Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial

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Summary

Background Despite advances in the treatment of Hodgkin lymphoma with the introduction of PET-adapted regimens, practical challenges prevent more widespread use of these approaches. The ECHELON-1 study assessed the safety and efficacy of front-line A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in patients with stage III or IV classical Hodgkin lymphoma. The primary analysis showed improved modified progression-free survival with A+AVD. We present an updated analysis of ECHELON-1 at 5 years, an important landmark for this patient population.

Methods ECHELON-1 was an international, open-label, randomised, phase 3 trial done at 218 clinical sites, including hospitals, cancer centres, and community clinics, in 21 countries. Previously untreated patients (≥18 years with an Eastern Cooperative Oncology Group performance status of ≤2) with stage III or IV classical Hodgkin lymphoma were randomly assigned (1:1) to receive A+AVD (brentuximab vedotin, 1·2 mg/kg of bodyweight, doxorubicin 25 mg/m² of body surface area, vinblastine 6 mg/m², and dacarbazine 375 mg/m²) or ABVD (doxorubicin 25 mg/m², bleomycin 10 U/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m²) intravenously on days 1 and 15 of each 28-day cycle for up to six cycles. Stratification factors included region (Americas *vs* Europe *vs* Asia) and International Prognostic Score risk group (low, intermediate, or high risk). The primary endpoint was modified progression-free survival; this 5-year update includes analysis of progression-free survival as per investigator assessment in the intention-to-treat population, which was an exploratory endpoint, although the 5-year analysis was not prespecified in the protocol. This trial is registered with ClinicalTrials.gov (NCT01712490) and EudraCT (2011-005450-60), and is ongoing.

Findings Between Nov 19, 2012, and Jan 13, 2016, 1334 patients were randomly assigned to receive A+AVD (n=664) or ABVD (n=670). At a median follow-up of 60·9 months (IQR 52·2–67·3), 5-year progression-free survival was 82·2% (95% CI 79·0–85·0) with A+AVD and 75·3% (71·7–78·5) with ABVD (hazard ratio [HR] 0·68 [95% CI 0·53–0·87]; p=0·0017). Among PET-2-negative patients, 5-year progression-free survival was higher with A+AVD than with ABVD (84·9% [95% CI 81·7–87·6] *vs* 78·9% [75·2–82·1]; HR 0·66 [95% CI 0·50–0·88]; p=0·0035). 5-year progression-free survival for PET-2-positive patients was 60·6% (95% CI 45·0–73·1) with A+AVD versus 45·9% (32·7–58·2) with ABVD (HR 0·70 [95% CI 0·39–1·26]; p=0·23). Peripheral neuropathy continued to improve or resolve over time with both A+AVD (375 [85%] of 443 patients) and ABVD (245 [86%] of 286 patients); more patients had ongoing peripheral neuropathy in the A+AVD group (127 [19%] of 662) than in the ABVD group (59 [9%] of 659). Fewer secondary malignancies were reported with A+AVD (19 [3%] of 662) than with ABVD (29 [4%] of 659). More livebirths were reported in the A+AVD group (n=75) than in the ABVD group (n=50).

Interpretation With 5 years of follow-up, A+AVD showed robust and durable improvement in progression-free survival versus ABVD, regardless of PET-2 status, and a consistent safety profile. On the basis of these findings, A+AVD should be preferred over ABVD for patients with previously untreated stage III or IV classical Hodgkin lymphoma.

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Introduction

Patients with advanced classical Hodgkin lymphoma are primarily treated with multi-agent chemotherapy regimens.[1] The most common front-line regimen used globally is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), but around 30% of patients with advanced disease have refractory disease or relapse after treatment with ABVD.[2] Intensified regimens such as

Research in context

Evidence before this study

We searched PubMed to identify novel regimens that improve outcomes for patients compared to ABVD. We identified 68 articles in PubMed published between Jan 1, 1990, and Dec 15, 2020, using the search terms "Hodgkin" or "HL" or cHL"; and "ABVD"; and "stage III" or "stage IV" or "advanced"; and a filter for randomised controlled trials. A manual review of these articles confirmed that studies published in the past 20 years that used ABVD as a comparator have primarily evaluated treatment with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) or its intensified version, escalated BEACOPP (eBEACOPP). Although eBEACOPP has been associated with reduced rates of early progression in some studies, this treatment regimen increases the risk of acute and late toxicities, including myelosuppression, haematological malignancies, and infertility. Given the potential risks associated with BEACOPP and other bleomycin-based regimens, PET-adapted approaches have been developed to try to improve efficacy while minimising exposure to bleomycin by targeting more intensive therapy to those patients who need it. The phase 3 ECHELON-1 study showed that treatment with the A+AVD regimen (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) provided a durable efficacy benefit over ABVD, with a manageable safety profile, obviating the need for a change in therapy based on PET results after two cycles of treatment and eliminating bleomycin-associated pulmonary toxicity.

Added value of this study

In this 5-year follow-up of the ECHELON-1 study, A+AVD continues to show a progression-free survival improvement over ABVD. This updated analysis of ECHELON-1 is clinically meaningful as previously published data suggest that most benefits related to progression-free survival, including reduction in deaths related to disease, occur within the first 5 years after front-line therapy. Furthermore, this clinical benefit comes with no evidence of an increased risk of infertility or secondary malignancy, both of which can be evident at 5 years in studies of intensified chemotherapy regimens.

Implications of all the available evidence

At 5 years, the results of the ECHELON-1 study confirm that A+AVD provides a durable progression-free survival benefit independently of PET status, without the risks associated with regimens containing bleomycin or requiring a change in therapy. On the basis of these findings, A+AVD should be considered a preferred front-line treatment option for patients with advanced classical Hodgkin lymphoma.

eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) have been associated with improvements in efficacy for patients with advanced disease; however, eBEACOPP has also been associated with both increased short-term toxicities, including myelosuppression, as well as long-term toxicities such as infertility and secondary malignancies, and therefore is only a suitable option for fit patients younger than 60 years of age.[3,4]

PET-adapted strategies customise treatment intensity according to the risk of induction therapy failure, to improve outcomes in the minority of patients who are at high risk and mitigate toxicity in low-risk patients.[1] These strategies most commonly restrict use of more intensive regimens such as eBEACOPP to patients at highest risk of primary refractory or relapsed disease; alternatively, they can involve de-escalation of treatment in patients at lower risk of treatment failure to a less intense regimen. The level of risk is determined on the basis of lymphoma status at the time of an interim PET scan done after two cycles of therapy (PET-2).[1] In a recent clinical trial of patients with classical Hodgkin lymphoma, use of a PET-adapted approach showed suboptimal response durability in PET-2-negative patients, indicating that PET-2-negative status is an imperfect indicator of which patients have an acceptable outcome with standard-dose therapy.[5] Additionally, longer-term data have shown that escalation to BEACOPP is associated with long-term toxicities in PET-2-positive patients, including a high rate of secondary malignancies.[5] PET-adapted strategies can also be challenging to implement in some settings, as they require a change in treatment regimen for some patients as well as timely availability and expert standardised interpretation of PET scans.[6] Thus, for patients with advanced-stage classical Hodgkin lymphoma, there is an unmet need for a treatment regimen that can be used in patients of all ages and provides a durable efficacy benefit while avoiding bleomycin and eBEACOPP and the need for a change in therapy based on interim PET assessment.

