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Date of Request: JULY 22nd, 2021

NCCN Guidelines Panel: Hodgkin Lymphoma

On behalf of Seagen Inc, we respectfully request the Hodgkin Lymphoma Guidelines Panel evaluate the enclosed data from the 5-year analysis of the phase 3 ECHELON-1 trial recently published in *Lancet Haematology*[1] for the purpose of updating the brentuximab vedotin + AVD recommendation on page 11 (HODG-5) of the Guidelines for the primary treatment of patients with Stage III–IV classical Hodgkin lymphoma.

Specific Changes: We request NCCN Hodgkin Lymphoma Guidelines Panel:

- Update the category of evidence for brentuximab vedotin + AVD (defined as BV+AVD) to 2A level of evidence for all patients ≥18 years of age with newly diagnosed Stage III or IV classical Hodgkin lymphoma (cHL).
- Update the recommendation for BV+AVD regimen to preferred in parity with PET-2 response adapted ABVD in the same patient population.

FDA Approval: ADCETRIS (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine.[2]

Rationale:

Request 1: The current NCCN Guidelines Version 4.2021 list the BV+AVD regimen as useful in certain circumstances, with a category of 2B for all subgroups of patients except those with no known neuropathy, IPS 4+, or bleomycin contraindicated.[3] The results of the phase 3 ECHELON-1 study demonstrated superiority of BV+AVD to ABVD and led to the FDA approval for the treatment of all patients ≥18 years of age with previously untreated Stage III or IV cHL in March 2018. [2,4] The 5-year update confirmed a durable progression free survival (PFS) benefit to BV+AVD (84.9%) versus ABVD (78.9%) independent of disease stage, age, baseline International Prognostic Score (IPS) risk, or interim PET2 status.[1] BV+AVD demonstrated a promising long term safety profile, a low rate of secondary malignancies, a high rate of resolution and improvement of peripheral neuropathy (PN) (85% BV+AVD, 86% ABVD), and no observed effect on the rate of pregnancies compared to ABVD.

We respectfully request that the Panel consider that this durable 5-year PFS advantage and long-term safety data across all subgroups in a phase 3 trial as relevant data to update the category of evidence for BV+AVD to 2A level of evidence for all newly diagnosed Stage III or IV cHL patients.

Request 2: The current guidelines list PET-2 adapted ABVD, supported by RATHL and SWOG0816 studies, as preferred therapy in patients with newly diagnosed Stage III or IV cHL.[3] Per this treatment approach, PET-2 negative patients are de-escalated to AVD and PET-2 positive patients are to escalate to escBEACOPP. Long term data on PET2 adapted therapies for Stage III and IV cHL from SWOG S0816 and RATHL studies are limited to patients ≤ 60 years of age due to toxicity concerns.[5,6] Additionally, the inclusion of patients with Stage II cHL in RATHL further illustrates the limitations of data for ABVD in advanced stage disease.[6] Approximately 25% of PET2-negative ABVD treated cHL patients in S0816 experienced relapse within 5 years, and those patients escalated to escBEACOPP had a high rate of secondary malignancies (14%).[5] Moreover while the RATHL trial demonstrated similar rates of 3 year PFS for PET2 negative patients treated with AVD or ABVD, approximately 42% of the study population had Stage II disease which makes applicability to just Stage III and IV patients challenging.[5] Additionally, PET adapted strategies have been difficult to implement in the community setting given limitations of real time acquisition of Deauville scores that are needed for PET2 adapted management strategies.[7] Thus,

for patients with Stage III or IV cHL, there had still remained an unmet need for a treatment regimen that could be used in all ages with a durable efficacy benefit regardless of PET2 status which BV+AVD fulfills. Finally, it is desirable for patients to avoid bleomycin-associated pulmonary toxicity in ABVD or escBEACOPP or the potential for infertility or secondary malignancies with escBEACOPP.[1]

BV+AVD provides a straightforward front line treatment option that compares favorably to contemporary PET adapted strategies without requiring a change of therapy based on interim PET assessment or exposure to bleomycin.[1]

Clinical Evidence: ECHELON-1 was an international, open label, randomized, phase 3 trial done at 218 clinical sites in 21 countries.[1] Previously untreated patients 18 and older with Stage III or IV cHL were randomized to receive 6 cycles of BV+AVD (n=664) or ABVD (n=670). At a median follow-up of 60.9 months, rates of PFS per INV were 82.2% with BV+AVD and 75.3% with ABVD (HR: 0.68; 95% CI: 0.53-0.87; *P*=0.0017) (Figure 1). Among adolescent and young adult (AYA) patients <40 years (58% of enrolled patients), PFS was 86.3% in the BV+AVD arm (n=396) and 79.4% in the ABVD arm (n=375) (HR: 0.64; 95% CI: 0.45-0.92; *P*=0.013).[8]

