FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Afternoon Session

Wednesday, July 12, 2017

12:34 p.m. to 3:29 p.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jennifer Shepherd, RPh

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Grzegorz S. Nowakowski, MD

Associate Professor of Medicine and Oncology

Mayo Clinic Rochester

Rochester, Minnesota

Brian I. Rini, MD, FACP

Professor of Medicine, Lerner College of Medicine

Leader, GU Program

Department of Hematology and Oncology

Cleveland Clinic Taussig Cancer Institute

Cleveland, Ohio

Bruce J. Roth, MD

(Chairperson)

Professor of Medicine

Division of Oncology

Washington University School of Medicine

St. Louis, Missouri

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Gary Gordon, MD, PhD

Vice President, Oncology Development

AbbVie, Inc.

North Chicago, Illinois

TEMPORARY MEMBERS (Voting)

Catherine M. Bollard, MBChB, MD

Professor of Pediatrics and Microbiology,
Immunology Chief, Division of Allergy and
Immunology
Director, Program for Cell Enhancement and
Technologies for Immunotherapy
Children's National Medical Center
The George Washington University
Washington, District of Columbia

Bernard F. Cole, PhD

Professor
Department of Mathematics and Statistics
University of Vermont
Burlington, Vermont

Timothy P. Cripe, MD, PhD, FAAP, CPI
Professor and Chief
Division of Hematology/Oncology/BMT
Nationwide Children's Hospital
The Ohio State University
Columbus, Ohio

James L. Gulley, MD, PhD, FACP
Chief
Genitourinary Malignancies Branch
Center for Cancer Research
National Cancer Institute (NCI)
National Institutes of Health (NIH)
Bethesda, Maryland

Larry W. Kwak, MD, PhD

Vice President and Cancer Center

Associate Director, Translational Research &

Developmental Therapeutics

Director, Toni Stephenson Lymphoma Center

Dr. Michael Friedman Professor

Department of Hematology and Hematopoietic Stem

Cell Transplantation

City of Hope National Medical Center

Duarte, California

Gianna McMillan, MA

(Patient Representative)

Los Angeles, California

Alan Rein, PhD

Head

Retroviral Assembly Section

HIV Dynamics and Replication Program

National Cancer Institute at Frederick, NIH

Frederick, Maryland

Malcolm A. Smith, MD, PhD

Associate Branch Chief for Pediatric Oncology

Cancer Therapy Evaluation Program

Division of Cancer Treatment and Diagnosis

NCI, NIH

Bethesda, Maryland

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE), FDA

Acting Director, Office of Hematology & Oncology Products (OHOP)

Office of New Drugs (OND), CDER, FDA

Wilson W. Bryan, MD

Director, Office of Tissues and Advanced Therapies (OTAT)

Center for Biologics Evaluation and Research (CBER), FDA

Maura O'Leary, MD

Medical Officer, Team Leader Clinical Hematology Branch (CHB)
Division of Clinical Evaluation & Pharmacology/Toxicology (DCEPT)
OTAT, CBER, FDA

Marc Theoret, MD

(*Afternoon Session Only)*
Acting Associate Director of Immuno-Oncology Therapeutics
OCE, FDA

Bindu George, MD

(*Afternoon Session Only)*
Branch Chief Clinical Hematology Branch (CHB)
DCEPT, OTAT, CBER, FDA

Donna Przepiorka, MD, PhD

(Afternoon Session Only)

Team Leader

Division of Hematology Products

OHOP, OND, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(12:34 p.m.)

DR. ROTH: Thank you for your patience. We'll start the afternoon session, which will be dedicated to clinical issues, specifically efficacy and safety. And we'll start with the applicant's presentation this afternoon. Again, Dr. Hirawat?

Applicant Presentation - Samit Hirawat

DR. HIRAWAT: Thank you, Dr. Roth.

Good afternoon. Again, I am Samit Hirawat, head of oncology global development unit at Novartis. This afternoon, we will focus on the efficacy and safety results observed in our clinical development plan, and Dr. Grupp will provide his clinical perspective. But first, I'd like to recap some of the key points we've discussed.

As Dr. Hunger described, more than 600 children and young adults in the U.S. are faced with relapsed or refractory ALL every year. Their treatment options are limited and are associated with poor outcomes and high toxicity. Diseases

like pediatric ALL are why we are vested in CAR T-cell therapy, and CTL019 offers a new hope.

Over the past five years, we have developed a highly reproducible and safe manufacturing process, established quality criteria that correlate with positive outcomes, and instituted a rigorous chain of identity protocols.

Regarding some of the discussion this morning, we would like to reiterate that we routinely achieved greater than 98 percent T cells in the final product. We have never detected any B cells or other contaminating cells other than occasional trace amounts of NK cells in batches made by Novartis.

In addition, we have performed extensive characterization of T-cell phenotypes on every infused batch and have evaluated this data against clinical outcome measures. We have identified no other attributes that provide greater assurance of product quality than the ones we have already discussed. For example, we have seen that there is no relationship between CD4-CD8 ratios and efficacy

or safety, and these data have been submitted to the agency. With this background in mind, I will now review the data supporting the clinical efficacy of CTL019.

The BLA submission is based on three key trials. The pivotal trial, B2202, is a global multicenter trial. There is a supportive study, B2205J, a multicenter trial conducted in the United States. We also have a supportive trial, B2101J, a phase 1-2 trial conducted at a single center in the United States.

B2101J was the earliest study of CTL019 starting in March 2012 for pediatric and young adult ALL patients. It established the feasibility of CTL019 manufacturing and use in the clinical setting with a high rate of durable complete remissions.

The on-target effect of cytokine-release syndrome was absorbed early on in this trial. And as the principal investigator, Dr. Grupp introduced the use of tocilizumab to reverse the toxicity. We'll discuss CRS in more detail later in our

presentations.

The first patient in this trial was also the first pediatric patient to receive tocilizumab for CRS. She was 6 years old at the time. She remains in complete remission today, more than five years later.

The overall remission rate in B2101J was 95 percent. This more than doubled the results seen with other available therapies shown this morning by Dr. Hunger; 49 of 52 patients, or 89 percent, with CR or CRi were MRD negative after CTL019.

The complete remission in this trial are durable. In fact, the duration of remission for responders in B2101J study have not been reached. Estimated relapse-free data two years is approximately 60 percent. Overall survival was also prolonged with a median duration of 33 months.

Turning now to data from our pivotal study, B2202, B2202 was a global multicenter trial. It was conducted at 25 sites across 11 countries. Patients were consented and screened, and eligible

patients were enrolled into the trial. During the period of manufacturing, the patients were stabilized as needed with bridging chemotherapy.

Before the patients were infused with CTL019, they received lymphocyte-depleting chemotherapy. After the infusion, patients are followed for response and safety assessment for 5 years. There is additional long-term safety follow-up ongoing for these patients for up to 15 years.

The treatment is a single intravenous infusion. The dose used in the phase 2 study was based on the experience from previous trials. Of particular note, remissions were seen across all doses used in those prior trials. Patients less than or equal to 50 kilograms received weight-based dosing, and those greater than 50 kilograms received a fixed dose.

Patients eligible for the study had relapsed or refractory B-cell ALL with at least 5 percent bone marrow lymphoblasts. Patients included in the study ranged from age 3 years at the time of

screening to age 21 years at the time of initial diagnosis. Patients were excluded if they had received prior anti-CD19 therapy.

The primary endpoint of the study was overall remission rate within 3 months after CTL019 administration as assessed by an independent review committee. Overall remission rate was the sum of the patients who had either a complete remission or CR or a complete remission with incomplete recovery of bone marrow function or CRi. Overall remission rate required that no clinical evidence of relapse could be observed at least 4 weeks after initial achievement of CR or CRi.

The key secondary endpoint was the remission rate for patients who achieved a minimal residual disease or MRD-negative bone marrow within that 3-month period. Other efficacy endpoints you will see today are duration of response and overall survival.

To assess efficacy, the leukemic blasts were evaluated in the bone marrow, peripheral blood, CSF, and extramedullary regions at defined

intervals, as shown here. The sample size was based on the premise that 76 patients would provide greater than 95 percent power to reject a null hypothesis of 20 percent under the alternative hypothesis that the overall remission rate is at least 45 percent.

An interim analysis was planned after the first 50 patients either were infused or completed 3-month follow-up or had discontinued earlier. The primary endpoint was considered met at the interim analysis if the one-sided p-value was less than 0.0057. The key secondary endpoints are tested sequentially to control overall alpha.

Overall, 88 patients were enrolled, of whom 16 discontinued prior to CTL019 infusion. At the time of the updated analysis, 4 patients were awaiting CTL019 infusion. That leaves 68 patients who received CTL019 infusion. Of these, 19 have discontinued the study but have been followed for survival. So now, there are 49 patients who remain in the study and are being followed for safety, efficacy, and overall survival.

The patient population in study B2202 is representative of the overall relapsed/refractory B-cell ALL population in clinical practice. The median age in the trial was 12 years and ranged from 3 to 23 years of age. About half the patients were female.

Most of the patients in the trial were white, though other races were represented. Patients had received a median of 3 prior lines of therapy, and 59 percent of the patients had received a prior stem cell transplantation. Nine percent of the patients had primary refractory disease. The median morphological blast count at the time of enrollment was 73 percent.

This slide shows the various analyses sets we'll discuss today. Overall, 107 patients were screened and 88 were enrolled. The full analysis set and the safety set include all 68 patients who were infused with CTL019. 63 patients were included in the updated efficacy analysis, and they were the basis of the BLA submission. Both the interim and the updated efficacy analyses were

performed with patients receiving US-manufactured CTL019.

The interim analysis included 50 patients who had been followed for 3 months. The primary and all key secondary endpoints were met. The final analysis for patients with US-manufactured product, which is the main focus today, was performed when 63 patients had completed either 3 months of follow-up or had discontinued earlier.

It's worth noting that at the time of this final analysis, 50 patients were followed for at least 6 months or discontinued earlier. The study is ongoing, and it will evaluate additional patients who receive CTL019 manufactured by our European facility.

Here, we see the efficacy result for the final analysis with U.S. manufacturing. 83 percent of the patients achieved a remission, either CR or CRi. The results of the primary and key secondary efficacy endpoints were consistent between the interim and the final analysis. At the time of the interim analysis, this study met both the primary

and the key secondary endpoints. The overall remission rate was 82 and is now 83 percent. Most of the patients achieved a complete remission, and all patients who achieved a remission achieved MRD-negative bone marrow.

We performed a sensitivity analysis for overall remission rate, which included the 16 patients who enrolled but were discontinued prior to CTL019 infusion. Now, you have the 63 patients included in the primary analysis plus the 16 for a total of 79 patients. The response rate in this analysis is 66 percent, and the lower bound of the confidence interval excludes 20 percent. Of note, there is 100 percent concordance between the independent review committee and the investigator's review of remissions.

To address the question of whether time from enrollment to infusion might impact remissions, we performed an additional sensitivity analysis. With a median time of infusion of 42 days, the data show that ORR was similar among patients treated before

or after the median wait time.

We also looked at subgroups in the trial. The overall remission rate is consistent across all subgroups, including those based on age, gender, race, or ethnicity. High remission rates were also observed in patients who had prior stem cell transplantation, those with high or low marrow burden at baseline, and those with complex karyotypes. And the duration of remission is prolonged; 75 percent of patients were relapse-free at 6 months, after the onset of their remission. The median duration of remission has not been reached.

Looking now at the entire analysis set of 68 patients for overall survival, the overall survival is 89 percent at 6 months and is 79 percent at 12 months.

We will next look at clinical pharmacology. This cellular kinetic profile is for an individual patient from study B2202. It represents the CTL019 transgene as measured by qPCR. Immediately following the infusion, CTL019 cells distribute

throughout the body, followed by a rapid expansion of cells until around day 11. This is then followed by a decline over time.

Overlaid here are the data for the 50 patients included in the interim analysis set. Responders are shown in the black and non-responders in red lines. As you can see, there is individual variability across all patients. These data are consistent with observations in B2205J and B2101J studies, where persistence or presence of transgene has been measured beyond two years.

Summarizing the kinetics among all patients in B2202, we saw an increase in expansion among the responding patients compared to those with a non-response.

Turning now to dose finding, responses were observed across the entire dose range administered in the clinical trials of CTL019. In fact, overall remission rates were similar across all dose quartiles. Dose had no apparent impact on the development of CRS or neurological toxicity.

To summarize our efficacy results, the

primary endpoint in study B2202 was met. The updated analysis show an 83 percent overall remission rate. Results were consistent between the independent review committee and the local investigator's assessment, and the sensitivity analysis and subgroup analysis were consistent with the primary analysis.

