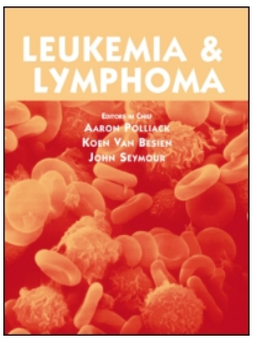

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Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy

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ORIGINAL ARTICLE

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Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy

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ABSTRACT

We investigate the impact of granulocyte-colony stimulating factor (G-CSF) primary prophylaxis (G-PP, $N = 83$) versus no G-PP ($N = 579$) on safety and efficacy of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A + AVD) in the ECHELON-1 study of previously untreated stage III/IV classical Hodgkin lymphoma. G-PP was associated with lower incidence of ≥ grade 3 neutropenia (29% versus 70%) and febrile neutropenia (11% versus 21%). Fewer dose delays (35% versus 49%), reductions (20% versus 26%), and hospitalizations (29% versus 38%) were observed. Seven neutropenia-associated deaths occurred in the A + AVD arm; none received G-PP. A + AVD with G-PP was associated with decreased risk of a modified progression-free survival event by 26% compared with A + AVD alone (95% CI: 0.40–1.37). G-PP reduced the rate and severity of adverse events, including febrile neutropenia, reduced treatment delays, dose reductions, and discontinuations, and may thus improve efficacy outcomes. These data support G-PP for all patients treated with A + AVD.

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KEYWORDS
Hodgkin lymphoma; brentuximab vedotin; frontline therapy; growth factor; primary prophylaxis

Introduction

ECHELON-1 is a global, open-label, randomized, phase 3 study that compared brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A + AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for the frontline treatment of stage III or IV classical Hodgkin lymphoma (cHL) [1]. The primary outcome of the trial was modified progression-free survival (modified PFS), defined as the time to progressive disease, death, or use of subsequent anticancer therapy following an incomplete response at the end-of-therapy as assessed by an independent review facility (IRF). As previously published, treatment with A + AVD was associated with a 23% reduction in the risk of a modified PFS event versus ABVD, and a 2-year modified PFS of 82.1% versus 77.2%, respectively (hazard ratio (HR) 0.77; 95% confidence interval (CI) 0.60–0.98). A + AVD was associated with an increased rate of febrile neutropenia and peripheral neuropathy, and a decreased rate of pulmonary toxicity compared with ABVD. Febrile neutropenia was associated with seven of nine on study deaths on the A + AVD arm, none of whom received G-CSF primary prophylaxis (G-PP) prior to onset of neutropenia. Primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) effectively mitigated febrile neutropenia in the A + AVD arm,

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Supplemental data for this article can be accessed here.

similar to the effect of G-PP in treatment regimens for other hematologic malignancies, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the treatment of non-Hodgkin lymphoma [2,3].

This paper presents additional exploratory analyses of the ECHELON-1 study that evaluate the impact of primary prophylaxis with G-CSF on adverse events and A + AVD treatment modifications. These analyses include an examination of the impact of G-CSF on the safety and efficacy of A + AVD. In addition, these analyses further investigate adverse events of clinical interest in the use of A + AVD for treatment of Hodgkin lymphoma, including pulmonary toxicity, neutropenia, and peripheral neuropathy.

Materials and methods

Trial design

Patients in the ECHELON-1 study (NCT01712490) were randomized 1:1 to treatment and stratified by region and international prognostic score (IPS) to receive A + AVD or ABVD, which were administered intravenously on days 1 and 15 of each 28-day cycle, for up to six cycles. Brentuximab vedotin (1.2 mg/kg) was administered intravenously over 30 min within approximately 1 h after the completion of AVD therapy. A detailed study design, including patient eligibility and demographics, response assessment, and results have been published previously [4].

