FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

(pedsODAC)

Thursday, June 18, 2020

10:00 a.m. to 11:49 a.m.

Topic 1

Morning Session

Virtual Meeting

Meeting Roster

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Consultant Management

Office of Executive Programs, CDER, FDA

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(Consumer Representative)

(Participation in Day 1 Topic 1 and Day 2 Only)

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C O N T E N T S

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good morning, and welcome to day 2 of the Pediatric ODAC meeting. Can everybody hear me?

CDR BONNER: Yes, we can hear you.

DR. PAPPO: Thank you.

For the media and press, I would like to announce the FDA press contact is Nathan Arnold, and his email is nathan.arnold@fda.hhs.gov, and his phone number is 301-796-6248.

My name is Alberto Pappo, and I will be chairing today's virtual meeting. I will now call the morning session of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to order.

We'll start by going down the meeting roster and introducing ourselves. We will once again use a call/respond method in which I will call the panel member to prompt the member to speak, and the

panel member will have a chance to introduce him or herself into the record. So we will just wait for the slides to load to show the pictures of the panel members.

David Mitchell?

MR. MITCHELL: Yes, Doctor. Thank you. I'm David Mitchell. I'm a consumer representative, and I'm also a cancer patient with multiple myeloma.

DR. PAPPO: Thank you. My name is Alberto Pappo. I'm a pediatric oncologist at St. Jude Children's Research Hospital, and I'm the chairperson of the Pediatric ODAC.

Dr. Cheng?

DR. CHENG: Good morning. Jonathan Cheng. I'm the industry rep, and I'm with Merck Pharmaceuticals.

DR. PAPPO: Dr. Catherine Bollard?

DR. BOLLARD: Yes. Hi. I'm Catherine Bollard. I'm from Children's National and The George Washington University in Washington, DC.

DR. PAPPO: Dr. Steven DuBois?

DR. DuBOIS: Hi. I'm Steve DuBois from

Dana-Farber Boston Children's, a pediatric oncologist.

DR. PAPPO: Dr. Ira Dunkel?

DR. DUNKEL: Good morning. My name is Ira Dunkel. I'm a pediatric neuro-oncologist at Memorial Sloan Kettering Cancer Center in New York

DR. PAPPO: Dr. Julia Glade Bender?

DR. GLADE BENDER: Good morning. I'm Julia Glade Bender also of Memorial Sloan Kettering in New York, and I am a pediatric oncologist.

DR. PAPPO: Dr. Richard Gorlick?

DR. GORLICK: Good morning, everyone. I'm Richard Gorlick, the division head of pediatrics at MD Anderson Cancer Center in Houston, Texas.

DR. PAPPO: Dr. Theodore Laetsch?

DR. LAETSCH: Good morning. I'm Ted Laetsch, a pediatric oncologist at UT Southwestern Medical Center in Dallas, Texas.

DR. PAPPO: Donna Ludwinski?

MS. LUDWINSKI: Hi. Donna Ludwinski from Solving Kids's Cancer in New York. I'm a patient representative.

DR. PAPPO: Dr. Andy Kolb?

DR. KOLB: Yes. Hi. This is Andy Kolb. I'm a pediatric oncologist at the Nemours Center for Cancer and Blood Disorders in Wilmington, Delaware.

DR. PAPPO: Dr. Katherine Janeway?

DR. JANEWAY: Hi. This is Katie Janeway. I'm a pediatric oncologist and sarcoma specialist at Dana-Farber and Boston Children's in Boston, Massachusetts.

DR. PAPPO: Dr. Naynesh Kamani?

DR. KAMANI: Hi. Good morning. I'm Naynesh Kamani, pediatric immunologist and bone marrow transplanter at Children's National in Washington, DC.

DR. PAPPO: Dr. Tobey MacDonald?

DR. MacDONALD: Good morning. This is Tobey MacDonald. I'm a pediatric neuro-oncologist at Emory University and Children's Healthcare of Atlanta.

DR. PAPPO: Dr. Leo Mascarenhas?

DR. MASCARENHAS: Good morning. I'm Leo

Mascarenhas. I'm a pediatric oncologist at Children's Hospital Los Angeles in the University of Southern California.

DR. PAPPO: Dr. Will Parsons?

DR. PARSONS: Hi. I'm Will Parsons. I'm a pediatric oncologist and deputy director of Texas Children's Cancer Hematology Centers, Baylor College of Medicine in Houston, Texas.

DR. PAPPO: Dr. Elizabeth Raetz?

(No response.)

DR. PAPPO: Elizabeth, are you on mute?

DR. RAETZ: Sorry. Good morning. This is Elizabeth Raetz. I'm a pediatric oncologist at New York University.

DR. PAPPO: Dr. Nita Seibel?

DR. SEIBEL: Hi. I'm Nita Seibel. I'm a pediatric oncologist. I'm in the clinical investigations branch of CTEP at the National Cancer Institute.

DR. PAPPO: Dr. Malcolm Smith?

DR. SMITH: Good morning. I'm Malcolm Smith in the Cancer Therapy Evaluation Program at the

National Cancer Institute of Pediatric Oncologists. Thank you.

DR. PAPPO: Dr. LaToya Bonner?

CDR BONNER: Good morning. This is LaToya Bonner. I am the DFO for this meeting.

DR. PAPPO: Dr. Gregory Reaman?

DR. REAMAN: Good morning. I'm Gregory Reaman, associate director for pediatric oncology in the Oncology Center of Excellence in CDER's Office of Oncologic Diseases.

DR. PAPPO: Dr. Denise Casey?

DR. CASEY: Good morning, everyone. I'm a pediatric oncologist at FDA, Division of Oncology 3.

DR. PAPPO: Dr. Leslie Doros?

DR. DOROS: Hi. I'm Leslie Doros, FDA Division of Oncology 3, pediatric oncologist.

DR. PAPPO: Dr. Megan Zimmerman?

DR. ZIMMERMAN: Good morning. This is Megan Zimmerman. I'm a pediatric oncologist and clinical reviewer at FDA.

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 for 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. 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, the 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.

We will now proceed with the FDA introductory remarks from Dr. Greg Reaman.

Introductory Remarks - Gregory Reaman

DR. REAMAN: Good morning. I'd like to welcome the expert advisors as well as our pharmaceutical company sponsors to day 2 of the Pediatric Subcommittee of the Oncologic Disease Advisory Committee.

Again, as in the past, our focus for these meetings are really to accelerate the timely development of novel anti-cancer agents with potential applicability to one or more pediatric cancers. At the present time, the only pediatric legislative initiative that is relevant to cancer drug development in children is the Best Pharmaceuticals for Children Act.

We will hear presentations and discuss two products in early development under INDs in an attempt to maximize the agency's authority under the Best Pharmaceuticals for Children Act, which is

a voluntary program utilizing the written request mechanism. The products for discussion will be a novel engineered cell therapy, a CD30 CAR-T cell product from Tessa Pharmaceuticals and a menin inhibitor SNDX-5613 from Syndax.

Company presentations and expert panel discussions and recommendations will serve to help inform the review divisions of the Office of Oncologic Diseases and the Office of Tissues and Advanced Therapies in CBER, as well as the Oncology Center of Excellence, as to whether written requests for pediatric assessment should be issued based on the degree of unmet clinical need and potential public health benefit to children; the quantity and quality of both nonclinical and adult clinical data to support pediatric investigations; and finally, an assessment as to whether or not an appropriately designed clinical trial in children provides a favorable benefit-risk.

So again, I would like to thank you all and acknowledge your patience with the technology that we are forced to work with during [inaudible -

audio fades], and, again, we appreciate your participation in this meeting. Thank you.

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

Dr. LaToya Bonner will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, sir.

The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members of the committee and temporary voting members of the subcommittee 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 the subcommittee's compliance with the 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 of the committee and temporary voting members of the subcommittee 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 special government employee services outweighs his or her potential financial conflict of interest and 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 discussions of today's meeting, members of the committee and temporary voting members of the subcommittee 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 investment; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

For today's agenda, information will be presented regarding pediatric development plans for two products that are in development for an oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies if appropriate.

The product under consideration for this session is CD30.CAR-T, presentation by Tessa Therapeutics. This is a particular matters meeting during which specific matters related to CD30.CAR-T will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee

members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 (b)(3) for Drs. Ira Dunkel, Theodore Laetsch, and Leo Mascarenhas.

