

Seattle Genetics, Inc.
21823 30th Drive SE
Bothell, WA 98021

Date of request: April 15, 2019

National Comprehensive Cancer Network
Hodgkin Lymphoma Guideline Panel
3025 Chemical Road, Suite 100
Plymouth Meeting, PA 19462

NCCN Hodgkin Lymphoma Guideline Panel:

On behalf of Seattle Genetics, Inc., I respectfully request the NCCN Hodgkin Lymphoma Panel review the enclosed updated data and new analyses relevant to the use of brentuximab vedotin (ADCETRIS[®]) in combination with doxorubicin, vinblastine, and dacarbazine (BV+AVD) as frontline therapy for patients with Stage III or IV classic Hodgkin Lymphoma (cHL).

FDA indication: ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage 3 or 4 classical Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine.¹

Rationale:

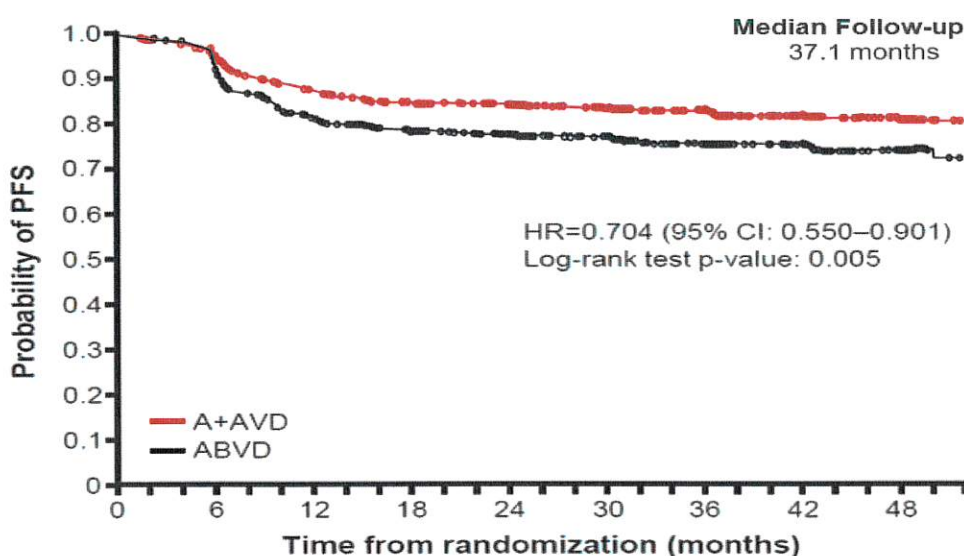
The results of the ECHELON-1 study, a large, randomized, global, phase 3 trial of brentuximab vedotin plus AVD demonstrated superiority to ABVD and led to the FDA approval for the treatment of all adult patients with previously untreated Stage III or IV Hodgkin lymphoma (HL) without restriction to any subgroup in March 2018. Updated results with an additional 18 months of follow-up and multiple new analyses have recently been presented at ASCO 2018 and ASH 2018. These updated results and additional analyses further support the utility of BV+AVD for all Stage III or IV patients, regardless of International Prognostic Score (IPS) risk status. Given the evidence in a large, well-conducted, randomized, phase 3 trial that BV+AVD is superior to ABVD, we respectfully request that the NCCN Hodgkin Lymphoma Committee reconsider their current recommendations and include BV+AVD as an option for all Stage III or IV patients with Hodgkin lymphoma, regardless of IPS risk group.

Clinical Evidence:

Efficacy results with extended follow-up

Results of the ECHELON-1 study with an additional 18 months of follow-up were presented at the ASH 2018 Annual Meeting.² With longer follow-up (median 37.1 months), the intent-to-treat (ITT) progression-free survival (PFS) benefit for BV+AVD as compared with ABVD was maintained (Hazard ratio [HR]=0.70; p=0.005), with an absolute difference of 7.1%, PFS at 3 years was 83.1% vs 76% (Figure 1).

Figure 1: PFS per Investigator with Extended Follow-up²



Efficacy results by PET2 status

A new analysis of efficacy by PET2 status and with longer follow-up from the ECHELON-1 study were presented at ASH 2018 using the traditional PFS endpoint in all patients and in those age 60 or younger.² This dataset now allows for a more direct comparison to the same population of Stage III or IV patients 60 years or younger reported in the RATHL study (comparison presented in Appendix 1). As demonstrated in Table 1, the ECHELON-1 study demonstrates improved efficacy in the overall population and in those aged ≤ 60 years for 3-year PFS. In the subgroups defined by PET2 status, BV+AVD also demonstrates improved efficacy for PET2 negative patients and for PET2 positive patients compared to ABVD.