Assessments/statistics

The primary endpoint of the study, modified PFS, was defined as the time from randomization to first documentation of progressive disease (per Cheson et al.) [5], death due to any cause, or confirmed non-complete response at completion of frontline therapy (end of treatment Deauville score $\geq$3) and receipt of additional anti-cancer therapy. This was assessed by a blinded IRF. All efficacy analyses are post hoc and were summarized using Kaplan–Meier's methodology. A stratified Cox regression model was used to estimate the HR and the 95% CI for the treatment effect.

Safety was analyzed in patients who received at least one dose of study drug and were summarized descriptively. The Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 was used to describe severity and type of adverse events, with grading defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

Dose modifications and the use of G-CSF

The ECHELON-1 protocol permitted the use of G-CSF for the treatment or prevention of neutropenia. G-CSF product selection, dose selection, and timing were at the discretion of the investigator per their institutional guidelines. After enrollment of 75% of study participants and review of the data, the independent data and safety monitoring committee (IDMC) recommended that all patients randomized to A + AVD receive prophylactic growth factor support beginning with cycle 1 due to the higher incidence of febrile neutropenia observed in the A + AVD group [4]. A Dear Investigator Letter detailing this recommendation was sent to all study investigators following the IDMC decision. In addition, the study informed consent form was updated and all patients on the treatment phase were reconsented.

For the purposes of this analysis, G-PP was defined as G-CSF by day 5 of cycle 1 of treatment. Receipt of G-CSF at any time after day 5, cycle 1 was defined as G-CSF secondary prophylaxis.

The study recommended brentuximab vedotin dose modifications for patients with peripheral neuropathy (Supplemental Table S1). Guidelines for managing $\geq$-grade 3 non-hematologic toxicities (other than peripheral neuropathy) using dose delays and management of $\geq$ grade 3 hematologic toxicities were also provided (Supplemental Table S2).

Oversight

The study protocol and all amendments were approved by the institutional review board or ethics committee at individual sites and adhered to the International Conference on Harmonisation Good Clinical Practices. All patients provided written informed consent. A steering committee, the IDMC, and the study sponsor oversaw the conduct of the trial. Data were analyzed by sponsor statisticians and interpreted by academic authors and sponsor representatives. All the authors vouch for the completeness and accuracy of the data and adherence of the trial to the protocol.

Results

Demographics

The ECHELON-1 study enrolled 1334 patients, with 664 randomized to receive A + AVD and 670 to receive ABVD. The two study arms were generally well balanced at baseline, as previously published [4]. Of the 499 patients treated with A + AVD who were enrolled prior to the IDMC recommendation for the addition of

G-PP, 42 (8%) received G-PP. After the IDMC recommendation, 41 of 163 patients (25%) enrolled and randomized to A + AVD received G-PP, for a total of 83 patients (13%) on the A + AVD arm.

Within the A + AVD arm, the demographics of patients who received G-PP (*N*= 83) were comparable to those of patients without G-PP (*N* = 579) (Table 1). A + AVD patients who either did or did not receive G-PP had comparable disease characteristics.

Overall, 81% of patients in the A + AVD arm received G-CSF during the study. Among patients in the A + AVD arm who received G-PP, median time to the first use of G-CSF was 0.3 weeks (range: 0.1–0.7 weeks). Among the 579 patients who did not receive G-PP, 453 (78%) received G-CSF at a later stage of treatment, with a median time-to first use of 2.3 weeks (range: 0.9–25.6 weeks) (Table 2). Long-acting (pegylated) formulations of G-CSF were used at a higher rate among patients treated with A + AVD who received G-PP (34%) than those who received G-CSF but not G-PP (18%).

Safety

The overall rate of adverse events for patients was lower among patients in the A + AVD arm who received G-PP than those who did not receive G-PP (90% versus 100%, respectively). Patients who did not receive G-PP experienced higher rates (≥5% difference for adverse events occurring in ≥20% of patients in either arm) of neutropenia (73% versus 35%), nausea (54% versus 46%), vomiting (34% versus 27%), peripheral sensory neuropathy (29% versus 24%), pyrexia (28% versus 23%), peripheral neuropathy (27% versus 19%), alopecia (27% versus 22%), and stomatitis (22% versus 13%), compared with patients who received G-PP (Supplemental Table S3). Bone pain (25% versus 18%), a known adverse event associated with G-CSF, and constipation (47% versus 41%) were the only adverse events with an increased incidence (≥5% difference, ≥20% in either arm) for patients who received G-PP versus patients who did not receive G-PP.

