

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
  
PEDIATRIC SUBCOMMITTEE OF THE  
ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Wednesday, June 20, 2018

8:00 a.m. to 4:10 p.m.

FDA White Oak Campus  
Building 31, the Great Room  
10903 New Hampshire Avenue  
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Lauren Tesh, PharmD, BCPS**

4 Division of Advisory Committee and

5 Consultant Management

6 Office of Executive Programs, CDER, FDA

7  
8 **ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)**

9 **Alberto S. Pappo, MD**

10 *(Chairperson, pedsODAC)*

11 Member and Head, Division of Solid Malignancies

12 St Jude Children's Research Hospital

13 Professor of Pediatrics

14 University of Tennessee Health Science Center

15 Memphis, Tennessee

16

17

18

19

20

21

22

1 **Courtney J. Preusse, MA**

2 (Consumer Representative)

3 Senior Research Administrator and CLIA Operations

4 Director

5 Clinical Research Division

6 Fred Hutchinson Cancer Research Center

7 Seattle, Washington

8

9 **ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS**

10 **(Non-Voting)**

11 **Phuong Khanh (P.K.) Morrow, MD, FACP**

12 (*Industry Representative*)

13 Executive Medical Director, Amgen Oncology

14 Therapeutic Area Head, US Medical Organization

15 One Amgen Center Drive

16 Thousand Oaks, California

17

18

19

20

21

22

1       **TEMPORARY MEMBERS (Voting)**

2       **Steven G. DuBois, MD**

3       Director, Experimental Therapeutics

4       Dana-Farber/Boston Children's Hospital

5       Associate Professor of Pediatrics

6       Harvard Medical School

7       Boston, Massachusetts

8

9       **Ira Dunkel, MD**

10      Attending, Pediatric Neuro-oncology

11      Memorial Sloan Kettering Cancer Center

12      New York, New York

13

14      **Julia Glade Bender, MD**

15      Associate Professor of Pediatrics at

16      Columbia University Medical Center

17      Associate Director, Division of Pediatric

18      Hematology, Oncology and Stem Cell Transplantation

19      Medical Director, Developmental Therapeutics and

20      Precision Medicine Programs

21      New York, New York

22

1 **Katherine A. Janeway, MD, MMSc**

2 Associate Professor of Pediatrics

3 Harvard Medical School

4 Senior Physician and Director Solid Tumor

5 Service, Pediatric Oncology

6 Dana-Farber Cancer Institute/Boston Children's

7 Hospital

8 Boston, Massachusetts

9  
10 **E. Anders Kolb, MD**

11 Director, Nemours Center for Cancer and Blood

12 Disorders

13 Alfred I duPont Hospital for Children

14 Wilmington, Delaware

15  
16 **Theodore W. Laetsch, MD**

17 Director, Experimental Therapeutics Program

18 Children's Health

19 Assistant Professor of Pediatrics

20 Division of Hematology-Oncology

21 University of Texas Southwestern Medical Center

22 Dallas, Texas

1     **Donna M. Ludwinski**

2     *(Patient Representative)*

3     Research Program Advisor

4     Solving Kids' Cancer

5     New York, New York

6  
7     **Tobey J. MacDonald, MD**

8     Professor of Pediatrics

9     Emory University School of Medicine

10    Director, Pediatric Neuro-Oncology Program

11    Aflac Cancer & Blood Disorders Center

12    Children's Healthcare of Atlanta

13    Atlanta, Georgia

14  
15    **Rajen Mody, MD, MS**

16    Ruth Heyn Professor of Pediatric Oncology and

17    Communicable Diseases

18    Interim Division Director, Pediatric

19    Hematology/Oncology/BMT

20    Director, Pediatric Phase-I and Experimental

21    Therapeutics Program

22    Ann Arbor, Michigan

1 **Kathleen A. Neville, MD, MS, MBA, FAAP, FCCP**

2 Professor of Pediatrics

3 University of Arkansas for Medical Sciences

4 Chief, Section of Clinical Pharmacology and

5 Toxicology

6 Director, Experimental Therapeutics Program

7 Co-Director, Pediatric Precision Medicine Program

8 Little Rock, Arkansas

9

10 **Elizabeth A. Raetz, MD**

11 Professor of Pediatrics, NYU School of Medicine

12 Director, Division of Pediatric

13 Hematology/Oncology

14 Stephen D. Hassenfeld Children's Center for Cancer

15 and Blood Disorders

16 New York, New York

17

18

19

20

21

22

1     **Nita Seibel, MD**

2     Head, Pediatric Solid Tumor Therapeutics  
3     Clinical Investigations Branch, Cancer Therapy  
4     Evaluation Program/Division of Cancer Treatment and  
5     Diagnosis, National Cancer Institute (NCI)  
6     National Institutes of Health (NIH)  
7     Bethesda, Maryland

8  
9     **Malcolm A. Smith IV, MD, PhD**

10    Associate Branch Chief for Pediatrics, Clinical  
11    Investigations Branch, Cancer Therapy Evaluation  
12    Program/Division of Cancer Treatment and  
13    Diagnosis, NCI, NIH  
14    Bethesda, Maryland

15  
16    **Brenda J. Weigel, MD, MSc**

17    Professor  
18    Division Director, Pediatric Hematology/Oncology  
19    University of Minnesota  
20    Developmental Therapeutics Chair  
21    Children's Oncology Group  
22    Minneapolis, Minnesota

1       **SPEAKER (Non-Voting)**

2       **Lia Gore, MD**

3       *(Participation in Topic 2)*

4       Professor of Pediatrics, Medical Oncology, and  
5       Hematology

6       Chief, Pediatric Hematology/Oncology/Bone Marrow  
7       Transplant

8       The Robert J. and Kathleen A. Clark Endowed Chair  
9       in Pediatric Cancer Therapeutics and the

10      Ergen Chair in Pediatric Oncology

11      Children's Hospital Colorado

12      Center for Cancer and Blood Disorders

13      Aurora, Colorado

14

15      **FDA PARTICIPANTS (Non-Voting)**

16      **Gregory Reaman, MD**

17      Associate Director Oncology Sciences

18      Office of Hematology and Oncology

19      Products (OHOP)

20      Office of New Drugs (OND), CDER, FDA

21      Associate Director for Pediatric Oncology

22      Oncology Center of Excellence, FDA

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

**Amy Barone, MD**

Medical Officer  
Division of Oncology Products 2 (DOP2)  
OHOP, OND, CDER, FDA

**Diana Bradford, MD**

Medical Officer  
DOP2, OHOP, OND, CDER, FDA

**Sandra J. Casak, MD**

Senior Staff Fellow  
DOP2, OHOP, OND, CDER, FDA

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Alberto Pappo, MD	14
5	Conflict of Interest Statement	
6	Lauren Tesh, PharmD, BCPS	17
7	<b>Topic 1: Target List</b>	
8	Implementing FDARA 2017 Provisions:	
9	Facilitating Precision Cancer Medicine for	
10	Children	
11	Gregory Reaman, MD	23
12	Clarifying Questions	42
13	Charge to the Subcommittee	55
14	Questions to the Subcommittee and Discussion	56
15	<b>Topic 2: FDARA Implementation</b>	
16	<b>Speaker Presentation</b>	
17	Scientific and Logistical Considerations in	
18	Applying "The List"	
19	Lia Gore, MD	82
20	Clarifying Questions	111
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	<b>Guest Speaker Presentations</b>	
4	Implications of the 2017 FDA Reauthorization	
5	Act on Pediatric Cancer Drug Development:	
6	An Industry Perspective	
7	Lisa Bollinger, MD	122
8	Clarifying Questions	133
9	Investigator Perspectives on New Agent	
10	Prioritization and Challenges with	
11	Multiple Same In-Class Agents	
12	Elizabeth Fox, MD	151
13	Clarifying Questions	179
14	Industry Perspective on Prioritization of	
15	Pediatric Relevant Targets and Molecules	
16	Hubert Caron, MD, PhD	192
17	Clarifying Questions	222
18	Open Public Hearing	234
19	Charge to the Subcommittee	245
20	Questions to the Subcommittee and Discussion	245
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	<b>Topic 3: Mechanisms to Assure</b>	
4	<b>Efficiency and to Enhance Global</b>	
5	<b>Coordination Through International</b>	
6	<b>Collaboration</b>	
7	Recommendations for International	
8	Collaborations and Coordination	
9	Gilles Vassal, MD, PhD	264
10	Addressing Challenges to Global	
11	Coordination	
12	Christina Bucci-Rechtweg, MD	277
13	Clarifying Questions	304
14	Charge to the Subcommittee	316
15	Questions to the Subcommittee and Discussion	316
16	Closing Comments	
17	Gregory Reaman, MD	348
18	Adjournment	352
19		
20		
21		
22		

1                   P R O C E E D I N G S

2                   (8:00 a.m.)

3                   **Call to Order**

4                   **Introduction of Committee**

5                   DR. PAPP0: Good morning. I would like  
6 first to remind everyone to please silence your  
7 cell phones, smartphones, and any other devices if  
8 you have not already done so. I would also like to  
9 identify the FDA press context, Sandy Walsh. If  
10 you are present, please stand.

11                   I would like to ask all the members seated  
12 around here to please introduce yourselves with  
13 your name so we can put them in the record. We can  
14 start right there.

15                   DR. REAMAN: Gregory Reaman, FDA.

16                   DR. CASAK: Sandra Casak, FDA.

17                   DR. BRADF0R: Diana Bradford, FDA.

18                   DR. BARONE: Amy Barone, FDA.

19                   DR. NEVILLE: Kathleen Neville, University  
20 of Arkansas for medical sciences in Arkansas  
21 Children's.

22                   DR. WEIGEL: Brenda Weigel, University of

1 Minnesota.

2 DR. JANEWAY: Katie Janeway, Dana Farber  
3 Cancer Institute.

4 DR. KOLB: Andy Kolb, Nemours Center for  
5 Cancer and Blood Disorders.

6 DR. MacDONALD: Tobey MacDonald, Emory  
7 University, Children's Healthcare of Atlanta.

8 DR. TESH: Lauren Tesh, designated federal  
9 officer.

10 DR. PAPPO: Alberto Pappo, St. Jude  
11 Children's Hospital.

12 DR. DuBOIS: Steve DuBois, Dana Farber and  
13 Boston Children's.

14 MS. PREUSSE: Courtney Preusse, Fred Hutch.

15 DR. LUDWINSKI: Donna Ludwinski, Solving  
16 Kids' Cancer, patient representative.

17 DR. RAETZ: Elizabeth Raetz, NYU Medical  
18 Center.

19 DR. DUNKEL: Ira Dunkel, Memorial Sloan  
20 Kettering.

21 DR. MODY: Rajen Mody, University of  
22 Michigan.

1 DR. SEIBEL: Nita Seibel, NCI.

2 DR. BENDER: Julia Glade Bender, Columbia  
3 University.

4 DR. LAETSCH: Ted Laetsch, University of  
5 Texas Southwestern and Children's Health in Dallas.

6 DR. MORROW: P.K. Morrow, Amgen industry  
7 representative.

8 DR. PAPPO: Thank you very much.

9 For topics such as those being discussed at  
10 today's meeting, there are often a variety of  
11 opinions, some of which are quite strongly held.  
12 Our goal is that today's meeting will be a fair and  
13 open forum for discussion of these issues and that  
14 individuals can express their views without  
15 interruption. Thus, a gentle reminder, individuals  
16 will be allowed to speak into the record only  
17 recognized by the chairperson. We look forward to  
18 a productive meeting.

19 In the spirit of the Federal Advisory  
20 Committee Act and the Government in the Sunshine  
21 Act, we ask that the advisory committee members  
22 take care that their conversations about the topic

1 at hand take place in the open forum of the  
2 meeting. We are aware that members of the media  
3 are anxious to speak with the FDA about these  
4 proceedings. However, the FDA will refrain from  
5 discussing the details of this meeting with the  
6 media until its conclusion. Also, the committee's  
7 reminded to please refrain from discussing the  
8 meeting topic during breaks or lunch. Thank you  
9 very much.

10 Dr. Lauren Tesh will have read the Conflict  
11 of Interest Statement for the meeting.

12 DR. TESH: Dr. Smith, can you introduce  
13 yourself for the record, please?

14 DR. SMITH: Malcolm Smith, NCI.

15 **Conflict of Interest Statement**

16 DR. TESH: Thank you.

17 The Food and Drug Administration is  
18 convening today's meeting of the Pediatric Oncology  
19 Subcommittee of the Oncologic Drugs Advisory  
20 Committee under the authority of the Federal  
21 Advisory Committee Act of 1972. With the exception  
22 of the industry representative, all members and

1 temporary voting members of the committee are  
2 special government employees or regular federal  
3 employees from other agencies and are subject to  
4 federal conflict of interest laws and regulations.

5 The following information on the status of  
6 this committee's compliance with federal ethics and  
7 conflict of interest laws, covered by but not  
8 limited to those found in 18 USC Section 208, is  
9 being provided to participants in today's meeting  
10 and to the public.

11 FDA has determined that members and  
12 temporary voting members of this committee are in  
13 compliance with federal ethics and conflict of  
14 interest laws. Under 18 USC Section 208, Congress  
15 has authorized FDA to grant waivers to special  
16 government employees and regular federal employees  
17 who have potential financial conflicts when it is  
18 determined that the agency's need for a special  
19 government employee's services outweighs his or her  
20 potential financial conflict of interest or when  
21 interest of a regular federal employee is not so  
22 substantial as to be deemed likely to affect the

1 integrity of the service which the government may  
2 expect from the employee.

3           Related to the discussion of today's  
4 meeting, members and temporary voting members of  
5 this committee have been screened for potential  
6 financial conflicts of interest of their own as  
7 well as those imputed to them, including those of  
8 their spouses or minor children, and for purposes  
9 of 18 USC, Section 208, their employers. These  
10 interests may include investments, consulting,  
11 expert witness testimony, contracts, grants,  
12 CRADAS, teaching, speaking, writing, patents and  
13 royalties, and primary employment.

14           Today's agenda involves the review and  
15 discussion of a list of molecular targets for which  
16 evidence and/or biologic rationale exists to  
17 determine their potential relevance to the growth  
18 or progression of one or more pediatric cancers,  
19 and a list of those targets deemed unlikely to be  
20 associated with the growth or progression of  
21 pediatric tumors.

22           These lists are expected to fulfill the

1 statutory obligation of the Food and Drug  
2 Administration Reauthorization Act, FDARA, and  
3 provide some guidance to industry and planning for  
4 initial pediatric study plan submissions for new  
5 drug and/or biologic products in development for  
6 cancer in accordance with the amended provisions of  
7 the Pediatric Research Equity Act.

8           The committee will review and discuss  
9 considerations other than specific relevance that  
10 FDA will include in decision-making with respect to  
11 the need and timing of pediatric evaluation of  
12 specific new drug and biologic products. The  
13 committee will discuss possible criteria and  
14 mechanisms for the prioritization by sponsors and  
15 the clinical investigator community of selected  
16 targeted new agents for pediatric evaluation,  
17 especially in the setting of multiple same in-class  
18 agents.

19           Preliminary discussion will focus on  
20 approaches to coordination and collaboration for  
21 pediatric clinical investigations of new agents  
22 that might be pursued to efficiently accommodate

1 international regulatory requirements in global  
2 pediatric product development. The open public  
3 hearing sessions are Topic 1, Target Lists; Topic  
4 2, FDARA Implementation; and Topic 3, Mechanisms to  
5 Assure Efficiency and to Enhance Global  
6 Coordination through International Collaboration.  
7 This is a particular matters meeting during which  
8 general issues will be discussed.

9 Based on the agenda for today's meeting and  
10 all financial interests reported by the committee  
11 members and temporary voting members, no conflict  
12 of interest waivers have been issued in connection  
13 with this meeting. To ensure transparency, we  
14 encourage all standing members and temporary voting  
15 members to disclose any public statements that they  
16 may have made concerning the topic at issue.

17 With respect to FDA's invited industry  
18 representative, we would like to disclose that  
19 Dr. P.K. Morrow is participating in this meeting as  
20 a nonvoting industry representative acting on  
21 behalf of regulated industry. Dr. Morrow's role at  
22 this meeting is to represent industry in general

1 and not any particular company. Dr. Morrow is  
2 employed by Amgen.

3 With regard to FDA's guest speakers, the  
4 agency has determined that the information to be  
5 provided by these speakers is essential. The  
6 following interest is being made public to allow  
7 the audience to objectively evaluate any  
8 presentation and/or comments.

9 Dr. Elizabeth Fox has acknowledged several  
10 clinical research grants with Ignyta, Merck, and  
11 Novartis, with no personal direct funding. In  
12 addition, she serves on the Data Safety Monitoring  
13 Committee for Helsinn, Inc. regarding supportive  
14 care.

15 Dr. Hubert Caron has acknowledged that he is  
16 employed by Roche and owns stock in the company.

17 Dr. Christina Bucci-Rechtweg has  
18 acknowledged several grants and stocks as part of  
19 employment with Novartis Pharmaceuticals  
20 Corporation.

21 Dr. Lisa Bollinger has acknowledged that  
22 she's employed by Amgen. As guest speakers,

1 Bollinger, Fox, Bucci-Rechtweg, Caron, and Vassal  
2 will not participate in committee deliberations,  
3 nor will they vote.

4 We would like to remind members and  
5 temporary voting members that if the discussions  
6 involve any other topics not already on the agenda  
7 for which an FDA participant has a personal or  
8 imputed financial interest, the participants need  
9 to exclude themselves from such involvement, and  
10 their exclusion will be noted for the record. FDA  
11 encourages all other participants to advise the  
12 committee of any financial relationships that they  
13 may have regarding the topic at issue that could be  
14 affected by the committee's discussions. Thank  
15 you.

16 DR. PAPP0: Thank you very much.

17 We will not proceed with an FDA presentation  
18 from Dr. Greg Reaman.

19 **FDA Presentation - Gregory Reaman**

20 DR. REAMAN: Thank you, Dr. Pappo.

21 I'd like to, on behalf of the FDA, just  
22 extend a welcome to all of our advisors and to

1 those guest speakers who have traveled. I'd also  
2 like to acknowledge and welcome those colleagues  
3 from the European Medicines Agency who are  
4 participating remotely, Drs. Franca Ligas, Ralph  
5 Bax, and Gunther Egger, and members of the EMA's  
6 pediatric committee, Koenraad Norga, Alessandra  
7 Janker, Jaroslav Sterba, and Sara Galluzo.

8 We're here today to talk about implementing  
9 the new PREA provisions in FDARA 2017 in an attempt  
10 to make precision cancer medicine in children a  
11 reality. I think everyone is aware of the fact  
12 that there are challenges with cancer drug  
13 development in pediatrics, which widely leverages  
14 adult drug discovery and development. There are  
15 limited opportunities for extrapolation and limited  
16 preclinical testing, early preclinical testing in  
17 pediatric models, both of which will hopefully  
18 change as a result of this legislation.

19 The impact of the existing legislative  
20 initiatives, PREA and BPCA, which support pediatric  
21 drug development and support it well in many other  
22 clinical areas, has really been markedly less

1 obvious in oncology given that the paradigm for  
2 cancer drug development is shifting and utilizing  
3 histology agnostic approaches and focused on  
4 targeted agents, many of which are likely  
5 applicable to cancers in children.

6 I think the most recent evidence of the  
7 immediate mandate for evaluating targeted agents in  
8 children come from these two papers recently  
9 published together in Nature, which evaluate  
10 pan-cancer genome transcriptome analyses of  
11 collectively about 3,000 pediatric cancers across a  
12 variety of histotypes, including acute leukemias,  
13 which definitely demonstrate differences in  
14 mutational burden and differences in specific  
15 genetic and epigenetic drivers. And roughly half  
16 of the various genetic abnormalities are distinct  
17 from those seen in adult cancers.

18 Nevertheless, there is significant  
19 expression of those targets, up to 40 percent and  
20 higher, of targets in pediatric tumors that are  
21 also expressed in many adult cancers and targets  
22 involving the MAP kinase pathway cell cycle control

1 and PI3K/AKT signaling pathway as the lead  
2 contenders.

3 Drs. Pfister and Grubner actually looked and  
4 evaluated and defined what were actually  
5 potentially druggable events in pediatric cancers  
6 in their study from the International Cancer Genome  
7 Consortium and found that 52 percent of the genomic  
8 drivers, or genetic abnormalities, or targets were  
9 potentially druggable with currently approved drugs  
10 or drugs in development. I think this certainly  
11 justifies our need to evaluate these targeted  
12 agents earlier in children.

13 So just as a bit of background, the two  
14 legislative provisions that we have are PREA, the  
15 Pediatric Research Equity Act, and BPCA, or the  
16 Best Pharmaceuticals for Children Act, PREA is  
17 mandatory, requires studies only on indications  
18 under review and orphan indications are exempt.  
19 And essentially, PREA has had no relevance to  
20 pediatric cancer.

21 BPCA is voluntary. Studies are done in  
22 response to written requests issued by the agency

1 to sponsors. They may expand and generally do  
2 expand indications, and again, historically these  
3 have actually been issued many years after the  
4 approval of a drug in the adult population. And  
5 despite our efforts to issue a written request  
6 earlier in the development timeline, it's not had a  
7 great deal of impact on changing those timelines.

8 The RACE for Children Act fortunately amends  
9 PREA, and it was incorporated RACE for Children  
10 Research Acceleration for Cure and Equity, was  
11 incorporated as Title V of the FDA Reauthorization  
12 Act, or FDARA, enacted last August. It  
13 requires -- not a voluntary but requires evaluation  
14 of new molecularly targeted drugs and biologics  
15 intended for the treatment of adult cancers and  
16 directed as a molecular target substantially  
17 relevant to the growth of progression of a  
18 pediatric cancer. And I think we've had some  
19 difficulty with the term "substantially relevant"  
20 in defining substantial relevance; more about that  
21 later.

22 As we implement how we're actually going to

1 apply this law to decision-making, I think there's  
2 an opportunity to actually create degrees, levels,  
3 and grades of substantial relevance, which should  
4 hopefully make things a little bit more clear for  
5 all stakeholders.

6 The statute describes the types of studies  
7 which are required. These are not full pediatric  
8 development plans, so these are very distinct from  
9 the pediatric investigation plans in the European  
10 Union. They're defined in the statute as  
11 molecularly targeted pediatric cancer  
12 investigations that will provide clinically  
13 meaningful study data using appropriate  
14 formulations regarding dosing, safety, preliminary  
15 efficacy that may possibly inform potential  
16 pediatric labeling. We interpret this to be early  
17 phase studies, phase 1, 1B, phase 2 studies, and  
18 there is no requirement for a commitment a longer  
19 term development or evaluation.

20 The important feature of this legislation  
21 also is the elimination of the orphan exemption for  
22 pediatric studies for cancer drugs that are

1 directed at relevant molecular targets. The  
2 definition we actually went over at our last public  
3 meeting. We tried to keep this as broad as  
4 possible.

5 The statutory requirements for the FDA are  
6 to establish with the National Cancer Institute and  
7 update regularly and post on the FDA website a list  
8 of relevant targets. We have a year to do that.  
9 We've done that. We went over that list, reviewed,  
10 and discussed in April of this year.

11 Establish a list of targets that lead to  
12 waivers, and we interpret this as leading to  
13 automatic waivers. And at this point in time, an  
14 automatic waiver would be appropriate for drugs  
15 that inhibit those targets, which are considered  
16 non-relevant to the growth or progression of a  
17 pediatric cancer.

18 Work with NCI and the pediatric subcommittee  
19 of ODAC, you all, our internal pediatric review  
20 committee and sponsors, experts, and advocates to  
21 implement the legislation and to make decisions  
22 about required studies.

1           To convene an open public meeting. This is  
2 the second open public meeting that we've done  
3 within the year, and issue a guidance on  
4 implementation in two years.

5           So where are we? I mentioned that we had  
6 the first meeting in April. We're here today for  
7 final review and comment on the target lists, the  
8 relevant target lists and those that would lead  
9 immediately to waivers; applying the target lists  
10 and a process for prioritization, including same  
11 in-class agents; how we would work with external  
12 constituents, all stakeholders; a process to  
13 support international collaboration and  
14 coordination given that pediatric cancer drug  
15 development is global in nature. And we have  
16 non-aligned regulatory requirements and processes  
17 and timelines, so we really need to coordinate and  
18 collaborate.

19           Our internal planning has been coordinated  
20 through our Office of Hematology and Oncology  
21 Products in the Oncology Center of Excellence along  
22 with a number of other offices in the FDA. The

1 focus here, I will point out again, is on  
2 accelerating appropriate initial pediatric  
3 evaluations and not merely increasing number of  
4 pediatric phase 1 studies. So as we think about  
5 this, talk about this, and deliberate through the  
6 day, please keep this in mind.

7 The focus here is not just studying every  
8 drug and studying many, many drugs in the phase 1  
9 setting and children, but really accelerating the  
10 timeline for initial evaluation of those agents  
11 that appear to be appropriate. We've been advising  
12 sponsors of new conditions and requirements for  
13 their initial pediatric study plans for new  
14 applications with plan submission dates after  
15 August 18, 2020 when the full implementation of the  
16 law goes into effect.

17 Prior to the open public meeting, there was  
18 a meeting sponsored by the Friends of Cancer  
19 Research, a workshop that was really a forum for  
20 scientific discussion and multistakeholder  
21 exchange. We considered a framework for defining  
22 relevance and came up with a classification tool to

1 organize our totality of evidence. It's not a  
2 perfect classification. There's a great deal of  
3 overlap, but it made sense at the time, as we were  
4 dealing with a large number of potentially relevant  
5 targets

6 We talked briefly about additional factors  
7 which would impact the decision-making and some  
8 anticipated consequences. The discussion again was  
9 not focused on any specific diseases or strategies  
10 for therapeutic investigation in the single disease  
11 area, and there were no regulatory policy  
12 decisions, again, other than focusing on the  
13 justification for studies to accelerate initial  
14 evaluation and not just increase numbers of phase 1  
15 studies.

16 The target lists have been, as you can  
17 imagine, a subject of much discussion. Developing  
18 these is a statutory requirement to  
19 purportedly -- and I say purportedly -- address  
20 regulatory uncertainty for industry and guide, but  
21 not dictate early decision-making.

22 Designation as relevant is not an absolute

1 or an exclusive requirement for decisions related  
2 to pediatric evaluation, so we can require studies  
3 of products even if the target is not on the list.  
4 And a target may be on the list and waivers may  
5 actually be likely for some of those products, even  
6 though the target is considered relevant.

7 We envision that target lists are not going  
8 to restrict the authority or the flexibility of the  
9 FDA. The relevant molecular targets were created  
10 or defined independent of whether an agent or  
11 biomarker was currently available.

12 Candidate target lists were constructed  
13 within the OCE with input from other offices at the  
14 FDA and with the NCI, and input from quite a large  
15 number of international content experts mostly  
16 using published peer reviewed literature, abstracts  
17 and publicly available databases. There was no  
18 prespecified minimum evidence base given the  
19 variability in the types of targets that we were  
20 including.

21 At the meeting in April, the NCI posted a  
22 request for information so that the target lists

1 were reviewed at that time, and multistakeholders  
2 had the opportunity to provide comments for the  
3 addition or deletion of targets on the list. I'm  
4 not going to go through all of these. They're  
5 actually I think in the written materials that you  
6 have, but the gene abnormalities were probably the  
7 best validated and available by review of the NCI  
8 Genomic Data Commons, St. Jude PeCan data portal,  
9 the International Cancer Genome Consortium, the  
10 INFORM project, and the Pediatric PeCan.

11 There are quite a number of these, again no  
12 specific agents were defined or discussed. We  
13 classified another group as related to cell  
14 lineage. Most of these would be appropriate for  
15 immunotherapeutic approaches to pediatric cancers,  
16 monoclonal antibodies, antibody drug conjugates by  
17 specific T-cell engagers, and TCRs, and CAR-T  
18 cells.

19 Another group of targets not on the cancer  
20 cells but on normal immune cells or cells in the  
21 tumor microenvironment supporting cancer growth,  
22 this is an area that I think is still begging for a

1 biomarker to define those populations in both  
2 adults and children who are going to respond to  
3 some of these agents, and then a whole host of  
4 other targets, some of which may actually have a  
5 genetic base, some of which may not, but most of  
6 which are thought to interfere with normal cell  
7 growth differentiation and development and are at  
8 least in consideration for development of drugs in  
9 the cancer space. They have potential  
10 applicability to a number of pediatric tumors, and  
11 some of these are actually currently being  
12 evaluated in children; so again, another sizeable  
13 list.

14           The automatic waiver lists, those which we  
15 would consider not relevant to pediatric cancer,  
16 are listed here. It's small. It may not give  
17 quite the degree of regulatory certainty that  
18 industry is looking for, but I should point out  
19 that there are other waiver considerations which  
20 can and will be used in decision-making. So I  
21 think other waiver considerations for why we would  
22 not require a study, even though a target was on

1 the relevant list, would be if the target were to  
2 be associated with a serious developmental  
3 toxicity. Here, however, we might consider partial  
4 waivers age-dependent partial waivers, a case in  
5 point being bone growth abnormalities with  
6 smoothed inhibitors. And limiting evaluation to  
7 patients who are skeletally mature would hopefully  
8 avoid the toxicity seen in younger children.

9 Another obvious waiver consideration would  
10 be a second or third in-class product unless  
11 there's compelling evidence of substantial  
12 differences in efficacy, safety, PK profiles, or  
13 formulation to warrant additional pediatric  
14 studies. And then the current waiver  
15 consideration, feasibility and practicability due  
16 to small study populations may be addressable by  
17 limited study requirements and innovations in study  
18 design and conduct.

19 So rather than doing full-scale pediatric  
20 studies, including a pediatric cohort on an initial  
21 adult first in-human study to define dose and look  
22 for signals of activity, or even embed a pediatric

1 study or cohort within an adult study as we've  
2 currently advised a sponsor in a written request to  
3 do in a very rare subset of high-grade gliomas.

4 So as far as publishing and updating the  
5 lists, our plan at this point is to hold  
6 semi-annual public workshops, and this will  
7 hopefully provide an opportunity for stakeholders,  
8 clinical investigators, sponsors, advocates to  
9 advise on updating the lists and obviously discuss  
10 issues related to implementation and  
11 decision-making.

12 I think enabling ongoing recommendations for  
13 additions and deletions, we actually plan to open a  
14 docket for comments on the existing targets and  
15 suggestions for additions and deletions. And  
16 hopefully following this meeting, shortly after,  
17 we'll post the list of candidate molecular targets  
18 on the Oncology Center of Excellence website under  
19 the pediatric oncology program, and the web address  
20 is listed here.

21 Other considerations for decision-making and  
22 prioritization likely are going to be variable by

1 the target class and perhaps even the diseases in  
2 question and prevalence of target expression in  
3 either a single disease or across multiple  
4 histologies and evidence that target inhibition,  
5 modulates tumor growth, and I think this could  
6 certainly be used as a criteria for defining a  
7 level or degree of irrelevance.

8 The extent of unmet clinical needs or  
9 potential public health impact, so studying  
10 multiple anti-CD30 antibodies in mature B-cell  
11 malignancies in children probably isn't going to  
12 have a great deal of public health impact, and  
13 therefore we would likely not require studies.  
14 Availability of access to the agent, obviously,  
15 availability of predictive response biomarkers.  
16 This would be very helpful in thinking about the  
17 study design and conduct.

18 All of this is really going to require  
19 collaboration between industry, clinical  
20 investigator, community, and regulators. This  
21 multistakeholder input is required to inform FDA  
22 decision-making, and that's what we hope and expect

1 will be accomplished through these open public  
2 workshops or meetings.

3 Other considerations will be any evidence of  
4 clinical or preclinical activity, the toxicity  
5 profile, as I mentioned earlier, doing a potential  
6 benefit-risk assessment; formulation, obviously a  
7 major issue; multiple agents in class, and there's  
8 going to be required some transparent evaluation of  
9 selection criteria in the precompetitive space  
10 between investigators and sponsors about which  
11 agents when they are multiple in-class should be  
12 and can be evaluated in a limited pediatric  
13 population. And I think rare pediatric cancers now  
14 are not well supported by current study platforms.  
15 And again, this is an opportunity to enroll early  
16 on adult studies when we're looking at a histology  
17 agnostic or tissue agnostic development plans.

18 Looking at uniform international master  
19 protocols for biomarker directed studies will  
20 provide efficiency and hopefully high quality data.  
21 We will look to increase to the extent possible  
22 extramural input in any decisions we make, but

1 obviously we have to respect the proprietary  
2 considerations of industry in doing so. We might  
3 be able to at these open public hearings have early  
4 pipeline presentations from industry as part of  
5 this collaboration. I think this speaks heavily to  
6 the need for an industry initiated public-private  
7 partnership, which we've been discussing probably  
8 for the last 10, 12, maybe 15 years, to help  
9 facilitate and accelerate pediatric cancer drug  
10 development.

11 So I think successful implementation is  
12 going to require transparency. We'll do our best  
13 to be as transparent as we can to address potential  
14 adverse consequences. What's going to be required  
15 is initiating early preclinical testing  
16 initiatives. This may require effective industry  
17 academic collaboration when necessary, and I think  
18 this is another potential important role for  
19 public-private partnership.

20 We have to recognize emerging scientific  
21 discovery, so what's on a list today may not be on  
22 a list two weeks from now, or a month from now, or

1 a year from now. I think most important is global  
2 development is really going to require  
3 international collaboration in designation of  
4 relevance in prioritization and decision-making  
5 regarding study feasibility and conduct. And we  
6 really need to support and expand robust publicly  
7 shared data sets of genomic, proteomic, and  
8 preclinical testing data.

9 Priority setting for relevant targets  
10 through periodic international multistakeholder  
11 workshops I think is important. We currently have  
12 pediatric cluster calls monthly with the EMA, the  
13 PMDA in Japan, and the TGA in Australia and Health  
14 Canada to talk about pediatric investigation plans  
15 and study plans and provide written commentary to  
16 sponsors when requested and appropriate.

17 I don't think that's sufficient; I think  
18 it's very helpful, but I think having a process  
19 similar to the EU's ACCELERATE platform, which is  
20 really multistakeholder, including investigators,  
21 regulators, and sponsors. And there's a clear move  
22 on the part of ACCELERATE to expand this to include

1 international representation, so we are working  
2 with them to accomplish that. And obviously to  
3 support and encourage international trials when  
4 possible, we have to avoid duplication and  
5 competition.

6 With that, I will close and answer any  
7 questions if there are any.

### 8 **Clarifying Questions**

9 DR. PAPP0: Thank you very much, Dr. Reaman,  
10 We will now take clarifying questions for  
11 Dr. Reaman. Please remember to state your name for  
12 the record before you speak.

13 Steve?

14 DR. DuBOIS: Steve DuBois. Thank you for  
15 that, Greg. How will FDA define a first in-class  
16 agent? Is it the first to the clinic, first to  
17 declare an adult dose, first to approval? How  
18 will that be determined? Because there's obviously  
19 downstream consequences of what's second in class.

20 DR. REAMAN: Right, a very good question. I  
21 don't have an exact definition. How we would see  
22 them now is first in class, the first application

1 that comes in for an adult indication that would  
2 trigger, since it would be for a new indication, an  
3 initial pediatric study plan. So it's sort of  
4 first come/first served.

5 That may not be the best way to actually do  
6 this, which is why I think there needs to be some  
7 discussion pre competitively with sponsors who are  
8 developing same in-class agents with investigators  
9 in the event that there are real differences that  
10 would justify selecting one over another. It may  
11 be that just saying a second in class may not be  
12 too much, but I think once we start getting to  
13 third, fourth, and fifth in the case of checkpoint  
14 inhibitors, we're not doing anyone a favor here.

15 DR. PAPPO: Ira?

16 DR. DUNKEL: I wanted to ask for  
17 clarification about two points that you made, one  
18 being the formulation issue. Of course as you're  
19 very aware, it's not uncommon that the  
20 tablet/capsule formulations make it difficult to  
21 study agents in young children, and I'm wondering  
22 how or if the new legislation addresses that.

1           The second issue is you talked about  
2 bringing pediatric phase 1 trials earlier in the  
3 process, and I wonder if you could discuss what the  
4 FDA believes the most appropriate time would be.  
5 For example, does there always have to be  
6 completion of an adult phase 1 study before an  
7 agent can start an pediatric phase 1 evaluation?

8           DR. REAMAN: To answer the first question, I  
9 think the statute clearly says inappropriate  
10 formulation, so it may be an appropriate,  
11 extemporaneously, used formulation for  
12 investigational purposes that may then require, if  
13 we issue a written request, an appropriate  
14 formulation, which could and should be marketed.  
15 But it is going to be a challenge and it may be  
16 that does become a deciding factor about whether we  
17 can or can't evaluate certain agents in the  
18 pediatric population or at least the ages of  
19 children that can be evaluated.

20           So to answer the second question, which was  
21 timing of pediatric phase 1 studies, there is no  
22 hard and fast rule. We feel, and as a group, the

1 subcommittee of ODAC, the pediatric subcommittee,  
2 developed a consensus statement that clearly  
3 defined that pediatric phase 1 studies should be  
4 started immediately after the identification of a  
5 safe dose in the adult population. But in some  
6 situations they could start earlier, and we could  
7 even use a preclinical nonclinical data to justify  
8 starting studies without adult experience.

9 DR. PAPPO: PK?

10 DR. MORROW: So you discussed the interest  
11 of the FDA in an industry-initiated, public-private  
12 partnership. I wanted to get your criteria or  
13 thoughts in terms of success and framework of such  
14 a partnership.

15 DR. REAMAN: I don't really have a framework  
16 fully developed, but I think we'll know it when we  
17 see it. Right now, all we've done is talk about  
18 it, and it goes back to a meeting that pharma and  
19 bio had with I believe Friends of Cancer Research  
20 several years ago. Actually, maybe it was with the  
21 Children's Cause for Cancer Advocacy several years  
22 ago. That was great discussion but no follow

1 through and no real changes. I think now we have a  
2 mandate to follow through with this. We have to  
3 collaborate. We have to corroborate, industry,  
4 investigators, regulators. And the only way we can  
5 really do this is through such a public-private  
6 partnership in my estimation

7 DR. PAPPO: Nita?

8 DR. SEIBEL: Greg, maybe you could expand a  
9 little. You mentioned the master protocols. In  
10 some situations, if an agent is included in a  
11 master protocol and 20 patients are tested, and  
12 nothing is seen, then there's no reason to do a  
13 pediatric phase 1. So does that replace it in some  
14 places?

15 DR. REAMAN: Yes. I think that would  
16 replace it. The master protocol would be the  
17 pediatric phase 1, 1B or 2 study.

18 DR. PAPPO: I have a question. The  
19 prioritization of same in-class agents, for example  
20 MEK and BRAF inhibitors, there are three combos now  
21 that are approved. Is this going to move forward  
22 between COGs, the multiple consortiums, and

1 investigator initiated studies? Is there going to  
2 be a specific agent that will be identified and  
3 then the other ones that will just have waivers or  
4 is there going to be a process to identify that?

5 DR. REAMAN: I think we can't change what's  
6 already in progress. There are multiple same in-  
7 class agents already being studied. There are  
8 commitments. There are plans. And depending on  
9 the results of those studies, there may be labeling  
10 that moves forward. I think we need to prevent  
11 something like that from happening in the future,  
12 either prevent it or at least not require sponsors  
13 when there are same in-class agents.