All patients with CR or CRi had minimum residual disease negative bone marrow. Responses are durable. The median duration of response has not been reached, and 75 percent of patients were relapse-free at 6 months. The survival probability is 89 percent at 6 months and 79 at percent at 12 months. These results are consistent for all key secondary endpoints across the trial. The pivotal trial data confirm the encouraging results observed in the prior studies. Thank you.

Now, I'd like to invite Dr. Lebwohl back to the podium to share our safety data and the pharmacovigilance data. Dr. Lebwohl?

Applicant Presentation - David Lebwohl

DR. LEBWOHL: Thank you, Dr. Hirawat.

I'd like to turn to the safety seen with CTL019. This shows the safety populations from each of the three studies, the pivotal study B2202, and the supportive trials, B2205J and B2101J.

The safety data were pooled from the two multicenter trials as shown here, so it will be a total of 97 patients in the safety analysis. Studies B2202 and B2205J had nearly identical study designs and enrolled a similar patient population. Both trials used a single infusion, and standardized lymphodepleting regimens, and the same safety reporting conventions. Data from these two studies were pooled to allow a more robust safety analysis in a larger population of patients.

Safety was maintained with a comprehensive training program before any sites started. This included training on leukapheresis with a stem cell lab and clinical centers. It also included education for the patients and families. Important to the safety is that we maintained a chain of identity for patient material.

Prior to infusion, all patients had

influenza testing, assessment of their performance status and disease status, and laboratory testing. Following CTL019 infusion, the sites monitored and managed adverse events such as cytokine-release syndrome and neurologic events.

Looking again at the study design that Dr. Hirawat showed you earlier, I want to point out that there are three safety reporting periods. The first is during bridging chemotherapy. This therapy is used to control the disease during manufacturing between enrollment and the initiation of lymphodepleting chemotherapy.

The second is after the administration of lymphodepleting chemotherapy, which is required for most patients. And the third and main reporting period is after infusion of CTL019.

123 patients were enrolled in the two trials, of which 22 patients discontinued prior to CTL019 infusion. 97 patients were infused, and the infusion was pending for the remaining 4 patients. Of the 22 patients who discontinued prior to CTL019 infusion, 9 patients' products could not be

manufactured, 7 of which were due to intrinsic cell factors. Of the deaths prior to infusion, 5 were due to ALL, 3 due to infection, and 2 caused by organ failure.

I'll tell you next about the safety of all patients following enrollment. Grade 3-4 adverse events occurred prior to lymphodepleting chemotherapy and are summarized here. The most common events were febrile neutropenia and anemia. These are commonly observed events in patients with ALL who are receiving multi-agent chemotherapy.

Now, here are the grade 3-4 adverse events occurring following lymphodepleting chemotherapy, but prior to CTL019 infusion. The most common events are cytopenias and febrile neutropenia. These are also commonly observed in patients with ALL receiving multi-agent chemotherapy.

CTL019 is a single infusion and the adverse events differ between the first 8 weeks and the time after that. 69 percent of patients had a serious adverse event that was suspected to be related to CTL019 in the first 8 weeks, but the SAE

rate goes down to 4 percent after 8 weeks.

Similarly, for grade 3-4 adverse events, most are in the first 8 weeks, with 72 percent of patients having a suspected event. This goes down to 19 percent after 8 weeks.

With this time frame in mind, adverse events of special interest were assessed within the first 8 weeks after infusion. As we saw in earlier trials, cytokine-release syndrome was the most common event. The other thing we watched closely were cytopenias, which had not resolved by day 28. Let's look at these events in more detail.

Cytokine release syndrome is an expected on-target effect. It is considered to be a consequence of cell expansion with CTL019 as well as the activation of T cells and tumor cell killing. The presence of a high tumor burden at baseline or early fever may be predictive for severe CRS, and the most common symptoms are shown here.

In our trials, we instituted a CRS management algorithm that results in CRS

improvement and resolution in almost all patients. There were no deaths due to refractory CRS.

The median time to CRS onset was day 3, but it started as late as day 22. The median duration was 8 days. 44 percent of the patients were admitted to the intensive care unit with a median stay of 8 days; 34 percent of patients received systemic anti-cytokine therapy, which for most patients was tocilizumab, an antagonist for the IL-6 pathway. Patients received other supportive measures, including 16 percent who were intubated at some point in their course.

This is the proposed CRS algorithm, including our plan prescribing information. We will restrict the use of CTL019 to trained and certified clinical centers, and we'll provide educational materials to physicians, nurses, caregivers, and patients.

Patients who have symptoms are managed in the first line with oxygen, hemodynamic stabilization, and treatment for febrile neutropenia. If there is further deterioration,

they are treated with tocilizumab as well as hemodynamic and respiratory support. As a third line, we recommend considering steroids and additional dosing with tocilizumab.

Other alternatives are available, including siltuximab, which interrupts the IL-6 pathway, as well as anti-T-cell therapies and other agents. This algorithm was used in the clinical trials and optimized over time. Of note, only 6 percent of patients with CRS received fourth-line management and no patients required fifth-line CRS management.

Some patients had prolonged cytopenias following infusion with CTL019. 48 percent experienced grade 3-4 thrombocytopenia, and 61 percent reported grade 3-4 neutropenia at 28 days. But overall, these cytopenias resolved quickly, with about two-thirds of the cases resolved by 4 months after infusion.

Grade 3 neurologic events were reported in 11 percent of patients, but no grade 4 events were observed. The most common events at grade 1 and 2 was confusional state, and this was often seen in

the setting of cytokine-release syndrome. There were no cases of cerebral edema in this study.

In addition, there were 2 deaths due to secondary neurologic events, which aren't included here. One was a case of cerebral hemorrhage and one was a case of embolic stroke due to mucormycosis.

Prolonged B-cell aplasia is an expected on-target effect of CTL019 therapy. All patients who achieved CR/CRi developed B-cell aplasia. Long-term data from B2101J suggests that B-cell aplasia may persist for greater than 3 years. B-cell aplasia is managed with immunoglobulin replacement and other standard measures.

The most common serious adverse event is cytokine-release syndrome. We also see febrile neutropenia, hypotension, and pyrexia. Within the 30 days after CTL019 infusion, there were 2 deaths due to leukemia, 1 death due to cerebral hemorrhage, and 1 death due to an infected embolic stroke. After 38 days, 30 days, the most common cause was leukemia, but there are 3 other cases,

one of a patient with encephalitis, a patient with bacterial respiratory tract infection, and a patient with systemic mycosis. Patients remain at risk for infection, so we're recommending close monitoring for signs and symptoms of infection.

Health-related quality of life was assessed with a child-friendly questionnaire in patients 8 years or older. The patient-reported quality of life among responding patients to CTL019 improved compared with their baseline status.

These improvements far exceeded the minimal clinically important differences. In fact, the EQ VAS scores at 3 months are comparable to the normative means for the general population. By this measure, patients return to a similar quality of life as healthy children, despite the toxicities experienced following infusion.

A long-term safety study is continuing for all patients in the clinical trials. Per FDA guidance for gene therapies, the study will monitor for delayed adverse events and efficacy for up to 15 years following treatment.

In the commercial setting, patients will be followed long term using a registry. This observational trial will collect information on adverse events and efficacy and will monitor B-cell levels as a surrogate for persistence.

RCL will be monitored in the long-term follow-up of the clinical trials, and as part of the registry, Novartis will conduct an investigation should an unexpected event be observed.

As we work to bring this new therapy to the medical community, we have proposed a careful selection of sites for the safe use of CTL019. With 30 to 35 initial sites, we will achieve access for patients throughout the United States. All sites must be FACT accredited and accredited for allogeneic stem cell transplantation.

Novartis will train centers on processes for cell collection, cryopreservation, transport, chain of identity, safety management, and logistics for CTL019. We will also provide educational resources for patients and caregivers.

We are also proposing a REMS. The goal of the REMS is to assure safe access for patients by mitigating the risks of CRS and neurologic events. Implementation of the REMS is a joint responsibility of Novartis and the sites.

Novartis will be responsible for ensuring an authorized representative is designated at each site. We will provide training for the site personnel on the key adverse events, and we will ensure that only certified prescribers can order CTL019.

The sites' designated representative should ensure that all staff complete their training and knowledge assessments and verify availability of anti-cytokine medications. Given the early risk of CRS and the need for early intervention, the site will ensure that patients stay close to the treatment center for 3 to 4 weeks after infusion.

To summarize, the safety profile of CTL019 is well characterized and can be managed effectively. CRS is an on-target toxicity that is limited to the first 4 to 6 weeks after infusion,

and there have been no refractory or fatal cases.

A treatment algorithm for CRS has been optimized in three clinical trials. Neurologic events are transient and occurred within the first 30 days following infusion. Other adverse events of special interest are manageable with best supportive care.

B-cell aplasia in responding patients has been managed with immunoglobulin replacement therapy. There have been no replication-competent lentivirus observed in any patients, and there has been no insertional oncogenesis observed in any patients. Thank you.

We will now turn to Dr. Grupp to discuss his clinical perspective. Dr. Grupp is the director of the cancer immunotherapy program, chief of the section of cell therapy and transplantation at Children's Hospital of Philadelphia, and professor of pediatrics at the Perelman School of Medicine at the University of Pennsylvania. Thank you.

Applicant Presentation - Stephan Grupp

DR. GRUPP: Thanks, everyone. I appreciate

the chance to talk about the clinical perspective. In addition to the titles that David mentioned, I also have relevant experience with cell therapy and specifically with CTL019. I have been treating patients with this particular drug for over five years. I have led the CHOP single-site center B2101 that you have heard about and also had the privilege to run the study steering committees for both B2205 and B2202. My disclosures are that I have research support from Novartis, but I have no personal financial interest in the outcome of the study.

I think that we've seen Dr. Hunger talk about the unmet medical need in these patients. We've heard from a parent this morning, and I think it's very clear to all of us that although pediatric ALL is a terrific success story and that modern therapy for pediatric ALL works very well for a large number of the patients, the patients who are left behind when chemotherapy doesn't work are in really tough shape. And these are patients that are very hard to treat.

I see this as a pediatric stem cell transplanter, who over the past 20 to 25 years have been trying to get these patients into transplantable remissions so that they can then access therapy that may be curative for some of them.

Our experience is that these relapsed patients are harder and harder to get into remission. This is absolutely the trend in these kids for sure. As chemotherapy got better, the folks that we treat and try to treat with relapse are harder and harder to treat.

I think a key point that Dr. Hunger made is that it's very hard to get these patients to a point where they can get transplanted. We do not transplant patients in pediatrics if they are not in remission. And so this means hitting them with very intensive chemotherapy over, and over, and over again as we drive them past what is a clinical remission and down to an MRD level that's actually acceptable for transplant, which requires weeks and months in the hospital and extraordinary levels of

morbidity and the potential for mortality in these patients. And many of them lose their access to transplant not only because of inadequate disease response, but because of clinical events related to all that chemotherapy.

So it's very hard to get these patients to the point where we can actually transplant them in the transplant centers. So for that reason, the current treatment options are just not adequate.

Now, you saw a part of this slide from Dr. Hunger earlier looking at prior studies for relapsed ALL, and now I can put CTL019 in context. It's a similar-sized study with 68 patients, a high number of patients with three or more prior regimens, so heavily pre-treated, and this is absolutely our experience in these patients. You've heard the overall response rate of 83 percent, all of which were MRD negative.

The median overall survival in these patients compares very favorably at almost 17 months. The 12-month overall survival, 79 percent, again very favorable. Then as our

focus is on safety, the recognition that early mortality within 30 days also compares favorably to both clofarabine and blinatumomab at 3 percent.

Now, as I mentioned, we've been running a trial at Children's Hospital of Philadelphia in the University of Pennsylvania, testing this as a single-site trial. We started in 2012 with the first trial, the first ALL patient, and we've seen 95 percent complete response rate in infused patients on this trial, most of whom were MRD negative; again, the median overall survival in this group of patients with longer follow-up, 33 months.

This was a study in which we learned how to use tocilizumab to control cytokine-release syndrome, and this was a key finding because steroids are not adequate to treat cytokine-release syndrome. It's really the understanding that the IL-6 pathway is instrumental in the key toxicity of these patients that allowed us to treat these patients safely. This led to a CRS grading scale, so we could actually understand CRS a little bit

better, and a toxicity management approach, which was further codified in collaboration with Novartis for the multi-site trials.