Adverse events of ≥ grade 3 severity were also less common in A + AVD patients who received G-PP (57%) than those who did not receive G-PP (87%). This difference was largely due to the lower rate of ≥ grade 3 neutropenia. In addition, serious adverse events were less common among patients treated with A + AVD who received G-PP (33%) than those who did not receive G-PP (44%). Patients who received G-PP also had a lower rate of hospitalizations than those without (29% versus 38% with at least one hospitalization).

Table 1. Demographics and disease characteristics were comparable between A + AVD patients with and without G-PP.

	A + AVD	
	G-PP (*N*= 83)	No G-PP (*N*= 579)
Median age, years (range)	34 (18, 78)	35 (18, 82)
Sex, *n* (%)		
Male	43 (52)	334 (58)
Female	40 (48)	245 (42)
Stage at initial diagnosis, *n* (%)		
Stage II	0	1 (<1)[a]
Stage III	29 (35)	207 (36)
Stage IV	54 (65)	370 (64)
Not applicable	0	1 (<1)
IPS risk factors, *n* (%)		
0 – 1	20 (24)	121 (21)
2 – 3	47 (57)	306 (53)
4 – 7	16 (19)	152 (26)
Extranodal involvement at initial diagnosis, *n* (%)	54 (65)	355 (61)

G-PP: primary prophylaxis with G-CSF; IPS: international prognostic score.
[a]This patient had a major protocol violation.

Events of clinical interest

Neutropenia

Within the A + AVD arm, patients who received G-PP had a lower incidence of neutropenia (35% versus 73%). This difference was consistent for higher grades of neutropenia: ≥grade 3 neutropenia occurred in 29% of patients who received G-PP versus 70% of patients without; ≥grade 4 neutropenia occurred in 22% and 51%, respectively (Figure 1(A)).

The incidence of febrile neutropenia in the A + AVD arm was lower in patients who received G-PP (11%) than those without (21%). This association remained when the analysis was limited to onset during cycle 1,

Table 2. Summary of G-CSF administration in the A + AVD arm.

	A + AVD (*N*= 662)		
	G-PP (*N*= 83)	No G-PP (*N*= 579)	All (*N*= 662)
Patients receiving G-CSF, *n* (%)	83 (100)	453 (78)	536 (81)
G-CSF by duration of action, *n* (%)			
Long acting (pegylated)	28 (34)	107 (18)	135 (20)
Short acting (non-pegylated)	61 (73)	416 (72)	477 (72)
Median time-to-first-use of G-CSF, weeks (range)	0.3 (0.1–0.7)	2.3 (0.9–25.6)	20.4 (0.1, 34.0)

A + AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; G-PP: primary prophylaxis with G-CSF; G-CSF: granulocyte-colony stimulating factor; IPS: international prognostic score. Overall, 81% of patients received G-CSF, even if they did not receive primary prophylaxis.

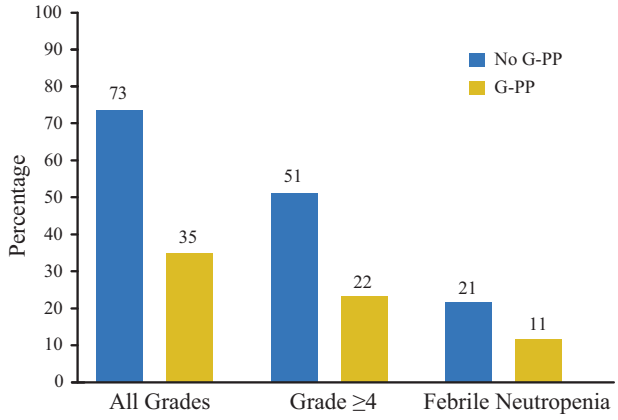

Figure 1. Overall, G-PP decreased the incidence of neutropenia and febrile neutropenia.

where febrile neutropenia occurred in 1% of patients who received G-PP versus 11% in those without. Advanced age was the only baseline risk factor found to be associated with an increased risk of febrile neutropenia.

