Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial

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Summary

Background Based on the encouraging activity and manageable safety profile observed in a phase 1 study, the ECHELON-2 trial was initiated to compare the efficacy and safety of brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30-positive peripheral T-cell lymphomas.

Methods ECHELON-2 is a double-blind, double-dummy, randomised, placebo-controlled, active-comparator phase 3 study. Eligible adults from 132 sites in 17 countries with previously untreated CD30-positive peripheral T-cell lymphomas (targeting 75% with systemic anaplastic large cell lymphoma) were randomly assigned 1:1 to receive either A+CHP or CHOP for six or eight 21-day cycles. Randomisation was stratified by histological subtype according to local pathology assessment and by international prognostic index score. All patients received cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² on day 1 of each cycle intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally, followed by either brentuximab vedotin 1·8 mg/kg and a placebo form of vincristine intravenously (A+CHP group) or vincristine 1·4 mg/m² and a placebo form of brentuximab vedotin intravenously (CHOP group) on day 1 of each cycle. The primary endpoint, progression-free survival according to blinded independent central review, was analysed by intent-to-treat. This trial is registered with ClinicalTrials.gov, number NCT01777152.

Findings Between Jan 24, 2013, and Nov 7, 2016, 601 patients assessed for eligibility, of whom 452 patients were enrolled and 226 were randomly assigned to both the A+CHP group and the CHOP group. Median progression-free survival was 48·2 months (95% CI 35·2–not evaluable) in the A+CHP group and 20·8 months (12·7–47·6) in the CHOP group (hazard ratio 0·71 [95% CI 0·54–0·93], p=0·0110). Adverse events, including incidence and severity of febrile neutropenia (41 [18%] patients in the A+CHP group and 33 [15%] in the CHOP group) and peripheral neuropathy (117 [52%] in the A+CHP group and 124 [55%] in the CHOP group), were similar between groups. Fatal adverse events occurred in seven (3%) patients in the A+CHP group and nine (4%) in the CHOP group.

Interpretation Front-line treatment with A+CHP is superior to CHOP for patients with CD30-positive peripheral T-cell lymphomas as shown by a significant improvement in progression-free survival and overall survival with a manageable safety profile.

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Introduction

Peripheral T-cell lymphoma is a heterogeneous group of aggressive non-Hodgkin lymphoma, accounting for approximately 10% of all non-Hodgkin lymphoma cases in the USA and Europe and as high as 24% in parts of Asia.[1] The most common peripheral T-cell lymphomas are the so-called nodal peripheral T-cell lymphomas, which include peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase (ALK)-positive or ALK-negative systemic anaplastic large cell lymphoma. These subtypes are usually treated similarly with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens.[2,3] However, anthracycline-containing regimens result in low complete remission (CR) rates and poor progression-free survival and overall survival.[4–6] Even with the more favourable ALK-positive systemic anaplastic

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*Authors on the steering committee contributed equally to the oversight of the study, including study design and maintaining the quality of study conduct

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Research in context

Evidence before this study

Peripheral T-cell lymphoma is a heterogeneous group of rare, aggressive lymphoproliferative disorders that represent approximately 10–15% of non-Hodgkin lymphoma cases worldwide.

Clinical outcomes for patients with previously untreated peripheral T-cell lymphoma depend upon histological subtype but are typically poor. Most subtypes of peripheral T-cell lymphoma are treated similarly with combination chemotherapy, most commonly cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisone (P; CHOP) or CHOP-like regimens.

Several of the peripheral T-cell lymphoma subtypes express CD30, most notably systemic anaplastic large cell lymphoma, for which CD30 expression is a hallmark of the diagnosis. Brentuximab vedotin is an antibody–drug conjugate with shown efficacy in the treatment of relapsed or refractory systemic anaplastic large cell lymphoma. Additionally, combination treatment of brentuximab vedotin with CHP (A+CHP) in a phase 1 trial showed encouraging activity and a manageable safety profile. Given the results of brentuximab vedotin monotherapy in the relapsed and refractory systemic anaplastic large cell lymphoma setting, and its tolerability when combined with CHP, the ECHELON-2 trial was designed to assess the efficacy and safety of A+CHP versus CHOP in patients with previously untreated CD30-positive peripheral T-cell lymphoma.

We searched the scientific literature to identify reports of patients with peripheral T-cell lymphoma given brentuximab vedotin or CHOP chemotherapy. We searched PubMed from June 1, 2012, to Oct 01, 2018, using the terms ("ADCETRIS" or "Brentuximab vedotin" or "BV") AND ("CHOP" OR "CHP") AND ("PTCL" or "MTCL") and identified no other clinical trials of brentuximab vedotin in combination with CHP. Additionally, no reports had been published from randomised, prospective, phase 3 clinical trials establishing the superiority of any regimen over CHOP in untreated patients with peripheral T-cell lymphoma.

