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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****ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)****LaToya Bonner, PharmD**

Division of Advisory Committee and  
Consultant Management  
Office of Executive Programs, CDER, FDA

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*(Participation in Day 1 Topic 1 and Day 2 Only)*  
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Member and Head, Division of Solid Malignancies  
St Jude Children's Research Hospital  
Professor of Pediatrics  
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3 *(Industry Representative)*

4 Vice President and Oncology Therapeutic

5 Area Head, Merck Research Laboratories

6 Oncology Clinical Research

7 North Wales, Pennsylvania

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9 **TEMPORARY MEMBERS (Voting)**

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12 Professor of Pediatrics and Immunology

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14 The George Washington University

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12    Pediatric Oncologist

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1     **Richard Gorlick, MD**

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4     Robert A. Mosbacher Chair of Pediatrics

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13    Sidney Kimmel Medical College at

14    Thomas Jefferson University

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17    Nemours/Alfred I. duPont Hospital for Children

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1     **Theodore W. Laetsch, MD**

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3     Norma and Jim Smith Professor of Clinical Excellence

4     Eugene P. Frenkel, M.D. Scholar in Clinical Medicine

5     Harold C. Simmons Comprehensive Cancer Center

6     University of Texas Southwestern Medical Center

7     Experimental Therapeutics Program Leader

8     Children's Health

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12     *(Patient Representative)*

13     New York, New York

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16     Aflac Endowed Chair for Pediatric Neuro-Oncology

17     Professor of Pediatrics

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17       Hematology Centers  
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2     Professor of Pediatrics

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

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11    Associate Director for Pediatric Oncology

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14    Associate Director for Oncology Sciences

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18    **Denise Casey, MD**

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

2                   (10:00 a.m.)

3                   **Call to Order**

4                   **Introduction of Committee**

5                   DR. PAPPO: Good morning, and welcome to day  
6                   2 of the Pediatric ODAC meeting. Can everybody  
7                   hear me?

8                   CDR BONNER: Yes, we can hear you.

9                   DR. PAPPO: Thank you.

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

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

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

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

5 David Mitchell?

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

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

13 Dr. Cheng?

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

17 DR. PAPPO: Dr. Catherine Bollard?

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

21 DR. PAPPO: Dr. Steven DuBois?

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

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

3 DR. PAPPO: Dr. Ira Dunkel?

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

7 DR. PAPPO: Dr. Julia Glade Bender?

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

11 DR. PAPPO: Dr. Richard Gorlick?

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

15 DR. PAPPO: Dr. Theodore Laetsch?

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

19 DR. PAPPO: Donna Ludwinski?

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

1 DR. PAPPO: Dr. Andy Kolb?

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

6 DR. PAPPO: Dr. Katherine Janeway?

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

11 DR. PAPPO: Dr. Naynesh Kamani?

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

16 DR. PAPPO: Dr. Tobey MacDonald?

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

21 DR. PAPPO: Dr. Leo Mascarenhas?

22 DR. MASCARENHAS: Good morning. I'm Leo

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

4 DR. PAPPO: Dr. Will Parsons?

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

9 DR. PAPPO: Dr. Elizabeth Raetz?

10 (No response.)

11 DR. PAPPO: Elizabeth, are you on mute?

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

15 DR. PAPPO: Dr. Nita Seibel?

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

20 DR. PAPPO: Dr. Malcolm Smith?

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

1 National Cancer Institute of Pediatric Oncologists.

2 Thank you.

3 DR. PAPPO: Dr. LaToya Bonner?

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

6 DR. PAPPO: Dr. Gregory Reaman?

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

11 DR. PAPPO: Dr. Denise Casey?

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

15 DR. PAPPO: Dr. Leslie Doros?

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

18 DR. PAPPO: Dr. Megan Zimmerman?

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

22 DR. PAPPO: Thank you very much.

1           For topics such as those being discussed at  
2 today's meeting, there are often a variety of  
3 opinions, some of which are quite strongly held.  
4 Our goal is that today's meeting will be a fair and  
5 open forum for discussion for these issues and that  
6 individuals can express their views without  
7 interruption.

8           Thus, as a gentle reminder, individuals will  
9 be allowed to speak into the record only if  
10 recognized by the chairperson. We look forward to  
11 a productive meeting.

12           In the spirit of the Federal Advisory  
13 Committee Act and the Government in the Sunshine  
14 Act, we ask that the advisory committee members  
15 take care that their conversations about the topic  
16 at hand take place in the open forum of the  
17 meeting.

18           We are aware that members of the media are  
19 anxious to speak with the FDA about these  
20 proceedings, however, the FDA will refrain from  
21 discussing the details of this meeting with the  
22 media until its conclusion. Also, the committee is

1 reminded to please refrain from discussing the  
2 meeting topic during breaks or lunch. Thank you.

