FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Morning Session

Thursday, June 20, 2018

9:00 a.m. to 11:17 a.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good morning. We're going to get started. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Amanda Turney. If you are present, please stand.

My name is Alberto Pappo. I'm a pediatric oncologist, and I will be chairing today's meeting. I will now call the morning session of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. REAMAN: Gregory Reaman from the Oncology Center of Excellence.

DR. CASAK: Sandra Casak, FDA.

DR. DREZNER: Nicole Drezner, FDA.

DR. SINGH: Sonia Singh, FDA.

DR. KAMANI: Naynesh Kamani, Children's National, Washington, D.C.

DR. LAETSCH: Theodore Laetsch, UT Southwestern.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. RINI: Brian Rini. I'm a GU medical oncologist from Cleveland Clinic.

MS. PREUSSE: Courtney Preusse, consumer rep.

MS. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer, patient advocate.

DR. BENDER: Julia Glade Bender, Memorial Sloan Kettering, pediatric oncologist.

DR. SMITH: Malcolm Smith, the National Cancer Institute.

DR. DUNKEL: Ira Dunkel. I'm a pediatric neuro-oncologist at Memorial Sloan Kettering and

chair the Pediatric Brain Tumor Consortium.

DR. BOLLARD: Cath Bollard, Children's National and George Washington University, Washington, D.C.

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

DR. PAPPO: Thank you very much.

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the

meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

Lauren?

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

The agenda for the morning session involves the review and discussion of the Food and Drug Administration Reauthorization Act, FDARA 2017, mandated relevant molecular target list now posted on the FDA website, https://www.fda.gov/aboutFDA/oncology centerofexcellence/pediatric oncology.

The FDA is required by statute to review and update the previously approved published list. The focus of the discussion will be limited to target two classes included in the Relevant Pediatric Molecular Target List: 1) targets linked to cell lineage; and 2) targets

on normal immune cells and cells in the tumor micro environment. Planned introductory presentations will be on, 1) cell-based therapy approaches to childhood cancer; and 2) novel membrane antigen determinants in pediatric tumors.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by

Amgen.

Regarding FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Crystal Mackall has acknowledged that she holds stocks in Allergy Therapeutics and Lyell Immunopharma. She is also the founder of Lyell Immunopharma. She receives consulting fees from Lyell Immunopharma and Unum Therapeutics. Dr. Mackall is a scientific advisor to Unum Therapeutics and Apricity. She receives royalties from the NIH for the CD22 CAR that was licensed by Juno Therapeutics.

Dr. Kristopher Bosse has acknowledged that he is involved in two NIH grants, and his role in these grants is a researcher, principal investigator, and co-investigator. The U54 CA232568 grant is for the discovery and development of optimal immunotherapeutic strategies for

childhood cancers. This is a multi-institutional center grant to discover new immunotherapeutic strategies for children's childhood cancers, as part of the Pediatric Immunotherapy Discovery and Development Network. The award period for this grant is from September 1, 2018 to August 31, 2023.

The KO8CA230223 grant is on targeting the GPC2 oncoprotein with immune-based therapies in neuroblastoma. The major goal of this project is to define the mechanisms, underlying aberrant GPC2 cell surface expression, and oncogenicity and neuroblastoma, and to determine the efficacy and safety profile of GPC2 targeting immunotherapeutics. The award for this grant period is July 9, 2018 through June 30, 2023. In addition, Dr. Bosse holds patents that are focused on the discovery and development of immunotherapies for cancer, and he receives research funding from Zymeworks and Tmunity.

As guest speakers, Dr. Mackall and Bosse will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have had regarding the topic at issue that could be affected by the committee's discussions. Thank you.

DR. PAPPO: Thank you very much, Lauren.

We will proceed with an FDA introductory remark from Dr. Greg Reaman.

FDA Introductory Remarks - Gregory Reaman

DR. REAMAN: Good morning. I'd like to extend my welcome to all of you also and express our, appreciation for your willingness to help us as we comply with some legislatively mandated obligations here.

As a little bit of background, we're really

here today to talk about some requirements related to legislative initiatives, and the fact that the Pediatric Research Equity Act, which supports drug development in children, has really been markedly less obvious -- in fact, it's been totally absent -- in the cancer arena. We all know and recognize that many targeted cancer therapies are likely equitable to children. A recent passing of the RACE Act, the Research to Accelerate Cures and Equity, essentially amends the Pediatric Research Equity Act.

Just a bit of background, there are two major pieces of legislation in the U.S., which guide drug development in children, PREA, which requires mandatory studies for the specific indication under review. That is a new drug for the treatment of breast cancer has to be studied for breast cancer in children.

Drugs that are developed for rare situations where there's orphan designation are exempt from any of the PREA requirements. Most of the cancers that may actually cross the adult and pediatric age

divide receive orphan designation, so they're exempt from the pediatric requirements.

The Best Pharmaceuticals for Children Act is the major piece of legislation that we've tried to use, to the best of our ability, to initiate early studies. These are totally voluntary, and as you know, this afternoon, we'll actually discuss a product where there may be consideration for the issuance of a written request.

The Race for Children Act was passed in August of 2017 and incorporated as Title V, Section 504 of FDARA, the FDA Reauthorization Act. It requires evaluation of new molecularly targeted drugs and biologics intended for the treatment of adult cancers, but directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer.

The legislation further defines what these molecularly targeted pediatric cancer investigations are. They must provide clinically meaningful study data using appropriate formulations regarding dosing safety and

preliminary efficacy to inform potential pediatric labeling, and most importantly, it eliminates the orphan exemption for pediatric studies.

The agency interpreted molecular target quite broadly, as demonstrated here, a molecule in human cells intrinsically associated with a particular disease process, etiology, progression, and drug resistance. There must be evidence that by addressing the target with some intervention, a desired therapeutic effect is produced in altering the disease process.

The current implementation status we've had since 2017, with planning and implementation coordinated through multiple FDA programs: the Office of Hematology and Oncology Products and the Oncology Center of Excellence; the Office of Pediatric Therapeutics; the Office of Clinical Pharmacology; the Division of Pediatrics and Maternal Health; the Office of Regulatory Policy; and the Office of Chief Counsel.

We are mandated to have an open public meeting. We've actually had two open public

meetings, where we reviewed the initial candidate target list and a subsequent one to review and finalize that list.

The lists are actually posted on this website. For the last year and a half, we've been advising sponsors of the new conditions and requirements for their initial pediatric study plans, which must be submitted and agreed to prior to a new drug or a new biologic licensing application with plan submission dates after August of 2020.

Guidances, we have two guidances that have been written. They're in clearance and have been in clearance for quite some time, and we anticipate draft publication some time within the next several months.

The framework for defining relevance is pretty straightforward: presence of the target in one or more pediatric cancers, not necessarily prevalence dependent; target function, as I mentioned previously; nonclinical evidence, general and pediatric specific that target inhibition and

affects tumor growth; clearly adult clinical experience and any pediatric clinical experience that might be available; availability of predictive or response biomarkers; the localization of targets for immunotherapy-directed interventions; and therapeutic agent availability or in development.

The target lists we envision as statutory requirements to address regulatory uncertainty for industry, and we envision these as a guide, not a dictate, for decision-making regarding early evaluation of specific products and the initial pediatric study plan or iPSP submission.

The designation is relevant and is neither an absolute nor exclusive requirement. We can require studies of drugs if the target is not on the list. Just because a target is on the list doesn't mean that we're automatically going to require an early pediatric study.

They're not envisioned to restrict authority or flexibility. The candidate target list was constructed by the Oncology Center of Excellence and the pediatric oncology medical officers with

input from the National Cancer Institute, and was actually done collaboratively with the NCI and with significant input from international content experts in two open public meetings. We utilized published peer-reviewed literature, abstracts, and public databases, and there was no prespecified minimum requirement for evidence based.

There are four classes of targets not meant to be exclusive, and there's a significant overlap between these targets, but we utilized this classification for ease of thinking about this and presenting in public forum: targets associated with specific gene abnormalities; targets associated with cell lineage determinants; and targets on normal immune cells and cells within the tumor microenvironment, and both of these classes might lend themselves to immunotherapeutic interventions to a number of pediatric tumors; and another large group of other targets that are essentially pathways and functional mechanisms present in both normal as well as cancer cells that actually form the basis for therapeutic interventions.

We're here today because another mandate is updating the lists and publishing the lists. I've mentioned already where the lists are, on the FDA website. We have decided to hold semiannual public meetings, and this is one such meeting, to get some input on recommendations for additions to the target lists or deletions, and utilizing both internal and external advice panels. We've had open for several months now an open docket for comments,. To date, we've received no a recommendations for additions or deletions.

This is the list. I think they're in your briefing packages, the targets associated with specific cell lineage determinants that we'll consider today, so we're looking for any suggestions for things that should be added or things that no longer would be considered relevant; then targets on normal immune cells and cells in the tumor microenvironment that might be appropriate for immunotherapeutic exploitation.

With that, I would just like to thank our guest speakers, Drs. Crystal Mackall and Kristopher

Bosse, from Stanford and the Children's Hospital of Philadelphia, respectively, who are going to open our discussion with some background on where we are with development of some agents relative to these two classes; and more importantly, I think, then, where we are currently, the future, and the potential. Thanks.

DR. PAPPO: Thank you very much, Dr. Reaman.

Before we proceed, I just wanted to ask Anne to introduce herself for the record. She just joined us.

DR. ANGIOLILLO: Thank you. Good morning. My name is Anne Angiolillo from Children's National Medical Center and George Washington University School of Medicine.

DR. PAPPO: Thank you very much.

We will proceed with a guest presentation from Dr. Crystal Mackall.

Guest Presentation - Crystal Mackall

DR. MACKALL: Good morning. Thank you for the opportunity to be here and present to the committee and to the public. I took Greg's charge

to provide an overview of where we stand in terms of developing immunotherapies for children's cancers, with an emphasis on targets.