14 There may be reasons for doing it, and in  
15 that case, we have voluntary mechanisms through  
16 BPCA and the written request process where we could  
17 incentivize a sponsor if there is a reason for  
18 evaluating another same in-class product.

19 I think Dr. Kolb maybe had a question.

20 DR. KOLB: Thanks, Greg.

21 DR. REAMAN: Go ahead.

22 DR. KOLB: Toby was first.

1 DR. PAPPO: Please don't forget to state  
2 your name, please.

3 DR. MacDONALD: Toby MacDonald.

4 Greg, in my experience, contacting some of  
5 the pharma, there is a time where they do not know  
6 there's an indication for pediatric cancer. And  
7 I'm wondering is there a way for the FDA to somehow  
8 get the knowledge to them.

9 DR. REAMAN: Well, part of the, I think, the  
10 process of posting the lists, the lists are  
11 associated with references and references to  
12 databases that they can explore. I think also it's  
13 going to be incumbent upon sponsors to do some of  
14 this research and investigation on their own in the  
15 event that they have to submit a study plan that  
16 either includes a plan for a study or provides a  
17 justification for why a study is not feasible, or  
18 highly impractical impracticable, or potentially  
19 unsafe.

20 DR. PAPPO: Ed?

21 DR. REAMAN: And again, I think this is  
22 something that we would clearly depend on the

1 investigator community to help with as well. So  
2 there could be a series of publications that would  
3 be helpful to industry. But again, this is  
4 evolving science, and how rapidly can things be  
5 published to successfully, and efficiently, and  
6 effectively inform industry, I'm just not clear.

7 DR. MacDONALD: Sorry, a quick follow-up.  
8 Could there be a subcommittee of pediatric -- a  
9 variety of multispecialists who could look at what  
10 they're developing and bring it back to them and  
11 say this is a target in this disease of which you  
12 had no idea that this was --

13 DR. REAMAN: I would hope that industry  
14 would take that advice. I mean, clearly they have  
15 advisory boards. Do they all have pediatric  
16 advisory boards, so there may be a role there? I  
17 know some forward-thinking companies do, and I  
18 think it's been very evident in the kinds of study  
19 plans that we have seen. So that may be a real way  
20 of accomplishing that.

21 DR. PAPPO: Ed?

22 DR. KOLB: Thank you. Andy Kolb.

1           Thanks, Greg, for the talk and for your  
2 leadership in bringing this forward. There are  
3 aspects of the Act that will be diminished with the  
4 current level of coordination between the FDA and  
5 the EMA, and I'm thinking specifically about the  
6 PIP process and second and third in-class  
7 exemption.

8           Do you have a sense of what the timeline  
9 will be to coordinate better with the EMA so that  
10 the European statutes don't undercut some of the  
11 efforts that you're trying to move forward here?

12           DR. REAMAN: Sure. I don't have a good  
13 timeline. We've been talking about this already.  
14 They're participating remotely as part of how we're  
15 going to deal with this. And I'm not sure that  
16 we're going to prevent everything, but I think  
17 thinking about it early could actually be  
18 beneficial.

19           I think one way that we could help is if  
20 this legislation actually results in earlier phase  
21 1-2 experience in children, it could actually  
22 inform the pediatric investigation plan process in

1 the EU, which requires a full development plan from  
2 early phase through a more definitive evaluation.  
3 And I think making some joint decisions about what  
4 products could/should be studied and how, and  
5 studying them jointly on both sides of the  
6 Atlantic, I think could make things much more  
7 effective and efficient as well.

8 DR. PAPPO: Brenda?

9 DR. WEIGEL: Dr. Reaman, I have a question  
10 with regards to updating and adjusting the lists in  
11 a fluid manner. You mentioned there's going to be  
12 the opening of a docket, an FDA docket for -- and  
13 I'm assuming that's going to be public access for  
14 anyone.

15 What do you envision the vetting of the  
16 content of that docket to be within the FDA, and  
17 how is that information going to be transparent and  
18 utilized to add/delete things from the lists?

19 DR. REAMAN: I don't have that all worked  
20 out yet, but I see it as having our internal  
21 process, and then some expert external advice. We  
22 could do it as part of the pediatric subcommittee

1 of ODAC meetings. We could do it at the  
2 semi-annual open public workshops. But clearly,  
3 there has to be some vetting, and that will be  
4 something to think about. We're open to  
5 suggestions.

6 DR. PAPPO: Katie?

7 DR. JANEWAY: Katie Janeway, Dana Farber. I  
8 actually have the same question as Brenda, but I'll  
9 use my time to extend on that vein of questioning.

10 In the context of a new product, when you're  
11 assessing the relevance of the molecular target,  
12 will there be a process for obtaining outside  
13 opinion if this potential target has not been  
14 previously considered; in other words, hasn't been  
15 thought about in the context of this legislation?

16 DR. REAMAN: We always have the opportunity  
17 to seek outside opinion and advice. Sometimes it's  
18 a little bit complicated if there are conflicts of  
19 interest with the sponsor. So sometimes the people  
20 who may have the most expertise in a particular  
21 area -- in this case with a specific target maybe  
22 in a specific disease -- may have shared that same

1 information with the sponsor, which would make it a  
2 little bit difficult for us to get advice from the  
3 same individual. But there clearly is more than  
4 one expert in most areas in pediatric oncology.

5 So I think there are definitely ways of  
6 safely and without any conflict of interest getting  
7 an outside opinion. This is a testament of one way  
8 that we do get outside opinion through the  
9 pediatric subcommittee.

10 DR. PAPPO: Julia?

11 DR. GLADE: Thank you. Julia Glade Bender  
12 from Columbia University.

13 Greg, thank you very much. I'd like to  
14 revisit a question that was asked by Dr. Dunkel  
15 regarding formulation, in the sense that it's clear  
16 that it is part of the legislature, but it's not  
17 clear that there is any advice that's being offered  
18 to pharmaceutical industry about the process of  
19 developing a pediatric appropriate formulation.  
20 And the question is whether the FDA will be able to  
21 offer advice or recommendation so that each time  
22 that this comes up, we don't have to sort of

1 reinvent the wheel about the steps involved in  
2 developing a pediatric-appropriate formulation and  
3 bioavailability testing in adults, et cetera.

4 DR. REAMAN: Sure. Yes, and that would  
5 certainly be part of the guidance that we are  
6 required to develop. I mean, it's something that  
7 we have already thought about. It's something that  
8 we already have some templated language when we  
9 issue written requests with respect to  
10 investigational formulations and evaluation of  
11 bioavailability usually in the adult  
12 healthy volunteers or at least in the adult  
13 population.

14 DR. PAPPO: Any additional questions for  
15 Dr. Reaman?

16 (No response.)

17 DR. PAPPO: Thank you very much.

18 We have no registered open public hearing  
19 speakers for this specific session, and therefore  
20 we will now proceed with the charge and questions  
21 to the subcommittee and panel discussions. I would  
22 like to remind public observers that while this

1 meeting is open for public observation, public  
2 attendees may not participate except at the  
3 specific request of the panel. We will start with  
4 the first question.

5 **Charge to the Subcommittee**

6 DR. CASAK: This is about the target lists.

7 "Title V of the FDA Reauthorization Act,  
8 FDARA 2017, assigns FDA to establish, publish, and  
9 regularly update lists of molecular targets  
10 considered on the basis of data the FDA determines  
11 to be adequate to be substantially relevant to the  
12 growth or progression of pediatric cancers. New  
13 drug products directed at these targets may trigger  
14 the requirement for pediatric investigations. As  
15 well, a list of targets considered not relevant has  
16 been developed.

17 "Comment on the process utilized to  
18 construct the list, the classification of molecular  
19 targets, the factors utilized to designate a target  
20 as relevant or non-relevant and indicate your  
21 concurrence with the lists as currently  
22 represented."

1                   **Questions to the Subcommittee and Discussion**

2                   DR. PAPP0:  If there are no questions or  
3                   comments concerning the wording or the question, we  
4                   will now open the questions for discussion.

5                   I had one minor question.  Tumor mutational  
6                   burden, is that something that will be included at  
7                   some point or it will just be a surrogate based on  
8                   other analysis?

9                   DR. REAMAN:  I think it's both a surrogate,  
10                  and I guess it could be included as a specific  
11                  target as well.

12                  DR. PAPP0:  Katie?

13                  DR. JANEWAY:  I have a comment and then a  
14                  question.  So my comment is just that although the  
15                  landscape papers that were recently published are  
16                  fantastic, they contain only 3,000 cases and some  
17                  especially rare tumors are missing.  And most of  
18                  the data we currently have is from specimens  
19                  obtained at the time of diagnosis; so just a  
20                  statement that there's a need for continued  
21                  acquisition of data regarding molecular targets in  
22                  pediatric cancers.

1           The question I have is on the excluded list  
2 of targets, I noted of VEGF and VEGF receptor, and  
3 I'm just interested in a little bit more  
4 information if it's possible to provide that, of  
5 how those ended up on the excluded lists.

6           DR. REAMAN: I think they ended up on the  
7 excluded lists because there's been significant  
8 clinical evidence to question their activity in  
9 multiple different pediatric tumors in pediatrics  
10 in general, not looking at the specific pediatric  
11 cancers. But again, I remind you that if there's a  
12 reason, just because it's on the automatically  
13 waived list or we consider it not relevant, if  
14 there is sufficient interest and other preclinical  
15 evidence that would refute what we've seen  
16 clinically, it's certainly something that could be  
17 evaluated and investigated. And it also doesn't  
18 preclude our issuing a written request for study of  
19 a new VEGF inhibitor.

20           DR. JANEWAY: Thank you.

21           DR. PAPP0: Any additional comments? Steve?

22           DR. DuBOIS: Could you just clarify the

1 requirement for pediatric investigations? In some  
2 cases, will that be a requirement for an industry  
3 sponsor to conduct a nonclinical investigation, and  
4 is that included in the legislation?

5 DR. REAMAN: The requirement is clinical  
6 investigations. It may be that a nonclinical  
7 investigation would be required to support a  
8 sponsor's justification for not doing a pediatric  
9 clinical evaluation. But there's nothing in the  
10 legislation that requires industry to do  
11 nonclinical studies.

12 But clearly, there's an implied need for  
13 preclinical studies, and this could be and probably  
14 is best accomplished, or could be a very well  
15 accomplished, by collaborating between industry and  
16 academic investigators. They do it beautifully in  
17 Europe with the ITCC P4 platform with a number of  
18 industry sponsors working together with  
19 investigators to do preclinical studies, so I don't  
20 see why we can't do the same thing here.

21 DR. PAPPO: Elizabeth?

22 DR. RAETZ: Elizabeth Raetz, NYU. Given the

1 scope of the lists, have there been any discussions  
2 about potential prioritization within the  
3 subclasses of targets that you've identified?

4 DR. REAMAN: We've not prioritized, and I  
5 think that's something that investigators and  
6 industry working with us, we clearly need to be  
7 informed on what are the priorities of patients and  
8 investigators to best help patients, which is the  
9 only reason this legislation was passed.

10 DR. PAPPO: Toby?

11 DR. MacDONALD: Toby MacDonald. The way  
12 the list is currently, it looks like these are  
13 single entity abnormalities. But targeting a  
14 single molecular alteration, rarely if ever, is  
15 sufficient. So is there a plan to develop  
16 combination of synergistic and synthetic lethal  
17 type lists that might be more helpful for  
18 preclinical development?

19 DR. REAMAN: There is not as a result of  
20 this legislation. It clearly is something that I  
21 think would be beneficial from the perspective of  
22 rational clinical trial design considerations, and

1 hopefully that would be something that would come  
2 from the academic community and maybe working with  
3 industry. But there's nothing specific in the  
4 statute which talks about combinations, and we  
5 clearly recognize that combinations, particularly  
6 in pediatric oncology, are going to be necessary.  
7 And again, the focus here, and I think the intent  
8 of this legislation, was early initial evaluation  
9 of single relevant drugs.

10 DR. PAPPO: Julia?

11 DR. BENDER: I wanted, again, to go back to  
12 Dr. Janeway's question just because of the VEGF and  
13 the VEGF-R. I agree absolutely why they are on the  
14 prospective list of excluded because we've done a  
15 lot of studies in the past. But they don't fail  
16 the substantially relevant tests, and they're also  
17 in pediatric use to a large extent. So the data  
18 that was generated was important.

19 So the question is, now prospectively, at  
20 what point, or maybe there needs to be additional  
21 language about when we say it's not substantially  
22 clinically relevant, or there is already sufficient

1 clinical data for that target?

2 DR. REAMAN: I think we probably used the  
3 latter to define relevance here. But maybe there's  
4 an argument for it not being sufficient clinical  
5 data, and that these were all in multiply relapsed  
6 patients across a spectrum of diseases and was the  
7 exposure really of significant or appropriate  
8 duration to really evaluate efficacy.

9 So this is an opportunity to take them off  
10 the automatic waiver list of if there's a rationale  
11 to do so. And again, just because they're on there  
12 doesn't mean that they can't and shouldn't be  
13 studied. But we'd be certainly open to removing  
14 them if that's your recommendation.

15 DR. PAPPO: Ted?

16 DR. LAETSCH: I had a different question.  
17 Maybe, Katie, if you want to come in first, then  
18 I'll --

19 DR. JANEWAY: So I guess I raised the  
20 question because in common use in the clinic and  
21 certainly supported by clinical trial evidence is  
22 multi-tyrosine kinase inhibitors in relapsed

1 sarcomas, and it's unclear -- I think there's  
2 preclinical data to suggest that VEGF and VEGF  
3 receptor are important in those diseases. It's  
4 unclear whether there's a relationship between  
5 those two things because they are multi-tyrosine  
6 kinase inhibitors.

7           So this is the reason I raised the question.  
8 I think additional correlative biology, new agents  
9 that are maybe more specific, more tolerable, might  
10 answer that question. So I guess I'm sort of  
11 addressing -- Julia's, actually, paper is cited for  
12 that. By the way, I want to make an aside comment  
13 that I think including the evidence and the  
14 citations in the lists is fantastic. It's a great  
15 resource.

16           So that is why I raised the question. And I  
17 agree it's difficult. I don't think there's a  
18 clear answer. I don't disagree that there is  
19 clinical data to suggest that the current agents  
20 make this not a relevant target, but I worry about  
21 future investigation.

22           DR. REAMAN: I don't think we want to

1       jeopardize future investigation. I'm hearing that  
2       maybe we should reconsider this. Again, we didn't  
3       walk down from any mountain with two tablets or  
4       anything, so I believe that we could amend the  
5       list. That's one of the recommendations here. I  
6       agree that it might be a relevant target. It  
7       should be a relevant target. It's just that the  
8       agents that we've had to evaluate its relevance  
9       from a therapeutic perspective I don't think have  
10      really panned out.

11             DR. CASAK: It may be a point that we were  
12      really focused on early investigations, and we did  
13      not include -- or we excluded VEGF because we  
14      didn't think further moving -- we already know the  
15      safety. We may not know right now efficacy in  
16      combination, et cetera, but it's a very good  
17      suggestions, so thanks.

18             DR. PAPPO: Ted, do you still have a  
19      question?

20             DR. LAETSCH: I was going to sort of ask  
21      that question, but more generally, about as we get  
22      more data on the clinical experience with agents in

1 each of these classes, how are we going to decide  
2 whether that data is relevant to that single agent  
3 alone or to the entire class? And when do we  
4 decide that there is enough, either negative or  
5 positive evidence that we stop requiring further  
6 studies of other agents in that class?

7 DR. REAMAN: Good question. But again, I  
8 think it's a little bit beyond what we do here  
9 because the reason for the list is for early  
10 preliminary evaluations. It doesn't really impact  
11 what's done later. So if there's still a reason to  
12 evaluate a drug in the phase 1 setting, or phase 2  
13 setting hasn't had a sufficient activity signal in  
14 combination, it certainly doesn't preclude those  
15 kinds of studies.

16 I think you raise a good point. If there is  
17 reason to keep it on the list because of  
18 anticipated synergy or observed synergy in a  
19 clinical trial setting, then it can stay on the  
20 list.

21 DR. PAPPO: Raj?

22 DR. MODY: Rajen Mody, University of

1 Michigan. My question is regarding molecular  
2 lists, and I think we discussed that in the April  
3 meeting. I'm looking at PTEN, and it seems to be  
4 missing from the list, PTEN deletion. And maybe  
5 I'm missing that it was added on later on, but I  
6 can't seem to find it.

7 DR. REAMAN: That was one that had the RFI  
8 up on the NCI website to post anything. That  
9 wasn't something that came in that I'm aware of.  
10 So that's also something that can be added if  
11 there's a reason to do so.

12 DR. JANEWAY: Katie Janeway, Dana Farber. I  
13 second Rajen's suggestion.

14 DR. REAMAN: Okay. Yes, I don't see it on  
15 here.

16 DR. PAPPO: Brenda?

17 DR. WEIGEL: Brenda Weigel, University of  
18 Minnesota. I have more of a comment than a  
19 question. I want to go back to, I think, some of  
20 the discussion from the April meeting and also the  
21 concept of the list is it's a fluid list that is  
22 really I think a guide for development rather than

1 an absolute, a requirement.

2 I think one of the real opportunities here  
3 is to be as inclusive as possible, to go back to  
4 what Dr. Reaman just said, to have the impetus to  
5 do very early investigation in pediatrics, which is  
6 really the goal of the legislation. And I think  
7 it's not to say that it's going to work or not work  
8 in pediatrics; it's to say we should look at it in  
9 pediatrics.

10 So I think erring on the side of being as  
11 inclusive as possible very early on is really what  
12 we need to do, and it may serve as an impetus, both  
13 for industry and academics, to actually look at  
14 doing more research to really investigate the  
15 utility of these pathways, targets, agents in  
16 pediatrics.

17 So I think sort of shifting the gear a  
18 little bit of saying this may be an opportunity to  
19 enhance investigation for pediatric cancers, and we  
20 should be as inclusive as possible and try not to  
21 be exclusive.

22 DR. PAPPO: So I will try to summarize our

1 discussion. We still have another question. The  
2 first issue is consider adding a PTEN and also  
3 tumor mutational burden to the current list. The  
4 second issue that was brought up is that the two  
5 pan-cancer analyses that have been published so far  
6 lack certain histologies, and certainly additional  
7 information would be needed to perhaps update to  
8 the current target list.

9 The other question revolved around the  
10 exclusion of VEGF and VEGF receptors, and they're  
11 currently listed on the automatic waiver list,  
12 especially within the context of multi-tyrosine  
13 kinase inhibitors that appear to be very active in  
14 sarcomas. So it would be worthwhile reconsidering  
15 removing them from this automatic waiver list.

16 There was another comment as to whether the  
17 pharmaceutical companies are going to be mandated  
18 to perform nonclinical investigations or  
19 preclinical investigations, and as of the current  
20 standing of the legislation, that is not part of  
21 it, if I'm correct.

22 Is that correct, Greg?

1 DR. REAMAN: They're not mandated and we  
2 can't mandate it. It's in their best interest to  
3 comply with the legislation to consider preclinical  
4 studies in a pediatric setting.

5 DR. PAPPO: There was another comment as to  
6 whether there has been a specific process that has  
7 been identified to prioritize a specific identified  
8 target. And the current answer is no, but it's  
9 something that you'll be working on

10 There was a question about the potential for  
11 developed lists that list either combination agents  
12 or synthetic lethality agents. And at this stage,  
13 this is not yet in the legislation, but everybody  
14 feels that it would be beneficial for sure and to  
15 be considered in the future.

16 There was another comment about -- there  
17 were a lot of comments, so sorry for that.

18 (Laughter.)

19 DR. PAPPO: There Was a comment as to when  
20 is enough data enough to say that this agent should  
21 proceed or not, and at this stage, this is beyond  
22 the scope of the legislation. And I have one more

1 that I cannot read my writing, but it was something  
2 related to a lack of sufficient data in relapsed  
3 disease, and when do you say that this is okay to  
4 put on the list or put on the waiver list.

5 Yes, go ahead, Malcolm.

6 DR. SMITH: I had a couple of other comments  
7 to add to those on your list.

8 DR. PAPPO: Please.

9 DR. SMITH: One regarding the combinations.  
10 There are, for example, DNA damage response  
11 modifier type agents or targets that are on the  
12 list. For example, ATR is on the list. So that's  
13 the type of agent that you probably would develop  
14 in combination. So as far as I know, the law is  
15 silent in terms of this is a target that's  
16 potentially relevant, and how it would be developed  
17 is something that the FDA, the research community,  
18 would have to establish with the companies that  
19 were developing the agent.

20 So I don't think there's any preclusion of  
21 that kind of work, and some of those targets are  
22 already on the list.

1           Regarding the VEGF, I think part of the  
2 question is we've studied maybe 10 VEGF targeted  
3 agents in children. If there's an 11th one that we  
4 haven't studied yet, does FDA need to mandate one  
5 of these molecular studies or have we studied  
6 enough?

7           So I think maybe it should be on the list,  
8 and maybe it's a separate question as to whether it  
9 should be studied. But I would vote that we don't  
10 need to study it, probably, unless there's  
11 something really novel about it.

12           DR. PAPPO: Noted.

13           Yes, Greg?

14           DR. REAMAN: I think this speaks to coming  
15 up with a system of degrees or classes or levels of  
16 relevance. If we have 10 studies with clinical  
17 experience, we ought to be able to use that. But  
18 then again, if there's a specific reason for  
19 exploring the 11th, then it's something that could  
20 be considered.

21           DR. PAPPO: We will now move to the second  
22 question.

1 DR. CASAK: Please comment on the process  
2 proposed for formally updating the lists least at  
3 semi-annual public workshops, the methods for  
4 nominating potential future candidate targets, and  
5 the required transparency in multi-stakeholder  
6 discussions to determine relevance. Comment on  
7 additional measures to assure timely discussion of  
8 emerging science and its clinical translation,  
9 which has the potential to expedite drug  
10 development to improve the care and outcome of  
11 children with cancer.

12 DR. PAPPO: If there are no comments or  
13 questions concerning the wording or the question,  
14 we will now open the question for discussion.

15 DR. DuBOIS: Steven DuBois. A couple of  
16 issues about the next-in-class agents, I guess a  
17 question about the level of transparency. So if an  
18 agent is given a waiver because it's second or  
19 third in class, how will that information get out  
20 to the world? And related to that, often the  
21 second and third generation drugs, or in-class  
22 drugs, may actually be better drugs. So with the

1 VEGF in mind, if we had stopped at sunitinib, maybe  
2 we wouldn't be so happy.

3 So if there is a waiver because of a second  
4 or third in class, is there an opportunity to sort  
5 of revisit that if a much better drug comes along?

6 DR. REAMAN: I would say the waivers are  
7 going to be product specific. So how that gets out  
8 to the world isn't from the agency. Our  
9 communication with the sponsors is confidential.  
10 So if sponsors elect to make that information  
11 public, they can do so. But it wouldn't  
12 necessarily preclude a third in class that does  
13 have some properties that would warrant  
14 investigation to either a study required or a study  
15 that could be done on a voluntary basis through the  
16 written request mechanism.

17 DR. DuBOIS: But there's not a way, in terms  
18 of updating the lists and keeping it current, that  
19 agents that have been given a waiver, that that  
20 process somehow feeds back to the lists.

21 DR. REAMAN: The lists that we were mandated  
22 to develop our lists of targets, so not lists of

1 drug products or biologics. And that I think we  
2 have to keep -- I don't think we can do that. The  
3 target wouldn't have to change -- I mean, wouldn't  
4 have to come off the relevant lists if people still  
5 felt that there was a reason for exploring further.  
6 But we wouldn't put a specific agent and identify  
7 compounds by name or industry sponsors by name.

8 DR. PAPPO: Brenda?

9 DR. WEIGEL: Brenda Weigel, University of  
10 Minnesota. I want to go back to what Dr. Reaman  
11 presented as what's the process for updating the  
12 lists because this is an ongoing fluid process, and  
13 I think that's one of the real challenges.

14 I like the idea of the FDA docket. I think  
15 that's a great idea, and I think that is public.  
16 It's open. Anyone can add information to that. I  
17 think then the key is how is that information  
18 vetted, processed, and how then is that going to  
19 link to changes in the lists.

20 My thoughts on that are kind of twofold.  
21 One is clearly that's all going to come into the  
22 FDA, and it may be that that information is

1 summarized. And a good use of the pediatric ODAC  
2 would be to say let's look at a summary of that  
3 content with references because we have regular  
4 meetings. And then at the twice-a-year meetings,  
5 anything that's felt to be of relevance coming out  
6 of those is put forward for public vetting.

7 I think then there's transparency. There is  
8 also evidence based because I think one of the keys  
9 is how is evidence going to be weighed, and I think  
10 we have to actually really look at what is the  
11 publicly available evidence. So I think that there  
12 could be a stepwise process. And it may be that  
13 the list is formally updated twice a year because  
14 the targets aren't going to change that quickly.

15 But that may be worth something to think  
16 about, is that rather than sort of things come and  
17 go at will, is there's a real public vetting twice  
18 a year, and then formally things are taken on or  
19 off the lists, because I think the FDA has the  
20 discretion, as Dr. Reaman has said, regardless of  
21 what's on the lists, to have conversation with  
22 industry at any time to look at an investigation.

1 So I think that it's a balance between that and  
2 public availability.

3 DR. PAPPO: Ted?

4 DR. LAETSCH: I just wanted to follow. Ted  
5 Laetsch from University of Texas Southwestern in  
6 Dallas. I just wanted to follow up on Steve  
7 DuBois' question about the second and third  
8 in-class agents and your comment that formulation  
9 will be one of the things considered to determine  
10 whether those need to be studied.

11 Does that mean that industry sponsors will  
12 be required to attempt to make a pediatric  
13 formulation for those second and third in-class  
14 agents if the first in-class agent doesn't have an  
15 optimal pediatric formulation, or how will that be  
16 determined?

17 DR. REAMAN: That's a sponsor decision.

18 DR. PAPPO: Julia?

19 DR. BENDER: Julia Glad Bender. I have a  
20 question about when a sponsor is required to look  
21 at the target list and do a pediatric study. The  
22 question is perhaps for those second and third

1 generation. If they're looking for a second  
2 indication, do we go back and ask the same  
3 questions about pediatrics once we have more data  
4 on their first indication to say perhaps that's the  
5 better drug, and now we should go back and ask?

6 DR. REAMAN: I'm confused. Are you talking  
7 about indications for the same agent or indications  
8 for next generation? The next generation is a new  
9 application and a new molecular entity.

10 DR. BENDER: Right. No. So I'm asking for  
11 a second indication of a drug that's already been  
12 indicated for something else.

13 DR. REAMAN: Good question. So the  
14 legislation is very specific. These are for new  
15 applications, original applications. So  
16 supplemental applications would not trigger a  
17 requirement for a pediatric evaluation.

18 DR. PAPPO: Any additional comments or  
19 questions?

20 DR. KOLB: Andy Kolb. I noticed on the  
21 lists -- and I missed this before -- you have  
22 several specific targets in the class of MLL

1 fusions. I think we could expand that to include  
2 NUP98 fusions, ETS fusions. I think there  
3 are -- and when I viewed the lists, I wasn't  
4 thinking about it in those terms. But I think MLL  
5 is probably the most well described and well known,  
6 but with 40 different fusion partners, the targets  
7 may be quite broad.

8 I think you could say the same with ETS and  
9 NUP98, to name a few. And I think adding those  
10 fusions to the list as the category, recognizing  
11 that multiple targets will fall under that umbrella  
12 I think is important to represent.

13 DR. REAMAN: So would you suggest adding all  
14 of the currently known fusions or just broadening  
15 it to MLL fusions or ETS fusions?

16 DR. KOLB: I think that there are lead  
17 fusion partners like MLL, like ETS family, like  
18 NUP98, that probably define a distinct biological  
19 class. And currently, the targets and the drugs  
20 that can target those are not as well known. I  
21 think they're known in MLL to some degree, but not  
22 as well known in the other fusions.

1 DR. REAMAN: Okay.

2 DR. PAPPO: Malcolm?

3 DR. SMITH: Malcolm Smith. There were  
4 several additional targets that were submitted, and  
5 I'm sure they're on some lists at FDA, but they  
6 weren't on the list that was circulated, and I do  
7 want to just bring those up. The NUT midline  
8 carcinoma fusions were ones, and along the lines of  
9 what Andy Kolb was saying, there are a number of  
10 different fusions, but they all end up causing  
11 midline carcinoma, the fusion for fibrolamellar  
12 hepatocellular carcinoma.

13 The DNAJB1-PRKACA fusion is another one.  
14 And then CD206 as an M2 macrophage surface marker  
15 would be in the kind of non-cancer cell target  
16 class. And then finally, there are several  
17 antigens or proteins like PSA, PSCA, and PSMA that  
18 are prostate specific that could be in the  
19 non-relevant list.

20 DR. REAMAN: They're on there.

21 DR. PAPPO: But was not included, correct,  
22 on the list?

1 DR. REAMAN: I thought it was. We'll make  
2 sure it gets in.

3 DR. PAPPO: We have time for two more  
4 comments, one for Ted and one for Katie.

5 Ted?

6 DR. LAETSCH: I was just going to make one  
7 quick additional comment. I'd also recommend RET  
8 fusions, RET point mutations there and also KIT  
9 fusions -- sorry, mutations. Yes, they're not KIT  
10 fusions.

11 DR. PAPPO: Katie?

12 DR. JANEWAY: I have a couple additions as  
13 well, which I think are not there, although it's a  
14 little bit hard to make sure you've seen  
15 everything, CCND1, 2, and 3; CCNE1. Ted mentioned  
16 KIT, which was on my list, and STAG2, and there's  
17 histone 1H13B.

18 DR. PAPPO: A final quick question.

19 MS. PREUSSE: Hi. Courtney Preusse,  
20 consumer rep, Fred Hutch. A quick question. I may  
21 have missed this, but will there be any sort of  
22 subclassification of molecular targets by new

1 diagnosis versus relapse recurrence?

2 DR. REAMAN: That wasn't planned. Much of  
3 the data that we have are in relapsed patients,  
4 although there are clearly now some and in newly  
5 diagnosed patients. But we have sort of included  
6 them as an aggregate, so not looking at newly  
7 diagnosed versus relapsed.

8 DR. PAPPO: We only have three minutes to  
9 summarize, so getting to question number 2, there  
10 were a number of new potential genes that partner  
11 with other genes that define a specific class that  
12 perhaps should be reconsidered on the list. Just  
13 an example, it's not the one in CCD206 [ph] RET  
14 fusions, KIT mutations, CCND1, 2, 3, CCNE1, STAG2,  
15 and histone 1H13B.

16 There was a question as to how to deal with  
17 second and third generation compounds and whether  
18 there is an opportunity to revisit the list and the  
19 waiver. And from what I could gather, this is  
20 going to be primarily related to the sponsor.

21 Correct me if I'm wrong, Greg, or I don't  
22 know if there's going to be a specific mechanism to

1 evaluate that, correct?

2 DR. REAMAN: I'm sorry --

3 DR. PAPPO: I'm sorry.

4 DR. REAMAN: -- I missed --

5 DR. PAPPO: In the discussion that we had  
6 about second and third generation drugs and how  
7 they are going to be incorporated, is it possible  
8 to revisit the waiver and is it possible to revisit  
9 the lists if there's a specific indication for  
10 those?

11 DR. REAMAN: I don't think there's a need to  
12 revisit the list necessarily, unless something  
13 should be taken off the list because of the  
14 experience with one product in that class. But it  
15 wouldn't preclude it coming back on the list if a  
16 new product became available for which there was a  
17 rationale to study it.

18 DR. PAPPO: And the final comment was on a  
19 process for updating the list, and one of the  
20 recommendations was that although the docket is a  
21 very good idea to put in potential compounds and  
22 potential targets, it would be very helpful to

1 actually vet this process by having a formal review  
2 of the specific target or the specific agent at the  
3 twice yearly meetings, and then vetting that  
4 specific target or agent at those meetings.

5 Did I leave anything out or anybody that is  
6 really telling me you said the wrong thing?

7 (No response.)

8 DR. PAPPO: So good. Okay.

9 So now we will take a 10-minute break.

10 Panel members, please remember that there should be  
11 no discussion of the meeting topic during the break  
12 amongst yourselves or with any member of the  
13 audience, and we will resume at 9:40 am.

14 (Whereupon, at 9:30 a.m., a recess was  
15 taken.)

16 DR. PAPPO: We will proceed with topic  
17 number 2, FDARA implementation, and we will now  
18 proceed with the speaker presentation by Dr Lia  
19 Gore.

20 **FDA Presentation - Lia Gore**

21 DR. GORE: Good morning. It's a pleasure to  
22 be here, and I'm grateful for the challenge that

1 Greg presented to me to talk about some both  
2 scientific and logistical conditions that we should  
3 think about when trying to figure out how to apply  
4 the lists, and I think the conversation in the last  
5 questioning session really brought out many of the  
6 questions that I hope we can elucidate a little bit  
7 here.

8           So the outline and what I'd like to speak  
9 about today is simply to break down things into  
10 some scientific challenges that are really  
11 biologically driven, and then to think about some  
12 very practical applications or logistical  
13 considerations that we should consider. Finally,  
14 give a couple of just target examples of things  
15 that, again, I think the panel outlined their  
16 challenged considerations in the question session  
17 previously, and then finish with a few reasons that  
18 I think we can be optimistic about what this may  
19 bring to drug development in pediatric oncology.

20           Scientific challenges, biology is becoming  
21 more and more complex. Some basic considerations  
22 really are that targets differ by disease, and

1 adult cancer biology is very different, and  
2 treatments that are being developed for adult  
3 cancer types differ from what we may need in  
4 pediatric oncology. The vast majority of pediatric  
5 cancers involve aberrations and developmentally  
6 important pathways or genes and non randomly  
7 occurring fusions, as we talked about previously.

8 Overall, pediatric tumors have very few  
9 mutations per tumor, and fusion proteins are very  
10 prevalent in pediatric cancers and to date have  
11 been harder to target, in general. Those diseases  
12 that are considered more adult type cancers seem to  
13 have a higher mutational burden and lower frequency  
14 of fusions, and as a result, they may be more  
15 either amenable to or readily targeted by certain  
16 approaches that they're getting lots of attention  
17 today in drug development.

18 So the panel below, in the lower half of  
19 this, is a kind of a hallmark paper that really  
20 represents a range of tumor mutational burden for a  
21 variety of different tumor types. And we know that  
22 with an increase in capacity to identify molecular

1 aberrations in the tumors that we're studying, we  
2 have the capacity to understand how that might  
3 influence the targets that we're trying to attack.

4           There is still now a lack of knowledge  
5 between the molecular definitions of disease in  
6 both pediatric and adult cancers, so we can't apply  
7 what we know necessarily about adult cancers to  
8 pediatric cancers just by assumption. Pediatric  
9 tumors overall tend to be sort of cleaner. They're  
10 a little bit more simpler monogenic diseases and a  
11 little bit more homogeneous in most malignancies  
12 than adults, and they tend to have fewer copy  
13 number abnormalities and what we would consider  
14 lesions per pediatric tumor.

15           So if we look at the diagram on the bottom,  
16 along the X-axis is just a variety of different  
17 tumor types and along the Y-axis is the number of  
18 somatic mutation frequency. In the solid bars in  
19 kind of that fuchsia color are diseases that are  
20 typically considered more pediatric in nature, and  
21 you can tell that they're at the left end of the  
22 panel, meaning that they have fewer molecular

1 aberrations per tumor.

2           The ones in the dotted lines, however, are  
3 ones that pediatric cancer physicians and adult  
4 cancer physicians share with patient populations,  
5 and those are things like AML, glioblastoma  
6 multiforme, and DLBCL. But I would argue also that  
7 within the group of diagnoses overall, there's  
8 still quite a few variations among those tumor  
9 types, so it's hard to say that a GBM in a child  
10 for instance is like a GBM in adults. In fact, we  
11 have lots of reasons to believe that those are  
12 fairly different. So it's important not just to  
13 take diagnostic groups, but to really dig into the  
14 molecular underpinnings of those specific tumors.

15           One of the things that I study most is  
16 pediatric acute lymphoblastic leukemia, so I  
17 thought I would just give a couple of examples of  
18 some genomic subgroups that are under active  
19 consideration right now as therapeutic targets, and  
20 why we are learning more about them, and why they  
21 still present a challenge to us clinically to  
22 treat.

1           So we know that there's a group of mutations  
2           in pediatric ALL that have particularly adverse  
3           outcomes, at least with the therapies that we've  
4           used to date, and those treatments are targets of  
5           PTEN, the IL7 receptor, JAK mutations, RAS  
6           mutations, those of NF1 or TP53, and AKT.

7           There's still some confusion around MDM2 as  
8           a target, and that is specifically that we do not  
9           entirely understand efficacy and outcome results  
10          when inhibiting P53 in patients with wild type  
11          versus mutant clones, and MDM2 as a target is a  
12          very specific example of this, that even though  
13          there are now thousands of patients who have been  
14          treated with MDM2 inhibitors with adult cancers,  
15          we're still not exactly quite sure how to apply  
16          this for pediatric tumors.

17          One of the things that a pediatric  
18          oncologist will tell you is that severe  
19          hyperdiploidy in patients with ALL is a  
20          particularly adverse prognostic factor, and we know  
21          now that about 80 percent of hypodiploid patients  
22          have TP53 mutations, so this again is a target

1 opportunity, but one that we have not risen to the  
2 occasion to be able to address quite adequately  
3 yet.

4 IL7 receptor signaling overall we know  
5 drives steroid resistance, and this depends on  
6 transactivation of a particular domain, R3C1 [ph].  
7 We know that there is a small molecule inhibitor  
8 that has been applied successfully to children with  
9 cancer and that it can sensitize steroid-resistant  
10 cells. But in a patient population that really  
11 needs additional therapies that are more promising,  
12 those with T-cell ALL and in particular those with  
13 relapse T-cell disease, ruxolitinib does not seem  
14 to affect T-cell blasts as well as it does other  
15 types of malignant cells.

16 Similarly, we know that AKT activation and  
17 phosphorylation is observed in about 85 percent of  
18 T-cell ALL. But to date, targeting AKT has been  
19 really either an indirect or an upstream target  
20 effect. So as we think about how to apply these  
21 targets, it's not as straightforward even when we  
22 know a very strong disease and target relationship.

1           Another challenge that I think we have to  
2 consider is how do we apply the technology that  
3 seems to be exploding in our daily lives. There is  
4 ever-advancing technology in genomic landscape that  
5 makes the available data on molecular targets rise  
6 exponentially and seemingly logarithmically every  
7 day. The good news for that is that there are an  
8 increasing number of platforms that we can use to  
9 study these molecular aberrations, which means that  
10 the cost for those studies in genomic testing  
11 overall has decreased substantially.

12           What that also means is that even though we  
13 have an increasing number of targets, this does not  
14 make things clearer for us necessarily, so we  
15 really have to dig into not only the targets but  
16 the platforms very specifically as we figure out  
17 how to apply these. It's also important to  
18 understand that not all targets that we currently  
19 define are identified by these next-generation  
20 sequencing technologies, so we have to think about  
21 how technology can keep up with what we're also  
22 learning about tumor biology.

1           Current technologies depend on an enormous  
2 amount of bioinformatics information and  
3 interpretation of the data, and as the data explode  
4 logarithmically, so does the need for  
5 bioinformatics and careful analysis. Despite their  
6 sort of super-human skill set, bioinformaticians  
7 are still human beings, and there's a very  
8 different interpretation of the same data sets at  
9 times, and we have to really understand what that  
10 means if we're trying to compare data, for  
11 instance, from one platform to another and from one  
12 bioinformatician to another. This does not make  
13 our jobs any easier, but it's something that we  
14 have to keep in mind.