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

5 **Introductory Remarks - Gregory Reaman**

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

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

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

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

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

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

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

3 DR. PAPP0: Thank you very much, Dr. Reaman.

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

6 **Conflict of Interest Statement**

7 CDR BONNER: Thank you, sir.

8 The Food and Drug Administration is  
9 convening today's meeting of the Pediatric Oncology  
10 Subcommittee of the Oncologic Drug Advisory  
11 Committee under the authority of the Federal  
12 Advisory Committee Act, FACA, of 1972. With the  
13 exception of the industry representative, all  
14 members of the committee and temporary voting  
15 members of the subcommittee are special government  
16 employees or regular federal employees from other  
17 agencies and are subject to federal conflict of  
18 interest laws and regulations.

19 The following information on the status of  
20 the subcommittee's compliance with the federal  
21 ethics and conflict of interest laws, covered by  
22 but not limited to those found at 18 U.S.C. Section

1 208, is being provided to participants in today's  
2 meeting and to the public. FDA has determined that  
3 members of the committee and temporary voting  
4 members of the subcommittee are in compliance with  
5 federal ethics and conflict of interest laws under  
6 18 U.S.C. Section 208.

7 Congress has authorized FDA to grant waivers  
8 to special government employees and regular federal  
9 employees who have potential financial conflicts  
10 when it is determined that the agency's need for  
11 special government employee services outweighs his  
12 or her potential financial conflict of interest and  
13 when the interest of a regular federal employee is  
14 not so substantial as to be deemed likely to affect  
15 the integrity of the services, which the government  
16 may expect from the employee.

17 Related to the discussions of today's  
18 meeting, members of the committee and temporary  
19 voting members of the subcommittee have been  
20 screened for potential financial conflicts of  
21 interest of their own as well as those imputed to  
22 them, including those of their spouses or minor

1 children and, for purposes of 18 U.S.C. Section  
2 208, their employers. These interests may include  
3 investment; consulting; expert witness testimony;  
4 contracts, grants, CRADAs; teaching, speaking,  
5 writing; patents and royalties; and primary  
6 employment.

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

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

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

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

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

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

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

15 The waivers allow these individuals to  
16 participate fully in today's deliberation. FDA's  
17 reasons for issuing the waivers are described in  
18 the waiver documents, which is posted on FDA's  
19 website at [www.fda.gov/advisorycommittees/  
20 committeesmeetingmaterials/drugs/default.htm](http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm).  
21 Copies of the waivers may also be obtained by  
22 submitting a written request to the agency's

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

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

16 We would like to remind members and  
17 temporary voting members that if the discussions  
18 involve any other products or firms not already on  
19 the agenda for which an FDA participant has a  
20 personal or imputed financial interest, the  
21 participants need to exclude themselves from such  
22 involvement and their exclusion will be noted for

1 the record. FDA encourages all other participants  
2 to advise the subcommittee of any financial  
3 relationships that they may have with the firm at  
4 issue. Thank you.

5 DR. PAPP0: Thank you very much, Dr. Bonner.

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

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

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

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

5 We will now proceed with Tessa Therapeutics'  
6 presentation.

7 **Industry Presentation - Ivan Horak**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1           The subsequent two studies, a study at the  
2           University of North Carolina and Baylor College of  
3           Medicine, is the main component of my presentation.  
4           On this slide is the design and the number of  
5           patients who were treated. This is two parallel  
6           phase 1/phase 2 trials for 59 patients under the  
7           procurement of the T cells. However, from the 59,  
8           15 were not treated for various medical and  
9           nonmedical reasons, which are very well articulated  
10          in the blue box.

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

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

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

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

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

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

1 therapies.

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

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

14 The protocol is very similar to a response  
15 rate with an anti-PD1 antibody and BV as a third-  
16 and fourth-line therapy. Three-quarters of the  
17 patients responded to the treatment, but what was  
18 surprising was the high level of the CR rate,  
19 56 percent, and 8 percent of the partial responses.

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

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

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

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

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

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

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

12 [Indiscernible] in progression-free  
13 survival. At 1 year PFS, it was 38 percent for  
14 total group. Now when you compare the  
15 fludarabine/bendamustine, 57 percent of the  
16 patients had the PFS for 1 year and Flu/Cy  
17 21 percent. It seems, again, a small number of the  
18 patients, there is some curve separation.

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

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

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

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

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

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

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

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

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

1           You can see this high dose going up to  
2           200 million cells in bende/fludarabine. You can  
3           see a significantly higher area under the curve.  
4           There is a pretty significant difference between  
5           bendamustine and fludarabine continued regimen at  
6           the same cell, and again, is a small number of the  
7           patients.

