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NCCN T-cell Non-Hodgkin's Lymphoma Guideline Panel:

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

Specific Request: Please consider including the results from the phase 3, randomized ALCANZA trial as additional evidence supporting the use of brentuximab vedotin in patients with CTCL, including mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL).

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: CTCL is a rare, heterogenous group of T-cell lymphomas associated with reduced quality of life.[2] Several systemic therapies for CTCL are available; however, no randomized trials have previously established a preferred regimen. Additionally, while several single-agent and combination regimens may be used to treat CTCL, most achieve a modest response of limited duration.[3-7] As a result, there is a clear need to identify agents that demonstrate clinical activity and improve patient outcomes in this setting.

Data Summary:

A phase 3, randomized, open-label, international clinical trial (ALCANZA) investigated the efficacy and safety of brentuximab vedotin (n=64) versus physician's choice of methotrexate or bexarotene (n=64) in patients with CD30-expressing MF and pcALCL (NCT01578499).[8] Patients were randomized 1:1 to receive either brentuximab vedotin 1.8 mg/kg IV every 3 weeks or physician's choice of oral methotrexate 5 to 50 mg/week or oral bexarotene 300 mg/m^2/day for up to 48 weeks or until disease progression or unacceptable toxicity. The primary endpoint was the objective

response rate lasting at least 4 months (ORR4) by independent review as measured by a global response score using the ISCL/EORTC consensus guidelines. Secondary endpoints included complete remission (CR) rate, progression free survival (PFS), change in burden of symptoms/patient-reported quality of life (QoL) (as measured by the validated Skindex-29 QoL tool), duration of response, pharmacokinetics, immunogenicity, and safety.

With a median follow-up of 17.5 months, a statistically significant improvement was seen in the brentuximab vedotin arm for ORR4 and PFS.[8] For the intent-to-treat population, the ORR4 was 56.3% in the brentuximab vedotin arm versus 12.5% in the control arm (P<0.0001), while the median PFS was 16.7 months in the brentuximab vedotin arm versus 3.5 months in the control arm (HR=0.27; 95% CI, 0.169 to 0.43; P<0.0001).

Treatment-emergent adverse events (AEs) reported in ≥15% of patients in the brentuximab vedotin arm included peripheral neuropathy (67%), nausea (36%), diarrhea (29%), fatigue (29%), vomiting (17%), pruritus (17%), pyrexia (17%), alopecia (15%) and decreased appetite (15%).[8] Treatment-emergent AEs reported in ≥15% of patients in the control arm included fatigue (27%), hypertriglyceridemia (18%, reported in 30% of patients treated with bexarotene), and pyrexia (18%). Grade ≥3 AEs were reported in 41% of patients treated with brentuximab vedotin and 47% of patients in the control arm. Treatment-emergent grade 3/4 AEs reported in the brentuximab vedotin arm included peripheral neuropathy, fatigue, diarrhea, nausea, vomiting, and pruritus; treatment-emergent grade 3/4 AEs reported in the control arm included hypertriglyceridemia (reported in 22% of patients treated with bexarotene), pruritus, fatigue, and pyrexia.

Four patient deaths were reported in the brentuximab vedotin arm within 30 days of the last dose of therapy; 3 of the deaths were unrelated to study drug as determined by the investigator, and included disease progression (n=1), pulmonary embolus (n=1) and sepsis (n=1). One death occurred in a patient with pcALCL who developed multiple organ dysfunction syndrome attributed to tumor necrosis at visceral disease sites caused by brentuximab vedotin. Overall, with a median follow-up of 23 months, 16 deaths occurred in the brentuximab vedotin arm and 14 deaths occurred in the control arm.

The results from the ALCANZA trial, the first phase 3 trial investigating a new systemic agent against an active comparator, demonstrate that treatment with brentuximab vedotin provides improved efficacy versus methotrexate/bexarotene in patients with MF and pcALCL. These data are further supported by two previous phase 2 studies demonstrating the clinical activity of brentuximab vedotin in CTCL, including activity in patients with CD30-expressing and CD30-non-expressing disease and activity in patients with lymphomatoid papulosis (LyP) and Sézary syndrome (SS).[9,10] Results from the ALCANZA trial that were presented at the 2016 American Society of Hematology Annual Meeting can be found in the enclosed supporting references. A manuscript containing additional results from the ALCANZA trial is anticipated for publication in early June 2017. Once published, the manuscript will be provided to the NCCN T-cell Non-Hodgkin's Lymphoma Guideline Panel for further consideration.

Sincerely,

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References:

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