We also saw patients who have long-term persistence of CTL019 cells, and this led us to the thought that it might be possible to use this in some patients as definitive therapy and not go on to bone marrow transplantation after they achieve a remission.

This then took us to the B2202 trial. Now, this was the first global trial of a cell therapy, the first global multicenter trial. It was also, very importantly, supplied by Novartis supplies, so this was the actual pharma supply that will be used in commercial use, so a global supply chain able to supply 25 centers, 11 countries across the globe from the United States.

You've already heard the overall response rate. And the most common question that I got in the years that I was describing the experience at CHOP and Penn was, "That's great. You're doing that at a single center. You have a dedicated

team." I have fantastic people that I work with. We have an ICU that's very used to taking care of these patients. "What does this look like when other people start doing it? Can you do the same thing? And more importantly, not only can you achieve the same efficacy, can you make it work safely?"

I think that was the key learning from this study, that we could absolutely do that. We had a clear toxicity management program. We are able to train sites, that Novartis was able to train sites on the approaches that we had started to learn at Children's Hospital Philadelphia.

So this is the result from the B2202 trial. And with the follow-up that we have currently available, this looks quite promising. But again, in the name of trying to sort of compare this to a single-site experience, you can make a visual comparison to the duration of response curve from the single-site trial.

So that's shown in yellow or orange, depending on how that projects, and then we have in

blue the 2202 multi-site trial. And you can see that the shapes of the curves are quite comparable. And there's a sense in the longer follow-up that we have available in B2101 that there is a plateau in the curve.

One of the striking things in watching patients get this therapy is that across a very broad range of patient characteristics, the outcomes are very similar. So patients with refractory disease go into remission. Patients with lower disease burdens go into remission, but also patients with higher disease burdens also go into remission. I think that that's extremely important.

As a transplanter, half to two-thirds of these patients had already had a transplant and had a recurrence after that transplant. Those patients do equally well. Patients with very difficult cytogenetics and other characteristics indicating very high clinical risk go into remission.

It's interesting to see in a small group of patients with Down's syndrome. Down's syndrome

patients can be a very tough group to treat. They're very intolerant of high-dose chemotherapy. Transplant can be really challenging for these patients. It's a small group of patients, granted, but they seem to do equally well with this cell therapy.

Safety. Cytokine-release syndrome is the principal toxicity. You've heard about this over and over again. This is expected with CTL019 therapy. It's expected to the point where some parents with a patient with a low disease burden will say, "I'm worried because my child does not look sick. They don't have a fever yet. Are we going to see a response to the therapy?"

You can see responses to this therapy without fever, without cytokine-release syndrome, but 80 to 90 percent of the patients experience some degree of cytokine-release syndrome. And that can go from fever and muscle aches to very significant clinical instability.

The thing that we learned that was the most prognostic for this was disease burden. So the

T cells can get on top of really significant leukemia burdens that require significant T-cell proliferation, significant cytokine release, and that causes the cytokine-release syndrome.

Also, patients with high disease burden tend to get sick faster than patients who are febrile and then have hypotension within a day or two are typically the patients who have the tougher time with CRS. We learned how to grade this. We learned how to treat this. And IL-6 blockade was really the key.

Now, neurologic events are really an issue here. This trial did not see significant neurologic events, but unfortunately, there was another trial that was halted because of several instances of cerebral edema in these patients.

So we've looked at the neurologic events very carefully. And what I would say from my perspective is we didn't see any grade 4 events, but what we see are essentially three things. We see seizures in very small numbers of patients. We see delirium in patients who have high spiking

fevers, which are quite characteristic of cytokine-release syndrome and are due to the fever, due to the CRS, and also due to the medications that the patients are getting during that time. And then we see a very characteristic encephalopathy that's characterized by an awake patient who isn't speaking. That lasts for two or three days. It resolves typically over another few days, and has resolved entirely without any therapy in all the patients that we've seen. And that is really the characteristic encephalopathy that we see in these patients.

So we just manage these patients with supportive care. We have not treated the encephalopathy, and in the very small number of patients with seizures, we've treated with appropriate anti-seizure medications.

Now, neutropenia and infections, these are ALL patients with very extensive prior therapy that we're giving chemotherapy to. All the centers that treat patients like this are very comfortable treating patients with febrile neutropenia. They

have their own protocols, and they do a great job with this. This management is, I think, very well laid out in everyone's care pathways.

There are patients who have prolonged neutropenia, which is past day 28, which is more than you would expect from the chemotherapy, and is some mixture of prolonged prior neutropenia in these patients, and the chemotherapy that we have given them for lymphodepletion, and some inflammatory side effect of the CTL019 cells.

In those patients, you have to continue to monitor them appropriately for a febrile neutropenia leukemia patient to make sure that there aren't infections, and we do see infections in some of these patients.

We also see B-cell aplasia that requires immunoglobulin replacement. And with adequate immunoglobulin replacement, we have not seen infections in these patients.

So I want to give you a patient example. This is a 12-year-old young lady who was initially diagnosed at age 7 with high-risk ALL. She had a

white count of 68,000, went promptly into remission, received typical ALL therapy.

Three months after completion of her therapy, so a relatively late relapse, she had a relapse. She went back into remission with retrieval chemotherapy, went to unrelated donor transplant, had mild graft-versus-host disease. So from a transplanter's perspective, that is the best possible scenario.

Two years after her transplant, unfortunately, she relapses again, and now we see the problem. This is a young lady we could not get back into -- we weren't treating her at that time, but her physicians were not able to get back into remission, no response to reinduction with multiple regimens.

This patient was enrolled with active disease and infused with CTL019, had 20 percent ALL on enrollment marrow, so refractory disease at that point, went into an MRD-negative CR, day 28, excellent CTL019 proliferation, remains in remission, remains in B-cell aplasia.

I think the striking aspect of this is that these patients, when they're left alone and are not requiring further therapy, get back to their function very quickly. They're going back to school, they're getting back to their lives because these are kids, and they typically can recover very quickly if we just could leave them alone. And we're able to in many of these cases.

So from my perspective, I think we've hit over and over again the urgent need for higher rates of durable remissions in these patients. These patients have refractory disease. They've been treated over and over again. They are developing comorbidities, and we don't have other treatment options. We've shown you that we have high remission rates with CTL019, deep remissions because they're MRD negative.

As a transplanter, you get this patient into an MRD-negative remission, transplant now is an option for this patient. But in many of these patients, we actually have foregone transplant in an attempt to use CTL019 with full discussion with

the family and the referring physicians as definitive therapy in a number of these patients.

I think that prospect is extremely exciting, and it's really because of the durability of both remissions and of the cell persistence in these patients. I think we understand the adverse events. We've treated so many patients at this point that we have a pretty good understanding. We see rapid returns to normal quality of life.

So from my perspective, I think this really does involve an important treatment option for pediatric and young adult patients with relapsed/refractory B-cell ALL. And with that, I'll turn it back over to Dr. Lebwohl.

Applicant Presentation - David Lebwohl

DR. LEBWOHL: Thank you, Dr. Grupp.

Now I'd like to provide a few closing thoughts on behalf of our team. In the trials we've shared today, we have demonstrated a consistent high rate of remission, and we've shown that these remissions are durable.

Here, you see the data from B2101J extending

beyond three years. For the duration of remission, the median has not yet been reached. When we overlay the duration of remission from B2202 and B2205J, we see the duration of these trials looks very similar to B2101J so far.

I've been working in oncology drug development for more than 20 years, and I've never seen anything like this. It's truly a paradigm shift in a setting with an enormous medical need. Across our program, we've shown that CTL019 therapy results in a high rate of remission, which is durable. There is also a prolonged overall survival relative to currently available therapies.

The safety profile of CTL019 is well characterized and generally manageable with appropriate site training and some patients requiring ICU care. And Novartis is committed to comprehensive pharmacovigilance and risk management to ensure safe use.

CTL019 has the potential to be definitive therapy. It has shown prolonged remissions and improved quality of life in pediatric and young

adult patients with relapsed/refractory B-cell ALL with many patients not requiring further therapy.

on these data, we conclude that CTL019 offers a positive benefit-risk profile. Moreover, it represents a new hope for patients. Thank you, and we will be pleased to answer your questions.

DR. ROTH: Thank you, Dr. Lebwohl.

We'll proceed now with the FDA's presentation, and we'll start with Dr. O'Leary.

FDA Presentation - Maura O'Leary

DR. O'LEARY: Good afternoon. My name is Maura O'Leary, and I am the clinical reviewer for this BLA. The proposed indication for tisagenlecleucel is the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia or ALL.

Novartis has discussed the disease background, current therapies, and key aspects of the study design. My presentation will introduce the issues for discussion by the committee and limit the discussion of the study design to the

risk mitigation measures, efficacy and safety results, and the proposed pharmacovigilance study.

FDA seeks the opinion of the committee with regard to potential postmarketing considerations to mitigate short-term risks from cytokine-release syndrome and neurotoxicities, as well as the committee's opinion regarding long-term follow-up. We are also asking the committee to discuss and vote on the overall benefit-risk profile in patients with relapsed or refractory B-cell precursor ALL.

CAR therapies are associated with life-threatening toxicities such as cytokine-release syndrome. To minimize risk to subjects, Novartis implemented broad risk mitigation measures during study B2202, including a stipulation that subjects meet safety criteria prior to tisagenlecleucel infusion. A novel CRS grading system to address severity of toxicities was implemented.

The cytokine-release syndrome treatment algorithm was complex, requiring a sequential and timed approach to administration of rescue

treatments, supportive care measures, and ICU monitoring. To implement these risk mitigation measures, clinical study sites were selected and trained. These sites were then closely monitored to ensure that protocol-specified measures were followed and that safety and reporting was timely.

Prior to the infusion of tisagenlecleucel, subjects were required to meet protocol-specified safety criteria. These criteria included a negative test for influenza, adequate pulmonary and cardiac function, no active infections, and ensuring that tocilizumab, an anti-interleukin 6 receptor inhibitor, was available on site prior to the infusion. There is evidence that tocilizumab may ameliorate cytokine-release syndrome.

Tertiary care centers with multi-disciplinary teams and appropriate supportive care facilities were selected as clinical study sites. These were primarily pediatric transplant centers. Expertise with thawing and infusion of cellular therapy products was required.

Clinical sites were required to have

tocilizumab on site prior to the infusion and administer treatment for cytokine-release syndrome based on the cytokine-release syndrome treatment algorithm.

Subjects and their families were educated about the early signs of short-term toxicities such as CRS and were required to stay close to the treatment site for 3 to 4 weeks after the infusion. Clinical sites were prepared to triage and hospitalize subjects rapidly.

Long-term follow-up for adverse events will be performed for up to 5 years after tisagenlecleucel administration under the study B2202. Monitoring for an additional 10 years will be under the study A2205B.

The primary objective is to monitor for potential risks or events specific to this product such as replication-competent retrovirus, or RCR, and the development of new malignancies.

Long-term safety monitoring may be performed at the investigational site or at remote sites between 2 and 5 years after tisagenlecleucel

infusion. Annual visits for physical exams and RCR are planned for B2202 subjects with visits every 6 months for transgene persistence. However, once 2 consecutive samples are negative for RCR or persistence, samples will be collected and stored.

For the next 10 years, annual monitoring or archiving of samples for RCR and transgene persistence will be performed. Survival status will be collected every 6 months.

Novartis has adequately described the study baseline characteristics and subject disposition, but I would like to reiterate the efficacy results. Sixty-eight subjects were infused with tisagenlecleucel as of the date of cutoff.

For the purposes of this BLA, the primary efficacy population consisted of 63 subjects for whom the tisagenlecleucel was produced at the U.S. site. The overall remission rate, which included complete remission and complete remission within complete hematologic recovery, is 82.5 percent. All of these remissions were minimal residual disease negative.

This graph illustrates the duration of response for the 52 responders. Each green line represents a subject with a complete remission. Each orange-yellow line represents a patient with a complete remission with incomplete hematologic recovery. The X-axis provides the months since the initial response. Median follow-up was 4.8 months, and the median duration of response has not been reached.

The graph shows that responders maintain their remissions; 29 of 52 responding subjects were still in remission at the time of the last assessment prior to the date of cutoff for efficacy without additional therapy.

Twenty-three subjects were censored. The red squares represent 5 subjects censored for new cancer therapy. The black diamonds represent 11 subjects censored for relapse. The blue squares represent 6 subjects censored for stem cell transplant, and the clear square represents 1 subject censored for inadequate assessments after documented response.

I will now review the safety results for B2202. In particular, I will focus on deaths on study, cytokine-release syndrome, neurotoxicity, additional adverse events of special interest, and pharmacovigilance.