By all accounts, immunotherapy has really been a revolution in the way we approach cancer patients, especially I think in the adult arena. You can see there that so much press has been given both in the lay and scientific press, and most of that has been driven by the success with immune checkpoint blockade, well illustrated by the award of the Nobel Prize in 2018 to Jim Allison and Takira [sic - Tasuku] Honjo for developing immune checkpoint inhibitors.

Of course, when these waves happen in adult oncology, the job of the pediatric oncologist is to figure out how we use these therapeutics, if we can, for the benefit of children. I think even though we're a decade into this, I think we still have a very unclear idea of whether and how we can use this novel class of therapeutics for children.

Part of its biology because -- much of it I think is biology. This is essentially a new

classification in terms of the many ways you can classify cancers. This is one where you bin them according to how many mutations the cancers have that turn out to be targets for potential immune recognition, and those cancers with the most mutations happen to be those that are also responsive to the immune checkpoints. While of course there are other factors that modulate responsiveness to that class of therapeutics, this is standing the test of time as an important biomarker.

So when you look at the span of human cancer and you say what are the bookends here, you've got melanoma and lung cancer on the far side with the most mutations, and then you've got diseases like rhabdoid tumor and Ewing sarcoma on the pediatric side as the least mutated of the cancers.

If indeed, it requires mutations, and plenty of them for immune checkpoint inhibitors to work, this really leads to the concern that this may not be a class that has value for pediatric cancers. Even among the histologies that have high

checkpoints, it tends to be the patients that have the highest burden that benefit.

Many of our pediatric tumors are on the left side of this curve, and now let's look at what is the data with the immune checkpoints. There isn't too much data published. We did the first trial with a ipilimumab, and as far as I know, it's the only single-agent trial with this agent.

This was published in 2016. We enrolled 30 children. About half of them had melanoma and about half had sporadic pediatric tumors of the more common histologies. We went up pretty high on the dose, and we did observe that the agent acted very similarly with regard to autoimmune toxicity as it did in adults, and the pharmacokinetics were no different than adults.

So we really believed that biologically, the agent was acting in the same way, but disappointingly, we saw no evidence for objective responses in 11 metastatic melanomas.

The response rate in adults using RECIST is relatively low. That could be that we missed it in

11, but I think that's unlikely. Then of course, perhaps the more important question, because of the pediatric tumors that are more common, we saw really no responses.

Now, there were autoimmune toxicities, and they were mostly at the very high dose levels. The patients who developed autoimmunity actually seemed to have some longer survival. Whether it was causal or not, we don't know. But again, it appears that ipilimumab works the same in children as it does in adults, but rather that the children's cancers simply are not as, quote/unquote "immunogenic."

Then of course PD-1, which really is the major immune checkpoint inhibitor, PD-1 blockers and PDL-1 blockers, the major class in adults. Those results haven't yet been published, but the studies with single-agent PD-1 blockade have largely been completed in sporadic pediatric tumors.

Again, we see that the agent behaves very similarly in children and adults with regard to

tolerability and with regard to pharmacokinetics, but we did not see impressive responses. Even in Hodgkin's disease, we don't, I don't think, understand this, but the level of response was not the rate that we saw in older adults that reported with Hodgkin's disease.

There are some studies ongoing with combining immune checkpoints, and I think we still don't know whether there might be some mileage we can gain there. I will say there have been some sporadic responses with that, and time will tell. We do know, I think, that checkpoint inhibition is a single therapeutic maneuver and has limited impact in sporadic pediatric cancers.

And additional reason to believe that it's not because the drug works any differently is this rare germ line predisposition syndrome called biallelic mismatch repair, where children are born with mutations and DNA mismatch repair genes and almost invariably develop cancers within the first decade of life. It turns out that these cancers have very, very high levels of mutations, even

higher than any adult cancer, so we're talking about mutations now above a hundred mutations per megabase. In fact, when you treat those patients with PD-1 blockade, you do see impressive responses.

The question that remains unresolved is whether -- and I don't see if I have a pointer here -- the area between 10 and 100, that it's classified as hypermutant. It's not ultra hypermutant, but there are about 4 or 5 percent of sporadic pediatric cancers that do have somewhere between 10 and 100 mutations per megabase.

Those numbers have been associated with response to checkpoint blockade in adults. We don't really know what the minimal cutoff is, and, frankly, measuring mutational burden varies, depending on the assay that you use. So these things aren't cast in stone, but there still may be some room for activity.

We still have unanswered questions. I don't think pediatrics should declare the use of these checkpoint inhibitors a negative in pediatrics. I

think there still are some questions, but we do have to be careful that we don't -- we've already treated many, many patients, several hundred, with these checkpoint inhibitors without good responses. So we have to think, I think, hard about what are the trials that should be done in the future with these agents.

I think one of the major unanswered questions is whether this combination checkpoint, CTLA4 and anti-PD-1 in molecularly stratified populations and designated hypermutant, may show activity. This trial we are hoping to get launched very soon in the Pediatric Cancer Immunotherapy Trials Network.

The other issue that comes up with regard to the discussion of targets is whether novel combinations of immunotherapies can induce responses. Some reason to think this could be the case is there's some emerging data in neuroblastoma models of low immunogenicity cancers, fully murine models now, where you use antibodies plus anti-PD-1. With or without radiation, we're

starting to see some signals in preclinical models.

There was a recent report in pancreatic cancer, the PRINCE study. It's very preliminary, but pancreatic cancer is also one of those diseases where single-agent checkpoint inhibition hasn't been effective and also sort of low mutational burden. But when you combine anti-CD40 with anti-PD-1 and chemotherapy, there were some recent preliminary data presented at ACR.

I think there's reason to have continued interest in these class of agents, but we're left with a conundrum because there are hundreds of potential combinations. As Greg pointed out, and the purpose of this meeting, the RACE Act will make many more of these agents available for study.

I get calls all the time now from companies with their immunomodulator that they want to study in children, which is good. We're happy to have companies interested, but the truth is we cannot study all of them. So now we have to become, I think, much more sophisticated with our ability to prioritize what trials are done in children.

Because we haven't had access to drugs in the past, frankly we haven't had a lot of practice prioritizing, and prioritization is really tough business.

I would argue that combinations that demonstrate efficacy in preclinical models that mirror the low mutational burden of pediatric solid tumors, in an intact immune system, should be prioritized, but we still need more of those model systems.

I think that combinations that demonstrate efficacy in adult low immunogenicity tumors should be prioritized; just because you think it might be a good idea and it has activity in melanoma, not necessarily a combination, that we should prioritize in children.

I also think there are other checkpoints. I just wanted to mention CD47 because there's been some exciting data that Robbie Majzner, a junior investigator in our group, has developed. It's an example of a novel checkpoint. CD47 turns out to be a checkpoint for macrophages. Tumors express

CD47. It gives macrophages a don't eat me signal. If you block CD47 on tumors that also express an eat me signal, you get phagocytosis. It turns out that our old friend dinutuximab induces induction of these eat me signals on neuroblastoma and on osteosarcoma. So when you combine these agents together in preclinical models, you get very nice synergy.

So we need to keep an open mind about what checkpoints we're talking about. It may be that in pediatrics, 47 is a very important checkpoint, so really continuing to understand the biology is really important.

You can bin immunotherapies into those that you use in the immunogenic tumors, where you're really just trying to amplify something that already exists, or you can say I'm going to be a synthetic biologist. I'm going to create something that would hijack the immune system to make an immune response when it otherwise wouldn't.

I think a good example of that type of synthetic immunotherapy are chimeric antigen

receptors, which many of you have probably already seen. They basically incorporate some kind of antigen specificity usually from an antibody, and allows the T cell then to recognize a cell surface molecule. Once that's recognized, the T fires because of the signaling domain that is integrated into the CAR.

When CAR T cells were being first tested, many of us thought they were going to be too complicated, and I'll get into that, but clearly there's been a watershed moment in this field, and remarkably with pediatrics at the front and center. The approval of Kymriah for pediatric B-cell ALL was the first FDA-approved cell therapy for the treatment of cancer and the first gene therapy approved in the U.S. It had this unusual developmental path of being approved in children before it was approved in adults.

We still don't have a CD19 CAR approved for adults with leukemia, which is the first time the adults have found themselves with this arbitrary cutoff based on age, and maybe that will cause some

changes in -- I think we could probably get this done. It would be really, really important. Of course, we have adults that need it and don't have access. These arbitrary designations around age provide real barriers; and first therapy with an outcome-based payment model. There was also I think a very robust acceptance within the community to try to figure out how to do this, use CAR T cells earlier in therapy, so there will be a study ongoing.

I want to point out that, really, the approval of CD19 CAR has caused a watershed, a true watershed, in this business around cell and gene therapy, and I think it's going to continue to impact pediatric oncology in very meaningful ways. Before CD19 CAR was approved, what I would hear is crystal cell therapy will never work.

Even if it did, how would you commercialize it? Bispecific antibodies do the same thing. Why do you need cells? Autologous products from cancer patients? That's not going to work. They're too immunosuppressed. It's going to take too long to

make the product. These are aggressive diseases and it's too expensive.

Today what I hear is it's too expensive, and I think it remains a major issue. How can we scale up products for all patients who need it? This is especially with regard to the lymphoma story and adults, and could we get an off the shelf? Could it really work for solid tumors?

How good are the CD19 CARs? Well, it's great to see that about half of the patients who receive these, their tumors develop resistance to all of our standard agents for ALL. But while 80 to 90 percent go into remission, it looks like many of those patients will relapse.

We still have major challenges around manufacturing delays, some toxicity, although that's getting better. But we're really seeing a high rate of relapse. Especially in the Novartis trial, the vast majorities were because of this old problem of tumor heterogeneity. These tumors can live without the epitope that the CAR recognizes. So if you put all of your pressure on one target,

guess what? The tumor comes back lacking that target.

It points out the need for additional targets, and this is the CD22 CAR that was developed in my laboratory and has been studied by Nirali Shah at the Pediatric Oncology Branch. This CAR shows very nice activity. A vast majority of these patients had already received CD19 CAR, then developed this CD19 negative mediated resistance, but went back into remission with the CD22 car.