The ECHELON-1 study showed significantly improved modified progression-free survival (as per the independent review facility) with A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) than with ABVD for front-line treatment of patients with stage III or IV classical Hodgkin lymphoma.[7] In the 3-year update of the ECHELON-1 trial, investigator-assessed 3-year progression-free survival was 83·1% (95% CI 79·9–85·9) in the A+AVD group and 76·0% (72·4–79·2) in the ABVD group.[8] The progression-free survival benefit was independent of disease stage, age, prognostic risk factors, and PET status. Although the rate of febrile neutropenia was higher with A+AVD than with ABVD in the primary analysis, primary prophylaxis with investigator's choice granulocyte colony-stimulating factor (G-CSF) reduced the rate to a level comparable to that of ABVD.[7,9] Peripheral neuropathy was more frequent with A+AVD (67%) than

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with ABVD (43%) in the primary analysis, and the 3-year update showed continued improvement in both groups. Ongoing peripheral neuropathy (mostly grade 1 or 2) was reported in 25% of patients in the A+AVD group and in 11% of patients in the ABVD group. The rate of secondary malignancies with A+AVD did not exceed that of ABVD. These outcomes are similar to data reported from PET-adapted strategies with a similar follow-up period; importantly, ECHELON-1 included only patients with stage III or IV disease and also recruited patients older than 60 years.

Although earlier analyses of the ECHELON-1 study showed a durable efficacy benefit and manageable safety profile after 3 years of follow-up, we did an additional analysis at 5 years, as this is an important milestone for assessing survivorship, including long-term safety and survival, in this patient population. Despite the low rate of relapse after 5 years in historical datasets,[10,11] recent attempts to further improve efficacy in front-line therapy of classical Hodgkin lymphoma have generally evaluated intensification of chemotherapy, which can come with safety trade-offs including risks of secondary malignancies and infertility. We hypothesised that, in the ECHELON-1 study, A+AVD will continue to show a durable efficacy benefit over ABVD at 5 years, with a manageable safety profile.

Methods

Study design and participants

ECHELON-1 was an open-label, international, randomised, phase 3 trial that compared the efficacy and safety of A+AVD versus ABVD in patients with advanced classical Hodgkin lymphoma. The study was done at 218 clinical sites, including hospitals, cancer centres, and community clinics, in 21 countries (appendix pp 8–12); details of the study design have been described previously.[7] The study enrolled patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 2 or greater and with previously untreated stage III or IV classical Hodgkin lymphoma, histologically confirmed according to the current WHO classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, not otherwise specified). The complete eligibility criteria are in the appendix (pp 1–2).

See Online for appendix

The study was done in accordance with regulatory requirements and the protocol was approved by institutional review boards and ethics committees at individual sites. All patients provided written informed consent. The protocol is available online.

For the **protocol** see https://clinicaltrials.gov/ProvidedDocs/90/NCT01712490/Prot_000.pdf

Randomisation and masking

The randomisation scheme was generated by the sponsor. Before administration of study drugs, a randomisation number was assigned to each patient. The randomisation schedule also included study-specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated. Patients were randomly assigned (1:1) to receive A+AVD or ABVD. Stratification factors included region (Americas *vs* Europe *vs* Asia) and International Prognostic Score (IPS) risk group (low, intermediate, or high risk).

ECHELON-1 was an open-label study; neither investigators nor patients were masked to treatment assignments. The independent review facility was masked to treatment assignments, and the sponsor was masked to treatment assignments for efficacy outcomes.

Procedures

Patients received either A+AVD (brentuximab vedotin, 1·2 mg/kg of bodyweight; doxorubicin 25 mg/m² of body surface area, vinblastine 6 mg/m², and dacarbazine 375 mg/m²) or ABVD (doxorubicin 25 mg/m²; bleomycin 10 U/m²; vinblastine 6 mg/m², and dacarbazine 375 mg/m²) intravenously on days 1 and 15 of each 28-day cycle for up to six cycles (appendix p 5).[7] Use of G-CSF for treatment or prevention of neutropenia was permitted in both groups at the discretion of the investigator as per their institutional guidelines.[9] After 75% of enrolment was complete, a recommendation was made for primary prophylaxis with G-CSF for patients who would receive A+AVD in order to mitigate the increased risk of febrile neutropenia observed in patients enrolled earlier.

CT and PET scans were done at screening and after completion of two cycles of therapy. PET-2 status was assessed with the Deauville criteria with central review. A PET-2-negative status was defined as a Deauville score of 1, 2, or 3. A Deauville score of 4 or 5 was considered PET-2-positive, with an optional switch to alternative front-line therapy for patients with a Deauville score of 5.[7] At the time of the 3-year analysis, re-adjudication by the independent review facility was ongoing for some PET-2 scans. Adjudications have since been completed and are reflected in the data presented in this 5-year analysis.

Initially, CT scans were done every 3 months for the first year of follow-up and then every 6 months. The protocol was amended on July 16, 2018, approximately 15 months after the primary analysis, and CT scans were no longer required during the extended monitoring period. As per the same protocol amendment, patients were intended to be followed up for survival until death or for a minimum of 10 years after enrolment of the last patient.

Post-treatment follow-up assessments for new primary malignancies and other safety events were done every 3 months until 36 months after the end of treatment and then every 6 months. Safety was assessed with the Medical Dictionary for Regulatory Activities (version 19.0) and National Cancer Institute Common Terminology Criteria for Adverse events (version 4.03). Peripheral neuropathy was monitored for resolution and improvement; events were investigator-assessed and reported. Improvement was defined as a decrease of at least one grade from worst grade with no higher grade thereafter. Use of subsequent

anticancer therapies and the incidence and outcomes of pregnancies among participants and their partners were assessed. Patients could be discontinued from the study for the following reasons: loss to follow-up, study termination by the sponsor, withdrawal by the patient, death, or at the investigator's disrection.

