 263:18;310:21;328:10	movement (2) 301:11;322:6	multinational (1) 185:6
moderators (2) 154:4;162:4	morbidity (3) 15:12;173:16; 295:19	mortality (1) 15:12	moving (14) 26:15;27:10;30:14; 35:3,14;36:19;47:19; 83:2;149:22;160:7; 198:18;203:21;285:7; 356:14	multiple (23) 20:9;25:16;26:3,22; 30:4,11;48:5;114:13; 118:17;140:12;144:9; 148:16;163:14; 181:13;186:6;220:1; 225:19;228:21;255:5; 285:21;353:14; 368:18;369:22
modern (4) 128:21;138:18; 368:12,14	more (194) 12:9;15:15;17:8; 37:2;40:10;43:17; 44:18;51:11;55:17,20; 58:17;62:6,8;63:19, 21:64:20;66:8,20; 67:2,18;69:19;73:6, 11,22;74:5,16,18; 77:14;80:14;81:18; 85:10,11;87:20;90:10, 17:91:21;94:6;95:3; 97:3;99:18;100:10;	most (66) 9:4;13:2;47:13; 48:1;53:11,13;74:10; 81:4;95:13;114:5; 115:13;118:2;130:1; 137:13;141:21; 145:15;147:19; 152:19;168:4;177:9,9; 187:6,10;196:11; 206:5,18;222:1; 225:16;226:15,15,17; 234:5,11,15;236:17; 243:11;245:10; 252:20;266:20;268:7, 22;275:3;292:1; 295:14;305:10; 308:15;310:5,6,17; 319:15;342:7;344:9; 345:21;357:12; 358:16;360:20;361:3; 363:6;364:3;368:5,7; 379:3,14;380:21; 381:2,11	MRI (20) 38:4,5;52:7;73:11; 77:2;126:12,14; 127:17;130:1;131:2; 133:6;156:10;270:12; 324:5;334:13,17; 335:1;346:21;348:14; 352:18	multisite (1) 132:4
modernize (1) 260:22	modifed (1) 136:12	Moss (2) 299:7,8	MRIIs (6) 43:3,5,8;196:1; 299:13;370:21	must (3) 123:20;240:8;265:4
modulate (2) 287:8;367:8	modulators (1) 287:14	much (82) 12:5;17:19;20:1,6; 23:20;29:9;32:19; 37:3;54:2;67:18,19; 68:14;70:15;73:6,11; 74:5,16;75:22;77:20; 83:12;84:15;117:13, 17;129:4,13;138:6; 152:7,10;153:10; 161:14;163:5;164:22; 176:6;179:19;181:15; 184:16;199:8,20; 201:18;203:12; 204:15;207:14; 214:11;225:6;234:1; 241:5;248:9,11;	mutations (13) 27:2;31:12;86:18; 89:12;90:7,21;91:5; 92:8;122:21;198:4; 312:20;328:15;332:4	
moment (4) 265:16;316:10; 319:1,4	momentum (2) 301:12;302:9	mostly (7) 47:12;68:12;136:2, 3;251:21;252:3,4	mute (1) 8:12	myeloma (1) 12:15
money (1) 306:16	monitor (3) 177:3;267:18; 304:15	mother (1) 349:7	myself (8) 40:11;50:17;81:13; 132:18;206:7;295:17; 349:7;371:19	name (26) 18:14;20:5;37:15; 44:20;77:21;84:16; 125:22;145:8;148:3; 151:14;155:22;163:5; 176:3;178:3;185:2; 197:8;221:18;233:16; 248:20;249:3;251:16; 252:10;310:4;334:7; 349:3;371:20
monitored (2) 323:12;384:1	monitoring (3) 126:13;272:14; 303:22	motivate (1) 233:2	name's (1) 186:2	N
monoclonal (1) 111:3	monotherapy (2) 105:12,15	motivated (2) 185:8;369:11	Nancy (14) 10:22;49:1;82:17; 84:3;98:6;133:21;	
month (10) 95:9;96:10;128:10; 247:13;268:9,11,14, 18;312:12;383:22	months (29) 25:19;30:20;32:2; 34:21,22;39:8,18,19, 21;40:20;41:2;48:2,4; 67:17;161:9;178:7,12; 179:3,8,14,16;216:17;	motivating (1) 340:15	Nancy's (1) 151:18;274:12; 275:21;356:22;357:5; 358:19;363:12;383:10	
		motor (2) 211:19;213:6		
		mouse (4) 114:22;115:4; 141:1;144:8		
		move (37) 23:12;30:9;36:14; 54:7;68:21;82:11;		
		83:7;103:21;131:21; 138:1;162:6;175:9; 189:1;190:5,6;203:20; 215:5;233:2,11;241:2; 243:1;260:13;276:3; 278:5;285:5;292:18;		

367:1	59:15;60:14,15;62:10;	nerve (5) 245:11,15,18;246:5, 6	147:20;297:18; 307:22,22;312:14; 336:6	63:3;68:18;87:12; 93:12;184:13;259:5; 326:20;383:10
narrow (1) 313:19	64:8;65:4,10;67:19; 68:1,5;70:5;71:5,10;	nervous (2) 92:10;243:8	neurosurgeon's (2) 47:10;316:19	nicely (3) 19:2;344:2;355:14
nasty (1) 222:6	75:6;76:3;82:8;85:4, 10,10;86:6;89:14;	neuro (1) 206:4	neurosurgery (8) 71:22;72:3;73:4; 120:16;145:12; 221:20;256:7;306:3	Nicole (6) 374:20;375:12; 376:1,13;377:6,7
National (10) 8:9;10:13;14:19; 96:5;97:18;181:12; 270:11;312:2;375:8; 377:10	92:6;94:19;96:1,6; 103:19;107:4;117:3, 11:118:4,21;122:1; 124:19;128:17; 131:18;135:19;	neurocognition (4) 47:18;48:7,13,14	neurosurgical (5) 22:20;23:18;47:20; 48:16;176:2;184:19; 203:7;282:14;338:14; 353:10	NIH (2) 69:1;320:3
nationally (2) 87:17;96:10	137:18;149:14;158:2; 162:1;163:17;167:12;	neurodegenerative (1) 347:14	neurotoxicities (1) 50:2	Ninety (1) 166:15
natural (4) 54:19;182:4;192:4; 357:18	170:4;174:7;177:15; 182:6,7;186:15; 188:11;193:14,17;	neurologic (7) 35:3;52:1;120:4; 146:1;205:11,16; 259:3	neurotoxicity (2) 23:4;48:9	nitty-gritty (1) 176:13
naturally (2) 40:7;190:13	194:6,16;201:18; 202:22,22;203:12;	neurologically (1) 135:2	nivolumab (4) 33:3;49:14;60:1; 310:13	
nature (3) 65:11;118:20;222:9	204:11;211:17;214:1; 218:18;221:8;226:12, 13;228:2,11,21;233:5,	neurologist (1) 388:14	Nobody (5) 38:19;245:21; 341:13;362:1;370:9	
naturopathic (1) 244:8	7,10,11;241:21; 254:14;264:18; 265:14;268:16;	Neurologists (3) 211:5,11;388:5	nobody's (2) 67:8;249:13	
naught (1) 49:19	269:17;274:3;277:19;	neurology (1) 215:14	node (5) 92:18,20;93:2; 170:13;327:10	
NBTS (1) 11:10	281:12;282:5;284:7;	neuro-oncologist (7) 18:16;43:20;46:19; 149:4;246:9;366:4; 388:14	nodes (1) 93:4	
NCCN (1) 125:2	285:2,5,6;287:3,13, 15;293:12;294:21;	neuro-oncologists (4) 50:12;211:11; 354:20;366:6	noise (1) 131:19	
NCI (7) 96:11;114:7;176:5; 211:15;322:6;356:9, 11	295:10;296:22; 297:10,12;298:17; 301:2;305:20;307:15; 308:10;313:13;	Neuro-Oncology (9) 10:16;15:1;18:2,5; 56:9;104:10;150:10; 176:8;382:9	none (1) 111:16	
NCIC (1) 104:14	316:11;321:12; 323:15,18;330:4; 331:4;333:3;337:3,4;	neuropathologist (1) 149:4	non-eloquent (1) 267:7	
NDOUM (9) 68:22;69:1;320:1,2, 2;337:6;362:2,6;363:9	338:8;342:15;343:20; 346:2;348:10;351:21; 354:4;355:11;359:9; 365:1;367:11;372:3,5;	neuroprotective (1) 252:20	non-enhancing (3) 130:18;140:10,15	
near (1) 136:20	384:2,16,20,20;385:5, 7,12;387:19	neuropsychologist (1) 185:3	nonetheless (3) 193:4;213:20; 242:11	
nearly (2) 317:21;381:15	needed (4) 70:13;73:15; 175:18;331:9	neuropsychologists (2) 50:12;221:3	noninferiority (1) 148:11	
necessarily (19) 116:15;131:8; 135:21;152:12; 196:15;208:21; 261:22;262:21;267:8; 271:15;285:18;292:3; 315:8;352:14;354:10; 357:11;366:1;368:19, 22	needing (1) 53:12	neuropsychology (1) 221:1	noninvasively (1) 56:7	
necessary (5) 65:7;254:15;270:9; 350:3;373:10	needle (3) 276:4;285:6;295:18	neuroradiologist (2) 149:5;334:8	non-IO (1) 367:6	
neck (5) 247:10,10,13;248:2; 325:18	needs (13) 26:13;58:16;65:18; 116:2,2;119:4;160:5; 165:8;166:20;187:8; 263:5;337:1;384:6	neuroradiology (1) 221:7	non-measurable (3) 208:7;238:19,20	
necrosis (1) 338:15	negative (4) 24:22;25:10;85:19; 222:8	neurosurgeon (13) 46:7;69:16;73:18; 74:4;141:7;145:9; 146:9;148:2;149:3; 293:6;299:1,8;305:19	non-mutational (1) 122:21	
need (147) 9:17;15:15;17:12; 19:21;26:10;29:12; 35:9;38:18;39:12; 42:11;45:12;13;49:3, 4;50:1;52:21;56:20;	Nelson (1) 299:8	neurosurgeons (13) 50:11;69:3,7,10; 74:6,12;146:20;	non-neuro-oncology (1) 43:5	
	neoadjuvant (2) 113:1;147:14		nonprofit (1) 391:19	
	neoplasm (1) 9:5		nonprofits (1) 392:13	
	nephrectomy (1) 317:22		non-randomized (3) 36:20;262:12; 360:13	
			nonsignificant (1) 172:1	
			non-small (6) 26:17;27:5;30:7; 49:21;109:2;285:14	
			non-squamous (1)	

288:22	343:19	151:13;162:10; 181:11;203:20; 204:10;205:14; 216:19;229:13; 232:12;237:22;240:7; 263:14;270:15;271:1, 10;281:3;303:22; 305:7;328:2;336:22; 384:1	149:3;161:1;163:6; 182:18;206:7;8;217:4, 16;243:21;246:19,20; 249:4;252:11;257:3; 268:1,5;290:10;297:5; 305:18;306:12,20; 308:5;309:12;310:9; 320:3,8;352:17; 379:16;381:20;382:6	318:8,14;319:14; 323:22;325:9;328:5; 330:20;332:14; 333:10,13;334:8; 338:9;340:6;342:16; 343:17;346:8,15; 347:10,22;348:14; 353:2,17;357:5,20; 358:8,16,16;359:13; 360:20;361:19; 365:15,17;367:19; 368:3;370:14;374:9, 22;377:12,18;378:12; 384:13,22;385:17; 386:17;387:3,21; 389:10
non-statistically (1) 226:20	numerically (1) 108:12			
Non-target (3) 134:21;135:6,13	numerous (2) 11:3;389:16			
nor (1) 93:5	nuts (1) 249:21			
normal (9) 45:19;87:21;88:17; 106:1,5;113:18;114:9; 117:6;247:17	Nuwam (1) 145:11			
normally (1) 268:15	O	offense (2) 305:22;306:2		
Northwestern (2) 198:11;252:11	Oak (1) 12:6	offer (4) 60:15;219:7;241:6, 9		
Notably (2) 109:15,18	objection (1) 270:7	offered (1) 313:10		
note (3) 108:18;112:20; 275:12	objective (13) 166:10;168:13; 203:4;219:2;225:21; 234:16;240:3;294:14; 295:9;360:21;361:2; 362:14;384:11	offering (2) 225:12;377:2		
notebook (1) 89:18	objectively (1) 218:18	office (3) 246:9;343:2;349:4		
notes (2) 357:7;389:4		officer (2) 233:17;375:13		
notice (1) 180:16		offline (1) 205:21		
noticing (1) 377:17		often (24) 19:9;25:17;45:18; 72:7;73:11;86:8,21; 99:20;122:7;146:4; 171:6;193:7;204:5; 226:15;235:17; 237:11;264:2;271:11; 284:12,14;313:12; 318:20;357:16;358:5		
notion (2) 54:10;261:11		oftentimes (1) 184:7		
Novartis (2) 283:14;320:18		old (9) 30:18;39:10; 180:19,19;244:13,13, 22;330:21;331:10		
novel (3) 13:14;188:17,22		older (2) 122:18;324:15		
November (2) 29:16;382:10		oligometastases (1) 148:12		
novo (3) 87:10;102:11;156:4		oligometastasis (1) 146:18		
Novocure (1) 10:20		oligometastatic (1) 22:10		
now's (1) 256:16		ommayas (1) 199:2		
NRAS (5) 310:15,16,16,18; 311:4		once (8) 60:9;127:22;		
nuances (1) 43:7		195:13,17;205:9; 236:5;302:9;382:7		
nuclear (1) 166:20		oncogenes (1) 27:7		
nude (1) 95:20		oncogenic (4) 27:1;89:11;94:12, 16		
number (32) 8:12;9:5;23:5;25:4; 27:15,20;48:21;49:12; 56:10,17;60:10;72:13; 80:13;86:13,15;97:20; 101:6;102:18;103:21; 111:11;115:4;116:1; 118:20;147:17;199:8; 212:3;333:20;334:3,4; 344:7;367:21;384:8		oncologist (44) 13:1;43:6;44:21; 46:6,7;47:8;50:18; 69:1,16,17;83:18; 84:4;102:8;111:1;		
numbers (3) 103:11;295:1;				

8:3;61:17;64:22; 248:12;336:3,7	163:17;188:5;191:8; 222:20;223:20;233:5, 11;334:16	159:6;173:12;182:19, 22;184:18;185:17; 188:18;190:20;194:7; 202:16;207:10,11; 215:10;217:5;218:20;	230:20;231:2;268:19; 283:4;358:9;373:3; 390:17	OXPHOS (3) 95:18,21;97:17	
opens (1) 246:15	ordinarily (1) 216:18	outweighing (1) 214:12		P	
operate (1) 38:18	organ (3) 235:22;250:9,14	ovarian (1) 92:17			
operated (1) 73:5	organization (1) 181:9	over (48) 14:12;15:13;26:21; 27:18;38:16;49:10; 61:13;82:15;99:15; 103:13;110:8;114:12; 128:22;138:8;144:21; 148:7;151:9,9,9; 155:19;159:3;162:14; 175:1;198:13,15; 199:18;215:9,16; 216:11;230:11; 233:21;250:19; 256:10;290:17; 299:16;328:9,12; 344:3;358:9,19;371:6, 9,10;376:17,18,19; 381:7,19			
operating (1) 147:5	organizations (7) 10:9,17;14:9,21; 374:9,22;391:20				
operation (1) 146:12	organize (1) 98:11				
operational (1) 169:1	organizing (2) 14:8;301:20				
opiate (1) 172:8	organs (1) 257:17				
opiates (1) 173:20	original (3) 115:3;220:8;371:6				
opinion (5) 128:12;149:21; 224:15;379:13,20	originally (1) 336:10				
opinions (3) 19:20;244:16,18	ORR (2) 235:6;361:20	outcome (14) 40:7;167:16; 168:21;169:15;176:8; 177:6;185:18;201:13; 202:8;219:16;222:14; 227:4;258:22;361:22			
opportunities (10) 8:19;9:21;26:9; 27:3;29:22;36:13; 123:3;192:6;332:11; 356:10	OS (1) 172:1	outcomes (29) 28:19;33:19;34:22; 46:17;53:5,9;59:8; 75:15;96:7;104:21; 120:5;168:16,17; 169:4,11;173:10; 174:19;176:13; 177:18;193:10; 200:20;201:5;202:1,3; 210:22;217:22; 265:12;367:9;390:21			
opportunity (26) 9:20;20:7;29:8,12; 37:11;44:4;60:17; 63:13;68:18;81:15; 116:12;162:2;176:7; 186:11;201:22;243:3; 282:7;294:8,19; 297:19;298:11;304:1; 362:11;390:18,20; 391:4	osimertinib (4) 63:5,7;183:13; 331:15	outlandish (1) 148:8			
opposed (5) 178:6;190:1; 211:21;219:16;278:15	osmotic (1) 336:14	outlet (1) 128:16			
optimal (3) 17:6;23:9;385:6	others (10) 71:12;95:4;123:17; 133:21;206:22;234:7; 337:5;355:1;375:20; 390:19	outlets (1) 128:19			
optimize (2) 46:12;50:13	other's (1) 309:6	outline (1) 259:16			
optimizing (1) 35:11	otherwise (10) 146:20;154:5; 187:13;189:6;192:9; 212:21;221:13;259:9; 273:14;328:17	outlined (2) 39:5;200:14			
option (5) 77:12;179:21; 214:22;337:15,17	out (121) 17:17;19:20;23:12, 17:26;19:27;2:31:2; 39:1;40:21;47:11; 48:3;55:20;60:13; 62:4,10;66:4;69:5,22; 70:20;73:15,19;75:1; 77:12;84:21;85:6; 88:22;89:1;91:18,19; 96:20;102:16;105:22; 111:16;114:11;115:1, 10;117:11;118:7;	outnumber (1) 9:8			
options (15) 9:18;21:20;40:10; 63:17;179:6;188:5; 292:14;313:10,15; 314:3,9;319:18; 328:13;343:6;366:13	outnumbering (1) 9:6	out-of-the-box (1) 9:22			
oral (1) 41:10	outpatient (1) 323:13	outpatient (1) 323:13			
orbis (1) 334:22	output (1) 125:17	outside (12) 122:10;124:16; 206:3,16;224:4;			
order (13) 99:22;100:13; 131:20;132:22;136:6;	oxidative (1) 93:16	oxidative (1) 93:16			

