Christian Wade, Ph.D.
Associate Director, Medical Affairs
Seattle Genetics, Inc.
21823 30th Drive SE
Bothell, WA 98021
425.527.2668
cwade@seagen.com
Date of request: 5 September 2014
NCCN Guidelines® Panel: Hodgkin Lymphoma

On behalf of Seattle Genetics, Inc., I respectfully request the *National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma Panel* to review the enclosed data to include use of ADCETRIS® (brentuximab vedotin) as a single agent for the front line treatment of elderly patients with classical Hodgkin lymphoma who are ineligible for or who have declined conventional chemotherapy.

Specific Changes: Recommend brentuximab vedotin as a treatment option for the front line treatment of patients with classical HL, aged ≥60 years who are ineligible for or have declined conventional combination chemotherapy.

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 (sALCL) 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.

RATIONALE

Background

Patients 60 years of age and above comprise a substantial portion of the population with hematologic malignancies. It is estimated that 20% of patients with HL are at least 60 years of age.[2,3] Older patients with newly-diagnosed HL have a worse prognosis compared with younger patients.[4] Comorbidities in older patients are associated with greater treatment-related toxicities, can prevent delivery of standard-intensity chemotherapy, and may limit the duration of therapy.[5]

Engert et al. conducted a comprehensive retrospective analysis of 4,251 HL patients (in early favorable, early unfavorable, and advanced stages), 372 (8.8%) of whom were over age 60; the older cohort had a 15% rate of grade 3/4 infection vs. 6% in those age 60 or younger, and 6% rate of fatal infection vs. 0.6% for younger patients. In that same analysis, the treatment-related mortality rate was 34% for the older patients vs. only 2% for younger patients. The overall survival (OS) was 65% vs. 90%, respectively; the rate of freedom from treatment failure (FFTF) was 60% vs. 80%, respectively.[6]

Brentuximab vedotin

Brentuximab vedotin (ADCETRIS®) is an anti-CD30 antibody conjugated to monomethyl auristatin E (MMAE). Efficacy has been shown in the treatment of relapsed HL with an objective response rate (ORR) 75%, complete remission (CR) rate 34% with manageable toxicity in a pivotal phase 2 study.[7]

Data supporting the use of brentuximab vedotin in elderly patients are derived from distinct analyses of 64 elderly patients, range 61-92 years of age, from two ongoing phase 2 studies, and one published retrospective analysis performed in patients with relapsed or refractory CD30-positive hematologic malignancies who received at least one dose of brentuximab vedotin among seven clinical trials.[8-10]

In a phase 2, open label ongoing study, Yasenchak et al. reported interim results of a single-agent brentuximab vedotin for frontline therapy of both early and advanced stage treatment-naïve HL (Stage I-IV) patients who were deemed ineligible for or declined conventional combination chemotherapy. Nineteen patients aged ≥60 years were enrolled and evaluable for response at the time of the analysis. Objective responses were observed in 89% (n=17) of patients with brentuximab vedotin monotherapy (12 CR, 5 partial remission [PR]); 2 patients had stable disease (SD). The median duration of treatment was 18 weeks (range, 11-38).[8]

Patients with ECOG status ≤3 receive brentuximab vedotin 1.8 mg/kg every 3 weeks (q3w) for up to 16 cycles; patients with SD or better at the end of therapy may continue beyond cycle 16. At baseline, patients (N=19) had a median age of 78 years (range 64-92 years); 9 (47%) had B symptoms, 9 (47%) had advanced stage disease, and 12 (63%) had moderate age-related renal insufficiency (CrCL ≥30 and <60 mL/min).[8]

Brentuximab vedotin was generally well tolerated in this elderly population. Adverse events (AEs) occurring in ≥10% of patients regardless of relationship to therapy included peripheral sensory neuropathy (PSN), fatigue, diarrhea, peripheral edema, pruritus, alopecia, nausea, urinary tract infection, constipation, muscle weakness, rash, and maculo-papular rash. AEs related to brentuximab vedotin occurred in 15 patients; most of these events were Grade ≤2 except for Grade 3 PSN, rash, neutropenia, and orthostatic hypotension, each of which occurred in 1 patient. Two patients experienced a serious AE considered related to brentuximab vedotin; one had orthostatic hypotension and the other pyrexia. Two patients discontinued the study due to AEs, one due to orthostatic hypotension and the other peripheral motor neuropathy. Grade 3 laboratory abnormalities include elevated alkaline phosphatase, AST, bilirubin, and glucose, and low hemoglobin, neutrophils, phosphate, and potassium, each of which occurred in 1 patient, and decreased lymphocytes, which occurred in 2 patients.[8]

This phase 2 study is ongoing and has been amended to evaluate the activity and safety in combination with dacarbazine. Data from this study have been submitted to the American Society of Hematology Annual Meeting in December 2014. We anticipate that the primary outcome measure will be complete by the end of 2015 (NCT01716806).