Outcomes

The primary endpoint for ECHELON-1 was modified progression-free survival (time from randomisation to progression, death, or non-complete response and use of subsequent anticancer therapy) as per the independent review facility.[7] The independent review facility was disbanded after the primary analysis, and progression-free survival as per investigator assessment in the intention-to-treat population, a prespecified exploratory endpoint for the study, was assessed at 5 years. Progression-free survival was defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first. Progression-free survival as per investigator assessment was a prespecified endpoint for the trial and collection of data on subsequent therapies, peripheral neuropathy, secondary malignancies, and pregnancies was pre-planned; however, this analysis at 5 years was not prespecified in the protocol. Post-hoc analyses of progression-free survival at 5 years were done within prespecified subgroups defined by age, region, IPS risk group, cancer stage at baseline, baseline B

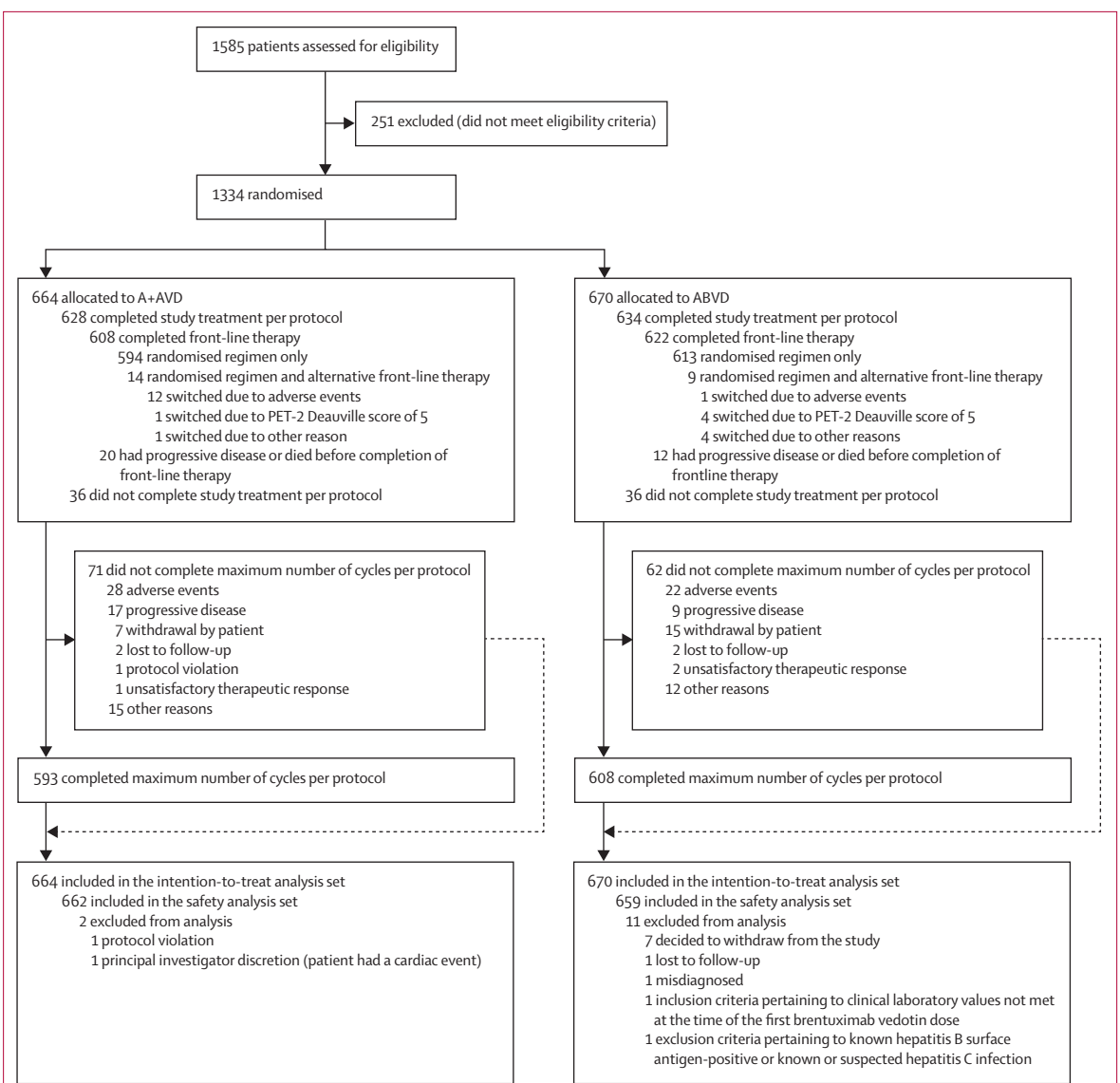

Figure 1: **Trial profile**
A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. PET-2=PET scan after two cycles of therapy.

symptoms, baseline extranodal sites, ECOG performance status, sex, and PET-2 status. The key secondary endpoint was overall survival. A pre-planned interim analysis of overall survival has been published.[7] As defined in the protocol, the final analysis of overall survival will be done once 112 deaths have occurred. Other secondary endpoints were: the rate of complete remission as best overall response reached at the end of the randomised regimen as per independent review facility assessment based on the Revised Response Criteria for Malignant Lymphoma; adverse events, serious adverse events, assessments of clinical laboratory values, and vital signs measurements; event-free survival; disease-free survival; overall response rate; duration of response as per independent review facility; duration of complete remission as per independent review facility; proportion of patients not in complete remission who received irradiation; complete remission rate as per independent review facility at the end of front-line therapy; proportion of patients with PET-2 negativity; patient-reported outcomes as per European Organization for Research and Treatment of Cancer QLQ-C30; pharmacokinetic variables for brentuximab vedotin, monomethyl auristatin E, and total antibody; and the presence of antitherapeutic antibodies to brentuximab vedotin. Results for these secondary endpoints have been previously reported and are available online.

For the **results of the secondary endpoints** see https://clinicaltrials.gov/ct2/show/NCT01712490

	A+AVD group (n=664)	ABVD group (n=670)	Total (n=1334)
Sex			
Female	286 (43%)	272 (41%)	558 (42%)
Male	378 (57%)	398 (59%)	776 (58%)
Median age, years	35 (26–51)	37 (27–53)	36 (26–52)
Age group, years			
<60	580 (87%)	568 (85%)	1148 (86%)
≥60	84 (13%)	102 (15%)	186 (14%)
Region			
Americas	261 (39%)	262 (39%)	523 (39%)
Europe	333 (50%)	336 (50%)	669 (50%)
Asia	70 (11%)	72 (11%)	142 (11%)
Ann Arbor stage at initial diagnosis			
Stage II*	1 (<1%)	0	1 (<1%)
Stage III	237 (36%)	246 (37%)	483 (36%)
Stage IV	425 (64%)	421 (63%)	846 (64%)
Not applicable, unknown, or missing	1 (<1%)	3 (<1%)	4 (<1%)
International Prognostic Score			
0–1	142 (21%)	141 (21%)	283 (21%)
2–3	355 (53%)	357 (53%)	712 (53%)
4–7	167 (25%)	172 (26%)	339 (25%)
ECOG performance status			
0	376 (57%)	378 (57%)	754 (57%)
1	260 (39%)	263 (39%)	523 (39%)
2	28 (4%)	27 (4%)	55 (4%)
Not obtained or missing	0	2 (<1%)	2 (<1%)
Extranodal involvement at diagnosis			
Yes	411 (62%)	416 (62%)	827 (62%)
1 extranodal site	217 (33%)	223 (33%)	440 (33%)
>1 extranodal site	194 (29%)	193 (29%)	387 (29%)
No	217 (33%)	228 (34%)	445 (33%)
Unknown or missing	36 (5%)	26 (4%)	62 (5%)
Patients with any B symptom	400 (60%)	381 (57%)	781 (59%)
PET-2 status			
Positive	47 (7%)	58 (9%)	105 (8%)
Negative	588 (89%)	578 (86%)	1166 (87%)
Unknown or unavailable	29 (4%)	34 (5%)	63 (5%)

Source: Connors et al, 2018.[7] Data are n (%) or median (IQR). A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. ECOG=Eastern Cooperative Oncology Group. PET-2=PET scan done after two cycles of therapy. *Patients in this category had a major protocol violation.