144:16;220:1;224:15, 19;358:1	partnering (2) 10:8;385:15	214:4;215:16,17; 216:4,4,10;223:16;	63:9,12,14,16,21;65:4, 8,11,15,22;66:3,11,21;	270:3,10,13;271:1; 272:4,9,12,15;273:9,
parallels (1) 218:4	partners (2) 378:20;389:1	235:5,8;237:19; 242:16,17,18;243:6,9;	67:1,3,7,14,18;68:4, 15;69:16,22;70:1,6,	11,12,19;274:8; 277:11,19;278:1,11,
parenchymal (1) 134:2	parts (4) 126:6;162:8; 176:19;253:17	244:12;246:13;248:6, 15;250:1;268:14,17;	15,16;71:8,10,12,17; 72:8,9,13,20;73:5,8;	19,21;279:6,15,19,20; 22;280:7,14;281:18;
parent (1) 381:3	passages (1) 114:13	269:6;278:17;280:13, 15,18,22;282:4;284:6;	74:6;75:6,8;76:11,15; 77:2,6,14;78:4,9,22;	282:9;283:18;285:4,4, 15,17;286:2,15,17,21;
parietal (1) 91:19	passion (1) 252:14	19;301:16,21;302:11; 303:14,18;306:5,11,	79:3,13,16,19;80:11, 13,21;81:1,6,8;82:5,6;	15,17;286:2,15,17,21; 287:3,3;288:9,17,19;
park (1) 360:14	passionate (1) 255:22	21;308:7,15,19;309:4; 310:4,6,17;313:7,8,11,	84:21;85:13,18,19; 86:1,8;87:2,14;90:15;	289:7;290:19;291:1,4, 22;292:2,12,21;
parsimonious (1) 84:11	past (9) 42:17;62:21;75:21; 183:4;198:13;199:19; 216:18;229:21;256:10	16;314:1,5,6;315:11; 317:19,21;323:11;	91:2,3;94:8;96:4,19, 20;97:4;98:16,22;	293:20;294:3,20;
part (48) 37:18;39:4,6;48:7; 56:11;61:1;71:6;72:9; 74:5;76:17;77:7;80:5; 88:4,6,14;94:14; 96:21;127:2;128:1; 132:12,19;133:16; 141:8;148:19;162:8,9, 9;178:17;207:22; 224:22;225:1;232:9, 21,22;255:22;258:17; 265:16;289:4;297:19; 301:20;325:19; 333:16;346:7,16; 348:7;359:8;363:13; 365:2	paste (4) 279:4;281:22; 331:2,6	330:14;340:4;342:1; 343:17;344:12,22;	99:12;100:15;101:7, 11,17,21;102:2,6,11,	295:1,5,8,10,14;296:2, 3,4,7,14,18,21;297:9;
Pat (6) 114:7;144:6;264:6; 279:1;298:7;330:21	patched (1) 392:22	345:17,22;346:4; 348:8;349:7;350:10;	22;104:17,20;105:17, 19;106:4,4,8;107:18;	303:3,5,22;304:14,17; 305:12;306:17;307:4,
Patchell's (1) 146:12	path (3) 129:8;312:5;384:12	360:16;363:2;364:2; 368:2;372:8,19,20;	108:19;109:3,7,9,17, 20;110:3,17;111:18;	17;308:4,11,22;309:9, 15,22;310:6,22;311:4,
pathologically (1) 126:9	patched (1) 392:22	376:11;377:19,21; 378:3,10;379:1,10;	112:2,22;22;113:4,9, 10;115:20;117:8;	5;312:2;315:2,7,13, 20;316:2,4,317:5,7;
pathology (3) 218:21;229:11; 312:6	pathway (11) 87:15;90:18;97:15; 142:5;154:15,16; 163:19,20;312:7; 372:1,10	381:2,2,14,17;382:5, 13,14;386:5;389:4;	118:9;119:1,8;120:8;	318:4,20;319:19,19;
participation (6) 8:15;340:9;380:3,7, 10;383:7	pathway (11) 87:15;90:18;97:15; 142:5;154:15,16; 163:19,20;312:7; 372:1,10	390:1;391:8,14; 392:13	121:2,13,16;122:8;	321:1,2,5,9,20;322:16,
particular (18) 12:18;13:22;26:7; 27:2;28:5;29:12;36:1; 53:15;78:16;124:8; 173:3;180:6;181:17; 212:6;256:9;281:1; 380:18;382:18	patient (167) 9:15;12:3;14:21; 31:5;36:17;37:9;40:2; 50:4,10;65:7;67:16; 68:1;71:18;72:5; 75:16;76:19,22;77:8; 81:20;85:1,2;86:11; 87:9;88:22;90:2; 91:16;92:12,16,17; 93:6,14;95:5;110:19; 113:12;114:20;120:4; 121:22;136:7;137:3; 138:9,14,17,20;139:2, 4,8,11;143:17;156:1; 157:18;158:6;159:8, 17;161:1;164:4;	40:1,13;41:1,15,16; 42:1,13;43:1,15,16; 44:8,14,17;45:15,17, 19,21;46:3,4,13,15; 47:19,21,22;48:2,4;	125:9;131:14;134:22; 140:3,8,9;141:2,19, 22;142:2,21;144:15;	21;323:6,7,16;324:2, 3,6,8,18;325:2,4,15, 21;326:4,13,13;
particularly (22) 23:6;28:15;30:8; 63:22;70:7;105:17; 121:15;123:15;126:3, 11,20,22;132:3;133:8; 147:10,12;192:20; 205:17;259:8;260:7; 354:14;363:20	patient (167) 9:15;12:3;14:21; 31:5;36:17;37:9;40:2; 50:4,10;65:7;67:16; 68:1;71:18;72:5; 75:16;76:19,22;77:8; 81:20;85:1,2;86:11; 87:9;88:22;90:2; 91:16;92:12,16,17; 93:6,14;95:5;110:19; 113:12;114:20;120:4; 121:22;136:7;137:3; 138:9,14,17,20;139:2, 4,8,11;143:17;156:1; 157:18;158:6;159:8, 17;161:1;164:4;	48:3,8;19:2,10; 21:5;22:9;23:2,8;	145:13,20;146:4; 148:13;149:6;158:1;	327:15;328:7,12,13, 18;329:2,14,21;330:1,
parting (1) 230:16	pathway (11) 9:10,19;11:14,15, 16;13:2,5;15:16;16:9, 11,17;17:22;19:13; 21:5;22:9;23:2,8;	24:11,13,18;25:22; 26:16;27:5,6,8,10;	159:5;160:21,22;	6;333:15;334:1,13;
partner (1) 10:9	patient (167) 9:15;12:3;14:21; 31:5;36:17;37:9;40:2; 50:4,10;65:7;67:16; 68:1;71:18;72:5; 75:16;76:19,22;77:8; 81:20;85:1,2;86:11; 87:9;88:22;90:2; 91:16;92:12,16,17; 93:6,14;95:5;110:19; 113:12;114:20;120:4; 121:22;136:7;137:3; 138:9,14,17,20;139:2, 4,8,11;143:17;156:1; 157:18;158:6;159:8, 17;161:1;164:4;	28:3,8,19,20;29:1,4,7, 10,13,17;30:1,13,19;	162:21;164:12;	335:8;336:19;337:4;
partnered (1) 97:5	patient (167) 9:15;12:3;14:21; 31:5;36:17;37:9;40:2; 50:4,10;65:7;67:16; 68:1;71:18;72:5; 75:16;76:19,22;77:8; 81:20;85:1,2;86:11; 87:9;88:22;90:2; 91:16;92:12,16,17; 93:6,14;95:5;110:19; 113:12;114:20;120:4; 121:22;136:7;137:3; 138:9,14,17,20;139:2, 4,8,11;143:17;156:1; 157:18;158:6;159:8, 17;161:1;164:4;	31:1:4,8,13,14,17,20;	167:21;172:19;	338:12;339:6;340:10;

388:19;391:17	12:11,16;20:9;	278:9	PET (8)	physical (2)
Patrick's (1)	21:16;53:6;55:18;	perfusion (5)	52:15,17;106:3,12;	38:8;173:12
208:1	61:14;69:6;75:14;	127:17,19;133:6;	126:12;137:12,14,15	physician (5)
pattern (4)	79:9;82:2;83:3;96:11;	136:22;137:5	325:18	45:1;84:17;167:6;
89:8,16,19,20	99:20;100:5;114:18;	perhaps (22)	PFS (7)	303:15;346:17
Paul (13)	118:21;129:17;	12:12;67:1;100:13;	109:11;157:22;	physicians (2)
23:11;47:15;	138:11;140:22;	107:3;182:21;184:4;	171:19;203:6;259:6;	60:15;307:21
101:14;163:4,6;	150:15;151:12;157:5;	187:13;188:20;	361:20;363:16	physician's (6)
202:12;215:7;222:18;	158:16,18;177:13;	217:10;228:22;	363:22;364:16;	365:16,18,20;366:14
228:4,5;361:10;	181:3;207:10;214:16;	272:14;306:6;314:7;	physiology (2)	126:19;145:21
368:12;390:19	222:20;223:7,8;	335:4;339:18;340:5,7;	PI3 (7)	87:15;90:20;95:11,
pause (2)	241:11,13;248:19;	344:13,14,15;383:11,	12:97:15;154:16;	12:97:15;154:16;
252:2;274:4	254:6;255:5;260:20;	13	312:6	312:6
pay (2)	261:3,10;265:7;271:6,	period (11)	pharma (16)	pick (4)
244:8;350:13	17;273:3;274:4,22;	45:19;75:5;136:5;	37:9;255:15,19;	215:15;284:15;
payers (1)	276:17;279:17;280:3;	268:4,10,17;274:14;	256:19;274:11;	306:8;359:9
187:12	282:21;283:3;284:14;	318:17;387:12;390:2;	276:18;279:3,4;	picking (1)
paying (1)	286:17;291:3;305:11;	391:9	280:10;281:5,6;282:8;	56:15
158:18	317:17;323:19;	peripherally (1)	283:1;326:7;335:18;	picture (4)
payload (1)	333:19,20;335:14;	199:4	354:9	48:8;172:18;
111:4	347:18;353:4;355:2;	peritumoral (1)	pharmaceutical (4)	225:17;387:3
Pazdur (8)	365:4;379:3;380:18;	124:4	97:6;144:3;340:14;	piece (2)
11:22;12:1,3,5;	386:2;387:22;388:1	permanent (1)	350:16	128:1;378:7
14:18;18:18;20:7;	people's (2)	248:1	pharmaceuticals (1)	piecemeal (1)
83:19	67:4;327:9	328:1	257:1	147:10
PD-1 (1)	per (2)	person (10)	pharmacy (2)	pieces (3)
60:2	21:6,8	105:13;150:7;	350:5,9	133:2,5;224:16
pediatric (3)	percent (54)	152:1;200:22;245:12;	pharmas (1)	piggy (1)
181:20;217:4,8	9:10;24:15;31:13,	249:19;308:14;346:8;	344:22	140:20
pediatrics (1)	22:32:4,16;33:5,8,21;	349:1;381:12	phase (57)	piggyback (2)
252:13	41:2;49:19,21,22;	personal (5)	74:15;80:10;	194:9;333:7
peeled (1)	85:17,19,20,22;86:2,	139:4;177:7;187:5;	100:19;111:17,17;	piggybacks (1)
147:16	3;90:19;94:6;100:19;	215:12;381:1	140:19;143:21;	150:15
Peggy (1)	104:17;105:20;	personality (1)	145:15;158:8;175:21,	PIK3CA (4)
341:22	109:15;110:3,5;	255:6	22,22;176:1;189:16,	90:8,21;95:14,15
Peggy's (1)	111:14;112:10;113:6;	personally (5)	22:19;1:3;192:19;	PIK3R1 (1)
317:18	121:16;135:4,11;	139:4;20:20;70:1;	194:10;197:4;198:16,	90:21
pelvic (1)	161:9;166:15;170:8,	152:12;330:13	16,19;199:7,11;200:6,	pilots (1)
170:13	14;177:1;244:15;	perspective (42)	7,12;20:1;19;205:13;	70:13
pelvis (1)	263:20,21,22;265:21;	58:7;66:5,6;76:22;	249:19;263:9;267:21;	pioneered (1)
170:12	267:3;269:4,5;282:17;	138:17;140:7;143:17;	268:21;269:2,9,16,20;	114:7
pembro (2)	295:20;334:4,4;	159:8,15;187:5;189:3,	272:15;273:7;279:13;	pioneering (1)
61:3,12	379:16;380:6,9;381:9	15,16;192:13;200:11;	280:8,12,21;290:16;	122:16
pembrolizumab (6)	percentage (3)	202:11;212:10;	291:9;292:9,11;298:9,	pipeline (1)
32:13;40:13;41:3;	273:11;339:19,20	253:15;255:19;263:1;	17,18;300:8;315:6;	369:13
49:13,20;62:1	percentile (1)	266:3;274:11;283:1;	331:2;339:2,7;359:4;	pitched (1)
penetrant (2)	186:22	296:11;300:15;303:2;	391:22	184:3
95:12;144:5	perception (2)	304:22;313:15;	phases (8)	pitfalls (1)
penetrate (5)	64:11;382:5	316:20;340:14;342:1,	78:5;99:13;111:19;	150:12
51:16;100:1;	perennial (1)	7;360:9;364:2;	199:9;227:11;264:13;	pivotal (1)
106:19,22;142:9	140:2	377:20;378:3;381:14;	295:7;329:15	197:3
penetrates (1)	perfect (6)	382:5,6,14;389:4;	PhD (1)	PK (2)
100:7	70:6;174:3;189:20;	390:1	221:19	104:11;348:15
penetration (28)	213:5;297:22;389:7	perspectives (3)	phenomena (1)	place (15)
56:3,12,14;86:16;	perfectly (2)	11:18;354:22;	55:16	15:18;46:16;53:16;
99:6,9,18;103:22;	77:11;259:1	377:12	phenomenon (2)	64:7,20;79:21;95:6;
104:3;105:3,7;107:9,	performance (6)	persuade (2)	145:10;205:10	138:1;192:16;287:8;
12,14,20;108:15;	101:18;102:17;	241:11;242:9	phone (2)	293:14;302:13;307:3;
112:16;116:5,7,22;	103:1;109:4;172:12,	persuading (1)	8:13;261:11	319:13;344:3
139:21;140:13;	13	354:13	phosphorylation (1)	placed (1)
144:17;152:9;160:4;	performed (1)	pesky (1)	93:16	
264:11;328:21;383:12	17:9	180:8		
people (69)	performs (1)			