So it tells us a lot about you can make CARs to other targets that are also quite active; that intrinsic resistance of the tumor cells probably are not what's going on; rather it's this target modulation.

It's really great to see this, and this is the Pediatric Oncology Branch, and the NCI is trying to get this moved forward and made more readily available. We'll be opening a study at Stanford with this because it is an unmet need, sort of an orphan disease, CD19 negative leukemia.

But the truth is most of these remissions

have not been durable. It's been a bridge to transplant, and the relapse now is associated not with complete loss of the target but simply selection of cells that express lower levels of the target. It turns out the CAR T cells need a lot of target.

You can see the difference in activity there based upon modest differences in target level, 2000 versus 4,000 molecules. It can mean the difference between being able to control the tumor; there's your 4,000 molecules on the right and 2000 molecules per cell in the middle. So we've got to be able to engineer these things when we want to be able to go after low antigen density.

It raises the prospect of rather than allowing the tumor to become resistant to one agent and have to come in with another agent, can't we do them at the same time? So there's a lot of activity in the CAR T cell space to engineer these cells to have multi-specificity. It's one of the reasons people are excited about this class of agents, is because they are readily engineered to

address the problems of resistance that are observed.

Just to show you there, you can do CAR T cells with a bivalent receptor. You can give two pots of cells. You can co-express. We don't know the best way to do it, and you can see this is all institutions in our St. Baldrick's Stand Up to Cancer pediatric dream team that are studying this, and hopefully we'll learn.

This is the data from a patient treated at Stanford with a lymphomatous B-cell ALL treated with a double CAR. You can see it does have activity. It's an early-phase trial, so our primary objectives remain safety and feasibility with a secondary objective of its response rate. We do have really significant clinical activity and acceptable toxicity without 19 negative escapes so far. We'll see over time, though, whether it really is able to prevent 19 negative escape. I think it's way too early to know that.

All of this that we're learning about what happens when you give CAR T cells for childhood

leukemia is going to inform how we can make these therapeutics more functional for solid tumors, because we know that many of the challenges we're seeing in leukemia are going to be even greater, the same problems, but even greater challenges in solid tumors, especially around heterogeneous antigen expression, but also intrinsic T cell dysfunction and the suppressive microenvironment and the poor trafficking.

So again, our St. Baldrick's Stand Up to Cancer team has been very active in defining targets for solid tumors, and this gets to our discussion today. Of course, we all know that GD2 is a target on neuroblastoma. Not all of us recognize, but indeed the data demonstrates it's also expressed consistently on osteosarcoma, albeit at lower levels, but we're hoping that it's targetable for that disease.

Then we recently discovered with Michelle Monje at Stanford that this is very highly expressed on diffuse intrinsic pontine glioma. It's quite remarkable that it's 2019, and we're

only learning this. To me, it is really indicative of how little we know about the cell surface of pediatric tumors, especially solid tumors. Our tumor biologists often tell us about mutations and oncogenes, but this is not something that they are routinely cataloging.

Given how many antibody derivatives there are for therapy today, understanding what the cell surfaceome looks like and how it's modulated with therapies is really, really valuable for developing immunotherapeutics.

GPC2, another target that you'll hear from Kris today, came out of John Maris' and Kris's group, a discovery that this is highly differentially expressed on neuroblastoma, medulloblastoma, and several other cancers, including adult cancers, that really can be an entirely new target because they mine the surfaceome.

PAPPA, this is, Greg, a new one for your list. I don't see it on the list. We published on this earlier this year. This is highly

differentially expressed. In Ewing sarcoma, it basically cleaves IGF1 from its binding protein and ensures that Ewing sarcoma has a ready supply of IGF1, and it's expressed then on the cell surface, and we're hoping that we can target it with CARs. We're still working on it.

B7H3, this is another molecule that is very highly overexpressed on pediatric tumors compared to normal tissue, recently published, and we have some exciting data in ATRT coming soon, I hope.

Here's the DIPG data. Again, we all know it's a terrible disease. It highly differentially expresses GD2. Therefore, when you use the GD2 CAR, even though it's in the brain, systemic administration, at least in xenograft models, is enough to clear those established tumors.

We do have some deaths in these animals that were quite sobering due to tumor swelling and hydrocephalus, but we do not believe that the GD2 CAR is targeting the neural tissue. Here is some evidence of the normal histology in these mice, and of course, GD2 is the same in mice and humans after

clearance of the tumor. So even though we know there's low levels of GD2 on the brain, CARs appear to be able to thread a therapeutic window because of this requirement for high antigen density.

We are, hopefully in the next couple months here, going to get our clinical trial of GD2 CAR T cells open for DIPG. We're going to have to treat patients before recurrence because the post-progression survival is so short. We're incorporating a suicide domain into the CAR in case we do need to suicide these cells, and we're using other approaches. We hope to deal with what may happen, the increased intracranial pressure, so that patients Ommaya reservoirs and very close monitoring.

Here's some of the data using a CAR targeting B7H3, getting regression of osteosarcoma xenografts, Ewing sarcoma xenografts, and medulloblastoma.

I think, to summarize, the surfaceome of human cancer is incompletely cataloged. Some solid tumors express really high levels of surface

antigens that would be amenable to a whole array of antibody-derived therapeutics, including CARs, and these deserve prioritization for clinical trials in solid tumors.

The other point to make, it should be obvious, but I think we just haven't talked about it enough that people understand this thing isn't random. Tumor biology, just like the oncogenes, drive the signaling pathways of tumors. They also drive the surface phenotype. We've talked about the GD2 ganglioside being overexpressed in DIPG, and of course we know on other solid tumors. But we think that there are plenty more that can be found if we only look for them.

Just to kind of make the point, there are a lot of CARs out there. That list right there is my list of clinical trials that are open now or soon to open. The vast majority, many of these, are highly expressed in pediatrics. So this is an area where I think we are positioned to hopefully make some gains for our refractory pediatric tumors.

But it's not just about new targets. It's

also about new ways of making CARs. You can go through all of this, but there's a lot of different platforms that we think can be used to make these CARs more effective against the solid tumors, using instead of T cells and K cells, et cetera.

I also just want to, in speaking about the CAR T cells, make a point about -- there are all the scientific issues that remain to be addressed, and that's what our team and many of the investigators across Europe and North America are working on to make cars work better, especially in solid tumors. But we also have a lot of challenges around manufacturing, high cost, and limited availability.

Despite these challenges, the field is really booming. Cell therapy now represents the largest number of agents under study in the immune oncology space. This is from a report in Nature Reviews Drug Discovery. They're saying that there are more than a thousand active agents in global cell therapy, in the pipeline. There are 130 CD19 CARs under study. This is sort of like we were

with PD-1 a while ago. I don't think we need 130 CT19 CARs under study, but we do need more trials in solid tumors, and about half of the trials are in solid tumors.

The FDA is anticipating that this phase of growth is going to continue to increase. They anticipate by 2025, there will be approving 10 to 20 cell and gene therapy products per year. These are the companies in the space. And that's incomplete, but just to show you how many of the private sector are investing.

I want to make this point about manufacturing of CAR T cells because I think it's really important, especially for pediatrics. We all are hopeful that there may someday be an off-the-shelf version, hundreds or thousands of products from a super donor. But we still have to be able to engineer it to not cause GVH and not be rejected. It will drive the price down if that happens, but we aren't there yet. I think time will tell. There's a lot of investment. It likely will happen, but it's not going to be in the next

five years, I don't think.

Centralized manufacturing is the current way that we're getting CAR T cells. We send the apheresis to Morris Plains in New Jersey. Novartis makes the CAR; it comes back, and you have to pay $475,000 for this product. This is very costly. There's is immense pressure to bring the cost down, and we are concerned that for the rare indications that pediatrics is, this costly approach is not likely to be a driver for any kind of a margin.

There's also the idea of distributed manufacturing. Here, hospitals would manufacturer individualized products using automated platforms. The regulatory approval would apply to the construct being used and the process being used to generate it. You can think of it sort of like bone marrow transplantation, which is, of course, the most effective immunotherapy we have to date, and large academic medical centers deliver bone marrow transplantation.

So thinking about using CAR T cells for rare indications, which would particular be pediatrics,

having our large academic medical centers be able to produce these for our children I think is really important if we're going to be able to administer these and really reap the benefits of the science that's being done. There are a lot of automated platforms; here are some of them, the Miltenyi Prodigy, the Lonza Cocoon. All of this is really quite automated and could be done in major academic medical centers.

CAR T cells have made their debut. In pediatric oncology, they've driven a paradigm shift in the field of cancer cell therapy and gene therapy. There are a lot of challenges that remain, both scientific and practical, but the science and the emerging technology is very robust.

The FDA, academic medical centers, and private sector are betting that the field is going to grow dramatically in the next 5 to 10 years. We believe that a technological developments will drive down cost, and children with cancer, all bets, all indications are that these children's cancers are developmental aberrancies, and as such,

they look different on the cell surface than postnatal tumors.

So we think that there are a lot of lineage targets, as Greg referred to them, that we could be using in the context of CAR T's or other antibody-derived therapeutics. There are some of the acknowledgements. I did want to acknowledge Robbie Majzner who has done that exciting work with CD47, and I'll stop there. Thanks.

(Applause.)

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Mackall.

We will now take clarifying questions for Dr. Mackall. Please remember to state your name for the record before you speak, and we only have about five minutes for questions, so go ahead. State your name please.

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering. Thank you for the excellent talk. Coming from the brain tumor perspective, can you comment on what we know or what your thoughts are

about where the CAR cells should be delivered for brain tumors; intravenous, intrathecal, intratumoral?

DR. MACKALL: Yes. We're doing some pretty focused efforts on that currently, as are several other groups. Trafficking is a problem for T cells into solid tumors, whether they be in the brain or they be anywhere else. In fact, I think one of the reasons leukemia is so responsive is T cells get into the marrow quite well.