Table 1: **Key characteristics of the intention-to-treat population**

Statistical analysis

We calculated that a planned sample size of 1240 patients (260 modified progression-free survival events) was required to provide 90% power at the primary analysis to detect a hazard ratio (HR) of 0·67 for the primary endpoint (modified progression-free survival) at a one-sided significance level of 0·025 with a log-rank test.[7] For the 5-year analyses presented here, the data cutoff date was Sept 14, 2020. Progression-free survival was assessed with the Kaplan-Meier method. Patients with no events were censored at the last available contact. The intention-to-treat population comprised all randomly assigned patients, and patients were analysed according to the treatment they were randomly assigned to receive. The safety population comprised all patients who received at least one dose of study drug, and patients were analysed according to the actual treatment they received. p values were calculated with a stratified log-rank test to compare progression-free survival between the two treatment groups. p values are nominal and not adjusted for multiplicity. HRs (A+AVD *vs* ABVD) and 95% CIs were based on a stratified Cox's proportional hazards regression model, with treatment as the explanatory variable in the model. Stratification factors included region and baseline IPS risk group. No stratification factors were used in the subgroup analysis. Statistical analyses were done with SAS (version 9.4).

This study is registered with ClinicalTrials.gov (NCT01712490) and EudraCT (2011-005450-60), and is ongoing.

Role of the funding source

This study was designed by the funders with contributions from JMC, JR, AY, AG, WSK, and SMA. The funder provided the study drug and participated in regulatory and ethics approval, safety monitoring, data collection, data analysis, data interpretation, statistical analyses, and writing of the manuscript.

Results

Between Nov 19, 2012, and Jan 13, 2016, 1334 patients were randomly assigned to receive A+AVD (n=664) or

ABVD (n=670; figure 1). Baseline disease characteristics and patient demographics have been described previously and were similar between treatment groups and PET-2 status subgroups.[7] Key baseline and demographic data are summarised in table 1. The median age of patients was 36 years (IQR 26–52), and 771 (58%) of 1334 patients were younger than 40 years of age. The median follow-up time was 60·9 months (IQR 52·2–67·3). The number of confirmed deaths did not reach the prespecified number to trigger analysis of overall survival.

The estimated 5-year progression-free survival per investigator assessment in the ITT population was 82·2% (95% CI 79·0–85·0) in the A+AVD group and 75·3% (71·7–78·5) in the ABVD group (HR 0·68 [95% CI 0·53–0·87]; p=0·0017; figure 2A, table 2). The rate of late relapses was similar in the two groups: since the 3 year analysis, there were three new progression-free survival events in the A+AVD group (all progressive disease or relapse) and seven new events in the ABVD group (three progressive disease or relapse, four deaths).

5-year progression-free survival per investigator assessment was generally higher with A+AVD than with ABVD across prespecified subgroups, including age, PET-2 status, IPS risk group, and disease stage (table 2; figure 2B; figure 3; see the appendix pp 3–4 for progression-free survival by stage).

Treatment with anticancer therapy after front-line treatment was assessed (appendix p 6). Overall, fewer patients in the A+AVD group (133 [20%] of 662) received at least one subsequent anticancer therapy than in the ABVD group (156 [24%] of 659). 42 (6%) of 662 patients in the A+AVD group and 57 (9%) of 659 in the ABVD group had high-dose chemotherapy plus an autologous haematopoietic stem-cell transplantation.