244:15	82:13;94:7;103:14;	210:11;218:11	187:13,21;189:3,7;	45:2;164:6,9,11
places (4)	104:3,6;105:2,21;	portfolio (1)	191:9;192:3;207:13;	predictive (1)
82:9;176:22;231:2;	107:8;111:16;112:20,	38:1	209:12;215:10;	115:13
242:7	22:113:11,16;115:8,	pose (3)	225:21;257:21;	predispose (1)
plan (5)	12:118:7;121:12;	78:1;157:9;345:7	276:21;292:22;	122:22
10:8;72:10,11;	134:21;138:14;143:9,	posed (1)	302:19;303:2;315:7;	predisposition (1)
176:20;239:21	9;147:8;157:14;	207:5	330:8;366:15;368:4;	198:3
planned (3)	158:4;180:11;188:17;	posing (1)	384:10	preferentially (1)
71:22;97:19;237:14	192:5;202:2;204:19;	315:12	power (3)	266:9
planning (3)	207:3;211:3;215:20,	posit (1)	202:3;288:5;365:1	pre-imposed (1)
10:9;11:9;386:3	21:216:21;218:21;	295:17	powered (1)	335:4
plasma (1)	219:19;222:17;	position (1)	353:11	preliminarily (1)
105:9	224:12;237:2;238:1;	341:13	powerful (2)	155:17
platelets (2)	260:3;263:17;269:3,5;	positive (21)	46:11;243:4	preliminary (1)
250:5;278:16	279:1;282:13;286:4;	10:5;24:21;25:12,	practical (8)	376:2
platform (1)	296:19;298:2,6;299:8;	16:39;15:41;12:85:17;	217:21;266:13;	preparation (1)
46:14	301:7;306:3;308:22;	21,22;86:4;101:18;	277:1,3;308:11;347:8;	11:6
play (3)	309:4;328:22;346:15;	111:6,11;113:9;189:3;	360:1;367:16	prepare (1)
37:20;188:11;336:5	352:4,13;353:19;	206:13;256:9,12;	practically (1)	11:5
played (1)	356:2;382:1;387:11;	266:15;284:22;299:16	353:2	preparing (1)
37:19	390:9,12	possibility (6)	practice (13)	175:11
playing (2)	pointed (3)	142:7;143:6;	54:3;55:10;220:22;	prerogative (2)
41:5;132:18	23:11;26:19;188:18	150:20;284:17;341:7;	223:3;255:7;269:1;	64:14;81:19
plays (2)	points (24)	354:12	279:7,12;286:22;	prescribe (1)
50:5;139:1	8:11;24:2;29:4;	possible (22)	287:2;323:13;354:18;	334:16
please (11)	30:4;49:1;76:6;	14:22;45:15;72:1;	364:17	prescribed (3)
8:12;19:17;161:20;	112:18;152:17;	78:6;126:8;158:9;	222:1,3;223:19	
197:7;230:13;235:9;	157:21;186:10;188:2;	160:3;211:13;252:18;	presence (5)	
249:1;293:4;298:4;	216:22;220:2;237:16;	257:11;264:2,3;	109:13;235:18;	
316:9,13	258:2;263:16;281:16;	269:11;270:1;291:18;	239:14;281:19;357:13	
pleasure (2)	283:6;299:14;328:1;	303:17;321:19;	present (9)	
119:20;162:19	329:8;367:1;389:3,22	351:18;354:19;	19:18;31:12;	
plenary (2)	poised (1)	380:15;392:16;393:2	109:21;135:14;	
347:22;348:4	301:4	possibly (5)	247:12,13;291:14;	
plenty (1)	pool (1)	160:8;246:10;	366:1;382:8	
173:10	139:11	336:5;351:13,14	Presentation (18)	
plot (1)	pooling (1)	post (1)	14:15;18:12;20:4;	
31:19	101:14	105:15	27:16;50:20;84:14;	
plug (7)	poor (11)	post-contrast (2)	98:6;117:16;121:14;	
62:3;84:20;92:6;	53:5,9;98:16;101:7;	127:9;130:7	125:21;155:22;163:3;	
95:3;128:15;299:10;	191:15;192:22;	poster (1)	4,232:12;233:15;	
376:3	241:19;258:19,22;	103:5	374:8;375:5;377:7	
plurality (1)	265:12;365:7	posterior (5)	presentations (2)	
50:21	population (39)	147:4;208:19;	153:3;157:20	
plus (13)	9:17;53:11;75:17;	211:19;212:5;213:5		
59:22;102:4;158:9;	102:6;109:15;110:19;	postmarketing (1)		
161:9;168:10;169:6;	113:12;181:20;182:6;	164:14		
230:19;239:7,7;	192:3,10;202:14,15;	post-radiosurgery (1)		
240:16;337:21;349:6;	205:20;212:18;	268:9		
367:7	239:18,19;260:7;	post-tissue (1)		
pluses (1)	262:19;263:11,22;	295:21		
167:11	264:5;265:1;280:22;	potent (1)		
pm (3)	282:5;284:7;287:16;	55:8		
231:4;232:2;393:5	288:4,7;289:14;	potential (19)		
podium (2)	322:18;340:5;363:2;	36:8;39:4;68:10;		
82:16;148:9	372:8,19,20;389:15,	116:14;117:2;145:17;		
point (89)	15,19	166:4;167:17;188:15;		
19:14;24:6;25:10;	populations (5)	191:6,8;266:7;294:4;		
31:2;40:9;55:8;56:22;	181:19,19;192:21;	299:12,12;311:1;		
57:3,4,9,20;59:10;	201:9;387:6	354:8;362:16;366:19		
60:22;61:5;64:6,11;	portending (1)	potentially (26)		
67:10,13;69:5;73:3;	227:8	15:14;44:10;67:7;		
74:22;75:8,20;81:5;	portends (2)	94:3;168:18;171:3;		

pressure (2) 145:18,19	357:21;370:7,14; 379:18;380:8,12	349:9;353:2 procedure (3) 167:7;169:15,18	154:18;166:21; 171:15;172:1;182:4; 202:20;203:16,17; 204:18,22;215:22; 216:7,15;229:8; 238:11;240:2,4; 269:13;275:1;384:1	14;173:1;218:5,6; 225:4;228:5;351:9; 352:11
presumably (1) 111:21	principles (1) 123:20	procedures (2) 165:21;167:2	prostatectomy (1) 218:11	prostatectomy (1) 218:11
presurgical (1) 106:13	prior (9) 63:14;124:10; 130:10;178:16; 217:19;238:10; 255:11;269:2;279:4	proceeded (1) 244:19	protectant (1) 176:2	protectant (1) 176:2
pre-tissue (1) 295:21	priori (3) 78:14;79:8;80:2	process (10) 11:10;39:4;74:14; 181:18;260:18;315:5; 325:8;334:2;347:20; 363:22	protection (1) 54:19	protection (1) 54:19
pretreated (1) 105:19	priorities (1) 379:11	processing (1) 221:8	proteomic (1) 87:13	proteomic (1) 87:13
pretty (14) 121:21;166:10; 167:5;168:22;206:10; 224:6;234:1;280:4; 300:3,5;321:5;324:5; 337:13;376:5	prioritize (3) 26:12;115:5,16	producing (1) 196:9	protocol (20) 15:7,9;109:18; 129:12;132:13,20; 137:21;199:18;200:2; 223:17;224:2;273:20; 274:1,5;282:1;297:7; 331:7;335:11;384:21; 386:21	protocol (20) 15:7,9;109:18; 129:12;132:13,20; 137:21;199:18;200:2; 223:17;224:2;273:20; 274:1,5;282:1;297:7; 331:7;335:11;384:21; 386:21
prevalence (4) 100:17;109:17; 228:16;265:20	Priscilla (11) 59:16;18;60:17; 84:14;17;104:8; 113:13;122:15; 197:14;287:11;333:2	Product (10) 8:8;233:3;266:4; 284:5,7;331:18;369:9; 392:5,10,11	proliferating (1) 137:10	protocols (7) 17:13;130:1;131:1; 251:22;254:7;296:20; 334:21
prevalent (2) 260:8,9	privileged (1) 186:11	productive (3) 12:21;14:3;17:18	prolong (2) 164:3;217:11	prove (3) 116:22;286:8,10
prevent (5) 99:3;152:18; 173:19,20,22	Priya (4) 62:22;96:14; 198:10;200:8	Products (7) 233:18,20;251:20; 253:10;284:12; 331:19;371:21	prolongation (1) 217:19	proven (3) 24:7;258:6;373:9
preventative (1) 326:10	Priya's (1) 200:18	professional (1) 244:20	prolonged (1) 259:6	proves (1) 47:22
prevented (1) 124:13	PRO (2) 169:8;283:1	professor (1) 126:1	promise (1) 300:1	provide (9) 15:17;21:14;36:12; 132:5;189:5;219:5; 286:1;299:9;316:1
preventing (6) 143:1;167:1,2; 169:13;173:15;355:18	probably (48) 12:7;21:9;22:2; 42:11;55:2;58:10,16; 60:11;66:19;79:4; 113:5;114:5;117:9; 145:1;163:20;186:10; 16:188:11;18:190:9; 192:6;206:22;209:21; 216:12;222:1,7; 243:10;254:4,16; 256:3;268:16;279:18;	profile (6) 66:1;170:1;172:10; 14:190:17;381:1	promises (1) 136:20	provided (6) 16:8;19:2;26:19; 27:3;234:21;378:17
prevention (10) 107:22;110:12; 112:17;116:10;117:2; 143:4;152:15;218:16; 326:17;383:14	profiles (1) 78:13	profiles (1) 78:13	pronounce (1) 125:11	providers (1) 221:5
previous (6) 105:18;132:15; 194:5;202:3;320:19; 380:11	prognosis (7) 101:17;102:22; 191:16;192:21;193:2; 241:19;365:7	profile (6) 66:1;170:1;172:10; 14:190:17;381:1	pronouncing (1) 207:6	provides (4) 35:17;46:13;137:5; 340:6
Previously (8) 48:1;133:15;159:6; 191:19;201:17;238:8; 9;292:21	prognostic (3) 102:16;258:19; 288:20	program (6) 41:10;50:7;68:13; 73:4;186:6;255:8	proof (6) 32:13;36:5;45:7; 141:17;142:5;190:15	providing (2) 16:16;376:22
primarily (7) 23:1;47:1,10;50:19; 129:15;182:18;253:13	programs (2) 218:20;376:20	proper (3) 99:3;110:10;340:8	properly (2) 342:5;343:9	provoke (1) 331:8
primary (65) 9:8;23:13;46:21,22; 55:5,13;61:22;86:19, 22:87:4,9,21;88:5,17, 22:89:4,9;90:1,4,9,13; 91:7,8;92:2,9,17;93:1, 7,10,20;94:2;96:22; 97:11;109:10;110:6; 125:14;129:14;140:3; 159:20;160:5;163:13, 22:165:2;172:2; 173:6;186:7;200:13; 203:5;205:16;206:3, 16:216:3,5;265:11; 267:11;329:11; 332:16,18;333:6;	progress (11) 33:16;57:17;79:20; 102:4;128:18;129:8; 133:3;136:1;203:3; 268:20;278:2	progress (11) 33:16;57:17;79:20; 102:4;128:18;129:8; 133:3;136:1;203:3; 268:20;278:2	prophylactic (1) 355:21	provoking (1) 139:14
	problem (25) 12:18;21:4;30:16; 34:18;36:1,3;47:18; 50:22;51:4;56:17; 75:12;82:3;83:5; 109:17;124:9;138:12; 173:21;232:6;246:1; 279:11,14;305:14; 333:5;334:15;389:17	progressed (6) 27:18;32:4;38:14; 60:2;204:7;237:20	proposed (1) 149:9	Powell (54) 162:15,18;192:11; 206:2,8;213:1;222:17; 226:1;232:17;241:5; 248:11;249:1;251:14; 252:9;259:13;265:15; 271:4;272:17,20; 273:1,18;276:13;
	problematic (2) 213:11;246:7	progressing (8) 24:14;30:1;79:20; 207:21;242:5;292:22; 300:14;303:3	pros (2) 119:16;201:14	283:8;285:8;289:18;
	problems (4) 167:18;184:19;	progression (29) 13:4;86:16;108:9; 110:7,11;121:18; 122:1;141:21;153:8;	prospectively (1) 148:10	298:3,22;299:4,22;
			prostate (11) 123:18	302:14;304:18,20;
				305:22;308:13,17;
				310:3;311:9,13,22;
				312:17;313:2;314:10,
				19,20;321:21;322:5;

340:11;347:10; 354:11;362:3;365:2	376:3 puts (1) 341:12	quite (29) 11:3;26:20;32:21; 33:20;75:4;102:5; 103:2,12;105:2,10; 107:8;119:21;125:16; 127:16;148:17;160:1; 166:18;170:14,19,20; 188:2;200:7;220:8; 252:5;284:8;313:19; 339:11;344:2;351:14	126:4,4,22;133:17; 135:16;160:15; 171:22;174:11; 210:18;224:16	259:2;263:6,9;280:21; 291:16;307:5;352:12; 354:13;358:6;373:10, 13
proximal (2) 202:18;203:5	putting (5) 184:13;233:12; 235:2;267:3;350:16		radiographs (1) 113:17	range (5) 25:19;34:20; 111:13;230:3;314:2
pseudoprogression (3) 55:17;124:5;136:17	puzzle (2) 128:1,2		radiolabeled (1) 106:3	ranging (1) 275:7
psychology (2) 220:22;341:2			radiologic (1) 59:1	RANO (39) 10:15;16:15;17:3; 18:2;61:8;66:14;80:5; 84:6;97:1;125:12; 132:21;133:21,22; 134:7,19;136:10,12; 137:21;149:9,13,21; 150:14;160:17;184:3; 194:6;201:20;207:6,8; 216:2;239:7,7,7,8; 240:16;322:2;369:20; 384:4,13;385:14
public (6) 8:14;19:15,16; 145:12;349:21;350:8			radiologists (3) 150:9,10;334:20	rapid (2) 159:22;189:1
publication (1) 80:8	Q		radiology (4) 43:10;126:1;320:9; 369:22	rapidly (6) 26:21;68:16;74:8; 137:10;207:21;245:4
publications (1) 175:4	Q&A (1) 8:21		radionecrosis (2) 124:10;136:18	rare (4) 64:12;167:19; 206:10;250:10
published (9) 16:15;49:9;88:15; 93:13;95:8;103:8; 143:14;184:4;222:9	quaint (1) 147:22		radionucleized (1) 137:13	rarely (2) 12:16;342:11
pull (2) 369:21;370:6	qualification (1) 270:1		radiosurgery (32) 22:8;28:4;47:2,15; 48:12;49:11,16;55:11; 63:6;73:6,7,9,20;	rarity (1) 170:3
pulled (3) 246:20;370:9,10	quality (16) 22:20;43:11;120:4; 184:10,15,18,19; 214:9,15;235:11; 291:12,17;324:12; 367:12;379:7;381:12		radiation (96) 21:21;22:7,22; 30:12;34:10;40:14,19; 42:9,21;46:7;47:12, 14,17;48:10,18;50:11; 55:13,16;68:2,5; 69:17;75:2,9;77:4; 82:7;91:20;101:14; 102:8;105:18;126:16; 146:8,22;149:3; 173:19;210:1;214:18;	radiotherapy (13) 22:5,18;23:9,17; 213:10;252:17;253:5; 269:15;290:11; 291:15;355:13,16;
pulling (1) 42:20	quantify (2) 131:10;174:10		radiating (1) 22:15	rate (42) 33:8;39:7;55:2; 104:18;111:14; 164:16,17;169:3;
pumps (1) 128:19	quantifying (1) 128:2		radiation (2) 146:16;210:2	170:7,7,8,8;171:1; 174:11;193:19;194:7;
purpose (5) 208:3;290:9;302:6; 329:12;359:5	quantitate (1) 120:6		radiated (3) 238:8,9;271:2	16;203:4;212:4,5,7; 222:8;228:13;229:2;
purposes (1) 328:4	quantitative (2) 220:13;378:11		radiating (1) 22:15	230:3;234:17,21;
pursue (1) 379:21	QUEEN (8) 37:15,16;70:18; 82:22;138:10;145:13; 176:14;389:6		radiation (96) 21:21;22:7,22; 30:12;34:10;40:14,19; 42:9,21;46:7;47:12, 14,17;48:10,18;50:11; 55:13,16;68:2,5; 69:17;75:2,9;77:4; 82:7;91:20;101:14; 102:8;105:18;126:16; 146:8,22;149:3; 173:19;210:1;214:18;	radiotherapy (13) 22:5,18;23:9,17; 213:10;252:17;253:5;
pursuing (5) 260:15;288:17,18; 289:2;380:17	Queen's (1) 75:1		radiation (2) 146:16;210:2	269:15;290:11;
push (4) 18:7;244:5;279:16; 280:6	quest (1) 39:14		radiated (3) 238:8,9;271:2	291:15;355:13,16;
pushed (2) 69:12;319:14	question's (1) 153:14		radiating (1) 22:15	rails (1) 356:4
pushes (1) 343:17	quibble (1) 327:10		radiation (2) 146:16;210:2	205:14
pushing (6) 38:15;130:20; 142:12;282:3;295:18; 313:22	quick (15) 35:16;81:19;82:13; 154:2,3,9;157:9,10; 200:4;229:5;232:4; 272:3;311:17;332:12; 355:9		radiated (3) 238:8,9;271:2	rain (1) 178:6
put (44) 38:11;42:10;65:22; 71:1;72:9;75:3;78:9; 79:3;80:5;84:20; 111:12;114:12,18,22, 22:117:18;119:2; 140:7;148:6;191:8; 207:10;212:15;213:3; 225:8;227:12;232:19, 20:250:1;261:6; 267:22;270:18;273:7; 278:1;279:17,19; 286:17;307:3;323:1; 345:22;349:16; 350:15;353:22;363:3;	quicker (1) 29:9		radiated (3) 238:8,9;271:2	raise (2) 112:19;244:19
	quickly (13) 39:9;61:16,19; 63:11;65:5;202:21;		radiations (1) 292:3	raised (2) 139:15;147:12
	211:5;280:11;310:2; 348:19;375:21; 378:21;381:18		radiation (2) 146:16;210:2	raises (2) 107:11,19
	quiet (1) 247:18		radiation (2) 146:16;210:2	raising (2) 112:15;233:7
	quit (1) 319:9		radiation (2) 146:16;210:2	rally (1) 355:2
			radiation (2) 146:16;210:2	Ralph (7) 374:20;375:5,11;
			radiation (2) 146:16;210:2	377:8;378:4,20;
			radiation (2) 146:16;210:2	381:19
			radiation (2) 146:16;210:2	randomization (4) 112:5;365:21;
			radiation (2) 146:16;210:2	366:9;384:16
			radiation (2) 146:16;210:2	randomize (1) 263:10
			radiation (2) 146:16;210:2	randomized (24) 28:17;30:10;34:5;
			radiation (2) 146:16;210:2	67:11;77:5;104:18;
			radiation (2) 146:16;210:2	109:9;148:10;167:20;
			radiation (2) 146:16;210:2	235:11,17;239:12,13;