The deaths that occurred prior to infusion were mainly related to disease progression, 6 subjects. However, infections were also a major cause of death. Treatment-related deaths that occurred post-infusion were related to disease progression in 7 subjects, infections in 3 subjects, and 1 death from intracranial hemorrhage, secondary to coagulopathy with resolving cytokine-release syndrome.

Overall, 78 percent of the subjects experienced cytokine-release syndrome. The median time to onset was 3 days, and it lasted for a median of 8 days. The median time to grade 3 or 4 cytokine-release syndrome was 6 days, with a peak incidence of all grades of cytokine-release syndrome on day 7.

Cytokine release syndrome severity was

associated with high tumor burden, which was defined as 50 percent of bone marrow blasts at the time of screening.

Neurotoxicity was characterized by one or more symptoms of encephalopathy seizures, depressed level of consciousness, difficulty swallowing, muscular weakness, or aphasia; 30 patients or 44 percent of the subjects experienced neurotoxicity; 10 of the patients or 15 percent of the subjects experienced grade 3 neurotoxicity.

A majority of the severe that is grade 3 neurotoxic events were associated with grade 3 to 4 cytokine-release syndrome events. There was no grade 4 neurotoxicity. There was 1 grade 5 intracranial hemorrhage due to coagulopathy. Neurotoxicity was reversible, but required close monitoring.

Sixty-eight subjects have been treated with tisagenlecleucel; 53 subjects developed cytokine-release syndrome with 32 as grade 3 or grade 4. Tocilizumab, an IL-6 receptor blocker, may ameliorate the cytokine-release syndrome response.

One subject with grade 2 was treated; 7 of 14 subjects with grade 3 were treated; and 18 of 18 with grade 4 were treated; 14 subjects who were treated with tocilizumab also received corticosteroids and 5 subjects received siltuximab.

This slide shows the extent of supportive care required for the subjects who experienced cytokine-release syndrome or severe neurotoxicity. Thirty-one subjects required ICU admissions with a mean duration of 11 days. This included treatment for fever, hypotension, and other complications.

Twenty-seven subjects had grade 3 to 4 infections requiring broad spectrum antibiotics for bacterial, viral, and fungal infections; 10 subjects required assisted ventilation; 7 subjects were dialyzed for a mean time of 11 days.

In addition, subjects were placed on seizure prophylaxis for potential neurologic events, and measures were taken to maintain airways in patients who were encephalopathic or obtunded.

Additional adverse events of special interest included febrile neutropenias, prolonged

cytopenias, and infectious complications, which included viral reactivation and opportunistic infections. These events resolved over 3 to 6 months.

In this heavily pre-treated population, there is a pre-disposition towards cardiac toxicity, particularly congestive heart failure. Although a normal echocardiogram was required for enrollment, there were 4 episodes of congestive heart failure, 3 of which were severe. Although reversible, treatment for congestive heart failure has continued in some of these patients post-discharge. Hemophagocytic lymphohistiocytosis occurred in 3 subjects, usually concurrent with their cytokine-release syndrome.

Tisagenlecleucel also has the potential to destroy normal B cells, and therefore can cause hypogammaglobulinemia and require replacement therapy with intravenous immunoglobulin.

Coagulopathy, particularly hypofibrinogenemia, was also associated with cytokine-release syndrome and solely resolves after

the cytokine-release syndrome has improved. Coagulopathies with the low fibrinogen, with prolonged cytopenia increases the risks of life-threatening bleeding such as intracranial hemorrhage.

On this slide, we review the long-term safety results. The median overall survival has not been reached. The median follow-up time for survival for B2202 is 6.9 months. There were no events related to the generation of replication-competent retrovirus, RCR. Persistence of the CD19 transgene was observed up to 366 days in subjects who experienced overall remission on B2202.

While therapeutically this may be advantageous, it also requires intravenous immunoglobulin supplementation for hypogammaglobulinemia due to the decrease in normal B cells. In addition, there is potential for malignant transformation.

In summary, the most notable adverse events related to tisagenlecleucel were severe cytokine-release syndrome, neurotoxicity, and prolonged

cytopenias with infectious complications. Deaths were related to progressive disease and infectious complications.

There were no fatal cytokine-release syndrome or neurotoxic events. However, there were serious cytokine-release syndrome events in 47 percent of the subjects and serious neurotoxicity in 15 percent of the subjects.

There is a potential long-term risk from replication-competent retrovirus and insertional mutagenesis with result in secondary malignancies. Transgene persistence has been documented for up to a year.

Novartis has proposed a pharmacovigilance plan with two components, a postmarketing observational registry study that is intended to evaluate the short-term and long-term risks of treatment with tisagenlecleucel. This includes standard-of-care follow-up for the known toxicities of tisagenlecleucel therapy and B cell precursor ALL. Active surveillance is not planned for CD19 transgene persistence or RCR.

Adverse events such as serious opportunistic infections, neurologic, hematological, hypogammaglobulinemia, rheumatologic disorders, and other unexpected delayed adverse events from treatment of childhood leukemia such as disorders of cognition, growth, and reproduction will be documented per standard of care. If a second malignancy does occur, Novartis will attempt to obtain tissue for evaluation.

Novartis has in addition proposed a risk mitigation plan specific for treatment sites that is focused on training for healthcare providers, education for patients, and essential services that are needed.

This is a brief outline of the proposed prospective observational postmarketing study. Monitoring would include standard-of-care exams and laboratory assessments of ALL and follow-up for the acute toxicities of tisagenlecleucel.

Study endpoints include adverse events, adverse events of special interest, growth and development outcomes, reproduction and pregnancy

outcomes, and disease outcomes such as overall remission rate and overall survival. The study includes monitoring for long-term follow-up for up to 15 years after the administration of tisagenlecleucel.

We ask the committee to consider risk mitigation measures to address the short-term and long-term toxicities of tisagenlecleucel. Please consider whether the risk mitigation procedures that were included in study B2202 were helpful in protecting the safety of the subjects and whether similar procedures would be useful if this product were approved for marketing; treatment sites for tertiary care, pediatric transplant centers with expertise in cell therapy.

Training of sites included adequate preparation and pre-infusion. For example, tocilizumab was on site; reassessment of clinical status after lymphodepletion as well as training on the recognition of treatment of cytokine-release syndrome and neurotoxicities.

In summary, the primary efficacy results

were an overall remission rate of 82.5 percent, all of which were MRD negative. Study B202 required site training, cytokine-release syndrome treatment per an algorithm, and site monitoring.

The safety issues that the FDA seeks the opinion from the committee relate to short-term risks of serious adverse reactions, namely cytokine-release syndrome and neurotoxicity. Although reversible, these reactions require early recognition, a timed and sequential use of medications, and supportive care measures to prevent these life-threatening events from progressing.

Patient or caregiver understanding of the risks are necessary to facilitate early intervention and the long-term adverse reactions related to the potential risks of secondary malignancies from RCR and insertional mutagenesis. The FDA seeks the committee's recommendation regarding the duration and types of postmarketing monitoring if tisagenlecleucel is approved.

I'll now go over the discussion questions.

These are the specific questions we are asking the committee to address, discussion question 3. Please discuss risk mitigation measures for the serious risks of cytokine-release syndrome and neurotoxicity with tisagenlecleucel.

Discussion question 4. For the tisagenlecleucel IND studies, the FDA requires 15 years of follow-up to monitor for subsequent malignant transformation. Given the possibility of the generation of replication-competent retrovirus and insertional mutagenesis, please discuss the duration of follow-up and the type of assessments that you would recommend for patients who receive marketed tisagenlecleucel.

Lastly, question 5 is the voting question. Considering the efficacy and safety results of study B2202, is the benefit-risk profile of tisagenlecleucel favorable for the treatment of pediatric and young adult patients age 3 to 25 years with relapsed, second or later relapse, or refractory, failed to achieve initial remission after two induction attempts, B-cell precursor

acute lymphoblastic leukemia.

I appreciate your attention and look forward to the committee's discussion of the issues. Thank you all, to all of my FDA colleagues for their help in the review of this BLA, and I will now turn the discussion over to Dr. Roth.

Clarifying Questions to the Presenters

DR. ROTH: Thank you, Dr. O'Leary.

We'll now proceed with clarifying questions both for the applicant and the agency. Please, if you have something to say, please show Jen, and we'll try to go through these sequentially. And again, state your name for the record when you ask a question.

So let me start off with one. I want to talk about the neurotoxicity. I got a little bit of mixed messages. I think Dr. Grupp referred to some cases of cerebral edema, and I think Dr. Lebwohl said that there weren't any. So were there some?

DR. LEBWOHL: There were no cases of cerebral edema with CTL019. What was coming up and

mentioned often is that there are other cases with other vectors that are occurring, not with the CTL019 program. So that's why the question came up.

DR. ROTH: So let me ask you whether you have a different mechanism of the toxicity for neurotoxicity other than CRS. And if not, if we think it's a component, I was wondering why the recommendations for intervention are more conservative in terms of holding off on anti-IL-6 or steroid intervention.

To me, a grade 3 CNS toxicity is scarier than fever. So I was just wondering if you thought there was a different mechanism of action that didn't warrant, or if you have evidence that intervention with tocilizumab or something else is not as effective in abrogating that toxicity.

DR. LEBWOHL: The mechanism isn't understood for the neurologic events. They are sometimes associated with cytokine-release syndrome, but they're not always associated, and there hasn't been good evidence that tocilizumab reverses that.

I'll ask Dr. Grupp for his clinical perspective on this.

DR. GRUPP: Yes. I completely agree that one of the transformational things in being able to treat patients with cell therapy is our understanding of the IL-6 pathway's importance to cytokine-release syndrome.

If you look across the different products that are in clinical development right now, I think that we all see about the same thing with CRS, but we see stuff that's very different from a neurotoxicity standpoint, and I think, mechanistically, that's very hard to sort out.

The fact that many patients, what we observed to be encephalopathy, get that with grade 3 or 4 cytokine-release syndrome mean they've already gotten tocilizumab, but it didn't prevent the encephalopathy. Now, that's hard to analyze prospectively, but it gives you the sense that we don't prevent this sort of very reversible but definitely notable neurotoxicity with tocilizumab.

So I would say, when I stated that most of

these patients had had not received therapy, it was because they didn't seem to require therapy and because it wasn't obvious what to do. You could certainly treat these patients with steroids, but that's entirely speculative because we don't have a lot of experience with that.

So I think from a mechanistic standpoint, there's a lot to understand. And then I think that one of the issues in terms of understanding mechanisms is that at this point in time, although you need a lot more patients to really understand this, there seems to be a sense that CAR T-cell products with a CD28 co-stimulatory domain may be more at risk for the more significant types of neurotoxicity, including cerebral edema than we've seen with a 4-1BB CAR. But again, I think that there is a lot to learn in this particular area.

DR. ROTH: Thank you. Dr. Bollard?

DR. BOLLARD: Sorry for all the questions. So just some questions regarding the first presentation. Can I just clarify firstly that the lymphodepleting regimen that you're using for B2202

is standard for all?

DR. LEBWOHL: It's standard in B2202 for all patients, yes.

DR. BOLLARD: With that protocol, okay.

DR. LEBWOHL: They would receive fludarabine and Cytoxan, yes.

DR. BOLLARD: So then for your eligibility criteria for that protocol, you say you have to be greater than 5 percent bone marrow lymphoblasts to be eligible. So what time point is that done? Is that done pre-lymphodepletion to chemo? Is it done post pre-bridging chemo? Is that done pre-CTL019?

DR. LEBWOHL: Yes. So that's done at screening and enrollment, so before additional therapy is given. So we did not obtain bone marrow after the bridging therapy or lymphodepleting therapy.

DR. BOLLARD: So you don't know immediately prior to T-cell infusion, correct?

DR. LEBWOHL: That's correct.

DR. BOLLARD: Right. My next question is related to slide CE-29. In other studies that have

come out of U Penn, they have shown non-responders; you don't see an expansion of transgene-modified T cells. But it's interesting to me on this graph that your three non-responders have dramatic expansion of the transduced cells and the blood.

How do you explain that?

DR. LEBWOHL: That's correct. We do see expansion. I'll have Dr. Thudium discuss this.

DR. THUDIUM: As you pointed out -- I'm Karen Thudium, Novartis clinical pharmacology. What I want to show you here today is data coming from all three trials, and this is showing the persistence, represented by the black line, in the responding patients. The non-responding patients are presented in the red lines.

What you can see is that there's a limited expansion in the non-responding patients, and you see the long-term persistence in the responding patients.