In the A + AVD arm, seven of the nine deaths that occurred within 30 days after the last dose of study drug were associated with neutropenia. Notably, none of these patients had received primary prophylaxis with G-CSF before the onset of neutropenia, with the exception of one patient who entered the trial with preexisting neutropenia.

Peripheral neuropathy

In the ECHELON-1 study, the rate of peripheral neuropathy was higher among patients in the A + AVD arm (67%) than in the ABVD arm (43%) [4], although the median time to first onset of peripheral neuropathy was similar (A + AVD: 8 weeks, range 0–29 weeks versus ABVD: 7 weeks, range 0–32 weeks). Discontinuation of treatment among patients with peripheral neuropathy was 10% in the A + AVD arm versus 4% in the ABVD arm.

Among patients in the A + AVD arm, patients who did not receive G-PP had a higher incidence of peripheral sensory neuropathy (29% versus 24%) and peripheral neuropathy (27% versus 19%) compared with patients who received G-PP (Supplemental Table S3).

As of April 2018 (median follow-up of 30.6 months after end of therapy, range: 0–72.2 months), 59% of A + AVD treated patients in ECHELON-1 had a complete resolution of peripheral neuropathy, with an additional 17% experiencing improvement. Among patients with continuing peripheral neuropathy, 90% was grade 1/2. Among patients with peripheral neuropathy at the end of treatment, the median time to resolution was 28 weeks (range: 0–160 weeks).

Pulmonary toxicity

The overall rate of pulmonary toxicity, defined by a MedDRA standard medical query (SMQ) for interstitial lung disease, was lower in the A + AVD arm (2%) than in the ABVD arm (7%). Within the A + AVD arm, the incidence of pulmonary toxicity was low overall: 1% (one of 83, 1% ≥grade 3) among patients who received G-PP versus 2% (11 of 579, <1% ≥grade 3) among A + AVD patients without G-PP (Figure 1(B)).

Treatment exposure

Overall, relative dose intensities (RDIs) were numerically increased for patients treated with A + AVD who received G-PP, with the most notable difference in brentuximab vedotin exposure (Table 2). The median RDI of brentuximab vedotin for patients who received G-PP was 93.7 (range: 8.3–116.2) versus 89.0 (range: 8.1–118.9) in those who did not receive G-PP.

Similarly, brentuximab vedotin dose delays were less common in patients who received G-PP than those without (35% versus 49%), as were dose delays for doxorubicin (37% versus 50%), vinblastine (35% versus 50%), and dacarbazine (37% versus 49%) (Supplemental Table S4). Receipt of G-PP also decreased the frequency of dose reductions, which occurred in 20% of patients who received G-PP versus 26% in those who did not receive G-PP. Rates of permanent brentuximab vedotin discontinuation were similar between the two groups (10% with G-PP versus 11% without), as were discontinuation rates for doxorubicin, vinblastine, and dacarbazine.

Efficacy

A + AVD patients who received G-PP had a 41% decrease in the risk of a modified PFS event compared with ABVD arm (HR 0.586, 95% CI: 0.32–1.08) (Figure 2(A)). Additionally, A + AVD patients who received G-PP had a 26% decrease in the risk of a modified PFS event versus those without G-PP (HR 0.74, 95% CI: 0.40–1.37) (Figure 2(B)). The 2-year modified PFS rate for A + AVD patients with and without G-PP were 84.6% (95% CI: 73.7–91.3) and 81.7% (95% CI: 78.1–84.8), respectively.