One of the things we've learned is that, actually, they get into the brain pretty well. I showed you that data with DIPG, systemic administration, even into the brain stem. However, if you compared administration systemically to administration intraventricularly, or intratumorally, you need about a log less cells to get clearance if you do the regional delivery.

Furthermore, we've learned that they get in there more quickly. There are less inflammatory cytokines when they're delivered regionally, and the CSF cytokines are similar. Remarkably, they

also traffic out of the brain after you deliver them there, so you don't seem to pay a price on persistence.

So this is an area of very immense research, and I think you'll see some publications come out over the next year. The City of Hope made the initial observation, and I think all of us are really seeing the same thing.

While we're going to start with a DIPG with systemic administration, we're also going to have an adult GBM trial on the heels of that, where we administer intracerebro ventricularly. I think that Seattle is already doing that with, I believe, the HER2 CAR in brain tumors, so we're going to see more of that.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's. Thanks so much, Crystal. I really appreciate the content. A couple of questions; one, I didn't see PAPPA on your list of coming soon CAR T cell trials. Is that because of the rarity of the disease, that it seems to be just maybe Ewing specific? Are there technical

challenges in targeting that? What are your thoughts on why that's not on the coming soon list?

DR. MACKALL: We just haven't had a CAR to work yet. We're still working on it. I mean, it takes a year and a half or so to get a CAR at work. Hopefully, we'll figure it out, but it's just on the list of to-do's. But there are antibodies, and there may be ADCs, and other ways to target PAPPA, too.

DR. DuBOIS: Great. Then there is some data from Medical Oncology about TIL content as a potential predictor of response to immune checkpoint inhibition. Are there particular pediatric tumors that are characterized as having high TIL burden?

DR. MACKALL: You know, infiltrating lymphocytes has been a really challenging biomarker because, indeed, in melanoma, infiltrating CD8s is one of the markers of response.

When you look at kids' tumors, mostly they're full of macrophages and myeloid cells; why we're so interested in the 47 story. There are

lymphocytes in there, but it's still quite -- compared to a melanoma, it's much lower. So they are cold tumors. Even though there's some lymphocytes in there, they're cold. Among the tumors, Robbie Majzner and John Maris and I published a cancer paper; you can look at it. We looked at 500 samples, and maybe glioblastoma had a little more, but it was all still in that cold space.

Interesting, there's a paper that is going to be coming out soon about rhabdoid, where maybe rhabdoid has kind of more cells in there than you'd think. It's so funny because it's such a low mutational burden. So there may still be some principles to learn. But in general, all the pediatric tumors are cold as far as I understand, except Hodgkin's

DR. PAPPO: Alberto Pappo. I had two very quick questions. How predictive are the preclinical models where you're studying currently CARs, since they do not have an intact immune system?

DR. MACKALL: Yes, a couple things to say about that. I don't know who says it, all models are bad; maybe Bill Weiss. All models are bad. This is where we have to start. There is no perfect model. For evaluating a CAR T cell, what you want to know is can it find the tumor? Can it proliferate? Can it kill the tumor?

In our hands, and I think the field generally agrees, that xenografts have been very useful. They're a step beyond what you can do in vitro for looking at the fitness of the T cell. As far as no immune system there, they do have the myeloid compartment, and we've shown that the myeloid cells do suppress the T cells.

The NSG mouse is myeloid replete. Okay. But when you're talking about checkpoints, no, there's no way. One of the concerns is the PPTP program, especially, is all xenografts. There are no fully murine models yet that I'm aware of in that program. So you really can't model the checkpoint combinations without the fully murine models.

Furthermore, if you model them with a tumor that doesn't reflect -- for instance, we did this once with a rhabdo, M39M, you can look it up, and we saw checkpoint responses with a rhabdo, and we looked at a combination and demonstrated it. But it turns out M39M expresses the male antigen, and we did all this in female mice. In alveolar rhabdo, you don't have that male antigen.

So you've got to be very careful that the antigens you're talking about are reflective of what the antigen load is like in humans. I think we're starting to get there as people get more sophisticated, but we've got to be very careful about modeling the checkpoint combinations.

DR. PAPPO: I had another very quick question. Given the gloomy data with checkpoint inhibitors in pediatrics, one would think that they are dead. Do you think that there is any role in trying to modify the epigenetic landscape of T cells to try to see if we can boost the immune response of those T cells already exhausted, or you think that it's not worth proceeding with those

clinical trials?

DR. MACKALL: Well, that's a big question. That's a big question. The epigenetic landscape, we're really trying to modulate that in the CAR T's, because we agree exhaustion is a problem there. I don't know if, quote/unquote, "exhaustion" is what's limiting responses in our pediatric tumors to checkpoint; I think there just aren't enough antigens. So what we need is probably a combination of innate immune activation and the checkpoint inhibition in the right cocktail, in the right tumor, in the right patient.

So I think it's more we have to stimulate more, and it's not necessarily an exhaustion problem, but we could talk about that for a long time.

DR. PAPPO: Thank you.

DR. BOLLARD: Crystal, that was an outstanding overview of the field, and in particular of the CAR T cells. I'm being a little bit provocative. I'm not sure if you heard Steve Rosenberg's comment at ASGCT this year, but he made

the very bold statement that he could not see how CAR T cells would make a great impact for solid tumors, so I would like to hear your opinion about that.

Then, really speaking to what the previous two members spoke to, there are other T cells in the adaptive response to intracellular tumor-associated antigens. Can you see a way where they could be also beyond checkpoint inhibitors enhanced and partnered with a CAR T cell approach?

DR. MACKALL: Yes. Let me take that in two parts. Steve and I have had several spirited discussions about that. I think we have to look at the data, and the data pretty clearly shows that CAR T cells require high antigen density. Therefore, when we see differential expression of cell surface molecules and we see in preclinical models where there is mouse expression of the target but no evidence for toxicity, we just have to look at the data.

That said, there's no substitute for a clinical trial, so time will tell. But predicting

the future in general is something that we maybe shouldn't do.

The other T-cell issues, absolutely. Engineered TCRs, they really can be very potent. I've been a leader in developing the New York ESO-1 TCR in synovial sarcoma, which hopefully GSK is going to really go after approval now. We've got very meaningful long-term responses in half of the patients treated, and that's just fantastic.

The problem is we had to screen, for that trial that we published, about 110 patients to treat 12. So the problem is we don't have a T-cell receptor for every HLA allele. I wish the companies to just make us more T-cell receptors so we have them for patients. It's just very difficult to develop a therapy for a pediatric rare tumor, and then you make it rarer by saying it's only going to be a third of that rare.

TILs, I don't know. We don't have a lot of TILs in there. I think NK cells, definitely. Let's see whether the NK cells are going to make a hit. There's some investment now. So I certainly

don't want to predict the future. Let's go by the data, and there's some exciting data out there on NKs for sure.

DR. PAPPO: We have time for two more questions. It's going to be Greg and Anne, and then the other questions we can come back at the end of Dr. Bosse's talk.

DR. REAMAN: Crystal, I just want to also echo, this was fantastic, great overview. And I was pleased to hear that the CAR T approach sort of supersedes TILs, at least in the pediatric space.

Two questions; the combinations, I think you've definitely warned us about combinations of checkpoint inhibitors. But just following up on the epigenetic manipulation, what about other opportunities to make cold tumors hot and sequencing low-dose radiation or cytotoxic chemotherapy followed by checkpoint inhibition?

DR. MACKALL: Yes, that is what we need to do. The whole immuno-oncology world, adult, they're trying to figure out how to do that in diseases like pancreatic. There's a trial opening

in the Parker Institute to make just cold tumors hot, looking at combinations.

I think there, we want to kind of follow on their heels. We want to watch that data like a hawk. And when you see a signal, then I think pediatrics should jump in. But to an extent, we have to let them sift through the dozens of combinations to find the winner or get some good models.

DR. REAMAN: I think watching like a hawk is good advice, and we don't want to jump in because we can't jump in, because we don't have the numbers of patients that will allow us to evaluate every combination. But I think there may be some unique pediatric specific combinations that we ought to really be thinking about.

DR. MACKALL: Yes. Certainly, the dinutuximab, for instance, leveraging that, some of that preclinical data looks exciting. I agree.

DR. REAMAN: Just one other quick question. Based on the cell surfaceome and findings, what guides the decision to develop a CARs versus ADCs,

versus naked [ph] antibody approaches, other than the specific expertise and interest of investigators?

DR. MACKALL: Yes. Obviously, you ask 10 different people, you'll get different answers. For me, I think that when it comes to CNS, the CARs have a major advantage because although we've all been told it's a sanctuary site, the truth is those CAR T cells get in there. The CD19 CAR get in, and the preclinical models, and we have the opportunity for regional administration.

So there, I think antibodies don't cross well in ADCs.

Small fragments may cross, but I'm just concerned that will always be a problem. But for peripheral solid tumors, I think that in many ways, bispecifics in the ADCs, they're a lot easier to develop and administer. So unless you have a good reason to use a CAR, maybe you need that persistence. Then maybe you say you take the simpler therapeutic first.

DR. PAPPO: Sorry. We're going to have to

move on, but I promise you, we'll try to get your questions.

It's my understanding that Dr. Shah is here. I would ask for her to please join us at the table and introduce herself before we proceed with the next speaker.

DR. SHAH: Nirali Shah, NCI.

DR. PAPPO: Thank you. We will now proceed with our next guest speaker presentation, Dr. Kris Bosse.

Guest Speaker Presentation - Kris Bosse

DR. BOSSE: Let me say thank you for giving me the opportunity to talk here. It's a hard act to follow. I kind of wish I could go first before Crystal, but I'll do my best. I'm going to give you a little more of a ground view of antigen discovery and what we've been doing at CHOP. Thankfully, Crystal introduced a lot of the introductory slides.

I'll first start with saying this is very much a team effort. This is some of our team at CHOP with our leader in the middle there, Dr.

Maris, who couldn't be here today. A lot of this work is done by members of my lab but also graduate students doing some work, and Amber you can see in the middle there pointed out. I'll have the opportunity to talk a little bit about their work.