15           Then finally, turnaround times are improving  
16 for the molecular testing that's being done,  
17 however, it is still not real-time data, and we  
18 still have to understand what to do between the  
19 time of testing and the time to apply this to  
20 patient utilization.

21           We're pleased to see that one of our  
22 panelists has actually provided the figure on the

1 left side of this slide, so Dr. Mody and his  
2 colleagues presented a very beautiful article last  
3 year about what occurs in a variety of different  
4 tumors and what are the technologies that we can  
5 use to assess different aberrations in the cells  
6 that we're trying to understand.

7 At the center of this converges the  
8 molecular data that have clinical impact that we  
9 need to understand, and on the right side of this  
10 slide, I've listed just some basic facts to  
11 illustrate that our technologies and the available  
12 platforms differ and how they're being applied  
13 differ. FoundationOne testing for instance is a  
14 nice gene panel by targeted capture, which are a  
15 little over 300 genes on any given day, and the  
16 turnaround time for that is about two weeks.

17 Dr. Janeway's GAIN and iCat2 panel and the  
18 oncopanel, about 300 genes as well. There is the  
19 option to add in both array compared to genomic  
20 hybridization, FISH studies, and other  
21 histochemistry studies to evaluate in more detail  
22 what a particular tumor aberration might look like,

1 and the turnaround time is somewhere between two  
2 and four weeks for the full testing.

3 Parallel to that at Dana Farber as well is a  
4 LEAP leukemia consortium, that looks at a gene  
5 panel called the Rapid Heme Testing Panel, that  
6 looks at 95 focus genes active in leukemias. And  
7 it may also include additional infusion testing or  
8 other drug screen assays depending on the  
9 identification of aberrations. Turnaround time for  
10 the actual panel itself is quite brief, it's less  
11 than 5 days, but to include all of the analysis and  
12 the sort of curation of the data, it takes another  
13 week or two.

14 Finally, the pediatric match protocol is an  
15 amplicon gene panel conducted through Project Every  
16 Child at the National Cancer Institute in the  
17 Children's Oncology Group using OncoMine. There  
18 are 143 genes that are evaluated in about two to  
19 three weeks of turnaround time.

20 In parallel, CureSearch convened really a  
21 survey of pediatric oncologists, scientists, and  
22 other experts in the field to say what are the most

1 important targets you can think of? And this  
2 occurred just a little bit over a year ago. It was  
3 presented at the CureSearch summit in February of  
4 last year.

5 Along the left side is listed the things  
6 that practicing oncologists thought would be the  
7 most targetable where should we focus our efforts  
8 kinds of genes, and that's a list that's very  
9 familiar to many people in the room. The right  
10 side of that column is really what's the current  
11 status. For PI3 kinase for instance, there are  
12 adult studies right now that are not necessarily  
13 that promising for certain targeted tumor  
14 populations, so the future of the application to  
15 PI3 kinase inhibitors in pediatrics is a little bit  
16 more challenging.

17 BRAF and MEK have gotten a lot of attention  
18 in pediatric studies right now. There are multiple  
19 ongoing studies. I think the last count, there  
20 were somewhere around 100 studies of PD and PD\_L1  
21 one targeted agents. So the question is -- again  
22 getting back to the earlier conversation -- what is

1 next in line, how many studies did we need to do  
2 with these agents, and what can we or should we not  
3 extrapolate from one to another?

4 CDK4/6 is a rising target for pediatric  
5 tumors and BCL-2 has active studies ongoing. MDM2,  
6 as I said, is a little bit unclear about how we're  
7 going to interpret those data and in which  
8 populations, but there is a pediatric study  
9 planned. I think many people would agree that if  
10 we could effectively target Myc, that would take  
11 care of a lot of challenges that we have today.  
12 And similarly, EZH2 is a very clean target for a  
13 select patient population. Early studies of that  
14 compound in children have been very promising for  
15 some patients. It has undergone some challenges in  
16 recent weeks, but I think that will continue to  
17 move forward well.

18 The CureSearch summit actually prioritized  
19 these agents, both the single agents, and they  
20 looked at combination strategies, and finally added  
21 the EWS-FLI1 fusion, MLL-RK [ph], MT2A as it is now  
22 known in PARP, as additional targets that would be

1 of interest to pediatric studies. So as we think  
2 about the lists of targets that were developed that  
3 Dr. Reaman presented earlier and those lists that  
4 are sort of identified as hot spots in clinical  
5 practice, it sets our challenges out for us.

6 Another thing for us to be aware of is that  
7 even when we have a phenomenal target and a  
8 phenomenally well-defined biologic driver, it  
9 doesn't always work as well as we would like. And  
10 the example I'd like to use is that of a small  
11 molecule inhibitor of DOT1L called pinometostat,  
12 which is a very clean, very specific inhibitors of  
13 DOT1L.

14 The reason that that's relevant is that  
15 KMT2A fusion or MLL fusion proteins recruit a  
16 histone methyltransferase called DOT1L, and it  
17 causes hypermutation at a specific location of  
18 target genes that enhance the leukemogenesis or  
19 pro-leukemic potential for cells and genes. DOT1L  
20 is absolutely necessary for the development and  
21 maintenance of these rearranged leukemias, and  
22 pinometostat is a very specific potent and

1 selective small molecule inhibitor.

2           With all of that biology in our favor,  
3 pinometostat still did not give us the kind of  
4 results that we would like to see in patients with  
5 KMT2A rearranged leukemias, and that tells us that  
6 we still have a lot of work to do; not that the  
7 science wasn't right and that didn't look  
8 promising, but simply that it is not as  
9 straightforward as we'd like to even hope that it  
10 could be.

11           So the question is what do we do next with  
12 information like this, and then do we go back and  
13 evaluate a very clean biologic pathway that should  
14 work and it doesn't work the way we'd like it to?

15           Processing logistical and practical  
16 considerations that I think we can't underestimate  
17 the importance of, one is that there are a limited  
18 number of institutions that can conduct pediatric  
19 studies well and cleanly, and it requires a lot of  
20 work and effort. That also means that it's very  
21 difficult to access these sorts of centers and  
22 trials for patients who may need to travel. It

1 causes a lot of strain on the families. It causes  
2 an incredible amount of challenge for people to get  
3 to the place where their trial might be available.

4 Historically, there have been some  
5 regulatory endpoints that have sometimes been  
6 challenging in a new era of therapies, and I think  
7 we've seen some very nice evolution lately of what  
8 this could look like in a new generation of  
9 therapies. And that is we can't necessarily judge  
10 success or failure on overall survival necessarily.  
11 We need to take a little bit more carefully about  
12 what other endpoints may be meaningful and how to  
13 apply them.

14 Randomized trials are always favored, but  
15 randomized trials are not always possible. And  
16 there seems to be an evolution toward clinical  
17 benefit and overall response for a number of new  
18 agents, and those are particularly useful when used  
19 in combination with valid historical comparisons  
20 and cohorts of data.

21 We know that a lot of our current therapies  
22 and a lot of the targeted therapies that were

1 discussed and will be discussed at this meeting are  
2 less often now traditional cytotoxics. They're  
3 more biologically driven, and as a result, complete  
4 response or rate at which complete response might  
5 be attained may be a different endpoint for us to  
6 think about, and we have to question how we want to  
7 apply that.

8 A lot of newer endpoints that are being  
9 considered and more commonly used in clinical  
10 trials for pediatric oncology right now include  
11 things like progression-free survival, clinical  
12 benefit, and modulation of targets. I think also  
13 at the ASCO meeting earlier this month was a great  
14 example of trials that now show that you can have  
15 some examples of noninferiority for instance, where  
16 you may have clinical benefit, toxicity advantages,  
17 quality-of-life advantages that also have non-  
18 inferior results compared to more traditional  
19 therapies or surgical interventions for instance.

20 So I think those are important to think  
21 about as we consider clinical trials as we're  
22 developing this and what our appropriate endpoints

1 might be for the patient population in whom we are  
2 trying to most benefit.

3 Financial challenges are ones that we can't  
4 ignore, and traditionally, investment in pediatric  
5 trials has lagged behind those in adults. Just  
6 practically, the vast majority of drug development  
7 will really only go forward if there's a potential  
8 adults indication, and a lack of a market for drugs  
9 and pediatrics does exist. It's difficult to  
10 recover research and development costs once a drug  
11 is on the market, so that has led to lots and lots  
12 of social conversation around drug pricing, drug  
13 documentation, and marketing, and the majority of  
14 those costs are still borne by the companies that  
15 develop compounds.

16 An additional thing that we've touched on  
17 very briefly this morning is that pediatric  
18 formulations are necessary for many of our  
19 patients, but they are costly to develop, and it's  
20 estimated to cost at least a million dollars to  
21 develop some pediatric oral formulations. If  
22 there's a limited market for that, you can see how

1 that would be difficult to both employ simultaneous  
2 testing, pharmacology testing, and additional  
3 safety that might be required. And that sometimes  
4 has limited implementation of pediatric trials  
5 simply either relatively or absolutely and has  
6 delayed the development of some compounds in  
7 pediatric oncology.

8 Another consideration is really access to  
9 and what are the operations and practical  
10 considerations. At any given time, there are at  
11 least 8[00], or 900, or a thousand compounds in  
12 development for cancer overall. That's a lot of  
13 compounds, and in fact, we've occasionally said  
14 that there are more drugs in development for cancer  
15 than there are certain diagnoses per year in  
16 children by quite a bit.

17 The relatively small number that is  
18 available for pediatric trials definitely has  
19 another set of implications for how we would set  
20 about looking at these most appropriately, and a  
21 problem of the success that we have also is that  
22 the vast majority of children with cancer today are

1       cured of their disease. And that means that  
2       overall there are a relatively small number of  
3       patients in whom we can apply phase 1 and early  
4       phase drugs to use the data that we have and the  
5       access to these exciting compounds in a thoughtful  
6       way that poses challenges to clinical trial design  
7       as well as data interpretation, and the pace at  
8       which we can acquire data for patients on these  
9       trials.

10               Another challenge is that pediatric patients  
11       who are enrolled in early phase trials are  
12       typically very heavily pretreated. They've been  
13       through many rounds of chemotherapy, surgery, and  
14       radiation. They may have had multiply relapsed or  
15       significantly refractory disease, and that is a  
16       patient population in which it requires a lot of  
17       effort to take good care of them, and they may have  
18       untoward complications that could potentially limit  
19       our toxicity evaluations in the new agent.

20               Many of these patients traditionally have  
21       had a shortened life expectancy and challenging  
22       disease-free survival outcomes, and this not only

1 is unfortunate for the patients and their family,  
2 but it actually imparts a pretty significant  
3 difference in our ability to follow the effects of  
4 these agents in inhibiting important pathways if  
5 we're trying to look at the long-term outcome for  
6 these patients.

7           If we think about moving some of these  
8 compounds up front to the front line or early phase  
9 treatment, we want to know what happens to  
10 inhibiting these pathways after 10 or 15 or  
11 20 years. And that is a very significant  
12 difference in pediatrics than most of our adult  
13 colleagues have to acknowledge.

14           Overall, I think what all of these things  
15 tell us is it requires a lot of expertise, it  
16 requires a lot of focused effort, and it requires  
17 very large teams to be able to evaluate all of the  
18 important factors that we have to consider. And  
19 that, again, brings more costs and burden of  
20 treatment implementation for all of the centers  
21 that are participating in these both very excitedly  
22 and very willingly.

1           There are some societal and ethical  
2 challenges that I think we have to raise. One is  
3 that we know that drug development in children's  
4 has traditionally lagged behind that for patients  
5 over age 18, and there are very good reasons for  
6 that. There is substantial concern for exposing  
7 what we would consider some of our most vulnerable  
8 citizens to unknown risks.

9           We know that there are studies that require  
10 biomarkers that we need to assess most adequately  
11 by doing either serial sampling or serial biopsies  
12 and that historically has been very difficult to do  
13 in children for the concern of putting them through  
14 painful or unnecessary procedures if they may not  
15 benefit from the treatment which they are  
16 receiving.

17           I think we've received a number of very  
18 positive indications that there's very real  
19 potential for benefit for children now with some of  
20 these compounds, and there has been an evolution to  
21 rethinking whether or not that restriction on  
22 serial sampling and biopsying is really ethical if

1 we could offer them a therapy for which they do  
2 stand a chance of benefit.

3 I think there's another consideration that's  
4 a little bit of the elephant in the room and that  
5 people do have a challenge to think about what  
6 happens if a child has a bad event on a clinical  
7 trial and we don't have a host of data to support  
8 this, or it may be an untoward event that has  
9 unfortunately just occurred.

10 There has been historically reluctance to  
11 invest in applying drugs to pediatric trials if  
12 there's the potential risk that a very bad public  
13 relations event could happen if a child had a bad  
14 event on those and further potential killing of  
15 that drug if there's a bad event with a child that  
16 may actually limit the ultimate access that other  
17 patients have to a promising agent just simply  
18 because something bad happened, and that's an  
19 important event for us to think about how we both  
20 deal with that societally and ethically.

21 So I want to actually draw this to a close  
22 by thinking that there are some very good reasons

1 for us to be optimistic. It's always easy to pick  
2 apart the problems and pick apart the difficulties,  
3 but I think there is some significant and  
4 substantial reason that we should be optimistic.

5 I think we've seen an evolution, and over  
6 the last 10 years I've argued repeatedly that  
7 cancer is becoming a chronic disease for many  
8 patients. We may never cure somebody entirely of  
9 their disease, but we could turn this into a  
10 disease that looks very much like diabetes or  
11 hypertension. And if you are compliant with your  
12 appropriate therapy, you may keep your cancer at  
13 bay for many, many years.

14 As I've told a lot of patients, cancer that  
15 does not grow and divide and metastasize and cause  
16 organ dysfunction might not kill you. And it's an  
17 important thing to think about this as we're  
18 thinking about what our appropriate endpoints are.  
19 What if cancer becomes a disease that people live  
20 with more effectively? That's a very different  
21 concept in pediatric oncology, and it requires a  
22 frame shift in how we think about things.

1           I think the newer legislation that was  
2 presented earlier today and all of the work that's  
3 being done really offers great advantages over what  
4 we've done. There has been a learning curve to  
5 legislating pediatric oncology, and I think it's  
6 important to acknowledge that, first of all,  
7 because we are substantially better off today than  
8 we have been. But these legislative actions also  
9 have limitations, and I don't think we can expect  
10 any one piece of legislation to fix everything. So  
11 I think we have to be realistic, and I think we  
12 have to continue to work to try to define the  
13 appropriate degrees of how we're going to  
14 intervene.

15           New approvals and new applications are  
16 actually dramatically exciting as we think about  
17 what goes forward. There are a number of approvals  
18 recently that have been really relatively age  
19 agnostic or have allowed access for younger  
20 patients under the age of 18 to agents which are  
21 extremely promising. And I suspect that most of  
22 the members around the table can identify examples

1 in which they have used an adult drug in a child  
2 and had a very good outcome.

3 Similarly, I think agents are now getting  
4 tumor-type specific agnostic approvals. And that's  
5 also very exciting as we think about the tremendous  
6 explosion in biologic knowledge that we have the  
7 advantage to apply something that might be a little  
8 bit untraditional but with very strong biologic  
9 rationale, and therefore impact a disease that we  
10 may not have even anticipated an improvement in.

11 This is a brief chart to get back to the  
12 therapy and prioritization review of targeted drug  
13 pairs, and I think it's important. Just as an  
14 example, I don't expect people to actually see the  
15 detail, but to understand that there's a wide agent  
16 class that's been evaluated. They have been  
17 subject to scoring systems and look at some  
18 potential biomarkers for which these targets may be  
19 able to be applied in pediatric oncology.

20 There are some example biomarkers that are  
21 listed in the second to the last column for the  
22 right, and then I wanted to include the priority

1 for the pediatric MATCH trial in terms of how these  
2 were included or not included for a variety of  
3 reasons. I think this is just an example, and I do  
4 think it's important to recognize that these lists  
5 are not static in any way. They need to continue  
6 to be evaluated.

7           Similarly, along here there were some agents  
8 on the left chart, some agents that were excluded  
9 from the initial evaluation. That is simply, if  
10 you'll notice along these, that there are either  
11 very uncommon targets or targets and biomarkers  
12 that are not known, so it's difficult to know how  
13 to apply them. On the right-hand side are some  
14 example histologies or tumor types for expansion  
15 cohorts. It's important for us to think about how  
16 these apply as we continue to evolve knowledge as  
17 we go forward.

18           Challenging things to think about and I hope  
19 what will set the stage for later discussions today  
20 are really our tremendous exposure to knowledge  
21 about the cancer genome has led to increases not  
22 only in the molecular targeted agents that are

1 being developed, but in the sophisticated  
2 technologies and sequencing that we have the  
3 capacity to interrogate biologic pathways to  
4 understand more about what's happening in real  
5 time.

6 This is truly a new age of biomarker-driven  
7 personalized therapy, and as we learn how to direct  
8 agents, it will allow us to be able to give  
9 patients drugs for which they are most likely to  
10 respond and from which they can most likely derive  
11 benefit. So I think it's important to consider the  
12 limitations. We've talked about some of them  
13 already. We need to think about how to handle  
14 multiple tissue or tumor collections.

15 We need to really recognize the importance  
16 of disease heterogeneity and complexity, and the  
17 influence of things like the epigenome, the  
18 proteome, the microbiome, and all kinds of other  
19 omes that we haven't even defined yet; to think  
20 about as we increase our knowledge, we have also  
21 increased how we photo divide, and subdivide, and  
22 develop micro cohorts of disease and how we need to

1       classify them together in order to develop expected  
2       responses. Similarly, we need to define pediatrics  
3       a little bit differently. We need to think about  
4       ethical challenges that will rise as we discover  
5       germline mutations. We need to think about costs,  
6       and we need to think about availability and  
7       formulation.

8               This is a quote I think from a thoughtful  
9       article that was published last year, and it  
10       recognizes that as we have had successes and  
11       failures in the development of targeted agents,  
12       we've done this one step at a time. And I think we  
13       can see that the mathematical modeling of what we  
14       have presented in front of us and the challenges  
15       for the explosion of new applications and new drug  
16       development really does require that we shift our  
17       paradigm, be creative and be collaborative in how  
18       we think about how to do this most effectively  
19       because at the end of the day, there is a patient  
20       at the other end of these discussions that depends  
21       on us to do this correctly.

22               My personal acknowledgements are those here.

1 I have the privilege of working with really  
2 wonderful people, both in my own institution and  
3 across not only the country but across the globe;  
4 and again, most importantly, the patients and  
5 families that we see every day and trust us to take  
6 these responsibilities very seriously. And I think  
7 this effort that's going on will allow us to  
8 continue to do honor by them and the effort that  
9 they have placed in trusting us. Thank you.

10 (Applause.)

11 **Clarifying Questions**

12 DR. PAPPO: Thank you very much, Dr. Gore.

13 We have a few minutes left to take some  
14 clarifying questions. Please remember to state  
15 your name for the record before you speak.

16 DR. KOLB: Lia, you had mentioned access to  
17 phase 1 development, phase 1 trials as a challenge.  
18 If we're going to increase the number of phase 1  
19 trials through the RACE Act, how do we address that  
20 challenge?

21 DR. GORE: That's the million-dollar  
22 question, right? I think Dr. Kolb has a very valid

1 question. The concern is that if we have more  
2 drugs than we have patients, how are we going to do  
3 that? I think part of it is that as we get to  
4 tumor type or histology, biologically driven trials  
5 rather than a trial for neuroblastoma or a trial  
6 for Ewing sarcoma, if we get to biologically  
7 driven -- this is an inhibitor of a pathway that we  
8 know is active in these groups -- it will allow us  
9 to be more creative about our trial design, and we  
10 can probably be more effective and more efficient  
11 in enrolling patients on trials where there's  
12 biologic rationale.

13 I do think that our study design, our  
14 statistics, are going to have to evolve as we think  
15 about this. The way we used to do trials is not  
16 effective or efficient anymore in this era, so I  
17 think we're going to have to think about that more  
18 carefully.

19 Dr. Janeway?

20 DR. PAPP0: Katie?

21 DR. JANEWAY: Lia, one of the most  
22 challenging aspects of biomarker defined clinical

1 trials is getting the right patients to the right  
2 trial. You talked about availability of molecular  
3 diagnostics and the sort of challenges of  
4 navigating different types of molecular  
5 diagnostics. I think maybe you didn't mention or  
6 I'm interested in your thoughts on is actually  
7 trial matching, so finding the trial for the  
8 patient, because in our current paradigm, we don't  
9 list trials by genes or gene variants make you  
10 eligible for that trial, and there isn't an easy  
11 way to search or access that information.

12 Do you have thoughts about that?

13 DR. GORE: I think you're absolutely right.  
14 I think one of the things that you didn't talk  
15 about is how hard it is to get genomics on a  
16 particular patient sometimes, and we know that  
17 there are many patients that are limited in their  
18 ability to get the best diagnostics available  
19 because insurance won't cover it, or they don't  
20 allow third-party payers, or there is some great  
21 delay.

22 So that's the social side of this, right?

1 Just to get even the information is still  
2 challenging for a significant proportion of our  
3 patients. So under the best of possible  
4 circumstances, we have access to this information.  
5 I think it's a place where we could have a more  
6 national effort, more sponsored ability to have  
7 databases that are more searchable, more  
8 accessible, a real-time possibility of getting that  
9 information. It's almost impossible to have  
10 everything captured at any given time. And even if  
11 we do, clinicaltrials.gov for instance is a great  
12 start, but it's not enough.

13 I think even if you know there is a trial,  
14 it may not be open. There may not be a slot.  
15 There are all kinds of other sort of practical  
16 application considerations. And I didn't even go  
17 into that because it is very complicated, but I  
18 think there are probably things that we can do  
19 better to make the information more publicly  
20 available.

21 DR. JANEWAY: One major limitation of  
22 clinicaltrials.gov is that the eligibility criteria

1 that are gene or gene variant related are not a  
2 searchable field, actually, so it's a descriptive  
3 entity within that very valuable repository of  
4 clinical trials.

5 DR. GORE: And I think we've probably all  
6 had the experience where we have looked for our own  
7 trials on databases and websites. We can't even  
8 find out if that's our own trial, let alone  
9 something else that might be an option for our  
10 patients. And if we can't navigate that, that's  
11 probably really challenging for somebody that is  
12 coming at this without of knowing how to look for  
13 it. Absolutely.

14 DR. PAPPO: Ira?

15 DR. DUNKEL: I have a comment, although it's  
16 more for the FDA staff maybe then for Dr. Gore. I  
17 think you've provided a really important service.  
18 Some of you have authored papers and statements  
19 saying that adolescents should be included in  
20 relevant adult trials. I just came back from an  
21 adult brain tumor meeting, though, and although  
22 these were highly academic clinical researchers,

1 this was completely foreign to them. So I just  
2 wanted to mention that I think this needs wider  
3 dissemination.

4 DR. PAPPO: You want to --

5 DR. REAMAN: I'll just comment that -- thank  
6 you. We did publish a paper suggesting that this  
7 is something that should be considered. We just  
8 recently, as of last week or the week before,  
9 published a guidance as well. So it's available  
10 for sponsors and investigators, including  
11 adolescents, on appropriate disease and  
12 target-appropriate studies.

13 DR. PAPPO: Elizabeth and then Malcolm.

14 DR. RAETZ: Lia, thank you for the excellent  
15 talk. Just in terms of your comments that you made  
16 about efficiency of trial design, I was wondering  
17 if you could comment on any strategies that you've  
18 thought about combinations, particularly for  
19 disease processes where a single agent activity has  
20 been somewhat of an issue and a challenge.

21 DR. GORE: Sure. For those that didn't hear  
22 Dr. Raetz's question, it related to trial design

1 and thinking about some approaches that might help  
2 solve some of these issues, single agent versus  
3 combination, those kinds of things.

4 I think there is always a tricky balance  
5 between how to structure, for instance,  
6 single-agent windows and then rolling to  
7 combinations. How to move some drugs up front if  
8 they look particularly promising can be very  
9 challenging because you don't want to, in some  
10 cases, introduce a new agent that may compromise  
11 what we know to be a standard baseline population  
12 response for certain patients.

13 I do think a very simple thing that we could  
14 do, if we're trying to introduce a new agent into  
15 combination studies, for instance, if we have a  
16 backbone that's a relatively accepted backbone for  
17 a particular disease type or tumor type, but we  
18 know that there is the potential that a new agent  
19 targets something that has been discovered  
20 recently, one of the things that has been  
21 challenging I think is when we're looking at the  
22 window period of what data we're trying to

1 understand and acquire from a new agent, sometimes  
2 there has been a tendency to require single-agent  
3 windows to be very long, sometimes wonder 1 or 2  
4 months, and then allow rolling over to combination  
5 therapy.

6 I think we are getting to the point where  
7 those very prolonged single-agent windows might not  
8 be either as helpful as we thought they might be or  
9 they might actually compromise the ability to  
10 actually see activity of a drug that may have more  
11 potential efficacy in combination.

12 So I think we can consider some models, for  
13 instance just as a simple example, where that  
14 single-agent window for pharmacokinetics or  
15 pharmacodynamic evaluation could be much shorter  
16 and still not compromise evaluating the integrity  
17 of the drug, both for safety and activity reasons,  
18 but also roll in response modifiers to look at  
19 single agent versus combination.

20 I think we can probably accelerate some of  
21 the things that we've done more slowly in the past.  
22 That might be one approach. And then again, tumor

1 type agnostic, biologically-driven studies so that  
2 we're not lumping everybody together, but at the  
3 same time, that we have the opportunity to evaluate  
4 a promising compound in multiple tumor types  
5 simultaneously.

6 DR. PAPP0: One final question. Malcolm?

7 DR. SMITH: Malcolm Smith. A beautiful and  
8 thoughtful presentation, Lia. I wanted to query  
9 you a bit on your comments about the chronic  
10 disease paradigm. I see that for CML plexiform  
11 neurofibromas, that those will probably be treated  
12 as chronic diseases. It's harder applying that to  
13 aggressive ALL or AML.

14 I guess when I think of the transformative  
15 agents from imatinib and nelarabine, ATRA, arsenic,  
16 and more recently the CAR-T cells and  
17 larotrectinib. What everyone is excited about is  
18 that they make the tumors really get smaller or  
19 they induce complete remissions.

20 So I guess it seems to me that's still the  
21 coin of the realm and that there's not -- that's  
22 still our goal. So maybe we would take something

1 else if it was the best we had, but I don't see  
2 that there's a real change in what we really want  
3 from a new agent or a new treatment.

4 DR. GORE: Very appropriate, and I think I  
5 absolutely agree with you. I do think that we  
6 should think about our response definitions,  
7 though, if we have -- for instance, treatment  
8 beyond progression is something that we now do in a  
9 lot of adult phase 1 studies where we're able to  
10 then introduce into -- for instance, a single-agent  
11 phase 1 study, a patient develops some isolated  
12 brain met.

13 We don't necessarily take them off that by  
14 protocol. A protocol may allow for that patient to  
15 get single-fraction brain radiation and allow them  
16 to continue on, because if we know that this is a  
17 biologic agent that isn't going to work instantly,  
18 it requires a long runway to be able to see the  
19 biologic effect.

20 If we take that patient off and they go on  
21 to get radiation anyway, we may have limited our  
22 ability to understand what natural history of

1 inhibiting that pathway or that gene might be. And  
2 if we can allow for a more creative trial design  
3 where we say isolated progression in one area  
4 doesn't mean that the patient isn't benefiting from  
5 inhibiting that target or that pathway in a whole  
6 bunch of other parts of where they have disease.

7           So I absolutely agree with you. We still  
8 should want to cure patients, and we should want to  
9 cure them strongly and deeply and well, is how  
10 we've described it. But at the same time, I think  
11 we have to think about what do we remove patients  
12 from study for and why, and what could we  
13 potentially think about modifying as we think about  
14 those responses, so that we understand that we give  
15 patients an opportunity, a sufficient duration of  
16 time exposed to an agent to understand if they're  
17 really going to benefit from it.

18           So I think part of the question is, again,  
19 to think carefully and cleanly about what that  
20 means, and that does allow patients to live with  
21 their cancer for a longer period of time. So we  
22 may not be able to use our same judgment criteria

1 for what we have traditionally.

2 Thanks for asking the clarification.

3 DR. SMITH: And that's a great point, and I  
4 think just in our preclinical testing, for some  
5 agents, we clearly see a progression before we see  
6 a response, especially the epigenetic modifiers  
7 that may take a week or two to actually modify the  
8 transcriptional machinery.

9 DR. GORE: Right, or four months.

10 DR. SMITH: So certainly having the response  
11 criteria match the mechanism of action of the agent  
12 in terms of timing is critical.

13 DR. PAPPO: Thank you very much, Dr. Gore.

14 DR. GORE: Thank you.

15 DR. PAPPO: We will now proceed to our next  
16 presentation, Dr. Lisa Bollinger.

17 **Guest Presentation - Lisa Bollinger**

18 DR. BOLLINGER: Good morning. I'm  
19 Dr. Bollinger, and today I will be talking about  
20 the implications of the 2017 FDA Reauthorization  
21 Act on Pediatric Cancer Drug Development from the  
22 perspective of industry. I have the disclosure

1 information that I am employed full time by Amgen.

2 I'm going to start with a brief overview of  
3 BPCA and PREA that you heard a lot about from  
4 Dr. Reaman this morning. They are intended to work  
5 together in order to maximize the information in  
6 labeling on dosing, safety, and efficacy for  
7 products that may be used in the pediatric  
8 population. The law requires that even if studies  
9 are negative or uninterpretable, study information  
10 is still placed in labeling because information has  
11 been deemed critical.

12 We know in the pediatric population we don't  
13 often have chances to repeat studies over and over  
14 again until we get positive studies. Because of  
15 the limited amount of information that gets out  
16 there in the pediatric population, it is important  
17 for all study results to be included in labeling.  
18 And it's also important to note that PREA and BPCA  
19 are not mutually exclusive. Those products that  
20 are required to be studied under PREA can also  
21 qualify for exclusivity under BPCA, although it  
22 should be noted that we have increasing numbers of

1 biologics that are being developed for oncology  
2 therapy, and because of the way that the  
3 legislation applies exclusivity to biologics, fewer  
4 companies actually seek exclusivity for these  
5 programs.

6           Pediatric oncology studies have actually  
7 been required by the agency now under BPCA or PREA,  
8 and you can see some examples are arsenic, which  
9 Dr. Smith mentioned earlier, imatinib, and  
10 panitumumab. These are examples from the early  
11 2000's, and a lot of things have changed since the  
12 early 2000's in regards to the legislation.

13           For one, we've had stronger infrastructure  
14 and documentation by the agency in how this  
15 legislation is applied. In addition, since the  
16 early 2000's, we've had improved knowledge of tumor  
17 biology that's informing treatment, and precision  
18 medicine has delivered more targeted therapies.  
19 Because of the targets that are identified, these  
20 products may qualify for orphan drug exclusivity,  
21 which is actually a critical regulatory pathway for  
22 development of medicines in small populations.

1           Remarkable progress has been made in our  
2 understanding of genomic landscapes for pediatric  
3 cancers, and products approved for use in adult  
4 cancers can provide a health benefit for pediatric  
5 patients. Despite the lack of PREA requirements  
6 for these orphan products, many of them are  
7 actually studied in the pediatric population  
8 anyway, although they're not always performed for  
9 regulatory review nor product labeling, so that's a  
10 big disconnect.

11           If the studies are conducted and they're not  
12 conducted under a requirement or under an incentive  
13 program by the FDA, they often aren't submitted for  
14 independent review and may not be included in  
15 labeling.

16           I actually went back and looked at Drugs at  
17 FDA approval letters and did a sampling and saw  
18 that there were approximately 77 new BLAs or NDAs  
19 that were approved since 2012. I picked the date  
20 2012 because that was the most recent  
21 reauthorization of both PREA and BPCA, and there's  
22 really good documentation in the database at Drugs

1 at FDA about decisions that were made on those  
2 products. About 26 applications were waived on the  
3 basis that the disease did not occur or was rare in  
4 the pediatric population, and another 50  
5 applications were exempt because of orphan  
6 designation.

7 Now, when I cross-reference these 77  
8 products to clinicaltrials.gov, about 62 percent of  
9 them had clinical studies listed in the pediatric  
10 population. But again, the regulatory utility of  
11 those studies are unknown. In other words, it's  
12 not known if those are being conducted by the  
13 sponsor for submission to the agency or if they're  
14 being conducted as independent research studies by  
15 investigators.

16 As we know, PREA was changed under FDARA,  
17 and we are now required to study molecularly  
18 targeted drugs if they're intended for the  
19 treatment of an adult cancer and directed in  
20 molecular targets substantially relevant to the  
21 growth or progression of the pediatric cancer, and  
22 also, it eliminated the exclusion for

1 orphan-designated products.

2           Now, these legislative changes do bring new  
3 opportunities. For one, PREA now allows industry  
4 an early opportunity to discuss these pediatric  
5 studies in oncology with the FDA. In addition, the  
6 smallest study populations will require the  
7 development of innovative study designs, and I  
8 think that this will cause a lot of advancement in  
9 the way that we study drugs not only in the  
10 pediatric population but in the adult population as  
11 well. It's also a chance for closer collaboration  
12 between NCI, COG, other collaboratives, FDA,  
13 industry, and advocacy groups. And you heard  
14 Dr. Reaman talk a lot today about public and  
15 private work to do in this area.

16           One of the other benefits is that because  
17 studies submitted in response to PREA are required  
18 to be included in labeling, the independent  
19 regulatory review of data and availability and  
20 labeling may increase access to these products for  
21 patients. But of course with legislative changes  
22 also come challenges.

1           One of the first challenges that we've heard  
2 a lot of discussion about today is what molecule  
3 should be studied, and as we all know, this  
4 legislation requires lists. The lists in the  
5 legislation are a list of products that have  
6 substantial evidence that the products would work  
7 on a pediatric target and another list of products  
8 that should be automatically waived.

9           The chance to make these lists may represent  
10 an opportunity for stakeholders to come together to  
11 discuss emerging science, but regardless of whether  
12 or not products are on the lists, each one of the  
13 therapies that are being developed must be  
14 independently assessed for the opportunity to  
15 provide benefit in the pediatric population.

16           So it's not clear if we will continue to  
17 have this list or how much benefit it will provide  
18 to us in deciding which products need to be  
19 studied, or if it will go the same way as the other  
20 lists that have been required in previous  
21 legislation like BPCA. We used to have lists for  
22 drugs that needed to be studied or lists of generic

1 drugs that needed to be studied. So we'll see if  
2 this actually has utility in helping us determine  
3 which products should be studied.

4 Now, what the list doesn't do is it doesn't  
5 help us prioritize. Many of these products share  
6 the same molecular targets, and studies could be  
7 competing for the same small pool of patients. And  
8 because recruitment in pediatric trials is  
9 difficult and many centers must be opened,  
10 pediatric studies are often international by  
11 nature, and that does require some level of  
12 harmonization. We'll have to have ongoing  
13 surveillance of pipelines to ensure that the most  
14 promising therapies are studied first.

15 Oftentimes, FDA and NCI are often aware of  
16 pipelines across companies, so perhaps we can work  
17 with them as we decide which therapies revolve into  
18 studies and which ones to come off. I will say  
19 that at Amgen, one of the things we are doing is  
20 working with internal experts as well as looking at  
21 external experts that we can collaborate with to  
22 assess which ones of our products in our portfolio

1 may benefit the pediatric population, and then to  
2 also determine what types of nonclinical studies we  
3 can do to further investigate the potential.

4           There was also a safety requirement. We do  
5 want to make sure that we do have some safety  
6 information before we move into the pediatric  
7 population to assure that we have all the  
8 information we need to help us determine if the  
9 benefit will outweigh the risk.

10           That being said, there are always inherent  
11 risks for patients participating in clinical  
12 trials, and we have a recent adult example of  
13 studies of immunotherapies used in combination with  
14 other drugs that were actually placed on hold while  
15 safety concerns were examined.

16           We also know from all the previous studies  
17 in pediatrics, including non-oncology studies, that  
18 we have identified adverse events that are unique  
19 to or amplified in the pediatric population, and we  
20 know that some toxicities are hard to predict based  
21 on what we know from adult studies or preclinical  
22 models.

1           Of course, industry is always looking for  
2 regulatory stability. The intent of the  
3 legislation was not to provide prescribed  
4 directions for implementations, and lists certainly  
5 don't provide certainty. As Greg mentioned  
6 earlier, whether a drug is on the list or off the  
7 list, it will have to be evaluated independently to  
8 see if it will be required to be studied in the  
9 pediatric population.

10           As science advances, it will be incumbent  
11 upon the FDA to more clearly define what therapies  
12 will have study requirements, because while  
13 regulatory certainty is an ideal that's hard to  
14 realize, business uncertainty is not sustainable.

15           Industry must be able to plan for the study  
16 requirements for a given therapy over time; number  
17 one, to be able to plan the studies. And this is  
18 going to be more labor intensive now because as we  
19 know, the FDA has been really forward thinking in  
20 reducing cycle times of drug development, as well  
21 as in reviewing the products for approval. So that  
22 actually compresses the amount of time that

1 industry has to reach an agreed upon pediatric  
2 study plan with the FDA.

3           Of course, we always have to plan for costs.  
4 While that's not the primary driver for pediatric  
5 studies, we do know that from a business  
6 standpoint, we do have to plan for these  
7 investments, which could range anywhere from \$1  
8 million to \$35 million depending on the types of  
9 studies that need to be performed.

10           So where does that lead us? It leads us  
11 exactly back to places where we've been before.  
12 More than 20 years ago, people said that pediatric  
13 studies in any therapeutic area could not be  
14 conducted, and what we know now is that there are  
15 over 700 products with pediatric information and  
16 labeling largely based on clinical studies in the  
17 pediatric population. There will be challenges in  
18 prioritizing products to study, and the best minds  
19 are poised to solve the challenges presented by  
20 this new legislation.

21           The new requirements may provide an  
22 opportunity for increased collaboration across

1 industry, academia, and government, so I'm going to  
2 end on this positive note as well. Thank you.

3 (Applause.)

4 **Clarifying Questions**

5 DR. PAPPO: Thank you very much,  
6 Dr. Bollinger.

7 We will now take clarifying questions for  
8 Dr. Bollinger. Please remember to state your name  
9 for the record before you speak.

10 DR. SEIBEL: Thank you, Dr. Bollinger, for  
11 that perspective, which was very helpful. I guess  
12 I'm a little -- and this question or comment is  
13 both for you and for Greg perhaps, but you alluded  
14 to these previous lists that have been present.

15 Is there anything different about this list  
16 that will distinguish it from the ones in the past,  
17 where it sounds like they've really failed?

18 DR. BOLLINGER: I do think that there may be  
19 some subtle differences. One is that this is one  
20 therapeutic area, although all cancers are  
21 obviously very different. And I do think it is an  
22 opportunity for all stakeholders to come together

1 and really discuss what's emerging in the science.

2 I think the one thing that's not different  
3 is that the FDA doesn't have to stick to what's on  
4 the list or not on the list, so there's going to  
5 have to be independent assessment of every therapy  
6 along the way. So I think time will tell whether  
7 or not the investment of time and energy into  
8 making these lists is going to be fruitful, but we  
9 will certainly be using these lists as we embark on  
10 this journey to develop these products in kids.