116:2,11	22:105:21;107:7,16;	14:375:15;377:15;	211:15;252:20;	98:13
rationale (2)	110:15,18;113:11,18;	379:9,11,14,20;	372:16;373:11	refer (1)
30:9;297:10	115:4,19;117:7,18;	382:12,13;383:3,10;	74:5	306:19
rationally (1)	118:4,12;119:12,21;	385:9,18;386:14;	recess (2)	reference (1)
177:19	120:13;121:10;	387:1,8,17;388:1;	161:17;231:4	313:6
rats (1)	122:16,19;123:6,18,	389:6,17,22;390:12,	recharacterize (1)	referred (2)
105:7	18;124:19;125:13;	22;391:5,10;392:7,9,	323:15	213:19;308:11
Ray (1)	126:7,9,17;127:1,5,	20	recharacterizing (1)	referring (2)
147:7	12;128:2,8,13,17;	realm (2)	323:5	197:3;222:20
reach (1)	129:3,5,8,13;130:5,15,	25:12;147:19	refine (1)	79:22
106:14	22;131:2,21;133:2;	real-world (2)	reflect (4)	125:4;127:18;
reached (2)	134:2;136:21;137:20;	258:5,5	390:22;391:6	
102:1,2	138:15;139:8;142:16;	reanalyzing (1)	reflects (2)	125:4;368:2
reactions (1)	143:22;144:19;	371:11	254:17	
381:4	152:11,11,17;153:7,	rearranged (2)	refractory (5)	29:18;98:20;
read (3)	10;156:12,17;157:18,	108:6;109:2	192:20;365:4;372:20	
166:17;268:7;270:8	22;159:21;160:9;	rearrangement (2)	reframing (1)	260:18
readily (1)	162:2,4;163:22;166:5;	102:21;103:1	275:16;384:3	
220:14	169:19;171:19;	reason (32)	recommend (1)	139:22;340:10
readout (1)	174:16;175:18;	52:9;68:14;75:18;	recommendation (1)	regarding (1)
352:13	182:15,22;183:10,19;	155:15;199:20;201:7;	322:3	164:13
ready (3)	184:1;185:8,16;	210:10;254:11;	recommendations (6)	regardless (5)
301:16,16,19	189:14;190:2;193:1;	265:17;271:16,17,21;	8:19;129:4;132:21,	109:20;208:20;
real (14)	194:6;198:18;199:7;	272:6;279:2;288:15;	22:384:4,5	272:11;312:6;362:20
22:13;24:8;30:5;	200:1,12,22;201:8,21,	289:1,3,7;294:9;	reconsent (1)	regards (5)
66:13;125:4,4;252:14;	22;202:13,14;203:8;	297:13;298:8,15,16;	274:4	186:16;188:3,9,19;
254:20;288:15;	12,14;204:5;205:4,19;	304:2;317:10;323:1;	record (3)	190:14
302:20;313:6;321:14;	210:8;211:1,5,18;	324:9;329:14;370:6;	312:14;361:5,9	
354:12;375:17	212:18;213:7;215:21;	388:9,12;390:5	recording (1)	regimen (1)
realistic (2)	216:2,4,21;217:6,13,	reasonable (3)	20:19	309:20
9:21;389:12	17,21;218:9;220:3;	165:17;195:19;	records (1)	regimens (9)
reality (5)	222:22;223:7;225:6;	196:6	368:16	25:17,17;31:16;
67:17;99:14;227:5;	10;227:11;230:5;	reasonably (1)	recruited (1)	34:1;36:8,9;188:14,
323:7;340:3	232:13,22;233:10;	164:8	106:4	16;222:4
realizable (1)	241:20;242:22;	reasons (11)	recurred (1)	region (3)
135:16	243:13;244:4;246:10;	75:13;131:4;	156:6	211:9,22;212:6
realize (6)	247:2;249:8,10,12,22;	200:14;223:21,22;	recurrence (6)	regional (3)
19:5;79:21;207:6;	250:12;251:4,5,10;	226:3;241:13;284:15;	112:13;113:5;	91:11;92:19;93:2
220:4;280:4;370:8	252:16;253:4,6;	289:8;325:12;339:17	196:4;244:16;310:10;	regionally (2)
realized (1)	259:10;261:6;263:5,	rebut (2)	327:7	88:19;91:14
175:17	15,21;264:9;268:4;	197:10;284:9	recurrences (1)	regions (2)
realizing (1)	269:7,7;275:5,16,19;	rebuttal (1)	113:3	97:11;211:12
192:13	276:4,18;278:4;	293:9	recurring (1)	region-specific (1)
really (333)	280:11;286:2,4;	Recap (3)	386:16	188:21
11:17;13:6;14:6;	289:15;290:17;291:6,	159:1;229:17;	recycle (1)	registration (9)
17:18;20:8;21:18;	7,9;292:14;296:1;	314:19	254:6	31:3;81:2,7;108:22;
23:1,5,11,19;24:2,10,	298:16;299:5;301:12,	recapitulate (3)	red (2)	111:17;228:8,19;
19,21;25:7,11;26:18,	13;307:6;308:21;	92:14;115:2;155:11	89:3;91:20	296:7;359:4
19:27;3,8,10,14,15,22;	309:5;313:5,11;	recapitulated (1)	reduce (6)	registration (9)
28:1;29:12,21;30:3;	314:21;315:1,22;	102:9	23:3;24:7;76:13;	41:20;58:12;
32:22;34:7,14;38:8;	316:1;321:7,12;328:4,	receive (4)	77:15;384:7;392:15	175:22;182:14;190:2;
40:1;42:4,19;43:9,22;	11;329:13;330:15,15;	44:15;58:20;	reduced (1)	198:16;201:11;234:1;
44:2,5,12;45:2,13,14,	331:15;332:1,17;	354:17;359:22	170:13	239:11
18:46:1,11,13,14;	333:3,10,14;335:6;	received (5)	reducing (2)	regroup (1)
47:5,13;51:6,10;52:5,	337:9;343:14,21;	71:19;105:18;	169:12;193:18	123:21
18;53:17;54:2,6;	345:1;347:8;348:19;	183:7;278:20;379:15	reduction (3)	regular (8)
56:15;57:1;61:18;	352:9;353:10;354:17;	receiving (1)	194:1;227:7;240:17	77:3;172:5,16;
63:13;64:16,19;65:16,	355:10,19;356:3;	141:22	reexamine (1)	351:7,15;352:1;
18;67:8,19;68:3,6,8;	357:20,21;359:15;	recent (2)		
75:19;76:3,18;77:7;	360:3;361:13,22;	101:2;168:4		
80:20;83:13;98:11;	363:1;365:7;366:7;	recently (10)		
100:12;101:5,10;	367:3,22;371:15;	49:9;66:14;102:9;		
102:6;103:12;104:4,	372:2,5,16,22;373:5,	182:9;184:4;190:20;		

372:15;390:17	206:21;228:17;359:10	14:5;264:1;284:2; 310:7	356:19	result (7)
regularly (1)	reliable (2)	representing (2)	respect (4)	15:5;61:20;75:15; 129:13;133:11;
254:12	93:4;97:13	24:15;186:5	169:17;288:14	237:20;381:16
regulate (1)	reliably (1)	represents (1)	respond (12)	results (12)
223:3	151:8	345:9	67:3;98:21;213:1; 272:13;273:12;	28:10;32:19;68:9; 100:14;142:8;159:17;
regulated (1)	relied (1)	reps (1)	289:19;299:6;308:13, 18:319:11;335:10;	161:7;212:19;334:18;
387:17	151:7	325:2	345:12	373:1,4;382:7
regulator (1)	relies (2)	request (1)	responded (2)	retain (1)
160:11	217:21;372:2	370:2	283:10;319:9	391:8
regulators (6)	reluctant (1)	require (9)	responders (1)	rethink (1)
187:12;223:3; 224:14;272:18; 302:17;345:11	204:10	32:17;18;33:3;20; 52:12;114:15;299:20;	318:8	115:18
regulatory (23)	rely (4)	306:18;373:13	responding (6)	rethinking (2)
118:5;22:119:5; 163:1;181:9;16; 193:22;232:12;15; 233:8;21;266:8;271:5, 21;279:15;285:8; 296:11;303:1;351:3;7; 352:5;360:9;11	86:19;22;126:11; 171:8	required (11)	41:1;57:17;71:16; 122:9;261:18;295:2	160:2;232:18
rehab (1)	remain (2)	15:4;99:7;104:1; 107:10;112:16;116:9;	response (102)	retrospective (3)
350:9	59:8;183:18	130:13;149:16;166:5;	29:19;33:4;44:2; 47:5;49:4;5,8;18;	123:13;291:2;
reinforce (1)	remains (3)	221:13;256:14	52:16;57:6;63:9;	368:19
21:2	58:10;193:5;206:12	requirement (2)	66:12;97:1;104:17;	reveal (4)
reinforced (1)	remark (1)	131:15;274:7	105:19;108:12;17;	191:8;192:1,7;
24:2	248:20	requirements (2)	110:4;111:14;119:18;	220:20
reinforcing (2)	remarkable (1)	150:2;315:16	126:3;13,21;22;128:6;	revealed (1)
29:21;64:6	72:14	requires (5)	133:16;17;134:8;19;	245:4
reinvigorate (1)	Remarks (2)	43:1;12;127:3; 235:11;323:5	135:3;144:10;149:11;	reversibly (1)
72:17	8:3;241:9	requiring (5)	22;151:1;154:2;	335:17
reiterate (2)	remember (7)	131:2;213:16; 237:4;267:7;357:15	164:16;17;170:6;7,7,8,	review (9)
138:14;157:20	102:2;177:7;	rerun (1)	14;171:1;10;173:8;9;	20:22;24:11;43:3;
rejected (1)	216:17;234:19;256:2;	370:15	174:11;192:16;	122:18;220:5;238:17;
380:16	274:18;318:22	research (15)	193:19;194:7;15;	251:19;22;386:8
relapse (2)	remiss (1)	10:1;12;12;15;16:7;	196:4;201:2;12;15;21;	reviewer (1)
112:15;206:15	138:13	23:3;39:6;48:3;88:3;	202:18;203:4;14;	18:15
related (17)	remission (1)	157:18;204:2;252:14;	207:19;209:14;212:2,	reviewers (1)
33:13;140:6;21;	327:15	349:10;376:22;384:4	2,4,5,7;217:7;228:12,	207:18
152:8;173:14;184:19;	renal (2)	researcher (1)	14;229:1;230:3;18;	reviewing (1)
190:16;201:1;215:21;	90:3;181:22	349:13	234:10;16;17;20;21;	221:9
222:18;254:2;291:11,	rep (1)	researchers (1)	235:1;6;239:4;240:3;	revolutionized (3)
15;20;311:11;380:7;	138:9	250:20	20;273:15;294:11;	30:22;32:9;22
10	repeat (4)	resect (3)	295:9;298:13;313:21;	revolving (1)
relates (5)	270:12;275:22;	70:17;141:6;6	360:22;361:2;10,13;	350:6
65:3;207:13;	276:1,7	resectable (1)	362:10;13;363:15;	reward (1)
252:22;268:21;291:21	report (4)	292:7	367:8;12;368:3;	340:21
relationship (11)	156:9;10;370:10;	resected (1)	372:13;15;18;373:2;	RFA (1)
186:17;22;187:14;	380:3	87:13	384:11	156:6
190:20;191:2,6;12,14;	reported (7)	resection (10)	Rhun (2)	
212:11;20;381:1	23:21;115:10;	71:19;73:9;114:21,	34:14;59:10	
relative (3)	120:4;143:12;13;	21:134:11;147:11;15;	rib (1)	
115:9;11,21	211:16;307:6	195:7;295:11;16	245:8	
relatively (10)	reporting (1)	reserved (1)	rich (3)	
25:18;40:12;84:11;	159:16	23:1	162:20;229:20;	
92:4;97:12;101:1;	represent (6)	reset (2)	348:4	
134:9;166:10;168:12;	145:11;256:19;	45:13;311:17	Rick (1)	
310:1	263:21;316:19;	residual (3)	11:21	
relevance (1)	322:17;346:9	112:5;145:2;164:13	rid (1)	
217:8	representation (1)	resistance (1)	275:5	
relevant (7)	84:12	45:5	ridiculous (1)	
107:12;155:4;	representative (2)	resistant (1)	329:22	
190:19;196:12;	91:12;378:13	39:21	RIELY (11)	
	representatives (1)	resolution (2)	50:17;18;54:9;	
	386:6	130:15;131:15	65:19;68:17;75:11;	
	represented (4)	resources (1)	77:17;79:6;82:10;	
			333:10;348:7	
			right (40)	
			28:20;33:21;38:16;	

