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NCCN T-Cell Lymphomas Guideline Panel:

On behalf of Seattle Genetics, Inc., I respectfully request the NCCN T-Cell Lymphomas Guidelines Panel review the enclosed data for inclusion of ADCETRIS® (brentuximab vedotin) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for the frontline treatment of patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified (PTCL-NOS).

Specific Request: Please consider including ADCETRIS in combination with CHP (A+CHP) as a preferred treatment regimen with Level 1 evidence for the frontline treatment of patients with systemic ALCL and other CD30-expressing PTCLs, based on the results of the phase 3, ECHELON-2 study.

FDA Clearance: ADCETRIS is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.[1]

ADCETRIS in combination with CHP was recently approved for use through the Oncology Center for Excellence Real-Time Oncology Review pilot program, which is designed to allow for a more efficient review process for drugs that are likely to demonstrate substantial improvements compared to currently available therapies in trials with easily interpretable endpoints.[2,3] ADCETRIS is also indicated for five other indications related to Hodgkin lymphoma and other T-Cell lymphomas.[1]

A summary of the unmet need in patients with PTCL and the ECHELON-2 study results are included below for review and consideration.

Rationale: Peripheral T-cell lymphomas are a rare heterogeneous group of lymphoid malignancies that account for approximately 10% of all non-Hodgkin lymphomas. While there remains no standard frontline treatment regimen, the most common PTCL subtypes are usually treated similarly with the multi-agent chemotherapy CHOP, or CHOP-like regimens.[4,5] One reason that an optimal therapy for PTCL remains to be determined is that results from most studies are difficult to interpret owing to retrospective analysis, inclusion of subgroups with varying prognosis, and small patient numbers.

Although CHOP, or CHOP-like regimens are commonly utilized, anthracycline-containing regimens typically result in poor progression-free survival (PFS) and overall survival (OS) outcomes for most previously untreated PTCL patients; depending upon histological subtype, 5-year OS can range from 7% to 70%.[6] Thus, PTCL represents a group of lymphoid malignancies with a high unmet need, with a specific need for treatment regimens which demonstrate an improvement in overall survival as assessed in large, randomized clinical trials. While alternative or intensified combination

chemotherapy regimens have been studied, the results generally exhibit increased toxicity and have failed to demonstrate superiority over CHOP.[7-12]

CHOP plus etoposide (CHOEP) is the PTCL frontline treatment option that some clinicians believe may offer a treatment advantage compared to CHOP; however, CHOEP has not been compared to CHOP in a prospective, randomized trial.[13-15] A retrospective subset analysis from completed prospective trials demonstrated a 3-year event free survival (EFS) advantage for CHOEP compared to CHOP (75.4% versus 51%); however, these results were from a subset of younger, more favorable patients, with the greatest benefit observed in patients with ALK-positive sALCL. Further, there was no OS advantage for patients treated with CHOEP, but there was an increased rate of Grades 3 and 4 hematologic toxicities, including leukopenia, thrombocytopenia, and anemia.[14,15]

Clinical Data: ECHELON-2 is a phase 3, multicenter, randomized, double-blind, double-dummy, randomized, active controlled trial comparing the efficacy and safety of A+CHP with CHOP as frontline treatment in subjects with previously untreated CD30-expressing PTCL.[1] ECHELON-2 enrolled 449 subjects with sALCL, PTCL-NOS, AITL, ATLL, or EATL who were randomized 1:1 to receive 6 to 8 cycles of A+CHP (n=223) or CHOP (n=226) administered as 21-day cycles. The majority of subjects had Stage III or IV disease (81%) and received 6 cycles of A+CHP or CHOP therapy (70% and 62%, respectively). The primary endpoint was PFS per Independent Review Facility (IRF), with a key secondary endpoint of OS.

The hazard ratio for PFS by IRF for the intent-to-treat (ITT) population was 0.71 (95% CI: 0.54, 0.93; P=0.011) in favor of subjects who received A+CHP compared to CHOP, with a corresponding median PFS of 48.2 months (95% CI: 35.2, not estimable) in the A+CHP arm versus 20.8 months (95% CI: 12.7, 47.6) in the CHOP arm.[1] At a median follow up of 41.9 months for the A+CHP arm and 42.2 months for the CHOP arm, A+CHP demonstrated a statistically significant improvement in OS compared to CHOP (HR 0.66 [95% CI: 0.46, 0.95; P=0.024]), with the median OS not estimable for either arm at the time of primary analysis.

While the study was not powered to compare efficacy between each individual histological subtype, it is important to note that the OS benefit with A+CHP is consistently observed across all histologic subtypes enrolled in the ECHELON-2 trial.[16]

The safety profile was comparable between the A+CHP and CHOP arms, with serious adverse reactions occurring in 38% and 35%.[1] There were also similar rates of any grade febrile neutropenia (19% versus 16%) and any grade peripheral neuropathy (52% versus 55%) for A+CHP and CHOP, respectively. As the rate of febrile neutropenia approached 20% in the A+CHP arm, the use of G-CSF primary prophylaxis is recommended, consistent with ASCO and NCCN guideline recommendations.[17,18]

Summary: Patients with PTCL have a high unmet medical need as patients have poor OS associated with a lack of effective treatment options. The FDA has recently approved A+CHP for all patients with CD30-expressing PTCLs based on the results of the ECHELON-2 trial. In addition to demonstrating a significant improvement in PFS, ECHELON-2 is the first prospective trial in PTCL to show an OS benefit over an established standard therapy, CHOP. The data from the ECHELON-2 trial, including statistically significant and clinically meaningful improvements in PFS and OS compared to the current standard of care, demonstrate that A+CHP is a practice-changing treatment option for patients with previously untreated sALCL and other CD30-expressing PTCLs.

Sincerely,

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