Dr. Dunkel's waiver involves consulting interests with three companies for which he received remuneration between $0 to $5,000 per year from two companies and between $10,001 and $25,000 per year from a third company.

Dr. Laetsch's waiver involves his employer's research contract funded by the Children's Oncology Group.

Dr. Mascarenhas' waiver involves his employer's research contract funded by AstraZeneca.

The waivers allow these individuals to participate fully in today's deliberation. FDA's reasons for issuing the waivers are described in the waiver documents, which is posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's

Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857 or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to discuss any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms 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 subcommittee of any financial relationships that they may have with the firm at issue. Thank you.

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

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meetings, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Tessa Therapeutics' presentation.

Industry Presentation - Ivan Horak

DR. HORAK: Good morning. Thank you very much, Dr. Pappo, Dr. Reaman, members of the ODAC, and members of FDA. I'm Ivan Horak with Tessa Therapeutics in Singapore, and on behalf of the company, we are very grateful for the opportunity to present our CD30.CAR-T program here and get input from ODAC members.

Tessa Therapeutics is a biotech company which is global but is headquartered in Singapore, which is focusing on the CAR-T technology and virus-specific T-cell platform. We received the AMA designation for relapsed and refractory recurring classical Hodgkin lymphoma early this year, and we'd like to discuss this program at this meeting.

Hodgkin lymphoma is a highly curable disease, and the majority of the patients are cured with first-line therapy and various variations of the first-line therapy, which is usually the combination of multiple agents. After a small fraction of the patients relapse, they advance to high-dose chemotherapy with a bone marrow transplant.

The third- and fourth-line therapy are usually reserved for anti-PD1 antibody or brentuximbab vedotin. But there is no approved treatment for BV [ph] or the PD-1 antibodies. Therefore, there is a high unmet medical need, so therefore there is a small fraction of patients who may benefit from novel therapeutics.

On this graph, it's a well-known phenomenon of the bimodal expression or incidence of Hodgkin lymphoma, where the incidence is high in young adults and patients, and then it's increasing over the aging patient population. It is clear with the light bar that the incidence, although it is very high for young adults, the death rate or mortality

is significantly low, and then it increases with the age of the patients.

Now, in addition to Hodgkin lymphoma, which are universally CD30 positive, there are other substantive non-Hodgkin lymphomas which might be relevant for the pediatric patient population, primarily anaplastic large-cell lymphoma, which is almost 100 percent CD30 positive, and we present a meaningful fraction of the patients, patients with non-Hodgkin lymphoma.

The second subgroup, which is an increased incidence, especially in CD30, are the diffuse large B-cell lymphoma, which represent the meaningful subset of the non-Hodgkin lymphoma in the pediatric patient population. Other CD30 positive non-Hodgkin lymphomas are probably less relevant for the discussion. On the subsequent slide, you can see a summary of the various aspects of the CD30 and the lymphoma, so it's on a high-level perspective.

As I mentioned, CD30 is the universal expression of Hodgkin and the stem blood cells.

This is a well-validated target primarily through the antibody drug conjugate BV, which got approval for Hodgkin lymphoma as well, of course, some substantive non-Hodgkin lymphoma.

It is that [indiscernible] from BV and some other studies using cell therapy and antibodies that CD30 is a safe target, and actually it is universally expressed on the various tumors primarily of Hodgkin lymphoma and some non-Hodgkin lymphoma. It can be expressed on activated T cells, a small number of the L genome [indiscernible], and actually what is clear from the study, which I will present, on the keratinocytes.

T cell therapy we believe is an exciting opportunity to fill the vacuum for patients or opportunities for patients who failed third-line therapy for Hodgkin lymphoma.

On slide number 9, you can see the picture and design of the CD30 construct. The CD30 construct is a single-chain FV, which is both generated from the HRS3 mutant antibody. It has a

linker, which is the CH2CH3 linker, which has the antibody ADCC or Fc receptor component. It's a transmembrane and cytoplasmic tail of CD28 and the CD3 zipper chain, so it will be probably a classical type 2 CAR-T cells.

On the right side of this slide, it's a very general high-level picture of PBMCs going through CD3/CD28 activation, ultimately a transaction of CD30, an extension of the T cells in the presence of the IL-7 and IL-15.

Let me just talk about the clinical experience, primarily in adults, but in a small number of the pediatric patients with this construct.

On the next slide, there are three clinical trials, one published in totality, which is the first trial published in the Journal of Clinical Investigation in 2017 from Carlos Ramos. This is an interesting study because it's using CAR-T for Hodgkin, non-Hodgkin lymphoma but without lymphocyte depletion. In spite of LD therapy, 3 out of the 9 patients achieved complete remission.

The subsequent two studies, a study at the University of North Carolina and Baylor College of Medicine, is the main component of my presentation. On this slide is the design and the number of patients who were treated. This is two parallel phase 1/phase 2 trials for 59 patients under the procurement of the T cells. However, from the 59, 15 were not treated for various medical and nonmedical reasons, which are very well articulated in the blue box.

On the right side of this, you can see 44 patients receive infusion; 26 patients at the University of North Carolina and 18 patients at the Baylor College of Medicine. These are all patients with the classical Hodgkin lymphoma who failed multiple lines of prior therapies, and I will talk about it later.

What is important is there are three different types of lymphocyte depletions. A small group of the patients at UNC received only bendamustine as the lymphocyte depletion with the fludarabine. The additional two groups, one at UNC

and one at Baylor, received a combination of fludarabine; at UNC a combination of fludarabine with bendamustine. At Baylor, it was a traditional flu/cy regimen, so 18 patients in both arms.

The next slide is a demographic baseline of the patients who were treated by this protocol. It is not a surprise that the majority of the patients at the initial diagnosis were stage 3 and 4. The median age of the patient is not very surprising, it's likely predominantly male patients. What is surprising is that a number of the prior therapies may be in this age, ranging from 5 to 17.

Two-thirds of the patients received bridging chemotherapy prior to receiving T-cell therapy. The majority of the patients received prior BV therapy or 93 percent. A significant number of the patients received chemotherapy with anti-PD1 antibody, between three-quarters and up.

The majority of the patients got their high-dose chemotherapy in stem-cell transplants and/or support and 25 percent of the patients received allotransplant on the top of the prior

therapies.

The dose of the cell therapy was – the initial dose escalation started with 20 million cells going to 200, and 200 per meter squared. At UNC, the start was a little bit higher, 100 million cells per meter squared going to 200.

Our next slide is the high level of the clinical responses. In the first column, you can see the total group, and then the subsequent columns are showing according to a different lymphocyte depletion therapy. Going from the first high level, the response for a patient who failed multiple lines of therapy is pretty high.

The protocol is very similar to a response rate with an anti-PD1 antibody and BV as a third- and fourth-line therapy. Three-quarters of the patients responded to the treatment, but what was surprising was the high level of the CR rate, 56 percent, and 8 percent of the partial responses.

That really compares very nicely with the even less patients with BV or anti-PD1. For instance, for illustration, anti-PD1 antibody is

usually around 16 percent, 16, 1-6, complete remission and BV around 33 percent. It was surprising that bendamustine, a small number of the patients had no response whatsoever.

So really, the fludarabine was an important component of the lymphocyte depletion therapy. It seems in a small number of the patients that bendamustine with fludarabine provided a high number of the complete remission compared to Flu/Cy regimen.

This slide I would like to show the plot showing the patients and duration of responses. On the right side, you can see, if it's visible on your screen, the previous therapies highlighting the key important prior therapy, including BV anti-PD1 antibody and the transplant. On the right side, you can see the duration of responses.

Maybe the duration of response for patients from complete remission was basically [inaudible – static]. After first infusion, we followed up [inaudible – static] in February 2020 [inaudible]. Fourteen out of the 29 patients received CR

[inaudible – static] one-year survival, 94 percent.

The next slide, I would like to focus on the differences between the type of lymphocyte depletions. On the left panel, you can see progression-free survival of patients receiving fludarabine containing lymphocyte depletion, so Flu/Cy or benda/fludarabine. On the right side is really the distribution between, on the top on the red line, a patient who failed bendamustine/fludarabine and on the blue side a patient who received fludarabine and cytoxan.

[Indiscernible] in progression-free survival. At 1 year PFS, it was 38 percent for total group. Now when you compare the fludarabine/bendamustine, 57 percent of the patients had the PFS for 1 year and Flu/Cy 21 percent. It seems, again, a small number of the patients, there is some curve separation.