61:3;63:6;79:1;82:9; 83:8,10;116:20; 144:17;151:22; 154:12;161:14;202:7; 209:8;221:15;227:5; 230:22;246:4;247:4; 265:9;268:17;270:19; 271:6,9;274:5;286:6; 290:18;301:21; 304:18;309:13; 310:12;314:15; 325:17;329:17; 336:16;352:20;354:9; 360:7	rooms (1) 341:15	salad (1) 231:1	scanning (2) 122:8;327:9	130:16;133:16;150:1; 151:3;153:18;154:11; 162:9;171:12;207:22; 214:2;215:21;232:8; 16;238:4;243:16; 247:5,8;260:5;289:4; 293:3;310:11,13; 335:12;350:1;363:13; 377:9;379:13,20; 387:5
rightly (2) 102:5;193:11	Ross (3) 26:15;80:6;119:20	saleable (1) 220:14	scans (10) 38:11;52:17;131:3; 135:16;180:20;221:7; 334:13;370:10,13,21	
rigorously (2) 323:11,12	round (1) 213:9	salivary (1) 91:17	scenario (4) 191:9,14;206:10; 303:6	
rising (1) 21:10	routine (3) 54:3;126:12;384:3	same (37) 16:16;46:6;65:15; 73:19,21;88:22;92:1;	scenarios (2) 175:20;373:12	
risk (18) 25:1;76:11,13;99:2; 112:12,22;166:3; 168:12;169:5;174:4; 191:14;244:15; 259:12;277:5;295:20; 315:12;343:21;389:15	routine (5) 17:2,4;121:21; 127:17;329:22	133:20;135:8;141:4; 20:142:19;174:11; 185:21;201:5;220:11; 237:13;258:4,12;	secondary (11) 100:2;201:10; 203:6;220:10;225:9; 259:4;290:21,21; 326:16;330:9;359:11	
risk-benefit (1) 165:17	row (1) 261:22	280:8;286:1;294:21; 299:8;309:5;312:6; 324:14;331:5;333:5;	schedule (1) 84:10	
risks (1) 118:14	Roy (1) 146:12	338:18;342:8;358:2; 362:13;370:12,13; 379:17;381:3;387:17	scheduled (1) 237:12	
RNA-seq (1) 93:15	RP (1) 218:16	sample (8) 87:9;91:7,13;92:2; 94:2;218:14;239:17; 378:17	Schelsky (1) 348:5	
road (3) 210:11;292:3,5	rules (2) 276:21;304:12	samples (2) 91:9;92:5	school (2) 245:2;318:6	
roadmap (1) 17:14	run (11) 45:1,17;115:3; 150:11;179:14; 225:19;292:15;356:9; 11;369:16;386:1	sandwich (1) 231:1	science (7) 255:14,20;278:14; 18;312:10;376:10; 390:19	
robust (3) 8:22;30:5;361:13	running (8) 60:4;81:14;96:17; 228:1;255:7;332:14; 349:4;375:6	Sarah (1) 11:10	scientific (2) 297:10;392:5	
robustly (1) 315:4	rushed (1) 246:3	satisfied (1) 152:20	scientifically (2) 390:5,9	
robustness (1) 361:11		satisfying (1) 363:7	scientist (2) 45:1;84:17	
role (15) 8:22;22:5;25:21; 34:10;47:9;50:5;74:4; 12;138:22;160:20; 255:17,17;319:18; 336:5;338:1		Saturday (1) 245:18	scientists (1) 331:20	
roll (1) 302:3		saw (15) 31:21;33:4,7;36:7; 49:18;50:20;52:10;	scope (3) 206:4;217:6;224:4	
rookie (1) 27:21		57:2;89:16;100:17; 155:10;273:15;296:4; 13;362:13	scratch (1) 371:5	
room (26) 46:5;64:17;96:12; 158:17;217:1;230:10; 232:20;233:9,10; 243:12;260:21; 266:17;294:10;297:7; 300:3;301:10;305:15, 17;311:18;316:10; 334:9;340:12;355:1; 377:12;389:13;392:7		Sawaya (1) 147:7	scream (1) 245:2	
		saying (21) 52:19;130:21; 180:12;181:2;197:10;	screen (8) 76:22;77:2,16; 188:5;265:6,7;306:17; 335:9	
		211:18;219:9;248:12; 256:4;261:3;276:18;	screened (1) 326:14	
		324:17,18;327:13;	screening (10) 28:8;75:21;77:6;	
		332:22;340:17;	188:4;325:10,17;	
		345:19;346:14;352:6;	326:13;334:13;335:1;	
		361:11;388:2	352:18	
		scan (16) 52:15;86:12;127:4;	screenings (1) 73:11	
		133:12;166:17,18;	search (1) 343:10	
		170:11;179:2,18;	searches (1) 101:1	
		238:1;245:17;247:3;	seats (4) 8:5;82:16;161:20;	
		268:14;269:19;	232:5	
		334:17;346:21	Seattle (3) 10:20;41:9;243:20	
		scanned (1) 346:10	Second (39) 8:13;51:5;52:22;	
		scanners (1) 132:9	60:22;98:21;99:5,17;	
			105:2;118:7;127:8;	

364:18	387:6,9	80:18;86:2,9;94:9;	32:13;33:12;40:15;	silent (2)
selected (4)	separated (1)	111:5,8,9;133:3;	63:3;87:9,14;92:19;	69:4;245:2
51:18,19;102:6;	88:19	136:3;160:9;193:12;	94:4,22;95:13,21;	similar (10)
321:5	separately (4)	204:17;206:17;263:9;	105:16;143:10;	31:22;100:22;
selecting (5)	198:8;263:3;289:8;	280:20;281:20;305:2;	148:11;152:16;171:21	108:17;134:18;
42:18;98:9;101:5;	330:7	326:3;342:19;351:9;	136:13;166:13;175:3;	134:13;166:13;175:3;
104:22;366:8	separating (2)	352:11;362:12	204:4;332:4;384:22	204:4;332:4;384:22
selection (4)	28:2;295:7	settings (5)	63:8;89:18;97:17;	similarities (1)
113:15;155:13;	September (1)	45:12;129:20;	101:8,10;106:14;	173:1
238:5;284:10	40:20	185:7;192:21;260:8	152:17;267:13;312:10	Similarly (2)
selectively (1)	sequence (2)	several (5)	shown (11)	93:3;326:3
55:11	133:14;257:15	114:13;215:1;	25:20;33:18;47:15;	Simon (1)
self (1)	sequenced (1)	220:9;269:2;385:10	113:20;144:7;159:21;	77:21
344:10	91:14	sexual (1)	291:16;307:11,12;	simple (3)
self-identity (1)	sequences (6)	218:11	328:17;336:18	276:18;369:19,19
37:18	43:8;123:19;127:8;	Shah (2)	shows (5)	simpler (1)
Selig (35)	132:7;329:5;335:2	179:6;180:2	109:1;223:16;	303:6
11:8;14:20;64:13;	sequencing (4)	Shanthi (4)	235:13;288:2;320:12	simply (8)
74:19;81:11,13;83:7;	23:11;87:7;88:16;	233:15,17;252:3;	39:20;200:21;	113:16;146:16;
84:9;98:3;151:12;	123:14	263:8	202:19	151:19;152:21;
152:22;153:4;154:2,9;	sequential (1)	shape (2)	shrinkage (5)	213:17;245:19;
155:19;157:8,13;	136:14	38:8;361:22	134:21;196:10,13;	271:19;342:4
158:12;161:13,19;	serial (1)	share (4)	259:5;294:13	simultaneous (1)
214:2,14;227:18;	126:7	88:7;185:9;200:8;	41:1;52:18;268:16	123:14
228:1;230:13,16,19;	series (4)	334:11	shrunk (3)	single (16)
232:3;311:13;314:16;	111:12;143:13;	shared (7)	41:1;52:18;268:16	31:5;36:20;68:15;
316:9;345:7;374:2,19;	246:7;291:2	89:5,9;90:6,7;	shunted (1)	70:17;91:12;105:7;
382:12	serious (1)	91:22;176:14;252:14	71:8	134:5;146:11,13;
semantic (1)	388:8	sharing (1)	Sibley (1)	148:16;211:22;221:4;
276:9	serve (1)	92:20	182:19	254:4;308:14;353:15;
Senate (1)	377:5	Shelly (4)	sick (1)	362:15
349:6	served (1)	178:3;183:7;214:3;	281:19	single-agent (2)
send (2)	340:5	217:7	66:21;139:10	32:11;36:20
296:22;297:9	service (1)	shift (1)	side (14)	single-arm (8)
sense (27)	175:4	103:6	38:16,16;47:20;	164:17;192:15;
8:18;10:4;114:21;	services (1)	shock (1)	48:16;69:12;75:14;	360:10;361:7;362:7,
147:3;208:6,11,13;	376:21	381:5	146:10;180:13;	12;363:15;372:12
213:5;241:16,20;	session (39)	shooting (2)	199:20;222:6;262:3;	sit (5)
250:7;253:15;254:10;	8:21;20:3;81:21,21;	247:9,16	331:13;334:16;345:16	208:21;248:8;
267:4;269:10;274:21;	82:14;83:8,11,13,15;	short (5)	284:21;289:21;363:8	284:21;289:21;363:8
275:18,20;276:7;	110:15;159:1;162:2,7,	18:17;63:13;75:5;	site (12)	12:17;13:7;94:3;
300:7;301:2,2;315:6;	17,21;175:11;185:17;	161:20;259:9	112:15;117:3;141:21;	
322:19;338:21;361:3;	207:5;208:4;232:9,17;	shorter (2)	218:15;221:4;235:22;	
389:10	22:289:17;291:11;	39:19;198:20	240:11;336:17;347:7	
sensitivity (1)	311:16;315:22;316:5,	shorthand (1)	sites (12)	13:9;20:10;88:18;
90:20	12,21;317:1,2,12;	276:14	194:12,13,18;277:21;	89:16;92:13;97:2;
sensitizer (1)	320:22;348:4;350:20,	shortly (1)	278:12;298:9;326:1;	102:12;108:18;155:8;
104:19	22:353:17;355:15;	302:2	339:7;363:19	332:17;343:12;349:19
sent (2)	376:5	shot (1)	signals (3)	sitting (11)
245:20;314:7	sessions (3)	357:4	192:9;215:10;280:2	43:21;96:13;
sentiments (1)	159:4;236:18;348:1	shots (1)	179:18;189:11;	
62:13	set (23)	230:17	246:14;261:10;	
sentinel (1)	40:5;81:17;96:9;	shout (1)	268:18;299:1;309:13;	
327:10	118:2;127:8,16;128:7;	250:21	316:9;366:5	
separate (29)	129:6,7;138:1;154:14,	show (22)	situation (10)	173:3;174:15;
57:14;61:1,6,9;	20:162:3,4,11;167:20;	31:7;85:7,9;96:6;	195:15,16;275:13;	
145:21;146:5;260:10;	208:14;209:12;210:4;	99:9;108:2,4;142:21;	292:15;300:20;	
261:12,20;262:6,12,	228:12;278:4;349:10;	143:1;151:18;164:2;	342:22;353:20;389:17	
15,18;264:16;265:8;	359:8	172:19;196:2;271:11;	situations (3)	
273:19;276:20,21;	sets (2)	13,290:8,13,17;	196:16;361:2;	
284:3;286:5;288:16;	137:19;371:4	312:14;328:8;372:3;		
289:3;298:17;310:17;	setting (25)	376:9		
315:14;338:8;379:10;	19:15;65:6;67:9;	showed (16)		

384:11	smoothly (1)	264:22;277:9;280:1;	311:22	300:18;341:4
six (1)	375:7	321:4;325:12;331:7;	speaker (1)	Sperduto (2)
178:7	SNO (2)	334:21;336:11;356:2;	84:11	101:14;102:14
size (20)	376:3;385:14	361:11;367:14;	speakers (4)	sphere (1)
111:22;124:3;	snow (2)	373:11;386:13,13	20:18;42:3;69:8;	189:7
128:4;144:22,22;	178:7;346:17	somewhat (4)	153:2	Spillman (1)
147:18;149:16;150:2;	snuck (1)	12:19;112:13;	speaker's (1)	11:11
151:5,7,10;208:6,20;	125:8	122:18;211:7	124:2	spin (4)
209:7,21;239:17;	soap (1)	somewhere (1)	19:16;109:16;	132:1,10,14;133:13
261:16;282:4;288:5;	70:2	113:5	143:8;17;255:16,17;	spinal (1)
357:15	social (1)	son (1)	271:22;290:9;300:17;	245:6
sizeable (1)	310:7	318:5	305:9;306:4,16;	spine (4)
324:14	Society (11)	soon (7)	307:16;342:6;346:18;	131:16;245:6;
sizes (1)	8:10;10:13,15;	61:22;78:5;198:17;	353:2;360:3	246:3;252:12
130:14	14:20;18:1,5;181:12;	223:6;270:14;286:22;	speaks (2)	spirit (1)
skeleton (1)	344:20;375:8;377:10;	327:9	122:20;217:6	10:4
245:6	382:9	sooner (1)	special (7)	split (1)
skepticism (1)	soft (1)	45:22	11:13;12:10;13:7;	220:12
336:12	126:14	Sorry (7)	135:17;181:19;	spoke (1)
sketchy (1)	277:12	228:1;263:14;	199:18;200:2	spoken (1)
100:10	sole (1)	267:22;276:13;	specialist (1)	392:19
skin (1)	341:15;362:2;371:19	341:15;362:2;371:19	163:8	sponsor (1)
170:19	solely (1)	sort (40)	specialize (1)	220:5
skip (1)	117:7	24:10;27:6,16;54:6;	252:11	sponsored (1)
376:9	solid (15)	57:13;66:12;70:12;	specialized (2)	348:1
skull (1)	121:11;125:10;	75:22;80:2;99:14;	321:10;323:12	sponsoring (2)
247:11	156:15,20;206:5,18;	122:20;143:14;	specific (30)	374:9,22
slices (4)	251:21,22;253:12;	146:11;148:8,9;	14:5;78:11,11;	sponsors (7)
130:10,11,21;134:9	255:9,13;256:6;	152:11;185:21;	80:10,12;153:12,13;	13:19;14:21;171:4;
slide (10)	320:18;331:3;339:12	207:13;210:14;	155:16;194:18;211:8;	182:12;349:18,19;
28:16;108:19;	solid-tumor (1)	213:16;215:7;218:22;	12:229:8;253:20;	351:17
118:2;123:7,20;	62:17	222:18;231:1;257:9;	254:8;257:17;272:6;	sponsor's (1)
124:17;125:6;143:9;	solitary (1)	266:3,6,8;278:15;	287:9,16,18;298:19;	353:19
174:22;376:8	295:11	326:22;338:19;	309:20;314:4;328:6;	spontaneous (1)
slides (5)	solution (2)	341:11;351:1,19;	330:4;332:4;338:19;	114:15
84:12;118:2;	83:6;261:9	358:11;360:11;	351:19;360:17;367:4;	spontaneously (1)
122:17;243:17;375:14	solutions (1)	367:18;368:8;387:7;	369:14	114:10
slight (2)	277:10	15	specifically (30)	spot (4)
293:9;337:22	solvable (2)	sorts (1)	15:20;24:13;51:19;	212:15;232:21;
slightly (2)	83:4;138:13	222:21	68:13;79:2;100:20;	321:18;324:13
265:2;303:6	solve (1)	sought (1)	134:1;179:22;183:1;	spread (7)
Sloan (2)	82:4	379:13	187:1;194:11,15;	39:2;131:17;134:3;
299:9;331:5	somebody (7)	sound (2)	198:14;238:18;	147:9,16,16;385:13
slow (1)	39:7;319:21;337:7;	293:21;300:21	239:18;251:2;252:16;	spreads (2)
273:13	353:5,7;358:15;388:2	somebody's (1)	285:16;289:5;293:16;	55:20;302:10
slow-growing (1)	276:6	219:22;372:21	295:3;310:19;332:2;	squamous (1)
299:19	somehow (2)	space (20)	338:22;339:5;348:20;	288:21
slowly (3)	79:1;354:5	25:8,16;53:15;70:2;	356:21;362:18;383:9;	SRA (1)
179:16;245:3;317:8	someone (12)	74:17;127:15;139:18;	384:9	276:6
small (19)	73:17;141:4;165:4;	160:4;185:14,19,20;	spectator (1)	SRS (24)
42:8;55:1;56:10;	168:20;225:8;253:5;	192:6;218:9;221:3;	248:22	42:17;123:15;
70:13,15;72:13;76:19;	274:7;280:15;320:21;	247:19;257:1;281:5;	spectroscopy (1)	124:10;133:9;135:19;
79:18;131:13,21;	324:4,14,21	282:14,15,15	137:7	180:10;203:19;213:9;
132:18;141:8;165:16;	someone's (1)	span (1)	speech (1)	215:1;216:1,10,15;
177:19;207:19;	323:13	163:9	210:21	224:17;229:9;280:16;
264:14;267:6;339:19;	something's (2)	sparing (3)	speed (1)	306:14;309:7;352:22;
383:21	165:18;301:4	48:11;252:21;	273:16	353:4,14;367:7,7,9;
smaller (2)	sometimes (30)	355:20	spend (3)	387:10
73:13;208:3	19:18;28:1;53:6;	speak (13)	269:15;314:12;	SRS-ing (1)
smart (1)	63:11;65:5,19;122:12;	19:15,17;61:4;	355:19	203:1
348:15	126:12;156:21;	84:16;198:14;199:15;	spent (4)	SRS-to-1 (1)
smartly (1)	206:13;220:6;226:18;	227:19;248:5;255:18;	282:13;294:10;	280:14
387:19	237:15;239:8,8;253:3;	262:3;281:14;305:5;		

