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NCCN Guidelines® Panel: Non-Hodgkin Lymphoma

On behalf of Seattle Genetics, Inc., I respectfully request the *National Comprehensive Cancer Network (NCCN) Non-Hodgkin's Lymphoma Panel* to review the enclosed data to include ADCETRIS® (brentuximab vedotin) for patients with cutaneous T-cell lymphoma (CTCL).

Specific Changes: Recommend brentuximab vedotin as a treatment option for relapsed or refractory cutaneous T-cell lymphoma (CTCL).

FDA Clearance:
Brentuximab vedotin is approved 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.
- The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.

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

Rationale:
The acceptable treatment of CTCL can include topical and systemic therapies, alone or in combination. The decision on which therapy to use mainly depends on the clinical stage, TMNB classification, and major prognostic factors.

Data Summary:

Data supporting the use of brentuximab vedotin for CTCL are derived from two phase 2 studies.[2,3] In the first study, Krathen, et al. reported results of a phase 2 investigator-sponsored trial to evaluate the response rate of brentuximab vedotin in patients (N = 20) with stages IB-IVB CD30-positive and CD30-undetectableundetectabelundetectable mycosis fungoides and Sézary syndrome who failed at least one prior systemic therapy. Data were presented in an oral session at the 2nd World Congress of Cutaneous Lymphomas in 2013. The overall response rate (ORR) was 70% (n = 14). There was a statistically significant correlation between clinical response and stage. The ORR for patients who were stage IB (n=2), stage IIB (n=11), and IVA/B (n=7) was 100%, 91%, and 29%, respectively. The median event-free survival was 27 weeks (range, 2-74+).

Clinical responses were observed in patients with all levels of CD30 expression, including those with no detectable CD30 by IHC.

The most common drug-related adverse events (≥20% of patients) were peripheral neuropathy (75%), fatigue (60%), decreased appetite (30%), nausea (25%), alopecia (20%), dyspepsia (20%), and skin eruption (20%). Grade 3-5 AEs reported were peripheral neuropathy, skin eruption, neutropenia, pain, thrombocytopenia, acute renal failure, decreased white blood cell count, febrile neutropenia, hyperglycemia, lymphocytosis, pneumonia, pruritis, sepsis, and respiratory failure.

In a second study, Duvic, et al. evaluated the safety and efficacy of brentuximab vedotin in patients with cutaneous CD30-positive lymphoproliferative disorders in a phase 2 investigator-sponsored study. Latest data were presented at the 2013 American Society of Hematology Annual Meeting.

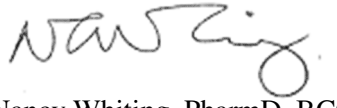
A total of 56 patients have been enrolled on study, of whom 54 were evaluable for toxicity (received ≥1 dose) and 48 were evaluable for efficacy (received >2 doses). Eligible patients had histologically confirmed CD30-positive disease within 12 months of treatment and progression after radiation or systemic therapy. The ORR was 73% (35/48); among patients with LyP, pcALCL, LyP /MF, ALCL/MF or ALCL/LyP the ORR was 100% (20/20). The median duration of response in mycosis fungoides patients was 32 weeks (range, 3-93). The overall survival rate had not been reached and the average progression-free survival (PFS) was 1.5 years. Of 54 patients who received at least one dose of brentuximab vedotin, the most common AEs reported were peripheral neuropathy (65%), fatigue (41%), and drug rash (27%). Most AEs were Grade 1/2. Grade 3 AEs reported included neutropenia (n=3), nausea (n=2), unstable angina or myocardial infarction (n=2), infection (n=2), fatigue (n=1), deep vein thrombosis (n=1), pulmonary embolism (n=1), abnormal liver function tests (LFTs, n=1), dehydration (n=1), and arthralgia (n=2). Four patients withdrew from the study due to AEs, which included infusion reaction, severe fatigue, unstable angina or MI, and ineligible cord compression. Two patients died, 1 due to sepsis and 1 due to urosepsis.

In addition to the two phase 2 trials, other investigators have described in case reports successful use of brentuximab vedotin for cutaneous T-cell lymphoma.[4]

There is also a randomized phase 3 trial (ALCANZA) evaluating brentuximab vedotin versus physician's choice (methotrexate or bexarotene) for the treatment of CTCL. Our goal is to complete enrollment in this trial by the end of 2014 or early 2015.

These studies evaluating the use of brentuximab vedotin as a single agent in patients with CTCL who have failed systemic therapy demonstrate efficacy and manageable toxicity in a difficult to treat patient population. Manuscripts from the phase 2 studies are in preparation, and we anticipate that they will be published shortly. We respectfully request that NCCN NHL panel members consider adding brentuximab vedotin as a treatment option for patients with CTCL who have failed at least one prior systemic therapy.

Sincerely,



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References:

1. ADCETRIS® (brentuximab vedotin) for Injection U.S. Prescribing Information. Seattle Genetics, Inc. September 2013.
2. Duvic M, Tetzlaff M, Gangar P, et al. Phase 2 open label trial of brentuximab vedotin (SGN-35) for CD30+ lymphoproliferative disorders and CD30+ mycosis fungoides. Oral presentation at the American Society of Hematology Annual Meeting. December 7-10, 2013; New Orleans, LA.
3. Krathen M, Bashey S, Sutherland K et al. Brentuximab vedotin demonstrates clinical activity in mycosis fungoides/sezary syndrome. Oral presentation at the 2nd World Congress of Cutaneous Lymphomas. February 6-9, 2013; Berlin, Germany.
4. Mody K, Wallace JS, Stearns DM, et al. CD30-positive cutaneous T-cell lymphoma and response to Brentuximab vedotin: 2 illustrative cases. Clin Lymphoma Myeloma Leuk. 2013 Jun;13(3):319-23.
5. Whittaker S, Dummer R, Scarisbrick J, et al. Phase 3 study of brentuximab vedotin versus physician's choice in patients with CD30-positive cutaneous T-cell lymphoma. The ALCANZA study. Poster presentation at the 6th Annual T-cell Lymphoma Forum. January 23-25, 2014; San Francisco, CA.