

Nancy Whiting, PharmD, BCOP  
Senior Vice President, Global Medical Affairs  
Seattle Genetics, Inc.  
21823 30<sup>th</sup> Drive SE  
Bothell, WA 98021  
425.527.2646  
[nwhiting@seagen.com](mailto:nwhiting@seagen.com)

Date of request: December 10, 2017

NCCN Hodgkin Lymphoma Guideline Panel:

On behalf of Seattle Genetics, Inc., I respectfully request the NCCN Hodgkin Lymphoma Guideline Panel review the enclosed data regarding the use of ADCETRIS® (brentuximab vedotin) in combination with Adriamycin (doxorubicin), vinblastine, and dacarbazine (AVD) for the frontline treatment of patients with advanced classical Hodgkin lymphoma (cHL).

Specific Request: Please consider including ADCETRIS (brentuximab vedotin) in combination with AVD (A+AVD) as a preferred regimen for the frontline treatment of patients with advanced cHL, based on the results of the phase 3, ECHELON-1 study.

A summary of the ECHELON-1 study results, affordability considerations, and reference list are included below for your review and consideration.

FDA Clearance: ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate indicated for the treatment of adult patients with:<sup>1</sup>

- Classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.
- cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- 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.

- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

Rationale: Approximately 30% of patients with advanced stage cHL are refractory to, or will relapse after frontline treatment with ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine).<sup>2-4</sup> Additionally, ABVD has an adverse event profile associated with several long-term toxicities, including treatment-related pulmonary toxicity.<sup>5</sup> New treatment options for advanced cHL are needed that will improve patient outcomes with a manageable toxicity profile.

A previous phase 1 study evaluating brentuximab vedotin in combination with either ABVD or AVD as frontline treatment for advanced cHL showed that A+AVD was well-tolerated and resulted in a 96% complete remission (CR) rate, with a 5-year failure-free survival and overall survival (OS) rate of 92% and 100%, respectively.<sup>6,7</sup> Based on these positive results, the ECHELON-1 trial evaluated A+AVD versus ABVD as frontline therapy in patients with Stage III/IV cHL.

### Clinical Data:

ECHELON-1, a phase 3, randomized, open-label, multicenter study, evaluated the efficacy and safety of A+AVD versus ABVD as frontline treatment in previously untreated advanced stage cHL.<sup>8-10</sup> A total of 1334 patients  $\geq 18$  years were randomized 1:1 to receive either A+AVD or ABVD on Days 1 and 15 of each 28-day cycle for a total of 6 cycles.<sup>8,9</sup>

The primary endpoint of the study was modified progression-free survival (PFS), defined as the time to progression, death, or receipt of additional anticancer therapy for patients who are not in CR after completion of frontline therapy, as assessed by an independent review facility (IRF).<sup>8-10</sup> Additional secondary objectives included a comparison of OS, CR rate and safety profile between the two study arms.

After a median follow-up of 24.9 months, 117 modified PFS events had been observed on the A+AVD arm and 146 modified PFS events had been observed on the ABVD arm per IRF.<sup>8,9</sup> A+AVD was associated with a statistically significant 23% reduction in the risk of a modified PFS event versus ABVD as assessed by independent review (hazard ratio [HR]=0.77 [95% CI: 0.60, 0.98]; P=0.035). The percentage of patients free from a modified PFS event at 2 years after randomization was 82.1% (95% CI: 78.7, 85.0) on the A+AVD arm versus 77.2% (95% CI: 73.7, 80.4) on the ABVD arm per IRF. This was consistent with investigator-reported 2-year modified PFS (81.0% [95% CI: 77.6, 83.9] versus 74.4% [95% CI: 70.7, 77.7] for A+AVD and ABVD, respectively; HR=0.73 [95% CI: 0.57, 0.92]; P=0.007). Results of the interim analysis of OS, the key secondary endpoint, and all other secondary efficacy endpoints trended in favor of A+AVD. Further, the benefit of A+AVD was observed consistently in the majority of pre-specified subgroups.

The safety profiles of A+AVD and ABVD were consistent with the known safety profiles for the single-agent components of each regimen.<sup>8,9</sup> There was an increased incidence of peripheral neuropathy (PN) in the A+AVD arm. PN was reported in 67% of patients receiving A+AVD versus 43% of patients receiving ABVD. Of patients experiencing PN in the A+AVD arm, 67% had resolution or improvement of PN at last follow-up. Additionally, there was an increased incidence of neutropenia and febrile neutropenia in the A+AVD arm. Neutropenia was reported in 58% of patients who received A+AVD compared to 45% of patients who received ABVD, while febrile neutropenia was reported in 19% and 8% of patients, respectively. The incidence of neutropenia and febrile neutropenia were mitigated in some patients who received G-CSF primary prophylaxis with A+AVD. In the 579 patients who did not receive G-CSF primary prophylaxis with A+AVD, the incidence of febrile neutropenia was 21% compared with 11% in the 83 patients who did receive G-CSF primary prophylaxis with A+AVD. Pulmonary toxicity was more frequent and severe with ABVD; Grade  $\geq 3$  events were reported in 3% of patients receiving ABVD versus <1% of patients receiving A+AVD.