11 DR. PAPPO: Julia?

12 DR. BENDER: Julia Glade Bender. Thank you  
13 very much for that really very interesting  
14 perspective. And regarding costs, I just want to  
15 make sure that both parties understand that many of  
16 us who do these trials for industry or for the  
17 children, to do the targeted therapies, this is  
18 actually a labor of love on the part of the  
19 institution because the internal costs to your  
20 institution is so much higher than the compensation  
21 that you get for doing these trials, that all of us  
22 who do them are required to go out and raise more

1 money in order to satisfy all of the regulatory  
2 requirements of doing these studies.

3           So I'm concerned that in some ways, while we  
4 try to gain access for kids, the economy is so  
5 different in running these pediatric trials that I  
6 wonder how the institutions are actually going to  
7 manage because if you're looking for the needles in  
8 a haystack, do you have to open up the farm? And  
9 that's part of the issue here that I think we're  
10 going to have to think about new mechanisms of  
11 activating trials for individual patients for rare  
12 targets at an institutional level so that we as  
13 institutions or investigators, who feel responsible  
14 to our patients to get them access, don't go under.

15           DR. PAPPO: Very good point. Elizabeth?  
16 Brenda?

17           DR. WEIGEL: Dr. Bollinger, thank you very  
18 much. One of the points that I didn't see your  
19 presentation but I wonder if you might comment on  
20 is that -- and you do state international  
21 collaborations. But also from a regulatory  
22 perspective, how much does -- the new American

1 requirements, FDA requirements, how does that  
2 balance with the thinking and development of  
3 meeting international regulatory requirements from  
4 an industry perspective?

5 DR. BOLLINGER: Certainly Drs. Fox, Caron,  
6 Vassal, and Bucci-Rechtweg will be talking both  
7 about prioritization as well as international  
8 studies following me later today. But we do have  
9 to look at how we work with the requirements in the  
10 European Union. I think that because of the  
11 cluster meetings, we will have more collaboration.  
12 And actually moving these studies earlier helps to  
13 harmonize the timing of how we prioritize and  
14 embark on these studies. There are still some  
15 differences that we'll need to work out, but again,  
16 I'm sure that we will over time be able to get  
17 through those hurdles as well.

18 Also, I'd like to say a lot of international  
19 collaborations that are starting up right now that  
20 are very exciting, really do aim to help bring  
21 these two programs together.

22 DR. PAPPO: Kathleen?

1 DR. NEVILLE: Thanks; really great talk. I  
2 thought it was very thoughtful.

3 Dr. Bollinger, my question for you -- and I  
4 know you can't speak for all of industry -- is I  
5 think increased collaboration and cooperation  
6 between sponsors would be a paradigm shift and how  
7 do you foresee that happening? How do companies  
8 collaborate while also protect their and answer to  
9 the shareholders?

10 DR. BOLLINGER: I think that is a very  
11 important question and one that we will have to  
12 work through. As we look at a lot of these  
13 therapies that are not used as sole therapies, a  
14 lot of them are used in combination. And one of  
15 the questions is going to be with the PREA  
16 requirements, how are we going to work with other  
17 companies to provide combination studies? But  
18 again, I think because in the pediatric space there  
19 isn't a large financial driver for getting the  
20 studies done and having the products labeled in the  
21 pediatric population, that there's probably a  
22 little bit more leeway for cooperation.

1           That being said, as hopeful as we all are,  
2           we always run into issues with protecting IP and  
3           making sure that our adult programs don't suffer  
4           because we're also doing pediatric programs.  
5           Again, I don't have any real clear answers, and I  
6           think because we're at the very beginning, we  
7           haven't had to struggle through some of those  
8           issues enough for me to tell you how we're going to  
9           define that. The only thing that I can say is,  
10          again, we've faced these hurdles in the past and  
11          have been able to overcome them, so I have no doubt  
12          that all of the companies working together, as well  
13          as all the great minds that are focused on  
14          developing cancer drugs for pediatric patients,  
15          we'll make this happen.

16                 DR. PAPPO: Any additional questions or  
17                 comments?

18                 (No response.)

19                 DR. PAPPO: I have a comment if that's okay,  
20                 Dr. Bollinger. As we move forward. I just think  
21                 that it would be very important just to remember  
22                 some of the successes and some of the disasters

1 that we have had trying to develop specific  
2 indications for pediatric tumors. I don't  
3 completely agree with your slide that said that  
4 recruitment to pediatric trials is difficult. I  
5 think that if you have the right target, the right  
6 population, you will have the patients.

7 A perfect example is what has happened with  
8 the NTRK inhibitor. There is a very rare  
9 population that has greatly benefited from this.  
10 There have also been very disappointing studies  
11 which took a long time to develop, and the two  
12 stories are the ipilimumab that was specifically  
13 for melanoma patients and opened almost two years  
14 after the drug was actually approved for adults.  
15 And the second one was vemurafenib also for the  
16 BRAF mutant, which was exclusively for pediatric  
17 melanoma.

18 If this would have opened earlier and it  
19 would have been just a blanket study for BRAF  
20 mutant tumors, perhaps this drug could have been  
21 incorporated earlier into the treatment of BRAF  
22 selected tumors. So it's just something for your

1 company to consider in the future as this  
2 legislation moves forward.

3 DR. BOLLINGER: Yes. Thank you very much  
4 for your input.

5 DR. PAPPO: Katie?

6 DR. JANEWAY: Very well said, Dr. Pappo.  
7 Katie Janeway from Dana Farber once again.

8 How can we get numbers that will answer this  
9 question? Because I agree with your statement that  
10 a accrual -- we gnash our teeth a lot about  
11 accrual, and we worry about accrual, and we do it  
12 so much sometimes that we shoot ourselves in the  
13 foot and slow ourselves down developing trials and  
14 actually answering the question by opening the  
15 trial.

16 But I don't know how we manage to get data  
17 that supports what you said. And what my sense is  
18 that my problem is not putting patients on trials.  
19 My problem is not having trials for patients that I  
20 see in my clinic who have relapsed cancer, but I  
21 don't know how to actually quantify that.

22 DR. PAPPO: I'm afraid I don't have an

1 answer. I don't know if you have an answer for  
2 that, Dr. Bollinger.

3 DR. BOLLINGER: I think I would say the  
4 answer probably depends on the type of tumor that  
5 you're looking at and how many centers that you're  
6 going to have to open. While some studies may  
7 enroll quickly, we also have the experience that  
8 many others don't.

9 One of the things that certainly will help  
10 is talking about this more and having these types  
11 of meetings where people become aware of the  
12 different studies that are ongoing. As you said,  
13 it's really hard to search clinicaltrials.gov, so  
14 perhaps one of the things that we need to start  
15 thinking about is a way to either improve that  
16 database or develop another one that could help us  
17 to figure out answers to these questions.

18 DR. PAPPO: Greg?

19 DR. REAMAN: And we just point out that the  
20 one important thing about the trials that are  
21 ongoing, despite the fact that there were no PREA  
22 requirements for pediatric evaluation, and

1 separating out whether they were industry-sponsored  
2 studies that might lead to labeling information or  
3 some positive regulatory decision versus  
4 investigator-initiated studies where data may not  
5 really impact any other patients, I think that's a  
6 real distinction that needs to be made.

7           Again, I just want to stress that we're not  
8 hoping or we don't intend to see this legislation  
9 result in increased numbers of studies, but just  
10 increased timelines for which studies are in fact  
11 discussed, considered, thought about, and initial  
12 evaluations of dose and looking for activity  
13 signals, because I think some of the things that  
14 were studied were studied long after the drug was  
15 approved in adults.

16           There are some real challenging examples,  
17 and I think very telling examples, with the orphan  
18 exemption of drugs for indications that span the  
19 pediatric and adult age groups that were approved  
20 for adult indications when the same disease occurs  
21 in children in two years, three years later we're  
22 still doing studies. So that's what this

1       legislation is really intended to change, I think.

2               DR. BOLLINGER:  And that is actually a  
3       really important point that also plays into the  
4       ability to recruit into studies.  I know what we  
5       have seen across the board is if a product is  
6       approved in the adult population, it's much easier  
7       for a pediatric oncologist to perhaps use that  
8       therapy off label in the pediatric population, and  
9       they may be less inclined to consider enrolling  
10      that patient in a clinical study.

11              We saw that with our own Neulasta, where it  
12      was being used as standard of care in the pediatric  
13      population.  So because of the gap and the time it  
14      was approved in the adult population and the time  
15      that the pediatric studies were initiated, we  
16      weren't able to enroll enough patients because  
17      clinicians believed that the product was  
18      efficacious.  So that's an extremely good point,  
19      that we do need to bring those timelines together  
20      in order to actually get better studies.  Thank  
21      you.

22              DR. PAPPO:  And that you saw also with the

1       vemurafenib and the ipilimumab trials.  Although  
2       they were international studies, the accrual was  
3       dismal because the drug was already approved and  
4       pediatric oncologists could prescribe it.  And  
5       there were really combinations that were coming  
6       along that were much more effective.

7                 Steve and then --

8                 DR. DuBOIS:  Actually, something to respond  
9       to one of Dr. Reaman's comments.  Do you anticipate  
10       not necessarily an increase in early phase trials,  
11       but a shift in the proportion that are industry  
12       sponsored rather than investigator initiated as an  
13       impact of this act?

14                DR. REAMAN:  I think they should be industry  
15       sponsored, and it's going to be a collaborative  
16       effort, obviously, between industry and  
17       investigators.  Given the patient population that  
18       we're dealing with, this will have to be a  
19       coordinated, collaborative venture.

20                DR. PAPPO:  Kathleen?

21                DR. NEVILLE:  Just a comment to add on to  
22       what Drs. Reaman and Bollinger said, that another

1 reason to move these studies earlier is the off-  
2 label use is often not paid for by insurance, and  
3 these agents are expensive. And what we consider  
4 adequate data are not considered adequate by  
5 payers.

6 We're running into this over and over, and  
7 we've been successful in having sponsors supply  
8 drug but the whole landscape is shifting. And  
9 until we get these studies done and until the  
10 landscape shifts to where payers are satisfied or  
11 need to be satisfied with the data we provide,  
12 there's going to be an access problem in addition  
13 to just access to trials.

14 DR. PAPPO: Donna?

15 MS. LUDWINSKI: I'm curious on both the FDA  
16 perspective and the industry perspective about  
17 moving these trials earlier, which we all agree  
18 should be done. What's the impact when these  
19 agents are dropped for adults? What do you expect  
20 is a likely outcome? Will there be more drugs that  
21 are shelved that might have shown some efficacy in  
22 children but they're dropped because of adults, and

1 it doesn't work?

2 DR. BOLLINGER: I'll go first just to say  
3 that if they do move up earlier and they start  
4 showing promise in the pediatric population, we'll  
5 still have the PREA requirement, although if the  
6 submission isn't made for the adult population, I'm  
7 not sure where that leaves us. But hopefully if do  
8 see signals, we'll proceed.

9 I know that even with a couple of our  
10 molecules that we abandon the adult trials, NCI or  
11 NIH was actually continuing to study the products  
12 in the pediatric population. But there is that  
13 little twist that if the application is not  
14 submitted for the adult population, then does the  
15 PREA requirement really apply because the PREA  
16 requirement comes into effect when the application  
17 is approved.

18 Right, Dr. Reaman?

19 DR. REAMAN: Actually, the PREA requirement,  
20 the requirement, yes, but the initial pediatric  
21 study plan, actually that requirement comes at the  
22 end of phase 2, so before an application comes in.

1 And most of those study plans, we would envision  
2 that trials are already designed and trials were  
3 already approved by the agency and maybe even  
4 enrolling patients.

5 But I wanted industry to go first with the  
6 response because we won't have a mechanism that  
7 provides the authority for the agency to do  
8 anything beyond that. But my hope and expectation  
9 would be that despite the fact that pediatric  
10 cancer may be a small market and a minimal force,  
11 it's still a force, and there are other orphan  
12 diseases that some companies have capitalized and  
13 used as significant forces to develop drugs for  
14 small populations.

15 So I would be hopeful that something that  
16 might be shelved for adult development where there  
17 is evidence of activity in the pediatric population  
18 would continue to be developed. And that's another  
19 potential role for public-private partnerships. I  
20 know I'm on a public-private partnership roll  
21 today, but that's what it's going to require.

22 DR. BOLLINGER: One of the other things that

1 we can consider is if the product is dropped for  
2 development in the adult population but continues  
3 in the pediatric population, there would be an  
4 opportunity for a pediatric priority review  
5 voucher. So there still are some incentives that  
6 would encourage industry to continue forth with the  
7 pediatric studies alone.

8 DR. PAPPO: Julia?

9 DR. VASSAL: So I think in terms of  
10 accelerating testing in children, we all look to,  
11 for example, the larotrectinib study as one of the  
12 perfect studies where pediatrics was involved from  
13 the get-go in the initial trial. But oftentimes  
14 when industry and adults are speaking together  
15 about the early phase trials, there's no  
16 pediatrician at the table, so the question is whose  
17 job is it at this point to bring up pediatrics  
18 early in the conversation. And it seems to me that  
19 at least one part of this legislation may be that  
20 it's actually industry's responsibility to request  
21 that when they're initiating a phase 1 study, that  
22 they asked their adult collaborators to involve the

1 pediatric oncologist who could contribute at the  
2 same time.

3 DR. BOLLINGER: Absolutely. And I do think  
4 it is on industry to look at their portfolio and  
5 see which products will be required to have  
6 pediatric studies. And one of the great things is  
7 that there are actually a lot of pediatric  
8 specialists within industry. I will say we're  
9 taking over the world, right? But there are a lot  
10 of pediatricians within industry to provide that  
11 advice, although it depends on what company you're  
12 talking about.

13 DR. PAPPO: Brenda?

14 DR. WEIGEL: Building on what Dr. Glade  
15 Bender mentioned -- Brenda Weigel, University of  
16 Minnesota -- I think one of the reasons that  
17 larotrectinib was so successful in that space was  
18 that a pediatric friendly formulation of an oral  
19 compound was developed very early and taken into  
20 the phase 1 trial at the onset of investigation.

21 So I think it comes back to an industry  
22 prioritization of formulation development as well.

1 If you really look at that, that's one of the  
2 reasons it was so successful to move forward.

3 I don't know, Dr. Bollinger, if you can  
4 comment on that is an industry commitment in  
5 certain circumstances, if it's oral, for a  
6 pediatric formulation. And I don't know if you can  
7 speak to in the timelines how that could affect the  
8 implementation of trials for children that are very  
9 young age as was exemplified in larotrectinib.

10 DR. BOLLINGER: That's a really great point  
11 and something that we will need to be considering  
12 in the early stages. What you may not know is that  
13 I actually oversee CMC regulatory at Amgen as well,  
14 and so I've had a lot of experience working with  
15 taking some of our oral formulations and turning  
16 them into pediatric friendly formulations. It's a  
17 lot more complicated than you would think,  
18 especially with solid oral dosage forms because  
19 there may be issues with solubility or other  
20 excipients that you have to put into the product  
21 that may not be great for pediatric patients. So  
22 oftentimes with the solid oral dosage forms, it

1 really does take a long time to produce a product  
2 that can be approved by the FDA.

3 Now, when you have a subcutaneous  
4 formulations or IV formulations, that's a much  
5 easier question to answer. But it is something  
6 that will have to be addressed early because of the  
7 time lag required to develop an age appropriate  
8 formulation in younger patients.

9 DR. PAPPO: The last question is Katie.

10 (Dr. Janeway gestures no.)

11 DR. PAPPO: Thank you very much,  
12 Dr. Bollinger.

13 DR. BOLLINGER: Thank you.

14 DR. PAPPO: We will now proceed to a guest  
15 speaker presentation by Dr Elizabeth Fox.

16 **Guest Presentation - Elizabeth Fox**

17 DR. FOX: Thanks, everyone, and thanks to  
18 the chair for this opportunity to speak and address  
19 you from the investigative perspective.

20 My disclosure information was discussed at  
21 the beginning of today's meeting. I would also  
22 like to state that all the data that I'll present

1 on slides today is publicly available, and the  
2 references to those studies, some of which were  
3 done very well by people in this room, are  
4 referenced on each slide.

5 My interpretation of this data and my  
6 opinions, however, are not intended to reflect the  
7 opinions of my institution or cooperative group  
8 affiliations or trial sponsors, and I will discuss  
9 many off-label uses, as is the first statement, in  
10 what we're trying to improve with the RACE Act.

11 We've talked today, and just as a reminder,  
12 research to accelerate Cures and Equity for  
13 Children's Act as part of FDARA 2017 mandates  
14 earlier discussion of pediatric plan for our  
15 oncology drug development or biologic products  
16 directed at specific molecular targets in cancer  
17 that our germane to children. As we've heard  
18 repeatedly this morning, the agents are classified  
19 using a list system, which is very fluid, which  
20 includes relevant, non-relevant, or other. I see  
21 this as an important next step in the opportunity  
22 for collaboration among U.S. government agencies,

1 the European Medical Association, PDCO, global  
2 pharmaceutical industries, academic investigators,  
3 patients, and policy advocates.

4 This issue is particularly important, as we  
5 can see on this slide, on oncology drug approvals  
6 over the decades with cumulative oncology, new  
7 molecular entities plotted as a function of the  
8 decade, and as you can see, the rapid exponential  
9 growth and annual average of oncology drug  
10 approvals. Back in the 1950's, the average was  
11 about one per year. Between 2011 and 2018, that  
12 average is nearly 11 per year.

13 When we look at this more closely at  
14 anti-cancer drugs, we can see that these are  
15 falling into the two classes we'd expect, this  
16 early rise of small molecules, primarily tyrosine  
17 kinase inhibitors, and in recent years the  
18 increasing prevalence of biologic agents. The  
19 chart on the left-hand side of the slide just looks  
20 at the mechanism of action and the generic name  
21 stem that helps us organize these drugs with some  
22 degree of precision.

1           This slide is well known to many in the room  
2 and reminds us that cancer is a rare disease in  
3 children. Each year, under 16,000 children in the  
4 United States are diagnosed with cancer, and it's  
5 important to remember that the average age of  
6 diagnosis is 6 years of age. If we look more  
7 carefully at how these 16,000 children are divided  
8 by diagnoses here in the color-coded pie graph and  
9 the corresponding color-coded chart, you can see  
10 that children with lymphoblastic leukemia comprise  
11 20 percent of those children diagnosed. And if we  
12 look a little bit more closely, we can see that the  
13 common age for those children is less than 8 years  
14 of age.

15           Skipping down the list, you can see that  
16 there's a subpopulation of children with AMO who  
17 are very young. Patients with neuroblastoma tend  
18 to be young. Patients with Wilms tumor and other  
19 kidney cancers tend to be young, but there is an  
20 older age population for some specific types of  
21 cancer of the kidney, and patients with  
22 retinoblastoma are also very young.

1           If we look a little bit more closely at  
2 Hodgkin's lymphoma, the other end of the spectrum  
3 for acute myeloid leukemias, osteosarcoma, Ewing  
4 sarcoma, thyroid cancer, and melanoma, these are  
5 older children and adolescents. Really beginning  
6 to speak to if you look carefully at the disease  
7 you'd like to treat or the molecular  
8 characterization, you may be able to understand  
9 what age group you should target, and this will  
10 directly impact questions such as formulation and  
11 patient access to drugs.

12           Finally, if you look at some of the other  
13 listed diagnoses here, you see that non-Hodgkin's  
14 lymphoma, rhabdomyosarcoma, and a few others have a  
15 large age range, zero to 19 years of age, which is  
16 how these 16,000 children were categorized in that  
17 age group. You can see these diagnoses span the  
18 entire age group. But if you were to look  
19 carefully at the subtypes of these types of cancers  
20 in children, you would see that these two have age  
21 distributions. And as we learn more about the  
22 molecular diagnosis of these, we are likely to be

1 able to really hone in on what age group we're  
2 actually talking about for new drugs.

3           So one of the tasks I was given was to talk  
4 about single agents same in-class prioritization.  
5 I think this is among the places where we may  
6 likely have the biggest impact for single and  
7 individual patients, but from a clinical trials  
8 perspective presents many challenges. As we think  
9 about single agents, same in class, we need to  
10 consider the unique aspects of biomarkers in  
11 cancers of children and adolescents; specifically  
12 what is the strength of the oncogenic driver in  
13 each of these specific diseases.

14           Finally on the prior slide, there were 16  
15 percent of the children who are diagnosed with  
16 cancer between the ages of zero and 19 years of age  
17 who are classified as having rare tumors. These  
18 are specifically rare tumors, and addressing those  
19 may be a place where single agents are particularly  
20 relevant as we've heard for larotrectinib. The  
21 number of agents in trials in this rare patient  
22 population will depend on the agent properties and

1 the efficiency of trial design. This relies on our  
2 endpoints, whether they're safety, dosing, or  
3 pharmacokinetics.

4 The status of the biomarker and companion  
5 diagnoses for these various molecular entities is  
6 going to be critically important to how we apply  
7 that to children and how we conduct these studies.  
8 And finally, a topic that we've touched on slightly  
9 but not really delved into is in pediatric cancers,  
10 we have disease-specific response criteria. How we  
11 declare complete response in a patient with  
12 neuroblastoma is very different than how we declare  
13 that in a patient with rhabdomyosarcoma.

14 From an investigative perspective, I really  
15 appreciate the acceleration of new agents into our  
16 patient population. Access is a major issue.  
17 However, I will remind everyone that the RACE Act  
18 for Children defines cures, and in my mind, it  
19 defines cures as the ultimate goal.

20 The majority of childhood cancers will  
21 require assessment of combinations. These we will  
22 need to look at disease-specific backbone therapy

1 because our current curative therapies are  
2 multimodality and cytotoxic. They come at the cost  
3 of high late effects rate, and we would love to be  
4 able to decrease the amount of cytotoxic drugs that  
5 we use, but that is going to be a process over  
6 time.

7 In addition, we're also very interested as  
8 investigators in combinations of targeted agents  
9 for pathway inhibition, which has been alluded to  
10 in this and I understand is likely beyond the scope  
11 of the list, but certainly as an investigator, the  
12 places where we're looking. Finally, as I  
13 mentioned, the consideration for aged distribution  
14 of specific cancers, histologic and molecular  
15 subtypes, should be carefully tracked over the next  
16 few years.

17 In terms of prioritization, there are a few  
18 key points that I think are worth highlighting  
19 here. The evidence of the target drug/response  
20 relationship will need to be looked at in order to  
21 determine how to move forward in children. We're  
22 going to be doing this with less data from trials

1 in adults if we accelerate the pipeline. That will  
2 likely mean an increased reliance on  
3 pharmacokinetic and pharmacodynamic endpoints in  
4 modeling.

5 In addition, physiologic based  
6 pharmacokinetic models and the assumptions that are  
7 used in those to help predict how to start doses in  
8 children need to be looked at carefully. I think  
9 there are emerging data on what some drugs are  
10 doing and some of our sponsors have done to try to  
11 use PBPK modeling, and we need to monitor that  
12 carefully. As I mentioned, the biomarker  
13 validation and companion diagnostics and the status  
14 at the time we enter into pediatric trials will be  
15 important, and I'll have an example of that a  
16 little later.

17 The resources for pediatric cancer specific  
18 animal models should be clearly addressed. As  
19 we've heard, this is likely going to be a private  
20 and academic partnership to bring these forward  
21 with some interesting cooperative groups in the  
22 mix, but I think this is going to be something

1 we're going to need to address as part of  
2 prioritization.

3 As we've heard, toxicity in children is  
4 something that we take very seriously, and the  
5 toxicity profile of new agents must be carefully  
6 looked at, primarily from developmental  
7 considerations and careful assessment of the role  
8 of juvenile toxicology, its pros, its cons, and its  
9 timing in relationship to the cost of those types  
10 of studies. Most importantly from a clinical  
11 perspective, the severity and reversibility of any  
12 toxicity is a key consideration. And finally, as  
13 we think toward combinations that are relevant to  
14 childhood cancers, we need to think about additive  
15 toxicity.

16 Finally, I think pharmacologic properties of  
17 each of the agents and assets need to be looked at  
18 as well as the formulation, and we'll discuss some  
19 examples shortly. And finally, I think agents  
20 where we have a goal for global collaborations  
21 could be and should be prioritized, particularly as  
22 we're working in smaller and smaller groups of

1 patients.

2           With respect to preclinical models, in my  
3 opinion, they are a prerequisite for  
4 prioritization. Some of the best practices that  
5 should be considered when looking at preclinical  
6 models are the selection of the models with  
7 fidelity of the oncogenic drivers of disease and  
8 their ability to evaluate the biomarkers in this  
9 preclinical setting.

10           Drug distribution should be considered;  
11 specifically do we need drugs that cross the  
12 blood-brain barrier for CNS penetration, central  
13 nervous system penetration, particularly for  
14 patients with brain tumors; validation of  
15 concentration thresholds and necessary duration of  
16 inhibition. Demonstrations of the relationship  
17 between target inhibition and activity is something  
18 that clearly belongs, at least in the starting  
19 point, in the preclinical realm.

20           Within our preclinical models, we need to  
21 demand clinically meaningful efficacy thresholds.  
22 Those thresholds cannot be determined in our

1 smallest of patients. Evaluation of pathway  
2 redundancy, innate and acquired resistance, these  
3 can be secondary steps after the initial  
4 prioritization but are really important to  
5 understanding how we're going to move drugs  
6 forward. And finally, if we're going to consider  
7 combinations, the mechanistic rationale for synergy  
8 should be fully explored.

9           Biomarkers are going to be an important part  
10 of how we move molecularly targeted agents into  
11 pediatric patients and are doing so now. As we've  
12 discussed, childhood cancer is a rare disease.  
13 Biomarker selection will further limit the number  
14 of eligible patients and that we have the need for  
15 resources for assessment of agents in pediatric  
16 preclinical and in silico models.

17           We may have to consider limited revalidation  
18 of biomarkers and companion diagnosis in our  
19 pediatric populations; as Dr. Gore discussed, the  
20 role of tumor biopsies and consideration for  
21 recurring tumor biopsies if they can benefit our  
22 patients, and the hope that someday maybe

1 circulating tumor DNA can be part of what we use in  
2 children.

3           The relevance of single genetic aberrations  
4 and genomic signatures from carcinomas in adults  
5 are going to be challenging to use in our pediatric  
6 population, and efforts to look for genomic  
7 signatures in pediatric cancers are going to be  
8 limited by the lack of genomic variability in those  
9 tumors. And finally, the complexities of fusion  
10 transcripts and multiple fusion partners, as was  
11 alluded to by Dr. Janeway, as we look at the  
12 different panels that we are using in our patients,  
13 are we really finding pediatric relevant targets  
14 and are we looking for them?

15           So as an example, I'd like to walk through  
16 the checkpoint inhibition in childhood cancer or at  
17 least a piece of this study. These are three  
18 studies that were presented at the American Society  
19 for Clinical Oncology meeting last year in 2017,  
20 and what you can see is three separate trials were  
21 done. The age for the enrolled patients was  
22 similar. Two of the three trials did not have

1 biomarker selection and did not ask for centralized  
2 PD-1 screening of archival tissues. The  
3 pembrolizumab study did. The adverse events were  
4 fairly comparable across the three agents, and the  
5 first look at the overall response rate in these  
6 patients was very similar and quite frankly  
7 disappointing.

8           When we look more carefully at the  
9 pembrolizumab study, which was biomarker selected  
10 or what we thought was a biomarker selection when  
11 this study opened, it was updated this year at  
12 ASCO, and it was clear that over 800 patients had  
13 tumors screened for this study to enroll 127  
14 patients. And in doing this, the response rate was  
15 still very low, and those responses were in the  
16 disease that we expected to have response,  
17 Hodgkin's lymphoma.

18           So checkpoint inhibition, where we started.  
19 We started with huge enthusiasm from studies in  
20 adults, and we had a lack of preclinical models  
21 that led to multiple large multistrada clinical  
22 trials in children. We were uncertain of biomarker

1 selection, but we certainly learned along the way.  
2 What we learned from these studies is that  
3 single-agent PD-1 or PD-L1 inhibitors are tolerated  
4 for short durations. Many of the children were  
5 exposed, but few had clinical benefit. One of the  
6 important things we learned, however, in this  
7 experience is that multiple studies can  
8 simultaneously accrue when the effort is global.

9           What we would still like to know, with  
10 respect to the Hodgkin's lymphoma cohort, some of  
11 these trials included those patients down to age 12  
12 of what we would consider adult trials, and the  
13 real question in my mind is, can we realize true  
14 collaboration between medical and pediatric centers  
15 overcoming the logistics, the different care  
16 aspects, and the different care models in order to  
17 allow patients in the older age groups to actually  
18 have access to these drugs? Can we define the new  
19 biomarker for PD-1 inhibition, hypermutated cancers  
20 in children, and will those children benefit? And  
21 finally the lingering question of will combinations  
22 work better?

1           So as I think about dose-finding trials or  
2 the earliest trials we're going to be likely asked  
3 to do as part of the RACE Act for Children, we  
4 think about whether we need to do dose escalation  
5 trials or what we would consider dose confirmation  
6 trials, meaning bringing the adult dose directly  
7 into children, and I've outlined a few points here  
8 that are worth considering.

9           We should consider dose escalation in  
10 scenarios where the recommended adult dose is  
11 determined by maximum tolerated dose; that is there  
12 is associated toxicity with this drug. And if this  
13 toxicity is part of a central nervous system  
14 complex or is irreversible or serious organ damage,  
15 we certainly need to understand what the lowest and  
16 appropriate dose is for children.

17           For drugs that are myelosuppressive, there  
18 are fewer and fewer of those in development,  
19 however, we do have to recognize the impact of our  
20 upfront prior therapy in children with relapsed  
21 cancers will impact the role for myelosuppressive  
22 therapy, not only in the future but our ability to

1 assess that in a phase 1 study or early phase  
2 trial.

3 Highly variable pharmacokinetics,  
4 age-related metabolism, or saturable clearance  
5 would lead us to think that perhaps dose escalation  
6 is necessary in a younger patient population. If  
7 we're going to test the formulation or an untested  
8 schedule, we may need to consider dose escalation.  
9 And for childhood cancer that requires a different  
10 target concentration to achieve an end result as  
11 determined in a preclinical model, we may need to  
12 escalate to get to that dose. And finally, as we  
13 heard earlier today, if there's a rationale for  
14 early combination, we could consider that in a dose  
15 escalation trial.

16 If we don't have these things, if the  
17 recommended dose in adults was determined by  
18 pharmacokinetics and was not an MTD, if the  
19 toxicity profile is easily reversible, if the  
20 pharmacokinetics are dose proportional and have  
21 limited variability, and the other factors here  
22 listed, I think we could begin to consider how many

1 trials we need to do or if we can just do a dose  
2 confirmation and immediately try to expand.

3 As we look at the challenges of same  
4 in-class comparisons, I will put up some of the  
5 data that's been presented in publication form by  
6 Dr. Laetsch, as well as abstract form this past  
7 year at ASCO regarding the NTRK inhibitors. As we  
8 know, the larotrectinib study was a biomarker  
9 enriched study. Twenty four patients had been  
10 published from that study; 17 had tumors that  
11 harbored NTRK fusions, and the median age was  
12 4.5 years.

13 As we look at entrectinib for those  
14 features, we see that this was not a biomarker  
15 selected dose escalation study. Sixteen patients  
16 were required, 3 of whom who had tumors which were  
17 fusion positive, and the median age was 10. The  
18 dose-limiting toxicities were really limited in  
19 larotrectinib, but a number of dose-limiting  
20 toxicities were found in entrectinib, and in fact,  
21 the dose of entrectinib that's recommended in  
22 pediatric patients is based on a maximum tolerated

1 dose. And it's 550 milligrams per meter squared  
2 daily, which compares to the adults recommended  
3 phase 2 dose of 600 milligrams per day, which is  
4 approximately equivalent to 350 milligrams per  
5 meter squared, so above the adult recommended those  
6 as a fixed dose.

7           The pediatric recommended phase 2 dose of  
8 larotrectinib is 100 milligrams per meter squared  
9 twice daily with a maximum dose of 100 milligrams,  
10 which is the adult recommended dose, and that is  
11 given twice per day. The most important thing to  
12 our patients is objective response, and through  
13 biomarker selection, larotrectinib produced  
14 objective response in the majority of patients with  
15 fusion-positive tumors. And in the entrectinib  
16 study, all three of the patients who had  
17 fusion-positive tumors did benefit from this drug,  
18 indicating the true need and actual data to support  
19 biomarker selection works, and patients can be  
20 enrolled.

21           The biggest difference between these two  
22 drugs, besides toxicity and the way the trials were

1 conducted, is, as Dr. Weigel pointed out earlier,  
2 the presence of an oral form solution and  
3 formulation for larotrectinib allowed them to  
4 target the appropriate population. You see that  
5 the median age on that study was 4.5 years compared  
6 to 10 in entrectinib. This is in large part  
7 because infantile fibrosarcoma is an important  
8 tumor for NTRK fusions, and those are young and  
9 infant patients who require the oral solution.

10 The pharmacokinetics of these two drugs were  
11 looked at in each of the trials, and target  
12 concentrations were easily achieved at the doses  
13 that were administered to pediatric patients.  
14 You'll notice in the larotrectinib study, the vast  
15 majority of patients got their target dose because  
16 they were able to accurately deliver it with their  
17 oral solution.

18 Formulation has been mentioned a number of  
19 times today, so I'll spend a moment talking about  
20 the important features of formulation. We  
21 recognize as investigators this is an expensive  
22 endeavor. We also recognize as pediatric

1 oncologists what it means to walk into a room and  
2 have a child spit and oral drug back at you.

3 (Laughter.)

4 DR. FOX: This graph on this slide is  
5 actually from an ALK inhibitor study where we  
6 looked at a series of different formulations,  
7 investigational formulations including powder in  
8 capsule, powder in bottle, the formulated capsule,  
9 which is the commercialized form of this drug, and  
10 a pure oral solution.

11 As you can see, when we looked at the dose  
12 normalized exposure area under the concentration  
13 curve on the Y-axis as a function of age and each  
14 of the different colored dots, there's really no  
15 association between these things, which really  
16 helps us to understand that these formulations were  
17 all from an exposure perspective interchangeable.  
18 They were not, however, interchangeable in the  
19 patient's mind.

20 Bioavailability is an important  
21 consideration, and small bioavailability comparison  
22 studies can be done within pediatric studies.

1       However, major bioavailability studies need to be  
2       done prior to pediatric testing. In part, we need  
3       to know if we're in the right target range.

4               Taste and palatability are critically  
5       important to our patients. They're critically  
6       important to the ability to get the drug to the  
7       patients, and some of the other things we've heard  
8       about, the concentration of the oral solution is  
9       important.

10              Taking large volumes of anything, even if it  
11       tastes good, is not going to go well in a 3 year  
12       old. The stability of that formulation, how it is  
13       prepared, what the expectations are for the family,  
14       and how it is administered, and if it has to be  
15       administered immediately after preparation, this  
16       can really constrain a formulation in the  
17       long term.

18              To look carefully at one example of how  
19       formulation impacts how we design trials and how we  
20       interpret the results, this is the drug  
21       cabozantinib, which was recently published. And in  
22       this is the pharmacokinetics. This was a

1 dose-finding study in children where the area under  
2 the concentration curve or exposure is plotted for  
3 each dose level.

4           You can see that although we endeavored to  
5 treat patients at three different dose levels, 30,  
6 40 and 55 milligrams per meter squared, the  
7 exposure in the actual patients when it was  
8 measured was highly variable and probably didn't  
9 differ.

10           When we looked at the average daily dose  
11 that was actually administered to these patients,  
12 you can see that because of the constraints of the  
13 formulation, cabozantinib being delivered as 20  
14 milligrams or 60-milligram capsules, that the  
15 actual daily exposures didn't differ in the first  
16 two dose cohorts. So this was an important lesson  
17 about what we think we're accomplishing with those  
18 escalation and the ability to deliver drugs.

19           Toxicity profile is an important  
20 consideration. As we move into the targeted  
21 therapy age, we can look at both small molecules  
22 and biologics. They are no longer primarily

1 myelosuppressive, but they do have a major impact  
2 on important features particularly for children  
3 such as metabolic changes, such as hyperglycemia,  
4 hyperlipidemia and dyslipidemia. Cardiac impact  
5 with arrhythmias, QT prolongations, changes in  
6 injection fraction, and the changes in growth and  
7 development are something we're all aware of.

8           Similarly for the biologics that are now  
9 later in development in pediatric patients, the  
10 cytokine release syndrome, neuropathies, and  
11 capillary leak, I think the lesson from biologics  
12 in children is that as pediatric oncologists, we  
13 can adapt and we can manage these toxicities with  
14 careful observation.

15           The unique toxicity of growth plate  
16 abnormalities is well described and known and an  
17 ongoing issue for many of these agents. Here is  
18 the comparison of pazopanib, a VEGF and  
19 multityrosine kinase inhibitor, and vismodegib, a  
20 smoothed inhibitor.

21           What you can see here is that for pazopanib,  
22 even though on therapy there was a widening of the

1 growth plates, and a fusion of the growth plates,  
2 that was reversible. However, for the smoothed  
3 inhibitor, it was not. And Dr. Reaman alluded to  
4 this in his opening comments, that this was managed  
5 not only by understanding the toxicity but also  
6 understanding the toxicity and limiting the age  
7 range of patients who could go on to those who were  
8 skeletally mature.

9 I think the best way to manage toxicity  
10 profiles, particularly if we move agents into  
11 children with less adult data, is that serial  
12 evaluations are very important, and the use of  
13 pediatric-specific grading criteria -- for example,  
14 things like hypertension and neuropathy -- are  
15 important considerations as we move forward.

16 So I would say the attributes in my mind for  
17 prioritization and collaboration include  
18 adaptability. The expected prevalence of biomarker  
19 and disease and the primary endpoint determine the  
20 number of sites that will be necessary to conduct  
21 these trials. And perhaps we can move into a model  
22 where additional sites are added after initial

1 safety cohort.

2 Agility. We need to have timely,  
3 scientifically and clinically relevant results and  
4 require shorter protocol lifestyles with rapid  
5 readouts of endpoints and outcome measures.

6 Allegiance. We all have allegiance. We  
7 need to recognize it. We need to recognize it as  
8 stakeholders. And as an investigator, the goal of  
9 cure rather than an individual drug or trial is  
10 very important to me, and I recognize others in the  
11 room may have other allegiances and goals.

12 Importantly, and as was alluded to, a  
13 mechanism to continue assessment of agents without  
14 adult indication is critically important,  
15 especially as we're going to move these evaluations  
16 up sooner, and the pediatric oncology population  
17 and our patients are going to want to have  
18 continued development of some of these agents.

19 Finally, alignment. There is already  
20 academic international alignment on goals and risk  
21 stratification and strategies that is happening.  
22 One example is the recently activated, newly

1 diagnosed hepatic tumors trial, which is an  
2 international trial to address the issues of  
3 hepatic tumors and treat those tumors, which are  
4 very rare, on several continents using the same  
5 risk stratification and the same outcome measures.

6 Notably, there are no investigational agents  
7 on that study, but it demonstrates that academics  
8 and pediatric oncologists are willing to work  
9 together to align our goals and to negotiate to  
10 have international standards.

11 Finally, the future of cancer therapy in  
12 children, increases in preclinical modeling, both  
13 in vivo and in silico, will be helpful to us. We  
14 expect that personalized individualized therapy  
15 will be based on tumor biology. We look forward to  
16 the day where cytotoxic chemotherapy with its acute  
17 and late effects can become extinct and  
18 increasingly a role for all molecularly targeted  
19 immunotherapy drugs through clinical trials.