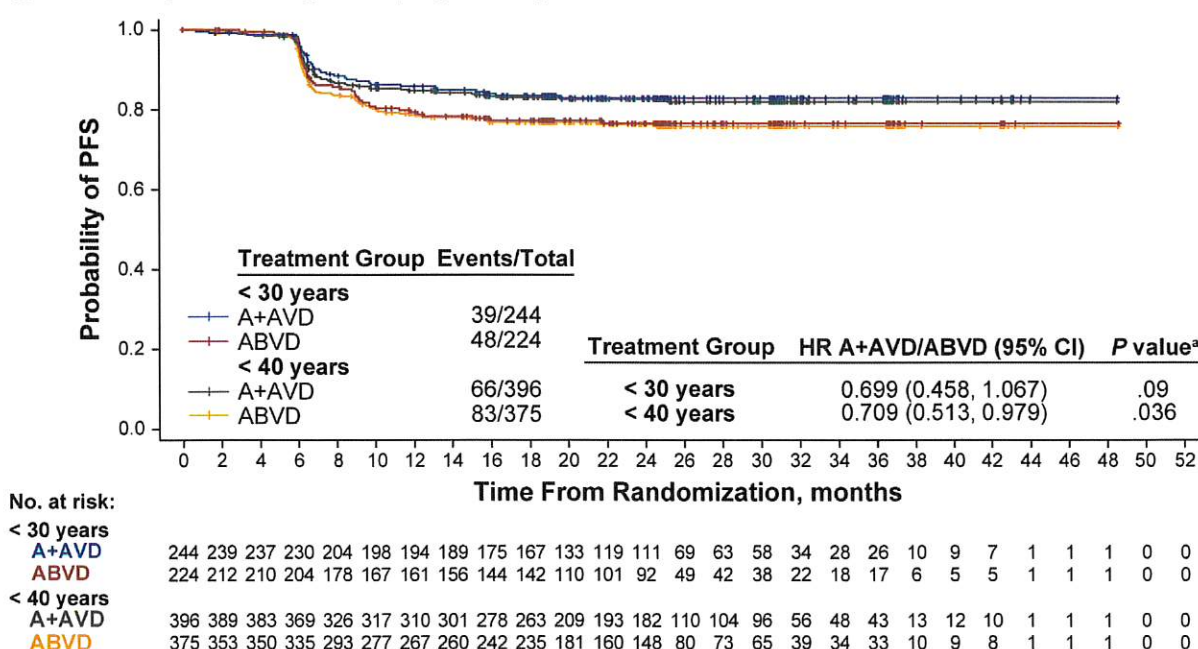
Table 1: PFS by PET2 Status²

	ECHELON-1 (Stage III or IV ≤ 60 years)		ECHELON-1 (Stage III or IV, all patients)	
	BV+AVD	ABVD	BV+AVD	ABVD
3-year PFS All patients	84.9%	77.8%	83.1%	76.0%
3-year PFS PET2- patients	87.2%	81.0%	85.8%	79.5%
3-year PFS PET2+ patients	69.2%	54.7%	67.7%	51.5%

Efficacy observed consistently in the AYA population

The ECHELON-1 study included adult patients and did not exclude patients based on an upper age limit. As such, 14% of patients enrolled on the study were over the age of 60. As the majority of newly diagnosed HL patients are in the adolescent and young adult (AYA) population, analyses of the efficacy of BV+AVD in this population were conducted.³ Consistent with the ITT population and the primary endpoint, PFS benefit was consistently observed in patients <40 years of age compared to ABVD with 30% reduction in the risk of a PFS event (HR=0.0709). Figure 2 also illustrates the benefit observed for patient groups aged <30 years (HR=0.0699) compared to ABVD. Of note, approximately 83% of AYA patients <40 years of age in ECHELON-1 were IPS 0-3.

Figure 2: PFS per Investigator by Age Group³



Efficacy observed consistently in all IPS risk groups

The current NCCN guidelines use IPS score as a differentiating factor in category of recommendation. IPS risk scores of 0-1, 2-3, and 4-7 were prespecified subgroup analyses of the ECHELON-1 study and it should be noted that BV+AVD demonstrated consistent treatment benefit across all IPS subgroups with hazard ratios less than 1 for all IPS risk score categories (Table 3).⁴ Furthermore, confidence intervals of all IPS subgroups overlap suggesting no difference in the treatment effect among these subgroups.

