FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
July 12, 2017

QUESTIONS

BLA 125646

Tisagenlecleucel

Applicant: Novartis Pharmaceuticals Corp

PROPOSED INDICATION: Treatment of pediatric and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)

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-γ production following stimulation by CD19+ antigen presenting cells.

   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-γ production and cytotoxicity upon stimulation)

   c. Any other measurements, such as T cell subpopulations (cell surface marker characterization), that could provide greater assurance of product quality.

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.

Clinical Discussion

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

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.

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)?