DR. BOLLARD: But are these patients relapsing at the time that you're finishing their monitoring?

DR. THUDIUM: That is correct. So if a patient is relapsing or if they're coming off the trial, there wouldn't be any additional samples measured. So essentially, what you see here is the last measurable time point that we have for a patient. It's conceivable that patients may still have transgene present. There wouldn't be samples collected.

DR. BOLLARD: I'm asking because some of these are pretty high, 10,000, 1,000 and above. And I go back to that concern, theoretical and maybe not theoretical concern that 4-1BB drives B-cell proliferation.

So do you know in all those patients that you didn't have transgene in the leukemia that they're relapsing with?

DR. LEBWOHL: What we know in these patients, if you're looking at the red curves, is these are patients who never responded. These are non-responders. So the blasts that are there are the blasts that were present from the start.

Dr. Grupp?

DR. BOLLARD: Can I just ask for your last slide, CC-3? You have got event-free survival, very impressive, 60 percent. Did you count LOBMT or getting other therapy as an event? Because I note from Dr. O'Leary's presentation that there actually was 10 out of your 40 CRs that got other therapy, including transplant.

DR. LEBWOHL: Yes. Per the standard conventions for FDA submissions, patients who receive new therapy are censored.

DR. BOLLARD: Okay. Thanks.

DR. LEBWOHL: Dr. Grupp would like to comment also on the B-cell question.

DR. GRUPP: Yes, because this has come up several times. There was one reported event, which has not been published yet but has been reported in meetings, where we had a patient who did indeed have the scenario that you're talking about, where they had a B-cell leukemia that had expression of the transgene.

In that particular case -- and it's the only case across all of the clinical programs that we've

seen -- that patient had a CD19-negative ALL cell collected. The CD19-positive ALL cells are collected as well, but are destroyed in the bag by the CAR T cells. But in those patients who do relapse, the most common mechanism of relapse is a CD19-negative leukemia.

That's what happened in that patient. That cell was indeed transduced, but that patient's transduced cell was his original leukemia. So any growth advantage that might have been conferred by the 4-1BB domain from the CAR in that particular cell was in a leukemia cell. That leukemia cell was already transformed. So I don't think the patient relapsed from that.

In the other CD19-negative leukemia, as we've seen, we have not seen CAR transgene clonally expressed on the surface of these cells, so that, as far as we know, is a singular event.

DR. BOLLARD: But I guess my question is, if you're not looking in all these patients, it would only take theoretically one cell to be -- it just goes back to my question about product purity.

DR. GRUPP: To answer that question, we did within the Penn program look across all the patients that we've treated and did look for other instances of B-cell recurrence with CAR expression, and that was the only case where we saw that across the leukemia cells.

You could find in some of the products very small numbers of transduced cells, but it wasn't what they were actually relapsed with. So I think across a fairly large number, although not across all of the programs, we didn't see that happen but once.

So there's no question that CD19-negative relapse is the issue that we do have to deal with. If these patients have CD19-negative ALL, it's not addressed by the CAR T cells. And so anywhere from two-thirds to 90 percent of our relapses are CD19 negative.

DR. ROTH: Dr. Gulley?

DR. GULLEY: Just a quick question about the impact of the steroids on the CAR T cells. So with T cells, steroids may be able to knock them down,

especially if they're naïve, but memory cells are perhaps more spared and effector cells are perhaps more spared.

What is known with the CAR T-cell product?

DR. LEBWOHL: We have looked at the effect of steroids, and Dr. Thudium will show that.

DR. THUDIUM: Karen Thudium, Novartis clinical pharmacology. So we have assessed the impact of tocilizumab on the expansion and persistence, and in general, we do not see a major impact. Essentially, the cells continue to expand and persist following administration of tocilizumab.

I'll show you here a slide that presents the transgene profile. It's indicated here by the different doses of tocilizumab that were administered. And you can see the blue line is representing patients that receive 1 dose of tocilizumab, and the red line is representing greater than 1 dose.

You can see that the lines are very similar across the expansion and persistence. So in

summary, we do not believe that tocilizumab has an impact on the expansion or persistence.

With respect to your question on the steroids, I want to highlight that -- and David can probably comment on this. But the steroids are given in small doses for short duration, and we did assess the impact on expansion and did not see any impact.

DR. ROTH: Dr. Smith?

DR. SMITH: Yes, questions in several areas. First related to the neurologic adverse events, there was a comment that resolution of symptoms occurs over weeks and can lag behind CRS recovery. I wonder if you can say more about what some of these slower evolving symptoms are, if there are any correlates, imaging correlates for example, of these slow-resolving symptoms, and if there's any evidence that these may be in fact persistent long term.

DR. LEBWOHL: We have seen no effect on imaging in terms of these effects, but I'll ask Dr. Grupp to comment on the persistent neurotoxic

events.

DR. GRUPP: I think looking across the broad experience, which includes the CHOP experience, where we have more follow-up in these patients, it lags behind CRS because often these patients actually experience the neurotoxicity when the CRS is over, which is to say their fever is gone is and they're no longer hypotensive if they were.

The typical time to completion of this, a resolution, rather, of this is, a week or so. There are a small handful of patients who had more prolonged neurotoxicity, and it has resolved in all of these patients. So I am not aware of a case where we have persistent neurologic deficits that have gone beyond -- that exist at this point in time.

DR. SMITH: What are those kind of things that persist?

DR. GRUPP: I can think of one illustrative case of a patient who had fairly significant neurotoxicity, word-finding difficulties, not speaking actually for several days. And that took

several weeks before that patient was actually speaking clearly and back to what his parents regarded as his neurologic baseline. So I think that would be fairly typical.

So it's often word finding and higher executive function. These patients have not been very carefully characterized by neurocognitive testing, so you could probably say something a lot more sophisticated than that, but this is what we observed clinically.

DR. SMITH: Relating to the B-cell aplasia, you provided data about the T last, and the range, in that. And does that T last have any relationship to B-cell recovery? Is there B-cell recovery or is B-cell aplasia the expectation?

DR. LEBWOHL: We do expect that there will be recovery, and we can show the recovery, let's say the time to recovery of B cells.

Don't we have a Kaplan-Meier for the recovery, shown here? So this is pooling data from both B2202 and B2205J. And what you see over a period of about a year is about a 30 percent

recovery of B cells in patients.

DR. SMITH: Is there any more you can say about the expectation, full recovery?

DR. LEBWOHL: No. In the very long term, we don't have the data over a very long term.

DR. SMITH: Related to the overall outcome, can you show us the EFS and overall survival curves for the enrolled patient population?

DR. LEBWOHL: Yes. Pull up EFS first, please. And that's shown here. So this is now 88 patients included. And as you see, there's a -- it's not there yet. We'll for that.

So this is a Kaplan-Meier curve of the event-free survival, now including all 88 patients who enrolled and the patients of course who could not receive therapy are non-responders and immediately have events. But looking at the additional patients, the overall median for all these patients is 10 months.

Looking at survival for all patients, it's shown here; 67 percent are still surviving, including the entire population in 12 months. And

you'll recall that the median for the best therapies today are about 7 months, and 67 percent survival at 12 months.

DR. SMITH: Final question is, do you consider the supportive care measures in the pivotal study were optimally applied, or were they still evolving during the pivotal study so that maybe they would be better today than they were during the time of the pivotal study?

DR. LEBWOHL: We do think, at the time of the pivotal study, they were fairly set by that time. We had both the single-center study as well as the multicenter, the first non-pivotal multicenter study.

What we were very happy to see is that we were able to show safety similar to what was achieved in the single-center study, expanding to 25 sites around the world. So we do believe that our training was quite effective in bringing that knowledge to many sites.

DR. ROTH: Dr. Nowakowski? Dr. Cole?

DR. COLE: Thank you for the presentations,

very interesting data. I was looking at overall survival, in fact, and the data shown for the study 2202 -- I don't know. Maybe we could look at the slide CP-4. Do you have slide CP-4?

DR. LEBWOHL: Yes.

DR. COLE: Thank you. So I was looking at the overall survival comparison there. We saw it for 1 minute, 1 second.

(Laughter.)

DR. COLE: There we go. So for the 12-month survival, 79 percent in study B2202 and then for the phase 1-2 study that came out in 2016 with blinatumomab -- I confess I'm not good at pronouncing these names -- 40 percent. And I was wondering if you could comment on any difference in the risk profile amongst the patients in these two different groups.

Two things come to mind. One is that in that phase 1-2 study, there seemed to be a higher rate of patients with refractory disease. I'm not sure whether that's protective or actually a risk factor.

The other thing that comes to mind is that necessarily there's a waiting period in B2202. You have to pass through the manufacturing process, which you might lose high-risk patients as a result of that.

I think that this comparison is important, and I'm glad you showed it. I'm also really glad you showed the quality-of-life data. I think these are really important data points. But I'd like to just get some comments from you about any difference in risk profile and how comparable you really think those two numbers are.

DR. LEBWOHL: Thank you. First I'll point out that it is difficult to compare across trials. These are coming from different places. But I think the most important feature you see here is the number of prior regimens. So for blinatumomab, only 7 percent of the patients had 3 or more regimens. In our study, 60 percent of the patients had 3 or more regimens.

So by the measure of prior treatment and amount of lines of therapy, certainly our trial

actually has a more severe group of patients.

I'll also say, of course, by showing the survival for the entire enrolled set, we are getting rid of that issue of the waiting in that these patients -- this is taking in all patients who approach clinical sites and wanted to be enrolled.

I'm going to point out that this has the possibility of getting better, of course, because we won't have the waiting period, the same waiting period in the commercial setting. But even looking at that, a 7-month median survival versus, here, 60 percent of the patients extending out beyond 12 months is quite a big difference.

DR. ROTH: Dr. Cripe?

DR. CRIPE: Thank you. First, I want to congratulate Dr. Grupp and his team for identifying the IL-6 pathway, which was, especially in the first patient, a stroke of brilliance.

I have a couple questions about the relapse patients, though, and that is, going back to those, are there any sanctuary sites for CAR T cells?

That certainly was a problem with chemotherapy in early days.

DR. LEBWOHL: We have seen no relapses in the CNS, and I'll ask Dr. Grupp to discuss this further.

DR. GRUPP: Yes. I think that, aside from the CNS, which I can address, we don't have enough experience with other extramedullary sites to really have a sense. The few testicular patients that we had treated were definitively treated in their extramedullary site, and therefore, I don't think we have a sense of that.

But the CNS, we actually have data on. Again, this was an exclusion in the B2202, but we have treated a number of patients with CNS 2 and now actually CNS 3 disease. We actually have done an analysis of this. What we've shown is that there is a great deal of expression of the CAR T cells in the cerebral spinal fluid. More than 95 percent of the patients have CAR T cells that are found in the CSF, so they get there.

We've seen initially patients with CNS 2A

disease on the day prior to T-cell infusion, where that has gone away. We've seen no CNS relapses, as Dr. Lebwohl mentioned. And then we've had a small number of patients, a handful of patients, that we've treated with overt CNS 3 disease, including MRI findings clearly indicative of both leukemic meningitis and leukemic inflammation and brain parenchyma and have seen those resolve with, in some cases, two or three years of follow-up after a CTL019 infusion.

So it doesn't appear that the CNS specifically is a sanctuary site. Other sanctuary sites are hard to actually address.

DR. CRIPE: And the patients who don't have the antigen, who either didn't respond, so you still have CD19 or relapsed with CD19, is there any reason to think that another batch might be effective? Have you thought about that? Has anyone gotten 2 doses?

DR. GRUPP: We have had, again, B2202 with single infusion, so I want to be very clear about that. But we have had investigational experience

with re-infusion. Shannon Maude at our center has done an incredible amount of work in this area.

So just to give different clinical scenarios, I would say the bottom line of what I'm about to say is that the jury is fully out on whether this is helpful or not. So we have had patients who didn't have an initial response, who got another dose of the same batch of T cells. And the cells that didn't grow the first time didn't grow the second time, and we don't get a clinical response, that's only a handful of patients.

We have had patients who have recurred with CD19-positive overt relapse, and we've retreated them with the same cells, and we've had some patients respond and some patients not respond.

We have had patients who have recurred with CD19-positive disease and got an alternative CAR product with a different CD19 binding domain and have seen patients respond under those circumstances.

Then there's also been a group of patients who we believe that an optimal time to hang on to

your B-cell aplasia and your cell persistence is 6 to 12 months, and this is very hard to measure. I mean, that's just an opinion.