The other point that Crystal made, which I think is a really important one for this type of work, is this, I think, can only really be done well with a large collaboration, and for us, it's now a 10-institution collaboration across the United States and Canada, and I think it allows us to do this work both from an antigen discovery standpoint, all the way to developing several different types of therapies.

The question about what therapy is the best, I'm not entirely sure we know. This gives us the opportunity to really take a target and make several different therapies in parallel, just given the wide expertise.

This is how I sort of envision how the cell surface landscape has changed since the invention of this team, almost a decade ago now. This is not

a complete list, and hopefully most of these targets are on the target list. In the blue are those targets that we've known about for a while, and the red are an incomplete list of some of the newer targets that we're working on in.

The circle targets are the ones, if I have a chance, to focus on today and what we're working on at CHOP; specifically just the neuroblastoma. What I show you today in neuroblastoma I think can really be applied across any different histotype.

I think the group here understands this well, the challenges, and we've made great advances with chemoradiotherapies in pediatric cancers, but there's much work to be done. Many of our cancer -- or almost all of our cancer survivors have really lifelong and life-altering morbidities. Relapsed cancers, for the most part, are incurable. We've changed the landscape a bit in ALL with CAR T cells, but neuroblastoma here in the bottom right, you can see is pretty much a death sentence when kids relapse.

Crystal introduced these data.

Immunotherapies have now been credentialed for pediatric cancers, both with CD19 targeted CAR T cells and dinutuximab or GD2 chimeric antibody for kids in neuroblastoma. Kids given the therapy up front is part of maintenance, but now it's actually become a very important therapy at the time of first relapse in neuroblastoma.

I think across our team, we feel very strongly that -- and this is, I think, why John and Crystal started this team 10 years ago -- there needs to be a focused pediatric immunotherapy effort and can't just simply be a trickle down from adult cancers.

I list some of the reasons here. But they're simply different cancers. A high-grade glioma in an adult is very different than a high-grade glioma in a child. Much of that is that there's a surfaceome. There's a different drill [indiscernible] into origin. There are different rotational/mutational burdens, as Crystal alluded to.

I think across both of these, there are

simply a lack of targets. I think, as Crystal alluded to, we're just beginning to understand the surfaceome. And it is a bit crazy to think that we didn't know GD2 was on DIPGs until very recently in that work that came out of Stanford. So I think we do need to do a deep dive, and I'll show you a very surface view of that today, but there's much work to be done.

The disease that I'm going to focus on for the rest of this talk, and I think doesn't need much of an introduction here, is neuroblastoma. The important part here is it's an embryonal cancer, so it's really a misappropriation of neural sympathetic nervous system development and of course occurs in young kids.

If you look at the diagram on the right, this is a complicated diagram just to say that the transcriptional program and the cell surface molecules that persist on these developing cells, and then our lost in postnatal and matures in sympathetic nervous tissues, actually persist then in neuroblastomas. So much of these lineage

restricted molecules or transcriptional programs are important in neuroblastoma and tumorigenesis, and many of these are good therapeutic targets, including immunotherapeutic targets.

This is the landscape of neuroblastoma in terms of phenotyping. As many of you know, some kids do very well with very limited therapy. The children we're talking about here are those with high-risk disease. They get two years of therapy, and again, we're only able to cure about 40 to 50 percent of them.

With all these challenges, we decided as part of the Stand Up to Cancer team, a few years ago when I was a post doc in John's lab, to take a very simple approach. Look at RNA sequencing data or RNA ray [ph] data -- now it's primarily sequencing data, and just compare tumors and normal tissues, and ask a very simple question, what's expressed in tumors? In a panel of normal tissues, there's a lot of good, normal tissue and RNA sequencing data available.

Then you can computationally predict what's

supposed to be on the surface. It's not perfect. There are different algorithms, many of which are imperfect for different reasons; then really to take a deep dive into that list of genes that comes out of that, find those that are lineage specific, study those genes in the lab, and really determine which are important in tumorigenesis, with the idea that, like the CAR T cell story, if you really choose to target a molecule that is important in tumorigenesis, the tumor will be less likely to be able to downregulate in that, and we'll see if that ends up being true; and then with a goal to find good targets that then, across our team, we can target with many different types of immunotherapies.

This has been published almost two years ago, and this is what the data looked like. Out of this algorithm, again, we looked at differential expression, predicted what's on the surface, and those genes highly expressed. We decided to work on this gene, glypican 2 or GPC2, and you can see the RNA sequencing data on the right. It's very

high in tumors and very limited tissue and expression. These are now adult normal RNA sequencing data. There is not a children equivalent of this yet.

This is a molecule that sits on the cell surface. It's thought to act as a signaling co-receptor. Very little is known about the biology, but we're also focusing on that in the lab. We're genomicists, hard molecular biologists, so we think a lot about where they sit in the genome and if they sit at areas of high copy number gain, which this does.

For us, although not a trickle down from adult oncology, it was reassuring that GPC, through a sister molecule, GPC2, was being developed as a immunotherapeutic target in several adult liver cancers, and actually pediatric liver cancers, too.

I'll go through this quickly. This has been published. We spent a long time thinking about how GPC2 behaves in neuroblastoma and the importance. And it ends up being that's a very important gene for cell growth. We don't know, again, what the

pathway's involved in yet, but if you deplete it, the cells die very quickly. If you overexpress it, the cells grow much better. It seems to be involved in some pathway, and it may be a win pathway or other pathways, but we just haven't figured that out yet.

Importantly, why these genes differentially express, why does GPC2 continue to be expressed in neuroblastomas and lost on all postnatal sympathetic nervous tissues, in part because it's driven by MYCN, so MYCN's amplified in about half high-risk neuroblastomas. It's a really important oncogene and high DNA copies.

You can see in some of this RNA sequencing data on the left that either tumors that have gain of this chromosome or make an amplification have much higher levels. We did some ChIP sequencing data to show that MYCN does bind the GPC2 promoter at [indiscernible] box. There are various things in the lab where you can knock down MYCN, and GPC2 gets downregulated and parallels.

In part, the transcriptional program in the

developing neuroblast persists in neuroblastomas and continues to drive expression of these lineage specific, in this case a cell surface gene that remains very differentially expressed.

Some newer data -- and this hopefully will come out soon -- is we spent a long time looking at -- these are patient-derived xenografts grown in immunocompromised mice. They have this interesting bimodal expression of GPC2, and it ends up being -- we think, and we have yet to fully prove this -- that these ultra-high GPC2 cells are have co-expression of other neuronal stem-cell markers, really getting at the biology of GPC2 being important in neuronal development, but then again lost in postnatal tissues.

I alluded to this at the beginning, that what's really great about this team is that we have people who are experts in binder discovery now at the University of Pittsburgh. They're able to work with the biologists and find specific binders that bind GPC2 or whatever, PAPPA, or whatever other protein we're interested in. Then we can quickly

make, really, any type of immunotherapy from those binders.

This is showing some of the published data. Here on the left, they were able to find this arbitrarily called D3 binder. It binds very specifically to GPC2. Again, getting to why we chose what therapy, this is sort of an arbitrary choice. It ended up being I think a good one, but we decided to make this antibody drug conjugate where we conjugated this antibody to these very potent DNA intercalators PBD dimers.

I won't go into too much of that data, but the in vitro data is very potent. The IC50s are in the single-digit picomolar value. Our in vivo data looks like this. You can give just one dose of ADC at the beginning of a study enrollment, and that completely ablates tumors. This is true across a number of genomically diverse PDXs.

The nice thing about this binder, which I will not show you the data for, it binds mouse GPC2. These mice are very healthy. They have no really clinical signs of any toxicities. We're

hoping to move this type of therapy to the clinic soon.

To get at the potency of this, we've treated some very large locally advanced tumors. You can see in the red lines there, you're able to ablate these tumors very robustly also, again, just with a few doses of ADC. And as expected, the ADC causes a lot of DNA damage and apoptosis. I won't show the data, but it actually also induces some immunogenicity, so thinking about combining these types of therapies with immune checkpoint blockades is actually a very interesting one.

Some newer data via collaboration from our Stand Up to Cancer team, we've been able to take this binder and fully crystallize it with GPC2. So now we know specific epitopes where this binds, which I think will give us a lot of flexibility as we make immunotherapies targeting GPC2. You can see on the left a diagram of that, and on the right, the epitopes are colored in green. GPC2 has folded, so it ends up being a confirmational epitope where it binds amino acids in the

N-terminus and the C-terminus of GPC2.

That's potentially very important because what I didn't tell you up front was not only do we think GPC2 is very differentially expressed, but we think there's a tumor-specific isoform. If you can see GPC2-1 there, that's a tumor-specific isoform, and GPC2-3 is the isoform that's found in most normal tissues and terminally truncated. The binding surface area is the part where you can see where the antibody binds GPC2. So it binds a large number of epitopes that are only found in the tumor.

As Crystal alluded to, we've spent a lot of time thinking beyond neuroblastoma and where else can we use these type of therapies in not only pediatric cancers but also adult cancers. This is just some data from the Cancer Cell Line Encyclopedia, where you can look at RNA sequencing across a number of different cancer cell lines, and neuroblastoma is also very high on the left.

One of the other things that popped out of this was small cell lung cancer. Again, getting at

lineage-restricted antigens, small cell lung cancer is neuroendocrine derived, very similar to neuroblastoma. So it's not very surprising that they have a very similar cell surface landscape as neuroblastomas. NCAM is an antigen. We spent some time on neuroblastomas, on small cell lung cancers. DL3 is another antigen on both tumors. We do see a lot of parallels between similar lineage-derived cancers across both pediatric and adult histotypes.

My lab has become a lung cancer lab, which is interesting at a pediatric institution, but we've spent some time really validating these findings in lung cancers, and this is just a xenograft we made. It's actually a MYCN amplified small cell lung cancer. You can see a very similar -- when you take these cells and put them in vivo, you get a rising of the stem cell population, which is interesting, but then you also see very similar potency to ABC in vivo for, again, some small cell lung cancer with GPC2 expression.