St (1) 217:15	22:129:2,6;130:6; 132:16;133:1	statistical (8) 192:12;225:7; 251:19;252:6;261:13; 263:1,4;304:10	192:7;204:15;232:6; 248:1;277:2;282:7; 294:22;302:12; 329:17,18;330:4; 337:1,2;352:8;353:21;	167:13
stable (16) 16:11;86:9,11; 94:10;135:2,6,7; 136:7;139:5;180:11; 191:21;236:10;242:6; 17:269:19;279:20	standing (2) 289:20;312:15	statistically (2) 171:21;226:12	337:1,2;352:8;353:21; 354:2;364:5;367:17; 384:14;385:10,387:18	stress (2) 50:9;104:6
stack (1) 294:16	standpoint (11) 98:18;153:14,20; 186:9;190:19;212:9; 214:21;271:5;307:16; 355:5;360:2	statistician (2) 225:13;251:17	stimulate (2) 58:1;234:3	stressful (1) 37:22
staff (1) 14:4	stands (1) 23:16	statisticians (1) 331:9	stressing (1) 113:11	striking (5) 33:5;34:19;152:16, 19:364:14
stage (24) 27:5;31:1;78:20; 102:11;104:16; 151:15;162:11;177:2; 178:9;190:1;194:4; 206:14;228:7,14; 230:1;242:13;244:14; 277:3;278:20;290:7; 298:10,12;317:11; 363:15	start (47) 22:4;30:10;58:9; 65:1;72:2;90:14; 114:18;117:19,20; 139:15;158:22;162:1, 22:176:4,20;189:13; 190:9;208:2;221:17; 223:8;230:21;232:12; 243:5,8;248:18;249:2; 255:21;261:21;262:2; 287:9;293:8;296:19; 320:15;321:7;324:9; 325:16;331:15;	statistics (2) 244:1;331:8	stole (1) 224:12	stroke (1) 131:4
stages (1) 194:17	status (12) 101:18;102:17,19; 103:1;109:4;135:9,15; 172:12;206:17; 224:18;388:7;390:7	stop (3) 125:18;189:8;274:2	strong (5) 73:4;166:7;167:15; 227:11;320:13	
staging (1) 325:17	stopped (1) 104:15	stronger (1) 219:6	strongly (3) 147:1;275:8;280:4	
stakeholders (3) 181:13;187:8,11	staying (9) 82:16;216:16; 232:6;244:3,6;374:11, 13,382:10;391:20	stopping (2) 276:21;304:12	struck (1) 248:12	
stand (4) 21:19;293:6; 316:17;341:9	steering (1) 10:21	stops (1) 325:17	structure (1) 246:15	
standard (28) 22:9;27:11;31:13; 34:5;46:9;75:13; 112:6;117:5;119:7,9; 132:15;138:1;146:22; 160:8;166:9;185:12; 218:22;230:5;259:11; 262:9;274:19;290:18; 305:3;325:15;331:1; 363:21;366:8;387:18	started (24) 8:10;44:1;45:19; 47:7;84:22;85:3; 160:17;161:14;	step (6) 51:5;284:19;334:2; 376:18;385:17,19	story (17) 43:22;44:4,6,18; 47:4;75:1;80:19;	structured (2) 368:21;369:6
standardization (6) 137:19;185:18; 222:4;368:9;386:18; 387:1	stepped (1) 246:20	stepped (1) 8:20;317:3;376:3; 381:19;383:1	structures (1) 128:20	struggle (6) 140:2;207:17; 268:22;302:8,17; 361:19
standardize (1) 368:10	starting (10) 20:13;25:12;96:5; 208:9;217:19;274:19; 294:15;311:20;312:2; 389:7	steps (5) 22:8;28:4;40:14,18; 47:14;49:16;120:15; 146:21;303:4;329:4	straight (1) 341:6	struggled (1) 306:8
standardized (13) 15:7;17:13;76:15; 131:22;132:2,7,12; 137:21;149:10; 159:13;322:7;368:21; 384:20	sterilize (1) 147:14	straightforward (1) 339:8	struggling (1) 32:6	
standardizing (3) 126:2;129:11; 160:14	steroid (1) 222:12	strain (1) 114:16	stuck (4) 226:18;245:16; 292:5;364:18	
standardly (1) 86:21	steroids (23) 32:17,18;33:4,20; 74:9,9;120:8,10; 135:1;167:4;173:18;	strains (2) 114:1,2	student (1) 221:19	
standard-of-care (3) 21:20;205:1;262:16	State (6) 26:16;38:14; 153:21;197:8;218:2; 349:6	strata (1) 198:7	studied (2) 254:22;266:6	
standards (14) 35:2,4;42:10; 128:12,15,17,18,21,	stated (3) 14:10;83:19;148:22	strategies (18) 9:22;17:2;23:3,15;	studies (64) 9:9;28:11;31:3,7; 33:12;35:13;36:21;	
	statement (8) 194:22;196:14; 209:22;258:12;264:8; 273:4;324:20;329:16	steroids (23) 32:17,18;33:4,20; 74:9,9;120:8,10; 135:1;167:4;173:18;	60:6;14;61:15,16;	
	still (44) 17:12;32:6;33:7,20;	strategize (1) 373:7	63:20;72:19,21,22;	
	States (3) 9:14;101:15;163:17	strategy (5) 99:4;136:9;197:16;	85:11;87:5;88:10;	
	stating (1) 305:3	stratification (5) 109:12;262:19;	95:4;108:16;111:15;	
	statistic (1) 244:2	sticking (1) 382:22	113:17,17;114:6;	
		still (44) 17:12;32:6;33:7,20;	117:6;151:11;159:22;	
		strategize (1) 373:7	175:21;198:19;200:5;	
		strategy (5) 99:4;136:9;197:16;	202:4;216:13;250:15;	
		stratification (5) 109:12;262:19;	267:2,21;268:21;	
		sticking (1) 382:22	269:2,9;272:11,15;	
		still (44) 17:12;32:6;33:7,20;	280:9;287:15;290:17;	
		strategize (1) 373:7	20:291:9;294:8;	
		strategy (5) 99:4;136:9;197:16;	307:6;309:18;321:1;	
		stratification (5) 109:12;262:19;	325:6,22;335:8;	
		sticking (1) 382:22	358:21;361:8;363:15;	
		still (44) 17:12;32:6;33:7,20;	364:9,21;365:1;	
		strategize (1) 373:7	371:13;373:5;385:3;	
		strategy (5) 99:4;136:9;197:16;	386:8,20;388:15	

study (91) 19:8;32:4;33:9,13; 59:12,22;61:12,17; 62:9;63:1,8,22;71:20; 78:21;87:6;88:15; 95:8;96:22;99:11; 103:7;104:20;105:12, 13:106:2,11,14; 109:15;110:13,16,17; 112:20;123:18;132:4; 152:17;157:22;159:9, 17:175:21;181:18; 197:15;198:22; 199:12,17;200:3,9,12; 201:11;203:20;222:9, 14:230:2;234:10; 236:10,20;238:10,12, 13:239:10;250:4; 263:9;265:8,13; 269:16,20;270:19; 271:7;273:5;277:20; 278:17;280:12,21; 286:17,20;292:11; 297:19;298:15,18; 325:4;335:10;341:1; 345:22;353:11;358:9, 10;359:13,14,14; 360:17;362:11,21; 373:8	101:11;103:15; 198:2;257:13 substantial (5) 103:2;112:10,12; 252:5;357:15 substantially (3) 101:12;103:16; 106:7 subtleties (1) 141:16 subtype (1) 101:18 subtypes (2) 25:4;26:22 subtyping (1) 157:15 success (3) 47:6;379:8;381:13 successful (4) 74:16;200:5;214:6; 365:3 successfully (1) 72:20 suddenly (2) 339:18;342:9 suffer (2) 333:5,345:1 suffice (1) 246:22 sufficient (3) 57:7;58:1;360:12 suggest (3) 9:11;94:14;295:6 suggestions (1) 162:5 suggests (4) 116:21;131:20; 257:19;379:19 Sul (17) 10:22;14:17;18:12, 13,14;74:19,21;207:2; 260:21;316:16; 324:19;326:18; 341:16;360:18; 362:18;366:10;385:21 Sul's (1) 213:2 sum (3) 134:12,14;135:4 summarize (6) 25:15;35:15;82:1; 311:15;314:21;379:1 summarizing (2) 25:2;314:12 summary (6) 23:21;26:18;229:4; 380:20;383:1;392:1 summer (3) 18:5;246:6;347:21 super (2) 118:12;225:21 supersede (1) 290:12	support (6) 120:22;212:19; 240:19;318:15; 342:20;362:16 supported (1) 147:1 supporting (1) 70:14 supportive (7) 167:2,8;180:17; 193:15;227:15; 236:12;307:8 supports (2) 155:17;251:18 suppose (1) 273:15 supposed (4) 129:22;134:10; 249:2;344:17 sure (33) 16:21;43:8;54:15; 58:18;60:19;65:14,21; 66:2;71:12;103:14; 169:2;172:17;190:11; 193:17;200:10; 225:15;232:9;249:13; 262:8;298:3,3;304:15; 308:9;322:5,11,11; 324:5;334:5;338:12; 346:12;352:4;363:3; 377:18 surgeon (1) 156:14 surgeons (2) 42:22;327:8 surgery (13) 38:22;42:18;72:6,7; 74:6;112:4;146:8; 229:9,10,16;292:6; 298:14;300:13 surgical (5) 71:18;92:6;146:10, 12;195:6 surprise (4) 341:17;378:8; 379:2,4 surprised (1) 122:12 surprising (2) 91:2,3 surprisingly (1) 168:15 surrogacy (1) 219:8 surrogate (24) 66:18;97:13; 120:21;164:5,7;168:2, 6;171:20;172:3; 187:18;189:8,18,20; 212:20;217:8;219:16; 222:14;224:20; 225:21;351:4,21; 368:1;369:3;372:5	surrogates (1) 93:5 surrounding (2) 44:10;171:10 surveillance (3) 28:7;218:20;267:19 surveilled (1) 76:15 survey (12) 376:11,19;378:6,14, 18;379:2,12;380:14, 21;381:21,21;382:7 survey-based (1) 375:17 surveyed (4) 376:17,18;378:19; 379:5 surveys (3) 376:16;378:11,11 survival (74) 22:21;25:19;30:19; 33:8;34:19;39:7;61:7; 94:21;95:2;98:17; 101:8,11,19;102:1,13; 103:3,9,15;110:7; 112:9;119:8,14,19; 146:14;148:13;160:8; 161:9;165:4,16,20; 166:4,8,10,12;167:14, 18;171:15;173:11; 177:14;184:12; 192:22;196:19; 200:13;201:19; 205:12;212:21;214:8, 8;216:6,8;218:7; 225:8,11;230:4;235:5, 8,11;249:16;259:1,8, 10;267:12,15;307:12; 357:19;358:6,12,17; 359:19,21;360:13; 364:16;365:8;391:5 survivor (1) 178:10 susceptibility (1) 133:6 susceptible (1) 165:10 Suzanne (1) 334:7 sweat (1) 286:19 swelling (1) 195:5 switch (4) 112:7;314:14,18; 348:19 Switzerland (1) 336:11 sympathetic (1) 242:8 symposium (1) 163:10 Symptom (6)	165:6;168:21; 174:18;215:15;230:6; 352:22 symptomatic (17) 50:4;72:8;146:19; 170:20;171:3;173:5; 177:5;209:6,9,10,20; 236:16;295:12;306:7, 10;325:13;357:14 symptoms (6) 68:5;171:5;177:14; 215:9,12;245:19 synchronously (1) 90:4 synergistic (1) 129:19 synergistically (1) 329:3 synergize (1) 150:22 system (5) 92:10;305:13; 342:20;344:11,11 systemic (54) 15:22;21:21;23:7, 20,22;24:3;36:6; 58:17;60:1;67:3; 72:12;73:21;76:4; 86:20;87:1;98:21; 108:12;115:22; 122:10;123:15; 124:11;125:9;146:2,3, 7,16;150:6;151:1; 176:2;195:15;196:3, 17;204:18;205:3; 207:3;236:3;237:8,20, 21;239:1;240:1,4,11, 21;269:2;270:2,22; 271:13;272:8;298:13; 309:16;336:5;337:18; 390:11 systemically (7) 137:14;195:17; 196:5;204:7;219:11; 270:4;272:13
T				
T1-weighted (3) 127:9;130:7;133:12 T2 (2) 127:3;130:17 T2-weighted (2) 127:4;335:5 table (2) 59:17;162:3 tables (1) 261:11 tail (1) 244:2 tailor (2) 335:1,11 take-home (3)				

30:5;41:16;174:1	target (19) 78:12;104:5,7,22; 116:2,11,18;131:12, 13:134:12,20;140:17; 144:4;238:6,7;312:22; 370:12,17,17	212:10;318:3 techniques (1) 256:7 technology (8) 87:7;139:10; 174:16;320:10; 335:15;339:20; 368:13;393:2	332:1 terrifying (1) 342:22 terror (1) 243:17 test (4) 114:3;142:11; 346:22;348:15	therapy (80) 13:15;21:21,22; 22:8,22;23:22;27:9, 12,12;29:19;30:12,17; 31:11,11,14;34:3,10; 45:20;50:5;67:3;68:7; 72:12,16;75:4;98:21; 113:1;115:22;122:10; 123:15;153:15; 172:18;177:22; 202:21;203:2;204:13; 211:17;213:15,22; 214:6;218:1;219:3,10, 12;258:13;260:12; 262:11,14,16;270:15; 280:17,19;281:1; 285:22;290:6,9; 291:20;292:1,14,20; 293:1,11;299:18; 300:12,13;302:19; 303:7,19;305:20; 309:17;315:8;327:17; 336:5;354:2;358:15; 365:5;366:8;367:13; 372:19;387:15,17
takeover (1) 241:2	targetable (2) 27:8;86:18	targeted (20) 25:9,13;26:4;27:9; 30:11,22;31:11,14; 34:2,9;86:20;87:1; 99:19;120:18;182:3; 204:3,16;293:16; 298:19;367:13	telling (4) 38:7;44:1;223:1; 224:2	
talented (1) 138:11		tells (2) 55:21;107:13		
tales (1) 183:18				
talk (60) 16:2,22;20:7;21:18; 22:1,4;26:10;31:10; 36:10;37:7;43:15; 44:18;46:7;47:13; 49:1;53:8;59:18; 60:17;63:19;85:7; 98:8,11;100:11; 117:14;118:8,13; 124:2;126:8,21; 144:20;149:9;152:2; 162:10,16;163:1,11, 22;176:13;178:22; 184:13;200:15; 209:20;210:9;232:15; 253:8;265:5;282:22; 285:9;314:16;320:5; 321:17;348:20,21; 356:7,20;358:5;366:2; 375:4;376:1;383:10	Temodar (1) 321:1	temozolomide (3) 104:9,12,19	tests (6) 228:10,12;345:16, 18;346:1;348:11	
talked (31) 15:13;29:15;35:7; 62:7;72:18;85:16; 119:13,17;120:9; 121:5;128:11,13,14; 136:21;138:20; 141:15,17;160:1,7,14; 173:18;229:6;271:10; 274:15;291:12;338:7, 10;339:3;341:20; 389:22;390:20	tasking (1) 162:3	template (2) 331:1,2	tests (6) 228:10,12;345:16, 18;346:1;348:11	
alking (42) 9:2;27:14,17;46:9; 58:22;69:13,20;70:3; 76:9;120:1;138:19; 179:5;181:2;182:7; 206:2,6;222:18; 239:11,19;249:12; 261:10;263:8;277:10; 286:5;294:13,14; 300:18;307:11; 314:15;321:8;328:21; 337:7;338:2;348:6; 350:21;354:11; 355:19;357:12; 362:20;364:2;365:22; 380:1	taste (1) 35:17	templated (1) 322:9	tests (6) 228:10,12;345:16, 18;346:1;348:11	
talks (11) 20:22;24:17;50:16; 81:17,22;82:15;83:10; 84:9;98:4;138:7; 328:10	Tatiana (8) 193:12;206:8; 207:20;227:1;228:4, 12;285:3;314:19	temples (2) 274:20;322:7	that'll (1) 316:5	
Tamoxifen (1) 247:1	Tatiana's (1) 346:8	temporally (2) 88:19;91:15	therefore (6) 51:21;52:2,21; 145:16;166:6;226:18	
tangible (1) 129:8	taught (2) 199:19;333:12	temporarily (1) 335:16	thick (1) 130:10	
	Tawbi (15) 202:10,10;249:2,4; 263:15;286:3;308:13, 19;310:5,10;364:10; 366:20,21,21;367:18	tend (6) 54:21,22;73:12; 127:20;277:8;323:3	Thin (2) 131:9;134:9	
	taxing (2) 380:5,17	tendency (1) 188:4	thinking (44) 10:1;28:15;39:10; 45:11,20;53:7;66:10; 82:2,8,11;86:6;90:15; 99:20;139:17;160:20; 174:6;189:11,14; 190:2;204:20;205:4; 208:4;241:17;247:14; 254:21;261:2,18; 278:3;285:2;287:9; 294:2;330:18;332:1; 338:7;344:12;346:16; 353:20;360:19; 363:20;364:8,20; 367:6;385:10;392:11	
	taxol (1) 223:8	terms (42) 15:17;21:20;35:4; 53:20;54:4;66:19;	therapeutic (24) 9:18;20:11;23:4; 26:12;27:3;35:22;	
	Taxotere (1) 223:8	74:13;78:17;82:2; 101:6;110:6,15;	36:13,22;45:5,14; 64:9;85:12;88:6;	
	T-cell (1) 170:21	111:14;112:8;115:9; 21:117:4;124:22;	89:14;94:18;97:3; 99:4;106:15;116:4;	
	TDM1 (6) 111:1,5,10,17;	128:3,4;141:15;	120:11,17;121:5;	
	112:7,10	152:13;176:18;184:9;	124:8;383:12	
	teach (2) 39:12;333:13	194:9;200:20;214:5, 14;264:4;266:3;	therapeutics (1) 126:14	
	team (10) 37:20;83:17;87:16;	267:21;271:7;277:11;	therapies (51) 15:16,22,22;19:12;	
	141:7;146:1,2;323:12;	279:13;315:13;	21:10;23:7,20;24:3;	
	331:20;376:13;392:3	317:13;319:16;	25:3,10,13,14;26:4;	
	teams (4) 145:21;146:5;	321:18;326:17;	29:18;30:11;31:1;	
	282:15;283:3	350:19;361:1;384:9	32:10;33:18;34:9,10;	
	tease (2) 182:22;184:18	Terri (1) 176:4	36:6;48:20;60:15;	
	technical (2)	terrible (3) 245:19;316:17;	67:7;86:20;87:1;	
		344:20	121:5,9,19;124:11;	
		terribly (1) 354:3	170:5;183:5,12,22;	
		terrific (6) 158:17;161:16;	204:11;253:18;269:3;	
		299:5;314:11,21;	292:11;293:12,15;	
			303:20;337:11,12,13;	
			346:3;359:22;387:16;	
			391:1,5,11;392:16	