So for the small handful of patients who don't have that kind of persistence, because the vast majority do, we've tested reinfusion to just maintain an area under the curve in a longer period of B-cell aplasia. And we've been able to re-establish B-cell aplasia in some of these patients, but it's very hard to tell whether that actually provided clinical benefit. And I think that's an area that requires very careful further study.

DR. CRIPE: In those who haven't responded at all, have you looked at PD-1 expression on the T cells, or PD-L1 on the leukemias, or other modes of Tregs, or MDSCs, or anything like that?

DR. GRUPP: Yes. We looked at a lot of things. The trouble is that some of the patients who didn't respond had checkpoint inhibitor expression, and some of them who did respond -- it's not obviously -- what it really looks

like -- Cath had raised the question about qPCR expansion, but in a single-institution study, where we had access to flow immediately, you don't see the same proliferation by flow.

So I don't understand, as Cath doesn't, and I understand the lack of understanding about this, but by flow, if you don't see proliferation, you don't see response. And so that seems to be a T-cell-intrinsic problem, but that again is an analysis that we had better access to at a single-institution center because you can carry the samples right to the lab, which really does make a difference.

DR. CRIPE: Another question I have relates to eligibility. I notice your study had a number of different eligibility criteria like prior CD19 therapy was an exclusion. Is there any reason to think that that should be maintained in the marketing setting or even some of the other criteria, pulmonary lung cardiac function, or is that going to be left to the discretion of the treating physician?

DR. LEBWOHL: What we believe is the most important thing is that the patients have CD19 present. So if a patient has another therapy that eliminates their CD19, we think that would not be good. But for CD19-positive B-cell ALL, really a broad group of patients have a possibility of benefitting.

DR. ROTH: Dr. Rini?

DR. RINI: The same question about the CRS management algorithm that's on your slide CS-13, if you're able to pull it up. And it was really about the tocilizumab. And I'm wondering if there's any experience with using it even earlier almost as prophylaxis like we do for tumor lysis syndrome.

I'm not really giving that drug, so I don't know a lot about its inherent side effects, or cost, or things like that. But it just seems like all the experts have said that that's a critical pathway, it's a critical drug for managing. And I'm just wondering if there's any even institutional experience and/or program experience with even moving into prophylaxis, or looking at

timing of that in relation to degree of CRS, or something like that.

DR. LEBWOHL: It certainly is a very reasonable idea, and moreover, there is a single-center study going on with the early use of tocilizumab by Dr. Grupp. We're giving the early tocilizumab with the first sustained fever in patients who have a high tumor burden, so these are the patients at highest risk of CRS. So we will be following to see if that can reduce the rate of severe CRS.

DR. RINI: One quick follow-up. You had mentioned one of the proposed strategies is to ensure that patients and caregivers stay within 2 hours of the center for 3 to 4 weeks after the infusion. How do you ensure that? How do you operationalize that to make sure?

DR. LEBWOHL: Yes. So this is a matter of training and education. We will be certifying the sites as mentioned. There will be a representative at the site who makes sure all the personnel at the site is trained. And part of that training is that

they will be instructing their patients that they do need to be close by for those 3 to 4 weeks.

In addition, patients will have tools. Patients will have wallet cards telling them what they should be doing, coming in for a fever, of course, but also staying near the site for that period of time.

DR. ROTH: If I could build on what Dr. Rini said, I think that's critically important information that both steroids and anti-IL-6 therapy does not appear to blunt the proliferative response, if I'm quoting you correctly, because I think there is the perception by some treating physicians that I've spoken to that you want to hold off on those things so you don't negate the effect.

I think that sometimes could potentially be to the detriment of a patient, that you want to hold out, whereas I would argue for the same thing. If 90 percent of people are experiencing some CRS, why not intervene early if it's not affecting the clinical response in a negative way, as far as we

know to date.

DR. LEBWOHL: As far as we know, we don't. Of course, the challenge of looking at patients who get tocilizumab or don't, those are the patients with the greatest expansion, the patients receiving tocilizumab. So the effect on efficacy might be confounded by that.

DR. ROTH: Let me ask one more, to step back, a broader question. In the era of a living biologic, does the 30-day MRD-negative versus positive still have the same relevance in terms of prognostic value? Namely, if you have MRD positivity at 30 days, are those 19-negative cells, or is there a possibility with this living drug that that may be premature to see maximum effect?

DR. LEBWOHL: As you saw, we didn't have any examples of responders who are MRD positive in our pivotal trial, so we don't have much information on patients who are MRD positive at the end of treatment.

Dr. Grupp, do you have examples of that?

DR. GRUPP: I guess one answer to your

question is that patients who aren't in remission at day 30 won't be afterwards. So we don't have any real experience with patients who are evolving their way to a better response by day 30.

The issue of flow MRD, which is the United States standard, is interesting in a world where you're destroying all the CD19-positive cells. But the central labs that perform the MRD -- specifically the University of Washington does this for COG -- has learned how to read these.

So you do occasionally -- this gets very technical, but you do occasionally see patients who have what may be CD19-negative MRD, but it is just common lymphoid progenitors, the very earliest B cells, and that can go away because it was never leukemia in the first place.

If you're doing next-gen sequencing, you would miss that signal because of course you aren't doing it by flow. You're actually looking for the leukemic sequencing signature.

So the answer is, from a leukemia standpoint, if you truly are MRD positive at

day 30, that's a bad sign, whether it's CD19 positive or CD19 negative.

DR. ROTH: Thank you. We have other questions. Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I'd like to compliment the applicant for development of postmarketing study and the registry to capture safety and efficacy in a real-world situation.

I wonder, in this study, if you could clarify if you're planning on enrolling patients who received the product or also patients who intend to receive the product, meaning underwent apheresis. What is the cutoff point for enrollment in this study?

DR. LEBWOHL: I'll put up the study again. The study would only be for patients who were infused with CTL019.

DR. NOWAKOWSKI: I think, based on some of the discussions which we had, that many patients aren't able to undergo, this will affect the efficacy with cancer length of the patients. You could consider enrolling all the patients, at least

the patients who underwent apheresis, to capture manufacturing failure rate as well as other events, which are cured before infusion, which precludes patients from receiving therapy.

DR. LEBWOHL: We certainly will have information on manufacturing success rate because that is what we'll be doing. We'll be manufacturing the product and then looking at the success rate. And we'll think about your idea of whether we can get information about more information about those patients.

DR. ROTH: Any other questions? Dr. Cripe?

DR. CRIPE: Could you put up slide BH-12 again, B-H, boy, Harry? I don't know. Bravo, Hotel, thank you.

So you have a patient there on the bottom that had proliferation of the transgene at month 8, 9, 10, a couple of spikes, and it looks like maybe ramping up to that point. So in the effort of trying to learn from every patient, could you tell us more about that? Do you think that the leukemia is relapsing and then it's restimulated production

of the clone, or what explains that?

DR. LEBWOHL: We'll ask Dr. Grupp about that patient.

DR. GRUPP: That, as you correctly point out, is the patient who had the transduced leukemia cell and who relapsed. So that increase in transgene expression is the patient's leukemia, and that's that one singular event.

DR. ROTH: Any other questions?

(No response.)

DR. ROTH: Then let's take a break. I have it as 2:20 now. Let's do a 20-minute break and reconvene at 2:40.

(Whereupon, at 2:17 p.m., a recess was taken.)

DR. ROTH: Let's go ahead and get started. There are a couple of housekeeping items before we go to the open public hearing. I noticed some difficulties technically with slides. And those are not the responsibility of the applicant, those are issues in the room, so I apologize for that.

Secondly, it is my fault I forgot that we

changed some personnel for the afternoon session. And for the record, we're going to go around one more time, introducing ourselves for the record, so if we could, start with Dr. Gordon.

DR. GORDON: Gary Gordon, AbbVie Oncology.

DR. BOLLARD: Cath Bollard, Children's National.

DR. CRIPE: Tim Cripe, Nationwide Children's, Columbus, Ohio.

DR. SMITH: Malcolm Smith, National Cancer Institute.

MS. McMILLAN: Gianna McMillan, patient representative.

DR. GULLEY: James Gulley, National Cancer Institute.

DR. RINI: Brian Rini, Cleveland Clinic.

DR. ROTH: Bruce Roth, Wash U in St. Louis.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. NOWAKOWSKI: Greg Nowakowski, Mayo Clinic.

DR. REIN: Alan Rein, National Cancer

Institute.

DR. COLE: Bernard Cole, University of Vermont, biostatistics.

DR. GEORGE: Bindu George, CBER, OTAT.

DR. PRZEPIORKA: Donna Przepiorka, CDER, Division of Hematology Products.

DR. THEORET: Marc Theoret, OCE, FDA.

DR. O'LEARY: Maura O'Leary, CBER, OTAT.

DR. BRYAN: Wilson Bryan, Office of Tissues and Advanced Therapies in the Center for Biologics.

DR. PAZDUR: Rick Pazdur, Oncology Center of Excellence.

Open Public Hearing

DR. ROTH: Thank you. We'll move on now to the open public hearing session. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure the transparency at the open public hearing session of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any industry group, its products, and if known, its direct competitors. For example, this financial information may include the industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

MS. SANTIAGO: Good afternoon. My name is Kristen Santiago, and I am here on behalf of the cancer support community, which I will refer to as CSC throughout my remarks. The Cancer Support Community does receive funding from Novartis, however, my presence here today was not supported in any way by Novartis.

CSC serves patients and their loved ones through a network of 150 affiliate sites and satellite locations as well as at the Cancer

Support Helpline, where patients and their families receive evidence-based programming, social, and emotional support.

We provide free programs, which include professionally-led support groups, educational seminars, nutritional workshops, and exercise and mind body programs. Our mission is to help people living with cancer regain a sense of control over their lives, feel less isolated, and restore their sense of hope for the future, regardless of their stage of disease.

In 2016, nearly 100,000 individuals, including patients and caregivers affected by relapsed/refractory B-cell ALL, made more than 900,000 visits to our centers across the country and around the globe. CSC is also home to the only research and training institute, where work is focused on understanding and elevating the patient and caregiver voice about the cancer experience.

My comments today reflect what we have learned from the Cancer Experience Registry through our research and training institute as well as what

we see in our locations around the country each day.

CSC serves people with all types of cancer, and we are seeing a high unmet need for children and young adults with relapsed/refractory B-cell ALL. ALL is a difficult disease with few effective treatments and ones that come with may have side effects. And there is much unknown about the long-term lifelong side effects of its existing therapies.

Given the growing patient population, severity of disease, and limited treatment options as having discussed today, additional novel treatments are needed in the portfolio of treatment options for patients with ALL.

The ultimate treatment decision should be made between the patient, caregivers, and the healthcare team following a thorough review, which includes examination of the risk-benefit profile as it relates to the patients' particular needs.

Because ALL affects children and young adults, CSC encourages the sponsor to continue to

monitor patients in a postmarketing study, which you plan to do, to continue to build the body of data on long-term side effects of the treatment, as it would be very meaningful for the patient as well as the caregivers to know what an individual may experience 5, 10, 25, or even more years down the road.

We know that the patient experience is much broader than the patient assessments of disease symptoms, treatment side effects, and physical functioning. And CSC encourages the sponsor to collect additional patient experience data to better understand what is actually really meaningful to patients as well as their caregivers.

This patient experience data should include information and concerns as related to disruption to daily and family life, which may be due to treatment regimen, concerns related to nutrition, financial impact, and others to provide meaningful feedback through the patient voice in real time about issues that may not be identified through the current measures.

Finally, given the high degree of patient care management needed for this population and this disease, the CSC would like to see a robust patient provider and caregiver education plans developed and implemented.

At the Cancer Support Community, we have learned a great deal from those we support, and we believe in the importance of value and of an educated and empowered patient. Since people with cancer often feel stigmatized, alone, and overwhelmed with grief, they feel stronger and more hopeful when they have more control of the best decisions for them.

Access to a full portfolio of treatment options as well as supportive care solutions helps arm them for making the best decisions for their personal situation.

Today, we ask that you carefully consider the challenges of those facing ALL and the need for a wider array of treatment options. We urge you to look at a broad range of treatment options that will encourage patients and caregivers to be

informed, empowered, and optimistic about their treatment. Thank you for the opportunity to speak today.

DR. ROTH: Thank you. Will speaker number 2 please step up to the podium and introduce yourself? Please state your name and any organization that you represent.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from industry, so I have no conflicts of interest.

The current therapy has an impressive overall remission rate. However, this rate was observed after only 3 months. The study has not yet reached the intended primary follow-up, which was 12 months.

We are concerned because 3 months was too short to determine most of the prespecified

efficacy endpoints, including overall survival. The short duration and lack of data on planned endpoints make it difficult to determine how effective this therapy actually is.