In a second ongoing phase 2 study in HL patients over age 60, Evens et al. presented interim results evaluating single agent brentuximab vedotin followed by doxorubicin, vinblastine, and dacarbazine (AVD) in 7 elderly patients (median age 73 years; range 61-88 years) with untreated advanced HL (stages II-IV). The treatment regimen includes brentuximab vedotin monotherapy (1.8 mg/kg) q3w for 2 cycles. Patients who achieve CR, PR, or SD then receive 6 cycles of AVD. Those who remain in CR or PR receive another 4 cycles of brentuximab vedotin as consolidation. Four patients achieved PR, 2 patients achieved SD with brentuximab vedotin monotherapy, and 1 patient died due to progressive disease.[9]

During brentuximab vedotin monotherapy, all 7 patients had Grade 3/4 AEs (5 patients experienced >1 AE). The Grade ≥3 AEs included acidosis, acute renal failure, acute respiratory failure, anemia, anorexia, dehydration, diarrhea, fatigue, hepatobiliary, hyperglycemia, hypoglycemia, hyponatremia, metabolism, multi-organ failure, nausea, neutropenia, other infection, pain, pancreatitis, pneumonia, urinary tract infection, and sepsis. One patient experienced a Grade 5 AE with acute pancreatitis 9 days after the second dose of brentuximab vedotin, and died 6 days later. This patient had no conventional pancreatitis risk factors (e.g. gallstones, alcohol, or other medications). Enrollment in this study was temporarily suspended then re-opened with mandated amylase and lipase analysis prior to brentuximab vedotin therapy.[9] Enrollment has resumed without recurrent safety concerns.

In addition to these two ongoing phase 2 trials, Gopal et al. have published a retrospective analysis of 38 older patients (≥60 years, median age 66 years) with relapsed or refractory CD30-positive hematologic malignancies who received at least one dose of brentuximab vedotin among seven phase 1 or 2 clinical trials, with an objective response rate (ORR) of 83% including 45% of patients achieving CR.[10] These results are similar to outcomes for younger patients (n=135) in the same studies as presented by Fanale et al.[11] In general, the safety profile in this subset of patients was similar to that in younger patients with PSN (60%), fatigue (58%), nausea (38%), anemia (30%), pyrexia (28%), diarrhea (25%) and neutropenia (25%) the most common adverse events observed in ≥25% of patients.

Brentuximab vedotin was administered every 3 weeks (at ≥1.2 mg/kg) for all trials except for one which evaluated the drug with dosing on Days 1, 8, and 15 of 28 day cycles (at 0.6-1.4 mg/kg). The majority of patients in this analysis received a dose of 1.8 mg/kg every 3 weeks. The median duration of brentuximab vedotin treatment was 24.6 weeks (range, 3.0 to 69.9), and patients received a median of 7.5 cycles (range 1-22). Patient demographics and baseline characteristics included ECOG 0/1 (n=38, 96%), at least 2 prior systematic therapies (median range 1-6), prior stem cell transplant (n=34, 84%), diagnosis sALCL (n=22, 55%), HL (n=16, 40%), and other (n=2, 5%).[11]

In summary, we present interim analyses of two phase 2 studies in patients with untreated HL who are 60 years of age or older. In one, brentuximab vedotin monotherapy (1.8 mg/m^2 q3w) is administered as front line treatment for older patients who are unable to receive standard combination chemotherapy. In the other study, patients receive single agent brentuximab vedotin followed by AVD then additional brentuximab vedotin. These data provide evidence of marked antitumor activity and a manageable safety profile in a subset of HL patients with few therapeutic options. Furthermore, a post-hoc analysis of relapsed and refractory patients over the age of 60 demonstrated efficacy and tolerability similar to that seen in younger patients.

We respectfully request that NCCN HL panel members consider adding brentuximab vedotin as a treatment option for front line HL patients over the age of 60 who are not candidates for conventional chemotherapy, a special patient population that has no standard treatment and is underrepresented in clinical trials.

Sincerely,

Christian Wade, Ph.D.
Associate Director, Medical Affairs
Seattle Genetics, Inc.

References:

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(SGN: VF: August 18, 2014)