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RESEARCH**

*APPLICATION NUMBER:*

**125399Orig1s000**

**OFFICE DIRECTOR MEMO**

### Office Director Decisional Memo

<b>Date</b>	August 19, 2011
<b>From</b>	<i>Pazdur</i> /Richard Pazdur, MD/  Richard Pazdur, MD
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	125399
<b>Supplement #</b>	
<b>Applicant Name</b>	Seattle Genetics, Inc.
<b>Date of Submission</b>	February 28, 2011
<b>PDUFA Goal Date</b>	August 30, 2011
<b>Proprietary Name / Established (USAN) Name</b>	Adcetris/brentuximab vedotin
<b>Dosage Forms / Strength</b>	Intravenous infusion given at 1.8 mg/kg every 21 days/ 50 mg single use vial
<b>Proposed Indication(s)</b>	Treatment of relapsed or refractory systemic anaplastic large cell lymphoma
<b>Action/Recommended Action for NME:</b>	<b>Accelerated Approval</b>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Karen McGinn, RNP/ Virginia Kwitkowski, RNP
Statistical Review	Kallappa Koti, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yanli Ouyang Ph.D./ Haleh Saber, Ph.D.
CMC Review/OBP and ONDQA Reviews and Micro	Bo Chi Ph.D./Colleen Thomas, Ph.D./Patricia Hughes, Ph.D./ Francisco Borrego, Ph.D./ Marjorie Shapiro, Ph.D./Patrick Swann, Ph.D./Kathleen Clouse, Ph.D./ Xiao Hong Chen, Ph.D./Janice Brown, Ph.D./Sarah Pope-Miksinski, Ph.D./Richard Lostritto, Ph.D.
Microbiology Review	See list above.
Clinical Pharmacology Review	A. Khandelwal, Ph.D. / Julie Bullock, Pharm.D.
DDMAC	Adam George, R.Ph.
DSI	Lauren Iacono-ConnOrs Ph.D./Jean Mulinde, M.D.
CDTL Review	Virginia Kwitkowski, RNP
OSE/DMEPA	Walter Fava, R. Ph., MEd./ Carlos Mena-Grillasca, R. Ph./Carol Holquist, R. Ph.
OSE/DDRE	
OSE/DSRCS	
Other - MHT	1. Tammie Brent-Howard RN, MSN/Karen Feibus, M.D. 2. Jeannie Best MSN, RN, PNP/ Hari Sachs, M.D.
IRT	IRT review team/Norman Stockbridge, M.D.

## 1. Introduction

On February 28, 2011, Seattle Genetics submitted BLA 125399 for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL), a sub-type of non-Hodgkin's Lymphoma. On the same date, the sponsor submitted BLA 125388 for the treatment of patients with relapsed or refractory Hodgkin Lymphoma. There is a separate Office Director decisional memo for the Hodgkin lymphoma application.

Brentuximab vedotin is a drug-antibody conjugate [(cAC10) conjugated to SGD-1006 via thioether bonds] directed against CD30. Brentuximab vedotin has 3 components: a chimeric IgG1 antibody cAC10 specific for human CD30, an antimicrotubule agent monomethyl auristatin E (MMAE), and a protease-cleavable linker that is covalently attached MMAE to cAC10. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex. Within the cell, MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

There are currently no FDA approved drugs specifically for systemic ALCL of which there are two types: anaplastic lymphoma kinase positive (ALK+) and anaplastic lymphoma kinase negative (ALK-) disease. The current standard of care for first-line treatment of ALK+ ALCL is CHOP, a combination of four chemotherapeutic drugs given every 14 to 21 days. The drug combination includes cyclophosphamide, doxorubicin, vincristine and prednisone. There is currently no recommended first-line treatment of ALK- ALCL although CHOP is frequently used. Relapsed ALCL (ALK+ and ALK-) is treated with a variety of combination regimens.

Males are affected more frequently than females, and the median age at diagnosis is 61 years with a range of 17–90 years. Although some subtypes may follow a relatively benign protracted course, most have an aggressive clinical behavior and poor prognosis. Symptoms of systemic ALCL include weight loss, night sweats, enlarged lymph nodes throughout the body (especially in the neck or armpits). The 5-year overall survival for ALK positive and ALK negative ALCL has been estimated at 70% and 49% respectively.

## 2. CMC/Device

The CMC and Product review teams recommend that this application be approved.

