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NCCN Guidelines® Panel: Hodgkin Lymphoma

On behalf of Seattle Genetics, Inc., I respectfully request the *NCCN Hodgkin Lymphoma Panel* to review the enclosed data to include brentuximab vedotin to salvage therapy prior to autologous stem cell transplant (ASCT) for patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL).

Specific Changes: Recommend brentuximab vedotin, as a single agent or in combination with bendamustine, as a salvage therapy option prior to ASCT for patients with R/R HL (in addition to "patients who have failed ASCT or at least 2 prior multi-agent chemotherapy regimens").

FDA Clearance: Brentuximab vedotin is a CD30-directed antibody-drug conjugate indicated for:

- The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.[1]
- The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.[1]

These indications are based on response rate. There are no data available demonstrating improvements in patient reported outcomes or survival with brentuximab vedotin.[1]

Rationale: Patients with R/R HL who achieve pre-ASCT complete remission (CR) with salvage therapy have improved post-ASCT outcomes.[2-8] Therefore, improving the quality of response to salvage therapy with manageable toxicity by administering brentuximab vedotin in the salvage setting is expected to lead to more patients being candidates for ASCT and improved outcomes after ASCT.

Data Summary:
Interim results from a phase 1/2 study of brentuximab vedotin combined with bendamustine as first salvage therapy in patients with R/R HL (N=23) have been reported. Among 13 patients evaluable for response, the objective response rate (ORR) was 92% with a CR rate of 77%. At the time of this analysis, 7 patients had undergone ASCT. The only treatment-emergent Grade ≥3 AE reported in >1 patient was lymphopenia (n=5; 22%). There were 6 treatment-related serious infusion-related reactions which resulted in a protocol amendment requiring routine premedication with corticosteroids and antihistamines.[9] Additional data from this study has been submitted for presentation at the American Society of Hematology Annual Meeting in December 2014.

In a phase 2 trial in patients with R/R HL, PET-adapted therapy with brentuximab vedotin with or without sequential augmented ICE (ifosfamide, carboplatin, etoposide), was evaluated as an alternative salvage therapy regimen prior to ASCT. Of 42 evaluable patients, 33 patients (78%) achieved PET normalization (Deauville ≤2), with 12 patients (28%) achieving PET normalization after 2 cycles of brentuximab vedotin alone and 21 patients (50%) achieving PET normalization after 2 cycles of brentuximab vedotin followed by augmented ICE. A total of 39 patients (93%) have been transplanted; with a median follow-up of 10 months, event-free survival was 92%. Adverse events

(AEs) related to brentuximab vedotin were mostly Grade 1 or 2 and included neuropathy (n=23, 55%) and rash (n=30, 71%). Serious AEs related to augmented ICE included febrile neutropenia (n=18, 43%), anemia, anorectal infection, bone pain, hyperglycemia, nausea, sepsis, thrombocytopenia, and vomiting (n=1 each).[10]

A retrospective analysis was performed to evaluate the use of brentuximab vedotin (1.8 mg/kg q3w) as first salvage therapy in patients who failed frontline therapy. This analysis included 3 patients from an expanded access program (EAP), and 11 patients from an ongoing investigator-sponsored trial. An interim analysis of 14 patients demonstrated an ORR of 85.7% and a CR rate of 50%. At the time of this analysis, 9 patients had completed ASCT and all achieved CR post-transplant. Grade 3-4 AEs included acneiform rash and UTI which were reported in 1 patient (7.1%) each. No febrile neutropenia was reported. The use of peripheral red blood cell transfusions, platelet transfusions, or growth factors was not required.[11]

In summary, these data provide compelling evidence that brentuximab vedotin can be used in the salvage setting to improve the quality of pre-ASCT responses and result in a high percentage of patients achieving ASCT with hematopoietic recovery. Furthermore, the evidence provided comes from three separate regimens (combination with bendamustine, single-agent administered weekly followed by sequential ICE if PET negative status is not achieved, and single-agent administered every three weeks). We respectfully request that NCCN HL panel members consider including these regimens incorporating brentuximab vedotin, as a salvage therapy option for patients with R/R HL. The enclosed references are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Sincerely,

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