This has been a fun road with this project.

We're at the point now where we're trying to move some of these therapies to the clinic, and then also optimize some additional therapies. This is a molecule -- I think in large part, because of our team, we've actually taken an approach, and I think we'll learn a lot from this, is what is the best therapy. Is it ADCs, or CAR T cells, or both? We're also making T cell engagers and bispecifics.

So I think we'll learn a lot from this molecule, which may be the ideal type of therapy, at least in this context.

I'm going to shift gears for the end of the talk, and just talk a little bit about some work done by Amber Weiner in the lab, again, very similar but a bit different. She's a graduate student close to graduating in John Maris' lab.

She's taken a very similar discovery approach to neuroblastoma lineage-restricted antigens, but she's built a really important step. That's in the top left, where she's spent a long time perfecting a sucrose gradient ultracentrifugation method, where she can

specifically isolate cell membrane proteins, and then throw them on a tandem mass spec and really identify which membrane proteins are highly expressed in both neuroblastoma cell lines, patient-derived xenografts, and tumors.

Then she's used the similar validation scheme that we've developed over the last few years. This is just a very small snippet of her data, but this is a panel of 10 patient-derived xenografts, and you can see from left to right the abundant protein. Then she's pointed out here some of the cell surface genes we're interested in, in neuroblastoma. You can see DLK1 is something that she decided to work on for a number of reasons I'll get into; GPC2, L1CAM, NCAM, et cetera.

Cell surface molecule has been known in neuroblastoma for a while, but no one thought about targeting it until recently. It ends up having this very differential expression. It's high in some tumors and nearly absent in others. What she's figured out is the reason for that is because there are a subset of neuroblastoma models that are

driven by a super enhancer element, DLK1.

You can see the super enhancer plots on the left. There are some models that have it, others that don't, and that correlates really perfectly with the expression of DLK1 in these models. On the right, you can see the H3K27, the subtle [ph] marks that correspond with that, the super enhancers.

By luck and by being aware of what other people in the adult world are doing, there's a company working on a DLK1 targeted antibody drug conjugate with a similar payload as what I showed you for GPC2. We've done several in vivo studies in the lab. You can see the IHC for DLK1 on the top left, and that correlates nicely with what you'd expect by RNA. It also correlates nicely with the response to the ADC. If you have the antigen, you respond; if you don't, you don't respond.

If you look in the bottom middle, the Felix PDX, some of those tumors started to come back. We re-dosed, and they continue to respond. So we

don't lose antigen, at least in this sort of dosing scheme, over time. These tumors continue to be responsive to the ADC.

To finish up -- I apologize; Mark makes some very complicated slides, so I'll try to give you the main points of them. Mark Yarmarkovich is actually now a graduate PhD student in John's lab and is joining as a post doc to finish up some of this work. He's done some really, I think, impressive work in challenging this central dogma I show here. And as Crystal alluded to, for decades, neuroblastomas and other pediatric tumors are thought to be cold tumors, and in partner, blastoma, the MYCN oncogene, as shown here, is thought to suppress MHC1 expression. Then, again, there's limited infiltrate of T cells.

Mark sort of ignored this data and said, well, is it possible to identify which peptides on neuroblastomas are presented via MHC, and are those then targetable with either TCRs or CAR T cells? Again, these are complicated sides, but what he essentially did was took neuroblastoma models with

patient-derived xenografts and primary tumors, and captured the MHC, alluded the peptides, and characterized them by mass spec.

This is a pipeline developed in Germany that he brought to the lab. Then he's compared this with healthy tumor MHC or healthy MHC antigen peptide databases. He has used a similar algorithm to really ask the question of all these peptides, which are interesting, use some gene expression, differential gene expression, that I showed you before. He then asked a lot of questions about are these presented on common or rare HLA alleles; are they on all tumors I looked at or just a portion? He then really thought about what types of genes are these, and does it make sense to target them.

What he found is, actually, a lot of the peptides he ended up prioritizing, and some of those are listed on the right, are all derived from lineage-restricted neuroblastoma genes. PHOX2B is really only expressed in neuroblastoma. It's not in many normal tissues, but also expressed in the developing nervous system. So a lot of these genes

are fitting that same mold. These are just now presented via MHC in their interest of other molecules.

This is a complicated graph to say that he's done the same thing in primary tumors. On the X-axis are peptides, and on the red are the percentage of tumors on the top. On the bottom are the percentage of normal tissues. You can see on the far right, there are peptides that are presented both in tumors and normal tissues, but what he really decided to focus on was on the box on the left.

Those peptides are only presented on a high number of tumors and not found in any normal tissues. When he did some genotology [ph] enrichment analyses, what came out was these are all genes associated with sympathetic nervous system development, so it makes a lot of sense.

Then our lab and others have really characterized a core transcriptional regulatory circuit shown here on the left. These are, again, nervous system development in neuroblastoma

specific transcription factors that drive a number of genes and important tumorigenesis. What he's found, with some work from Nate in the lab, is that many of these genes also drive many of the parent genes of the peptides he's finding. You can see the ChIP sequencing data on the right. So again, these are all driven by this transcriptional program that is sort of co-opted by the neuroblastoma tumors.

Then he's taken this a little further, and there's a lot of work to be done here. He's, again, worked within our Stand Up to Cancer team and found some binders that bind specifically to the peptides presented via MHC. There are a lot of binders that bind just to MHC, which he's had to remove from this discovery platform.

You can see on the right some ELISA data, where on the top there are some imperfect binders, where one binds the decoy and the peptide. The IGFBPL one doesn't bind either very well, but then A7 and F11, again, arbitrary names, seem to bind the peptide MHC but not that the decoy A protein.

He's taken this a little step further. Again, this is ongoing work where he's then engineered, as Crystal showed you, a CAR T cell using these binders, and is able to get transduction into those T cells, and they seem to bind IGFBPL1, which presented via MHC. He can treat these cells, and in addition, he's able to kill cells specifically that are IGFBPL1 positive in the right HLA background. He chose HLA, too, because it's one of the more common HLA molecules on people.

I'll just end there. I went through that quickly, so I'm happy to take questions. I think what we've developed in our platform at CHOP is -- all very neuroblastoma focus, but any of this I think can be moved across different histotypes, and really focusing on, postnatally express cell surface molecules, peptides presented via MHC, and they all seem to be genes that are important both in neuroblastoma development and in neuronal development.

I think the charge now is to move some of

these to clinical development with carefully done trials, where we can learn a lot about correlative biology. I personally think -- and my lab will focus on this for the next few years -- we're just scratching the surface, even just in neuroblastoma, and we haven't done these analyses across a number of other cancers. So I think there's a lot of work to be done there.

It's nothing magical. I think it's a lot of molecular biology, and finding good antibodies, and finding good targets, and diving both into how to target them, but also the biology of them will help us get some of these things to the clinic. So thank you, and I'm happy to take questions.

(Applause.)

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Bosse. We will now proceed with questions for Dr. Kris Bosse. Please remember to state your name for the record before you speak. After we're done with Dr. Bosse's questions, if there's time, we will have the other three members of the panel ask their

remaining questions to Dr. Mackall.

DR. DuBOIS: Steve DuBois, Dana-Farber. Thanks so much, Kris; really, terrific work. It's both uplifting and daunting. You've presented several very rational targets and several rational ways of targeting those targets, and this is a rare disease.

So how do we grapple with that to figure out the very best to move into the clinic straight away?

DR. BOSSE: I don't know the answer. It's a good question. You're a leader in this area. I think it's a rare disease, but I think there are also patients we see every week who have no therapeutic options. I think there's a balance, and I think we have to do well-designed preclinical studies, and then see if there's any hint of efficacy in humans.

We see many patients every week who were grappling to figure out what to try to get rid of their relapsed tumor. So I think there are limited patients but enough to explore some of these

therapies in a safe way.

DR. BOLLARD: Cath Bollard, Children's National. Again, a very elegant presentation, so thank you. Obviously, in solid tumors, one big obstacle to immunotherapy is MHC loss and neuroblastoma being a big problem for that.

How much work and investment should be done, in particular in neuroblastoma as well as other pediatric tumors, to really hunt out these MHC restricted epitopes, in reality, probably in vivo; or do you think it's worth exploring strategies, in vivo strategies, to upregulate MHC? I'd just be interested in your thoughts.

DR. BOSSE: I share the same -- I wouldn't say "concerns" the right word. Not only is there enough MHC presented peptide to be targetable, but then also the personalized nature of these therapies, just given the HLA background, has to be the same. I think those are challenges.

I'm excited to see the data that Mark comes up with, of whether these are targetable in our models, which do recapitulate the human tumor quite

well. So I think we could answer the are they targetable question. But it goes back to Steve's question, how do you choose which therapies, and if it's only going to be good for 20 percent or 30 percent of a rare tumor, is that something we should spend our time on?

I think Mark's work is very exciting and a proof of concept, but then we'll have to make some hard decisions of whether we would advance these to the clinic. But a large part will be dependent on the preclinical in vivo studies I think.

DR. LAETSCH: Ted Laetsch. Again, Kris, nice presentation. I know these targets were discovered as lineage specific, but when I look at your RNA-seq data for GPC2, for example, I notice there are some rarer subsets of other tumors that also have high expression. Do you think these should be developed in a histology-specific fashion, or do you think these should be developed in a biomarker-specific fashion, where high expressing tumors, regardless of histology, would be a potential target?

DR. BOSSE: I think with -- easiest biomarker would be GPC2 expression. I think we could very easily develop that as a clinical companion diagnostic via IHC. The question in my mind is why do these other subset of tumors express GPC2? Some of it is MYCN. As shown in lung cancer, MYCN similarly drives GPC2 expression. Some sarcomas, et cetera have MYCN amplified subsets.