Patients benefitted from BV+AVD independent of status at PET2, with HR of 0.66 for PET2 negative patients and 0.70 for PET2 positive patients, (Figure 2).[1] Similar outcomes were also observed for PET2 positive and PET2 negative patients in the AYA population.[8]

Figure 1. Overall PFS per INV at 5 years. Straus et al. *Lancet Haematology,* 2021;8(6):e410-e421.[1]

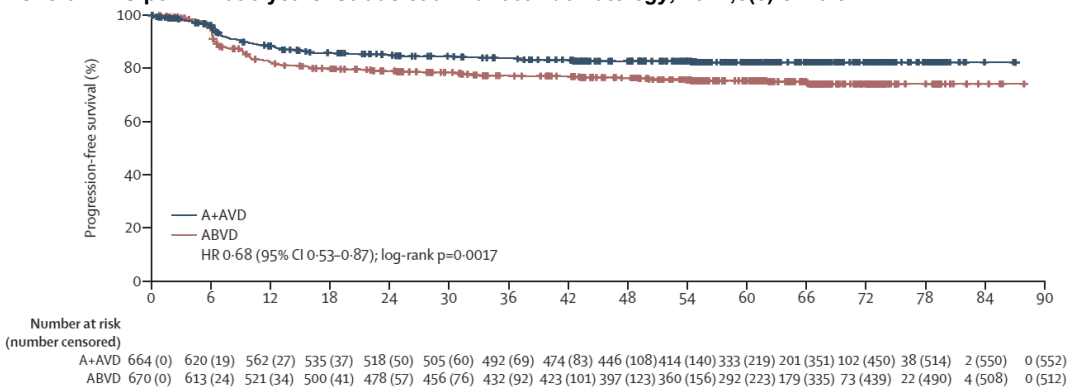
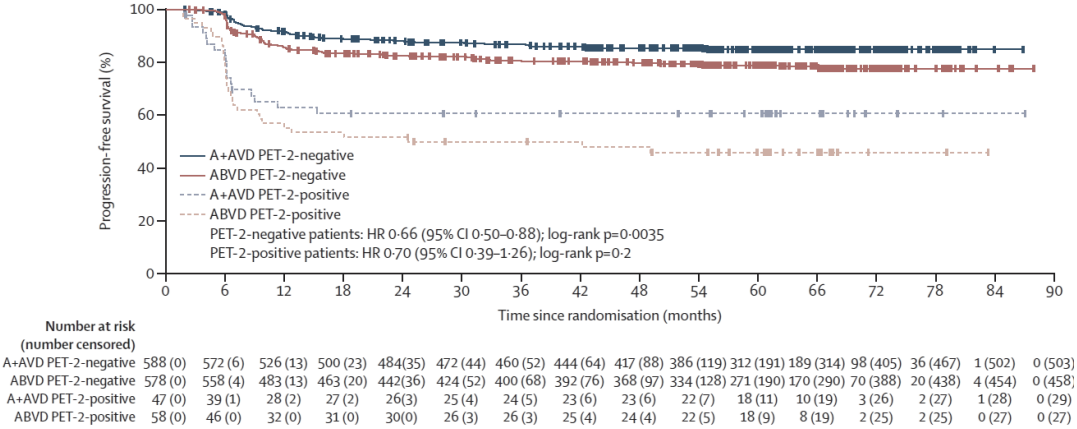


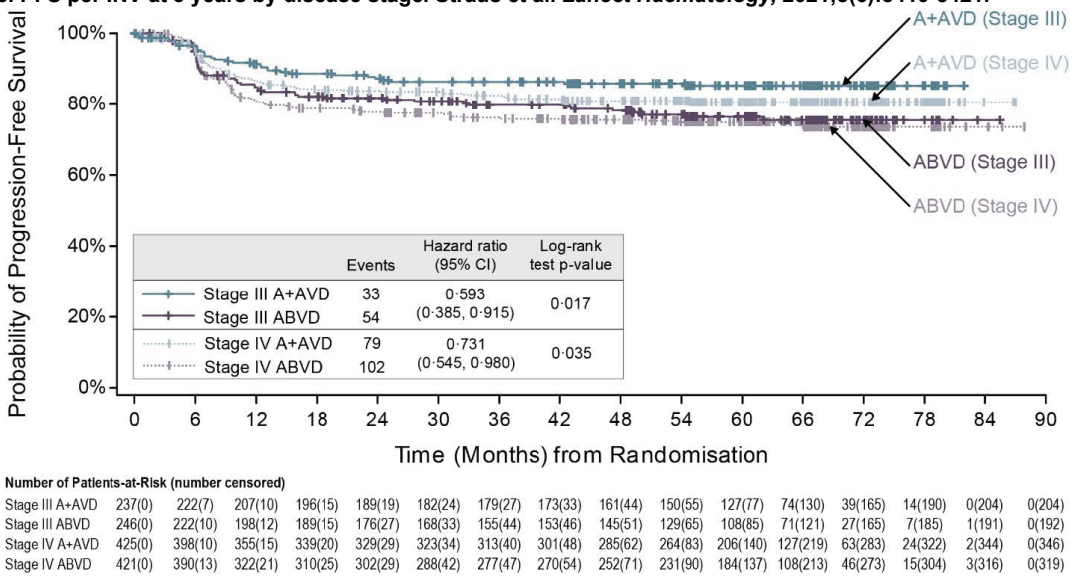
Figure 2. PFS per INV at 5 years by PET2 status. Straus et al. *Lancet Haematology,* 2021;8(6):e410-e421.[1]