20 We'll have to accept some of the challenges  
21 of looking at combination therapy and what it will  
22 mean to transition from a cytotoxic backbone to

1 more molecularly targeted drugs. As I've  
2 discussed, age appropriate formulations can be  
3 considered, and it doesn't necessarily have to be  
4 considered for every single drug we want to test  
5 earlier.

6 Finally, toxicity is always an important  
7 consideration for all stakeholders. Chronic oral  
8 outpatient therapy with targeted drugs -- so drugs  
9 with a long half-life -- means that we do have to  
10 watch some of these patients for longer to  
11 understand the toxicity profile.

12 Non-myelosuppressive, chronic non-hematologic  
13 toxicities will be prevalent in this group of  
14 drugs, and we'll have to watch carefully for the  
15 impact on growth and other development.

16 Finally, unknown late effects of this drug  
17 is something that will need to be followed possibly  
18 through registries as we expose children to these  
19 drugs and hope that we improve their quality and  
20 duration of their lives. So with that, I'd like to  
21 thank you.

22 (Applause.)

**Clarifying Questions**

1  
2 DR. PAPP0: Thank you very much, Dr. Fox.

3 We will now take clarifying questions for  
4 Dr. Fox. Please remember to state your name for  
5 the record before you speak.

6 DR. DuBOIS: Steve DuBois. Thanks so much,  
7 Beth. I wonder what your thoughts are on  
8 overcoming this challenge of novel-novel  
9 combinations when both agents are not owned by the  
10 same company.

11 DR. FOX: Thank you for that question,  
12 Dr. DuBois.

13 DR. DuBOIS: It's extremely straightforward.

14 DR. FOX: I want to be optimistic that as we  
15 see the single agent success stories like  
16 larotrectinib and the NTRK tumors, that we can move  
17 to a place where whether it's through some  
18 investigator initiated trials or other mechanisms  
19 in which patients get drugs, that we can garner  
20 enthusiasm for pathway inhibition. And in my mind  
21 that's truly what we have to show, whether that's  
22 through preclinical models or other ways with our

1 patients who understand those, what does it mean to  
2 inhibit the pathway? And I would hope that once we  
3 can determine that we really need to be able to  
4 inhibit multiple nodes on the pathway and through  
5 the legislative efforts to get us early data, that  
6 there may be an increasing opportunity for  
7 collaborations either within the industry or  
8 outside of industry to get those combinations to  
9 our patients.

10 DR. PAPPO: PK?

11 DR. MORROW: P.K. Morrow. I had a question  
12 for you about your slide related to doses and the  
13 dose confirmation trials. And my question was  
14 related to your criteria for non-myelosuppressive  
15 therapy, and the reason I'm asking is because  
16 oftentimes, particularly in the HE [ph]  
17 malignancies, we're able to accept some degree of  
18 myelosuppression, especially when it can be  
19 supported. And I just wanted to get your thoughts  
20 as to whether you would differentiate between the  
21 two types of malignancies for that.

22 DR. FOX: I certainly would. And

1 traditionally in dose-finding studies, we have  
2 separated hematologic malignancies from solid  
3 tumors precisely for that reason in that in the  
4 solid tumor population, myelosuppression is  
5 something we do need to be aware of, particularly  
6 if we want to move down the line into combinations.  
7 But in the hematologic malignancies, obviously that  
8 is not something we can either track, nor do we  
9 want to track.

10 DR. PAPPO: Elizabeth?

11 DR. RAETZ: Beth, thank you for a wonderful  
12 presentation. Just in terms of your thoughts about  
13 agility, I was wondering if you could comment on  
14 the process. So if an investigator at an academic  
15 medical center has what they believe to be  
16 promising preclinical data and they want to bring  
17 that to an industry partner potentially or to a  
18 cooperative group, retreating consortia, do you see  
19 that as a place where there could be some  
20 opportunities for greater efficiency, and any  
21 thoughts on how that process might be more  
22 efficient?

1 DR. FOX: I think that the ability to bring  
2 those ideas forward, in my experience and in  
3 talking to others who do a lot of preclinical work,  
4 the agreements that are set forward with whoever  
5 owns the asset or controls that asset are a very  
6 important key piece to this.

7 So when individual investigators in  
8 academics partner with pharma to test in a  
9 pediatric animal model or other models systems,  
10 agents and assets, if there were a mechanism to  
11 broaden those types of studies so that perhaps we  
12 could include other agents that aren't necessarily  
13 from the same sponsor or a way to compare those  
14 agents would be critically important.

15 That is a large ask in a time when there's a  
16 lot of proprietary information that needs to be  
17 protected, but I think it's going to become  
18 critically important, or if there were mechanisms  
19 to have similar -- and I know that through the  
20 PPTC, there are mechanisms to have potentially  
21 different labs working on using the same type of  
22 strategy to evaluate drugs, so the outcome is a

1 little bit more comparable.

2 DR. PAPPO: Ted?

3 DR. LAETSCH: Beth, thank you for a very  
4 nice -- this is Ted Laetsch from UT Southwestern.  
5 I just wanted to ask you your thoughts on trial  
6 design. And as we may be studying more agents if  
7 this legislation is successful and bringing more  
8 agents to phase 1, do we need to think about where  
9 we set the bar for those early trials in terms of  
10 early signals of efficacy -- noting larotrectinib  
11 as an example, but also crizotinib for ALK fusion  
12 tumors and CAR-T cells for ALL where there was very  
13 early evidence of lots of efficacy -- and avoid  
14 what we've potentially done with the PD-1  
15 inhibitors, where we have exposed hundreds of  
16 patients and use a lot of resources to study agents  
17 that show little efficacy, at least across the  
18 board, do we need to raise the bar in this setting?

19 DR. FOX: In my opinion, Dr. Laetz, I agree  
20 with your statement, and I would say that we do  
21 need to raise the bar. I think that biologic  
22 selection, using biomarker selection is going to

1 put us in a unique place to expect the bar to be  
2 higher. Where exactly that bar is, certainly we do  
3 not want to discount drugs that have -- for  
4 example, as Dr. Gore pointed out, we need longer  
5 periods of duration to know if they're really  
6 effective.

7 When we look back at the PD-1 and PD-L1  
8 inhibitor experience, if you look at how long  
9 patients were on study, very few of them continued  
10 on for a long period of time, one could say we just  
11 weren't patient enough with the drug. But I do  
12 think patients are one of our most valuable  
13 resources, and we have to respect that, and we have  
14 to respect how they move forward. I think the bar  
15 has to be a little bit higher in our clinical  
16 trials. I think it has to be a lot higher in our  
17 preclinical models.

18 DR. PAPPO: Toby?

19 DR. MacDONALD: Toby MacDonald. A lot of  
20 these targeted therapies also hit the normal host  
21 cells, namely the microenvironment cells, like  
22 tumor associated macrophage. These are not readily

1 addressable in preclinical models. Just what are  
2 your thoughts on how we can get at that side of the  
3 coin?

4 DR. FOX: Yes, I don't have a great answer to  
5 that question, Dr. MacDonald. I do have -- I'm  
6 thinking very heavily about the experience in the  
7 PD-1 inhibitors, where we accepted the fact that we  
8 didn't have good preclinical models and expose a  
9 large number of patients; so I think working  
10 towards some of those models or non-traditional  
11 models. I don't mean to imply that every drug  
12 needs to be in a mouse before it gets into a child.  
13 I'm just implying we need some indication as a way  
14 to say for our pediatric targets, this makes sense.

15 DR. PAPPO: Katie?

16 DR. JANEWAY: Very nice talk, Beth. Katie  
17 Janeway from Dana Farber Cancer Institute. One  
18 thing that I have grappled with since this  
19 regulation was passed and as we've developed the  
20 molecular targets of relevance list is the  
21 molecularly targeted agent where the biomarker is  
22 not yet clear and the biomarker is being assessed

1 in the context of early phase trials. The best  
2 example here probably is the DNA damage response  
3 inhibitors right now, ATR inhibitors, checkpoint  
4 inhibitors, PARP.

5 In that setting, the biomarker's not yet  
6 defined, but it will be defined in the context of  
7 the trial, and I worry that that will be to delay  
8 in incorporation into trials in pediatrics because  
9 we won't -- the testing for the biomarker is done  
10 in the context of the trial. We'll then have to  
11 catch up in figuring out whether that biomarker is  
12 present in children.

13 Do you have thoughts about how we do that?  
14 The best example of that is tumor mutational burden  
15 where -- or even PD-1 and PD-L1, where because kids  
16 were not included in those early trials, the  
17 biomarkers were never tested in our cancer types,  
18 so we didn't know how frequent they would be and  
19 whether or not they would predict response.

20 DR. FOX: Obviously, Dr. Janeway, that's an  
21 important question, and I would hope that in the  
22 RACE for Children Act and the mandate to begin

1 discussions earlier, that's part of the discussion.  
2 I think as pediatric oncologists and clinical  
3 trialists, we may need to consider that very  
4 heavily. And I have no problems with trying to do  
5 things in a non-biomarker; if we don't know what  
6 the biomarker is, should we make a leap that we do?  
7 Or should we just constrain the studies so we don't  
8 enroll 150 patients without a biomarker?

9 So could we do these things in parallel as  
10 we're learning more about the biomarkers and  
11 perhaps do a stage study where at the second stage  
12 of the study, before we expand to large patient  
13 populations, should they exist? We know precisely  
14 what the biomarker companion diagnostic is and how  
15 it relates to the pediatric patient population.

16 DR. PAPPO: Steve?

17 DR. DuBOIS: It seems to me that that really  
18 highlights the ongoing critical importance that  
19 academia and academic pediatric oncologists are  
20 going to continue to play in pediatric cancer, drug  
21 development, and biomarker development. So I think  
22 we're going to have to obviously continue to

1 publish our work on biomarkers and continue to pool  
2 our data into national resources, so that as new  
3 potential biomarkers become highlighted by studies  
4 in adults with cancer, we're able to very quickly  
5 say, oh yeah, that does seem to be relevant because  
6 here it is in this database that we've already  
7 built.

8 DR. PAPPO: Malcolm?

9 DR. SMITH: Right. And I think to the PD-1  
10 question, you know, even as these studies were  
11 being done, there were efforts of collecting  
12 pediatric tumors and analyzing for PD-1 by a number  
13 of companies. So it's really important to be doing  
14 that either prospectively before or in parallel. I  
15 do think there will be -- if we're going to be  
16 moving forward in children early, there is going to  
17 be this uncertainty like there was with the PD-1  
18 and PD-L1 targeted agents.

19 In retrospect when we look back, it's what  
20 tumor mutational burden seems to be really, really  
21 important, and our cancers don't have -- and the  
22 childhood cancers have low tumor mutational burden.

1 But going into it, that wasn't necessarily obvious,  
2 and there could be other hypotheses for why a  
3 checkpoint inhibitor might work against the tumor's  
4 expressing an embryonal antigen.

5 So I think there's both a risk and a  
6 potential for gain going in early, but there's  
7 certainly going to be more uncertainty like there  
8 was with the PD-1 and PD-L1 inhibitors.

9 DR. PAPPO: Donna?

10 MS. LUDWINSKI: Donna Ludwinski. I had a  
11 question about what is your opinion with affecting  
12 standard of care? So what's laid out here is  
13 introducing agents that might have efficacy early,  
14 but what is it going to take to do smarter phase 3  
15 studies so that it doesn't take 10 years to answer  
16 a question with this potential for lots of new  
17 agents? And I'm referring back to you pointed out  
18 the goal is cure, and I really appreciated that.

19 DR. FOX: So I think every investigator in  
20 this room would agree that having trials that take  
21 five-plus years to accrue and have endpoints that  
22 read out in three or four years is extremely

1 challenging for our patients. But I do think part  
2 of the answer to that question lies in how we do  
3 the study before phase 3. In some ways, phase 1, 2  
4 or 3 is becoming a little anachronistic, and I'm  
5 feeling a little dated using those terms.

6 But in terms of how do we compare and how do  
7 we get the very best agent to the most number of  
8 patients, I think part of that challenge is going  
9 to lie in the rarity of some of the molecular  
10 signatures and the molecular changes that we're  
11 trying to target. So when we talked about large  
12 MATCH studies or master protocols, those begin to  
13 address in my mind, in part, the logistical  
14 challenges of opening multiple studies.

15 In some ways, perhaps we could do more  
16 effective phase 3 studies with better endpoints,  
17 but we also probably need shorter protocol life  
18 cycles, not only in the phase 3 but also in the  
19 earlier phases 2 and dose finding.

20 DR. PAPPO: Any additional questions or  
21 comments?

22 (No response.)

1 DR. PAPPO: Okay. We will now break for  
2 lunch. We will reconvene in this room in one hour,  
3 approximately 12:40 p.m. Panel members, please  
4 remember that there should be no discussion of the  
5 meeting topics during lunch amongst yourselves or  
6 with any member of the audience. Thank you very  
7 much.

8 (Whereupon, at 11:42 a.m., a lunch recess  
9 was taken.)

10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

A F T E R N O O N S E S S I O N

(12:51 p.m.)

DR. PAPP0: Good afternoon. Welcome back.  
Please take your seat.

We will now proceed with a guest speaker presentation by Dr Hubert Caron.

**Guest Presentation - Hubert Caron**

DR. CARON: Thanks for inviting me to speak here. It really is a pleasure to be present at this meeting and meetings before to really help and push for the best implementation of new legislation. I'm going to talk today about the industry perspective of prioritization pediatric relevant targets and molecules. I'm a principal medical director at Roche/Genentech, and I lead the pediatric development group of our late-stage portfolio.

So I'm a full-time employee of Roche, I own some stocks, and I will not be discussing off-label use or experimental [indiscernible] use of any of our pipeline agents. Explicitly, this presentation describes our views on pediatric drug development

1 and not necessarily the views of companies or other  
2 entities.

3 I will be going through -- I'll skip the  
4 perspective on the current regulatory landscape.  
5 I'll do very short, one or two slides, on revisions  
6 to PREA because the presentation of Dr. Lia  
7 Bollinger -- has done this better than I can. I'll  
8 give you a vision on pediatric drug development,  
9 then I'll focus the majority of my talk based on  
10 pediatric target and molecule prioritization based  
11 on the MOA approach, pediatric developability, and  
12 then touch upon across company prioritization as  
13 well.

14 I'll give you a quick case study, how this  
15 works internally, but also how we can make this  
16 work externally, and then I'll end with the key  
17 messages.

18 The Research Equity Act and the revised PREA  
19 coming out of it, post-FDARA 2017 -- we're crystal  
20 clear as we implement it on both drugs and  
21 biologics. Pediatric studies will be mandatory in  
22 the future. That will be required to develop

1       molecularly targeted cancer investigation plans for  
2       those molecules which are on the lists but also  
3       potentially molecules which are not on the lists,  
4       and that the list of non-relevant targets is  
5       getting smaller and smaller.

6               It's important to realize that for pharma,  
7       there's a big change that our orphan exemption  
8       studies has gone. As you saw with the numbers  
9       Dr. Bollinger presented, it was a real big loophole  
10      in the previous regulation for pharma, that the ODD  
11      designation for the adult indication was a real  
12      quick possibility to go for a waiver in pediatrics,  
13      and this loophole is now repaired with the Research  
14      Equity Act.

15              What's also important to realize is that  
16      studies under the new legislation will have to be  
17      intention-to-file studies, and intention-to-file  
18      studies are very different from what in academia  
19      [indiscernible] trials. Intention to file requires  
20      much more rigor and other ways of implementing  
21      trials than for academic purposes only.

22              The change in landscape tells us that we

1 will be required to submit initial pediatric study  
2 plans for new market implications, submitted after  
3 August 2020, which is pretty quick from a follow-up  
4 point of view, and that those iPSPs have to outline  
5 clinical study designs to evaluate dose finding,  
6 safety, and efficacy of the drug. This will  
7 require relevant preclinical data that would  
8 require pediatric formulation.

9           Although we heard Dr. Reaman comment on the  
10 timing of the actual pediatric formulation used, we  
11 could potentially use a research-only formulation  
12 during phase 1-2, and then time the development of  
13 a definitive pediatric formulation underwritten  
14 request, which would be helpful because you've  
15 heard many times now during this meeting that  
16 pediatric formulation can be relatively easy, but  
17 solid-phase molecules are going to be pretty  
18 challenging and pretty expensive to develop a  
19 definitive pediatric formulation.

20           It might be difficult to get companies to do  
21 this without having any pediatric data. And to do  
22 this before any child has been dosed might be a bit

1 of a stretch, so then phasing it to start with an  
2 extemporaneous formulation for research purposes,  
3 and as soon as the molecule starts to become  
4 promising, then start redevelopment of a definitive  
5 pediatric formulation might be a good way forward.

6 The vision we hold at Roche for pediatric  
7 development is that we really want to provide  
8 children with unmet medical needs with innovative  
9 safe and life-saving therapies. Our mission to  
10 accomplish this vision are that we work towards  
11 early access to medicines with a strong scientific  
12 rationale for children, especially for children  
13 with high unmet medical needs that will increase  
14 treatment options through clinical trials aimed at  
15 pediatric product labeling for children with  
16 cancer. And sure enough, these activities will  
17 also work to ensure that we meet our regulatory  
18 obligations so we can facilitate timely  
19 registrations in adults.

20 Last but not least, one of our  
21 [indiscernible] missions, not only from watching  
22 the science folks but also from our regulatory

1 people and legal department, they said we're going  
2 to facilitate industry innovation and change in  
3 policies in collaboration with all the  
4 stakeholders, including regulatory authorities, to  
5 increase the potential for drug development in  
6 children with cancer.

7 Let's just say the big scheme of things we  
8 think of in Roche for the entire late pipeline in  
9 oncology is how are we going to make decisions here  
10 for children with cancer. The first step is that  
11 we will assess pediatric developability for all our  
12 oncology molecules in late stage to select those,  
13 which we prioritize for inclusion in our iMATRIX  
14 trial, and I'll come back to the details of that.

15 Then we develop phase 1-2 data for children,  
16 and then decide whether not an exceptional case,  
17 there's data potentially enough for direct labeling  
18 or that we add an additional sponsored pivotal  
19 trial or supported academic investigation pivotal  
20 trial. Or too often we'll have to terminate  
21 development due to toxicity reasons. But all of  
22 this is aimed at the endpoint of pediatric

1 labeling.

2 Here is the overview of the iMATRIX design,  
3 which is a gated phase 1-2 approach, which can go  
4 across molecules, which can go across broad  
5 indication of diseases, and which can incorporate  
6 early combinations as well. But the setup is  
7 similar or is identical for different molecules.  
8 It starts off with limited dose finding, including  
9 PK and safety until gate 1, either across all  
10 disease where it makes sense to go or a limited set  
11 of diseases depending on the context of the  
12 molecule and the adult data.

13 As soon as we establish a single molecule  
14 safe dose, then we branch out in different diseases  
15 or different clinical biological entities, where it  
16 makes sense to study the molecule for early  
17 efficacy. We've put an early gate 2 in place where  
18 after 10 to 12 patients, we will assess if there's  
19 a sufficient efficacy signal to move forward in  
20 additional cohort expansions or not.

21 At the end of full phase 2 expansion, the  
22 iMATRIX stops and is on its goals for phase 1-2.

1 And the [indiscernible] of the data will then go  
2 into discussions with academics and health  
3 authorities to decide on pivotal trials for the  
4 molecule in one or more indications.

5 The pediatric molecule developability relies  
6 on four major categories of questions or data. The  
7 first one from a pharma perspective is do we have  
8 or do we expect a regulatory obligation, which with  
9 revised PREA, that landscape has changed  
10 considerably. And it's not only the EU which is  
11 not driving these assessments, but it's also now in  
12 the U.S. with the new obligations very likely that  
13 the U.S. will deliver more obligations to pharma  
14 than Europe or at least earlier obligations to  
15 pharma to develop the molecules.

16 The second set of questions focus on  
17 molecule feasibility, do we see a strong match  
18 based on mechanism of action with pediatric  
19 biology; is this match then happening in diseases  
20 with a strong unmet medical need; is the safety  
21 profile we can deduct from our preclinical juvenile  
22 toxicity studies in the adult profile suitable to

1 move forward in children; and is the PK and  
2 formulation appropriate to be able to start  
3 development in children?

4 The pediatric clinical feasibility  
5 assessment relies mainly on feasibility, can we  
6 recruit sufficient patients for full phase 1-2  
7 development, which hinges on prevalence of matching  
8 patients, but also it's perceived improvement of  
9 standard of care, which really makes a major  
10 difference both in the endpoints we use and the  
11 statistical power, but also in the interest in  
12 academia to recruit patients into trials with  
13 agents with a large perceived improvement over  
14 standard of care.

15 Last but not least, are the competing  
16 molecules in class, either we don't go in pediatric  
17 development or where we expect pediatric  
18 development. And fourth, we checked the potential  
19 for capitalizing on incentives. It's not a major  
20 driver for pediatric development, but it does help  
21 if we can show that there's at least some  
22 likelihood of partial or recoup of the investments

1 we have to make in pediatrics.

2           What I'll focus on now in the next part of  
3 my talk is the more detailed approach and how do we  
4 match the MOA of a molecule with pediatric biology  
5 and what kind of methodologies to put in place both  
6 in the company but also in collaboration with  
7 academics and other companies, which could be  
8 useful for thinking about the list under the new  
9 revised PREA. It all relies on matching of the  
10 molecule biology on that side, and on the other  
11 side, the pediatric biology and actionability of  
12 the target in pediatrics. The stronger the match,  
13 the better the potential.

14           We use this set of questions to determine if  
15 the target is actionable in a pediatric setting.  
16 These questions are not unique. They're used in  
17 [indiscernible] medicine trials as well. It's a  
18 target activated in tumor of interest. Is tumor  
19 survival dependent on the target or the other way  
20 around. If you block the target or hit the target,  
21 does that lead to tumor kill? Less important but  
22 interesting to have is an idea on how resistance

1 occurs when you treat with molecules aimed at a  
2 target, and do we have information on combinations.

3 We categorized our targets in three main  
4 categories because that makes a difference in how  
5 we think about activation of targets, about tumor  
6 dependence on targets, and efficacy data. We  
7 defined this as tumor dependence targets, tumor  
8 delivery targets, and tumor microenvironment  
9 targets.

10 Then tumor dependence splits this in genomic  
11 aberrations and targets with expression, potential  
12 lineage to specific targets. Tumor delivery  
13 targets are mainly the ADCs, but also amino  
14 conjugates or antibodies used to deliver the  
15 molecule tumor target or other means of delivering  
16 to the tumor. And then tumor microenvironment,  
17 immunology, and angiogenesis are the major  
18 components there.

19 The target list is split what you've seen  
20 today in gene abnormality targets, cell lineage  
21 targets, which nicely overlap with our first tumor  
22 dependence classes, and then non-cancer cell

1 targets, which is both tumor delivery and tumor  
2 microenvironment. And the other targets we have  
3 not listed, but they mainly go under  
4 microenvironment or delivery targets as well.

5 For the target actionability, we split in  
6 three major activities. The one is systematic  
7 literature reviews of target actionability, and  
8 I'll show you more details on that. The second one  
9 is an additional in silico work to check for target  
10 prevalence in preclinical series to large  
11 databases. Dr. Reaman showed that there are more  
12 databases out there which we can tap into, both  
13 publicly but also in collaboration with academic  
14 groups.

15 When we have all these data analyzed on one  
16 of our targets or target pathways, we not only can  
17 identify where we have sufficient evidence to move  
18 forward in clinical trials, but also more often  
19 where do we have [indiscernible] evidence, and do  
20 we have gaps in our knowledge, and do we need to  
21 add additional preclinical proof-of-concept  
22 testing, which will then actually reach out to

1 other CROs or academic groups with the right  
2 expertise and the right models to develop  
3 additional data to help us move the molecule  
4 forward in the best way.

5 To structure our thinking on what is  
6 preclinical proof of concept, we came up with eight  
7 modules of data, which ideally would constitute a  
8 complete preclinical proof-of-concept data package.  
9 In practice, things are more patchy and we often  
10 don't have data in all eight modules.

11 Target activation status in clinical series,  
12 then we approve of in vitro models that raise  
13 molecular validation of tumor dependence. The  
14 third one is, as has been done, in vivo models  
15 showing that molecular means target dependence. So  
16 essentially, these are transgenic models that are  
17 in mouse or in zebrafish, or others; and then  
18 molecule sensitivity patterns in vitro, molecule  
19 efficacy data in vivo models, biomarkers, mainly  
20 predictive biomarkers, potential biological  
21 efficacy biomarkers. And then the resistance  
22 mechanisms we studied are rational combinations

1 tested in preclinical models.

2 The approach to target actionability reviews  
3 comes out of my time when I was still in academia  
4 until 2014 and was part of ITC, which is the  
5 European phase 1-2 consortium in pediatric  
6 oncology, where I was leading biology, which was a  
7 large clinical network of academic labs aimed at  
8 bringing these proof-of-concept data packages. And  
9 we didn't have to do the work all over again.  
10 There was potential to use the literature review.

11 The academia was also leading to the  
12 Cochrane group for systemic reviews and clinical  
13 care for pediatric oncology. So why don't we try  
14 to use the Cochrane approach to redo this for  
15 biology to find a way that we at least can  
16 describe, as objective as possible and as complete  
17 as possible, what do we know what do we not know  
18 about a target in pediatric oncology?

19 The steps start with finding reviewers,  
20 potentially two but prefer three or four reviewers  
21 so they can share the work, and then together  
22 perform a very sensitive literature search to find

1 all the papers there are in pediatric oncology on  
2 that target pathway, and agree on which are the  
3 relevant papers which describes the right target in  
4 pediatric tumors. The reviewers independently then  
5 take all those papers, review the papers, extract  
6 the main findings, and categorize the main findings  
7 based on the modules I showed early on and the  
8 disease type, which is described in the papers.  
9 Then particularly appraise the evidence in the main  
10 finding, and any paper can use 1 to 10 or so main  
11 findings.

12 Every main finding calls for experimental  
13 quality, so how strong and how well it's done, and  
14 on the other hand, what is the effect, what's the  
15 quantity of the evidence described in that paper?  
16 Then come back and independently check with the  
17 reviewers for discrepancies, and then adjudicate  
18 the discrepancies based on discussions. Then all  
19 of these main findings per disease per module are  
20 merged together in a final score on how strong the  
21 data are for that tumor, for that specific module.

22 All of this is supported by the R2 data

1 platform, which is in ITCCP4. I forgot to mention  
2 it is no longer academic work, which I took forward  
3 in Roche. This is now within the ITCCP4  
4 consortium, which is a large consortium with  
5 5 pharma, 11 academic sites, and 3 CROs working  
6 primarily on a PDX platform for standardized strong  
7 testing, clinical testing. But a part of the work  
8 they do is also aimed at target actionability, so  
9 we use those investigators to develop the  
10 methodology for these reviews and to also develop  
11 the bioinformatics support of performing those  
12 reviews.

13           So this R2 tool is a pretty intuitive and  
14 nice tool primarily aimed at analyzing genomic and  
15 transcriptomic and epigenic data, but those guys  
16 have also built the tool to support the reviews.  
17 So you can enter the paper references in the tool  
18 with all the reviewers, and each reviewer can  
19 extract its main finding and upload in this tool.  
20 Instead of uploading the [indiscernible] cell file,  
21 you upload them here and score them from quality  
22 and quantity, and then the reviewers can come

1 together. The tool will support checking the  
2 different main findings between reviewers and check  
3 for discrepancies in those findings, and then  
4 adjudicate.

5 We will put together to support and be as  
6 objective and as reproducible as possible. We put  
7 together guidance listings for the evidence quality  
8 in the 8 modules, and we also put together evidence  
9 quantity, rules or cutoffs, to help reviewers be  
10 reproducible in the way that's called, which  
11 doesn't mean these are the perfect truth, but this  
12 is the guidance we use. The endpoint is based on  
13 what reviewers make of it and what reviewers then  
14 discuss together, and what they adjudicate as their  
15 final agreed upon scoring of each of the main  
16 findings of each paper.

17 What then happens behind the scenes is all  
18 of those individual main findings, which address  
19 one disease and one of the 8 modules, those are  
20 merged, and then based on the quality and quantity  
21 scores, averaged across those main findings, and  
22 lead to a final score, which you see here in a kind

1 of heatmap.

2           There are two ways we can use these  
3 heatmaps, either with the 4 colors I show here,  
4 green as being sufficiently researched. Yellow  
5 with evidence, but it's patchy, it's not strong  
6 enough. Red is, yes, that's been research, but  
7 there is no support in that module for that disease  
8 for this specific target, and then white, it is  
9 missing evidence, so there is nothing.

10           What you can see is, for example, this is  
11 MDM2-TP53 review, where we split the target  
12 amplifications in three different findings, p53  
13 functional; is MDM2 amplified, is MDM2 highly  
14 expressed in clinical series. You see the  
15 neuroblastoma, for example. In general, P53 is  
16 functional. MDM2 amplifications occur at a rather  
17 low frequency, and high MDM2 expressions occur  
18 pretty frequently.

19           There is good vitro and vivo molecular  
20 dependence model data, so no molecules involved but  
21 molecular data involved. Compound efficacy in  
22 vitro is [indiscernible] with P53 status, but

1 in vivo, single molecule efficacy is not great.  
2 That's the red. But then in combinations, there is  
3 again strong P53 status dependent efficacy.

4 This is how this quickly reads. It serves  
5 nicely to come up with discussions on which disease  
6 has sufficient evidence to move forward into a  
7 clinical trial, also depending on the assessment of  
8 the medical need in that disease. In some disease,  
9 there is patchy evidence. For example, in synovial  
10 sarcomas, you will notice that there is some vitro  
11 work and some evidence from [indiscernible]  
12 expression, but there is no strong vivo work either  
13 for molecular tumor dependence or for compounds.  
14 So it will typically be a target disease to add  
15 additional data in collaboration before we move  
16 into clinical trials.

17 One more thing we have been adding is, for  
18 example, if you look at high grade gliomas or  
19 medulloblastomas, or neuroblastomas, we know there  
20 are several different biological subsets hidden  
21 under this one histotype. What we've been  
22 developing now is to ensure we can split the main

1 findings into different biological subsets. If you  
2 now would click on a disease name, it splits in 3  
3 or 4 subcategories, which are agreed upon by our  
4 academic experts in the ITCCP4 consortium as  
5 relevant biological subsets, so it can split  
6 quickly and see which evidence is for which subset.

7 On the other hand, if you would click on one  
8 of the colored squares, it will open up the  
9 underlying evidence. So here is the main findings,  
10 which constitute the green score for MDM2  
11 expression neuroblastoma. So you can quickly  
12 assess which are the individual papers and which  
13 are the main findings which underlie the combined  
14 green score here. And you'll see that for each  
15 main finding, there's a description, and the right  
16 upper-end corner, the main finding is the Q, which  
17 is the quality of the evidence score, which is  
18 minus 3 and plus 3, and then the extent of the  
19 data, minus 3 to plus 3, and then the product of  
20 those two in the colored box.

21 What we are currently doing is ensuring that  
22 we look at all academic investigators to ensure

1 that they agree on this methodology, which we've  
2 developed the neuroblastoma as a pilot; that all  
3 our academic investigators of the 11 institutions  
4 now are joining to review the methodology and the  
5 guidance tables so that we then can put together a  
6 white paper on this methodology, including one or  
7 two product reviews we have been performing, so we  
8 then can make this methodology, including R2  
9 support, available to external investigators or to  
10 anybody who wants to use it.

11 The timing is that we are finalizing the  
12 methodology over summer and that the paper should  
13 be written Q3 Q4, and submitted for publication  
14 before the end of the year. So as soon as we  
15 finalize the methodology, we're open to share this  
16 before publication of the paper with any interested  
17 investigators and/or rater authorities, or based  
18 [indiscernible].

19 So this is what I wanted to tell you about  
20 the target [indiscernible] reviews, which together  
21 with in silico work compose the basis of MOA-based  
22 rationale for pediatric development, which is an

1 important part of our pediatric developability  
2 assessment.

3 Here is the example of how we have  
4 structured our developability assessment in peds  
5 within the company. And again, you see the four  
6 categories I discussed with you earlier on: the  
7 regulatory obligations; the molecule feasibility;  
8 the clinical feasibility; and the incentives.

9 We tried to summarize this in one slide so  
10 you get a quick overview per molecule, but also  
11 this is an opportunity to go across our portfolio  
12 three to four times a year to see which molecules  
13 are either ready or strongly enough supported to  
14 move forward in pediatric development, or which  
15 molecules do we have as showstoppers for pediatric  
16 development, and do we need to put a regulatory  
17 de-risking [indiscernible] strategy in place.

18 What we're going to move towards next is  
19 prioritization across molecules and companies  
20 because this works internally, but this also works  
21 across companies and across molecules. And the  
22 example I'm going to use is the accelerate

1 multistakeholder strategy forums, which Professor  
2 Vassal will discuss in more detail. But this is  
3 our experience with how those forums worked with  
4 Roche participation.

5           The accelerate multistakeholder strategy  
6 forums either concern the molecules in the same  
7 class or disease specific forums with different  
8 molecules, different in ways, but then disease  
9 specific. They are truly multistakeholders. There  
10 is an independent organization organizing them, and  
11 they bring together academia-based advocates,  
12 pharma, and health authorities to exchange  
13 information on the molecules and the disease where  
14 they pertain to.

15           We have nicely formatted data showing, based  
16 on description of MOA, safety, pharmacokinetics,  
17 adult efficacy data, stage of adult development,  
18 and availability, or what's the formulation, and is  
19 it suitable for pediatrics, and is there pediatric  
20 formulation available? And then if available, do  
21 we have any pediatric preclinical data or pediatric  
22 clinical data?

1           This kind of formatting really helps in  
2 being able to think across molecules, because if we  
3 leave this to the different, say, molecule content  
4 owners or companies, the format differs widely, and  
5 then it becomes very difficult in a compressed  
6 fashion because these forums typically take a one  
7 and a half day, and if you then do 20 molecules, it  
8 becomes very difficult if there are different  
9 formulas all over the place. So this formatting  
10 thing really helps in being able to quickly go  
11 through different molecules and see similarities  
12 but also see differences between molecules.

13           Up until now, two of those forums have been  
14 run. We've participated in both. In January 2017,  
15 there was a forum on ALK inhibitors from six  
16 different companies, and in November of last year,  
17 there were an accelerated around a BNHL study  
18 forum, which was disease specific, where there were  
19 20 molecules discussed with different MOAs across  
20 15 companies. And in both instances, there was  
21 pretty clear output on what was the most likely  
22 strategy to be successful for children, where it

1 was a clear difference identified between molecules  
2 based on the stage of development, based on PK and  
3 formulation, and also based on preclinical efficacy  
4 data.

5 In September 2018, the preparation was  
6 ongoing to run a immuno checkpoint inhibitor forum,  
7 and Gilles will give much more detailed data on  
8 ACCELERATE, how it works, and what is the potential  
9 for connection between the groups represented here  
10 and ACCELERATE.

11 What I want to give to you is a flavor of  
12 how this works in practice and what has been  
13 happening with our BNHL portfolio and using  
14 ACCELERATE platforms as well as part of our, say,  
15 prioritization exercise there. We need a pediatric  
16 BNHL strategy because BNHL is a relatively rare  
17 disease and is very curable. So that mean that in  
18 relapse refractory BNHL, it's difficult to develop  
19 new molecules. And as you can see, there's a  
20 plethora of molecules targeting BNHL in adults,  
21 which makes prioritization something we need to do  
22 because we can't develop all those molecules in the

1 future, which constitutes an unmet medical need.

2 Here are numbers taken from Tom Gross'  
3 presentation at the ACCELERATE BNHL forum in  
4 November of last year. In adults, there was a  
5 pretty sizeable fraction of BNHL patients, and also  
6 prognosis in adults is less favorable than it is in  
7 pediatrics. In adults, we're looking at 54,000  
8 DLBCLs in Europe and about two-thirds of the number  
9 of patients in the U.S.

10 In pediatric, BNHL is much more rare. There  
11 are only 250 cases in Europe per year, and there's  
12 800 Burkitt lymphoma cases a year, which is pretty  
13 sizable. But if you take into account that with  
14 LMB chemotherapy and with the successful phase 3  
15 with Rituxan [indiscernible] 2 to LMB chemotherapy,  
16 we are now looking at 94 percent one year EFS,  
17 which essentially is cure. So that means that the  
18 relapse/refractory numbers in the middle column are  
19 going down considerably.

20 So we're looking at 40 relapse/refractory  
21 Burkitt patients and 12 DLBCL patients in Europe.  
22 Add to this about two-thirds of those patients in

1 the U.S. So we're looking at around 20  
2 relapse/refractory cases a year of very ill  
3 children who in general will relapse during  
4 chemotherapy or just after the chemotherapy, so a  
5 very difficult group to recruit into  
6 relapse/refractory studies only. You saw on the  
7 previous slide that there are more than 20  
8 molecules in development in the adult space, so  
9 really too many drugs to test and by far not enough  
10 pediatric patients to go around.

11 This was the basis for ACCELERATE to push  
12 for BHNL. And as I showed you, 20 molecules, 15  
13 companies, and the ACCELERATE organizers managed to  
14 compress the whole academic part of the description  
15 of the disease and the medical needs biology into  
16 half a day. The industry presentations took up  
17 about three-quarters of a day, and then there was  
18 one-quarter of a day left for very structured and  
19 good discussions on what comprised molecules with a  
20 potential to move forward in this space and what  
21 were molecules, which were deemed less relevant for  
22 the pediatric space.

1           In our own pipeline, Roche's three molecules  
2 are so-called BNHL-only molecules. So the MOA is  
3 such that it can only be developed in BNHL, and  
4 there are three or four more molecules where the  
5 MOA is broader, but rare are developments in BNHL  
6 as well. So those broader molecules we reason will  
7 go in other diseases, and we don't want to go in  
8 BNHL. But there are three molecules where the only  
9 development option is BNHL.

10           We used the same approach as I described for  
11 ACCELERATE, described earlier, to assess which of  
12 those molecules for us would be the most relevant  
13 for children and which molecules would be less  
14 relevant. We use a stepwise approach to test or to  
15 get feedback on our assumptions and our  
16 assessments.

17           First, we conducted a so-called pediatric  
18 oncology portfolio meeting with EMA, and then we  
19 had an advisory board a month later, and then we  
20 presented at the study forum from ACCELERATE in  
21 November. And this really helps to make our  
22 assessment of the molecules and the prioritization

1 much more explicit.

2           The feedback was pretty clear that only one  
3 class of molecules was deemed to be relevant out of  
4 the three molecules we have in the pipeline, which  
5 was in the T cell specific MOA. And it was also  
6 made clear that in Europe feasibility could not be  
7 a specific ground for a waiver, but with the right  
8 augmentation and the right discussion about  
9 relevance of the MOA and unmet medical needs, this  
10 could be considered, which is clearly different  
11 from the FDA position.

12           This worked quite nicely. In the end, it  
13 was possible to keep up our prioritization to move  
14 one molecule into the planning of clinical  
15 development and put two molecules on hold, on the  
16 back burner.

17           We were successful in negotiating this with  
18 the EU regulatory agency as well, which really  
19 helps, so we don't get a PIP situation as we had  
20 earlier on with the melanoma BRAF situation. So we  
21 now are able to focus our resources on a molecule  
22 not only for us but also to patient advocates and

1 academia, and this makes the most sense. And we're  
2 in the process of activating that clinical  
3 development.