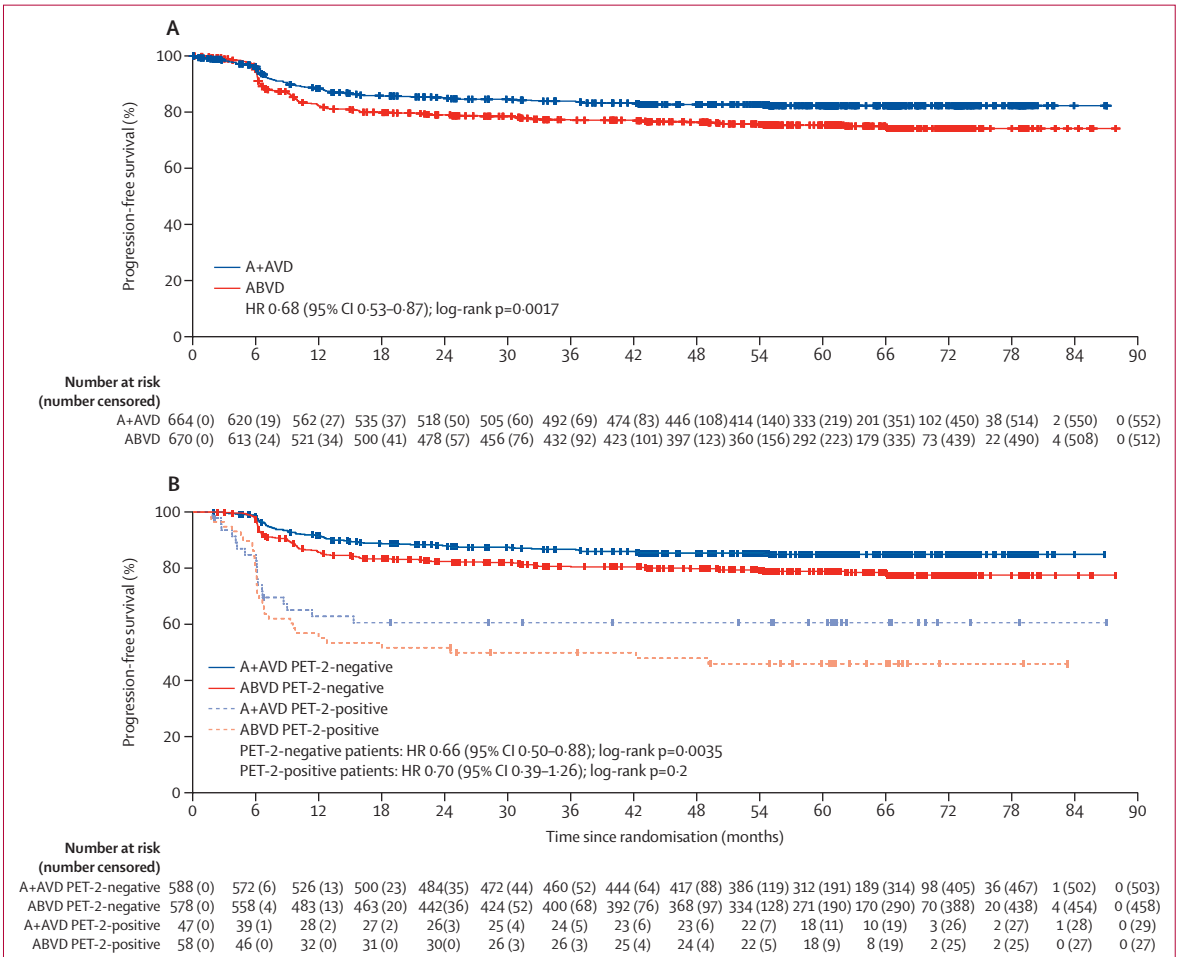

Figure 2: **Progression-free survival per investigator assessment in the intention-to-treat population**
(A) Patients treated with A+AVD or ABVD. A+AVD group: 16 deaths and 96 progressive disease events. ABVD group: 30 deaths and 128 progressive disease events. (B) Patients receiving A+AVD or ABVD by PET-2 status (positive or negative for active disease by PET scan after two cycles of therapy). A+AVD PET-2-negative subgroup: nine deaths and 76 progressive disease events. ABVD PET-2-negative subgroup: 26 deaths and 94 progressive disease events. A+AVD PET-2-positive subgroup: no deaths and 18 progressive disease events. ABVD PET-2-positive subgroup: three deaths and 28 progressive disease events. Tick marks indicate censored data. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. HR=hazard ratio.

	A+AVD group		ABVD group		HR (95% CI)	p value
	Number of patients	Progression-free survival (95% CI)	Number of patients	Progression-free survival (95% CI)		
All-patient analyses						
All patients	664	82·2% (79·0–85·0)	670	75·3% (71·7–78·5)	0·68 (0·53–0·87)	0·0017
PET-2-negative patients	588	84·9% (81·7–87·6)	578	78·9% (75·2–82·1)	0·66 (0·50–0·88)	0·0035
PET-2-positive patients	47	60·6% (45·0–73·1)	58	45·9% (32·7–58·2)	0·70 (0·39–1·26)	0·23
Patients <60 years						
All patients	580	84·3% (81·0–87·1)	568	77·8% (74·0–81·1)	0·67 (0·51–0·88)	0·0034
PET-2-negative patients	521	86·6% (83·3–89·3)	493	81·5% (77·7–84·7)	0·68 (0·49–0·93)	0·014
PET-2-positive patients	42	63·1% (46·4–75·9)	50	49·3% (34·7–62·3)	0·70 (0·37–1·33)	0·27
Patients ≥60 years						
All patients	84	67·1% (55·1–76·5)	102	61·6% (50·9–70·7)	0·82 (0·49–1·36)	0·44
PET-2-negative patients	67	71·9% (59·0–81·3)	85	64·9% (53·5–74·2)	0·72 (0·40–1·29)	0·27
PET-2-positive patients	5	40·0% (5·2–75·3)	8	25·0% (3·7–55·8)	0·92 (0·23–3·72)	0·91

p values were calculated with a log-rank test to compare progression-free survival between the two treatment groups. HRs (A+AVD *vs* ABVD) and 95% CIs were based on a Cox's proportional hazard regression model with treatment as the explanatory variable in the model. The all-patient analyses were stratified by region and IPS risk group; subgroup analyses were unstratified. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. HR=hazard ratio. PET-2=PET scan after two cycles of therapy. IPS=International Prognostic Score.

***Table 2*: Progression-free survival per investigator assessment at 5 years by PET-2 status and age in the intention-to-treat population**

Peripheral neuropathy occurred in 443 (67%) of 662 patients in the A+AVD group and in 286 (43%) of 659 patients in the ABVD group. At 5 years, 127 (19%) of 662 patients in the A+AVD group and 59 (9%) of 659 in the ABVD group had ongoing peripheral neuropathy. In the A+AVD group, 375 (85%) of 443 patients with peripheral neuropathy had either complete resolution (316 [71%] of 443) or improvement (59 [13%] of 443; appendix p 5). In the A+AVD group, 74 (11%) of 662 patients had maximum severity grade 1, 38 (6%) had maximum severity grade 2, 14 (2%) had maximum severity grade 3, and one (<1%) had maximum severity grade 4 ongoing peripheral neuropathy. Assessment of ongoing peripheral neuropathy with maximum severity of grade 3–4 was confounded in 12 of 15 patients in the A+AVD group (in three who died before resolution, four who were lost to follow-up, and five who withdrew from the study). In the ABVD group, 245 (86%) of 286 patients with peripheral neuropathy had either complete resolution (227 [79%] of 286) or improvement (18 [6%] of 286; appendix p 5); 39 (6%) of 659 patients had maximum severity grade 1, 16 (2%) had maximum severity grade 2, and four (<1%) had maximum severity grade 3 ongoing peripheral neuropathy. Among the patients in the ABVD group with grade 3 peripheral neuropathy, two patients were lost to follow-up and two died before resolution of peripheral neuropathy. The median time to complete resolution of peripheral neuropathy events that were ongoing at the end of treatment was 34 weeks (IQR 13–71) in the A+AVD group and 16 weeks (11–78) in the ABVD group. The median time to improvement for patients whose peripheral neuropathy did not completely resolve was 49 weeks (IQR 30–129) in the A+AVD group and 12 weeks (11–53) in the ABVD group.

Secondary malignancies were reported in 48 patients: 19 [3%] of 662 in the A+AVD group and 29 [4%] of 659 in the ABVD group (appendix p 7). In the A+AVD group, nine haematological malignancies and ten solid tumours occurred, including two cases of acute myeloid leukaemia (in patients aged 38 years and 29 years). In the ABVD group, 15 haematological malignancies and 14 solid tumours occurred, including one case of myelodysplastic syndrome (in a patient aged 71 years) and one case of acute myeloid leukaemia (in a patient aged 74 years).

Pregnancies were reported in 44 female patients and 31 partners of male patients in the A+AVD group and in 26 female patients and 30 partners of male patients in the ABVD group. 125 livebirths were reported among study participants and their partners (in 42 female patients and 33 partners of male patients in the A+AVD group, and in 21 female patients and 29 partners of male patients in the ABVD group). Among female patients, two or more livebirths were reported in eight patients in the A+AVD group and in three patients in the ABVD group. The proportion of pregnancies in female patients that were ongoing or resulted in a livebirth was 87% (52 of 60) in the A+AVD group and 75% (24 of 32) in the ABVD group. No stillbirths were reported.

