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NCCN Non-Hodgkin's Lymphoma Guideline Panel:

On behalf of Seattle Genetics, Inc., I respectfully request the NCCN Non-Hodgkin's Lymphoma Guideline Panel review the enclosed data and consider the inclusion of ADCETRIS® (brentuximab vedotin) for the treatment of patients with relapsed or refractory (R/R) angioimmunoblastic T-cell lymphoma (AITL).

Specific Request: Please consider the addition of brentuximab vedotin as a second-line and subsequent therapy option for AITL, in patients with and without intention to proceed to transplant.

FDA Clearance: ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate indicated for:[1]

- The treatment of patients with classical Hodgkin lymphoma (HL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- The treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.
- The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rationale: Patients diagnosed with AITL have a poor prognosis, with a median survival of less than 3 years.[2] Several single agent and combination regimens are used to treat R/R AITL; most achieve a modest response and have only been described in small patient populations or case reports.[3-9] There is a clear need to identify agents that demonstrate clinical activity and improve patient outcomes in this setting.

Data Summary:

A phase 2, open-label, multicenter study evaluated the efficacy and safety of brentuximab vedotin in patients with R/R non-Hodgkin's lymphomas (NHL).[10] A planned subset analysis of this study examined patients with mature T-cell lymphomas, including peripheral T-cell lymphoma, not

otherwise specified (PTCL-NOS) and AITL. Brentuximab vedotin 1.8 mg/kg IV was given on Day 1 of each 3-week cycle; patients who achieved at least stable disease were able to continue until disease progression, unacceptable toxicity or study closure. The primary endpoint was overall response rate (ORR) as determined by the investigator. Key secondary endpoints included safety, duration of objective response and progression free survival (PFS).

Thirty-five patients with mature T-cell lymphomas were enrolled, including 13 patients with AITL.[10] The ORR for patients with AITL was 54% (n=7), with 38% (n=5) achieving a complete remission (CR) and 15% (n=2) achieving a partial remission (PR). The median duration of response and PFS for patients with AITL was 5.5 months and 6.7 months, respectively.

Safety data was reported for all 35 patients with mature T-cell lymphoma enrolled in this study.[10] Grade 3 or higher adverse events (AEs) occurring in 2 or more patients were neutropenia (14%), hyperkalemia (9%), peripheral sensory neuropathy (9%), acute renal failure (6%), anemia (6%), dehydration (6%), disease progression (6%), pneumonia (6%), thrombocytopenia (6%), tumor lysis syndrome (6%), and urinary tract infection (6%). Six treatment-related Grade 4 AEs were reported in 3 patients, including pneumonia, sepsis, hyperkalemia, elevated lipase, confusion, and pulmonary edema. One Grade 5 event of acute respiratory distress syndrome was also reported. Three patients died within 30 days of the last brentuximab vedotin dose; 2 were disease-related and one was a 74-year-old patient with AITL who died due to acute respiratory distress syndrome that was deemed to be related to disease progression, infection, and study treatment.

These data provide evidence that brentuximab vedotin is a therapeutic option in the second-line or subsequent therapy setting for patients with AITL. The ORR of 54% compares favorably with other second-line agents currently recommended for the treatment of AITL by the NCCN Clinical Practice Guidelines for Non-Hodgkin's Lymphoma.[3-10] We respectfully request the NCCN Non-Hodgkin's Lymphoma Guideline Panel consider including brentuximab vedotin as a second-line or subsequent therapy option for AITL, in patients with and without intention to proceed to transplant. The enclosed references are submitted in support of this proposal.

Sincerely,

Steven Sesterhenn, MD, MBA
Senior Medical Director, Medical Affairs
Seattle Genetics, Inc.

References:

1. Seattle Genetics. ADCETRIS - brentuximab vedotin injection, powder, lyophilized, for solution. 2011 [rev. 2016 March]; http://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=3904f8dd-1aef-3490-e48f-bd55f32ed67f&type=display. Accessed April 27, 2016.
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10. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood.* May 15 2014;123(20):3095-3100.