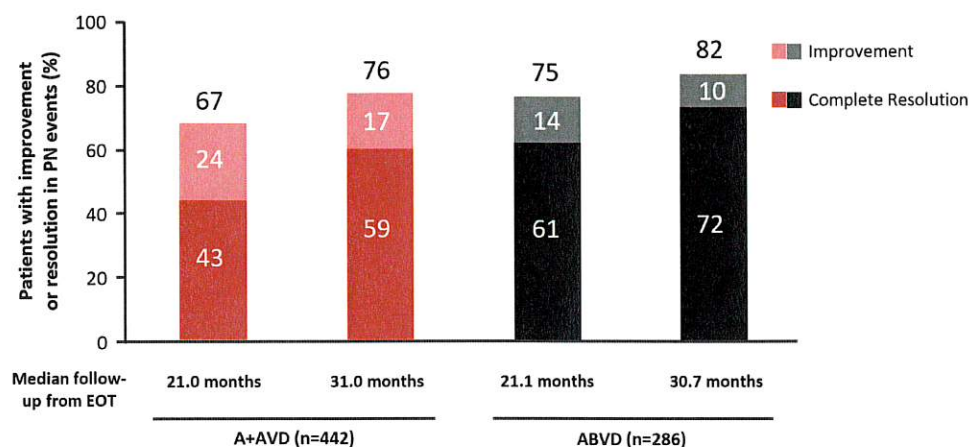
Table 3: Modified PFS per IRF Hazard Ratios by Baseline IPS Risk Score⁴

Subgroup	Event/N (%)		Hazard Ratio	(95% CI)
	BV+AVD n=664	ABVD n=670		
All patients (ITT)	117/664 (17.6)	146/670 (21.8)	0.77	(0.60–0.98)
IPS 0-1	22/141 (15.6)	25/141 (17.7)	0.84	(0.47-1.49)
IPS 2-3	57/354 (16.1)	68/351 (19.4)	0.79	(0.55-1.12)
IPS 4-7	38/169 (22.5)	53/178 (29.8)	0.70	(0.46-1.07)

Resolution of peripheral neuropathy

Evaluation of resolution of the peripheral neuropathy (PN) observed in the ECHELON-1 study with an additional 10 months of follow-up, representing a median follow-up from end of treatment of 30 months, was presented at the ASH 2018 Annual Meeting.⁵ As expected due to the inclusion of two agents known to be associated with PN, the rate and severity reported in the BV+AVD arm was higher than that in the ABVD arm. As demonstrated in Figure 3, 76% of patients treated with BV+AVD have now improved or resolved PN and 59% have complete resolution of all PN symptoms with extended follow-up. In both study arms, the majority of ongoing PN cases were Grade 1/2.

Figure 3: Resolution or improvement in PN events with continued follow-up⁵



Change in therapy based on PET2 status

The ECHELON-1 study was not a PET-adapted study as its study design was approved by the FDA to confirm the accelerated approval of BV in relapsed or refractory (R/R) HL prior to the availability of results of the RATHL and SWOG 0816 studies. However, investigators in ECHELON-1 were allowed to switch to an alternative chemotherapy during frontline therapy on the basis of PET2 status for a Deauville score of 5 (PET2 D5). Only 1 patient on the BV+AVD arm switched therapy due to PET2 D5 and only 4 patients on the ABVD arm switched therapy due to PET2 D5. Importantly, a switch in therapy for any reason other than progression was not considered an event. As presented in the Table 4 (REF: Supplementary Materials of the NEJM 2017 Connors), only 2.3% and 1.3% of patients on the BV+AVD and ABVD arms respectively, switched therapy for reasons other than progressive disease.

Table 4: Summary of Reasons for Switching to Alternative Chemotherapy during Frontline Therapy (REF: Supplementary Materials of the NEJM 2017 Connor)

Reason for switch	BV+AVD n=662 n (%)	ABVD n=659 n (%)
Any reason	15 (2.2)	9 (1.3)
PET 2 Deauville score of 5	1 (0.15)	4 (0.61)
Adverse event	12 (1.8)	1 (0.15)
Other	2 (0.30) [†]	4 (0.61) [‡]

[†]Reason was unspecified for both patients. [‡]Reasons included toxicity (n = 1), unsatisfactory response (n = 3).

Summary:

The current NCCN Hodgkin lymphoma guidelines consider PET-adapted ABVD therapy as the preferred treatment approach for all patients with Stage III or IV disease. Updated results and new analyses of the ECHELON-1 study continue to demonstrate superiority of BV+AVD over ABVD, as presented in Appendix 1. The 3-year PFS results obtained with BV+AVD for all patients, those who are PET2 negative, and those who are PET2 positive are superior to the results obtained with ABVD.² The superiority of BV+AVD is consistent across all IPS risk groups and of particular note in the AYA population <40 years of age for whom 83% were IPS 0-3.³ Importantly, the PN associated with BV+AVD continues to resolve and has completely resolved in more than half of affected patients.⁵ The current Category 2B rating for BV+AVD in patients with IPS 0-3 limits access to a highly effective and important treatment option for patients with advanced stage HL. Given these updated and new data, we respectfully request that the NCCN Hodgkin Lymphoma Committee reconsider their recommendations to include BV+AVD as an option for all Stage III or IV patients with Hodgkin lymphoma.