A detailed analysis of the safety and tolerability of A+AVD and ABVD in ECHELON-1 has previously been published, with additional details summarised in the appendix (p 8).[7,9]

Discussion

After a median follow-up of 60·9 months (IQR 52·2–67·3), A+AVD continued to show a robust and durable treatment benefit compared with ABVD, in terms of

progression-free survival, as a front-line treatment in patients with advanced classical Hodgkin lymphoma. The investigator-assessed progression-free survival at 5 years was 82·2% (95% CI 79·0–85·0) for patients in the A+AVD group and 75·3% (71·7–78·5) for patients in the ABVD group (HR 0·68; p=0·0017). These rates are similar to progression-free survival observed at 3 years: 83% (95% CI 79·9–85·9) in the A+AVD group and 76% (72·4–79·2) in the ABVD group.[8] The treatment benefit was similar across disease stages, IPS risk groups, and PET-2 response subgroups. The safety profile of A+AVD observed in this 5-year update continues to be predictable and manageable. The symptoms of peripheral neuropathy continued to improve or resolve over time in both groups, although more patients had ongoing peripheral neuropathy in the A+AVD group than in the ABVD group. Most ongoing peripheral neuropathy in this 5-year analysis was grade 1 or 2.

Several contemporary studies have evaluated different PET-adapted approaches, with the aim of further improving efficacy outcomes for patients with classical Hodgkin lymphoma while minimising exposure to intensive regimens such as BEACOPP. However, interpretation of findings across datasets for these trials can be challenging because of differences in aspects of trial design, including eligibility criteria, treatment regimens, and planned delivery of radiotherapy. In comparison with PET-adapted trials, ECHELON-1 excluded patients with stage II disease (in contrast to RATHL,[12] GITIL/FIL HD 0607,[13] HD18,[14] and AHL2011[15]) and included patients older than 60 years (in contrast to SWOG S0816,[5] GITIL/FIL HD 0607,[13] HD18,[14] and AHL2011[15]), a patient population of high unmet need as described by Evens and colleagues.[16]

RATHL,[12] SWOG S0816,[5] and GITIL/FIL HD 0607[13] evaluated the efficacy of initial ABVD with escalation to a BEACOPP-based therapy for patients classified as PET-2 negative. The RATHL study,[12] which evaluated ABVD escalated to BEACOPP or de-escalated to AVD, was a non-inferiority trial that enrolled a high proportion (42%) of patients with stage II disease. The 5 year progression-free survival for PET-2-negative patients in the ECHELON-1 study for A+AVD (84·9% [95% CI 81·7–87·6]) compares favourably to that of the RATHL study for PET-2-negative patients who were de-escalated to AVD (80·6%; 95% CI 76·2–84·2).[17] Additionally, 5-year progression-free survival with A+AVD for PET-2-positive patients younger than 60 years in ECHELON-1 (63·1% [95% CI 46·4–75·9]) was similar to 5-year progression-free survival in the RATHL study (65·7%; 95% CI 57·9–72·5) without the need for exposure to BEACOPP.[17] Similar results were seen in the GITIL/FIL HD 0607 trial,[13] which escalated PET-2-positive patients to four cycles of eBEACOPP followed by four cycles of standard BEACOPP with or without rituximab and, similarly to the RATHL study, enrolled a high proportion (36%) of patients with stage II disease. 5-year progression-free survival for PET-2-negative patients in the SWOG S0816 trial[5] was 76% (95% CI 70–81), a rate of relapse higher than that expected with ABVD, suggesting that a PET-2-negative status might not accurately identify all patients who can be potentially cured of their disease.

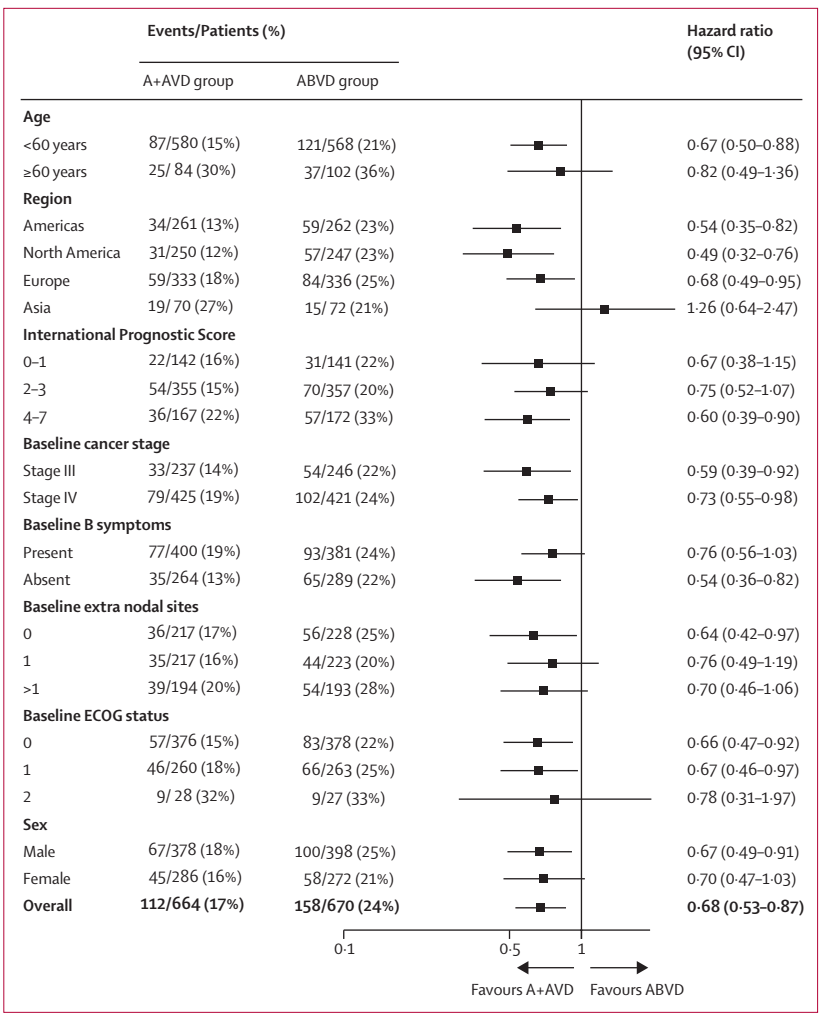

Figure 3: **Subgroup analysis of progression-free survival per investigator assessment**
Hazard ratios (A+AVD *vs* ABVD) and 95% CIs were based on a stratified Cox's proportional hazard regression model. A+AVD=brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. ECOG=Eastern Cooperative Oncology Group.