In addition, the treatment has very serious adverse events in the short term and many of the long-term adverse events are unknown. Short-term adverse events include 47 percent of patients experiencing severe CRS events that were life-threatening and required medical intervention.

There are clear short-term benefits, but also clear risks, so it is impossible to judge whether the benefits of this therapy outweigh the risks. A risk-benefit analysis is further complicated because it is based on a single one-arm study of 63 patients.

We understand that you may be reluctant to insist on a full year of data. For that reason, we strongly suggest that the FDA require at least 6 months of data on these patients before it makes a decision to approve this treatment or not. Three more months is not a very long time to wait, and

meanwhile we encourage the FDA to allow more patients to be added to the study.

The pivotal trial was designed with primary follow-up of 1 year and secondary follow-up of 5 years. As you know, after treatment is approved, patients are often lost to follow-up, making it difficult to interpret the results. This harms all patients because it means physicians, and patients, and family members lack the information they need to know if the treatment is likely to be beneficial or if they are risking serious side effects for at best a very short-term benefit.

It would be naïve to assume that any required postmarket research, or follow-up, or registry will answer the question of whether the benefits outweigh the risks. Post-market studies frequently fail to answer such questions, and in the meantime, new patients are exposed.

Before a new medical product is approved, the FDA needs sufficient data that the benefits outweigh the risks. To approve a product without sufficient data puts patients at unnecessary risk.

Keep in mind that patients in clinical trials are usually much more carefully monitored than patients in the typical healthcare setting. In addition, physicians and other healthcare providers are more carefully trained about the use and risks of new therapies in a clinical trial than other physicians. This means that the risks and benefits of this treatment might be quite different in the real world, and with only 3 months of data, it is not possible to make patients and their families reasonably aware of the risks and benefits of this treatment before they decide whether or not to try it.

This is a major issue for the panel and the FDA to consider. In the postmarket setting, the most severe risks are expected to be mitigated through REMS. A simple warning on the label or even a pamphlet discussing the risks could be easily ignored or overlooked. Training for providers and implementation of specific hospital procedures will likely be required.

Relapsed/refractory B-cell acute

lymphoblastic leukemia is a severe and heart-breaking cancer, especially as it affects children and young adults. New treatments are desperately needed. However, treatments should not be approved based on the hope that they will be shown to be safe and effective based on a small sample of patients studied for only 3 months. Patients and their doctors deserve to be able to trust that benefits outweigh risks for FDA-approved treatments.

We greatly appreciate the efforts of the FDA to ensure that this treatment can be manufactured consistently, develop methods to mitigate the known adverse events, and implement 15-year studies to monitor new events that may take a long time to emerge. However, it is important that the FDA is certain is that the treatment is safe and effective for at least 6 to 12 months before deciding whether to approve it. Thank you for the opportunity to share our perspective.

DR. ROTH: Thank you. Will speak number 3 please step up to the podium and introduce

yourself? Please state your name and any organization that you represent.

MR. McMAHON: My name is Don McMahon. I don't represent any organization. I just represent my son, and I am not financially gaining from any of this. And I promise I am not going to use the word tocilizumab even once while I stand up here. I think we've heard enough of those type of big long words today. Today, I'm just going to talk to you about Connor's Hope.

My son, Connor, was 3 years old when he was first diagnosed. His only dream at that point was to learn how to play hockey. That's really the only thing he ever wanted to do. It's what his older brother did. He wanted to join along with him.

Just two months after those pictures of him in that hockey mask were taken, he was diagnosed with ALL type B precursor. At the time of the diagnosis, he had 100 percent leukemia cells in his bloodstream. We were told we needed immediate surgery and immediate chemotherapy.

Two months later, after gaining 30 pounds from the drugs that he was taking, steroids, and losing his hair, he was incredibly uncomfortable and kind of embarrassed, even at 3. But being the true warrior that he is, for 3 years and 2 months, he battled that cancer and endured the effects of chemo all with that trademark smile.

Over the next 3 years and 2 months, Connor would have four hospitalizations, 66 appointments at the AFLAC Cancer Center in Atlanta, Georgia, two surgeries, 13 bone marrow aspirations, 23 spinal taps, and swallowed thousands of pills.

2008, cancer was behind him. He was a happy, healthy 7-year-old. Doctors told us that there was less than a .01 percent chance that this cancer would ever return, as long as he remained cancer free for 5 years from the date of the initial diagnosis.

But we're going to fast-forward eight years from that first diagnosis, and on March 23rd of 2013, his cancer came back, just two days before his 12th birthday. This time, it would be 2 years

and 6 months of chemo that would course through his veins, and yet he never stopped living his dream to play hockey and hoping that cancer would be a thing of the past.

However, this time, his cancer was nearly fatal, slipped into a coma, and he nearly died. And then he woke up. The first thing he did was ask me for a piece of paper. And while that's hard to read, I can promise you, what it says is, "When can I get this thing out?" He had been intubated and he couldn't speak.

Just a few short weeks after that, he was out of the hospital, big smile firmly intact, determined once again not to let cancer beat him. And a few weeks after that, he was back on the ice. Over the next 2 years and 6 months, he would have four more hospitalizations, 70 appointments at that AFLAC Cancer Center, 2 surgeries, 10 bone marrow aspirations, 17 spinal taps, and again swallowed thousands of pills.

His last chemo date was July the 2nd of 2015, right back where he belongs. He continued to

play in net, maintain excellent stats while undergoing that chemo during that second round. But now that cancer was over, he would really shine.

Living his life like your average 15-year-old until June of 2016, diagnosis number 3. This time we were told Connor only had a 30 percent chance of survival and that was if we did a bone marrow transplant. His mother and I were desperate. We needed something other than that traditional chemo and bone marrow transplant options, and that's when we heard about the CAR T cell. We knew that this was our chance to finally beat cancer. And to top it all off, all of that chemo had made Connor sterile.

So it was decision time. Connor was set to begin his bone marrow transplant on Monday morning. On Saturday night, when I first heard about CAR T-cell therapy, I reached out to Tom Whitehead. Tom's the father of patient number 1. That phone call changed all of our lives.

We were sitting in a pre-op room to begin

his surgery on Monday morning to do the bone marrow transplant, when my phone rang and it was Children's Healthcare of Philadelphia. Unfortunately, Connor had been denied their program, but he was accepted into the Duke University study.

So in July of 2016, we harvested his T cells for just 5 hours in a transfusion room. Those cells were sent to New Jersey to be reengineered, but he continued to play hockey while this process went on and did not have one day of downtime from his illness. A matter of fact, Connor played in net the day before he went to Duke.

Then we went for CAR-T. Doctors called Connor the healthiest cancer patient they ever saw. Even while getting his CAR-T, he continued to smile. Connor did have a reaction, and he battled fevers of over 104 degrees for 8 days. Three of those days, he was over 107 degrees.

He lost 30 pounds in about a month, but he was determined. He was able to get up and walk out of his room, and then he walked right out of the

hospital. Keeping Connor's hope alive just one day after leaving that hospital, he went back to deliver what he calls bags of hope. It's bags that he delivers to kids that are waiting in the hospital for their turn.

Less than 30 days after leaving the hospital, he was back in net. He finished the season with a 14-3-1 record and, of those 14 wins, 8 were shutouts. He only missed 50 days of being on the ice. His team also went to nationals, and they placed third in the country, where he scored his 8th shutout of the season while the goalie for the Dallas Stars sat on the sideline and watched.

There are also family effects. There's increased depression in all family members. There's increased divorce rates for parents of children with cancer; PTSD symptoms that can appear years after diagnosis due to the long treatment process. There's economic hardships that are placed on every family, siblings that feel alone and not as important as the child with cancer.

So you tell me, chemotherapy for Connor was

12 years with almost 6 of those getting chemo versus 3 months from start to finish and 4 days of chemo, 8 hospitalizations, weeks as an inpatient, 3 hospitalizations with a total of 10 days as an inpatient, 136 appointments at the AFLAC Cancer Center, and in 12 months less than 20 doctor's appointments; 4 surgeries versus 2 for his port to be put in and out; 23 bone marrow aspirations versus 3; 40 spinal taps versus 3; thousands of pills swallowed versus under 200 taken in home care.

So ladies and gentlemen, for the sake of these children, not only in the U.S., but all over the world, follow the example that the United States sets with world-class healthcare. Adopt and approve CAR T-cell therapy because, at the end of the day, that truly is Connor's hope.

DR. ROTH: Thank you for sharing your story. Would speaker number 4 please step to the podium and introduce yourself? Please state your name and any organization that you may represent.

MR. WHITEHEAD: Hello. My name is Tom

Whitehead. I'm a co-founder of the Emily Whitehead Foundation and Emily's dad, and I am not benefitting financially from participating here today in any way.

Good afternoon. It is an honor to share with you today how my daughter, Emily Whitehead, became the first child to be treated and cured of leukemia in the CTL019 trial at the Children's Hospital of Philadelphia.

Emily, our only child, was born perfectly healthy on May 2nd of 2005. She remained healthy up until May 28th of 2010, when she became sick overnight and was diagnosed with acute lymphoblastic leukemia. We learned that ALL is the most common type of pediatric cancer and that 90 percent of the children are cured with standard therapy.

The oncologist called it a garden variety type of leukemia and said that if we followed the standard protocol of 26 months of chemotherapy, Emily would be cured, and grow up, and grow old, and become a grandmother someday.

Emily had a very rough start, and after the first week of chemotherapy developed serious infections in her legs that almost took her life. But the chemotherapy worked and got her into remission after the first month.

She remained in remission for 16 months, then at a routine appointment for blood work, her oncologist called to tell us that her cancer had returned. We were shocked to hear that she had relapsed. He said that children rarely relapse while still getting therapy and that now she would need a bone marrow transplant and had less than a 30 percent chance of surviving.

Before moving forward, we decided to seek a second opinion at CHOP. The doctor there said that she would do the same type of bone marrow transplant as our home hospital recommended and that it was fine to return there to receive treatment since it was 2 hours closer to home for us.

Before we left, she mentioned that there was an upcoming clinical trial called CTL019 that uses

the patients' own immune system to fight cancer, however, the trial wasn't expected to be ready for several months and would not be ready in time for Emily. That's what she thought.

We decided to attempt a bone marrow transplant with an unrelated donor at our home hospital. The transplant was scheduled for February of 2012, however, just a few weeks before the scheduled date, we were devastated to find out that Emily had relapsed again. We tried another course of chemotherapy to get her back in remission, but instead, the leukemia continued to grow quickly.

Emily's oncologist said that the bone marrow transplant was no longer an option and it was time to take her home in hospice and enjoy the days we had left with her.

As a last hope, we called the Children's Hospital of Philadelphia again to see if there was any help they could offer us. The timing was perfect because they told us the CTL019 trial had started enrolling patients earlier than expected.

We transferred to CHOP, where we met Dr. Stephan Grupp and his amazing team for the first time. He explained the process and the risk involved with being the first patient in the CTL019 trial. We felt that this was the new approach we needed to fight Emily's leukemia, and it didn't take us long to decide to enroll her in the clinical trial.

Emily had her T cells extracted in March of 2012. This picture shows that happening. She was given the CTL019 modified cells a month later. Within days after the last dose, Emily experienced severe cytokine-release syndrome, but during that time, it was discovered that her interleukin-6 levels were very high, and one day, Dr. Grupp came in and asked if he could administer a drug called tocilizumab to try to reverse the negative side effects. It worked. Emily began to recover from the cytokine storm within a few hours.

Now, when other parents enter their children into this treatment, they are more comfortable knowing that the doctors figured out a solution for

Emily's storm so quickly.

We have since heard from many parents that tocilizumab has successfully worked to slow the storm in their child and it made their child's treatment more tolerable. Emily's bone marrow was checked just 23 days after the first infusion, and on May 10th of 2012, Dr. Grupp called me and said, "Tom, it worked. Your daughter is cancer free." That's the best call I ever received.

We took Emily home from the hospital on June 1st and, that August, she returned to elementary school. Six months after taking her home, her story went public, and we received media requests for interviews from all over the world. We also received calls from parents from all over the world, wanting to know how they could get their child into this trial.

We spent our free time outside of our normal jobs increasing awareness of this treatments so other patients who were told that their child was out of options can find it in time. Five years later, we still receive calls and messages from

parents around the world, looking for help and advice on how to get this treatment. We are reminded of the impact this has had every time we meet or hear from a family that the therapy has been a success for their child.