The treatment benefit of BV+AVD over ABVD was also similar across disease stages and IPS risk groups.[1] HR for patients with Stage III cHL was 0.59 and Stage IV cHL was 0.73; patients with Stage IV

disease receiving BV+AVD had improved PFS compared to Stage III patients receiving ABVD (Figure 3). Similar benefit was observed among patients with low, intermediate, and high IPS scores.

Figure 3. PFS per INV at 5 years by disease stage. Straus et al. *Lancet Haematology,* 2021;8(6):e410-e421.[1]



Number of Patients-at-Risk (number censored)

Stage III A+AVD	237(0)	222(7)	207(10)	196(15)	189(19)	182(24)	179(27)	173(33)	161(44)	150(55)	127(77)	74(130)	39(165)	14(190)	0(204)	0(204)
Stage III ABVD	246(0)	222(10)	198(12)	189(15)	176(27)	168(33)	155(44)	153(46)	145(51)	129(65)	108(85)	71(121)	27(165)	7(185)	1(191)	0(192)
Stage IV A+AVD	425(0)	398(10)	355(15)	339(20)	329(29)	323(34)	313(40)	301(48)	285(62)	264(83)	206(140)	127(219)	63(283)	24(322)	2(344)	0(346)
Stage IV ABVD	421(0)	390(13)	322(21)	310(25)	302(29)	288(42)	277(47)	270(54)	252(71)	231(90)	184(137)	108(213)	46(273)	15(304)	3(316)	0(319)

PN occurred in 67% (443/662) of patients in the BV+AVD arm and 43% (286/659) of patients in the ABVD arm.[1] At 5 years, PN continued to improve and resolve with 85% (375/443) of patients with PN in the BV+AVD arm achieving complete resolution (71%) or improvement (13%), and 86% (245/286) of patients from the ABVD arm achieving complete resolution (79%) or improvement (6%). Ongoing PN occurred in 19% (127/662) of patients in the BV+AVD arm, including 15 patients with grade ≥3 PN, compared to 9% (59/659) patients in the ABVD arm (four had grade 3 PN, with no reports of ongoing PN of grade 4). As assessment of PN is last observation carried forward, ongoing PN with maximum severity of grade 3/4 was confounded in 12 of the 15 BV+AVD patients by death prior to resolution (n=3), loss to follow-up (n=4), and withdrawal from study (n=5). Among patients <40 years of age, complete resolution occurred in 76% and 87% in the BV+AVD arm and ABVD arm, respectively, with improvement occurring in 12% and 3%.[8]

A lower rate of secondary malignancies was observed with BV+AVD versus ABVD.[1] There were 19 malignancies on the BV+AVD arm (9 hematological, 10 solid tumor) versus 29 (15 hematological, 14 solid tumor) on the ABVD arm. Among patients <40 years of age, seven and five secondary malignancies occurred in the BV+AVD and ABVD arms, respectively.[8] A total of 75 pregnancies were reported on the BV+AVD arm and 56 on the ABVD arm, indicating that BV is unlikely to have an increased impact fertility relative to ABVD.[1,8] No stillbirths were reported.

Summary: The 5-year update of the ECHELON-1 study shows a robust and durable PFS advantage of BV+AVD over ABVD in patients with Stage III and IV cHL at this important 5-year milestone independent of disease stage, age, baseline risk factors, or interim PET2 status.[1] These long-term data show that BV+AVD meets the need for a treatment regimen that can be used across all adult ages, including patients of childbearing potential, with a durable efficacy benefit while avoiding bleomycin, escBEACOPP, and the need to change therapy based on an interim PET2 analysis. In cHL the clear majority of relapses occur within the first 5 years,[9] therefore these results indicate that more patients may have been cured of their disease with BV+AVD. This data strongly supports BV+AVD being a preferred regimen with Category 2A level of evidence for all Stage III and IV patients with cHL.

Thank you very much for your consideration.

Sincerely,

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