21:67:8;138:13; 191:17;196:11; 207:12;214:19;248:1; 280:9;290:20;317:16; 318:13;331:13; 357:22;366:4	times (14) 78:10;85:2;128:11; 184:18;185:12,13; 225:8;281:17;349:5; 13;358:13;363:16; 367:21;387:22	38:10;40:16;93:22; 125:6;342:9;388:20, 21	toxicities (5) 33:13;52:1;53:20; 264:19,21	treat (21) 41:12;47:21;52:20; 62:17;71:21;118:6; 119:1;145:20;148:4,7; 209:1;246:4;252:15; 264:20;267:8,19; 268:12;270:21; 293:17;359:16;381:22
thought (25) 39:11;51:22;52:3; 81:18;124:19;139:14; 189:13;197:12; 207:10,10;230:19; 243:4;245:22;260:18; 262:5;283:3;285:3; 303:9;307:5;318:7,22; 345:10;352:16,20; 363:22	time-to-event (1) 165:12	tolerability (2) 184:14;188:10	toxicity (6) 53:22;190:16; 265:1;273:10,21; 276:22	treated (46) 16:11;27:9;28:2; 31:20;41:15;45:21; 49:10,13;68:15;95:20, 22;103:10;105:13; 112:3;124:13;146:8; 156:5,7;191:5,19; 195:2,12,19;206:14; 235:19;236:10; 239:15;247:21; 258:15;267:5;269:8, 18;270:13;271:14; 277:11;300:11; 307:18;313:21;321:9; 323:8;329:11;330:2, 14;342:10;383:20; 387:9
thoughtful (4) 182:12;216:1; 285:6;324:17	timing (7) 82:6;124:3;144:1,1; 151:4;165:11;387:15	tolerable (1) 204:14	toxicity-gathering (1) 277:3	treating (20) 46:21;54:12,12; 118:10;152:21; 183:10,15;196:2,14, 15,18;205:6;270:16, 22;333:18,19;359:5; 377:21,22;382:2
thoughtfully (2) 159:13;160:16	tiny (3) 245:9;299:7,19	tonight (1) 217:15	tractable (1) 221:14	treatment (56) 20:16;24:4;30:21; 40:22;41:6;48:6; 49:18;50:13;52:16; 65:5;69:11;72:2;75:3; 98:9;99:11,22;111:5, 10;145:17;148:11,16; 153:16;173:14; 196:20;205:18; 214:22;215:1;238:13; 239:20;240:9,11,13; 253:4;255:13;256:6; 257:6,6;266:18; 285:17;288:3;289:12; 305:16;313:18;314:6; 318:19,21;319:3,14; 321:13;358:8;365:15, 18,20;379:8,21; 380:15
thoughts (19) 51:4;67:5;139:22; 158:12,20;159:3; 176:5,10;177:7; 203:15;204:1;262:5; 303:8;321:22;322:3; 334:10;336:2,7; 356:22	tissue (10) 70:10;88:17;96:20; 116:4,6;126:14;294:5, 6;296:9;299:9	took (7) 38:5,12;39:16; 246:6;283:5;286:18; 370:15	traction (1) 391:12	treatments (19) 15:21;17:10,22; 18:8;31:8;37:3;39:5; 48:15;53:12;73:21; 153:17;222:16; 246:22;256:8;289:9; 380:11;381:13; 388:10,11
threaded (1) 336:16	title (2) 125:7;162:20	tool (1) 301:22	tradition (1) 317:6	tremendous (3) 29:22;103:19;
threatening (2) 145:15;344:9	TKI (1) 77:10	tools (2) 129:7;256:4	traditional (3) 131:22;134:7; 163:19	
three (11) 16:17;24:20;31:16; 38:1,2;164:19;199:17; 243:13;283:4;366:17; 376:16	today (75) 8:7;9:19;11:16; 16:1;17:7,21;19:7; 20:7,9;26:10;36:14; 42:3;43:15;50:9;69:8; 78:2;84:16;85:7;88:2; 90:16;106:11;120:1; 123:11,12;163:10,21; 172:22;175:10,11; 181:13;182:4;187:4, 21;199:21;232:14; 233:1,4,6,20;234:2; 243:8,10;248:8;251:6; 252:15;269:6;287:11; 293:8;312:15;317:2; 319:15;324:13;336:7; 341:17;342:17; 355:20;368:5;377:3, 12,15,18;378:9;379:9; 383:3,5;385:18;386:6, 17;388:22;389:13,16; 390:19;392:8,18,21	Tooma (1) 77:21	traditionally (5) 54:20;83:22;119:9; 151:6;351:5	
threshold (4) 147:5;265:1;275:6, 7	today's (2) 16:22;182:8	tossed (1) 352:20	trafficking (1) 57:8	
thresholds (2) 128:7;187:14	Todd (1) 11:11	total (4) 9:5;128:5;134:14; 313:14	train (1) 221:5	
thrilled (1) 57:1	together (36) 9:20;12:12,13,16, 19;26:6;36:22;42:20; 50:13;80:6;85:5,6; 87:16;111:12;114:18; 117:18;149:5;158:2; 181:3,13;186:13;	totality (5) 171:7;172:15; 174:8;230:5;363:4	trained (1) 150:9	
thriving (1) 123:4	tilt (1) 301:18	totally (5) 227:1;276:2;298:6; 369:17;372:19	training (2) 43:20;217:4	
throughout (8) 22:16;24:17; 131:14;230:8;263:18, 18;318:2;390:13	today's (2) 16:22;182:8	touch (5) 75:10;136:19; 160:10;207:2;350:19	trains (1) 81:14	
thus (1) 358:11	Todd (1) 11:11	touched (7) 43:22;44:5;113:13; 130:5;138:15,15; 387:7	trametinib (1) 31:18	
tie (1) 234:11	ties (3) 69:20;361:6;387:15	touching (1) 139:15	transient (1) 25:18	
tilt (1) 301:18	tilt (1) 233:20;246:21;263:2; 281:12;309:5;311:7; 316:14;348:10;	tough (3) 19:19;307:3,3	transitioned (1) 61:17	
Tim (2) 132:17;136:11	tim (2) 356:17;368:17; 377:11;389:2;391:21; 392:1,15	towards (3) 47:19;100:11; 160:17	translate (2) 55:14;235:7	
timeline (1) 266:20	told (7)	toxic (1) 34:1	Translating (1) 363:9	

390:18	357:1;359:10;364:4;	8,11,17,21;357:21;	158:8;187:21;208:13;	87:4,9,21;88:5;90:1;
tremendously (1)	365:3,11,22;366:2,12,	358:7;359:2;365:18;	216:1;226:6;227:12;	93:21;97:11;121:12;
20:21	16;367:15;368:11;	367:2,4;368:7,18,21;	248:5;250:12;251:8;	123:16;125:10,14;
trend (1)	370:4;372:12;380:2,7,	369:4,7,12;370:1,19;	254:16;255:16,18;	126:6;127:12,20;
172:1	10,18;390:16;391:14	373:13;380:4;383:8,9,	259:15;264:13;277:8;	155:7,12;166:9;
trepidation (1)	trialist (1)	19;384:5,9,15,17;	280:18;284:16,21;	170:10,17;173:6;
119:13	257:8	385:6,12;387:6,11;	291:3;292:6;294:16;	174:15;206:5,18;
trial (211)	trials (240)	390:2,3,7;391:13;	303:19;307:13;322:1;	209:13;251:21;252:1,
13:14;15:17;28:9,	15:10;17:4,6,8;	392:12	333:6;346:6;356:4;	13,15;253:12;292:6;
17:34:5;36:16,19;	24:11,16,18;25:5;	tribute (1)	389:18;391:3;392:4	299:15;310:19;331:3;
41:20;43:6;58:12,15;	27:15,20;28:13;29:11;	145:8	trying (36)	332:19;333:4;339:12;
59:22;60:4,9;61:3;	30:10;32:11;33:1;	tricky (1)	357:12	
62:22;63:6;65:6,15;	35:6,7,11,22;37:3;	353:13	tumor's (1)	
66:6,9;67:9,11,15;	40:3;41:14;42:16;	tried (15)	268:15	
68:8;70:15;71:14;	43:16;44:6;46:10,15;	16:5;40:12;48:22;	tumor-specific (1)	
72:7,10;75:9;76:21;	47:1;51:8,13;52:11;	56:1;62:20;67:8;73:3;	188:21	
77:5,10;80:7;81:2;	58:7,9;59:5;61:2,2;	80:5;178:19;185:19;	tuned (1)	
96:5,8,11,12,16;97:2,	62:5,6,11;64:22;65:8,	221:4;226:17;241:10;	382:10	
7,18;104:14,16,18;	17:67;20:68:11,18;	249:22;336:14	turbo (3)	
108:22;109:1,22;	69:21;74:15;75:7;	trigeminal (3)	132:10,14;133:13	
112:2;121:8;123:12;	76:13;77:15;81:7;	245:11,15;246:6	turn (11)	
125:1,3,5;142:12;	90:15;99:2;100:16,20,	trigger (3)	14:12;138:8;	
148:10;152:11;	22:101:6,22;107:18;	169:18;218:17;	162:14;224:13;	
158:14;159:7,13;	108:21;111:17;115:4,	219:3	230:11;237:7;238:20;	
163:21;164:1,2;165:1;	9,21;117:9,15;118:9;	triggered (1)	244:5;250:13;312:1;	
171:11,21;172:7;	129:15;130:4;140:12,	197:12	358:19	
174:7;175:3;178:1,18;	19:149:13,17,22;	triggers (1)	turned (1)	
179:5,22;180:2,4,12;	150:6,16;158:5;159:5;	218:22	247:15	
182:10;185:7;192:15;	160:21;161:5;164:14,	triple (3)	turning (2)	
195:8;201:19;205:2;	17:167:19;175:20;	24:22;25:10;85:19	233:13;250:15	
216:19;218:14;	176:21;177:16;	trivial (1)	Twelve (1)	
223:11,15,19;224:22;	182:14,14;184:3;	92:12	244:22	
225:4;226:13;228:8,	185:6,10;190:22;	trouble (3)	Twenty-four (1)	
19:232:18;235:17;	191:3;192:15;195:1,	267:13;279:18;	380:6	
236:6,7,9;237:4,22;	12;197:1;204:11,22;	350:5	two (74)	
239:5;242:21;248:4;	205:13;221:3,22;	troubles (1)	15:13;16:5;24:8;	
250:1;252:8;253:8;	222:15;224:5;225:19;	268:5	28:13;29:3;33:1;39:9;	
254:16,18;258:7,17;	228:22,22;229:7;	troublesome (1)	12,15;41:4;48:6;49:1,	
260:7;261:15,16;	233:22;234:2,3,18;	267:19	6;53:1;61:2;76:6;	
264:1;265:10;266:14;	235:12,12,18;236:16,	troubling (1)	77:13;83:8;98:12;	
267:6;270:10,11;	17:239:5,11,12,13;	245:10	107:2;118:13;122:3;	
271:12,20;273:7;	240:8,12,19;241:12;	truck (1)	147:14;155:7;167:22;	
275:1;277:12;279:7;	242:6;249:6,15;251:1,	391:3	168:9;171:11,15;	
17,19;284:2;285:4;	1,10;253:14,17;254:2,	true (16)	173:2;174:15;181:12;	
286:14,15;290:15;	5;258:4;18;259:2;	101:4,4,4,8;104:2,2;	186:6;193:18;194:4;	
291:16;295:12;	260:12,14;261:7;	122:3;124:18;130:22;	195:7;199:3;200:21;	
297:19;298:9,11;	264:7;266:10,21;	131:8;188:16;197:21;	202:19;206:16;	
302:7;303:21;304:3,	267:2;268:8;271:1;	212:13;308:8;321:2;	226:19;227:6,7,7,14;	
10,15;306:12,22;	272:5;277:14;279:3;	358:14	228:15;235:22;	
307:9;309:9;310:12,	280:7;281:5;290:8,22;	truest (1)	180:18;187:22;193:4;	
13;311:1,3,8,11,20;	293:21;294:2,16,19;	8:17	237:19;245:10;	
312:3,3,9,12;313:11,	295:3;296:8,15;297:4;	truly (4)	247:17;255:9,13;	
13;314:5;315:18;	299:14,21;302:4,9,12;	10:20;121:1;	256:2,6;259:5;287:12;	
317:10;318:20;	306:17;308:4,12,12;	288:14;305:17	292:4;293:18;296:4;	
321:17;323:10;	309:8;310:21;315:3;	trust (1)	297:20;311:5;318:1;	
326:11,15;329:19;	316:3,4;317:14;321:5;	244:6	320:19;333:6;336:17;	
330:5,5,6;334:19;	323:2;325:1;326:8;	truth (1)	343:4;362:10;374:8,	
335:3;338:13;342:13,	329:9,10,15,22;	308:6	21;375:8,12;377:10	
15;343:16;344:8,11,	330:12,13;331:3;	try (46)	tumors (57)	
16;345:4,18;346:17;	332:15,21;340:2;	16:12;23:14;25:6;	9:6,8;22:11,14;	
347:5;352:12,18;	341:19;342:2;343:1,7,	75:9;85:5,11;87:5,7,	28:18;29:17;38:13,13,	
353:19;354:14,14;	20;346:5;347:2,9,19;	17,18;88:6,12;89:1;	14;39:20;22;40:22;	
355:5;356:13,15;	348:4,20;352:7;356:8,	130:11;132:19;133:4;	46:8,21;50:11;54:12;	