There was no apparent association between peripheral neuropathy and modified PFS outcomes per IRF for patients treated with A + AVD who either completed therapy or developed peripheral neuropathy. Patients treated with A + AVD with and without peripheral neuropathy had 2-year modified PFS rates of

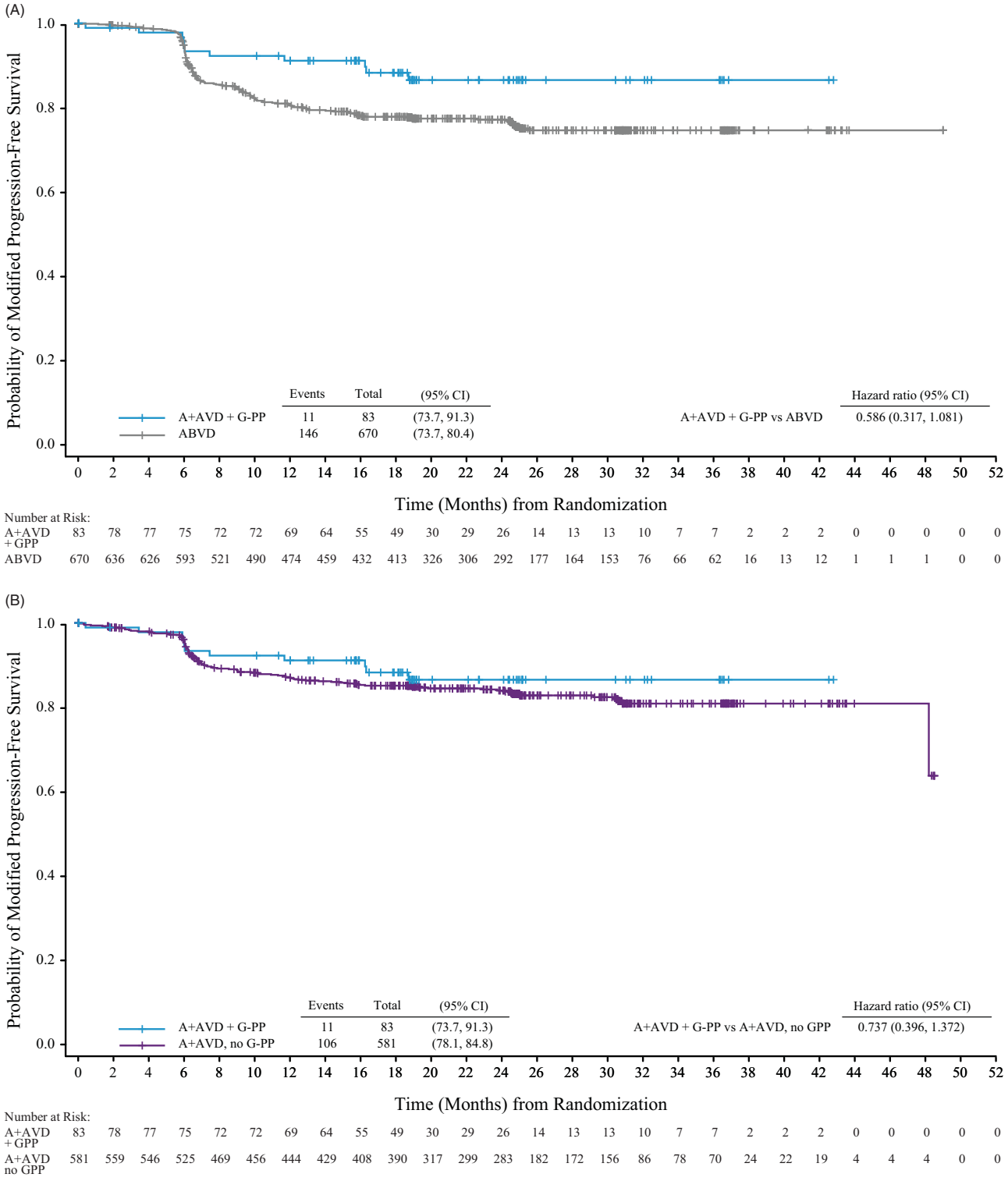

Figure 2. Kaplan–Meier's plots of modified PFS per independent review facility by primary prophylaxis with G-CSF (G-PP) by day 5 of the randomized regimen in the ITT population (A) patients treated with A + AVD plus G-PP had a 41% reduction in risk of a modified PFS event versus patients treated with ABVD (HR 0.586). (B) Patients treated with A + AVD who also received G-PP had a 26% decreased risk of a modified PFS event versus those who received A + AVD without G-PP (HR 0.737).