The safety profile of the CD30.CAR was really impressively good compared to, let's say the experience of CD19 CAR T. You can speculate what is the reason behind it, but let's just focus first

on the toxicities. The majority of the toxicities of lymphocytic patient therapy driven by Flu/Cy or benda/fludarabine. There are a few things which really stood out in the safety profile.

One is the cytokine release syndrome reached only grade 1 and was resolved spontaneously and didn't require any therapeutic intervention. The second one is very interesting in that 18 patients, where 41 percent had grade 1 to grade 3 toxicities which resolved spontaneously, were largely asymptomatic.

On their biopsies, it looks like spongiotic dermatitis with occasional involvement of the eosinophils. Very nicely documented by the study showed that on a skin biopsy there was by qPCR a low level of expression of the CD30 in keratinocytes that may be responsible for this toxicity. No CNS toxicity was noticed.

Now, one can speculate why there is a difference between CD19 and CD30. One possibility is a low tumor burden because the CD30 is expressed only on Hodgkin and the stem blood cells. Also,

the tumor volume is much lower than one would see with ALL or [indiscernible] based on lymphoma.

From a small group of patients, phase 1/phase 2, 3 patients account for pediatric category. Two were 15 years old and one 17 years old. They failed multiple prior therapies. Two achieved complete remission, one on the bendamustine and fludarabine and one on the FLY/CY.

Unfortunately, one patient on the Flu/Cy did not really respond to treatment. This patient was probably high risk anyway and required bridging chemotherapy. Two patients who had a complete remission, they waited for cell therapy, bridging therapy. Again, the safety profile was not really different compared to adults. Again, primarily, the toxicity was driven by the chemotherapy.

Interesting is the pharmacology in CD30. CD30 and cell persistence was followed by the two methodologies, flow cytometry and qPCR by the copy number. It is probably not surprising that cell extension and persistence was to some extent dose dependent.

You can see this high dose going up to 200 million cells in benda/fludarabine. You can see a significantly higher area under the curve. There is a pretty significant difference between bendamustine and fludarabine continued regimen at the same cell, and again, is a small number of the patients.

What is surprising is that the persistence of the cells did not correlate with responses. There's a clear dose response in the channel of the cells, so the more cells you give, it's not surprising that the peak and the area under the curve will be higher, so there will be dose-dependent increase of the area under the curve.

The pediatric patients, we had a very limited PK profile, so it's really hard to make too much from it. But it just showed that there is a pretty decent persistence of the cells over several weeks.

So actually I would like to go straight to a pivotal trial design which we submitted to FDA for evaluation. This we call the CHARIOT trial, which

is for patients with relapsed and recurrent Hodgkin lymphoma. In this study, we expect to enroll 82 adults to reach 66 evaluable patients. We expect a 20 percent dropout. It's a little bit on the high side, and we would like to enroll at least 5 pediatric patients.

It will be really interesting to discuss the severe but very limited experience with CD30.CAR. In the pediatric patient population, we would like to start and open for treatment up to age 12, and for the safety, tolerability, and efficacy justify and grow to a lower age population, although the incidence of -- probably can enroll this patient population to a lower age, let's say up to 5 might not be very high, with a high cure rate as I mentioned.

We expect to do a lymphocyte depletion therapy using bendamustine/fludarabine. We plan to provide 200 million cells per square meter per occupation/population [indiscernible]. We plan to dose based on a kilogram primarily for patients who are less than 50 kilograms of weight.

We open the opportunity to give a second dose if needed for patients who have some level of response, so it will be stable disease. But it can be done only between 3 to 6 months after the initial dose. There must be a tumor biopsy to show that the patient has Hodgkin lymphoma which is CD30 positive, and then there will be a long-term follow-up first on an every 3-month basis up to 24 months, and then every 6 months after, up to 15 years as required by FDA.

What is the primary endpoint? It will be response rate, which has to be assessed at 9 months follow-up. There are multiple secondary endpoints, some clinical and some exploratory, looking at the performance of the CD30 cells and looking at the imaging, the cytokine profile, immunological parameters, and circulating tumor DNA. For this we are going to assess safety profile as a very important endpoint for this patient population.

In a tumor, the statistics behind the study design and sample size, we would expect that, number one, the response rate will be evaluated by

the Independent Review Committee assessment. The target is the lower bound, and 95 percent confidence should be response rate over 30 percent. But the assumption is that the overall response rate will be 50 percent and a statistical power of 90 percent.

The sample size is 66 patients with a baseline radiographic assessment that will be evaluated for the primary efficacy analysis. We would like to enroll at least 5 pediatric patients, which will be analyzed separately.

Let me go to how we envision the study procedures. It will not be very different to any other cell therapies. The patients will be initially screened, and we expect the screening to be completed less than 28 days. Then we will draw the blood for cell preparation, and it may need the bridging chemotherapy, which will be allowed.

There will be a washout period prior to infusion of the cell therapy. There will be a baseline assessment. Prior to the cell therapy, the patient has an active disease, and then the

first evaluation of efficacy will be based on the Lugano 2014 or Bruce Cheson criteria, as we used to call it. It will be evaluated 6 weeks post-cell therapy and then repeat for subsequent to 4 months.

The first question for the pediatric order will be what is the experience of bendamustine/ fludarabine? Even in the adult patient preparation, bendamustine/fludarabine is not the most commonly used. The patient therapy, there is a significant experience with bendamustine for Hodgkin and primarily non-Hodgkin lymphoma. But the limited number of pediatric patients who received bendamustine, they tolerated the treatment very well. There's a limited experience in patients with Hodgkin lymphoma, acute lymphoblastic leukemia, acute myelogenous leukemia, but the safety profile is very similar to adult patients.

Treatment of the relapsed or refractory Hodgkin lymphoma usually use -- again, a small number of patient -- 120 milligram per meter squared for 2 days every 28-day cycle. In our protocol, we are using 70 milligrams of

bendamustine for 3 subsequent days. In terms of the PK profile in the pediatric patient population, it looks similar to adults. In fludarabine, there is plenty of experience in the pediatric patient population, and it's very well tolerated.

Now I would like to address the monitoring and primarily focusing on the pediatric patient population. Patients will be admitted for a CD30.CAR-T cell administration as recommended by many panels that have published data in the Annals of Oncology 2017, published by MD Anderson and the Nature Reviews Clinical Oncology, et cetera.

Patients will be monitored for 24 hours, at least, prior to discharge, and they'll be coming daily to a treatment facility for 10 days, excluding weekends. Patients might actually hospitalize, and it will be according to a local practice and will be monitored. After 10 days and discharge from the hospital, patients will have to be in a 30-minute driving distance to a treatment hospital that can be monitored frequently.

The primary reason for that is highlighted

on the subsequent slide. Clearly, there are two major concerns. One is the cytokine release syndrome, although we haven't experienced a grade 2 and higher in our program, but that still remains to be seen in larger patient populations. The cytokine release syndrome in the pediatric patient population requires special attention and has to be treated very aggressively.

The same goes with CNS, central nervous system toxicity, and the grading of the CRES generally used at the 50 criteria for adults is probably not very applicable to infants and definitely not to the young children population. So then they suggest to use CAPD or CARTOX-10 grading system, and that should be performed at least twice a day during the admission. Clearly doctors, nurses, and maybe the family members have less experience of the mental status of their children changing.

So the pediatric patient population will require the significant attention to two of these major potential risk of toxicities.

There are potential challenges of the clinical development of CD30.CAR-T in the pediatric patient population. One is obviously to find a sufficient number of patients and treat them by the protocol on the protocol. That will be definitely very important.

Significant attention has to be done to the volume of the blood required. The medical oncologists, they are very cavalier, and it's easier to draw the blood from adult patients. But clearly the children are not just small adults, but they have a special requirement, and the amount of the blood that will be drawn has to be very carefully assessed and used very carefully, even more carefully than adults.

It will be very important to get leukapheresis for T-cell production. We expect to get 30 mL, and based on our experience, they should provide a sufficient amount of T cells, which is the criteria to have more than one lymphocyte or more than 500 T cells in the blood, so that will be very important. What will be important is not to

only get the leukapheresis but using infectious disease testing and HLA typing just to be sure that we can identify correctly the patients.