CTL019 killed Emily's resistant leukemia in just 23 days and did what standard treatment couldn't do. It saved our daughter's life. This treatment has kept our family whole. Today, Emily is a typical healthy 12-year-old girl and is at the top of her class academically.

There are parents all over the world watching, waiting to hear that this treatment will be available to try before their child dies from cancer. We believe that when this treatment is approved, it will save thousands of children's lives around the world.

I hope that someday all of you on this advisory committee can tell your families for generations that you were part of the process that ended the use of toxic treatments like chemotherapy and radiation as standard treatment and turn blood

cancers into a treatable disease that even after relapse, most people survive.

Children fighting cancer need better treatments like CTL019 that are more effective and less toxic than chemotherapy and radiation so that they do not have to live the life-long side effects of their treatments.

The benefit we gained from this treatment far outweighed the risk. We were honestly more afraid of a full-body radiation that Emily was going to receive before a bone marrow transplant than we ever were of entering her as the first child in the CTL019 trial. Our daughter was going to die, and now she leads a normal life.

If you want to see what a cure looks like for relapsed ALL, she's standing right beside me, and it's because of this treatment. I would like to take this time to thank, personally thank, everyone that worked so hard for so many years to turn this treatment and have it ready for Emily when she needed it. There are amazing people working on this very hard and missing a lot of

times with their own families.

We are honored to attend this hearing and be a part of this process. We hope and urge you to vote in favor of this approval, and we're very thankful for you giving us time today to speak. So thank you very much.

DR. ROTH: Thank you, Mr. Whitehead, Emily.

(Applause.)

Questions to the Committee and Discussion

DR. ROTH: The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will now continue with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

If I could have the first question, please. Question 3 for discussion, please discuss the risk mitigation measures for the serious risks of cytokine-release syndrome and neurotoxicity with tisagenlecleucel.

Are there any comments on the phrasing of the question or any specific comments that you might have? Any discussion at all? Dr. Cripe?

DR. CRIPE: Do you want us to discuss this now or answers to this? Yes. So I'm going to start by saying that even though cytokine-release syndrome sounds really scary, our bone marrow transplant teams are used to dealing with this sort of thing every day.

The strategies that they've put in place to train people to qualify teams, much of which is already in place, FACT certification, teams used to dealing with ICU-type of situations, is nothing new to pediatrics. So their mitigation strategies to me are very good and very reassuring.

In addition, public speaker number 2 raised several points that I would argue may be true for

the adult cancer world, but in my experience, over two decades as a practicing pediatric oncologist, are really not true for pediatric patients.

So for example, patients are often "lost to follow-up," so we don't know what's going to happen to them. I would say that's not my experience. Patients are very rarely lost to follow-up. Not only do they have two parents, but often have extended families looking after them, making sure that they get to their appointments, or if not, they're put in someone's care to do so.

So we also have very mature long-term follow-up clinics that track patients down and get them back for their routine follow-ups very rigorously. So they're very rarely lost to follow-up.

Second point was, "Patients are monitored more carefully in clinical trials than the real world." In the pediatric world, most of our patients are on clinical trials. It's our standard practice to monitor them very carefully. And even when they're not enrolled on trial, we're typically

following a protocol that spells out very careful monitoring.

So again, I take issue with that statement. It may be true in the adult world, where most patients are not on clinical trials, but certainly not in the pediatric world. So I don't think that we're going to lose a lot of data, or not be following these patients, or not be following them closely because that's our standard practice. So I have no concerns with their risk mitigation measures.

DR. ROTH: Dr. Bollard?

DR. BOLLARD: So I completely agree with Dr. Cripe, and I think the team has done an outstanding job with these mitigation measures. I guess I just have a wider question regarding -- I really as a pediatric hematologist applaud the fact that this is coming to us in the pediatric setting. As you hear, there's an unmet need. It has changed the lives of many families and children.

If this goes to a postmarketing phase, though, there is the potential to open this up to

the older age group, who often aren't eligible for transplant, et cetera. I would be interested to know if Novartis has a plan for what risk mitigation measures they're going to instigate if they are approached by adult patients.

DR. LEBWOHL: David Lebwohl. So the use of this product would be restricted to patients up to 25 years of age, so we would not be able to produce material for patients older than that.

DR. ROTH: Dr. Smith?

DR. SMITH: Yes. I would also second Dr. Cripe, and I think the risk mitigation strategy is quite reasonable, and I think will provide protection for the children who will be treated.

I do think that the registry and establishing that will be very important because we are at an early stage in learning how to use these engineered T cells. There's obvious major and positive treatment effect in a substantial number of patients, but it's hard at this point to really know what the true response rate is in a real-world setting, and a registry will help with that.

I think monitoring of neurotoxicity, we're still at a very early stage for knowing the range of neurotoxicity that might occur, so the registry and really following up on episodes of neurotoxicity will be important.

Then monitoring for the duration of B-cell aplasia, some patients are recovering B cells, but it will clearly be less than ideal to be a decade or longer out and still be without B cells.

DR. ROTH: Dr. Cripe?

DR. CRIPE: My only issue with their mitigation plan is limiting it to 30 to 35 sites. I think that will put a burden on families who have to travel. Most patients who are in this type of a situation are best served at their own institution, where the people know them. Their psychosocial support team is there. The parents can stay in touch with their support systems as well.

I also think it will add time to product development, requiring a new team to get to know the patient and for the patient to travel. I think it could create social economic disparities, where

you're going to have areas, rural areas, et cetera, without access or who have to travel even further. You're going to have whole metropolitan cities without any option. And you're going to create inequities amongst hospitals, even within the same city.

So finally, I don't see it as a business plan. It limits your market penetration and allows other competitors to come into hospitals, the other hospitals that aren't the 30 or 35.

So I would like to see a plan to roll it out to all NMDP sites that are well trained to handle these kinds of patients.

DR. ROTH: I would like to take the contra approach to that in that I think the best risk mitigation strategy is experience with the drug. And I think that there are a limited number of patients. It may not seem that way at CHOP or somewhere else, but I do not think that one improves risk by having dozens of hospitals treat 2 patients a year.

That's just my personal bias. We've seen

that with other high-risk technologies, and I think there's no doubt that patients are better and well faster with fewer life-threatening toxicities when you've done 15 of these as opposed to one. So just for complete discussion, I would take a little bit of a contra approach.

Dr. Lebwohl, did you have a comment?

DR. LEBWOHL: Thank you for allowing me to speak. This is the initial group of sites. It's 31 to 35 sites, and it really is to ensure the safety of the initial period of treatment, taking the most experienced sites in an addition, adding enough sites that we have the geographic coverage.

But it is true. If we're seeing this is going well and going safely after 6 to 12 months, we will expand the group to a number of sites to make this more available.

DR. CRIPE: The technologies for apheresis are at all NMDP sites. The technologies for gene transfer and preparation of product is in the company, so that's not anything that's unique to the sites. When the product comes back, the

infusion and management of the sick patient is common amongst NMDP sites.

So I don't see -- unless Dr. Grupp or others can tell us something that they can uniquely do, that other top 20, top 30 hospitals in the country can't. You're already going to have expansion of sites from the ones that were already experienced in this, so I just don't see where your concern is going to be a problem. I can imagine the same discussion would have happened before bone marrow transplant came about, and now everybody does that.

DR. ROTH: Other comments?

(No response.)

DR. ROTH: If there's no further discussion to this question, we'll now begin the voting process. Please press the button on your microphone. I'm sorry. Question number 2, and then we will vote, which is what I meant to say.

(Laughter.)

DR. ROTH: Question 4 for the tisagenlecleucel IND studies, the FDA requires 15 years of follow-up to monitor for subsequent

malignant transformation. Given the possibility of generation of replication-competent retrovirus and insertional mutagenesis, please discuss the duration of follow-up and the type of assessments that you would recommend for patients who receive marketed tisagenlecleucel.

I'll open it up for discussion. Go ahead.

DR. CRIPE: Again, we follow our patients longer than that, and we're going to be happy to follow these patients that long and even longer, so we're not too concerned that anybody is going to be lost.

DR. BOLLARD: I would agree with that, and I think the 15 years is appropriate.

DR. ROTH: Dr. McMillan?

MS. McMILLAN: As a parent of a survivor of pediatric cancer, sometimes in follow-up, we are giving information to the care providers and they're not giving information back to us. So I would just encourage that you bring the parents and caregivers in as part of the team and that they are updated as to whatever is learned in the 15 years

as they unfold so they can also be monitoring their child.

DR. ROTH: Other comments?

(No response.)

DR. ROTH: Question 5. And before we take a vote, Dr. Kwak had to leave, so he will not be voting today. This is for vote. Considering the efficacy and safety results of study B2202, is the benefit-risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients ages 3 to 25 years with relapsed, second or later relapsed, or refractory, failed to achieve remission to initial induction or re-induction chemotherapy, B-cell precursor acute lymphoblastic leukemia, or ALL?

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before

the vote is closed.

(Voting.)

LCDR SHEPHERD: For the record, the vote is 10 yes, zero no, zero abstain, and zero no voting.

DR. ROTH: Now that the vote is complete, we will go around the table and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start with Dr. Bollard.

DR. BOLLARD: This is Catherine Bollard. I voted yes. This is a very poor risk patient population. This is an unmet need in the pediatric population. As you saw the data day, the clinical response was remarkable, and I think Novartis has done a great job putting together a plan for mitigating risk going forward.

DR. CRIPE: Tim Cripe. I voted yes. I think this is the most exciting thing I've seen in my lifetime and probably since the introduction of multi-agent total cancer care, as it was called then, for the treatment of childhood leukemia in the '50s.

DR. SMITH: Malcolm Smith. I voted yes, and I agree that this is a major advance and is ushering in a new era in treating children with relapsed and refractory ALL.

MS. McMILLAN: Gianna McMillan, patient representative. I voted yes. This therapy meets a dire unmet need and, on behalf of all parents, I am grateful for this advance.

DR. GULLEY: James Gulley, National Cancer Institute. You know, this is a novel therapy that has -- there's a strong unmet need for. There's a strong efficacy signal. There's a good risk mitigation strategy in place. And I voted yes.

DR. RINI: Brian Rini, Cleveland Clinic. I voted yes for all the same reasons that have been outlined. It seems like this is a potentially paradigm changing type of benefit with an obvious need. I think the parents who share their stories had a lot of courage, and I think that they're to be commended.

I think there's an adequate risk mitigation strategy, and I also think there's really enormous

academic opportunities to learn about this cytokine-release syndrome and how to manage them in an earlier use of IL-6 antibody, et cetera. And I think that the company is doing all the right things in that regard.

DR. ROTH: Bruce Roth. I voted yes. Clearly, a high-risk approach for a disease that has very few alternative options that also are associated with toxicity. And while I have some concerns about late toxicity, you have to be a long-term survivor to experience late toxicity, and I think that's what this drug gets us.

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes, although there are still a lot of unknowns in the long-term effects of the therapies, and we spent the morning discussing some of the manufacturing issues.

It is hard to argue with unprecedented clinical success, which we have seen in this population of patients. We do not really have other viable treatment options.

I found that the risk mitigation strategy

developed by the sponsor was very adequate and acceptable, and the site selection strategy as well was adequate to assure the safety of this cell therapy in the future.

This, along with the plans for it, prospective registry for those these patients postmarketing is very reassuring.

DR. REIN: Alan Rein. I voted yes because of the remarkable clinical successes, although it does seem to me there are some unanswered questions about long-term risks. And I'm glad to see discussion of a 15-year follow-up.

DR. COLE: Bernard Cole. I voted yes. As the statistical reviewer, I often get to talk about the most boring aspects of these kinds of studies, and I'm afraid I have to do some of that today.

The pivotal study was extremely well run. High-quality data were produced regarding the safety and efficacy of the CTL019. The applicant provided thorough analyses of the primary outcomes as well as a large collection of sensitivity analyses, including quality-of-life data. And all

of these showed positive benefit in terms of overall response that is substantial and robust.

The results were also verified by FDA, the limitation being a lack of a control group, and thus we can't be certain of the magnitude of the benefit, most importantly, in terms of overall survival.

Nevertheless, the strong and robust benefit in terms of response observed with CTL019 is favorable, and I think that's true in light of the risks and in light of the high level of unmet clinical need.

DR. ROTH: Thank you very much for your participation today. Panel members, before we adjourn, are there any last comments from the agency?

DR. PAZDUR: No.

Adjournment

DR. ROTH: Panel members, please take all your personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of.

Please also be green and turn in your name badges at the registration table on your way out so that they may be recycled. We'll now adjourn the meeting. Thank you very much.

(Whereupon, at 3:29 p.m., the meeting was adjourned.)