4           So with that, I'm going to leave you with  
5 the key messages from our perspective. We expect  
6 that the revised PREA will lead to the right  
7 approach from our perspective, more MOA-based  
8 rational pediatric drug development and; and  
9 earlier, that we will be forced to be more  
10 proactive and more early, which is a good thing;  
11 and that we really need a strong collaboration  
12 between regulators, sponsors, academic partners,  
13 and patient advocates to perform detailed  
14 preclinical proof-of-concept testing; ensure that  
15 we harmonize our study designs so we don't start  
16 competing our patients; and that we perform strong  
17 molecule prioritization to be able to successfully  
18 implement the new legislation in the U.S. and at  
19 the same time fulfill regulatory obligations in the  
20 EU.

21           We expect innovative trial designs;  
22 establishing clinical development matching

1       pediatric potential; use molecule developability in  
2       an explicit way; and shift mindsets to portfolio  
3       approaches based on MOA, which is really needed to  
4       ensure that we develop the right molecules for the  
5       right disease and thereby contribute to improving  
6       the outcome for children with cancer.

7               With that, I thank you for your attention,  
8       and I'm open to questions.

9               (Applause.)

10                               **Clarifying Questions**

11               DR. PAPP0: Thank you very much.

12               Before we proceed to clarifying questions  
13       for Dr. Caron, I would like to ask if there are any  
14       public hearing speakers here in the room, to please  
15       go register in the table across the hall and then  
16       come back.

17               We will now take clarifying questions for  
18       Dr. Caron. Please remember to state your name for  
19       the record before you speak.

20               Steve?

21               DR. DuBOIS: Thanks so much, and I've got a  
22       couple of questions. It's terrific that Roche has

1 an IPODD [ph] team because as an investigator, it  
2 makes it very clear who to talk to at your company.  
3 How common are these sort of dedicated teams? A  
4 lot of the pediatric oncologists I know who have  
5 gone into industry are sort of dispersed throughout  
6 industry and not clustered in a team really devoted  
7 to thinking about pediatric drug development.

8 So that's one question. Maybe we'll just  
9 start there, and then I can ask my second.

10 DR. CARON: Yes. As far as I know, we are  
11 the only dedicated team in the sense of having the  
12 responsibility for the full development of the  
13 portfolio in children. But talking to Mark Kieran,  
14 who recently moved to BMS, his expectation is that  
15 he will be putting together a similar team at  
16 Bristol-Myers-Squibb, so that's going to be helpful  
17 because I recognize the difficulty for academic  
18 investigators to connect with the right people in  
19 these huge pharma organizations.

20 In many other companies, there are true  
21 pediatric champions. I'm not aware of any, say,  
22 listing of who those people are in companies,

1 potentially something we could consider developing  
2 through ACCELERATE or through health authorities,  
3 because those tend to be relatively stable but not  
4 always known to all investigators that those are  
5 the people to reach out in the companies. And  
6 they're not necessarily the ones who are  
7 responsible for development because, in general,  
8 pharma is organized by molecule, but there are  
9 great assets to guide investigators to the right  
10 person for a molecule or for a set of molecules,  
11 and to align.

12           What will be helpful thinking from the  
13 pharma side is to return the favor and have the  
14 academic community coordinator as well. Because  
15 it's interesting to see, now that I'm in pharma,  
16 how much duplication occurs in communications.

17           One complicated molecule -- and my team is  
18 developing -- is also co-developing with another  
19 molecule from another company, and it's really  
20 interesting to see that we are being approached  
21 four or five times, but then the other company from  
22 the same people also get requests for their

1 molecule individually. And that really takes a lot  
2 of time to ensure that things calm down and we  
3 don't get different teams activating discussions.

4 So from both sides, I think that  
5 coordination of communication would be great. And  
6 I can take it on to work with ACCELERATE and/or bio  
7 and FDR [in] in Europe to see if we can come up  
8 with some kind of repository or listing for  
9 pediatric experts in different companies.

10 DR. DuBOIS: Terrific. And my second  
11 question was about the guidance that Dr. Reaman  
12 talked about this morning about encouraging  
13 adolescent age of eligibility to, quote, "adult  
14 clinical trials," or trying to move that age range  
15 down closer to 12 years of age. And I wonder if  
16 you might comment on how Roche-Genentech is  
17 thinking about that guidance moving forward.

18 DR. CARON: Given the fact that our vision  
19 is that we want to develop all our molecules where  
20 it makes sense in children, we are trying to push  
21 to be able to start up pediatric development  
22 earlier. So for the diseases where we're talking

1     pediatric tumors, the typical embryonal tumors and  
2     pediatric leukemias, it's not very useful to try  
3     and enroll one or two patients in an adult trial if  
4     we are planning on pediatric development.

5             We have disease I call overlap disease,  
6     Hodgkin's or sarcomas. There it depends on the  
7     patient's size. It depends on the adult  
8     development program. If in the adult development  
9     program, those diseases would already be in their  
10    development view, then it could make sense to lower  
11    the age range because those also have an  
12    epidemiology, which the majority of  
13    relapse/refractory cases will be over 12, and it's  
14    unlikely that we're going to put a  
15    pediatric-specific development together.

16            The third is adult epithelial  
17    tumors -- colorectal, breasts, where the indication  
18    is very, very low, which makes it impossible to  
19    develop specifically for children, but where labels  
20    in general are over 18, so access to molecules for  
21    those patient groups is very difficult. So there  
22    we are pushing to help our adult teams to lower the

1 age range to 12, which logistically is not as easy  
2 as we from a pediatric point of view think.

3 Sure enough, we can help with and with sense  
4 and with taking away the belief that it's dangerous  
5 to go in children and that they need different PK.  
6 For adolescents, that's not an issue. But finding  
7 the operational possibilities, general adult  
8 studies are much smaller in number of sites;  
9 finding overlapping site where we can include  
10 adolescents; and find a right co-investigator at a  
11 site. Then again, it's knowing the playing field.

12 DR. PAPPO: Brenda?

13 DR. WEIGEL: Dr. Caron, thank you very much.  
14 That was a great talk. My question actually is  
15 around the Cochrane-like methodology, and I love  
16 it. But do you have any data on timelines and  
17 learning curves? This is a process, and how much  
18 time it takes actually to get to that  
19 prioritization piece and the people involved in it  
20 that's required at training, or how has that been  
21 really implemented?

22 DR. CARON: So in general, the amount of

1 training, I would say we typically try to use  
2 pediatric oncologists to do those reviews, but  
3 essentially those are biology reviews. So what you  
4 need is oncologists who have enough biology  
5 knowledge to be able to perform those reviews.

6 On the other hand, it's the same time kind  
7 of methodology that occurs all the time. What I  
8 did at Roche is run a hallmarks of cancer course  
9 first to educate my clinical scientists, and then  
10 got them into reviews. But with the people who  
11 will be interested in these things in early drug  
12 development, the majority of people are involved in  
13 pediatric [indiscernible] medicine trials. The  
14 majority has been doing preclinical work  
15 themselves.

16 So I would think training is very limited,  
17 as such for the [indiscernible], what you do when  
18 you read an investigational paper and want to find  
19 out whether not for this specific patient a  
20 molecule A or B or C will be a good match. So I  
21 wouldn't say there's a lot of training involved,  
22 but the different mindset is to get all the

1 information and summarize all the information.

2 Now, it depends on the pathway. The MDM2  
3 one, it was 150 papers with three reviewers, and  
4 then there was about three to four main findings  
5 per paper. On the other hand, our 4/43:12 review  
6 was 12 papers or so, so it's relatively easy; PI3  
7 kinase, 350 papers, so it depends a bit. But  
8 that's where three reviewers come in handy. Larger  
9 reviews would take two to three months or so.  
10 Smaller reviews, a BID-4 review I did in two days  
11 because I had to talk to the company.

12 DR. WEIGEL: Because there wasn't much  
13 there, right?

14 DR. CARON: Yes.

15 DR. WEIGEL: And it's very -- I forgot to  
16 identify. Brenda Weigel. Thank you.

17 DR. PAPPO: We have time for two more  
18 questions. Kathleen?

19 DR. NEVILLE: Hi. I enjoyed your talk as  
20 well. One question is about the master protocol  
21 and have you used that just within Roche or are  
22 there any plans -- I'm going to go along the lines

1 of what I did with Dr. Bollinger. Are there any  
2 plans to roll that out to other companies or to do  
3 that collectively?

4 DR. CARON: So two things. Currently, we  
5 use this as stand-alone CTA-90 [ph] not because of  
6 the U.S. situation because there we potentially  
7 could handle this as a master protocol and bring in  
8 new molecules as amendments. But in Europe, the  
9 review process and amendment process doesn't allow  
10 to use major amendments as a process to bring in  
11 entire new molecules because there's not enough  
12 time and not enough discussion in that amendment  
13 procedure to allow for solid evaluation of a new  
14 molecule arm. So that's why we're currently  
15 using -- and two-thirds of our patients we recruit  
16 in Europe, so for us it's not feasible to run as a  
17 master protocol.

18 What we have done is template all the  
19 language and all the approaches we can, and we're  
20 completely open to sharing these templated things  
21 with other companies, and at the last ASCO, at, at  
22 least, two meetings with other companies to discuss

1 sharing. So anybody interested, please approach  
2 me. We're open to sharing.

3 With new insights coming from academia,  
4 where Dr. Vassal is running a precision medicine  
5 trial, he recently told me that he'd been  
6 successful in amending new molecular arms into his  
7 EASMARK [ph] trial. So if this holds for different  
8 countries, then we might reconsider and bring it  
9 again back as a master trial protocol.

10 We also explored potential collaborations  
11 with other companies to bring in different  
12 molecules from different companies into these CDAs  
13 or INDs or master trial. There was some  
14 interesting discussions on legal stuff and IP, and  
15 specifically sharing safety data and sharing  
16 investigative brochures across companies. But with  
17 the new RACE Act, there's a new drive, sort of new  
18 potential to open these discussions again and see  
19 if we can consult [indiscernible].

20 We see this coming now with our own  
21 development and working with another company for  
22 co-developing combinations. If we want to do good

1 combination studies, we cannot go with portfolio  
2 molecules only from whatever company. We need to  
3 be able to go across companies.

4 DR. NEVILLE: And to your point, it doesn't  
5 make sense for three companies to each be getting  
6 four and five phone calls if it's not in anybody's  
7 best interest, especially the patients.

8 DR. CARON: The discussions is one, but then  
9 putting a coordinated trial together with molecules  
10 from several companies, that will be interesting.  
11 We are doing so now for one of our future trials  
12 with one of our molecules, so the lessons we learn  
13 from that I'm going to bring into opening up new  
14 discussions with other companies to see if we can  
15 bring together pipelines and develop across  
16 pipelines.

17 DR. PAPPO: Donna, and then Greg, and then  
18 we're done with questions.

19 MS. LUDWINSKI: Donna Ludwinski. I'm  
20 curious about how you choose your topics for the  
21 strategy forums. I think that concept is a very  
22 exciting idea, and I was just curious how you're

1 choosing those and the timing.

2 DR. CARON: Roche is an active member of  
3 ACCELERATE, but we do not choose the topics.  
4 That's really a cross-stakeholder process where  
5 essentially the steering committee -- which is  
6 composed of 4 regulatory representatives, 2 out of  
7 the U.S. and 2 out of Europe; 4 patient advocates,  
8 2 out of Europe, 2 out of the U.S., 4 pharma, 2 and  
9 2; and 4 academia, 2 and 2. And the steering  
10 committee is the committee where these discussions  
11 about the next forum and the frequency of the  
12 forums takes place to avoid any shred of doubt  
13 about the independent way of how this is done.

14 So I'll leave this to Professor Vassal to  
15 comment in his next talk.

16 DR. REAMAN: I just wanted to follow up on  
17 Dr. DuBois' question about the adolescent guidance  
18 and one of the other potential benefits of  
19 enrolling adolescents on appropriate adult studies.  
20 And really the impetus for this was because of the  
21 orphan designation for many of the diseases that  
22 span the adult and pediatric age group, which

1       exempted PREA requirements for pediatric  
2       investigations. But enrolling adolescents on those  
3       trials allows us to potentially extrapolate data  
4       from older children, adolescents if you will, down  
5       to a younger age group.

6               So that's another possibility for  
7       accelerating, if you will, the evaluation and even  
8       potentially the approval of appropriate drugs for  
9       the pediatric population.

10                               **Open Public Hearing**

11               DR. PAPPO: Thank you very much. We will  
12       now move to the open public hearing session.

13               Both the Food and Drug Administration and  
14       the public believe in a transparent process for  
15       information-gathering and decision-making. To  
16       ensure such transparency at the open public hearing  
17       session of the advisory committee meeting, the FDA  
18       believes that it is important to understand the  
19       context of an individual's presentation. For this  
20       reason, the FDA encourages you, the open public  
21       hearing speaker, at the beginning of your written  
22       or oral statement to advise the committee of any

1 financial relationship that you may have related to  
2 the topics of this meeting.

3 Likewise, the FDA encourages you at the  
4 beginning of your statement to advise the committee  
5 if you do not have any such financial  
6 relationships. If you choose not to address this  
7 issue of financial relationships at the beginning  
8 of your statement, it will not preclude you from  
9 speaking.

10 The FDA and this committee place great  
11 importance in the open public hearing process. The  
12 insights and comments provided can help the agency  
13 and this committee in their consideration of the  
14 issues before them. That said, in many instances  
15 and for many topics, there will be a variety of  
16 opinions. One of our goals today is for this open  
17 public hearing to be conducted in a fair and open  
18 way where every participant is listened to  
19 carefully and treated with dignity, courtesy, and  
20 respect. Therefore, please speak only when  
21 recognized by the chairperson. Thank you for your  
22 cooperation.

1 Will speaker number 1 step up to the podium  
2 and introduce yourself? Please state your name and  
3 any organization you are representing for the  
4 record.

5 (No response.)

6 DR. PAPP0: Okay. We will go to speaker  
7 number 2.

8 MR. AGIN: Good afternoon. My name is  
9 Jonathan Agin, and I am the executive director of  
10 the Max Cure Foundation. I sit on the NCI Brain  
11 Malignancy Steering Committee. I'm an attorney by  
12 trade. I'm also a member of Oncokids Biosciences.  
13 I have no financial conflicts. Much of my comments  
14 are to thank the members of the committee and the  
15 advocacy community for coming together to try and  
16 push forward the efforts under the RACE Act.

17 I lost my daughter to DIPG, a diagnosis that  
18 has had little to no improvement since  
19 classification. So as a member of the advocacy  
20 community, as I've seen so many improvements moving  
21 forward, and then I look at other forms of  
22 childhood cancer that have had little to no

1 improvement, what we try and do is balance out the  
2 success stories with the failures. And I've been  
3 to meeting after meeting in the DIPG community  
4 where the first line of everybody's talk, or  
5 everybody's presentation, or everybody's paper  
6 talks about the dismal prognosis.

7 Juxtapose that with the great stories that  
8 are told about the 80 percent cure rate for  
9 childhood cancer, and we have to ensure that  
10 efforts such as the RACE Act are implemented in the  
11 most aggressive fashion possible without excluding  
12 those cancers which have had little to no  
13 improvement.

14 So whereas on the one hand, I want to  
15 applaud everyone for their efforts in moving this  
16 forward and in understanding the need to have such  
17 efforts from the clinical side of things, the  
18 regulatory side of things, and industry, I implore  
19 everyone involved in implementing the Act and  
20 implementing the strategies behind ensuring that  
21 pediatric drug development does not continue to  
22 lag, to act aggressively, and to ensure that

1 childhood cancers with poor prognoses like DIPG, or  
2 refractory disease, or recurrent disease,  
3 metastatic disease, anything that does not fit  
4 within that tight little pretty bow that can be  
5 captioned as 80 percent survivorship, I implore  
6 everyone to ensure that the Act is implemented  
7 aggressively to ensure that studies move forward  
8 without the amount of wiggle room for waivers so  
9 that drugs are developed, so there is access  
10 earlier to be able to test drugs.

11 I also fully believe that what the RACE Act  
12 does is provide a potential new channel or pathway  
13 for creation of commercialization avenues for drug  
14 development for rare disease populations. And I  
15 think that we'll see, hopefully in the coming  
16 years, avenues for financial resources to be  
17 provided into this avenue of drug development.

18 So at conference after conference and  
19 meeting after meeting, when people talk about  
20 limited disease populations, and they talk about  
21 the fact that for biotech and pharma companies, the  
22 revenue sources, the equation isn't there, I think

1 that through some of these new efforts and some of  
2 these efforts that I'm involved with, and other  
3 members of the advocacy community are involved  
4 with, there is going to hopefully be a new pathway  
5 for commercialization of drugs, which aren't moving  
6 across the goal line in the adult population, and  
7 avenues for incentivizing pharmaceutical companies  
8 and biotechs to develop drugs for smaller disease  
9 populations.

10 Other than that, I appreciate everybody's  
11 attention to this issue, and I think we're moving  
12 in the right direction. Thank you.

13 DR. PAPPO: Thank you very much.

14 (Applause.)

15 DR. PAPPO: Will speaker number 1 step up to  
16 the podium and introduce yourself? Please state  
17 your name and any organization you're representing  
18 for the record.

19 MS. GOODMAN: Thank you. My name is Nancy  
20 Goodman. I have no conflicts of interest. I am  
21 the founder and executive director of Kids v  
22 Cancer, and I'm also a parent of a child who died

1 with cancer. I can speak today on behalf of not  
2 only myself but on behalf of the many families  
3 whose children were afflicted by cancer and who  
4 joined together to advocate for the passage of the  
5 RACE for Children Act.

6           Until now, parents of children with cancer  
7 have watched in frustration as companies developed  
8 novel and promising cancer therapies often for  
9 adult indications only. And I know all of you here  
10 in the room, researchers and even pharmaceutical  
11 executives within industry, have shared my  
12 frustration that access to these experimental  
13 therapies has been quite limited for pediatric  
14 indications.

15           So in response to this concern, we the  
16 pediatric cancer community undertook academic  
17 studies to understand how this policy of the  
18 Pediatric Research Equity Act could be updated,  
19 what the challenges were, and why it didn't match  
20 the scientific advances we have now. We drafted a  
21 bill. We created a grassroots opportunity. We  
22 asked members of Congress to join, and they did.

1       Congressman Michael McCaul; Congressman G.K.  
2       Butterfield; Senator Michael Bennet; and Senator  
3       Marco Rubio were real advocates on our behalf, and  
4       we're grateful for their support.

5               We would also like to thank the FDA, which  
6       was instrumental and critical in the technical  
7       assistance it provided to structure the bill and to  
8       provide input into how this new proposed policy  
9       change would be implemented in their communications  
10      to members of Congress, and we are very grateful  
11      for FDA's support.

12             There are just a couple of substantive  
13      points I would like to add here with respect to the  
14      question today of public comments related to the  
15      guidance that the FDA will be directed to publish  
16      on the RACE for Children Act.

17             First of all, from an advocate's  
18      perspective, the best way to achieve studies that  
19      really will benefit kids is that we protect FDA  
20      authority to make the decisions that it determines  
21      should be made. So to that end, I hope that the  
22      FDA and the stakeholders will all agree that we

1 should interpret the statute to maximize FDA  
2 discretion, so that we don't have the situation  
3 again like we had before, where PREA did not match  
4 the science and we couldn't get pediatric study  
5 plans undertaken because cancers in kids and adults  
6 occur in different organs.

7           Going forward, we don't know where the gaps  
8 will be between the language we drafted and what  
9 scientific opportunities present themselves, and I  
10 really hope that we as a community can agree that  
11 maximizing FDA discretion will achieve the best way  
12 to get the best pediatric study plans for kids. We  
13 know historically looking back that FDA's use of  
14 discretion has been appropriately handled by the  
15 FDA and that we have a lot of confidence in their  
16 expertise, so I thank you for that.

17           I would just like to make one other comment.  
18 I understand that in advocating for the RACE for  
19 Children Act, many members of industry express some  
20 concern about clarity of the legislation, whether  
21 there would be a burden associated with  
22 understanding whether there were standards

1 associated, with whether a molecular target was  
2 substantively relevant to a pediatric indication,  
3 for example, or when a target was on an automatic  
4 waiver list.

5           Again, I just want to assure industry and  
6 ask FDA to continue to apply the processes and  
7 procedures that are already in place under the  
8 Pediatric Research Equity Act and that have been  
9 used by the FDA for non-cancer drugs since 2003.  
10 And those processes provide that the sponsor submit  
11 to the FDA an initial pediatric study plan, a  
12 proposed discussion of how to think about a  
13 particular drug product, and that the FDA and the  
14 sponsor together consider the particular facts of  
15 that drug product so that they can make the best  
16 determination of whether there should be a  
17 pediatric study plan.

18           This has worked since 2003, so there is no  
19 reason to think it can't work now, that the FDA  
20 looking at each initial pediatric study plan can't  
21 make a fulsome and robust and detailed analysis of  
22 whether there is substantial relevance and whether

1 a pediatric study plan should go on.

2 So thank you very much. I appreciate the  
3 opportunity to speak, and I want to thank in  
4 particular the medical officers of the FDA, but all  
5 of you here in working on this very exciting new  
6 venture.

7 DR. PAPPO: Thank you very much.

8 (Applause.)

9 DR. PAPPO: The open public hearing portion  
10 of this meeting has now concluded, and we will no  
11 longer take comments from the audience. The  
12 subcommittee will now turn its attention to address  
13 the task at hand, the careful consideration of the  
14 data before the committee as well as the public  
15 comments.

16 We will now proceed with the charge and  
17 questions to the subcommittee on panel discussions.  
18 I would like to remind public observers that while  
19 this meeting is open for public observation, public  
20 attendees may not participate except at the  
21 specific request of the panel.

22 Would you like to read the next question?

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

**Charge to the Subcommittee**

DR. BRADFORD: Please comment on the proposed additional considerations for which the FDA might engage with industry, clinical investigators, and advocates when making decisions regarding the requirement for pediatric studies of new drug and biologic products based on molecular mechanism of action and their timing.

**Questions to the Subcommittee and Discussion**

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question to discussion.

(No response.)

DR. PAPPO: I guess I'll take a first shot at it if nobody has -- I didn't interrupt anybody? No.

So one of the questions I have is what is the level of evidence that is going to be needed to incorporate a specific agent based on the target list that we have? We for example saw in the presentation from Roche that this IPODD committee identified, for example, rhabdomyosarcoma. If you

1 look at MDM2, there was a lot of variability on the  
2 expression of MDM2.

3 What are the metrics, and what is the role  
4 for the FDA or for this legislation to say this is  
5 a go or no-go, or is that left up to the sponsor  
6 and the investigator? And what is the minimal  
7 level of evidence that we will have to do to move  
8 this forward?

9 DR. REAMAN: Well, I think what was  
10 presented is somewhat tangential to what is  
11 actually required in this legislation, which is  
12 really evaluation of agents, not necessarily in a  
13 particular disease since we do know that some  
14 molecular targets, many of these actually cross  
15 various histologies. So what is mandated by the  
16 legislation is that if the target is relevant to  
17 the ideology, progression of a pediatric cancer, of  
18 one or more pediatric cancers, then a limited  
19 pediatric molecular target investigation is  
20 required.

21 So the level of evidence is something that I  
22 think would be discussed in each individual case

1 that comes before us with the sponsor's initial  
2 pediatric study plan. Hopefully, they have  
3 received input from clinical investigators and  
4 received adequate information to formulate their  
5 plan, which is then evaluated by the agency, and a  
6 plan to proceed with a pediatric investigation, or  
7 a justification for why there is no need or why a  
8 pediatric investigation should be waived. And that  
9 decision would then be made by the FDA.

10 DR. PAPPO: Brenda?

11 DR. WEIGEL: Brenda Weigel, University of  
12 Minnesota. I want to go back to I think a point  
13 that Dr. Fox and Dr. Caron made with regards to  
14 just how we move quickly into early-phase trials.  
15 And I think the real goal -- and I think Dr. Reaman  
16 made this point -- is that the real goal of this  
17 legislation is to move quickly into an early-phase  
18 trial. It's not the end goal of a big randomized  
19 phase 3 trial.

20 One of the issues -- and I come back to the  
21 figure that Dr. Fox demonstrated with the age  
22 distribution of pediatric tumors. And I think that

1 really should drive some of the thoughts here of  
2 how we move forward. And if the target is  
3 something that's really going to occur in very  
4 young children, that should drive a formulation  
5 discussion very early on.

6 I think if it's a tumor type, even if it  
7 spans all the ages but does occur in older children  
8 and adolescents, existing formulations developed in  
9 the adults may be sufficient to do that initial  
10 trial in the pediatric patient population at the  
11 same time when the formulation questions are being  
12 considered by the pharmaceutical industry.

13 So I think what we need to do is really come  
14 at this with as much information about the target,  
15 the age appropriateness, and recognizing the burden  
16 on industry of developing formulations, but also  
17 saying we can probably get enough signal  
18 information in some of the pediatric populations.  
19 But I think learning from the larotrectinib data,  
20 that in infants -- and if that's where you're  
21 really going to have your patient population -- we  
22 have to have formulations from the get-go. And I

1 think that requires the biology to be done in the  
2 preclinical space, and as much as we can encourage  
3 that, the better.

4 So I would encourage the FDA to really work  
5 with industry to say what do we know about the  
6 patient populations and require those early trials,  
7 those very first trials, in the setting that makes  
8 the most sense.

9 DR. PAPPO: Julia?

10 DR. BENDER: Julia Glade Bender. I'm  
11 wondering what the mechanism will be for the  
12 communication between the investigators and  
13 industry vis a vis this legislation in the sense  
14 that oftentimes, we don't know where an asset is in  
15 its pipeline, or there are multiple assets in the  
16 pipeline, and we don't know which will hit the FDA  
17 first because we don't know where they are in their  
18 development.

19 In order to -- I was struck by Dr. Caron's  
20 comment about companies getting calls from the same  
21 investigators, three different companies. And I  
22 think that's really because in the past, if you

1 wanted to test a drug, the drug you tested was the  
2 one you got, and we'd take any drug. So I'm  
3 wondering if there's going to be a mechanism to  
4 allow investigators to know where things are in  
5 terms of development so that we don't call  
6 everybody. If there's a lead compound, I've got to  
7 be honest with you, I usually find out from the  
8 financial literature. I find out from Reuters  
9 before I find out from the drug company. So I  
10 guess it's really about how that's going to be  
11 communicated.

12 DR. REAMAN: Unfortunately, I'm not sure  
13 that that's a mechanism that falls within the  
14 authority of the FDA. I suspect that now that  
15 there will be a requirement for companies to think  
16 about pediatric plans, so when appropriate, when a  
17 target is relevant, they'll have to start  
18 communicating with the investigator community,  
19 hopefully earlier rather than late; and if and when  
20 necessary, communicating with regulators at the  
21 same time. And hopefully doing this on a global  
22 perspective so that they speak with U.S. -- or

1 North American -- and European investigators, and  
2 other investigators from other parts of the world  
3 since products are globally developed.

4 But I don't think there's a mechanism that  
5 we can definitely put in place unless we use these  
6 open public meetings, which we have semi-annually,  
7 to talk about what drugs should remain on the  
8 lists, what we should be adding, and what we should  
9 be deleting. And some of that would, I imagine, be  
10 informed by what might be in the pipelines of  
11 various companies.

12 DR. PAPPO: Katie?

13 DR. JANEWAY: Katie Janeway, Dana Farber.

14 Dr. Reaman, in your comments, you mentioned,  
15 both under waiver considerations and also  
16 considerations for prioritization, about frequency  
17 of a particular molecular target. And I just want  
18 to issue a word of caution about frequency because  
19 our current estimates of frequency of potential  
20 molecular targets in pediatric malignancies are  
21 very imprecise given the number of tumor samples  
22 and the range of cancers that have been sequenced.

1           Also, many potential molecular targets are  
2 not recognized or identified and reported on until  
3 there's a good drug. For example, to use the topic  
4 that's come up many times, NTRK fusions, fusions  
5 are very hard to find and people weren't looking  
6 for them until there was a good drug. So I just  
7 want to be careful -- I think implementation of  
8 waivers for rare variance or rare genomic  
9 alterations and de-prioritizing something because  
10 of low frequency I think should be done very  
11 cautiously.

12           DR. REAMAN: That wasn't actually the nature  
13 of my comments. It really related to whether or  
14 not -- not from the standpoint of granting waivers,  
15 but in the context of prioritizing with limited  
16 numbers of patients. And it may necessitate  
17 waivers, but it really was a question of  
18 prioritizing. And I certainly agree with you that  
19 we may not have adequate numbers and adequate  
20 evaluation of the numbers of molecular targets  
21 related to specific gene perturbations, but we  
22 certainly have more than adequate knowledge about

1 some molecular targets and their recurrence in  
2 pediatric cancers like CD19 in ALL as an example.

3 So it was a question of prioritizing and not  
4 necessarily granting waivers just based solely on  
5 prevalence.

6 DR. JANEWAY: Thank you for that  
7 clarification.

8 DR. REAMAN: Sure.

9 DR. JANEWAY: One could even imagine being  
10 creative about trial design such that the first  
11 trial is really to assess the frequency. That  
12 could even be an end point, how frequently does  
13 this occur and how large is the patient population  
14 in pediatrics for which this is a relevant drug.

15 DR. REAMAN: But I will also say that one of  
16 the written comments that we received very late  
17 from the Pharmaceutical Manufacturers Association,  
18 PhRMA, the trade organization, in response -- we  
19 didn't really have a chance because it was received  
20 literally the day before the docket closed -- was  
21 about prevalence and their perception that just  
22 because the target has been demonstrated in a

1 single patient, that that would be enough or  
2 sufficient evidence to say that it's irrelevant to  
3 pediatric cancer.

4 So that was another reason for just  
5 expressing the importance or the reason for  
6 consideration of prevalence in decision-making, but  
7 really more from a priority setting perspective  
8 rather than absolute go/no-go decisions.

9 DR. JANEWAY: I do think we want to prevent  
10 the example at the PD-1/PD-L1, where you screen 800  
11 patients and find out there's a very small number  
12 of patients who actually have that biomarker. So  
13 you might even, as I mentioned before, think about  
14 trial design more broadly in terms of assessing  
15 biomarker in a particular patient population and  
16 deciding that it's actually not feasible; that  
17 that's actually an endpoint of your first pediatric  
18 study, that studying that target is not relevant.

19 DR. REAMAN: Absolutely. And there are many  
20 targets on these lists for which there are no  
21 existing biomarkers that I am aware of. So not all  
22 of these studies are going to be biomarker

1 directed. When there's a biomarker and when we can  
2 do biomarker-directed studies, I think it's  
3 appropriate to do so. But that again shouldn't be  
4 a limiting factor and a sole deciding factor.

5 DR. PAPPO: Malcolm?

6 DR. SMITH: Malcolm Smith. I had two  
7 things. One was a clarification from Dr. Reaman  
8 that I thought I heard the statement that molecular  
9 targeted pediatric cancer investigation should all  
10 be sponsored by industry.

11 So I just wanted to clarify what role the  
12 groups -- like the current Children's Oncology  
13 Group phase 1 consortium and other academic groups,  
14 what role the data that they generate in their  
15 clinical trials could play in meeting regulatory  
16 requirements for these molecular target pediatric  
17 cancer investigations.

18 DR. REAMAN: Well, the confusion might be  
19 around the word "sponsors" and "regulatory  
20 responsibility." The statute refers to industry  
21 requirements, and it's well recognized that many  
22 industry studies are actually performed by the

1 academic community. Clearly, in pediatrics, I  
2 would say most are performed by the academic  
3 community.

4 So studies performed by the COG phase 1  
5 consortium, other early-phase consortia, would  
6 certainly be included in here. But when we talk  
7 about sponsors, we're talking about sponsors who  
8 are planning to submit licensing applications. And  
9 it's for them that the requirement is who's the  
10 sponsor of the study, not necessarily who's  
11 conducting it.

12 DR. SMITH: Okay. Thank you.

13 DR. REAMAN: If that clarifies things.

14 DR. SMITH: Yes. And my second point was to  
15 get back to the issue you raised, Alberto, about  
16 prioritization. And I do think it's an issue that  
17 we really are going to have to grapple with as this  
18 is implemented. When you, again, look at that list  
19 of targets and then think of all the agents that  
20 might meet those targets, too many of the agents,  
21 if we brought them into the clinic, probably would  
22 have very little activity depending on how we did

1 it. Too many of the clinical trials that we did  
2 wouldn't be able to be completed, and then it would  
3 crowd out the most important clinical trials and  
4 the agents that really are kind of the cream of the  
5 crop.

6 So I think the prioritization issue is  
7 really going to be critical. I think the kind of  
8 strategy Dr. Caron described, while we may not all  
9 be able to do it in such detail, I think we'll all  
10 be trying to think of those factors as we say we  
11 really need to focus on this agent for this disease  
12 or for this molecular biomarker.

13 The final point, I think, is it will matter  
14 by disease, and the biomarkers tend to distribute a  
15 lot by disease. Not all are kind of agnostic to  
16 disease. And I think for certain things like ALL,  
17 the bar is very high, so I think unless an agent,  
18 you have some hope that it's going to be inducing  
19 remissions in a substantial proportion of patients,  
20 it's going to be really hard to interest people in  
21 studying that given the alternatives of various  
22 flavors of the CAR-T cells.

1           So for a disease like that, the bar is going  
2 to be very high. When you look at tumors like  
3 Jonathan Agin talked about with the DIPG, the bar's  
4 not going to be nearly as high, so I think that's  
5 another factor that we have to consider. But  
6 prioritization is really going to be the biggest  
7 challenge for the people around this table, FDA  
8 academic, and the pharma and biotech sector.

9           DR. PAPPO: Thank you for your comments.  
10 Courtney?

11           MS. PREUSSE: Hi. Courtney Preusse,  
12 consumer rep and Fred Hutch. Most, if not all, of  
13 the discussion so far from a layman perspective has  
14 been around drug development as well as clinical  
15 trial design, so I hope I'm not too off the mark  
16 with my commentary.

17           Re-reading the discussion point to comment  
18 to the FDA on additional considerations for drug  
19 development and new biologic products to support  
20 pediatric cancer, I just wanted to put out there to  
21 the entire committee to take into consideration  
22 other things that support the development of drugs

1 as well as could improve on diagnoses and perhaps  
2 longevity in these patients.

3 What I'm specifically referring to is  
4 attention to molecular diagnostics, attention to  
5 companion diagnostics, to point of care devices,  
6 things that will help us get deeper into the  
7 scientific questions as to what is causing  
8 these -- anyway, as well as support for  
9 bioinformatics.

10 We see in research studies enormous amounts  
11 of data come out of NGS testing, but then there's  
12 not always the manpower to support interpretation  
13 of that data. And finally, new essays around  
14 prescreening, some of these patient populations  
15 before the clinical trials even open, so that you  
16 know in advance whether or not those patients are  
17 actually going to benefit from the drugs and chemo  
18 sensitivity testing.

19 There's just so much more that goes into it  
20 beyond just the development of the compound, so I  
21 just don't want that to be omitted from the  
22 conversation. I hope that was helpful.

1 DR. PAPPO: I don't think we have any more  
2 time for questions. And I'm sorry, Kathleen. Is  
3 it a really, really important question? Okay.

4 DR. NEVILLE: It's just a quick comment, and  
5 I couldn't have been teed up faster. We've been  
6 sitting over here sort of thinking and talking, and  
7 this is a plea to regulators and advocates that in  
8 an investigator's opinion, there needs to be a  
9 paradigm shift of what is standard of care for  
10 biopsies at relapse. It's standard of care in  
11 adults. It is not standard of care necessarily in  
12 children, and it for sure is not allowed as part of  
13 research protocols.

14 We're sitting here saying we don't know the  
15 prevalence of molecular aberrations, in particular  
16 tumors, yet as an investigator, my hands are tied  
17 behind my back to get that information, and I think  
18 that will greatly slow us down. So as  
19 investigators, we're going to rely on advocates,  
20 industry, and regulators to help push this forward.

21 Thanks, Alberto.

22 DR. PAPPO: I hope you're not upset. Was it

1 a really, really important comment? Okay. If  
2 not -- I want to be fair.

3 (Laughter.)

4 DR. PAPPO: So I'm going to try to summarize  
5 some of the points. A lot of it was just  
6 discussion and clarification, but some of the  
7 points that were brought up is how to move some of  
8 these new compounds into phase 1 trials. One  
9 consideration should be age and the prevalence of  
10 that disease and a specific age group, and that  
11 could potentially dictate which agent is going to  
12 be moved for that specific population.

13 Similar to that, also the tumor type and  
14 what we expect of that specific drug, whether it's  
15 a very highly curable disease and if your bar is  
16 going to be very high to move that agent forward;  
17 or if you have a uniformly fatal tumor, that your  
18 bar is going to be relatively low, and that may  
19 affect how you prioritize a specific agent.

20 Another comment was about communication  
21 between investigators and industry. Although it is  
22 not a direct responsibility of the FDA to address

1 this issue, it is hoped that with this new  
2 legislation, it will be much easier to get  
3 information on which agents are on the pipeline and  
4 that there will be increased communication between  
5 investigators, the FDA, and the EMA.

6 The final issue that was brought up was that  
7 we are not aware -- or we really don't have a very  
8 good idea on the prevalence of specific targets in  
9 the pediatric population, and that perhaps a  
10 strategy of a protocol would be actually to try to  
11 validate or to interrogate what is the prevalence  
12 of a specific target in that population that is  
13 being studied to further plan future clinical  
14 trials.

15 The final comment was to consider other  
16 issues other than drug development itself to  
17 address the clinical trial enrollment and  
18 identification of patients for potentially useful  
19 drugs. And that would be by the development of  
20 molecular companions, expanding bioinformatic  
21 support, and developing novel essays, prescreening  
22 a population that we are pretty certain could

1 potentially benefit from a novel agent.

2 Did I quote everybody correctly? Did I miss  
3 anything, or does anybody want to say anything  
4 else?

5 (No response.)

6 DR. PAPPO: Okay. So now the good news is  
7 that we will now take a 10-minute break, and with  
8 all this water, we will need it. Panel members,  
9 please remember that there should be no discussion  
10 of the meeting topic during the break amongst  
11 yourselves or with any other members. We will  
12 resume at 2:15, 2:16, something like that.

13 (Whereupon, at 2:07 p.m., a recess was  
14 taken.)

15 DR. PAPPO: We will now proceed with topic  
16 number 3, Mechanisms to Assure Efficiency and to  
17 Enhance Global Coordination through International  
18 Collaboration. We will have guest speaker  
19 presentations by Dr. Vassal and Bucci-Rechtweg. We  
20 will hold all of our questions until those two  
21 presentations have been done, and we will start  
22 with Dr. Vassal.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

**Guest Presentation - Gilles Vassal**

DR. VASSAL: Good afternoon. Thank you for giving me the opportunity to share some thoughts on the collaboration and coordination at an international level. I am Gilles Vassal, a pediatric oncologist, and clinical research at Gustave Roussy comprehensive [indiscernible] cancer in Paris. I am president of the ITCC Consortium and chair of the ACCELERATE platform. I will not discuss any drug or any off-patent use of drugs.

We are in the 2018 specific paradox. On the one hand, there are many drugs developed in adults. So far over the last years, it has been waived for the pediatric development of disease of children and adults. And after 10 years of such development, we can say that too many waivers delay pediatric development [indiscernible]. And in addition, there is quite poor access to pediatric patients for those plans run by pharmaceutical companies.