Of the 13 on-treatment deaths that occurred in the ABVD arm, 11 were due to, or associated with, pulmonary toxicity.<sup>8,9</sup> Seven out of the 9 on-treatment deaths that occurred in the A+AVD arm were associated with neutropenia, all of which occurred in patients who did not receive G-CSF primary prophylaxis prior to the onset of neutropenia. Based on this observation, and the reduction in neutropenia and febrile neutropenia, we expect to recommend that patients treated with A+AVD receive prophylactic G-CSF beginning with the first treatment cycle.

While fertility was not formally assessed, similar numbers of pregnancies were reported in each arm, which suggests that there was no significant difference in the effect on fertility.<sup>8</sup> At the time of this analysis, a total of 78 pregnancies were reported among trial participants and their partners (42 in the A+AVD arm and 36 in the ABVD arm).

### Affordability Considerations:

Patients with advanced stage cHL seeking cure following failure of frontline treatment will require additional chemotherapy followed by autologous or allogeneic stem cell transplantation. These additional therapies result in a high economic burden. In ECHELON-1, the administration of A+AVD resulted in a 33% reduction in the need for subsequent chemotherapy or high-dose chemotherapy and stem cell transplantation compared to the patients who received ABVD.<sup>8</sup> A retrospective analysis of 795 cHL patients treated with a frontline regimen between 2011 to 2015 identified 33 patients who failed frontline therapy; among these patients, the average healthcare cost was \$198,000 after treatment failure for the first year alone.<sup>11</sup> A separate retrospective analysis demonstrated that the average total costs of autologous and allogeneic stem cell transplantation were \$390,159 and \$745,341, respectively, which included an observation window of 6 months pre- and 12 months post- transplantation.<sup>12</sup> These costs associated with the management of cHL patients who fail frontline therapy are important when considering the affordability of the A+AVD regimen.

### Summary:

The results from the ECHELON-1 study demonstrate that A+AVD as frontline therapy in previously untreated advanced cHL patients results in a 23% reduction in risk of a modified PFS event compared to ABVD, has a manageable toxicity profile, and completely eliminates exposure to bleomycin. We respectfully request that the NCCN Hodgkin Lymphoma Guideline Panel add A+AVD as a preferred treatment option for the frontline treatment of patients with advanced cHL.

Sincerely,



Nancy Whiting, PharmD, BCOP  
Senior Vice President, Global Medical Affairs  
Seattle Genetics, Inc.

### **References:**

1. ADCETRIS. [prescribing information]. Bothell, WA: Seattle Genetics, Inc; 2017.
2. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol.* 2013;31(6):684-691.
3. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med.* 1992;327(21):1478-1484.
4. Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score  $\geq 3$ , high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup trial. *J Clin Oncol.* 2016;34(17):2028-2036.
5. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with Adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer.* 1975;36(1):252-259.

6. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol.* 2013;14(13):1348-1356.
7. Connors JM, Ansell SM, Fanale M, Park SI, Younes A. Five-year follow-up of brentuximab vedotin combined with ABVD or AVD for advanced-stage classical Hodgkin lymphoma. *Blood.* 2017;130(11):1375-1377.
8. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for Stage III or IV Hodgkin's lymphoma. *N Engl J Med.* 2017:Dec 10 [Epub ahead of print]
9. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine (A+AVD) as frontline therapy demonstrates superior modified progression-free survival versus ABVD in patients with previously untreated Stage III or IV Hodgkin lymphoma (HL): the phase 3 ECHELON-1 study. *2017 ASH Annual Meeting, Final program & abstracts.* 2017:Abstract 6.
10. Ansell SM, Younes A, Connors JM, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL): ECHELON-1 study. *J Clin Oncol.* 2014;32(15):TPS8613.
11. Straus DJ, Bonafede M, Feliciano J, et al. Real world clinical and economic burden of patients with Hodgkin lymphoma (HL) who fail frontline (FL) therapy in the US. *2017 ASH Annual Meeting, Final program & abstracts.* 2017:Abstract 2128.
12. Bonafede M, Richhariya A, Cai Q, et al. Real-world economic burden of hematopoietic cell transplantation among a large US commercially insured population with hematologic malignancies. *Journal of Medical Economics.* 2017:Aug 07 [Epub ahead of print].