In an alternative approach, the HD18[14] and AHL2011[15] trials treated patients initially with eBEACOPP and de-escalated therapy for those who were PET-2-negative. AHL2011[15] capped the age of participants at 60 years and used a PET-adapted approach: initial treatment with eBEACOPP for two cycles followed by de-escalation to ABVD for PET-2-negative patients or an additional four cycles of eBEACOPP for PET-2-positive patients. PET-2-negative patients had a 5-year progression-free survival of 89·4% (95% CI 84·9–92·6); PET-2-positive patients had a 5-year progression-free survival of 68·2% (53·4–79·2).[15] Like AHL2011, the initial therapy in the HD18 trial[14] was two cycles of eBEACOPP but was followed by de-escalation to two additional cycles of

eBEACOPP for patients who were PET-2-negative or four or six additional cycles for PET-2-positive patients. 5-year progression-free survival was 92·2% (95% CI 89·4–95·0) for PET-2-negative patients receiving four more cycles and 90·8% (87·9–93·7) for those receiving six more cycles. In comparison, PET-2-positive patients who continued on six further cycles had a 5-year progression-free survival of 89·7% (95% CI 85·4–94·0). Overall, both AHL2011 and HD18 showed a trend towards improved 5-year progression-free survival compared to patients younger than 60 years treated with A+AVD in ECHELON-1, although the comparison with HD18 is limited by the categorisation of patients with a Deauville score of 3 as PET-2-positive.

Long-term safety, including the risk of reduced fertility and secondary malignancies, is important to consider when selecting a treatment regimen. Given the demographics of this patient population (almost 60% <40 years of age), the infertility risk is important to many. The negative impact on fertility from chemotherapy typically increases with age.[18] ABVD is generally not thought to be associated with a greater risk of premature menopause, and a case–control study showed no substantial effect on fertility for patients treated with ABVD.[19] ABVD also has less of an effect on male fertility than more intense regimens.[20,21] By comparison, treatment with more intensive chemotherapy regimens such as eBEACOPP has been associated with a higher rate of infertility, which is age-dependent, with women aged 30 years or older being at highest risk for sustained amenorrhea 4 years after eBEACOPP therapy.[20] A report of the German Hodgkin Lymphoma Study Group found that 38 (51%) of 74 women treated with eight cycles of eBEACOPP had permanent amenorrhea.[3] Male patients are also at high risk of infertility after treatment.[20,22] In men treated with six to eight cycles of BEACOPP or eBEACOPP, 88·8% had post-therapy hormone levels indicative of oligospermia. Although the PET-driven approach in the AHL2011 trial decreased this rate, the rate of oligospermia was 50%.[20,23] Decreasing the number of cycles of eBEACOPP has been postulated to lessen the effect on fertility; however, the PET-adapted SWOG S0186,[5] RATHL,[12] GITIL/FIL HD 0607,[13] and HD18[14] studies have not yet reported on the effect of fewer treatment cycles on fertility or pregnancies. In a fertility substudy of AHL2011,[23] the risk of infertility was reduced in the PET-adapted treatment group compared to the standard treatment group (in which all participants received six cycles of eBEACOPP), but was still associated with the total dose of alkylating agents or cumulative dose of etoposide. Although there are regional differences in practice guidelines, a premenopausal woman with symptomatic advanced-stage disease who will be treated with a PET-adapted therapeutic approach might face a difficult decision to delay initiation of chemotherapy to pursue oocyte or embryo cryopreservation given the potential higher risk of future infertility if therapy would need to be escalated to BEACOPP.[24] Given the standard definition of infertility,[25] in the ECHELON-1 study pregnancies were assessed as a surrogate for reproductive function, and a numerically higher number of pregnancies were reported in the A+AVD group than in the ABVD group, suggesting that A+AVD conferred no additional risk of infertility compared to ABVD.

Secondary malignancies were less common with A+AVD than ABVD, and myelodysplastic syndrome and acute myeloid leukaemia were rare in both groups. Secondary malignancy rates are influenced by both the chemotherapy regimen and the dose and field size of radiation; the incidence of solid tumours usually does not increase until 12–15 years after treatment. Patients treated with combined modality therapy present with both a higher rate (particularly of solid tumours) and a later peak incidence of secondary malignancies than patients treated with chemotherapy alone.[26] Exposure to subsequent therapy such as autologous or allogeneic haematopoietic stem-cell transplantation might also increase the incidence of secondary malignancies.[27] BEACOPP has been shown to increase the risk of secondary malignancies compared with ABVD. In a recent pooled analysis of four randomised trials, secondary cancers were reported in 4·0% of patients treated with ABVD, with no reported cases of myelodysplastic syndrome or acute myeloid leukaemia, and in 6·5% of patients treated with BEACOPP, with 13 cases of myelodysplastic syndrome or acute myeloid leukaemia.[4] Given this association, contemporary PET-adapted strategies have sought to limit exposure to eBEACOPP. Data from the HD18 trial[28] have suggested that secondary malignancies are correlated with the number of cycles of eBEACOPP, with a higher number of cycles of eBEACOPP being associated with higher rates of treatment-related acute myeloid leukaemia or myelodysplastic syndrome: 1% for six cycles and 0·5% for four cycles. The AHL2011 trial[15] also decreased the overall rate of secondary malignancies to 1% (five of 407 patients) in its PET-driven group, in which 346 (87%) of 410 patients received just two cycles of eBEACOPP. However in the SWOG S0816 trial,[5] PET-2-positive patients receiving eBEACOPP had a high rate of secondary malignancies: seven (14%) of 49 patients after 5 years of follow-up. This rate was higher than expected on the basis of the above results as well as for other contemporary studies, including RATHL[12] and GITIL/FIL HD 0607,[13] although the comparison is limited by the heterogeneity of treatment regimens and duration of follow-up.

In addition to PET-adapted chemotherapy regimens, treatment regimens that incorporate other newer agents, such as checkpoint inhibitors, are being evaluated in ongoing clinical trials, including SWOG S1826 (NCT03907488),[29] a phase 3 advanced-stage study comparing nivolumab plus AVD versus A+AVD; and SGN35-027,[30] a phase 2 study investigating treatment of patients with early and advanced-stage classical Hodgkin lymphoma with the combination of

brentuximab vedotin and nivolumab plus doxorubicin and dacarbazine.

Previously published studies have shown that relapses in classical Hodgkin lymphoma peak early, 12–18 months after treatment initiation. The relapse rate then decreases rapidly: less than 5% of patients who are disease-free at 5 years will have a relapse by 10 years.[11] A more recent publication analysing more than 1000 patients within the BC Cancer Lymphoid Cancer Database treated with ABVD or equivalent chemotherapy supports these earlier publications by showing that patients who are disease-free at 2 years have excellent outcomes independently of baseline prognostic factors, noting that IPS of 4 or greater and bulky disease were no longer prognostic in these patients.[10] The expectation that most patients remain disease-free after 2 years is reflected in the US National Comprehensive Cancer Network guidelines, which do not recommend routine surveillance imaging beyond this timeframe.[1] The time course of relapses in the ECHELON-1 study has been consistent with historical survival trends for patients with classical Hodgkin lymphoma: six relapses have been observed since the 3-year follow-up. Given the consistency of the progression-free survival estimates with A+AVD over time and with 5 years of follow-up data now available, few additional relapses are expected in ECHELON-1.