Another aspect that has to be carefully addressed are the potential toxicities related to leukapheresis. Children will very likely require the central venous catheter. They might be hospitalized for this. There are some toxicities associated, primarily citrate toxicity, and it has to be carefully calculated by the formulas. The central venous catheter may require sedation might we need to provide blood transfusion to patients.

[Indiscernible] in cell therapy probably more than any aspect of the cancer therapeutics. The quality and well-controlled manufacturing process is essential and is much more complicated than if it's a small molecule or even with antibodies. Tessa is working very closely with Baylor College of Medicine and UNC, and they are working to really transfer the academic process, which is obviously done in a GMP facility, but still it requires some additional tuning up by

industry.

So we have to enhance the control. We have to establish a robust quality control, correct characterization and quality of the GMP manufacturing facility, and establish a two-tier cell banking to really be sure that we have a high-quality and consistent manufacturing process.

With all of this, I would like to complete by saying that it seems to be that in spite of the great success of the Hodgkin lymphoma -- and it's really amazing where the field has got from 1970s, where much was published and ABVD today, but still there's an unmet need for the patient population.

CD30 is a well validated target for classical Hodgkin and for some managed lymphoma. There are very encouraging data from these two parallel phase 1/phase 2 trials. What is encouraging is that the efficacy is very encouraging and the safety profile is very well tolerated. The CD30.CAR-T received the RMAT designation, and we are working very closely with FDA to proceed to a pivotal trial. And with all

this, I would like to close, and thank you very much for the opportunity and for your input.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much for your presentation. We will now take clarifying questions for Tessa Therapeutics. Please use the raised hand icon to indicate that you have questions. Please remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak. It would also be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with "that is all of my questions" so we can move on to the next panel member.

We have Dr. Bollard.

DR. BOLLARD: Hi. It's Catherine Bollard here from Children's National, Washington DC. I'd firstly like to congratulate Tessa Therapeutics for an outstanding presentation. I do have some clarifying questions if that's okay.

The first one is, I note the murine portion

of the single chain. Do you have any data on immunogenicity of that murine portion and if you have any experience with retreatment in the event of that?

Secondly, I note that for your pivotal trial you've decided to select 72 hours as your timing for your baseline scans before lymphodepletion, which is laudable. I just would like to know from your previous data on the other three trials if that was always achievable, that 72-hour window prior to getting the scans, prior to the lymphodepletion.

Thirdly, do you have any hypothesis why CD30.CAR-T cell persistence was not correlating with response?

DR. HORAK: Thank you, Professor Bollard. I'm really glad. These are excellent, insightful questions. Going straight to your question about the hema [ph], the limited data which we have, there is no hema in this patient population. I'm not totally surprised. You know as well as the panel members that, number one, Hodgkin lymphoma is

a pretty immunocompromised environment by itself, but over the seven or many other cycles of the chemotherapy, I'm pretty sure that the immune system is not totally competent.

So no, there's a limited number. We are going to test it much more carefully and vigorously. We will try, but right now I don't have any information that there is a positive hema, at least the data available to test.

In terms of the test, this is a fantastic question. You know better than I do that the logistics of arranging 72 hours prior to treatment may not be trivial in many institutions, and we will discuss it with investigators more in depth. We probably will have to open as a window 3-plus maybe 1 or 2 days, but it's a very, very good question.

In terms of the CD30, the mechanism and the safety profile, I think why there is no correlation between the persistence and the response rate, it's very hard for me to address, but my speculation is that probably in hematologic malignancies, more

than solid tumors, probably the peak and extension of the cells will be more important than persistence. But this is just purely hypothesis. I don't have any data to support it.

Thank you very much for the questions.

DR. BOLLARD: Thanks.

Dr. Pappo, can I ask a follow-up to my question?

DR. PAPPO: Yes, of course.

DR. BOLLARD: For the immune response, that's good about the hema. I guess I was more asking about cell-mediated immune response. I'm sure you're aware that there have been actually restricted T-cell responses identified to the murine portion of the CD19 CARs that are not humanized, so I was really asking about that.

Has that been looked at?

DR. HORAK: I'm sorry. Thank you very much for your clarifying question. I don't have the data to support it one way or another, but it's excellent, and we'll definitely look into it. Thanks a lot.

DR. BOLLARD: Okay. Thank you very much. Thanks, Alberto.

DR. PAPPO: Thank you. The next person is Dr. Kamani.

DR. KAMANI: Thanks, Dr. Pappo. This is Naynesh Kamani from Children's National in Washington, D.C. I have a couple of questions, clarifying questions. First, obviously intrigued by the low incidence of cytokine release syndrome likely related to tumor burden, did you see a correlation between the type of lymphodepletion chemotherapy used and the incidence of CRS? Do you have data on the kinetics of lymphocyte recovery after receipt of the CD30.CAR-T cells in terms of how fast the lymphocyte counts recovered? Because that would obviously determine the susceptibility to opportunistic infections post-treatment.

A couple of other questions; you decided to assess the response rate at 9 months. I'm not sure I understood why you chose that as your primary endpoint. And finally, do you have any preclinical data, from cell lines or otherwise, CAR-T cells for

neuroblastoma cells lines? Because I know that a number of neuroblastomas will express CD30. Thank you.

DR. HORAK: Thank you very much, Dr. Kamani. Those are excellent questions. I will start with the last one. No, we don't have any data on neuroblastoma. We are really focusing on Hodgkin and non-Hodgkin lymphoma, but they are very interesting questions, and we should definitely look into it.

In terms of the lymphocyte depletion, there is no difference at least in cytokine release syndrome. Where there are clear differences, the type of the lymphocyte depletion and the skin toxicity, there was almost none in the bendamustine and there was 40 percent in the Fly/Cy regimen. So that was clearly a difference.

In terms of the lymphocyte recovery, it was pretty good, but I cannot give you a timing from the top of my head, but I can say there are no opportunistic infection, so I assume there was not really -- the longest recovery was actually on

bendamustine/fludarabine, and it was a 3-month recovery for thrombocytopenia. It was the longest durable, discernible side effect of LD therapy.

DR. KAMANI: Thank you. I have one question if I may, Dr. Pappo, one last question.

DR. PAPPO: Of course.

DR. KAMANI: So I assume for the proposed trial you will have a central manufacturing facility, is that correct, with the cells being collected at individual institutions and then being shipped to the central manufacturing facility for CAR-T manufacturing? If so, do you plan to have any specific guidelines or quality control for the leukopheresis procedures at individual institutions, and how do you intend to make sure that that is generally standardized? Thank you.

DR. HORAK: Fantastic. I'm sorry. I forgot to answer your question about the response rate, and my apology for that. Actually, the response rate, FDA was asking that they have to have durable responses. To have let's say 6 weeks as the primary endpoint when you use it based on Lugano

criteria, that's the earliest sign of [indiscernible], it will definitely not suffice.

There was a discussion between FDA and Tessa Therapeutics, and we landed on 9 months. The first discussion is between 9 and 12 months. So it's not that that was -- the response is done first time at 6 weeks post-therapy, but then the responses have to be durable. So a landmark analyses of the response rate will be a 9 months. So that will be the primary endpoint. I'm sorry. I just meet your question. I forgot to answer.

DR. KAMANI: Thank you.

DR. HORAK: In terms of your question about the manufacturing, you are absolutely correct. It will be sent for manufacturing in a GMP facility. Actually, Tessa is now working with the CRO to audit and inspect all the local facilities to be sure that we are using the standardized process. Actually this will, to some extent, address that we have, unfortunately, probably a mostly virtual meeting with all the site's investigators and study coordinators, and we'll be discussing again.

So we will have the biggest treat control in terms of the quality of leukopheresis, and actually the time, which we allow -- from the time of leukopheresis to bring it to a central manufacturing facility, expand the cells, and then cryopreserve it, that's probably something that will be very important, and primarily will be multisites, a global pivotal trial study. We expect to enroll the open sites not only in North America but in Europe as well, so it's very important. Thanks for the questions.

DR. KAMANI: Thank you.

DR. PAPPO: Next is Steve.

DR. DuBOIS: Steve DuBois from Dana-Farber, Boston Children's. I have a few questions, please. The first is with brentuximab, another CD30 targeting agent, and there have been reports of serious pulmonary toxicity. I wonder if that's -- I'm not a lymphoma expert, so I'm wondering is that thought to be due to the payload of that antibody drug conjugate or is that potentially an on-target effect? That might be

worth monitoring as part of your trial.