So that's probably part of the answer. I think at the end of the day, we'd have to have an enrollment that's based on proven expression, which we've done for other immunotherapies that have come down the pipeline. But we're really interested in understanding why there are a subset of high-grade gliomas -- I didn't show that -- express GPC2, and why is it only that subset. And again, it's probably -- and we haven't proven this -- due to those are the MYCN amplified tumors within each histotype.

DR. SMITH: Kris, a very nice presentation. I think the focus of looking at the alkylating

agent ADCs is probably an important one to pursue and getting beyond the tubulin and binding ADCs for a cancer like neuroblastoma.

One concern that I have, and if you could comment on this, is that the 1 mg per kg dose for a PBD ADC may be higher than -- or may be overpredicting what we might see in the clinic. So the question would be your thoughts on that, and the role of dose-response testing, and looking at activity in the 0.1-0.3 mg per kg range for these PBD ADCs to better assess what might happen in the clinic.

DR. BOSSE: Yes. I think it's a good question. There has been a lot of press about PBD with the DL3 experience. I think the one question is, is PBD the right payload? But I completely agree -- and I have a student in the lab doing this just now, comparing efficacy across different payload classes. And you're absolutely right, tubulin binders won't be effective in our types of cancers. So I think it will have to be in that class. Whether that's the right molecule or not, I

don't know.

We didn't do a lot of dose exploration. We used our initial studies as proof of concept, so I think we'd have to go back and do that with the ultimate therapy that we decide to bring into the clinic. But the payload question is a very good one. It's surprising to me that no one's ever done, at least as so far as I know, that type of very easy panel screen and cell lines that are pediatric relevant at least.

So we're doing that, and I think the data will be not terribly surprising but hopefully prove that putting DM1, DM4, or MMAE on our pediatric-specific antibodies are not the right thing to do.

DR. BENDER: Julia Glade Bender, Memorial Sloan Kettering. I want to thank both you Kris, and Crystal, for really some enlightening talks. It strikes me -- I was very impressed by the data that Crystal presented about tumor heterogeneity and breakthrough then, and relapse rates when you targeted a single antigen.

I think that the ADC approach, because of its bystander effects, may be better perhaps for solid tumors because I would think that the tumor heterogeneity problem would be worse in solid tumors maybe than leukemia, though that may be a naive idea. But I also worry, for example, with a target like GPC2, when you don't understand the actual biology of that molecule as well, what might be the resistance mechanism, and therefore the novel next epitope.

DR. BOSSE: To take your first question, I think the heterogeneity point is a very good one. I think CD19, although very homogeneously expressed, it's a bit heterogeneous in some patients, so even that's able to escape a low antigen expression. So absolutely, I think it's a problem for CAR T cells and solid tumors. There are ways to try to avoid that.

I agree with the bystander effect, and we see some of that. I didn't show that data, but we do see that with this ADC. It's payload dependent, and it's cell context, depending whether you're

able to pump out the drug and get to neighboring antigen negative cells. But I do think it's an advantage of this type of therapy for solid tumors.

You're absolutely right; GPC2, the resistance mechanism could involve changing pathways of tumorigenicity or how the tumor's growing. It's something we're looking into. I think as we test more of these therapies, both in our mouse models and humans, we'll hopefully have the biology studies teed up to understand if we don't see the effect we do, why that is.

So again, as part of this team and taking this from a very biology-driven approach, we'll try to think as prospectively as we can about that to understand if they do fail in the clinic, why is that. Is it just that we're relapsing with low antigen clones or is it something more complicated?

DR. REAMAN: Kris, a great presentation and beautiful work on the GPC2, which actually was the reason that it's on the relevant target list.

Two quick questions. One, given that many of the targets that you discussed seem to be

involved in the sympathetic nervous system differentiation, do you see a potential for toxicity, particularly in young children were they to become therapeutic agents in the future? If so, how would you go about evaluating that?

Then the other question, just to follow up on the heterogeneity, do you see co-expression of some of these in tumors, and would there be an opportunity to prevent escape by using combination immunotherapy approaches?

DR. BOSSE: I'll take your last question first. Yes. It's something we haven't gotten to yet, but we have the data with co-expression and the list of molecules we want to go -- and I think the technology is done in Crystal's lab, that we can easily, quote/unquote "make these type of constructs and study those questions." We just haven't done it, but I think that's an obvious next step, especially if we were to see relapse with antigen-low clones.

Your first question, I think when we were doing the GPC2 work, we were asked by several

reviewers to even take a deeper dive via immunohistochemistry into the nervous system tissues. In part of that work we did, we stained sympathetic ganglia, and spinal cords, and nerve tissues. Those all looked negative by IHC. So we feel like for these stem molecules, it's not expressed on the postnatal tissues.

But you're right; GPC2 is a perfect example. So I think we just have to do the studies. It's largely driven by IHC now. We fortunately have a large clinical resource where we can get these tissues and stain them, but it's antibody dependent, and the binder you're using may not be the same binder you use for IHC. So I think these all just have to be done very carefully.

Then, I think the ultimate the test is the human experience and to understand and do those studies very safely and carefully with the appropriate safeguards in place.

DR. PAPPO: Thank you very much to our speakers.

Now, we're going to take a 10-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience, and we will resume at 10:50 a.m. And once again, thank you very much to our speakers.

(Whereupon, at 10:39 a.m., a recess was taken.)

Questions to the Subcommittee and Discussion

DR. PAPPO: We're going to get started.

There are no open public hearing speakers, so we will now proceed with the charge and questions to the subcommittee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

If there are no questions or comments, we're going to start with the questions. I read the questions?

DR. REAMAN: I can read the questions, unless you'd like to read the questions.

DR. PAPPO: It sounds more influential if you do it.

DR. REAMAN: After listening to the presentations from our speakers and the discussion that we had around those presentations, what we are actually here to do is to look at the list of molecular targets associated with specific cell lineage determinants.

Is there anything that you heard, anything that you are aware of from emerging data that would make it necessary for us to consider adding a molecular target or a target to this list?

DR. PAPPO: So if there are no questions or comments concerning the wording or the question, we will now open this question for discussion, and we will show you the target list that was developed earlier for you just to see what's available.

Steve?

DR. DuBOIS: Steve DuBois, Dana-Farber. There are a few things that are on the other list, but we shouldn't ignore as potential immunotherapy targets. For example, ALK is already on the list

of molecular targets of interest, but I think certainly falls into this category. Likewise, CD99, IGF1R I think could be potentially added to the list.

DR. REAMAN: So let me just clarify a little bit. As I mentioned, at least the classification of the list was somewhat artificial, certainly not based in strong science. So there's a great deal of overlap. I think from the standpoint of what's on the list, what should be on the list, should really be thought about from the perspective of the legislative mandate that we received to develop two lists, relevant molecular targets and non-relevant molecular targets.

So from my perspective, anything that's on the relevant target list could be in one or more of a class. And you're absolutely right. Many of these could in fact be used as part of an immunotherapeutic approach. But where they reside in these sort of artificial classifications, is not something that we have to be too concerned about?

DR. DuBOIS: Thank you.

DR. BOLLARD: Cath Bollard, Children's National. I was curious why SurviveN is not on this list. Had you thought about that?

DR. REAMAN: I think it's on the list, but maybe not in the cell lineage determinants. I remember seeing -- I know SurviveN was -- I think it's probably on the other target list.

DR. BOLLARD: Okay, good.

DR. PAPPO: Based on the presentation, I think that we should add PAPPA for Ewing's.

DR. REAMAN: Correct; I mean, we would agree with that.

DR. PAPPO: A couple of other presentations from Dr. Bosse. I don't know how relevant IGFBPL1 is or is going to be, and if that should be included in the list based on his presentation.

DR. REAMAN: I would think that they're relevant targets with potential application to therapeutic evaluation and intervention. So I would think that GFBPL1, PHOX2B might also -- DLK1, DL3.

DR. PAPPO: That one's there already.

DR. REAMAN: Oh, it is? That's right.

DR. PAPPO: Yes, DLK1 is there.

Any more questions?

(No response.)

DR. PAPPO: I'm going to summarize those questions. It was brought up that there are some targets that perhaps should have been included in the specific cell lineage determinants, but Dr. Reaman explains that there's some overlap between the two lists, and they should be looked at as whether the target is relevant or not, independent of whether it's in table 1 or table 2.

It was also brought up that we should include SurviveN, so we will look at the other list in a few minutes; and if that's not there, that will be added. Also, we thought that it would be worthwhile including PAPPA, PHOX2B, IGF1BPL1 to the target list.

Is there anything I left out?

DR. BOLLARD: Sorry. SurviveN, it's there. It's on the list.

DR. PAPPO: Which one?

DR. BOLLARD: SurviveN.

DR. PAPPO: Okay. It is on the list.

DR. BOLLARD: Yes.

DR. PAPPO: Okay. Perfect. So that addresses that.

Is there anything else I left out or anything I've misinterpreted from our discussion?

(No response.)

DR. PAPPO: Then we will proceed to the next question.

DR. REAMAN: The next question is similar. Please discuss any new or emerging data that provides sufficient evidence that a relevant target currently on this list should be removed.

DR. PAPPO: We're going to show the list again.

DR. REAMAN: Sorry.

DR. PAPPO: Any takers?

DR. REAMAN: I must say it took a long time to come up with these questions here.

(Laughter.)

DR. REAMAN: So we now move to the other

class of relevant targets that we talked about, those on normal immune cells and cells in the tumor microenvironment. From what we heard and what you may know from emerging scientific data, are there additions that the committee would like to bring forward for discussion?

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question to discussion, and we will show you the list also. Cath?

DR. BOLLARD: I'm just interested. TGF beta receptor, did you think of that as a target?

DR. CASAK: It is on the list.

DR. REAMAN: It's not in this class, but it's definitely on the list, in another class.

DR. BOLLARD: Because it is on cells in the tumor microenvironment, just to clarify.

DR. REAMAN: We could probably move it.

DR. DuBOIS: There are some agents targeting IL-15 receptors, so I didn't see IL-15 as a relevant target.

DR. RINI: May I comment?