A limitation of this study is that although progression-free survival per investigator assessment was a prespecified analysis at 2 years, the 5-year follow-up analysis is a post-hoc analysis, including analysis of outcomes by PET-2 status and protocol-specified subgroups. Thus, any associated p values are descriptive. Furthermore, when comparing our data to the PET-adapted trial regimens,[5,12,13,15] beyond differences in patient populations the differences between trials in their classification of PET-2-negative and PET-2-positive patients (ie, categorising Deauville score 3 as PET-negative *vs* PET-positive) can make comparisons of 5-year progression-free survival by PET-2 status between ECHELON-1 and contemporary PET-adapted trials challenging as well as pose challenges with comparing outcomes among trials. Additionally, more limited data were collected on receipt of subsequent therapy, precluding a detailed analysis of response to salvage therapy between the two treatment groups.

At this important 5-year milestone, A+AVD showed a durable progression-free survival benefit versus ABVD that was independent of disease stage, age, baseline risk, or interim PET-2 status. A+AVD provides a straightforward front-line treatment option that compares favourably to contemporary PET-adapted strategies without requiring either a change of therapy based on interim PET assessment or exposure to bleomycin, which is known to increase the risk of pulmonary toxicity. A+AVD also showed a promising long-term safety profile, with a low rate of secondary malignancies, no observed effect on the rate of pregnancies compared to ABVD, and a high rate of resolution and improvement of peripheral neuropathy. As most relapses in classical Hodgkin lymphoma have been shown to occur within 5 years, these long-term outcomes with A+AVD versus ABVD suggest that more patients might have been potentially cured of their disease. A+AVD should therefore be considered a preferred treatment option for patients with previously untreated stage III or IV classical Hodgkin lymphoma.

Contributors

DJS, MD-D, JMC, SA, ÁI, MP, EL-M, TF, PS, KJS, NLB, JW, RR, PLZ, MH, JM, HJL, WSK, RA, SMA, AY, AG, MF, and JR participated in data collection. KF and RL accessed and verified the data. DJS, KF, RL, ML, and MF interpreted the data and drafted the manuscript. All authors reviewed the manuscript, had access to study data, and accept responsibility for the decision to submit for publication.

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DJS reports personal fees from Seagen and Takeda during the conduct of the study; and personal fees from Seagen and Takeda outside the submitted work. MD-D reports personal fees from Takeda during the conduct of the study; and personal fees from Janssen, AbbVie, Roche, and Servier outside the submitted work. JMC reports grants from Takeda and personal fees from Seagen during the conduct of the study. EL-M reports advisory board membership with Amgen, AbbVie, Astellas, Roche, Novartis, Janssen-Cilag, Sanofi, and Gilead outside the submitted work. TF reports personal fees from Seagen, Bristol Myers Squibb, Celgene, Karyopharm, AbbVie, Daiichi, Pharmacyclics, Janssen, Kite Pharma, and Takeda outside the submitted work. PS reports personal fees from Takeda during the conduct of the study; and personal fees from Roche Poland outside the submitted work. KJS reports honoraria from and consulting with Seagen during the conduct of the study; honoraria, research funding, and consulting with Bristol Myers Squibb; honoraria and consulting with Merck; honoraria and consulting with AbbVie; honoraria and consulting with Gilead; honoraria and consulting with AstraZeneca; honoraria and consulting with Novartis; and steering committee membership for Beigene outside the submitted work. NLB reports research funding from ADC Therapeutics, Affimed, Autolus, Bristol Myers Squibb, Celgene, Forty Seven, Gilead, Immune Design, Janssen, Kite Pharma, Merck, Millennium, Pfizer, Pharmacyclics, Roche–Genentech, and Seagen; advisory board membership for Roche–Genentech, Seagen, BTG, ADC Therapeutics, and Acerta outside the submitted work. JW reports grants and personal fees from Seagen during the conduct of the study; grants and personal fees from GSK–Novartis and Roche, personal fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Gilead, Janssen-Cilag, Servier, and Takeda outside the submitted work. RR reports personal fees from Seagen during the conduct of the study; advisory board membership for and consultancy fees from Bristol Myers Squibb, and research funding from Merck outside the submitted work. PLZ reports personal fees from AbbVie, Gilead, Eusapharma, Merck, Roche, Takeda, Kyowa Kirin, Janssen, and TG Therapeutics outside the submitted work. MH reports research funding from Takeda during the conduct of the study. JM reports personal fees and research funding from Pharmacyclics, Bayer, Gilead-Kite Pharma, Janssen, and Seagen; personal fees from Pfizer, Juno-Celgene, Bristol Myers Squibb, Kyowa, Alexion, Beigene, Fosunkite, Innovent, Pharmacyclics-Janssen, Acrotech-Aurobindo, Verastem, AstraZeneca, Genentech-Roche, and AbbVie; and research funding from Celgene, Merck, Portola, Incyte, Genentech, Millenium outside of the submitted work. HJL reports research funding from Bristol Myers Squibb–Celgene, Takeda, Seagen, Janssen, Merck, Oncternal, and Onyx during the conduct of the study; advisory board membership for Kite and Bristol Myers Squibb; and honoraria from Aptitude Health, Pharmacyclics, Cancer Experts, and Guidepoint. WSK reports research funding from Roche, Johnson & Johnson, Takeda, Kyowa-Kirin, Donga, Celltrion, and Pfizer. RA reports grants from Merck, Millenium, and Seagen; personal fees from Merck, ADC Therapeutics, Takeda, Bristol Myers Squibb–Celgene, and Seagen during the conduct of the study; grants from Agensys, Celgene, Forty Seven–Gilead, Genentech–Roche, Infinity, Janssen Pharmaceutical, Kura, Pharmacyclics, Regeneron, and Cyteir Therapeutics; personal fees from Kura, Karyopharm, Takeda,

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Data sharing

De-identified patient-level trial data that underlie the results reported in this Article will be made available upon study completion (current estimate January, 2026) on a case-by-case basis to researchers who provide a methodologically sound proposal. Additional documentation might also be made available. Data availability will begin after approval of the qualified request and end 30 days after receipt of datasets. All data requests can be submitted via email to CTDR@seagen.com and will be reviewed by an internal review committee. The data sharing policy of this clinical study's sponsor, Seagen, requires all requests for clinical trial data to be reviewed to determine the qualification of the specific request. This policy is available online and is aligned with BIO's Principles on Clinical Trial Data Sharing.

For the **policy** see https://www.seagen.com/healthcare-professionals/clinical-data-requests

For more on **BIO's Principles on Clinical Trial Data Sharing** see https://www.bio.org/blogs/principles-clinical-trial-data-sharing-reaffirm-commitment

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