



**Summary Minutes**  
**Oncologic Drugs Advisory Committee Meeting**  
**July 12, 2017**

The following is the final report of the Oncologic Drugs Advisory Committee (ODAC) meeting held on July 12, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and the Office of Tissues and Advanced Therapies, and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm547155.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

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The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 12, 2017 at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and Novartis Pharmaceuticals Corp. The meeting was called to order by Bruce J. Roth, MD, (Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Acting Designated Federal Officer). There were approximately 290 people in attendance. There were a total of five Open Public Hearing (OPH) speakers.

**Issue:** The committee discussed biologics license application (BLA) 125646 for tisagenlecleucel suspension for intravenous use. The application was submitted by Novartis Pharmaceuticals Corp. The proposed indication (use) for this product is for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

**Attendance:**

**ODAC Members Present (Voting):** Grzegorz S. Nowakowski, MD; Brian I. Rini, MD, FACP; Bruce J. Roth, MD (ODAC Chairperson)

**ODAC Members Not Present (Voting):** Harold J. Burstein, MD, PhD; Philip C. Hoffman, MD; Heidi D. Klepin, MD, MS; Vassiliki A. Papadimitrakopoulou, MD; Alberto S. Pappo, MD; Courtney J. Preusse, MA (Consumer Representative); Gregory J. Riley, MD, PhD; Alice T. Shaw, MD, PhD; Thomas S. Uldrick, MD, MS

**ODAC Member Not Present (Non-Voting):** Phuong Khanh (P.K.) Morrow, MD, FACP

**Temporary Members (Voting):** Catherine Bollard, MD; Bernard F. Cole, PhD; Timothy P. Cripe, MD, PhD; James Gulley, MD, PhD, FACP; Larry W. Kwak, MD, PhD; Gianna McMillan, MA (Patient Representative); Alan Rein, PhD; Malcolm A. Smith, MD

**Acting Industry Representative to the Committee (Non- Voting):** Gary Gordon, MD, PhD

**FDA Participants (Non-Voting):** Wilson W. Bryan, MD; Denise Gavin, PhD (*Morning Session Only*); Bindu George, MD (*Morning Session Only*); Xiaobin Victor Lu, PhD; Maura O'Leary, MD (*Afternoon*)

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*Session Only*); Richard Pazdur, MD; Donna Przepiorka, MD, PhD (*Afternoon Session Only*); Marc Theoret, MD (*Afternoon Session Only*)

**Acting Designated Federal Officer (Non-Voting):** Jennifer Shepherd, RPh

**Open Public Hearing Speakers:** Amy Kappen; Kristen Santiago (Cancer Support Community); Megan Polanin, PhD (National Center for Health Research); Don McMahon; Tom Whitehead (Emily Whitehead Foundation)

***The Agenda proceeded as follows:***

Call to Order and Introduction of Committee

**Bruce J. Roth, MD**  
Chairperson, ODAC

Conflict of Interest Statement

**Jennifer Shepherd, RPh**  
Acting Designated Federal Officer, ODAC

Introductory Remarks

**Wilson W. Bryan, MD**  
Director  
Office of Tissues and Advanced Therapies (OTAT)  
Center for Biologics Evaluation and Research (CBER)  
FDA

**APPLICANT PRESENTATIONS**

**Novartis Pharmaceuticals Corp.**

Introduction

**Samit Hirawat, MD**  
Head, Oncology Global Development Unit  
Novartis Pharmaceuticals Corp.

Unmet Need

**Stephen P. Hunger, MD**  
Children's Hospital of Philadelphia

Manufacturing

**Spencer Fisk, BSc**  
Head, Cell & Gene  
Technical Development & Manufacturing  
Novartis Pharmaceuticals Corp.

Lentiviral Vector

**James Miskin, PhD**  
Chief Technical Officer  
Oxford Biomedica (UK) Ltd.

Correlations Between Product Attributes and Clinical Outcomes

**David Lebwohl, MD**  
CAR-T Franchise Global Program Head  
Novartis Pharmaceuticals Corp.

**FDA PRESENTATION**

Tisagenlecleucel CMC presentation

**Xiaobin Victor Lu, PhD**  
Chemistry, Manufacturing & Controls (CMC) Reviewer  
Gene Therapies Branch (GTB)  
Division of Cellular & Gene Therapies (DCGT)  
OTAT, CBER, FDA

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Clarifying Questions to the Presenters