DR. PAPPO: Yes.

DR. RINI: In the adult world, hypoxia inducible factors, as a transcription factor upstream, a VEGF and VEGF receptor is targetable. There's a drug and drugs in development. I didn't know in the pediatric world if that would be potentially relevant.

DR. REAMAN: Definitely potentially relevant; so HIF-alpha.

DR. PAPPO: There is also one that is being developed for adults in pancreatic cancer called VISTA. I know there's something from MD Anderson, so I don't know if that should be included here. I don't know how relevant it is for pediatrics, but I know that they have an active trial at MD Anderson.

DR. SHAH: The only other one that I would mention is CSF1R signaling, which is macrophage colony stimulating factor receptor. That should be targeting the tumor microenvironment and may have some role there. There's a phase 1 trial at Pediatric Oncology Branch that's been looking at that.

DR. PAPPO: Any other questions? Donna?

MS. LUDWINSKI: Donna Ludwinski. There was a concept I know that was thought about in NAND for using CD105, the endoglin, but I don't know that that needs to be included in this list.

DR. REAMAN: Do you have any more specific information about what it is and what -- I mean, it's something that we can take back and search the literature and consider.

MS. LUDWINSKI: I think the company has pulled the drugs, so I don't know that it's that helpful. But I don't know if that's a relevant target.

DR. REAMAN: But the relevant targets, again, are relevant independent of whether there is a drug or a drug in development because we obviously can't predict the future. So this was CD105?

MS. LUDWINSKI: 105.

DR. REAMAN: Okay.

DR. BENDER: Yes, it's CD105, and endoglin is one of the compensatory pathways for VEGF

inhibition.

DR. PAPPO: I will try to summarize this discussion. It was recommended that TGF beta receptor be moved to this list of the immune cells and cells in the microenvironment; that IL-15 receptor should be added to the list, as well as HIF, VISTA, CSF1 receptor, and investigate a little bit further CD105 as a potential target for this list.

Any other things that I left off or anything else that you would like to add to this question?

DR. REAMAN: CSF1R is actually on the list in another class on here, but it is on the list.

DR. PAPPO: We will now proceed to the next question.

DR. REAMAN: Please discuss any new or emerging data that provides sufficient evidence for the deletion of a target on the list.

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

DR. REAMAN: Does anyone need to look at the

list again?

(No response.)

DR. PAPPO: I hear crickets. We'll move to the final question for this session. Dr. Reaman?

DR. REAMAN: Please discuss any specific recommendations for how best to evaluate and/or prioritize combinatorial approaches to evaluating agents directed at targets on normal immune cells.

I think this follows the discussion that we had after Dr. Mackall's presentation about the fact that response to single-agent checkpoint inhibitors have been somewhat disappointing in the pediatric space; so what kinds of combinations an how should we evaluate them going forward, or how could we evaluate them going forward?

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question to discussion. Cath?

DR. BOLLARD: I think it's important to understand that actually CAR T cell therapy is already a combination therapy. They're combining lymphodepletion with CAR T cells. So I actually

think, personally, the way forward is combination therapy even beyond chemo and T cell therapy.

The low-hanging fruit is certainly checkpoint inhibitors and T cell therapies, whether it be CAR T cell therapies or other immune-based therapies. But I go back to my question from the last speaker, MHC lost is a problem. And if we can look at strategies to upregulate MHC, I think that would be one; then certainly combining with epigenetic modifiers would be another; certainly in the heme [ph] malignancy space, another option to combine T cell therapy, for example, with the decitabine, that sort of age class of agent. That's my immediate thoughts.

DR. SHAH: I would add to that, specifically for CAR T cell therapy, I think we're going to continue to be plagued with the issue of antigen loss. So while there is combination therapy with lymphodepletion in CAR, we also have to think about rationally designing combination multi-antigen targeted strategies.

Crystal Mackall mentioned several that are

currently being tested with 19 and 22, which are the two most active ones that are used in ALL, but I think especially going into solid tumors, we'll have to think about how to do that.

Ultimately, you need to be able to show that you have single function or single antigen targeted activity, but then taking it to the next step, and how to quickly make that happen knowing that there are significant costs of vector production, and getting it through a phase 1 trial. But I think that's really what we need to do in terms of CAR T cell and having it be more durable remissions.

DR. DuBOIS: I think returning to Crystal's paradigm of one side of the slide turning cold tumors hot, I think we need to acknowledge that some of the agents that may turn a cold tumor hot may in and of themselves have anti-cancer activity. So that poses a regulatory issue I think for you to try to understand what is the novel agent contributing if it's being added, even to chemotherapy, or to radiotherapy, or PARP inhibition where there may be some activity of the

partnering agent.

DR. HOTAKI: Sorry. Before you speak, let me know so I can write your name down. We have a running list. Thanks.

DR. SMITH: Malcolm Smith. I'd go back to the combinations involving the checkpoint inhibitors. I think the first two comments highlighted that our primary interest will be in the engineered T cells, and combinations or bispecifics, and different combinations around that.

I would urge the kind of caution that was verbalized earlier about combinations involving checkpoint inhibitors and T cell activating agents that are designed to allow the immune system to recognize a neoantigen or something about the cancer cell.

If we really have a tumor that doesn't have neoantigens and appears to be invisible to the immune system, before we start making combinations, I think we really need some evidence that there is something that is being recognized. If it's not an

neoantigen, what is it?

Before we get deep into combinations, I think there should be a clear understanding that this is what we're targeting with this combination that will allow the immune system to recognize it. And I think the idea that chemotherapy might induce mutations is not a plausible one because you've got billions of cancer cells in the body. Chemotherapy is going to stochastically induce mutations in a few.

So that's not going to induce mutations. Maybe it will somehow allow something else to be recognized, but I think there should be a clear hypothesis and data for what the chemotherapy or the radiation is allowing the immune system to recognize in a pediatric cancer before we get well into these types of combinations.

DR. SHAH: Nirali Shah. The one thing that has not been mentioned is what the effect is of antibody-based targeting strategies and how that impacts either T cell-based approaches or other types of immune targets. So I think we need to

think about what role those have as we try to prioritize combinatorial approaches.

For instance, what is the impact of inotuzumab, which is a CD22 targeted antibody therapy, on CD22 CAR T cells and what those responses are or antigen lost thereafter. Similarly, we need to look at the impact of blinatumomab and what that pre-treatment could do to patients who subsequently go on to receiving CD19 CAR. So I think that there are going to be multiple examples of other antibody-based strategies and the interplay with that in T cell therapies maybe we have to study.

DR. PAPPO: Anybody else? Greg?

DR. REAMAN: I just wanted to point out that we're here really to talk about the Race for Children Act in Section 504 FDARA and the early evaluation of targeted agents, which really doesn't address the issue of combinations per se.

So despite the fact that it doesn't necessarily address targets or mean combinations, when there is information that's available from

either preclinical data or from limited adult clinical data, and if one or more of the agents in the combination is new, there could be a requirement for an early evaluation.

At the same time, when we evaluate new agents that might be coming in as a part of an initial pediatric study plan that are being developed for an adult cancer, and there's some lack of clarity about what the combination might be, we would probably defer decisions about requiring early evaluation until there's more definitive data to suggest that the presumed mechanism of action on a pediatric tumor is also going to require an additional agent, and what that agent should be, we'll have to make a decision.

So I think despite the fact that it's not spelled out specifically in the legislation, I think we want to be as rational and as clinically and scientifically appropriate in the decision-making about when to proceed and how to proceed with early evaluation of novel agents and early evaluation of novel agents that are going to

require combinations with something else.

DR. SMITH: Malcolm Smith. I think that's a good approach. I think also, just to highlight what Crystal Mackall said earlier, that there will be adult cancer studies of combinations, I think that's where we're going to learn of some of these new concepts, that stimulating new approaches to recognizing cold tumors may play out. I think until we see really good signals there, we're not going to be able, absent extraordinary preclinical data, to really make the advances in pediatric cancer.

DR. REAMAN: I just wanted to ask Dr. Bollard, could you just expand a little bit on specific approaches to addressing the MHC loss issue? I know they're probably more theoretical than anything, but just for some clarification.

DR. BOLLARD: Yes. I was hoping that some other clever people around the table would -- but certainly, there's the idea that interferon gamma will upregulate MHC. I don't think that exogenous use of interferon gamma is a realistic option, but

delivering the interferon gamma nanoparticle approach, T cell therapy approach, in a targeted way may enhance MHC class 1 upregulation.

So that's sort of the idea I was thinking of, but if there's a small molecule delivery system that can be utilized as well, that would be ideal, too.

DR. PAPPO: Any other comment?

(No response.)

DR. PAPPO: So I'll try to briefly summarize this discussion for question number 5. I think what caught my attention the most was what Malcolm said, that in order to develop combinatorial approaches, we really need to have very strong preclinical data or very strong data from adults, and try to define what are we specifically targeting and that there should be a hypothesis-driven approach prior to proceeding to just starting combination therapies.

I know the thing that caught my attention was also the possible upregulation of MHC, and you have addressed that already, so that could be a

potential avenue for tumors that have MHC loss. Another issue that was brought up was the combination of epigenetic modifiers to try to enhance T cell function. One issue that was brought up is when you start adding other therapies, whether it's chemotherapy or radiation, then that may represent a regulatory challenge because in the end, you may not know what did the trick and how effective your immune cell-based therapy really was. There was also talk about using combinatorial approaches with T-cell activation.

I think that's pretty much what I have. Let me know if I missed anything, or if I should add anything, or if I should reword anything I said, or if you don't want to sit with me at lunch because I said the wrong thing; one of those things.

(No response.)

Adjournment

DR. PAPPO: So now we will a break for lunch, and because we ended a little bit early, we're going to be here at 12:45, and then we will

start the afternoon session.

I would ask the panel members that there should be no discussion of the meeting topics during lunch amongst yourselves or with any member of the audience. Thank you very much, and thank you again to our great speakers.

(Whereupon, at 11:17 a.m., the morning session was adjourned.)