83.8% (95% CI: 79.8–87.0) and 84.5% (95% CI: 77.8–89.3), respectively.

Discussion

These analyses of the ECHELON-1 study support the recommendation for administration of G-PP starting with the first dose of A + AVD in cycle 1 and throughout treatment for patients with previously untreated stage III/IV cHL. Among the subset of patients treated with A + AVD, use of G-PP was associated with an improvement in the rates of neutropenia and febrile neutropenia, and fewer ≥ grade 3 events. Notably, although higher rates of neutropenia and febrile neutropenia were observed in patients treated with A + AVD, the use of G-PP effectively lowered the rate of neutropenia (30%) and febrile neutropenia (11%) to levels comparable to patients treated with ABVD (45% and 8%, respectively) [4].

The high rate of use of growth factors in this study also supports the use of G-PP, with 78% of patients in the A + AVD arm ultimately receiving at least one dose of G-CSF during treatment. Within the A + AVD arm, the median administration of G-CSF was only delayed by 2 weeks for patients without G-PP (2.3 weeks) versus those with G-PP (0.3 weeks). Therefore, delaying the administration of G-CSF does not ultimately reduce the need for G-CSF and increases the risk of neutropenia and febrile neutropenia.

The rate of febrile neutropenia among A + AVD patients with G-PP in ECHELON-1 was similar to those seen when G-PP is used with other regimens that combine a targeted agent with chemotherapy for the treatment of a hematologic malignancy, including R-CHOP for the treatment of non-Hodgkin lymphoma [2,3].

A key finding of the phase 1 experience of brentuximab vedotin in combination with ABVD was a contraindication for the concomitant use of brentuximab vedotin and bleomycin in the treatment of patients with frontline advanced Hodgkin lymphoma due to an increased incidence of pulmonary toxicity, including fatal events [6]. Following discontinuation or removal of bleomycin from the phase 1 study regimen (establishing A + AVD), no further pulmonary toxicity was observed. The findings from ECHELON-1 provide confirmation that a negligible rate of pulmonary toxicity is observed in patients treated with A + AVD, even when G-CSF is also used. Indeed, similar rates of pulmonary toxicity were observed in patients on the A + AVD arm with and without G-PP.

Dose intensity has been recognized as an important factor in achieving complete remission and long-term survival [7–10]. The use of G-PP with A + AVD was associated with fewer dose delays and dose reductions compared with patients who did not receive G-PP. In a post hoc analysis, a trend toward improvement in modified PFS by IRF at 2 years was observed among patients treated with A + AVD who received G-PP versus those without G-PP (84.6 versus 81.7%, respectively) (HR 0.737, 95% CI: 0.40–1.37). Maintaining dose intensity via the timely delivery of A + AVD with G-PP may have contributed to the observed improvement versus A + AVD without G-PP, as well as the additional benefit versus ABVD (HR 0.586, 95% CI: 0.32–1.08). However, other factors, such as small sample size in the A + AVD with G-PP subgroup and the high rate of secondary G-CSF use must also be considered.

Additionally, as peripheral neuropathy associated with brentuximab vedotin can be managed with dose delays and dose reductions, these analyses also demonstrate that the presence of peripheral neuropathy alone does not affect efficacy outcomes. A + AVD patients with and without peripheral neuropathy had 2-year modified PFS rates of 83.8% (95% CI: 79.8–87.0) and 84.5% (95% CI: 77.8–89.3), respectively. Among patients that experienced peripheral neuropathy, onset occurred earlier in the A + AVD treatment arm than it did in patients receiving monotherapy with brentuximab vedotin in the phase 3 AETHERA trial (median 8 weeks versus 13.7 weeks) [11]. As the study was not powered to detect safety or efficacy differences among patients receiving G-PP versus those who did not, limitations of this analysis must be considered. The modest sample size of the G-PP subgroup and a lack of stratification are also limitations of this analysis, although the baseline characteristics of the A + AVD with G-PP subgroup were similar to the ITT population. As G-CSF product selection, dose selection, and timing were at the discretion of the investigator per their institutional guidelines, it is unknown whether heterogeneity in the use of G-CSF on study may have contributed to the observed associations. Lack of available data, such as duration of therapy for some patients receiving non-pegylated G-CSF, also limit this analysis.