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee Discussion

**LUNCH**

**APPLICANT PRESENTATIONS**

**Novartis Pharmaceuticals Corp.**

Efficacy

**Samit Hirawat, MD**

Safety

**David Lebwohl, MD**

Clinical Perspective

**Stephan Grupp, MD, PhD**  
Children's Hospital of Philadelphia

Conclusion

**David Lebwohl, MD**

**FDA PRESENTATION**

BLA 125646 Tisagenlecleucel

**Maura O'Leary, MD**  
Medical Officer, Team Leader  
Clinical Hematology Branch (CHB)  
Division of Clinical Evaluation & Pharmacology/Toxicology (DCEPT)  
OTAT, CBER, FDA

Clarifying Questions to the Presenters

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

*Question to the Committee:*

**Product Quality Discussion**

1. **DISCUSSION:** During tisagenlecleucel development, the applicant established product quality specifications to assess Chimeric Antigen Receptor (CAR) expression and T cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and IFN- $\gamma$  production following stimulation by CD19+ antigen presenting cells.

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Please discuss the following aspects of the control of product quality of tisagenlecleucel with respect to identity, safety, purity and potency:

- a. The design of the CAR construct and viral vector.
- b. The assessment of CAR expression and T cell activity through
  - i. The number of transduced T cells
  - ii. The number of vector copies per cell
  - iii. Antigen-specific T cell function (e.g., IFN- $\gamma$  production and cytotoxicity upon stimulation)
  - iv.
- c. Any other measurements, such as T cell subpopulations (cell surface marker characterization), that could provide greater assurance of product quality.

**Committee Discussion:** *Several panel members discussed the heterogeneity of the product, but one stated that the potency was demonstrated by the clinical activity seen in the trials. It was also stated that patient specific products face unique challenges in the manufacturing process, but that the applicant has the proper chain of identity procedures in place. Another committee member stated that the manufacturing process for this type of product is very complex as the technology is rapidly changing and carries an inherent risk for manufacturing failure. Safety concerns were stated by two committee members in relation to number of cells infected during therapy and the possibility of long term mutagenesis and replication-competent lentivirus (RCL). Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of replication-competent retrovirus (RCR) and insertional mutagenesis. Strategies to address these concerns include vector design and product testing.
  - a. Please discuss how vector design impacts the risk of RCR.
  - b. Please discuss how vector design impacts the risk that insertional mutagenesis might cause secondary malignancies.
  - c. Please discuss the extent to which product testing can mitigate the risk of RCR and insertional mutagenesis.

**Committee Discussion:** *It was commented by a committee member that RCR is no longer a serious safety risk for tisagenlecleucel, but that insertional mutagenesis still needs attention. Another committee member stated that there is concern over batch to batch variability of the vector since there is no stable producer cell line for the vector. The committee member also stated that with regard to insertional mutagenesis, there is a wealth of information available on mature T-cells in vivo; however, because of heterogeneous cell populations in the starting patient leukapheresis materials, you can't guarantee that you are transducing mature T-cells only. In particular, small amount of stem cells could be transduced by the CAR expressing vector. There was another concern stated over virus present in the final product that has not been transduced. A few committee members stated concern for RCR and insertional mutagenesis based on the number of cells infected and the number of infections per cell. Please see the transcript for details of the committee discussion.*

**Clinical Discussion**

3. **DISCUSSION:** Please discuss risk mitigation measures for the serious risks of cytokine release syndrome and neurotoxicity with tisagenlecleucel.

*Committee Discussion:* Most committee members agreed that although cytokine release syndrome (CRS) is a serious and concerning event, the risk mitigations strategies that the applicant has proposed are adequate and reassuring. Several committee members commented that they applauded the fact that an unmet need is addressed by tisagenlecleucel. There was opposing viewpoints on limiting the number of clinical sites. One committee member stated that limiting the sites could be a barrier to treatment for some patients and would recommend expanding the number of sites able to administer the product. Another committee member stated that the best experience with risk mitigation strategies comes from experience, and that expanding the number of sites would decrease the number of patients treated per site. The importance of a registry was also discussed. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** 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.

*Committee Discussion:* Committee members stated that the 15 year follow up was appropriate and the length was not concerning. Another committee member stated that involving caregivers in the follow-up is important. Please see the transcript for details of the committee discussion.

5. **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 (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?

**YES: 10 NO: 0 ABSTAIN: 0**

*Committee Discussion:* Several committee members stated that tisagenlecleucel addresses an unmet need in this patient population, the complete response was remarkable, and that the plan for mitigating the risk of CRS is adequate. A committee member stated concern over unknown late toxicities, but that long term survival outweighs that potential risk. Another committee member stated that the trial was well run resulting in high quality data showing the results were favorable in light of the risks. Please see the transcript for details of the committee discussion.

The meeting on July 12, 2017 was adjourned at approximately 3:28 p.m.