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

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

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

1 is for patients with relapsed and recurrent Hodgkin  
2 lymphoma. In this study, we expect to enroll  
3 82 adults to reach 66 evaluable patients. We  
4 expect a 20 percent dropout. It's a little bit on  
5 the high side, and we would like to enroll at least  
6 5 pediatric patients.

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

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

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

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

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

1 the Independent Review Committee assessment. The  
2 target is the lower bound, and 95 percent  
3 confidence should be response rate over 30 percent.  
4 But the assumption is that the overall response  
5 rate will be 50 percent and a statistical power of  
6 90 percent.

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

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

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

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

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

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

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

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

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

22 The primary reason for that is highlighted

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

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

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

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

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

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

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

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

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

1 industry.

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

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

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

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

3 **Clarifying Questions from Subcommittee**

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

16 We have Dr. Bollard.

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

22 The first one is, I note the murine portion

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

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

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

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

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

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

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

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

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

5 Thank you very much for the questions.

6 DR. BOLLARD: Thanks.

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

9 DR. PAPP0: Yes, of course.

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

17 Has that been looked at?

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

1 DR. BOLLARD: Okay. Thank you very much.

2 Thanks, Alberto.

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

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

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

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

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

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

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

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

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

6 DR. PAPPO: Of course.

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

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

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

3 There was a discussion between FDA and Tessa  
4 Therapeutics, and we landed on 9 months. The first  
5 discussion is between 9 and 12 months. So it's not  
6 that that was -- the response is done first time at  
7 6 weeks post-therapy, but then the responses have  
8 to be durable. So a landmark analyses of the  
9 response rate will be a 9 months. So that will be  
10 the primary endpoint. I'm sorry. I just meet your  
11 question. I forgot to answer.

12 DR. KAMANI: Thank you.

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

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

12           DR. KAMANI: Thank you.

13           DR. PAPPO: Next is Steve.

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

1       worth monitoring as part of your trial.

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

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

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

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

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

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

22           So yes we are going very actively, not going

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

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

8 DR. PAPPO: Thank you.

9 Ted, you're next.

10 DR. LAETSCH: Hi. Ted Laetsch. Steve asked  
11 the majority of my questions. I guess the last  
12 question I would have was around your pediatric  
13 dosing. It looked like the potential of the target  
14 dose was lower for children if you do 2 x 10 to the  
15 6 cells versus 200 million cells per adult  
16 patients, and I just was curious about the  
17 rationale for that.

18 DR. HORAK: Excellent question. We talked  
19 to some pediatric oncologists, so we plan to use  
20 5 million per kilo. Yes, it might be a lower dose,  
21 but actually it did work very well in 2 out of  
22 3 patients. It's a very good question. Based on

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

7 I believe I answered the question.

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

10 DR. HORAK: Thank you very much.

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

22 Then to follow up a little bit on what Steve

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

10 Those were my questions.

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

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

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

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

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

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

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

19           DR. PAPPON: There was just the correlation  
20           between side effects and response. Did you see  
21           any --

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

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

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

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

20               DR. PAPPO: Thank you. No further  
21       questions.

22               Malcolm, you're next.

1 DR. SMITH: Thank you, Alberto.

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

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

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

22 The second question is true as well. The

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

5 DR. SMITH: Thank you.

6 DR. PAPPO: Next is Julia Glade Bender.

7 DR. GLADE BENDER: Thank you very much.

8 Julia Glade Bender. [Inaudible - audio gaps].

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

11 DR. GLADE BENDER: [Inaudible.]

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

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

16 DR. PAPPO: Much better.

17 DR. GLADE BENDER: Okay. I'm not a cellular  
18 therapy specialist, but just a few questions.

19 Thinking along the lines of Dr. Smith's question, I  
20 know you said that persistence was not predictive  
21 of response, but how about duration of response?  
22 Because ultimately that is an issue when used in

1 the relapse strategy without a consolidation plan.

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

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

14 DR. HORAK: Unfortunately --

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

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

18 In terms of [inaudible].

19 DR. PAPPO: It's still very choppy.

20 (No response.)

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

1 (No response.)

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

4 (No response.)

5 DR. PAPPO: Nita?

6 (No response.)

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

8 DR. REAMAN: Thanks, Alberto.

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

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

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

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

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

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

1 development.

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

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

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

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

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

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

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

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

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

16 DR. REAMAN: Thank you.

17 DR. HORAK: Thanks a lot for the question.

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

19 Julia, are you on the line?

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

22 DR. PAPPO: Much better, so go ahead with

1 your question.