My second question is if you have encountered cases with progressive disease after response where CD30 has been lost on follow-on biopsy? Then the third question is what is your recruitment strategy as it pertains to the patients age 12 to 17 years of age and how is that strategy playing out in terms of the types of clinical trial centers that you are planning to include as part of the trial?

DR. HORAK: Thank you [indiscernible]; excellent questions. Let me start with your pulmonary toxicity. I'm not aware that it happens with a naked antibody. I'm not aware that it happens with the CD30.CAR. I would be assuming that it's more payload related, but we definitely will be monitoring patients from all safety perspectives.

In terms of the CD30 load, that's a fantastic question. I'm sure it's driven by experience with CD19 and CD22. Number one, 90-plus percent of our patients have failed after the DD

therapy, and we had almost 60 to 75 percent complete remission and 88 percent response rate. There's sort of a clinical justification there must be CD30 there.

There are actually better examples. There is post-relapse, a few biopsies for patients, or actually after CD30.CAR. In all, the CD30 was there, and actually I'm not aware that somebody will be the mutation load if this patient has a mutation on the binding side of CD30, but there seems to be there is not. With the data available to me, I can say that CD30 loads are probably not a mechanism to escape resistance to a CD30.CAR-T, so it's not similar to CD19 or CD22.

I've shown the pediatric strategy, so I'm a big fan of pediatric patients working UNC starting my previous life. There are several clips in various pediatric institutions. We go after the major pediatric institutions where I hope that you will enroll at least 5 pediatric patients for this study.

So yes we are going very actively, not going

to the typical adult cancer institutions in lymphoma but specifically to institutions where they have the patients and hopefully they will be able to support our clinical trial. So thank you very much for the question.

DR. DuBOIS: Yes. Thank you. Alberto, no further questions for me. Thanks.

DR. PAPPO: Thank you.

Ted, you're next.

DR. LAETSCH: Hi. Ted Laetsch. Steve asked the majority of my questions. I guess the last question I would have was around your pediatric dosing. It looked like the potential of the target dose was lower for children if you do 2 x 10 to the 6 cells versus 200 million cells per adult patients, and I just was curious about the rationale for that.

DR. HORAK: Excellent question. We talked to some pediatric oncologists, so we plan to use 5 million per kilo. Yes, it might be a lower dose, but actually it did work very well in 2 out of 3 patients. It's a very good question. Based on

the PK profile, it's probably okay, but we didn't, in a very formal way, study the dosing of the CD30. So we are using the dose more coming from a CD19 CAR rather than our own PK/PD study, which we'll identify; so following more the approved the CD19 CAR.

I believe I answered the question.

DR. LAESTCH: Yes, thank you. No further question.

DR. HORAK: Thank you very much.

DR. PAPPO: I have a couple of questions. What is the approximate time, from the time of leukopheresis, to stemming the product, to getting it back; just for the panel members to have an idea of how long you would have to give some kind of bridging therapy? The other question I had is, was there any correlation with any of the side effects and response? Specifically, I was very intrigued about what you saw in the skin, that patients that have grade 3 skin reactions had a better chance of responding or not.

Then to follow up a little bit on what Steve

said, are you investigating any mechanisms of resistance other than CD30 downregulation to try to explain why patients did not benefit long-term, a significant proportion of them, from the CAR-T cell therapy? Finally, are you exploring other enhancements to your CAR-T cell, like adding additional co-stimulatory molecules to improve the activation, survival, and expansion of modified T cells?

Those were my questions.

DR. HORAK: Thank you very much. These are all fantastic questions. Let me maybe start with the vein-to-vein time. The vein-to-vein time is really driven by the two factors, unfortunately. One is to get enough cells and one to really get the testing. That's really so the testing piece could be sure that you have the quality attributes and you don't have mycoplasma, any [indiscernible], et cetera.

This is something that is under discussion. It depends on what type of testing will be allowed by FDA. It may have implications of the

vein-to-vein time. I would say it's probably around 5 to 6 weeks. These are all the testings. Can it be shorter? Maybe it will be testing as part of our discussion with FDA.

In terms of the mechanism of resistance, it's a fantastic question for cell therapy and a fantastic question for antibodies, for immunotherapy, et cetera. Yes, we will be definitely studying. We have interest in the biomarkers, although it's not really easy to come up with the biomarkers for 6-line therapy for Hodgkin lymphoma, so that will be something that we'll have to do and look into it.

We'll definitely ask the investigator to get a tumor biopsy, and you as a treating physician, you know better than I do that it's not easy, when the patient has a progressive disease, to get a biopsy from every patient. It will be extremely valuable, and we'll be very much interested to do some deep dive. We have a pretty active biomarker program in our company, so we're definitely very much interested.

Your last question is a very, very fundamental question, which we are very much interested in how to enhance the strength and the quality of the T cells to be even more robust. Yes, we are working on it. Hopefully in a couple of years, we'll come again to the pediatric ODAC, or maybe sooner, to present some of the strategies, not necessarily only autologous, but maybe other programs.

But at this moment I think for this particular program, I think we'll stick to CD30.CAR-T. We are not going to change the signaling molecule and we are not going to do any other alteration because that will definitely derail the focus an really harm the medical and patient population as soon as possible. But we are working on it as very important future programs. Thank you very much for the question.

DR. PAPPO: There was just the correlation between side effects and response. Did you see any --

DR. HORAK: I'm sorry. My apology.

Actually not. The side effect -- number one, in terms of the cytokine release syndrome, the majority were a grade 1, and the majority of responses, they're complete remission, so it's really tweaking a very small number.

In terms of the skin toxicity, it would not be a very good because a significant number of the patients had a complete remission of UNC, and there was no skin toxicity or almost none. So the majority of skin toxicities were driven inside cytoxan fludarabine, so it's very difficult to really come up with a correlation.

We have a grade 3 cytokine release syndrome or maybe we have a high [indiscernible] response. This kind of correlation we didn't see in a relatively small number of the patients. But we'll be monitoring it carefully in our pivotal trial and see what we can learn from it. Thank you very much for your question.

DR. PAPPO: Thank you. No further questions.

Malcolm, you're next.

DR. SMITH: Thank you, Alberto.

Malcolm Smith, NCI. First, thank you for your excellent presentation. My question is whether the CD30.CAR-T is being envisioned as providing a path to subsequent auto or allo transplant or alternatively as a curative strategy for the pediatric patients who might enroll in the study?

DR. HORAK: Dr. Smith, you are reading my mind. Thank you very much for the question. One of the major interest, or big interest, in the company is how we can bring this hopefully education and safe therapy to an early line of the therapy, primarily for a patient who may have a long-term sequelae like pediatric patients.

So yes, the goal is that after we enroll a certain number of the patients, we will look at the efficacy and safety profile and have a further discussion with FDA of how this can be introduced to early line of therapy and how the study design will look. Yes, that is definitely in our mind.

The second question is true as well. The

CD30.CAR is a springboard for our thinking to go to our program, yes, and actually the study will be hopefully open very soon. Thank you very much for your questions.

DR. SMITH: Thank you.

DR. PAPPO: Next is Julia Glade Bender.

DR. GLADE BENDER: Thank you very much. Julia Glade Bender. [Inaudible - audio gaps].

DR. HORAK: I'm having difficulty hearing you. I'm sorry.

DR. GLADE BENDER: [Inaudible.]

DR. PAPPO: We're having a little bit of difficulty hearing you.

DR. GLADE BENDER: Can you hear me better now?

DR. PAPPO: Much better.

DR. GLADE BENDER: Okay. I'm not a cellular therapy specialist, but just a few questions. Thinking along the lines of Dr. Smith's question, I know you said that persistence was not predictive of response, but how about duration of response? Because ultimately that is an issue when used in

the relapse strategy without a consolidation plan.

DR. HORAK: Thank you very much, Dr. Bender. That's an excellent question. As I mentioned, the study was still censored, what we presented, and even the data, which were accepted to the Journal of Clinical Oncology, there is still longer term follow-up. We'll definitely look at a correlation between durability of response and the persistence of the cells. It's an excellent question. Thank you very much.

DR. GLADE BENDER: And one other question. Is there a minimum dose at which to expect a response [inaudible].

DR. HORAK: Unfortunately --

DR. PAPPO: You're fading again, Julia.

DR. GLADE BENDER: Okay. Sorry. I apologize.

In terms of [inaudible].

DR. PAPPO: It's still very choppy.

