

**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Oncologic Drugs Advisory Committee (ODAC) Meeting**  
FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center  
(Rm. 1503), Silver Spring, MD

July 14, 2011

**DRAFT QUESTIONS**

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**BLA 125388**  
**Adcetris (brentuximab vedotin) for injection**

**APPLICANT: Seattle Genetics, Inc.**

**PROPOSED INDICATION:** for the treatment of relapsed or refractory (resistant to previous standard treatments) Hodgkin's lymphoma (HL).

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Seattle Genetics, Inc. submitted a biologics licensing application, BLA 125388, for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL). The primary basis for this application is clinical trial SG035-0003, a single-arm Phase 2 clinical trial. The study population consisted of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant. Brentuximab vedotin was given intravenously at a dose of 1.8 mg/kg every 21 days for up to 16 cycles.

The primary endpoint was Objective Response Rate (ORR), and the key secondary endpoints were Duration of Response and Complete Remission (CR) Rate. Responses were determined by an Independent Review Facility (IRF) using Sponsor-modified 2007 Revised Response Criteria for Malignant Lymphoma.

SG035-0003 enrolled a total of 102 patients. Seventy-five percent of the patients were between the ages of 18 to 39. Overall response rate was 73% with a median duration of 6.7 months. CR rate was 32% with a median duration of 20.5 months. Partial remission rate was 40% with a median duration of 3.5 months. Peripheral neuropathy and myelosuppression were the most common adverse events identified by the Sponsor.

The single arm design and small size limits the benefit-risk analysis. Efficacy results are limited to response rates and duration of responses. Time-to-event endpoints such as progression-free survival or overall survival cannot be adequately interpreted in a single arm trial. In addition, a single arm trial does not permit attribution of the adverse events.

The Sponsor was advised by the FDA as early as 2008 that a response rate with prolonged duration and an acceptable risk-benefit may support an accelerated approval.

For this application, consideration for accelerated approval would be consistent with regulatory actions taken in the past decade for similar hematology applications based on single arm clinical trials.

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**DRAFT QUESTIONS (continued)**

1. **VOTE:** The FDA has identified limitations of trial SG035-0003. Should the FDA grant accelerated, regular, or non-approval for Brentuximab vedotin for the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant?
  - A. ACCELERATED APPROVAL
  - B. REGULAR APPROVAL
  - C. NO APPROVAL
  - D. ABSTAIN
  
2. The AETHERA trial is a Phase 3, double-blind, placebo controlled, randomized trial of post-transplant therapy in patients with Hodgkin lymphoma.
  - Patients are not required to be in remission at the time of randomization, which raises concerns on the heterogeneity of the study population.
  - The risk-benefit assessment would be different between a patient with no residual disease (i.e., CR) compared to a patient with active disease.
  - The primary endpoint is progression-free survival (PFS).
  - The AETHERA trial is powered to detect a PFS hazard ratio of 0.667, corresponding to a 6 month improvement of PFS.

**DISCUSS:** Please comment on the following issues regarding the AETHERA trial.

- a. Should the inclusion criteria have been limited to patients with no active disease (i.e., CR) post transplant?
  
- b. What is the most appropriate primary endpoint in this trial (progression-free survival or overall survival) to demonstrate clinical benefit?