Product quality recommends an expiration dating period of 30 months for brentuximab vedotin drug product when stored at 2-8°C, an expiration dating period of (b) (4) for brentuximab vedotin drug substance when stored at (b) (4), and an expiration dating period of (b) (4) for cAC10 Intermediate when stored at (b) (4). Also, the stability protocols were acceptable and product quality recommends approval of the proposed release specifications for brentuximab vedotin drug product, brentuximab vedotin drug substance and cAC10 Intermediate.

There are no issues identified that preclude approval; however, there are several post-marketing commitments (PMCs) for product quality. Please refer to the action letter for these PMCs.

## 3. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues at this time that will preclude the approval of brentuximab vedotin for the proposed indications. Pharmacology and toxicology studies with brentuximab vedotin and/or MMAE were conducted according to ICHS9 and are considered adequate.

#### **4. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology and Biopharmaceutics team recommended approval, and there are no issues that would preclude approval.

#### **5. Microbiology**

The Microbiology team has not identified issues that would preclude approval of the BLA.

#### **6. Clinical/Statistical-Efficacy**

The main trial to support accelerated approval of this application, Trial SG035-0004, is a single-arm, multicenter, clinical trial enrolling 58 patients who had CD30-positive systemic ALCL and had previously received front-line, multi-agent chemotherapy regimens. This application is also supported by phase 1 data and a second phase 2 single arm study, SG0-35-003, in a related disease (Hodgkin lymphoma).

The primary efficacy endpoint in the systemic ALCL trial was ORR by Independent Review Facility. An ORR of 86% (95% CI: 77, 95) was achieved with a median duration of 12.6 months (95% CI: 5.7, NE). CR rate was 57% (95% CI: 44, 70) with a median duration of 13.2 months (95% CI: 10.8, NE). PR rate was 29% (95% CI: 18, 41) with a median duration of 2.1 months (95% CI: 1.3, 5.7).

Since almost three quarters of the population had ALK-negative disease, which confers a worse prognosis, the high response rate suggests significant clinical activity was attained for a large percentage of patients with limited treatment options.

#### **7. Safety**

Safety information for the HL and ALCL trials were reviewed and incorporated into labeling.

The most common adverse reactions ( $\geq 20\%$ ) noted in both trials were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting. Serious adverse events (SAEs) were reported in 31% of patients. The most common ( $>2\%$ ) SAEs reported were peripheral motor neuropathy, urinary tract infection, and abdominal pain. Refer to the prescribing information link below for further details of safety profiles of the individual trials.

Of note, a high percentage of patients reported to have unresolved residual neuropathy, therefore, further follow-up of this adverse event is recommended to determine whether the neuropathy is permanent or resolves very gradually.

#### **8. Advisory Committee Meeting**

On July 14, 2011, the Oncologic Drugs Advisory Committee (ODAC) met in the afternoon to discuss this application. ODAC voted unanimously in favor of accelerated approval for this application.

#### **9. Pediatrics**

Brentuximab is exempt from the requirement for pediatric studies for this indication because of orphan drug designation.

## 10. Other Relevant Regulatory Issues

There are no outstanding regulatory issues that would preclude approval of this application.

## 11. Labeling

All disciplines made recommendations for labeling which were incorporated.

## 12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action  
Accelerated Approval
- Risk Benefit Assessment

The risk benefit assessment favors approval of brentuximab vedotin for the treatment of patients with systemic Anaplastic Large Cell Lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The overall response rate was impressive. The responses were durable for those who achieved a complete remission (median: 13.2 months duration for CRs). The responses were not very durable for those whose disease achieved a partial response (median: 2.1 months for PRs). The safety data base was limited as only 58 patients were enrolled in SG035-004. The major adverse events were neuropathy and infusion reactions.

The Division had recommended an accelerated approval requiring randomized studies to be performed to better characterize the risk to benefit analysis. This was discussed at ODAC with a unanimous vote to support accelerated approval rather than regular approval. This data that will cover this accelerated approval to regular approval will come from randomized studies combining brentuximab to chemotherapy regimens in less refractory disease settings in both Hodgkin lymphoma and anaplastic large cell lymphoma. In addition, the submission of safety data from a randomized trial comparing brentuximab to placebo in a maintenance trial in Hodgkin lymphoma will be a post-marketing requirement.

The benefits and risks of brentuximab were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable for the recommended regulatory action of accelerated approval (see above). In conclusion, I concur with the review team's recommendation as well as the unanimous vote of the ODAC supporting accelerated approval.

- Recommendation for Post marketing Risk Management Activities  
Routine Surveillance
- Recommendation for other Post marketing Study Requirements/Commitments  
See action letter for PMRs and PMCs. Since this BLA is being approved under Accelerated Approval, the sponsor is required to conduct a confirmatory trial to be considered for full approval.