On the other hand, patients with cancer are rare, but they do not [indiscernible] poor access

1 to innovation. Around 10 percent of children with  
2 relapse malignancies have access to innovative  
3 drugs. So the goal is first to base the  
4 development of new drugs for children on science,  
5 matching the knowledge of the science and the  
6 biology of the tumor [indiscernible] with the  
7 mechanisms of action of the drugs in order to meet  
8 the needs of the patients.

9 But this cannot be done without  
10 prioritization, and prioritization should include  
11 biostatistical data but be considering the needs of  
12 the patient, which will be different from the  
13 disease to another one. But the other goal is also  
14 to incentivize the development of specific  
15 pediatric drugs targeting the alteration which are  
16 specific of the pediatric treatments.

17 Now, in 2018, we are a favorable regulatory  
18 environment. On one hand, the RACE for Children  
19 Act, and on the other hand, the implementation in a  
20 few weeks of the Revised Class Waiver List that is  
21 defining in which situation a drug systemically can  
22 be waived. This gives a very favorable regulatory

1 environment to drive the development of new drugs  
2 for children with cancer through science, meeting  
3 the needs.

4 A few years ago, we set up this figure  
5 proposing that at the time a drug is being  
6 evaluated at the preclinical level and enters the  
7 phase 1 setting in adults, generating biological  
8 and preclinical evaluation in pediatric cancer, we  
9 do know to provide sufficient information and the  
10 relevance of the target in order to define whether  
11 or not these drugs should be developed in children  
12 and be the subject of the pediatric development  
13 plan.

14 So early evaluation or mechanism of action  
15 relevant for us, crucial in this setting, to do  
16 that, we need first early pipeline discussions  
17 between scientists, pediatric oncologists, and  
18 pharma. This is not in the scope of FDA or EMA,  
19 but a real need of early interaction between the  
20 scientists, the pediatric oncologists, and pharma  
21 just to generate as expected with the evidence of  
22 the relevance of a target.

1           There is a need for easy access to data but  
2 also to high-quality clinical platforms. And  
3 finally, there is a need to agree on an  
4 international consensus on what is required in  
5 terms of biological data and preclinical data to  
6 define whether a drug should be developed further  
7 in children. The FDA target lists will guide this  
8 early discussion about the relevance of the target  
9 with regard to a drug being developed for adults.

10           In terms of easy access to the preclinical  
11 platform, there are at the moment two very  
12 important programs, one in the U.S., the Pediatric  
13 Preclinical Testing Consortium and one in Europe,  
14 the ITCC Pediatric Preclinical Proof-of-Concept  
15 Platform, two programs building the assets to  
16 generate preclinical evaluation of compounds. And  
17 recently, at the American Association for Cancer  
18 Research annual meeting, the two programs first met  
19 and defined how to collaborate and [indiscernible]  
20 these important assets to make the generation of  
21 preclinical data most systemically done to  
22 [indiscernible] sieve the decision on

1 [indiscernible] of the targets.

2 In addition, we will host in Europe at the  
3 end of September a meeting with international  
4 experts from academia, from industry, as well as  
5 regulators and advocates to define together the  
6 international scientific consensus on preclinical  
7 evaluations that can be used further as a guidance  
8 by the regulatory authorities.

9 Access to molecular data at diagnosis and at  
10 relapse is now feasible because we have generated a  
11 lot of molecular data for pediatric malignancies.  
12 I just mentioned in this slide, on one hand, the  
13 paper by Grobner in Nature gathering data from 961  
14 pediatric malignancies, which is now accessible on  
15 this website, but also data at relapse; as an  
16 example, the MAPPYACTS program in France and other  
17 countries, generating molecular data at relapse  
18 when patients are [indiscernible] tumor when their  
19 disease relapses or progresses, or the other  
20 program called INFORM developed in Germany, which  
21 is generating at relapse as well as molecular  
22 information.

1           There is a certain need for international  
2 cooperation to run trials where we are addressing  
3 rare diseases in rare patients. To this point what  
4 I think is very important to have in mind is that  
5 there is a quite nice track record of successful  
6 phase 3 academic trials run at the international  
7 level looking at Burkitt lymphoma, hepatoblastoma,  
8 osteosarcoma, and Ewing carcinoma [indiscernible]  
9 tumor. But in terms of academic trial, we are  
10 facing major regulatory and administrative hurdles  
11 that will need, if possible, to be addressed to  
12 facilitate this academic program at the  
13 international level.

14           In addition, most industry trials at the  
15 moment are international, so clearly in terms of  
16 implementation, it is already at the international  
17 level that it is done and it is feasible.

18           But the strong message is that pediatric  
19 oncology drug development is global, and the other  
20 point is that this is necessarily a  
21 multistakeholder endeavor. Indeed, it has been  
22 brand new for everyone around the table to figure

1 out how to develop drugs for children with cancer  
2 and make them available to marketing with  
3 organizations. This was a learning curve over  
4 years but that is now to be pushed forward and  
5 implemented in order to really make this a new  
6 regulatory environment most successful for children  
7 and adolescents with cancer.

8 With this background, we created in 2015 the  
9 ACCELERATE multistakeholder platform. This is an  
10 international platform with academia, with  
11 industry, with parents and patient advocates, and  
12 with regulatory burdens. And we have in this  
13 setting participants from Europe, participants from  
14 the U.S., and even participants from Japan. And  
15 the idea was really to get together all the  
16 stakeholders and figure out how to improve new  
17 oncology drug development for children.

18 The motive of this program is first, there  
19 is a value of working together. The principle,  
20 there is no blame, no shame of what was done. But  
21 the goal is to look at what was done to generate  
22 data and to find solutions. So we've been working

1 on several topics. One is the teenager  
2 participation in trials. The other one was the  
3 implementation of mechanism of action  
4 biology-driven early drug development in children  
5 with cancer. These together define the feasibility  
6 of running such plans.

7 But without, as we said, mechanism of  
8 action, driven development plans cannot be  
9 effective without prioritization of compounds among  
10 all those developed in adults. This is why we  
11 propose to develop a new type of asset, which is  
12 the Pediatric Strategy Forum that Dr. Caron already  
13 presented in his talk.

14 What is a forum? It's a scientific meeting  
15 to share information and to advance learning on a  
16 given topic with everyone around the table. This  
17 is meant to further inform subsequent decisions,  
18 including regulatory decisions. So it's not a  
19 regulatory meeting, but is a meeting where everyone  
20 is in the same room and discuss a topic, and to  
21 really add positive subsequent decisions.

22 In this meeting, we define the need for a

1 given population because clearly the need for new  
2 drugs for children with B mature and mature B-cell  
3 lymphoma is absolutely different from the need of  
4 new drugs for children with DIPG. And this meeting  
5 is to facilitate the prioritization. They don't do  
6 the prioritization, but they facilitate the  
7 prioritization. In this meeting, there is a  
8 dialogue and interaction with all relevant  
9 international stakeholders, and we make it visible  
10 on the website and will publish this in the  
11 peer-reviewed journal.

12 This program is called an agent  
13 [indiscernible] implemented by both the ACCELERATE  
14 platform and the European Medicines Agency. We  
15 demonstrated the proof of concept of this platform,  
16 the first one January 2017. And you're looking at  
17 ALK inhibition pediatric malignancies with a clear  
18 situation where there is evidence of the relevance  
19 of the target. There are many drugs approved or in  
20 development but not a single pediatric  
21 investigation plan in place, and clear activity in  
22 academic trials to treat anaplastic large cell

1 lymphoma and inflammatory tumors.

2           The second meeting was orientated on  
3 disease, and I will not go into the details. But  
4 this was clearly defining that in this population,  
5 94 percent cure rate can be achieved under  
6 treatment, and there is a need for defining how to  
7 address the development of 20 compounds.

8           Based on the positive -- the reason for  
9 these forums would be the third one, which will be  
10 in September, looking at checkpoint inhibitors in  
11 combination. And stemming from the facts which we  
12 see there are many PD-1 and PD-L1 inhibitors, which  
13 are approved and all in development and likely to  
14 be approved later on, where at the same time there  
15 is very limited activity in pediatric malignancies  
16 for the data already generated by such drugs, and  
17 those malignancies are qualified as cold tumors.  
18 So the key question is, should we stop evaluating  
19 these single agents? Should we move more rapidly  
20 to combination and what will be the best way to do  
21 so?

22           We are already anticipating and preparing

1 the fourth meeting in April 2019, which will  
2 address pediatric acute myeloid leukemias. Why?  
3 It's a rare condition. There are many drugs, and  
4 now there are plans, which at the time of their  
5 development, they need to set up phase 3 trials.  
6 And there are clearly not enough patients to really  
7 participate in all these trials.

8 So these forums are very much on a given  
9 topic discussing with each stakeholder at EMA,  
10 including the participation of the representative  
11 of FDA, of the cooperative group from the U.S., and  
12 in addition, U.S. advocates. Based on that, we  
13 propose in the context of the implementation of the  
14 RACE for Children Act, that this will be of value  
15 to have this forum further implemented and more  
16 systematically done.

17 The proposal that we made to both the  
18 European Medicines Agency and the FDA was to  
19 organize these forums based on the processes that  
20 were established over the last 12 months in a way  
21 that there will be a preparatory panel and team,  
22 and for each topic a dedicated program committee

1 with experts from the U.S. and from Europe, and  
2 from the cooperative groups in order to have a  
3 single international forum for each topic.

4 The principle is invitation of people  
5 following expression of interest for academia, for  
6 pharma, and for patient advocates. We propose that  
7 the venue will be in Europe and in the U.S., and  
8 the goal will be to do up to four forums in  
9 pediatric oncology per year. So we think that it  
10 could help discussing about the issue of many drugs  
11 for the same targets and how to best define the  
12 strategy for their development in the pediatric  
13 population.

14 In addition, we will reorganize the  
15 ACCELERATE platform to make the steering committee  
16 international, and this platform is working through  
17 interactive meetings and working groups. It's an  
18 international platform to facilitate and accelerate  
19 the development of pediatric oncology drugs, and we  
20 think that it can help to accelerate the  
21 coordinated global agenda in order to implement  
22 further the development in the new context of the

1 regulatory environment in the U.S. and in Europe.

2 The goal will be to engage more pediatric  
3 oncologists and scientists. The patient advocates  
4 are extremely present, and we are very pleased that  
5 they are working very closely with us. And we  
6 would very much like in this platform further to  
7 engage more pediatric oncologists and scientists  
8 because over the next year, clearly the new  
9 environment is an opportunity to completely change  
10 the way we develop drugs for children based on  
11 science, better meeting the needs of the patients  
12 in order to accelerate starting early the  
13 development of these drugs for these children.

14 In conclusion, I would say that the oncology  
15 drug development for children is definitely an  
16 international initiative and should be done through  
17 international collaboration to better meet the  
18 science and the needs of the patients. And we I  
19 think showed the value of working together with all  
20 stakeholders in what is now favorable regulatory  
21 environment, which I think will change  
22 significantly the landscape. I would like to thank

1 you for your attention.

2 DR. PAPP0: Thank you very much, Dr. Vassal.

3 We will now proceed to the presentation of  
4 Dr. Bucci-Rechtweg.

5 **Guest Presentation - Christina Bucci-Rechtweg**

6 DR. BUCCI-RECHTWEG: Good afternoon. I'd  
7 like to express my thanks to Dr. Reaman for the  
8 invitation to present to you today and also for the  
9 important discussion that we've been having so far.  
10 I've been tasked with addressing the challenges to  
11 global coordination.

12 This is a bit of a take from some of the  
13 previous presentations, but you're going to hear  
14 this presented from the context of how do we get to  
15 global cooperation on agreement of a plan to  
16 develop pediatrics. So it's going to turn a bit  
17 from the science focus to more the regulatory  
18 procedure, the regulatory process, and how we can  
19 actually get a place to in fact even getting to the  
20 point of us getting to our clinical trials.

21 For my conflict of interest, I am an  
22 employee of Novartis Pharmaceuticals, and I am a

1 stockholder of Novartis and that the opinions  
2 expressed in this deck are mine. They are not  
3 representing an industry perspective or even a  
4 company perspective.

5 What I'm going to do is set the scene, the  
6 context, in relation to the regulatory process, and  
7 then what I'm going to do is offer some  
8 considerations for how to implement a global  
9 solutions focused approach, looking at  
10 population-specific opportunities, need-based  
11 opportunities, and also to how we can better think  
12 about streamlining our regulatory pathways, and  
13 then I'll leave with just with a brief thought.

14 Our colleagues so far have done a wonderful  
15 job of spending every presentation previously  
16 talking about this slide. If you look at the dark  
17 blue, we've talked about the fact that in oncology  
18 drug development, there has been this escalation of  
19 pace around the knowledge that's been building  
20 regarding the underlying biological mechanisms  
21 promoting cancer cell growth. And then if you move  
22 to the light blue, this has clearly led to avenues

1 for promising new therapies. And you'll see in the  
2 future slides what this has been doing in terms of  
3 the opportunities for development of numerous  
4 products within certain therapeutic areas.

5 Then when we move to the orange, there's  
6 also been this explosion of understanding as it  
7 relates to genomics and certainly embracing of  
8 precision medicine, which has changed the ways  
9 we've thought about our pipeline, development in  
10 our pipeline expansion. And as a result of that,  
11 it's required us to really think about how to move  
12 the regulatory science base forward, thinking about  
13 smaller and ever smaller populations of patients  
14 for us to be able to evaluate within our  
15 development programs.

16 Critically, as we get to the dark red piece  
17 of the pie, this all needs to be integrated into  
18 the policy that we use as our guide to develop our  
19 therapies in the regulatory policy space, and  
20 importantly when new policies, such as what we've  
21 been discussing today related to the FDARA  
22 Section 504 changes to PREA, we have to understand

1       how best to incorporate all of this into the  
2       regulatory procedures that will help us get to  
3       agreement on the development of these programs.

4               This in particular is important because as  
5       previous speakers have mentioned, when you look  
6       just at immuno-oncology medications and you look at  
7       the promise in the pipeline, just within pharma's  
8       trade organization member companies, we have more  
9       than 200 potential compounds in our pipelines from  
10      phase 1 through the point of application being  
11      submitted, that we have to think about how to apply  
12      this new regulatory process, too.

13              When you think about what that means for  
14      pediatrics, we've even seen that within the  
15      pediatric oncology space, that for  
16      relapse/refractory ALL, we've even been able to see  
17      that these advances have been able to be made in  
18      this population with response rates that we could  
19      have only dreamed of 10 years ago but we're clearly  
20      seeing in the populations when we've got targeted  
21      therapies that can address the pediatric population  
22      of interest.

1           How do we think about this as companies when  
2 we have to put all of this into our considerations  
3 for how we build our pipeline development? I'd  
4 like to thank the IHME, the Institute for Health  
5 Metrics and Evaluation, for allowing me to use  
6 their data. This is a group with funding from Bill  
7 and Melinda Gates Foundation and whose data metrics  
8 are evaluated by the University of Washington.

9           What the IHME does is they calculate model  
10 and forecast based on metrics that are available  
11 through census data, vital statistics and surveys,  
12 publications, registries, and research and  
13 government data. For example, in the U.S., they  
14 use CDC data, and as a result, they're able to  
15 create a global health data exchange. In doing so,  
16 this is how places like the World Bank, the World  
17 Health Organization, is able to look across regions  
18 to really understand the global burden of disease  
19 and where to direct action in order to change  
20 outcomes.

21           So if you look at this slide, look all the  
22 way to the left, what you see is the world. And if

1 you look at the global burden of disease for  
2 children under the age of 5 and the causes of death  
3 in children, there clearly is a huge burden as a  
4 result of what you would expect in this population:  
5 malnutrition, infection. When you look to see  
6 where does neoplasm fall in terms of the world,  
7 there's a light blue bar that's in the middle. And  
8 what you have to look at is how is this disparate  
9 across the regions of the world.

10 So when we've be using global here today and  
11 international here today, we've been talking about  
12 the U.S. and the EU. And clearly there's a huge  
13 disparity in what is global even when we think  
14 about oncology. So we have to think about, when we  
15 are talking about very novel therapies and the race  
16 to ensure we can get to cure, or we can get to  
17 advancing disease, that what we are thinking about  
18 for the U.S. may not be applicable to other regions  
19 of the world where our development pipelines need  
20 to reach into and where access issues are actually  
21 even more profound for our patients who are  
22 desperate for our therapies.

1           There is a slide -- and you'll have access  
2 to these decks -- which goes through and ranks then  
3 where do these different impacts and the global  
4 burden of disease really fall in the rank order and  
5 how they're impacting the population. Neoplasms  
6 range from 6th to 13th in this population. But not  
7 surprisingly for all the experts in this room, you  
8 know that as we go to the 5 to 14 year olds, you do  
9 see a change. We do see a difference in terms of  
10 the global burden of disease.

11           Again, the world all the way over to your  
12 left, the U.S. immediately following, the European  
13 region is about the sixth bar in, but you do  
14 continue to see this great disparity between our  
15 regions. So as developers, when we think about the  
16 global coordination, the global cooperation,  
17 clearly we need the science to drive our strategic  
18 imperatives behind a pipeline, but we do have to  
19 think about these implications for other regions  
20 and where our therapies are going to reach into.

21           So what does this mean, then, overall?

22           Well, if we expand between immuno-

1 oncology -- again, go to the pharma organizations,  
2 member companies -- and we look at just the  
3 therapies that are in development for various  
4 cancers, there's in fact over 1100 at this point.  
5 And this is just, again, the pharma member  
6 companies across the phases of developments. We  
7 have to think about how do we best target to meet  
8 the needs of children that will have the greatest  
9 impact for populations around the world.

10 But this is critically important to  
11 understand. That's just a snapshot of pharma  
12 because if you actually look to the publicly  
13 available data that's in pharma projects, there's  
14 over 5,000 active drugs in development pipelines  
15 for anti-cancer therapist, 5,000. We have to think  
16 about a rational way to move forward and what makes  
17 sense for a pediatric populations because we hit a  
18 situation like this.

19 I acknowledge that this is pooling every  
20 type of variation that could be there for ALL, but  
21 when you look just in clintrials.gov, as in a  
22 snapshot, currently with what's in the database for

1 planned or active studies in and across all types  
2 of sponsorship, there currently is a requirement  
3 for 23,000 patients with ALL. And if you look at  
4 the U.S. pediatric patients diagnosed per year with  
5 ALL, we've got 2600 patients, or if we're looking  
6 at recurrent and relapsed pediatric patients per  
7 year, we have over 500 patients.

8 We can't possibly do this alone in the U.S.,  
9 and clearly we've already heard the statement made  
10 earlier that even these trials are not necessarily  
11 adequate to meet the needs of the patients that are  
12 actually in the clinic. So how can we target what  
13 we need to do to prioritize the right studies,  
14 prioritize the right products, to prioritize the  
15 right mechanisms to be able to in fact impact  
16 change?

17 I had mentioned global for us goes beyond  
18 the U.S. and the EU. This is a paper, the  
19 Financial Times, an article at April 2018, where it  
20 clearly notes -- and if you look at the data, the  
21 Chinese are now emerging as the industry leaders in  
22 the CAR-T space. And in fact, they're already more

1 clinical trials going on right now in China than we  
2 have in the U.S. In fact, there are 116 CAR-T  
3 studies going on in China alone as we speak. And  
4 this is not a surprise. We know what the  
5 population growth is in China and other regions of  
6 the world, and in fact, businesses are pivoting.  
7 There is a change in direction of how we're  
8 thinking.

9 So when we think global, we do have to think  
10 about the influences that go beyond the U.S. and  
11 the EU because this in fact will come more and more  
12 into play for strategies for products that we're  
13 bringing into our pipeline that will ultimately be  
14 available to us to develop for children.

15 I bring up the next slide as an example of  
16 this because as you look across the regions and you  
17 look at how there has been a clear maturation of  
18 the regulatory environment in many regions around  
19 the world, and as companies are beginning to change  
20 their strategic focus based on the emergence of  
21 populations around the world, we're seeing other  
22 markets besides the U.S. and the EU really emerge.

1           In Japan, I focused specifically because in  
2 the 2017 report on the R&D outcomes in marketing  
3 approvals, we saw that in Japan, 18 percent of the  
4 new active substances were approved in 2017 first  
5 in Japan. This changes our dynamics. We have to  
6 think beyond the U.S. and the EU. We can certainly  
7 drive the science with where there's a critical  
8 construction, but we do have to think about the  
9 other markets that are in play.

10           So how can we be solutions focused  
11 understanding this background context for  
12 regulatory strategy? Well, you think clearly we've  
13 heard both from our speakers at the microphone and  
14 the public session, and we've heard from our  
15 panelists and from our members of the committee.  
16 There are some population-specific approaches we  
17 need to take.

18           There are pediatric-only cancers, there are  
19 ultra rare cancers, there are cancers with high  
20 mortality despite research investment, and there  
21 are cancers that are occurring in both adults and  
22 children. And what we need to do is think about

1 solutions that can address all of these needs  
2 because a single policy solution will not possibly  
3 be able to address and solve the issues that we  
4 have.

5 So number one, we've heard very, very nicely  
6 from many of our speakers today about the role of  
7 cooperative groups and importantly how do we expand  
8 and continue to grow our global cooperative groups.  
9 But when we think about pediatric-only cancers such  
10 as retinoblastoma, we have to critically think  
11 about what are the market drivers because what is  
12 really needed for these cancers is a solution that  
13 will continue to drive interest from the innovators  
14 into this space. PREA will not be a solution to  
15 address this issue.

16 For ultra rare cancers such as infantile  
17 fibrosarcoma, clearly market drivers are at stake,  
18 but we also have to think, just as some of our  
19 speakers have spoken about, about non-traditional  
20 quantitative approaches, non-traditional design  
21 approaches. We have to think about the potential  
22 for introducing new regulatory pathways that we've

1 never seen before, such as dedicated pediatric  
2 regulatory pathways that are specific to  
3 pediatrics.

4           Importantly, when we think about these ultra  
5 rare cancers -- I'm going to go back to access very  
6 quickly because it's not on this slide -- we know  
7 right now that we have experiences in Europe where  
8 these alternative approaches are not necessarily  
9 leading payers to reimburse, so we have to think  
10 about those other forces that are out there. We  
11 can develop these therapies. We can get them to  
12 the market utilizing these alternatives and  
13 innovative approaches. But we need the other  
14 players to be engaged. Now, I'm talking about  
15 payers to be engaged, so that they understand this  
16 is our only solution to being able to get this  
17 information for patients.

18           Then we have the cancers with persistently  
19 high mortality such as DIPG. We need to take a  
20 concerted effort to really drive the research and  
21 understanding here, so we can use better target our  
22 molecules, so we can better target our designs to

1 find solutions, which means we need to make a  
2 concerted global investment in the foundational  
3 science to find the solutions.

4 Then finally for cancers occurring in both  
5 adults and children, I think that we've seen  
6 wonderful progress just with the last week with the  
7 FDA draft guidance for industry to consider the  
8 inclusion of adolescents and adult cancer drug  
9 development, but this is the first region in the  
10 world that has such a stated guideline. We have  
11 countries in Europe whose review bodies will not  
12 allow pediatric inclusion until there is adult data  
13 to proceed forward. Again, the environment around  
14 us can be a critical roadblock. We can't just  
15 focus on the science. We have to move the bodies  
16 that can sometimes get in the way of our making  
17 forward progress.

18 We also critically need to think how do we  
19 get to a place of regulatory agreement on key  
20 program design elements; not all of them, but key  
21 program design elements that will facilitate  
22 high-level pediatric plan agreement, and therefore

1 earlier movement of a pediatric plan through a  
2 development pipeline.

3           So we've heard quite a few speakers talk  
4 about global coordination as it relates to unmet  
5 need. We've talked about the fact that this is a  
6 highly competitive environment in cancer drug  
7 development. We've also talked about the  
8 complexities of early-phase drug development  
9 planning primarily because of two issues. Number  
10 one, when we're really early in investigational  
11 drug development or innovative drug development,  
12 we're working with a tremendous number of  
13 assumptions.

14           We don't have a lot of data in hand to drive  
15 some of our trial considerations, and secondly, we  
16 know right now there's an 80 percent attrition in  
17 early-phase drug development. So how can we target  
18 the right, the most likely to be successful, so  
19 that we can really preserve our precious commodity  
20 of patients for the right trials at the end of the  
21 day?

22           Then finally, we don't have a consistent

1 standard of care. That's okay because regionally  
2 there are regional-specific needs, but where can we  
3 agree in some of our key global markets on a  
4 standard that will allow us to have a harmonized  
5 approach to developing these therapies?

6 So number one, we have to continue the  
7 efforts that have already been started. I always  
8 love following Gilles, because he laid out exactly  
9 where we're going right now from the standpoint of  
10 internationally bringing the conversation together.  
11 We need to continue that engagement, but we need to  
12 move this forward. And again, we need to move  
13 beyond just thinking about the U.S. and the EU  
14 because there are other markets that are applied.

15 To that end, I'm going to focus on the EU  
16 because this is the only other region where there  
17 is required development work in pediatrics. And as  
18 everyone in this room I think is well, there's a  
19 very high number of discussions going on with the  
20 European Medicines Agency with companies, almost  
21 400 discussions last year alone on pediatric  
22 programs. And when we look at it by therapeutic

1 area, specifically at what therapeutic areas are  
2 these discussions taking place, with oncology  
3 alone, there were 17 pediatric plans agreed for  
4 commitments in pediatric oncology. So we do need  
5 to think about coordination between our regions.

6 So what does this look like for a company?  
7 To be frank, it's not a straight journey. It's  
8 very complicated for us to figure out how to go  
9 forward, who to move forward with first, who to  
10 speak with first so we can get the best advice to  
11 be able to proceed forward. So if we start with  
12 our product, we know we have two sets of  
13 regulations that compel research. We've got the  
14 European pediatric regulation, and then we've got  
15 the legislative vehicles and the U.S. under PREA  
16 and BPCA.

17 That this then brings us to actors, clearly  
18 the sponsor or the future applicant. And then  
19 within the European Medicines Agency, who do we  
20 target first? Do we target the pediatric  
21 committee, the scientific advice working party, the  
22 CHMP, or even the committee on orphan medicinal

1 products because many of these programs working on  
2 developing are going to go through comp. And at  
3 FDA, it's nice because we can work directly with  
4 the division.

5 But when we think about our strategy, our  
6 strategy shouldn't be based on what is PREA telling  
7 I have to do. When we're thinking as innovators,  
8 we're truly thinking about our product development  
9 strategy. It is an over-arching development  
10 program that may include a PIP, may include a PSP,  
11 and may include a written request, but frankly, our  
12 fundamental questions remain the same. We've got  
13 scientific advice questions that we need to  
14 understand about all aspects of our development  
15 program that may not be applicable to our pediatric  
16 committees, but more so about how we can get this  
17 compound to move forward.

18 So what does that leave us to do? Well,  
19 there are all these different meetings that we  
20 could potentially engage in depending on where we  
21 are. And depending on what type of product we  
22 have, we may be able to get into a special

1 regulatory advice pathway such as PRIME in Europe  
2 or the breakthrough pathway in the U.S. And there  
3 is an opportunity for parallel advice, and I'll  
4 come to that.

5 But ultimately will lead to the pediatric  
6 plan application, which once agreed could go  
7 through multiple iterations of modification and go  
8 through multiple iterations of amendment. And that  
9 ultimately will generate the data that will lead to  
10 the discussion about the applicability of this  
11 therapy, then, in the pediatric population through  
12 labeling.

13 So what does that look like in terms of the  
14 existing timelines and how do we get to the point  
15 of ultimately getting that pediatric plan  
16 application in? Well, if you go by the procedural  
17 timelines in Europe, if we want to seek scientific  
18 advice, it's going to be about a six-month  
19 timeline. And we would suggest this before we  
20 submit a pediatric plan because sometimes they're  
21 very critical questions that we need formulation  
22 guidance. Sometimes we need modeling and

1 simulation guidance. Sometimes we need preclinical  
2 safety guidance.

3           Once we've completed that scientific advice  
4 working a party discussion through a formal  
5 procedure, we're going to go back, we're going to  
6 regroup, and then we're going to put together a  
7 pediatric plan, and we're going to submit our  
8 pediatric investigation plan. And the procedural  
9 timeline to agree on a pediatric investigation plan  
10 is 10 months.

11           Well, if you look at the guidelines in the  
12 U.S., the procedural requirement to agree on a  
13 pediatric study plan under PREA is seven months.  
14 It's got a 210-day review clock on it. That's  
15 assuming you do not receive an inadequate response  
16 letter that will extend your timeline to agree, and  
17 a written request will take approximately three  
18 months. But you need to understand that it is very  
19 rare that these procedures run in parallel, and in  
20 fact they often run back to back.

21           Just by way of anecdote, the most recent  
22 pediatric program at Novartis that was completed

1 through a written request took approximately 18  
2 months to agree ultimately on a final written  
3 request. In the midst of that 18-month agreement  
4 process, we did receive agreement on our pediatric  
5 investigation plan, however, they were not aligned.  
6 It took an additional five years of multiple  
7 modifications and amendments for us to get to an  
8 aligned pediatric program, at which point we could  
9 complete our pediatric program and submit  
10 ultimately our written request.

11 So this is currently not very  
12 straightforward, and what we truly need is a  
13 pathway that helps us to get to some kind of global  
14 agreement at least on the scientific components  
15 that are going to underline our plans.

16 Why do companies want to seek this guidance  
17 early on, and why do we want to go through all of  
18 this work early on? This is data that was  
19 presented by on Regnstrom from the scientific  
20 advice office at EMA in 2017. And based on their  
21 analysis, what they see is when companies seek  
22 scientific advice -- and it is a when; it's not a

1 requirement. But when they do seek scientific  
2 advice and they build their development programs  
3 based on that advice that's received, they have a  
4 much higher likelihood of once an application is  
5 submitted of having a positive outcome.

6           So this is a critical reason why companies,  
7 who are knowledgeable about the process and know  
8 that they have questions for the complex diseases,  
9 want to engage and want to engage early so that  
10 they can understand these critical pieces that  
11 might undermine ultimately their ability to  
12 register their product.

13           So what do we currently have available to us  
14 in pediatrics between the global regulatory  
15 agencies? A wonderful project that was put out is  
16 the pediatric cluster, and it has been referenced.  
17 And through the pediatric cluster, which includes  
18 the FDA, the EMA, Health Canada, PMDA, and the  
19 Australian health authorities, is it facilitates  
20 the regulators' ability to speak to each other  
21 about pediatric programs that have been submitted  
22 through either the European process or the U.S.

1 process. And the hope is that it will enhance the  
2 science underlying the pediatric trials and avoid  
3 exposing children to unnecessary trials. But it's  
4 important to note this is for the regulators only.  
5 Companies are not engaged in the pediatric cluster.  
6 And we might not know even that our product was  
7 discussed in the cluster, so we don't have an  
8 opportunity to ask specific questions.

9 We more recently through the cluster  
10 process, a project called the Common Commentary  
11 process was put in place where companies could in  
12 fact seek a non-binding and informal comment that  
13 came from those cluster discussions. However, this  
14 is not a pathway, again, that allows for the direct  
15 engagement of companies, so we don't have an avenue  
16 to be able to really have that direct  
17 communication.

18 So what avenues do we have? Well, there is  
19 opportunity for parallel scientific advice. Again,  
20 this is between the EMA and the FDA to exchange  
21 views and scientific issues during program  
22 development. Clearly, it can increase the dialogue

1 between agencies and sponsors because this is a  
2 pathway that sponsors are actively engaged in  
3 discussion. And what it's intended to do is to be  
4 put in place for breakthrough drugs or to address  
5 important safety issues, and it can be used for  
6 oncology and for the pediatric population.

7 It's extraordinarily useful for products  
8 that are early in their development where there's  
9 limited precedence. Its purpose is focused on  
10 sharing information and perspectives. It is  
11 extraordinarily resource intensive for all parties  
12 involved, but I would posit as a company who's been  
13 through this process, even when we couldn't get to  
14 a place of alignment, it probably shaved three to  
15 four years off our development timelines because we  
16 knew exactly what the agencies wanted. And we  
17 believe that it's more important to have these  
18 difficult conversations up front. So what's  
19 desperately needed from a policy standpoint is a  
20 greater opportunity to have these types of forums  
21 where we can have this direct conversation with the  
22 regulators.

1           Now, bear with me because the European  
2 mutual recognition procedure is about approval. I  
3 put it up here only as a fact that in Europe, there  
4 was a clear understanding that with all the member  
5 states in the European Union where there were  
6 national procedures for a single member state to  
7 approve a therapy, there was an opportunity  
8 potentially to facilitate the already agreed  
9 approval for a product and to decrease the burden  
10 and the workload amongst other member states.

11           So this is a pathway that's used for  
12 purposes of approval, the mutual recognition of an  
13 approval between member states. And I'm using this  
14 as an example because what is to come with the new  
15 clinical trials regulation in Europe is a similar  
16 theme, but as it relates to agreeing to the  
17 scientific content of a clinical trial application.  
18 So it's getting to the point of the plan in the  
19 agreement.

20           Now, the clinical trial regulation went into  
21 force in 2014, but it's not been fully implemented  
22 because the database necessary for countries to

1 share the reviews of the opinion based on the  
2 review of the application that was handed to them  
3 currently is not completed, so it's hoped that this  
4 will go into effect in 2019. And this is the type  
5 of pathway that I think companies would be very  
6 interested in understanding if we could get to a  
7 place of mutual-ish recognition of a plan that's  
8 been agreed with a recognized competent health  
9 authority.

10 So from my perspective, when we're thinking  
11 about a cooperative, global regulatory pathway to  
12 agree on a pediatric plan, utilizing what we  
13 currently have and expanding it, refining current  
14 pathways that we have, or creating new pathways to  
15 help us get here would be something that I think  
16 would help us tremendously in the pediatric cancer  
17 environment, particularly because we know that  
18 other pathways have been able to do this for other  
19 life-threatening diseases. We know that these are  
20 small populations, so we have to be thinking  
21 innovatively.

22 There are extraordinarily complex treatment

1 paradigms that we need to be able to understand and  
2 are not so simple to discuss product by product,  
3 monotherapy by monotherapy. And because of the  
4 other questions that come along with these types of  
5 developments such as assay development and other  
6 considerations related to prioritization because of  
7 the molecular targeted approach, we do need to have  
8 some consideration of alternative pathways if we're  
9 truly going to get to a more efficient global  
10 cooperative framework to agree on a pediatric plan.

11           So my considerations I put out there are  
12 that there is need for a pediatric dedicated  
13 parallel, true scientific advice pathway and also  
14 easier, some type of pathway we can consider. I  
15 know this is a pipe dream. I know this is a blue  
16 sky request, but mutual recognition is something  
17 that has been done, has been shown to work in  
18 Europe, and I think at the end of the day when we  
19 really want to talk about global cooperation, this  
20 may be something that we should be talking about  
21 robustly as one of the next things that needs to  
22 come from a truly transatlantic trade agreement.

1           So just my parting thoughts for us to move  
2 with today, we clearly are embarking on a new  
3 journey, and we have an opportunity to facilitate  
4 truly meaningful change in how we develop medicines  
5 for children with cancer. Our population, because  
6 they are small, creates an opportunity, a clear  
7 opportunity, for global collaboration avenues in  
8 innovative approaches like we've not been able to  
9 utilize in the past.

10           What we know from other transformative  
11 change that has been successful is it requires  
12 trust. And I think we're finally getting to the  
13 place where we're all at least sitting around the  
14 table. We have to trust that we all want to get to  
15 the same objective, and we have to do this because  
16 the children and their families are depending on  
17 us. We need to see this change be meaningful.  
18 With that, I will conclude.

19           (Applause.)

20                           **Clarifying Questions**

21           DR. PAPPO: Thank you very much. We will  
22 now take questions for Dr. Vassal and Dr.

1 Bucci-Rechtweg. Please remember to state your name  
2 for the record before you speak.

3 Is it possible to put Dr. Vassal on  
4 the screen? There he is.

5 DR. VASSAL: Hi.

6 (Laughter.)

7 DR. PAPPO: Hello.

8 DR. BUCCI-RECHTWEG: Hi, Gilles.

9 DR. PAPPO: Questions?

10 DR. KOLB: Andy Kolb. That was fantastic.  
11 Thank you for that global perspective. As you see,  
12 you gave the example of the CAR-T cells being  
13 developed in China. In those emerging markets,  
14 what kind of threat does that propose to access in  
15 the areas where we're talking about, the EU and  
16 North America? Are you inferring that Chinese  
17 companies are developing drugs for Chinese children  
18 or that traditionally North American EU companies  
19 are going to China as opposed to the FDA and the  
20 EMA for market development?

21 DR. BUCCI-RECHTWEG: Yes. I think it's a  
22 little bit of a mixture of both, but I would say

1 the caution I want to put on here is that companies  
2 that are EU based or U.S. based are still going to  
3 continue to go to those regulatory agencies where  
4 they believe that they are going to get the best  
5 guidance for their ability to move forward with  
6 their products.

7 I think the critical piece to take away from  
8 that is that the emerging markets are clearly a  
9 huge business opportunity for companies, so if what  
10 we're seeing from those regulated agencies who are  
11 becoming much more mature and are very quickly  
12 trying to replicate what we have here in the U.S.  
13 that you might see companies that are pivoting and  
14 wanting to have some requirements that other  
15 agencies may be requesting of us.

16 So we need to not necessarily take on  
17 another market that might not be as mature from the  
18 science standpoint, but we need to keep those  
19 considerations in mind because they may be  
20 inferring some strategic steps and the sequencing  
21 of strategic steps.

22 MS. LUDWINSKI: This question is for you,

1 Dr. Vassal. At the ACCELERATE meeting, are you  
2 going to be involving payers or national health  
3 service representatives in going forward, or have  
4 you already?

5 DR. VASSAL: No. This has been one of the  
6 important messages that was discussed and advised  
7 at the last meeting, that the HDAs [ph] were not  
8 present. But I can tell that we have been trying  
9 over the last years really to have people from the  
10 HDA participating. So far it did not work, but we  
11 hope that in the near future, and especially the  
12 near next meeting, we will have people from the  
13 HDAs because we strongly believe that we need them  
14 on board as well, as well as the ethic committees  
15 really to share all the issues addressing, in  
16 addition, the topic of cost and reimbursement.

17 MS. LUDWINSKI: Fantastic. Thank you.

18 DR. PAPPO: Additional questions? Katie?

19 DR. JANEWAY: Those were excellent  
20 presentations, and I wholeheartedly agree with the  
21 concept of getting broad input for prioritization  
22 and alignment. I guess my question is can we

1 define when that's really necessary, and are there  
2 any concerns or how do we prevent such  
3 multistakeholder discussion from interfering with  
4 the pace of development?

5 DR. BUCCI-RECHTWEG: Go ahead, Gilles.

6 DR. VASSAL: Sure. This is a very important  
7 question. The program is a meeting as a point in  
8 the development. It is not early; it is not late.  
9 Rather, it's an issue that needs to be solved. And  
10 as you saw in the full project, the reasons for  
11 having a forum are not the same. So this is why we  
12 propose that these forums are being set up when  
13 there is a real need expressed by people from  
14 industry, from academia, regulatory people as well,  
15 and parents.

16 We propose in our suggestion for  
17 international pediatric forum to have a process for  
18 choosing the next forums in a way that we will  
19 contact each cooperative group to verify what are  
20 the key issues that need to be addressed. We would  
21 put on the website a possibility for anyone to make  
22 suggestion, and then this will be discussed in our

1 annual meeting with everyone from Europe, from  
2 U.S., including Japan, and then we implement it  
3 with FDA and the EMA.