Sincerely,



Roger Dansey, MD
Chief Medical Officer
Seattle Genetics, Inc.
rdansey@seagen.com
Phone: 425-527-4014

Appendix 1

Comparison of ECHELON-1 to PET-adapted approaches

While cross-trial comparisons can have limitations due to differences in trial design and patient populations, nevertheless in the absence of direct comparisons this approach may be useful for the NCCN Hodgkin Lymphoma Committee to consider in determining preferred regimen assignment. As demonstrated in Table A1, the ECHELON-1 study demonstrates improved efficacy not only in the overall population but also in all PET2 status subgroups compared to RATHL for 3-year PFS. Likewise, data for the prespecified subgroup of ECHELON-1 patients treated in North America has been recently published⁶; this new analysis allows for direct comparison to the SWOG 0816 trial conducted solely in North America. As shown in Table A2, the North American data from the ECHELON-1 study demonstrates improved efficacy not only in the overall population but also in the PET2 negative population compared to SWOG 0816 for 2-year PFS.

Table A1: PFS Cross Trial Comparison – ECHELON-1² and RATHL⁷

	ECHELON-1 (Stage III or IV ≤ 60 years)		RATHL (Stage III or IV, ≤ 60 years)			
	BV+AVD	ABVD	All Eligible Patients	ABVD	ABVD→AVD	ABVD→BEACOPP
3-year PFS All patients	84.9%	77.8%	79.8%	--	--	--
3-year PFS PET2- patients	87.2%	81.0%	--	82.1%	82.1%	--
3-year PFS PET2+ patients	69.2%	54.7%	--	--	--	63.9%

Table A2: PFS Cross Trial Comparison – ECHELON-1² and SWOG 0816⁸

	ECHELON-1		SWOG 0816		
	BV+AVD	ABVD	All Eligible Patients	ABVD	ABVD→BEACOPP
2-year PFS All patients	88.1%	76.4%	79.0%	--	--
2-year PFS PET2- patients	91.9%	81.0%	--	82.0%	--
2-year PFS PET2+ patients	54.5%	48.0%	--	--	64%

References (enclosed):

1. ADCETRIS [prescribing information]. Bothell, WA: Seattle Genetics, Inc; Revised Nov 2018.
2. Connors JM, Younes A, Gallamini A, et al. (2018). Brentuximab vedotin plus chemotherapy in patients with advanced-stage classical Hodgkin lymphoma (cHL): evaluation of modified progression-free survival (mPFS) and traditional PFS in the phase 3 ECHELON-1 study. *Blood* 132(Suppl 1): Abstract 2904. *2018 ASH, 60th Annual Meeting of the American Society of Hematology, San Diego, CA, Dec 01-04, 2018. Poster presentation.*
3. Crosswell HE, LaCasce AS, Bartlett NL, et al. (2018). Brentuximab vedotin with chemotherapy in adolescents and young adults (AYA) with stage III or IV Hodgkin lymphoma: a subgroup analysis from the phase 3 Echelon-1 study. *Blood* 132(Suppl 1): Abstract 1647. *2018 ASH, 60th Annual Meeting of the American Society of Hematology, San Diego, CA, Dec 01-04, 2018. Poster presentation.*
4. Connors JM, Jurczak W, Straus DJ, et al. (2018). Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med* 378(4): 331-44. *Manuscript.*
5. Radford J, Connors JM, Younes A, et al. (2018). Resolution of peripheral neuropathy (PN) in patients who received A+AVD or ABVD in the phase 3 ECHELON-1 trial. *Blood* 132(Suppl 1): Abstract 2921. *2018 ASH, 60th Annual Meeting of the American Society of Hematology, San Diego, CA, Dec 01-04, 2018. Poster presentation.*
6. Ramchandren R, Advani RH, Ansell SM, et al. (2019). Brentuximab vedotin plus chemotherapy in North American patients with newly diagnosed stage III or IV Hodgkin lymphoma. *Clin Cancer Res* 25(6): 1718-26. *Manuscript.*
7. Johnson P, Federico M, Kirkwood A, et al. (2016). Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 374(25): 2419-29.
8. Press OW, Li H, Schoder H, et al. (2016). US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol* 34(17): 2020-7.