178:18;189:7;190:21; 201:20;214:22; 228:15,16;230:2; 351:2;356:10;359:8, 13,14;379:20	303:15;360:9;381:12 undergo (4) 71:18;72:6;167:7; 169:18	85:4,9;103:19;170:4; 182:5,7;186:15;282:5 unplanned (2) 237:14,15	132:16,19;133:14; 138:15,15;238:5; 290:13;322:8;355:6; 379:5	271:17;288:22;313:19 utilization (5) 23:9;169:12,13; 173:15,16	
types (17) 19:12;26:6;29:13; 42:12;58:11;63:10; 65:11;72:21;100:17; 107:17;132:7;157:5; 167:12;168:19; 180:13;186:6;330:13	undergoing (2) 73:9;114:20	unsupervised (1) 153:11	ups (1) 180:21	utilizing (1) 141:2	
typical (2) 171:18;244:11	underlying (4) 116:3,17;124:21; 143:15	untapped (1) 60:17	upwards (1) 9:12	utmost (1) 215:3	
typically (10) 73:5;127:3,11,18; 130:9;164:15,16; 177:4;224:3;305:13	underrepresentation (2) 24:17;35:20	untreated (9) 28:3;109:3;196:7; 235:19;236:15; 239:15;292:22; 309:10;387:9	urban (1) 279:9	V	
tyrosine (1) 151:18	underwent (1) 195:6	unusual (3) 38:4,6;279:11	vacuum (1) 19:9		
	undiagnosed (1) 52:17	unvalidated (1) 202:7	valid (1) 151:10		
U	unequivocal (1) 135:13	up (114) 19:15,17;21:5,7; 27:9;37:13;38:11; 40:15;41:4;44:10; 53:1;56:15;60:4,11; 61:11,18;62:6;64:16; 65:13;66:13;67:15; 73:8;75:11,20;76:7,9, 14:8;1:22;82:1;95:16; 96:16;102:13;110:17; 128:8,9,20;130:6; 133:4,22;134:12,14; 141:13;147:21;148:7, 11:149:8;150:4; 158:13,13;174:6; 176:7;189:17;194:14, 17:197:9;201:17;	validate (4) 26:11;88:9;202:7; 369:3		
UCLA (1) 126:1	unestablished (2) 171:20;172:3	223:9,17;225:9; 227:20;228:2,9; 230:22,22;241:8; 245:20;246:8,16; 252:7;261:14;273:16; 278:5;279:1;283:5; 284:17;289:20;290:2; 293:6;306:8,15;311:9, 18:313:5;316:12,18; 320:15,21;330:17; 335:12,15;344:4; 345:10;348:12; 350:15,16,19;354:15; 358:8,18;362:7; 363:12,12;364:7,12; 366:5,22;369:14; 381:18;387:22;390:8, 18:391:4,20;392:19	validated (3) 200:11;372:3,6		
uh (1) 382:19	unidirectional (1) 150:19	upcoming (1) 142:11	validating (1) 92:4		
ultimately (8) 38:4;187:19; 212:13;228:18;255:8; 275:9;353:8;390:12	unethical (1) 344:19	upfront (4) 27:11;136:3; 193:14;326:3	valuable (1) 213:17		
Ultrasound (5) 335:14,16;336:4; 337:14,20	unfortunately (3) 180:9;305:19; 331:11	upon (21) 22:1;25:9,11;26:1; 29:15;42:20;76:14; 104:11;129:6,8;130:5;	value (10) 11:19;124:7;132:5; 133:13;137:5,15,20; 195:11;212:6;309:1		
ultrasounds (2) 56:4,5	uniform (1) 354:15		vanguard (1) 326:22		
um (1) 247:6	uniformly (2) 322:2,12		variability (4) 166:2;169:7; 226:17;385:4		
umbrella (1) 284:1	union (1) 186:12		variable (1) 19:11		
unanswered (2) 57:9;86:13	unique (16) 12:19;13:8;20:8; 36:11,13;45:4,11,16; 46:13;131:7;145:21;		variation (1) 28:6		
unassociated (1) 205:18	uniquely (4) 120:14;121:2; 255:18;390:15		variations (1) 384:12,13;386:19; 387:14;389:18,19		
unbeknownst (1) 370:8	United (3) 9:13;101:15;163:16		variety (5) 126:18;131:4; 133:21;137:12;253:12		
uncertain (1) 170:15	University (5) 243:21;249:5; 255:10,11;256:1		various (7) 12:18;14:9;111:15; 121:11;123:15; 336:14;356:16		
uncertainties (1) 361:12	unknown (1) 57:4		varying (1) 175:14		
uncertainty (3) 164:13;171:9,16	unless (7) 196:22;279:17; 329:13;330:15; 342:16;360:14;364:4		vascular (2) 127:21;137:6		
unclear (1) 183:19	Unlike (3) 126:5,17;131:11		vascularity (1) 127:19		
uncomfortable (1) 45:18	unlikely (2) 98:20;342:20		vasculature (2) 133:7,11		
uncommon (1) 91:4	unmet (14) 9:17;26:13;35:9; 52:21;56:19;59:14;		vast (2) 15:9;129:2		
uncover (1) 188:15			vastly (1) 227:15		
under (8) 40:19;117:10; 217:12;256:14;284:1;			VATS (1) 156:6		
			VEGF (1) 107:6		
			vehicle (1)		

95:21	vitro (1)	31:19	Wefel's (1)	198:12
vendor (2)	181:10	way (75)	353:9	White (1)
376:12;378:18	vivo (1)	46:11;52:15;59:4;	weigh (2)	12:6
vendors (1)	95:14	114:5;136:16;142:20;	252:21;253:1	whole (23)
132:2	voice (8)	145:14;148:4;160:3;	weighing (1)	42:18;62:16;75:2;
ventricle (1)	81:12,20;198:11;	165:21;183:10,15;	269:16	88:15;91:18;105:6;
147:6	227:22;229:13,14;	187:7;188:14,20;	weighted (1)	124:9;243:2,11;
verging (1)	282:2;386:7	189:5;190:17;191:22;	127:3	246:15;261:22;283:3;
40:18	voices (1)	198:12;203:9,10,10;	WEINSTOCK (12)	302:6;303:5;307:7,11;
verify (2)	83:21	209:11;211:14,20;	83:12,16;117:13;	326:10,12;334:22;
135:19;164:15	volume (5)	212:22;215:13,17,19;	138:6;139:13;145:5;	341:1;346:9;365:14;
versa (1)	85:1,2;128:6;335:4;	217:18;221:9;223:18;	158:19;159:1,2;	385:9
238:21	371:1	227:10;230:7;235:12,	350:17,18;352:10	whole-brain (25)
versed (1)	volumetric (1)	13:243:16,18;251:3;	Welcome (5)	22:7,18,22;28:4;
43:7	130:9	252:18;257:13,22;	8:5,7;12:5;14:17;	47:14;48:10;91:20;
version (2)	voluntary (1)	265:10;266:16;267:1;	232:14	146:22;213:10;
302:3;318:21	129:3	275:17,18;276:14;	well-controlled (1)	214:18;217:11,20;
versus (27)	volunteered (1)	281:6;290:2;293:10;	164:2	219:3,9;224:17;
13:9;28:3,17;34:5;	11:5	301:8;305:12;309:8;	well-proven (1)	280:16;351:1;352:21;
105:15;106:2;108:6;	vouch (1)	311:5;316:13;321:6;	353:3,6,13,21;355:8,	335:3,6,13,21;355:8,
17:118:15;123:14;	64:5	330:7;333:13;337:22;	13,16	
153:8;155:13;184:19;	vulnerabilities (1)	343:7;346:2;351:4,6,	wholly (1)	
198:16;207:15;208:4;	92:14	20,353:6;354:21;	68:19	
239:15;288:9,21;	vulnerable (3)	364:4;370:12,13,20;	who's (7)	
309:16;324:5,22;	9:16;181:19;389:14	371:14;382:3,22;	102:8;162:11;	
338:8;345:21;367:6;		387:18	217:15;317:13;	
371:14;387:9	W	ways (28)	322:21,22;352:17	
via (1)		22:9;45:20;48:10;	whose (3)	
159:13	wait (10)	51:19;65:14;76:15;	278:1;291:22;295:1	
viable (1)	45:19;72:6;213:12;	80:8,16;115:15;120:6,	who've (6)	
195:7	270:9,22;271:3,16;	6,16;135:22;158:1,1;	60:1;122:11;269:8;	
vice (2)	272:7;276:14;309:15	196:18;200:6;221:1,5;	274:8;300:13;303:3	
238:21;255:2	waiting (5)	234:11;287:1;294:3;	Wendy (11)	
Victoria (2)	45:18;177:6;	303:11;315:9;330:9;	8:22;11:8;14:12,20;	
43:18;224:10	179:18;309:7;349:1	355:17;363:3;370:16	81:13;82:22;217:6;	
video (1)	Walker (5)	wearable (2)	230:11;346:6;375:7;	
328:9	41:8,8;58:10;65:2;	168:18;174:20	388:20	
videos (1)	66:22	Weatherby (3)	weren't (2)	
11:6	walking (2)	243:6,7;300:16	60:5;69:3	
view (6)	173:13;210:21	webcast (3)	whatnot (1)	
19:12;195:14;	wants (9)	119:21;158:17;	213:6	
284:3;328:22;353:19;	197:13;199:21;	392:22	what's (33)	
382:1	261:21;262:1;282:8;	webinars (5)	12:10;22:1;33:5;	
viewpoints (1)	343:18;349:14;391:7;	20:19;21:15,17;	49:5;51:9;54:13;	
189:10	392:2	35:18;377:3	131:5;136:6;137:2;	
views (1)	warranting (1)	website (1)	140:14;142:13;	
11:18	390:15	20:20	151:10;153:12,13;	
vignette (1)	Washington (1)	weeds (1)	155:4;186:16;187:6,	
147:22	243:22	352:1	10,202:13;207:18;	
village (2)	washout (8)	week (5)	209:20;214:3;254:20;	
50:9;124:20	268:4,10,16;271:22;	222:10;276:6;	287:9;316:2,3;328:20;	
Vinai (1)	274:14,20;276:10;	295:14;300:20;364:17	331:1;348:16;360:6;	
252:10	387:12	weekend (2)	365:11;387:3,12	
violation (1)	watch (3)	246:1;300:19	whatsoever (1)	
223:18	35:19;247:6;267:9	weeks (18)	241:16	
visible (1)	watched (1)	34:22;49:17;65:6;	whenever (1)	
327:16	256:11	109:19;245:19;270:9;	223:4	
visit (1)	watching (3)	271:3;275:8,9,11,13,	whereby (2)	
12:8	136:8;179:17;	15,17;276:1;295:13;	188:9;191:14	
Visualase (1)	268:18	302:2;309:19,20	where's (1)	
337:8	water (1)	Wefel (5)	61:7	
vitally (1)	127:5	185:2,2;219:7;	Whereupon (3)	
159:8	waterfall (1)	220:17,20	161:17;231:4;393:5	

137:8;148:17;153:9; 163:6;166:14;183:22; 186:7;190:13;210:5; 223:10;291:8;293:18; 342:17;362:10;367:3	66:2;68:4,7;70:9; 77:22;79:12;125:12; 135:22;138:11; 199:12,18;243:16; 247:2;320:21;335:13; 347:19;376:13,14; 378:19;392:1	WSCollaborative (1) 11:9	Z	161:17
without (16) 22:21;28:20;29:4; 32:3;109:7;180:12; 192:2;200:22;257:22; 285:15;304:16; 311:17;315:10,17; 326:10;340:10	X	zero (2) 74:15;140:19		11:15 (1) 158:22
women (2) 256:11;279:9	xenograft (5) 95:5,9,18;96:2; 114:19	zillion (1) 345:22	11:20 (1) 161:13	115 (1) 158:16
Women's (1) 221:20	xenografts (2) 95:20;281:8	ZUCKERBERG (1) 342:3	119 (1) 286:22	119 (1) 286:22
wonder (6) 165:17;213:17; 215:18;227:18; 338:16;356:9	XRT (2) 218:11,16	Zuckerman (3) 317:18,19;339:10	12 (3) 39:9;161:9;283:9	12:31 (1) 231:4
wonderful (7) 26:18;85:5;179:8; 204:3;212:9;375:10; 376:6	Y	0 (2) 109:5;244:14	12:59 (1) 232:2	13 (1) 299:18
wonderfully (1) 180:17	Yael (2) 77:3;352:16	0.13 (1) 105:9	14 (2) 39:10;71:21	14 (2) 39:10;71:21
wondering (2) 139:21;156:18	Yamamoto (1) 148:3	1 (31) 9:9;24:15;41:13;	15 (5) 183:4;215:9; 229:21;286:15;317:21	15 (5) 183:4;215:9; 229:21;286:15;317:21
word (6) 8:18;64:18;81:19; 156:12;253:22;285:1	Yang (6) 186:2,2;190:9,12; 197:2;212:8	80:10;100:19,19;	150 (1) 49:10	150 (1) 49:10
words (3) 37:12;243:19;357:6	year (22) 9:13;21:6,8;34:6; 41:21;50:22;61:12,20;	101:6;111:17;130:13;	1500 (2) 24:11;87:20	1500 (2) 24:11;87:20
work (75) 9:20;43:12,13;44:3; 45:2;46:20;47:15; 49:6;50:13;57:6;58:1; 65:12,21;69:22;70:4, 6:71:7;79:9;80:3; 85:8;87:12;93:12; 95:17;97:16;100:8; 117:11;122:16;126:2; 133:3;136:1;144:7; 154:12,22;155:1,2,16; 156:18;157:3;177:12; 185:8;195:16,17; 197:4;201:17;213:13; 217:3;224:6;242:4; 250:14;251:17; 259:10,11;270:4,5; 279:18;281:7,8,9,12; 294:18;301:3,13,21; 310:18;320:18;327:8; 335:20;343:18; 356:17;363:10;375:1, 14;376:15;389:21; 390:14	62:2;103:9;125:16; 199:1;244:13,13,22; 247:5;255:6;256:21; 278:2;281:6;291:15; 375:16	13:134:9;149:16;	16 (2) 24:12;347:6	16 (2) 24:12;347:6
worked (6) 12:12;14:8;39:16; 256:1;282:13;378:17	years (47) 12:9;13:1;15:13; 16:4;26:21;38:2,2;	151:7;175:22;194:10;	170,000 (1) 21:5	170,000 (1) 21:5
working (26) 8:17;16:8;37:22; 40:22;43:10;48:21;	worried (3) 77:7;265:12;337:3	198:19;249:19;	180,000 (1) 9:12	180,000 (1) 9:12
	worries (2) 280:10;281:21	263:20,22;268:9,11;	1837 (1) 89:18	1837 (1) 89:18
	worrisome (1) 211:19	272:15;273:7;295:20;	19 (1) 380:9	19 (1) 380:9
	worry (11) 67:6;256:22,22; 280:12,13,21;281:16, 18;282:4,10;283:2	298:9;300:8;315:6;	1985 (1) 102:3	1985 (1) 102:3
	worse (1) 36:3	335:5;339:2,7;347:5	1990 (1) 146:13	1990 (1) 146:13
	worsening (1) 22:20	1.1 (1) 134:4	1997 (1) 148:2	1997 (1) 148:2
	worst (3) 48:13;277:19;354:5	1.5 (1) 73:17	1-millimeter (1) 324:13	1-millimeter (1) 324:13
	worth (1) 43:14	1/phase (1) 199:7	1's (1) 158:8	1's (1) 158:8
	wrap (5) 227:20;228:2; 320:15;351:10;381:18	1:00 (1) 230:22	2	2
	wrap-up (1) 382:17	10 (25) 9:9;12:9;47:7; 71:21;102:4,4;112:10;	2 (17) 22:12;34:20;40:17;	2 (17) 22:12;34:20;40:17;
	write (1) 336:22	100,000 (3) 9:12;21:7;250:6	100:19;101:20;	100:19;101:20;
	writers (1) 282:1	10-centimeter (1) 318:1	103:21;109:5;111:17;	103:21;109:5;111:17;
	written (5) 217:14;223:5; 275:19;282:1;380:13	10-fold (1) 60:12	199:7;244:15;280:19;	199:7;244:15;280:19;
	wrong (1) 279:10	10-minute (3) 158:21;162:10;	295:13;315:6;327:2;	295:13;315:6;327:2;
	wrote (3) 280:9;357:6;389:3	yous (2) 386:1;389:3	363:15;370:16,22	363:15;370:16,22
		Yung (2) 298:5,5	2.0 (1) 302:3	2.0 (1) 302:3
			2.2 (1) 170:12	2.2 (1) 170:12
			20 (12) 32:16;49:21;	20 (12) 32:16;49:21;
			11:14;113:6;121:16;	11:14;113:6;121:16;

135:11;177:1;256:3; 282:13;334:4;342:18; 348:22 200 (3) 376:17,18,19 2001 (1) 244:12 2006 (1) 297:6 2007 (2) 102:3;156:4 2008 (1) 156:5 2011 (1) 31:2 2014 (1) 15:1 2015 (2) 129:12;133:20 2016 (2) 40:20,21 2016-17 (1) 307:6 2017 (2) 41:4,6 2018 (4) 28:17;29:16;31:2; 378:17 204 (5) 33:8;103:7;258:7, 16:286:14 211 (1) 378:14 237 (1) 378:12 24-year-old (1) 86:10 25 (5) 9:10;85:20;148:9; 255:7;279:7 250 (2) 128:22;151:21 27 (1) 85:22 28 (2) 179:8,14 2-centimeter (1) 73:18 2-dimensional (3) 130:10,16;132:14	315:6;331:2;359:4; 365:5;367:10 3:57 (1) 393:5 30 (9) 49:21;85:17;135:4; 148:7;170:8;263:21; 269:3;314:12;353:7 302 (2) 171:11;225:4 35 (1) 86:1 3D (4) 131:9,15;132:10,11 3DT1 (1) 335:4 3-month (3) 274:20;275:6;276:4 3's (2) 158:9;197:4	6 6 (14) 25:19;39:18;48:2; 67:17;106:3;179:3,16; 244:13,22;302:2; 309:20;335:2;367:10; 381:7 60 (5) 33:5;101:19; 105:20;269:4;314:17 600 (2) 41:21;151:21 65 (1) 151:17 6-month (2) 136:5;276:5
		7
		4
		7 (8) 32:2;179:3,10; 180:19;219:1;256:10; 275:8;279:8 70 (2) 86:2;269:4
		8
		8 (3) 109:19;335:2;347:5 8:31 (1) 8:2 80 (2) 31:22;161:9 81 (3) 33:8;110:5;379:16 8-millimeter (1) 77:9
		9
3	5 (11) 41:2;60:11;85:2; 134:12,13;148:12; 217:13;280:16; 346:11;365:6;370:17 50 (13) 31:13;32:4;33:5; 41:2;49:19;85:19; 86:3;94:6;110:3; 111:14;113:6;170:13; 265:21 50/50 (1) 157:1 51 (1) 104:17 5-target (1) 370:22	9 (4) 178:12;216:17; 379:4;381:15 90 (1) 286:21 92 (1) 282:16 9th (1) 348:2