4           So it's very much at the point in  
5 development when there is an expression of needs  
6 because there is an issue that can be solved or  
7 improved by such a forum. So it's not early  
8 preauthorization activity. At the moment, there  
9 are drugs already generated and they're either  
10 coming or there are many company developments  
11 [indiscernible] that we don't know how to address.  
12 This is where this forum at a given point can  
13 really help in shaping the strategy further and  
14 helping the U.S. with the decisions.

15           DR. JANEWAY: Thank you for that  
16 clarification. And for the record, that was  
17 Dr. Janeway from Dana Farber.

18           DR. PAPPO: Any additional questions?  
19 Brenda?

20           DR. WEIGEL: Brenda Weigel, University of  
21 Minnesota. I want to echo thank you both for a  
22 fantastic presentation. I think this really

1 addresses an incredibly important topic. And  
2 Dr. Vassal just addressed, the forums are really a  
3 little bit later than a fair bit of what the RACE  
4 Act is targeting as sort of that really initial  
5 forum into early-phase trials in pediatrics.

6 I wonder if either of you have ideas of how  
7 and what mechanism could be put in place for  
8 increased collaboration at that sort of preclinical  
9 space. I think, Dr. Vassal, you did mention  
10 there's going to be this fall this first  
11 preclinical connection, but it's that  
12 industry/academia partnership even earlier in the  
13 process and how that might look, and how we could  
14 leverage some of the platforms that are already in  
15 place with ACCELERATE and other mechanisms.

16 DR. BUCCI-RECHTWEG: I'm happy first,  
17 Gilles, and then I'll punt over to you. I do you  
18 think that the existing forums -- there are  
19 existing forums that are in place, and I do think  
20 we do need to make a pivot to precompetitive space  
21 for early discovery and also early molecular target  
22 based work.

1           I do think that there are some existing  
2 relationships that are in place. We need to find  
3 ways that we can expand upon them, and when it  
4 comes to policy expansion, for ways to fund them.  
5 Because I think one of the critical pieces I know  
6 right now has been the fact that we can't get the  
7 appropriate funding into those spaces because  
8 there's, of course, again, not commercial drivers  
9 and individuals who are willing to invest in them.

10           So I think that this is one of the critical  
11 places that we need to direct our attention. What  
12 I can say from the standpoint of the work that  
13 we've done ourselves organizationally within  
14 Novartis is we can't state enough the importance of  
15 the early engagement in our truly novel  
16 innovation-based development that we're doing for  
17 pediatrics.

18           We can't do the work without collaboration  
19 with academia, with basic research, with  
20 platform-based development. That is what helps us  
21 to get to the point of being able to be efficient  
22 to work directly towards pediatric drug

1 development.

2 So I do think the opportunity is there. I  
3 think, Gilles, you're looking to make a pivot  
4 earlier, and I think that that's where we're going  
5 to need to focus if we're going to truly be  
6 successful in those forums being able to inform on  
7 the regulatory decisions, on what plans can be  
8 agreed to move forward.

9 DR. VASSAL: To the question, these forums  
10 are much meant to solve all the issues of  
11 prioritization. In my talk, I first addressed the  
12 issue of early evaluation of relevance of targets,  
13 and this early discussion, that pipeline discussion  
14 that we are proposing, is really a discussion  
15 between scientists and individual companies. And a  
16 forum is useful when there are already, for a given  
17 pathway, one or two drugs with information in the  
18 pediatric setting and many other compounds  
19 developed by other companies on the specific  
20 target.

21 It is echoing something that we identify  
22 through our ACCELERATE and [indiscernible] meeting

1 when discussing with regulatory people and members  
2 of PDCO, we understood that when any company comes  
3 with a proposal, they don't have a vision about  
4 what's going on with the other plan that has been  
5 approved before.

6 So the forum is at a time there is a  
7 relevant pathway or an issue in a disease,  
8 sufficient information to already discuss how to  
9 move forward and trying to figure out whether other  
10 drugs should be developed, and if yes, how. But  
11 clearly, in our forums [indiscernible], this will  
12 not solve all the issues. And what is very  
13 important is early interaction at the beginning of  
14 development of other drugs in order to regenerate  
15 the evidence of the early evaluation of these drugs  
16 in children.

17 Did I answer the question?

18 DR. WEIGEL: Yes, thank you.

19 DR. PAPPO: This is a question for  
20 Dr. Vassal. Is there a mechanism for updating the  
21 recommendations or the observations of the forum?  
22 Let's say that a fourth generation ALK inhibitor

1 comes along and it's highly effective against ALK  
2 with neuroblastoma, but the preliminary  
3 observations said that that was not the case. Is  
4 there a way to update this or how does it work?

5 DR. VASSAL: This is a very important  
6 question, how were they batched [indiscernible]?  
7 We don't have a standard authority procedure saying  
8 that every 6 months or 12 months and they need to  
9 choose. It will be indicated by case. But I take  
10 your example, in the ALK or inhibition malignancy  
11 forum, the ALK inhibition -- any pediatric  
12 malignancy -- sorry -- we clearly say that there  
13 were no data with the ongoing trials and the  
14 available drugs showing real activity on  
15 neuroblastoma or without mutation.

16 Clearly, one of the messages was that in  
17 this neuroblastoma setting, there was a need for  
18 further development of either options, either new  
19 ALK inhibitors that would prove to be, at the  
20 preclinical level, active in neuroblastoma, and  
21 more active than the other one, or other  
22 approaches, including combinations, including

1 monoclonal antibody and so on.

2           So clearly, we paved the way for one just to  
3 say in neuroblastoma, there is a need for more  
4 research because at the moment, there is no  
5 evidence that the drugs we have are active. So we  
6 did not plan on a regulatory basis -- on a regular  
7 basis, not regulatory, a regular basis to revive  
8 this forum after 6 months, but this will be on a  
9 case-by-case situation.

10           DR. PAPPO: Thank you very much.

11           Any additional questions?

12           (No response.)

13           DR. PAPPO: Thank you very much, both, for  
14 your excellent presentations. Thank you.

15           DR. VASSAL: Au revoir.

16           (Laughter.)

17           DR. PAPPO: So we do not have any open  
18 public hearing speakers for this session, so we  
19 will now proceed with the charge and questions to  
20 the subcommittee and panel discussions. I would  
21 like to remind the public observers that while this  
22 meeting is open for public observation, public

1 attendees may not participate except at the  
2 specific request of the panel. So we will go ahead  
3 and read the first question.

4 **Charge to the Subcommittee**

5 DR. BARONE: Please discuss transparent  
6 mechanisms for industry advocates and the academic  
7 investigator community to communicate and provide  
8 input to the FDA for purposes of eliminating  
9 unnecessary duplication of clinical trials in rare  
10 pediatric cancer populations of same in-class  
11 agents.

12 **Questions to the Subcommittee and Discussion**

13 DR. PAPP0: If there are no questions or  
14 comments concerning the wording or the questions,  
15 we will now open the questions for discussion.  
16 Malcolm?

17 DR. SMITH: Yes. So this is one of the more  
18 vexing challenges. At some point if we have three  
19 or four or five or six drugs in class, someone is  
20 going to say maybe we don't need to study another  
21 one. It could be a company that goes in and says  
22 we need a waiver. It could be FDA that says I

1 think we've done enough. We encourage you to ask  
2 for a waiver. If that process could be one that  
3 was made available to the community, that would be  
4 a way of spreading the word that, as of now, people  
5 may want to study additional drugs, but there will  
6 not be this required molecular target study.

7 DR. PAPPO: Ted?

8 DR. LAETSCH: I would just second what  
9 Malcolm said and something that Julia said before  
10 about it may be helpful to develop a list of  
11 targets that aren't relevant based on biology, like  
12 the prostate antigens and a separate list of  
13 targets that aren't relevant based on prior studies  
14 so that we can differentiate those and then perhaps  
15 seek input from the community to update those lists  
16 periodically and assess whether there are new  
17 agents that have such different activity in those  
18 particular mutations that they should be studied.  
19 But that list may be helpful.

20 DR. KOLB: I think the challenge might start  
21 even earlier. Most of these concepts and these  
22 discussions with our industry partners start years

1 before the trial, and there are many examples where  
2 we have all spent lots of time in developing  
3 concepts of same in-class trials, not knowing which  
4 one's going to hit the clinic first. We are  
5 limited by CDAs in open conversations about these  
6 trials that are in development, and I think having  
7 a forum where we could strategize on which is the  
8 lead compound, which one are we going to develop  
9 clinically, none of us are confident enough to put  
10 our eggs in one basket because those baskets  
11 frequently vaporize without our prior knowledge.

12 So I do think that this is a complicated  
13 issue, as Malcolm pointed out. I think once there  
14 is initiation of the regulatory conversations, it's  
15 maybe a little easier to be transparent. I think  
16 in the early drug development when you do  
17 preclinical testing, when you're trying to  
18 prioritize agents, it's much more challenging.

19 DR. PAPPO: Brenda?

20 DR. WEIGEL: Brenda Weigel, University of  
21 Minnesota. One small word of caution as I'm  
22 sitting here thinking, to build on both what Dr.

1 Smith and Dr. Kolb mentioned, is that this is a  
2 really challenging problem. And we don't know when  
3 we're heading into that first pediatric trial, when  
4 there are multiple agents potentially in class,  
5 which one is actually going to have legs, which  
6 one's going to actually be the better agent. We  
7 have no necessary basis with which actually even  
8 most times to make that decision as we're moving  
9 forward.

10 The one word of caution is that the last  
11 thing we want to do is have any of our industry  
12 partners think that if they wait, that their  
13 regulatory requirements will be less if they're not  
14 first, i.e., they won't have to support or do the  
15 pediatric work if someone else gets to the gate  
16 first. And I think that's not what we want to do.

17 So I think we have to be really thoughtful  
18 of how we really do this in a competitive space  
19 with industry and  
20 really hold all our industry partners to the same  
21 bar for developing drugs for children and not make  
22 it that if you're first, you're actually almost in

1 a way penalized because that's absolutely not what  
2 we want to do.

3 DR. PAPP0: Good point. Greg?

4 DR. REAMAN: I just wanted to get  
5 clarification about moving things from the relevant  
6 to non-relevant list based on clinical trial  
7 experience. Just tell me again how that would  
8 happen just so that I understand the process.

9 DR. LAETSCH: I don't know that I have that  
10 process fully designed, but I would go back to the  
11 examples of the VEGF inhibitors that were  
12 originally at least placed on the non-relevant  
13 list, not because we don't necessarily think  
14 they're relevant to the biology of pediatric  
15 cancer, but because there have been numerous  
16 studies with low response rates.

17 So I just was thinking that as time evolves,  
18 we are going to get more data on some of these  
19 classes of agents in pediatric cancer, and some of  
20 them hopefully will be positive, but some of them  
21 may be negative. And in that situation, at some  
22 point, I would imagine that, as Malcolm said, we

1 would feel like and the FDA would feel like it  
2 wasn't worthwhile to mandate an industry partner to  
3 study the fifth in-class of the same drug when it  
4 didn't work four times.

5 So I don't know how that would exactly work,  
6 whether it would be a discussion among advisory  
7 committee to the FDA to review that data  
8 periodically and update the list, but I think there  
9 would need to be a process as data becomes  
10 available, which we really don't have at the  
11 moment, to move agents that have not shown activity  
12 or classes of targets that have not shown activity  
13 off of that list.

14 DR. REAMAN: Because we had an earlier  
15 discussion about targets that we thought there was  
16 sufficient clinical activity demonstrating -- or  
17 clinical data to suggest that there was an activity  
18 and actually moving them back on a relevant list.  
19 So I'm assuming that things could, should work in  
20 both directions.

21 DR. PAPPO: Steve?

22 DR. DuBOIS: A couple of comments. On this

1 most recent topic, I think it's very much drug  
2 dependent. So if we had said, okay, we've treated  
3 some kids with NTRK fusions with crizotinib and saw  
4 very little activity, and we treated some kids with  
5 NTRK fusions with lestaurtinib and saw very little  
6 activity. And then along came larotrectinib, and  
7 would we really have said no -- we've ruled that  
8 out as an attractable target of interest in  
9 pediatrics on the basis of sort of weak TRK  
10 inhibitors. So I think there is going to be a  
11 little bit of nuance there I think.

12           Then to Brenda's point, just to agree  
13 completely, I think we do need a little bit of  
14 redundancy, probably not as much as we have with  
15 some classes of agent. But at the end of the day,  
16 we need some agents in each class to survive and to  
17 have some dosing and safety information so that if  
18 a drug ultimately doesn't get approved in an adult  
19 indication, or gets approved and pulled for some  
20 reason, that we have some data with another drug in  
21 class because there will be patients who need to be  
22 dosed safely with those agents.

1 DR. PAPPO: Malcolm?

2 DR. SMITH: And, Greg, I wasn't suggesting  
3 that they necessarily be considered not relevant,  
4 but just that since X number have been studied,  
5 maybe that's enough. that any others would be able  
6 to apply for waivers because of that. So I think  
7 there are two processes in which one you might use  
8 would be kind of open. But I think being able to  
9 publicize that this is what the status of this  
10 target is, is that waivers may be given -- not  
11 guaranteed but may be given -- because of the  
12 number of agents that have been studied, could be  
13 helpful.

14 DR. REAMAN: No, and I fully understand that  
15 waivers would be certainly appropriate in that  
16 situation. But as I mentioned earlier, our  
17 communication with sponsor about waiving a  
18 requirement is not something that we have the  
19 ability to share publicly. Sponsors can share  
20 that. So maybe that would be the mechanism, but  
21 it's not -- and that's why I was wondering about  
22 this list and how we would really affect that. But

1 those communications are really confidential,  
2 proprietary information, but I think encouraging  
3 sponsors to make that information available to help  
4 guide investigators and other sponsors would be  
5 very helpful.

6 DR. PAPPO: Donna?

7 MS. LUDWINSKI: Donna Ludwinski, Solving  
8 Kids' Cancer. I'm wondering, based on the strategy  
9 forums that both Dr. Caron and Dr. Vassal  
10 discussed, is there a way for the FDA to leverage  
11 those in order to reduce duplication, or is that  
12 purely European-centric at the moment?

13 DR. REAMAN: It has been European-centric,  
14 but I think you heard Dr. Vassal talk about  
15 expanding its scope internationally. But I think  
16 the strategy forum, I think they're very useful and  
17 very beneficial. But I just recall the experience  
18 from the last one that I was at talking about 15  
19 clinical trials being conducted by sponsors in  
20 relapse/refractory mature B-cell non-Hodgkin's  
21 lymphoma; 15 trials that were all bought into by  
22 European investigators who were leading these

1 studies. But it was really kind of late in the  
2 game.

3 What we're really talking about here is  
4 early evaluation of potential products of interest,  
5 potential products of interest based on their  
6 molecular mechanism of action and whether they  
7 exist or don't exist on a relevant target list.

8 So I think we might be able to convince  
9 ACCELERATE to devote one of the four planned  
10 strategy fora that they're going to have every year  
11 on early prioritization and maybe a review.

12 They've certainly seen the list of targets.  
13 They've weighed in on the list of targets that  
14 we've proposed. They've made additions. They've  
15 asked questions. They've recommended some  
16 deletions.

17 But I'm not sure that the strategy forum  
18 is -- I think what we do may inform the strategy  
19 forum, but I'm not sure that the strategy forum is  
20 going to be the best method of doing the kind of  
21 prioritization that is going to be required of us  
22 in early development of some of these products.

1           Again, we've tried to address this in a  
2           disease agnostic sort of setting, recognizing that  
3           uh, some targets are strictly associated with  
4           specific diseases, whereas others may not be. So  
5           it's a little bit difficult to wait for a strategy  
6           forum that's focused on a specific disease. It's  
7           also difficult to wait for our purposes to discuss  
8           multiple same in-class drugs. So if we wait until  
9           there are five or six ALK inhibitors before we have  
10          a strategy forum to discuss which one should we  
11          prioritize, does that mean we've waited until the  
12          fifth one before we even evaluated the first one?  
13          And that's another issue that I think we need to  
14          highlight here.

15                 There's definitely room for participation  
16                 globally in that, but as far as implementing the  
17                 mandates of this legislation, I'm not sure that the  
18                 strategy forum is going to be the right place as  
19                 it's currently constituted, and it may be that  
20                 there will be opportunities to change that. And  
21                 that's something that we'll have to talk to  
22                 ACCELERATE about.

1 DR. PAPPO: Toby?

2 DR. MacDONALD: On that note, I think on the  
3 preclinical development side, it'd be helpful if  
4 there's a mechanism in place by which a single  
5 investigator or platform could get multiple agents  
6 of the same class with which to test, so instead of  
7 going sequentially, we can do it in parallel. It's  
8 very hard. You get your one CDA, your one MTA, you  
9 test your one drug, and you publish that. And then  
10 if you compare it to another lab or European study,  
11 there's no cross-comparison or validation. So it  
12 will allow you to validate the target, and it will  
13 allow you to do head-to-head competition of the  
14 drug.

15 I think if there's a way that -- if I could  
16 get my hand on five drugs and test them together in  
17 the same model, in the same style, in the same dose  
18 and schedule, you could have much better  
19 prioritization of the drug that you think is  
20 working the best within that, -- it will probably  
21 be within that histology or within that pathway  
22 that you're looking at.

1 DR. PAPPO: Ted?

2 DR. LAETSCH: I should clarify. I don't  
3 mean to say that they wouldn't be relevant. I mean  
4 to say, like Malcolm said, if they've been studied  
5 multiple times, we need to sort of consider whether  
6 or not new studies are needed. And I would also  
7 echo what Steve said, that it is not just target  
8 but also agent and class. So larotrectinib is  
9 different than crizotinib, and then it's a highly  
10 specific TRK inhibitor. I'm not sure there are  
11 that many differences between the many PD-1 or  
12 PD-L1 blocking antibodies that are clinically  
13 relevant, so I think those considerations will be  
14 important.

15 DR. PAPPO: Julia?

16 DR. BENDER: Julia Glade Bender. I hope  
17 this is not a naive question, but sometimes I  
18 wonder what the pediatric ODAC role is in this, and  
19 could the pediatric ODAC itself get involved in  
20 early prioritization. I'm not sure what the  
21 nomination process is to come to a pediatric ODAC,  
22 but I wonder, in fact, if investigators could

1 actually nominate a target and put a call out to  
2 see if industry wanted to come talk to us if they  
3 had something in the pipeline.

4 DR. REAMAN: Well, as you may know, the  
5 pediatric subcommittee of ODAC has undergone a  
6 series of evolutionary changes. We several years  
7 ago changed to invite sponsors to come and discuss  
8 products so that we could think about issuing  
9 written requests early in the development timeline  
10 rather than waiting until two or three years after  
11 a drug was approved and then say, oh yeah, that's a  
12 great drug; let's see if we can study it in  
13 children.

14 We could certainly do that, and I think  
15 there's clearly a role for the pediatric  
16 subcommittee to help advise. The only difficulty  
17 with that is, again, when it's a specific sponsor  
18 and if our experts that we invite as members of the  
19 subcommittee have a relationship with one of the  
20 sponsors that might be presenting their product,  
21 that poses a real conflict, and we unfortunately  
22 sometimes can't get the experts that we really

1 need.

2           So there may be mechanisms outside of a  
3 formal advisory committee where we don't have -- I  
4 mean, not that we're looking for ways to skirt  
5 conflict of interest considerations, but where we  
6 could do it in more of a workshop setting. And  
7 that was part of my thinking about these  
8 semi-annual workshops. Now, maybe we need to have  
9 them more frequently than twice a year, and that's  
10 something that we could really think about and  
11 discuss.

12           DR. PAPPO: If there are no additional  
13 questions or comments, I'll try to summarize some  
14 of the salient points of this discussion. Anybody  
15 else have -- we still have one more question to go  
16 through.

17           So regarding the most recent question, the  
18 possible role of pediatric ODAC in early  
19 prioritization of agents, there could be a  
20 possibility of incorporating that in the future.  
21 Just be careful of the conflict of interest that  
22 you might have if you invite a specific sponsor

1 that has a relationship with a drug company.

2           There were a couple of discussions regarding  
3 the development -- a process for new agents for  
4 multiple drugs in the same class and how that could  
5 be done. And the overall strategy would be to try  
6 to develop a forum or some kind of process to make  
7 available to the community to help strategize which  
8 should be the lead compound. On the other hand, we  
9 don't want to wait for multiple compounds to be  
10 available until all of them have been developed.  
11 And if the first compound in its class is available  
12 and it's the only one that is currently ready for  
13 prime time, I think that should be evaluated.

14           Is that a fair statement, Greg?

15           DR. REAMAN: Yes.

16           DR. PAPPO: Okay. I think that's it. A lot  
17 of it was just back and forth. Any other things  
18 that I left?

19           (Laughter.)

20           DR. PAPPO: There were a lot of clarifying  
21 questions that Greg was able to answer that I don't  
22 think I should be summarizing, but if you wanted me

1 to -- I didn't write it down.

2 Anything else I left out. Ted? You're okay  
3 with your priority lists and all the agents and all  
4 that stuff? Okay. Let's go to the last question.

5 DR. BARONE: Please comment on process  
6 development aimed at enhancing international  
7 collaboration between clinical trial networks to  
8 facilitate global cancer drug development for  
9 children in light of currently nonaligned  
10 regulatory requirements.

11 DR. PAPPO: If there are no questions or  
12 comments concerning the wording or the question, we  
13 will now open the question for discussion.

14 PK?

15 DR. MORROW: Just as a follow-on to the  
16 discussion about the common commentary and the  
17 pediatric clusters, would there be a mechanism for  
18 which companies would be able to receive guidance  
19 that is not drug specific but rather target  
20 specific? That is saying if one has a specific  
21 target or disease state globally harmonized, what  
22 type of appropriate endpoints or backbones could be

1 utilized?

2 DR. REAMAN: That's certainly possible,  
3 although usually the cluster calls use, to develop  
4 an agenda, applications that have come either to  
5 the agency or to the EMA, applications, or study  
6 plans, or proposed pediatric study requests, or the  
7 EMA, their pediatric investigation plans or PIPs.  
8 But this sounds like not PIP or PDSP specific  
9 questions, a bit more general questions.

10 The cluster calls are organized by the  
11 Office of Pediatric Therapeutics. I think they  
12 would be open to facilitating collaboration and  
13 coordination. And again, they're monthly, and we  
14 block off three hours, so some of these discussions  
15 might take more than just the 20 or 30 minutes  
16 because sometimes we have a lot. But I think there  
17 may be a mechanism for doing that.

18 There may also be a way of accomplishing  
19 this through workshops, but that may be a little  
20 bit more difficult to get international colleagues  
21 and representation. And it clearly would be  
22 difficult to get people from the EMA to travel here

1 because we can't reimburse for that. And the same  
2 when we go there, we're not reimbursed. And there  
3 may actually be a mechanism that we could set up  
4 outside of the cluster calls, just within the  
5 Oncology Center of Excellence because there are  
6 adult agent and clinical trial cluster calls as  
7 well with multiple regulatory agencies.

8 So we could have a pediatric-specific one  
9 that really was not necessarily product focused but  
10 may be target or pathway focused. And it may  
11 involve or maybe could involve more than one  
12 company even, as well as regulators. So yes, we  
13 could certainly look into ways that we could  
14 accommodate something like that.

15 DR. PAPPO: I have a question for Greg. Is  
16 it realistic to think that it will be possible to  
17 harmonize the EMA and the FDA for a single  
18 application and be able to get all of the  
19 requirements for the two agencies, or that's not  
20 realistic?

21 DR. REAMAN: In your lifetime or in mine?

22 (Laughter.)

1 DR. REAMAN: I mean, harmonized is a  
2 difficult word because harmonization I think really  
3 requires legislative changes that lead to  
4 regulatory procedures and processes. And I don't  
5 think we're in the right place to truly influence  
6 legislation.

7 Having said that, I think there are ways  
8 that -- and we have, actually with the early part  
9 of PIP requirements and written request  
10 requirements, been able to harmonize and agree on a  
11 single international study or one study that's  
12 being done in the U.S. and another study that's  
13 being done in Europe. And the results of those  
14 studies would satisfy both regulatory agencies'  
15 requirements.

16 So there are ways to do it, but there's no  
17 single way to do it all the time. And it really is  
18 more a question of coordination rather than  
19 harmonization, I think, which to me means something  
20 very different that is not necessarily immediately  
21 achievable.

22 DR. PAPPO: Thank you. Elizabeth?

1 DR. RAETZ: Elizabeth Raetz. This is a  
2 question for Dr. Reaman, and forgive me if this  
3 might be naive as well. Have there been any  
4 thoughts about harmonization of strategies for  
5 trial design? Because you may have a number of  
6 different agents that have promise in a certain  
7 class, but sometimes there is disagreement about  
8 how to study them, whether there would be  
9 combinations or common platforms that are agreed  
10 upon globally.

11 Has there been any thought about also  
12 working on those sorts of issues?

13 DR. REAMAN: There have been. And again,  
14 not as part of what we're talking about here with  
15 implementation. But it's not uncommon that we get  
16 proposed pediatric study requests for evaluation of  
17 a new drug in a particular disease or diseases with  
18 a backbone. And it's a backbone that is not used  
19 in the U.S. but is used in Europe. I won't mention  
20 the diseases because you can maybe then figure out  
21 what I'm talking about.

22 So we have tried to work with the EMA and

1 work with sponsors to accommodate both, and  
2 sometimes it's getting feedback from the company  
3 that there are enough of U.S. investigators that  
4 would be willing to enroll patients even though  
5 it's not the quotes/unquotes "standard of care,"  
6 for lack of a better word, in this country and vice  
7 versa. And sometimes there are major changes to  
8 study design that are required to accommodate both  
9 backbones, and maybe even to the point of a  
10 randomized study looking at both with the new  
11 agent.

12 DR. PAPP0: Steve?

13 DR. DuBOIS: Steve DuBois. Most or all of  
14 what we've talked about today has centered around  
15 drugs that are being evaluated in adults and then  
16 making their way to children, and that will get us  
17 only so far. At a certain point, the hope of  
18 course is that for some of these targets that are  
19 truly pediatric specific, that there will be drugs  
20 developed, which really the first in-human study is  
21 a first in-child study. And I suspect that those  
22 would probably have to be international in scope,

1 or at least the broader development plan would have  
2 to be international in scope.

3 So how aligned are the regulations in terms  
4 of conducting a first in-human study in a child?

5 DR. REAMAN: I'm not sure that I know the  
6 answer to that. I know that it's not out of the  
7 question as far as the FDA's position. I'm not a  
8 hundred percent sure what the EMA's position is on  
9 that. And you're absolutely right. This piece of  
10 legislation is not going to solve all of the  
11 challenges with drug development for children with  
12 cancer, and the most promising agents that we'll  
13 hopefully be able to see developed are not ones  
14 that are repurposed for pediatric indications, but  
15 ones that are developed specifically for pediatric  
16 indications. And this legislation really has  
17 nothing to do with them.

18 Having said that, I think -- and the other  
19 non-alignment of our regulatory processes is that  
20 the pediatric investigation plans require  
21 consideration of the development of a product  
22 through its continuum, so not just early dose

1 finding and signal seeking, but real efficacy  
2 studies, comparative efficacy studies if necessary.  
3 So it may be that the earliest phase studies might  
4 be done here, which would actually inform the  
5 pediatric investigation plan, and that the more  
6 definitive studies could be designed so that they  
7 meet the regulatory requirements of both the EMA  
8 and the FDA. That's how I would possibly see  
9 things happening.

10 DR. PAPPO: Julia?

11 DR. BENDER: I just wanted to -- and this  
12 probably goes back to PREA and some of the points  
13 that Brenda was making about multiple drugs in  
14 class and things that are going on in Europe and  
15 going on here. And I wonder if the incentive to be  
16 the first one out is sufficient for the extra  
17 amount of burden it may put on the first one, and  
18 whether in fact incentives should be graduated  
19 not based on positive results but rather based on  
20 how many studies or how much work it took to get  
21 there.

22 DR. REAMAN: Well, just to clarify, there

1 are no incentives associated with PREA. PREA is a  
2 mandatory requirement to do studies. The only  
3 incentives are associated with BPCA and the written  
4 request mechanism. But I understand Dr. Weigel's  
5 point, and I would hope -- or I would suspect,  
6 maybe incorrectly, that if a drug were truly of  
7 interest to a sponsor, that being first in class  
8 wouldn't be jeopardized by considering that they  
9 may have to study this in the pediatric population.

10 Our intent is clearly not to jeopardize  
11 cancer drug development. I don't think that's the  
12 intent of this language. It's certainly our  
13 interpretation of the law. But I don't think that  
14 companies are going to wait to submit the  
15 applications just because they might be able to  
16 escape, if you will, the requirement for a  
17 pediatric investigation. But that might be a  
18 question that's better addressed to our industry  
19 representative.

20 DR. MORROW: I think I would concur that  
21 there's a strong desire to be first in class, so I  
22 agree.

1 DR. PAPPO: One more?

2 DR. BENDER: Even if in the end, they don't  
3 get the indication but they did all the appropriate  
4 pediatric testing, is there an incentive through  
5 the BPCA for that, a voucher or something like  
6 that?

7 DR. REAMAN: They could submit a PPSR, and  
8 we could maybe issue a written request. So a  
9 written request, describe in pretty vivid detail or  
10 extensive detail the studies that are required.  
11 And the studies don't have to be positive. It  
12 doesn't have to lead to an indication. Generally,  
13 we hope that it leads to information that could  
14 inform labeling with respect to toxicities, PK  
15 doses. But there are new guidelines or guidances  
16 that are preventing us from including even some of  
17 that information in labeling.

18 But the studies don't have to be positive,  
19 but if they are conducted and data are submitted  
20 within the timelines, and they meet the  
21 requirements of the written requests, then they  
22 could get exclusivity without a pediatric

1       indication, sure.

2               DR. CASAK: Just to clarify, sponsors need  
3       to submit the pediatric plan at the end of phase 2.  
4       In order to develop their own track for the  
5       indication they're looking, they need to submit a  
6       pediatric plan. So they are not going to wait for  
7       somebody else to submit theirs.

8               DR. BENDER: My only point is that we're  
9       trying to move the timeline earlier, so they may  
10      not know yet. So they're making an early  
11      investment -- if they make an early investment and  
12      that drug doesn't go all the way through, is there  
13      an incentive?

14              DR. REAMAN: You mean that drug doesn't go  
15      all the way through for their planned adult  
16      indication? There is no -- no, there's no  
17      incentive. No, there's no incentive.

18              DR. PAPPO: Raj?

19              DR. MODY: Rajen Mody, University of  
20      Michigan. I just wanted to follow up on Steve's  
21      point. We do have an example of an active agent in  
22      pediatric, dinutuximab, which received FDA -- if my

1 memory serves me correct -- in March 2015 an EMA  
2 approval in August 2015, so a rather short  
3 succession, so when you have an active agent. Even  
4 though I would say that there are some lessons in  
5 that, when we are considering for approval for FDA  
6 and EMA, it's important to look at what therapy  
7 patients receive previously, and the backbones are  
8 not the same. Even though there are differences,  
9 the EMA and FDA were able to grant approval in a  
10 very rather short succession.

11 DR. PAPP0: Good point. Nita?

12 DR. SEIBEL: So in some of the  
13 presentations, it was mentioned how the cooperative  
14 groups have done international trials but they  
15 haven't involved IND agents. So that's how they've  
16 been able to be done. So it seems like really  
17 industry has to sponsor the trial if it's going to  
18 be done internationally. But my question is, have  
19 you had any discussions on would it be feasible to  
20 do an international trial that isn't industry  
21 sponsored but more through the clinical trials  
22 network? The main problems obviously are

1 regulatory from the IND standpoint or they have to  
2 be companion trials.

3 DR. REAMAN: I don't think we've had any  
4 specific discussions with companies. I suspect  
5 that we will as they now may be required to do  
6 studies that previously they knew they were just  
7 going to be automatically waived because they were  
8 developing the drug for an adult cancer indication.

9 Now I think -- and they may well have to  
10 consider that the study would be international in  
11 scope, so their sponsorship of it, even though it's  
12 conducted through a cooperative group here and a  
13 cooperative group in other countries, and their  
14 requirement to supply the investigational drug I  
15 think would still exist.

16 DR. PAPPO: Brenda?

17 DR. WEIGEL: Brenda Weigel, University of  
18 Minnesota. Just building on Nita's comment -- and  
19 I think it speaks to some of the joint  
20 communications internationally between pediatric  
21 oncologists -- for non-industry sponsored  
22 international trials, the real work is to have, in

1 the current regulatory environment, parallel trials  
2 and matching the data collection, matching the  
3 eligibility, matching all of that. And that really  
4 gets down to the collaboration among colleagues.  
5 And I think that's very doable, but that is also  
6 the buy-in of our industry partners to say it's  
7 really two parallel trials and then merging of data  
8 sets.

9 So it is possible and certainly doable, and  
10 we certainly have experienced doing it, but that's  
11 the only way with the current IND system, as  
12 Dr. Seibel points out. So I think there are ways  
13 to do it. It speaks again to that international  
14 collaboration, international communication that  
15 needs to occur and the academic industry  
16 partnership around that to be clear of what the  
17 options are.

18 DR. PAPPO: Any additional questions or  
19 comments? Greg?

20 DR. REAMAN: I would just question the  
21 regulatory buy-in. Parallel studies and merged  
22 data sets aren't always the optimal way to go. In

1 the adult setting, there are many international  
2 studies, and a single data set is clearly  
3 preferable. And I think that is something that in  
4 an industry-sponsored study that's conducted  
5 internationally would be required and would be  
6 certainly preferred if there was really a plan to  
7 license or get an approval for a pediatric  
8 indication.

9 DR. PAPPO: Malcolm?

10 DR. SMITH: And I will just add to what  
11 Brenda and Greg said, that we are working out ways  
12 so that we conduct a single trial. There's an NCI  
13 sponsor on this side of the Atlantic and there's a  
14 company sponsor on the other side of the Atlantic,  
15 but it's a single trial with a single database. So  
16 that's a model that I hope would be satisfactory.  
17 So it's all complicated, but we're working out the  
18 procedures to do that.

19 DR. PAPPO: Any additional comments or  
20 questions?

21 (No response.)

22 DR. PAPPO: The two main topics that I was

1 able to get out of the discussion -- because most  
2 of the questions were addressed to you, and you  
3 gave an exceptional answer to all of them.

4 (Laughter.)

5 DR. REAMAN: So you can repeat them back.

6 (Laughter.)

7 DR. PAPP0: Not really. They were not  
8 related to the -- anyway, one was if there was any  
9 kind of guidance for companies for a target, what  
10 should endpoints and what should be the backbone.  
11 And I think that the answer to that is that some of  
12 this is addressed in the cluster calls and there  
13 are some workshops.

14 Then the most recent discussion was  
15 regarding international collaboration and trials  
16 that include an IND drug. And although there's not  
17 a specific mechanism right now, there are parallel  
18 trials that are being conducted at the same time in  
19 Europe and the U.S. in which the data is merged;  
20 although Malcolm mentioned that there is currently  
21 an initiative to try to come up with a mechanism to  
22 actually conduct those trials internationally.

1           Is that correct? Is that fair?

2           (Nods of affirmation.)

3           DR. PAPP0: Any additional things I missed  
4 other than all this stuff that you were kind enough  
5 to answer to everybody?

6           (No response.)

7           DR. PAPP0: Now, Dr. Reaman, on top of  
8 everything else, is going to provide the closing  
9 comments.

10                           **Closing Comments - Gregory Reaman**

11           DR. REAMAN: Well, I just want to say thank  
12 you to all of you for participating in this. This  
13 meets and is the end of our statutory requirements  
14 for open public meetings, so for that I can  
15 congratulate you. But it clearly does not mark the  
16 end of the work that you have to do, that we have  
17 to do, and that industry sponsors have to do in  
18 implementing this. It's not easy. It's not going  
19 to be easy. And I think we've said, I've said  
20 during the day a few times, that this is really  
21 going to take collaboration and multistakeholder  
22 collaboration.

1           We see the statutory requirements to the  
2 agency on the creation of the molecular target  
3 lists maybe a little bit differently than they were  
4 intended because we I think prioritize the  
5 potential public health benefits of children a  
6 little bit higher than regulatory certainty. But  
7 at the same time, we don't want to make that  
8 prioritization of the public health of children at  
9 the expense of regulatory certainty.

10           We've tried to do this by defining molecular  
11 targets as broadly as possible and keeping the  
12 required evidence base as indiscriminate as  
13 possible. But I think we are clearly committed, to  
14 the concept of designating levels or grades of  
15 relevance so that we can provide a little bit more  
16 information to industry in their regulatory  
17 planning.

18           I think we're definitely committed to the  
19 concept of successfully and responsibly and  
20 effectively implementing Title V of FDARA in such a  
21 way that we don't jeopardize cancer drug  
22 development in general, and that we don't deprive

1 access to promising therapies by adults.

2 This is going to require continued to work.  
3 We're committed to engaging outside experts for  
4 advice. We clearly don't have all of the expertise  
5 and mechanism to define evidence bases for defining  
6 relevance. We don't have all the information  
7 that's required for decision-making with respect to  
8 how we implement these lists and decide whether or  
9 not we're going to need studies.

10 I think we did accomplish today, and I thank  
11 you for that, a list of relevant targets, a list of  
12 targets that will lead to waivers. And I think the  
13 concept of automatic waivers as we move from  
14 indication-based to mechanism of action or  
15 molecular mechanism of action-based triggers for  
16 PREAW has changed our concept and needs to change  
17 industry's concept of automatic waivers.

18 The list will be updated with some of the  
19 comments that we heard today. VEGF receptors will  
20 come off the automatic waiver list and go back to  
21 the relevant list, and we'll add the PTEN, KIT.  
22 RET is actually already there. We'll add

1 mutational burden, CCND1 and 2, STAT2, and we'll  
2 expand the MLL and ETS fusions. And the BRD4 NTM1  
3 and BRD3 NTM1 I thought were on there; they're not.  
4 They'll be added also.

5 I think the other message is that we really  
6 need more industry academic investigator  
7 collaboration in the nonclinical or preclinical  
8 space. I would hope that we could emulate the  
9 European experience with the ITCC P4. And if  
10 ACCELERATE is willing to expand internationally, I  
11 would hope that the P4 platform could do the same.

12 We will work to our best capacity with  
13 ACCELERATE in priority setting, priority setting  
14 within the drugs that are available given the  
15 patient populations that we have to enroll on  
16 studies, as well as in the multiple in-class  
17 products. But I think we're going to need also  
18 another mechanism for coordination and  
19 collaboration internationally with early-phase  
20 evaluation of studies that hopefully will actually  
21 inform global development plans.

22 So again, thank you all for the discussion

1 and the input, but just to make it clear that your  
2 job's not done today because --

3 (Laughter.)

4 DR. REAMAN: -- we have until 2020 to  
5 actually successfully implement this. And we have  
6 started outlining a guidance for how we're going to  
7 implement this with which we will respectfully  
8 request some input as well, so thank you again.

9 **Adjournment**

10 DR. PAPPO: Thank you, Greg.

11 We will now adjourn the meeting. Panel  
12 members, please remember to drop off your name  
13 badge at the table, actually leave it over here, so  
14 that it can be recycled, and thank you very much.

15 (Whereupon, at 4:10 p.m., the meeting was  
16 adjourned.)

17

18

19

20

21

22