Although the sample size is modest, G-PP effectively mitigates the increased rate of neutropenia and febrile neutropenia and can be safely co-administered with A + AVD. Furthermore, the combination of A + AVD and G-PP was associated with a trend toward improved outcomes relative to A + AVD alone. Therefore, these analyses further support the use of G-

PP for all patients who receive A + AVD as frontline treatment for stage III/IV cHL.

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Data sharing statement: Qualified researchers may request access to certain data and related study documents consistent with the Principles for Responsible Clinical Trial Data Sharing. Further details about data requests can be found at http://www.seattlegenetics.com/patients-healthcare-professionals/clinical-data-requests or by emailing CTDR@seagen.com.

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DS reports advisory board membership and consulting with Seattle Genetics and personal fees from Takeda. GC reports consulting for Bristol-Myers Squibb, Celleron, Gilead, MSD, Pfizer, Roche, and Takeda, honoraria from Bristol-Myers Squibb, Celleron, Gilead, MSD, Pfizer, Roche, and Takeda, research funding from Amgen, Celgene, Celleron, MSD, and speaker's bureau fees and travel expenses from Roche and Takeda. JW reports advisory board memberships and consulting with Abbvie, Amgen, Bristol-Myers Squibb, Celgene, Gilead, Incyte, Janssen-Cilag, Novartis, Takeda, Servier, and Roche, honoraria from Abbvie, Amgen, Celgene, Gilead, Janssen-Cilag, Roche, Servier, and Takeda, research funding from GlaxoSmithKline, Janssen-Cilag, Novartis, Roche, and Takeda, and travel expenses from Roche. PZ reports advisory board membership with Bristol-Myers Squibb, Celgene, Celltron, Eusapharma, Gilead, Immune Design, Janssen, Kyowa Kirin, MSD, Portola, Roche, Sandoz, Servier, and Verastem, consulting with Eusapharma, MSD, Sanofi, and Verastem, and serving with the speaker's bureau at Bristol-Myers Squibb, Celgene, Celltron, Eusapharma, Gilead, Immune Design, Janssen, Kyowa Kirin, MSD, Portola, Roche, Servier, and Verastem. AGrigg reports advisory board membership and honoraria with Bristol-Myers Squibb, Gilead, Merck, Roche, and Takeda, consulting with Merck and Takeda, research funding from Seattle Genetics and Takeda, and travel expenses from Amgen. AS reports personal fees, research funding, honoraria, consulting, and speaker's bureau with Takeda, consulting with Bristol-Myers Squibb, and personal fees from Sanofi. TK reports research funding from AstraZeneca-KHIDI. LS reports advisory board membership with Kyowa Kirin, MSD, and Takeda, speaker fees from Takeda, conference expenses from MSD, and research funding from Varian and ViewRay. VB reports research funding from MSD, Roche, Seattle Genetics, and Takeda. AY reports honoraria from Abbvie, Curis, Epizyme, Janssen, Merck, Roche, and Takeda, and research funding from Bristol-Myers Squibb, Curis, Janssen, Merck, Syndax, and Roche, and consulting with Epizyme, Biopath, Xynomics, Roche, Celgene, and HCM. JC reports research funding from NanoString Technologies, Seattle Genetics, and Takeda. AFT and KF are employees of and have equity ownership in Seattle Genetics. IP and RL are employees of and have equity ownership in Millennium Pharmaceuticals. AGautam was an employee of Millennium Pharmaceuticals at the time this work was completed. AGallamini reports honoraria from Takeda. AI and SA had no conflicts to report.

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