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

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

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

22 Is there a cap in terms of the response? I

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

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

20 I'm sorry --

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

1 all. Thank you so much.

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

10 DR. PAPPO: We have Catherine Bollard.

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

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

20 DR. BOLLARD: Thank you.

21 DR. HORAK: Thank you very much.

22 DR. PAPPO: Donna?

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

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

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

22 So I do think that after we enroll a few

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

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

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

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

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

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

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

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

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

22 DR. SEIBEL: Well, there's been a

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

5 DR. HORAK: None. None in --

6 DR. SEIBEL: None? Okay.

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

11 DR. SEIBEL: Sure.

12 DR. HORAK: Thanks a lot.

13 DR. SEIBEL: Thank you.

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

16 (No response.)

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

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

21 **Questions to Subcommittee and Discussion**

22 DR. PAPPO: Okay. So if there are no

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

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

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

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

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

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

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

2 Malcolm, you're first.

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

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

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

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

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

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

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

1 patient population. Thank you.

2 DR. PAPPO: Thank you, Malcolm.

3 Catherine?

4 DR. BOLLARD: Thank you very much. I agree.

5 This is Catherine Bollard here. I agree with  
6 everything that Malcolm just said. The caveat I  
7 would just add to the children age group, or even  
8 less than that, is there is a percent of children  
9 in that group who present with Hodgkin but actually  
10 have an underlying immune deficiency that needs  
11 workup and probably allo transplant; so just to be  
12 aware of that as well.

13 DR. PAPPO: Thank you.

14 Julia?

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

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

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

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

11 Ted?

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

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

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

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

8 It appears that the mortality rate for  
9 Hodgkin is very low, especially in patients that  
10 are less than 15 years of age, therefore, there may  
11 be a challenge into recruiting into this clinical  
12 trial. Whether it's 15 years of age or older, or  
13 12 years of age or older, or if it's going to be  
14 age/weight-based, if the patient is, for example,  
15 11 years of age but meets the weight criteria, they  
16 should be allowed to be enrolled in the clinical  
17 trial.

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

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

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

9 (No response.)

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

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

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

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

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

6 DR. PAPPO: Thank you.

7 Malcolm?

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

10 DR. PAPPO: Okay. I'm sorry.

11 Ted?

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

22 So while Dr. Smith explained the small

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

6 I do think there is some concern about the  
7 variability of the [indiscernible] regimen.

8 Bendamustine or fludarabine, this is the only  
9 setting that I'm aware of using CAR-T cells where  
10 use with this has been used as a lymphodepletion  
11 regimen with bendamustine/fludarabine. To my  
12 knowledge, there's no data using fludarabine/  
13 bendamustine alone in combination with children;  
14 I'm not sure about adults either. So this would be  
15 data that may be important.

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

21 DR. PAPPO: Thank you very much.

22 Ted?

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

3 DR. PAPPO: Thank you.

4 Dr. Kamani?

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

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

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

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

1 12 years of age, with other indications such as  
2 ALCL to be entered only to allow us to gain more  
3 experience with that age group as well. In terms  
4 of the ability to collect cells, that should not be  
5 a problem per se.

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

13 DR. PAPP0: Thank you very much. I do not  
14 see any other hands.

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

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

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

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

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

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

22 DR. PAPPO: Does anybody want to tackle

1 that question? Steve? Go ahead, Steve.

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

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

16 DR. PAPP0: Julia, do you want to add  
17 anything to this?

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

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

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

19 DR. PAPP0: I think that site selection is  
20 going to be key, exactly what you're saying. We  
21 experience that with a rare tumor community. It  
22 takes a lot of work, and a lot of money, and a lot

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

8 Any other comments regarding Dr. Cheng?

9 Dr. Cheng, does that answer your question?

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

17 DR. PAPPON: Katie, you're next.

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

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

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

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

19 DR. PAPPO: Thank you, Katie.

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

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

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

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

1 facilitate all of the IRB procedures.

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

5 (No response.)

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

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

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

17 (No response.)

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

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

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

9               DR. PAPPO:  Thank you.

10              Leo, you're next.

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

14             DR. PAPPO:  Thank you.

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

17             (No response.)

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

1 12 years of age, that it should not offer a  
2 significant challenge.

3 Did I say that correctly, Cat?

4 DR. BOLLARD. Perfect. Thank you.

5 **Adjournment**

6 DR. PAPP0: I don't know if there are any  
7 additional comments or questions. You're going to  
8 have a really, really long lunch break. So if  
9 there is nothing else or nobody wants to add  
10 anything, we will now break for lunch.

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

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

22 Panel members, please remember that there

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

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

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