(No response.)

DR. PAPPO: Julia, are you still on the line?

(No response.)

DR. PAPPO: Okay. We will come back to Dr. Glade Bender in a minute. Next is Nita Seibel.

(No response.)

DR. PAPPO: Nita?

(No response.)

DR. PAPPO: Okay. Next is Dr. Reaman.

DR. REAMAN: Thanks, Alberto.

Dr. Horak, thank you for an excellent presentation. Just a couple of questions. Can you clarify that your pivotal study will not proceed until the commercial manufacturing process has been established? And if that is in fact the case, do you have a timeline for when that should occur?

DR. HORAK: Thanks a lot. This is an excellent question. Yes, we plan to deal with a commercial manufacturing process. We are working, but unfortunately COVID-19 changed our life in every aspect, not only the study conduct but in the preparation, manufacturing, and et cetera.

We are targeting the end of the year, but many things can change between now and then and

depends how the COVID-19 will proceed in Europe and in the United States. The target is to open it towards the end of the year, and I hope that we can stick to it. We are all very enthusiastic and working very hard to stick to the timeline.

DR. REAMAN: Okay. Thank you. Another question relates to the number of adolescent patients that you plan to enroll on this trial. Why was the number 5 selected is number one Number two, do you think 5 patients is sufficient for evaluation of efficacy? Even though much of the efficacy could be extrapolated from the adult experience, only 5 patients is a pretty sparse number for even assessment of short-term and long-term toxicity.

DR. HORAK: This is an excellent question and is a very forming [indiscernible] question. Unfortunately, I don't have any good justification for number 5. I think the concern is we want to have pediatric patients in the study. We have a history to really work very hard to include, as early as possible, children in our drug

development.

A concern which I have specifically is really the high curability and relatively low incidence of the Hodgkin lymphoma under age 12. The number of patients we can enroll will not be very easy. They are very much open minded to hear the input from pediatricians what would be a reasonable number of the patients to be treated to assess not only the efficacy, which I agree can be extrapolated from adults, but primarily the safety and long-term safety.

So it will be fantastic to get input from pediatric ODAC. It was arbitrary to pick up the number 5, I have to admit, and age 12, again, was really coming more from the discussion of some investigators that probably to get a younger patient population might be even less likely. But again, we would love to hear the opinion of pediatric ODAC.

DR. REAMAN: I think it's a somewhat disappointing arbitrary number. I would encourage you to think bigger. I guess I would also question

the age of 12, although, as you pointed out, the majority of patients with this disease are adolescents, but that doesn't mean that a hundred percent of children less than 12 with classical Hodgkin lymphoma are cured.

The other factor to consider here is that the real unmet need I think in classical Hodgkin lymphoma is not just in salvage therapy but in frontline therapy that may in fact be more efficacious and less toxic from the standpoint of cardiac toxicity and second malignancies related to radiation therapy, which are significant factors in the management of Hodgkin lymphoma.

I would just encourage you to think a little bit more extensively about the pediatric population as far as numbers and as far as the age groups that you would want to assess these cell products

DR. HORAK: Thank you very much, Dr. Reaman; an excellent point. I have to admit that we are all thinking of how to bring the CD30.CAR to the early line of therapy primarily for the pediatric patient population and for the elderly patient who

does not tolerate high-dose chemotherapy. Unfortunately, I do know that the long-term sequelae of the chemotherapy and primarily high-dose chemotherapy for children might be devastating over the lifespan they hopefully have ahead of them.

So the question will be, really, what is the minimum number of patients one would need from a late line of therapy to be courageous and to go to the second-line pediatric patient population, and that will be, really, a very interesting discussion. Definitely the company is very much interested to think big and think how to push CD30 to second line primarily in children. Yes, I one hundred percent agree.

DR. REAMAN: Thank you.

DR. HORAK: Thanks a lot for the question.

DR. PAPPO: I'll try to go back to Julia.

Julia, are you on the line?

DR. GLADE BENDER: Yes, I am, but I don't know if you can hear me any better.

DR. PAPPO: Much better, so go ahead with

your question.

DR. GLADE BENDER: Okay. Thank you. I was just going to ask about a minimal dose, effective dose, because I did notice that the one child with progressive disease had received a log fewer cells.

DR. HORAK: This is an excellent question. Unfortunately, it was not robustly studied, I would say, even for the adult patient population and definitely not for children. So yes, the general perception is looking at the peak of the cell expansion and the persistence is cell-dose dependent. So I would assume that more is better in this case, primarily when the treatment is very safe and very well tolerated, but what is the lowest level, I really cannot answer the question.

The lowest study, to my knowledge -- and maybe Professor Bollard knows this better -- I think was around 20 million, and that was borderline efficacious. So I think that when it comes to a dose in adults around 100 million, the efficacy is going up.

Is there a cap in terms of the response? I

really don't know. Tessa plans to open this year the study in non-Hodgkin lymphoma initially as a dose escalation study, where we in a very formal way will start the dose which we are using right now for Hodgkin, 200 million per meter squared, and try to dose escalate and see if there is any dose dependency.

But based on the data available to us, I unfortunately cannot answer the question of what is the lowest level. But probably we don't have to worry too much about the lowest level as long as we can get a T cell, which generally we were very successful, or our academic colleagues are very successful to generate a sufficient number of the T cells and see the safety is good. So probably we don't have to go lower. But again, I don't think that in children it was in a formal way studied, and in adults, very limited data in 2 or 3 patients per cohort.

I'm sorry --

DR. GLADE BENDER: Thank you very much. I was just afraid of underdosing children. That was

all. Thank you so much.

DR. HORAK: And if I may give an addition, that's the reason why we are doing a very formal dose escalation study of non-Hodgkin lymphoma. I worry that the patient with the larger tumor volume or tumor burden, they may benefit with a high dose. So again, to address your question, to prevent the underdosing of patients, but thank you a lot for your question.

DR. PAPPO: We have Catherine Bollard.

DR. BOLLARD: Sorry. Just to build on some of the other comments, especially about durability of the response, do you have any data in patients who have been retreated with the CD30 cell?

DR. HORAK: It's a fantastic question. I believe there are a couple and actually are very short in duration. One patient has stabilized and one patient has complete remission, which was a very short duration I think.

DR. BOLLARD: Thank you.

DR. HORAK: Thank you very much.

DR. PAPPO: Donna?

MS. LUDWINSKI: Thank you very much for this presentation. I would reiterate what Greg already brought up about considering lowering the age without assuming that all of those under 12 are going to be cured first time around, and also this issue about bringing this forward to frontline to reduce toxicity.

I had a question. I was intrigued to see that you had an allogeneic CD30 CAR that's in development using EBV-specific T cells, and I was curious about your development plan and how you see that fitting into this particular landscape.

DR. HORAK: That's a fantastic question one of my favorites. Thank you very much. Going back to your first question or the first comment, I see that really the goal, when I'm talking about the 5, I understand Dr. Reaman is concerned about the small number of patients. We just would like to see the safety is really, we think, to be as good as the whole disease and open it to age pretty much as low as it can go.

So I do think that after we enroll a few

patients and do feel more comfortable, we are more than happy to amend the protocol and go to a lower age. So that will be the first answer.

I think we are working on a development plan for CD30 allo DDST [ph]. You are a right. There are a lot of very exciting hypotheses behind the strategy, which was developed by some people around the risk, around ODAC, at Baylor College of Medicine and Sloan Kettering, so a lot of interest in this technology.

They plan to first go after CD30 positive lymphoma and not really specific for Hodgkin or non-Hodgkin. Then based on the activity, whatever we observed in the phase 1 program, we will make a determination where to go with it and in which subset of Hodgkin or non-Hodgkin lymphoma.

I think it's very likely that our CD30.CAR will be significantly ahead of our program, and therefore it's very likely that it will be the first, if we decide to and data support it, to push it through an earlier line of therapy. Trust me and trust the company, we have a significant desire

to bring it earlier. Unfortunately, our weakness from long-term toxicity and from Hodgkin lymphoma chemotherapy is definitely not pleasant. It's an excellent question and suggestion. Thank you very much for your questions.

DR. BOLLARD: Good. Thank you. No more questions.

DR. PAPPO: Okay. Nita, I see your hand is still up. Would you like to ask a question?

DR. SEIBEL: Yes, I have two questions. Nita Seibel from the NCI. First of all, have you seen any development of the CAR-HLH syndrome that's been described after some of the other CAR-T's such as CD22 that follows the cytokine release syndrome? And then secondly, can you expand or give more description about any cardiac toxicities that you've seen?

DR. HORAK: So the second one is easier. I cannot discuss any cardiac toxicities, but can you clarify? I'm not really sure I fully comprehend your first question.

DR. SEIBEL: Well, there's been a

description, particularly after CD22 CAR-T cells, that after cytokine release syndrome, that they've seen what is being sort of labeled as CAR-HLH or hemophagocytic lymphohistiocytosis.

DR. HORAK: None. None in --

DR. SEIBEL: None? Okay.

DR. HORAK: No. It's a very, very good question. Thank you very much. I'm sorry. I just didn't comprehend what you were fully asking. Sorry.

DR. SEIBEL: Sure.

DR. HORAK: Thanks a lot.

DR. SEIBEL: Thank you.

DR. PAPPO: I think we have one last question. Greg?

(No response.)

DR. PAPPO: Greg, do you have another question?

DR. REAMAN: No. I'm sorry. I didn't put my hand down. I apologize.

Questions to Subcommittee and Discussion

DR. PAPPO: Okay. So if there are no

additional questions, we will move to the next portion of the meeting. Today, there is no open public hearing session, so we will go straight to the charge and questions to the subcommittee and panel discussions.

After each question is read, we will pause for any questions or comments concerning its wording, then we will open the question for discussion.

I will ask the FDA to read the first question, please.

DR. ZIMMERMAN: Hi. This is Megan Zimmerman with FDA. The first point for discussion is: pediatric age groups include neonates from birth to age less than 1 month; infants, ages 1 month to less than 2 years; children, ages 2 years to less than 12 years; and adolescents, ages 12 years to less than 17 years.

Please discuss which pediatric age groups are candidates for study with CD30.CAR-T and which can reasonably be excluded.

DR. PAPPO: Okay. If you want to raise your

hand and try to address these issues, let me see.

Malcolm, you're first.

DR. SMITH: Thank you, Alberto. Malcolm Smith, NCI. Regarding the age range that might be studied with the CD30.CAR-T, I think it's important to take a reality check on how many patients might be able to enroll. To a first approximation, the number of patients who might be eligible for the study each year would not be much higher than the number of patients who die from Hodgkin lymphoma each year within the age range since this is a treatment that's given after failure of the likely curative therapeutic options.

When you look at mortality data for the U.S., for the most recent five-year period for which we have data and for children who are less than 15 years of age, and deaths attributed to Hodgkin lymphoma, it was two per year. Looking at 15 to 19 years, the deaths attributed to Hodgkin lymphoma was around seven per year.

So I think it's going to be really challenging to enroll certainly less than 15. I

think you can pick a number, 5. It may be desirable to get more than 5, but 5 may actually be a realistic number.

The second comment I would make in terms of moving this to frontline, because that was discussed during the presentation and moving into frontline, the pediatric setting, I think here, as well, is a kind of reality check. The activity of checkpoint inhibitors in Hodgkin lymphoma has generated this whole new line of promising therapeutic research.

There will be a generation of clinical trials attempting to incorporate these agents into the frontline setting, and these trials I'm sure will make attempts at minimizing or avoiding radiation exposure for as many patients, as well as ameliorating other long-term effects.

So I think a few years from now, we'll need to check on the results from these studies and the anticipated long-term effects based on the chemotherapy and radiation doses used in these studies to think about what are the needs for this

patient population. Thank you.

DR. PAPPO: Thank you, Malcolm.

Catherine?

DR. BOLLARD: Thank you very much. I agree. This is Catherine Bollard here. I agree with everything that Malcolm just said. The caveat I would just add to the children age group, or even less than that, is there is a percent of children in that group who present with Hodgkin but actually have an underlying immune deficiency that needs workup and probably allo transplant; so just to be aware of that as well.

DR. PAPPO: Thank you.

Julia?

DR. GLADE BENDER: Just to advocate for access, while I don't think it should be required, perhaps it could be allowed for children ages to less than 12. Again. I'm thinking actually more of an anaplastic large-cell lymphoma than of Hodgkin lymphoma.

In my recent experience, I've had several younger children, despite the novel therapies, that

still have a very difficult time with the anaplastic large-cell lymphoma. So perhaps widening eligibility for younger children, at least to get experience with this drug, might be of interest.

DR. PAPPO: I think that's going to be one of the questions that is coming, so we can address that issue when that question comes up, where we can incorporate this into other malignancies that have CD30 abnormalities.

Ted?

DR. LAETSCH: Hi. Ted Laetsch, UT Southwestern. I was just going to say something similar to what Julia said, which is that I agree completely with Malcolm that the number of patients, especially in the lower age ranges, will be very small, but I don't know that there's a strong rationale to put a hard cut at 12 years for eligibility if you're already using weight-based dosing, et cetera, for patients older than that.

So I would hate to exclude an 11 year old with Hodgkin who might potentially benefit from

this therapy. Obviously, the infants and neonates are a different group, and I think certainly would not be in the Hodgkin cohort.

DR. PAPPO: Thank you. I don't see any other questions. So if there are no additional questions, I will try to summarize the discussion for question number 1.

It appears that the mortality rate for Hodgkin is very low, especially in patients that are less than 15 years of age, therefore, there may be a challenge into recruiting into this clinical trial. Whether it's 15 years of age or older, or 12 years of age or older, or if it's going to be age/weight-based, if the patient is, for example, 11 years of age but meets the weight criteria, they should be allowed to be enrolled in the clinical trial.

Regarding the use of this therapy as frontline, I believe that we need to await the results of other clinical trials that are ongoing that may show promise with incorporation of immune check inhibitors in patients with Hodgkin disease.

Finally, we will discuss a little bit more in one of the next questions whether additional histology should be included in this kind of trial and whether the age range should be modified based on the histology.

Please let me know if I left anything out or if it's okay to move to the next question. Did I summarize everybody's comments accurately?

(No response.)

DR. PAPPO: It sounds like a plan. We're going to go to question number 2.

DR. ZIMMERMAN: This is Megan Zimmerman with FDA again. The second question has two components. Please discuss the variability of the preparatory lymphodepletion therapies and their potential applicability to the pediatric population, and please discuss CD30-positive malignancies other than classical Hodgkin lymphoma, which could be studied in pediatric patients.

DR. PAPPO: Okay. Julia, you go first.

DR. GLADE BENDER: I apologize. I had not put down my hand, but here is where my point is

relevant. I think we need experience in patients with other diseases like anaplastic large-cell lymphoma, and that might involve children that are younger in age than those with recurrent refractory Hodgkin disease.

DR. PAPPO: Thank you.

Malcolm?

DR. SMITH: I'm sorry, Alberto. I put my hand down from the previous question.

DR. PAPPO: Okay. I'm sorry.

Ted?

DR. BOLLARD: Yes, thanks. This is Catherine Bollard. Firstly, discussing CD30-positive malignancies other than classical Hodgkin, certainly pediatric ALCL is CD30 positive. COG has currently completed a study with the upfront use of brentuximab in this setting. The problem here is that most pediatric ALCLs also express ALK, so the ALK inhibitors such as crizotinib as high efficacy here, even in the single-agent setting for relapsed disease.

So while Dr. Smith explained the small

numbers of relapsed/refractory Hodgkin lymphoma patients in the pediatric setting who would be eligible, I would argue that it would be even less in the pediatric ALCL setting, which would make this challenging.

I do think there is some concern about the variability of the [indiscernible] regimen. Bendamustine or fludarabine, this is the only setting that I'm aware of using CAR-T cells where use with this has been used as a lymphodepletion regimen with bendamustine/fludarabine. To my knowledge, there's no data using fludarabine/ bendamustine alone in combination with children; I'm not sure about adults either. So this would be data that may be important.

That being said, the safety profile of your approach seems extremely reasonable, and given the data that you have so far, it would suggest that you should go with the standards and pro-depletion regimen of bendamustine/fludarabine, in my opinion.

DR. PAPPO: Thank you very much.

Ted?

DR. LAESTCH: Apologies, Alberto. I put my hand down.

DR. PAPPO: Thank you.

Dr. Kamani?

DR. KAMANI: Yes. This is Naynesh Kamani. In terms of the preparatory lymphodepletion therapy, I agree with Dr. Bollard that I'm not aware of bendamustine having been used in children as a lymphodepletion regimen, and this would be probably the first setting where it would be used.

Fludarabine, obviously we have a lot experience with it, but I agree with her that based on the prior experience with bendamustine and fludarabine, that would be the regimen that seems the one that we should go with for this trial.

In terms of the other malignancies, since we're talking about a very limited number of patients that are proposed, I doubt that there will be sufficient information to deduce effectiveness in Hodgkin lymphoma per se.

Based on that, I would consider allowing younger patients, definitely those between 2 and

12 years of age, with other indications such as ALCL to be entered only to allow us to gain more experience with that age group as well. In terms of the ability to collect cells, that should not be a problem per se.

So I think because the current indication is classical Hodgkin lymphoma but the number of patients that are being suggested is not going to tell us a whole lot about efficacy per se, I think I would include younger patients, if they qualify, based on their diagnosis, whether ALCL or other indications. Thank you.

DR. PAPPO: Thank you very much. I do not see any other hands.

Dr. Cheng? I'm sorry. Dr. Cheng?

DR. CHENG: Hi. Jon Cheng, industry rep, and I'm with Merck. I had a comment and then maybe a question for the panel.

Oftentimes in a study as being proposed by Tessa, it's an adult Hodgkin lymphoma study, and along adolescents, I think it is a desirable thing. However, when you start to go into pediatric

patients with lymphoma, it causes some operational challenges because oftentimes those are unique COG sites or children sites, so choosing the site gets to be a little bit trickier once you get to the younger pediatric population outside of the adolescents.

So oftentimes you're limited in the choices of how many sites you can go and your footprint that you want to use. So I'm interested in the panel's perspective, or do they have any thoughts, as to how to help industry be able to enroll not just adolescents but the younger patient population, knowing that oftentimes it's different investigators, different sites, and different clinics.

Oftentimes industry will choose an adolescent cutoff rather than a pediatric cutoff for that reason, not because we don't want to understand it in younger patients. It's just that it's operationally challenging to have those two pieces in the same study.

DR. PAPPO: Does anybody want =to tackle

that question? Steve? Go ahead, Steve.

DR. DuBOIS: Yes, this is something that's extremely important, so I'm glad you're bringing it up. It's kind of meaningless for a trial to be open down to age 16, 15, 12 or younger if the sites that are participating are exclusively large medical oncology centers.

I think what I encourage sponsors to think about is centers that have both a robust pediatric program and a robust medical oncology program under the same roof; so one IRB, one contract, and investigators who can participate both on the pediatric side and on the medical oncology side. But it's really a key question and a really tricky one.

DR. PAPPO: Julia, do you want to add anything to this?

DR. GLADE BENDER: Yes. Julia Glade Bender of Memorial Sloan Kettering. I want to second what Steve said, but I think what I am advocating here and what I think that Dr. Naynesh is advocating here is really -- Dr. Kamani, I'm sorry -- is it

possible, rather than to require the accrual of a certain number of patients within an age group, just to have it open but not have it hold up the whole study if it doesn't accrue, but just to maintain access so that we could learn more about safety in the pediatric space.

I think that impacts on what Dr. Cheng is saying because in that case, your involvement of centers isn't focused on can we get the adequate numbers of patients, but rather do we have a few centers available that could enroll a patient, because I think as pediatric oncologists, we're very good at referring to highly specialized centers if they have a trial open that is not open elsewhere to get access for a patient, but if there is no center that has a means to access a new agent for the younger patient, that's when we have a serious issue.

DR. PAPPO: I think that site selection is going to be key, exactly what you're saying. We experience that with a rare tumor community. It takes a lot of work, and a lot of money, and a lot

of personnel to open a trial in which you may not even enroll one patient a year. So I think that size selection should be carefully studies and perhaps having centers, like Steve was saying, that have the ability to have patients in the adult, young adult, and pediatric group would be advantageous.

Any other comments regarding Dr. Cheng?

Dr. Cheng, does that answer your question?

DR. CHENG: Yes, it does. Thank you, and that's very helpful. There aren't that many centers that, of course, do both, and a lot, as you know, of pediatric centers that do a lot of work [indiscernible] than Hodgkin are sometimes separate. But I do think it's a helpful starting point and helpful advice, so thank you.

DR. PAPPO: Katie, you're next.

DR. JANEWAY: Yes. I also wanted to comment on this topic. I am likewise very glad that this topic was raised in the context of this discussion. I agree with Dr. Glade Bender and Dr. DuBois and their comments about larger centers that have a

medical oncology and pediatric oncology component, but I wanted to provide another thought about this as well.

If you do want to reach pediatric centers, I think what we have learned from our trials in sarcoma is that it's actually important to begin this process of engaging either the pediatric, if the protocol's being developed mostly in medical oncology or medical oncology if it's being developed mostly in pediatric oncology, very, very early in the trial development process.

I think if you do that, you greatly increase the chances that you will be able to accrue successfully across the age spectrum. That's actually what we're doing in sarcoma now, is just to have working group calls that cross medical and pediatric oncology when we're developing trial concepts.

DR. PAPPO: Thank you, Katie.

I don't see any other hands up, so if that is okay with you, I'm going to try to summarize the discussion that we just had. Regarding other

potential malignancies that could be included in this trial includes patients with anaplastic large-cell lymphoma, and that would also raise the possibility of decreasing the age range to less than 12 years of age, although given the number of patients and the excellent therapies that are currently available, including ALK inhibitors, accrual might be problematic.

The second issue, as far as the appropriate regimen, there's not a whole lot of experience with bendamustine in this patient population, however, given the data that was presented, our two experts believe that this is a reasonable appropriate regimen for this specific protocol.

Finally, there was a lot of discussion regarding the operational challenges to recruit patients in these types of clinical trials. Some of the challenges that were raised was which site should be opening this trial, early engagement of pediatric investigators to try to increase accrual, and also see if there are centers that have combined adult and pediatric programs that could

facilitate all of the IRB procedures.

So let me know if I've summarized everything to your satisfaction, if I missed anything, or if anybody else wants to add anything.

(No response.)

DR. PAPPO: Okay. We will now move to the third question.

DR. ZIMMERMAN: This is Megan Zimmerman from FDA with the final discussion point. Please comment on manufacturing issues related to autologous CAR-T cell products in pediatric populations, including collection of leukapheresis material and pediatric sites' ability to contribute to or complete the manufacturing process.

DR. PAPPO: This question is now open for discussion. I think Cath is the first one.

(No response.)

DR. PAPPO: I have Catherine Bollard. Do you want to comment on this?

DR. BOLLARD: Sorry, Alberto. It's Catherine Bollard here. Sorry, I was on mute. I certainly think this question has really been

helped by the success of the CD19 CAR-T cell manufacturing program for pediatric patients in particular with ALL and more recently with diffuse large B-cell lymphoma. If we are restricting this to a patient population at 12 or older, the data from the CD19 CAR-T cell experience would suggest that it would not be any more challenging than adult populations.

DR. PAPPO: Thank you.

Leo, you're next.

DR. MASCARENHAS: Sorry. I put my hand down. I was going to say exactly what Cat Bollard said. Leo Mascarenhas, Los Angeles.

DR. PAPPO: Thank you.

Any other comments or any other questions? I don't see any hands up there.

(No response.)

DR. PAPPO: So based on what I've heard, given the experience that we now have with CD19 and with CARs for diffuse large-cell lymphoma, it appears, and it's become a relatively standard process for patients that are equal to or more than

12 years of age, that it should not offer a significant challenge.

Did I say that correctly, Cat?

DR. BOLLARD. Perfect. Thank you.

Adjournment

DR. PAPPO: I don't know if there are any additional comments or questions. You're going to have a really, really long lunch break. So if there is nothing else or nobody wants to add anything, we will now break for lunch.

It is my understanding that we need to keep the timing the way it is because of the sponsor's presentation that is already scheduled for early afternoon. So we will reconvene at 1:20 p.m. Eastern Standard time.

We will have to start right on time, and we want to try to keep that session -- I'm going to be a little bit strict with the time, the reason being that Dr. Reaman has another conflict at 3:30, and I have also another conflict at 3:30. So we will try to move along as best as we can.

Panel members, please remember that there

should be no discussion of the meeting topics during lunch amongst yourselves or with any members of the audience. Thank you very much, and we will see you back at 1:20. Thank you.

(Whereupon, at 11:49 a.m., the morning session was adjourned.)