Added value of this study

Previous trials that have attempted to improve upon CHOP have shown either no or only modest improvements in response rates or progression-free survival, often with high rates of toxicity. To our knowledge, this trial is the first randomised, double-blind study of a targeted drug combination treatment against standard therapy for this indication and is the first reported prospective phase 3 trial in previously untreated patients with peripheral T-cell lymphoma to show an overall survival benefit over CHOP chemotherapy. Our results show that A+CHP improved progression-free survival and overall survival compared with CHOP alone in patients with CD30-positive peripheral T-cell lymphoma. Importantly, these improvements in survival came without an apparent increase in toxicity.

Implications of all the available evidence

We consider these results to be potentially practice-changing and approval was granted in November, 2018, by the US Food and Drug Administration. Regulatory approval is being sought from additional health authorities worldwide for the use of A+CHP in the treatment of patients with previously untreated CD30-positive peripheral T-cell lymphoma.

large cell lymphoma, 5-year overall survival is less than 50% for older patients (>40 years) and those with adverse prognostic factors (International Prognostic Index [IPI] ≥2).[7] Despite intensified approaches in front-line therapy, such as the addition of etoposide to CHOP and consolidation with stem cell transplantation, patients are still at considerable risk of disease relapse or early progression,[8,9] underscoring the high unmet need in these patients. Moreover, few randomised studies that guide therapy in peripheral T-cell lymphoma are available (and they are underpowered and do not give clear conclusions), with management approaches primarily derived from phase 2 studies, retrospective series, and clinical experience.[4,7,8,10–12]

CD30 is universally expressed and is pathognomonic in systemic anaplastic large cell lymphoma. Among non-systemic anaplastic large cell lymphoma subtypes CD30 expression is variable, with estimates from approximately 58–64% in peripheral T-cell lymphoma not otherwise specified, 43–63% in angioimmunoblastic T-cell lymphoma, 55% in adult T-cell leukaemia or lymphoma, and 0–100% in enteropathy-associated T-cell lymphoma.[13,14] Brentuximab vedotin is an antibody–drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting drug monomethyl auristatin E. It has been approved for several indications, including the treatment of adults with systemic anaplastic large cell lymphoma and previously untreated CD30-expressing peripheral T-cell lymphoma (US Food and Drug Administration).[15] Based on the encouraging activity and manageable safety profile observed in a phase 1 trial[16] combining brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone (CHP [CHOP without vincristine] to eliminate the risk of overlapping neurotoxicity that could be worsened by delivering two microtubule-disrupting drugs), the double-blinded phase 3 ECHELON-2 trial was initiated to compare the efficacy and safety of brentuximab vedotin in combination with CHP (A+CHP) with standard CHOP for the treatment of previously untreated patients with CD30-positive peripheral T-cell lymphoma.

Methods

Study design and participants

ECHELON-2 is a double-blind, double-dummy, randomised, placebo-controlled, active-comparator phase 3 study done at 132 sites (including four satellite sites) in 17 countries across North America, Europe, Asia Pacific, and the Middle East (appendix). Eligible patients were aged 18 years or older and had previously untreated, CD30-positive (≥10% of cells by local review; appendix) peripheral T-cell lymphoma according to the WHO 2008 classification system[17] by local assessment. Eligible histologies were limited to ALK-positive systemic anaplastic large cell lymphoma with an IPI score of 2 or higher, ALK-negative systemic anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, adult T-cell leukaemia or lymphoma, enteropathy associated T-cell lymphoma, and hepatosplenic T-cell lymphoma. Histologies were assessed by a central pathology laboratory after enrolment. Key exclusion criteria were previous history of another primary invasive cancer or haematological malignancy and previous treatment with brentuximab vedotin. Full eligibility criteria are provided in the appendix.

The trial 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. Additional trial design details are provided in the protocol.

Randomisation and masking

Patients were randomly assigned (1:1) to the A+CHP or CHOP group. Randomisation was done centrally with an interactive web response system (IWRS) that assigned a unique patient randomisation number and did not specify the actual treatment assignment. Randomisation numbers and their corresponding treatment assignments were allocated to patients according to the randomisation list by sequential ascending block number and by sequential ascending randomisation numbers within the appropriate strata. The randomisation list was generated by the IWRS vendor, Bracket (San Francisco, CA, USA). Brentuximab vedotin and vincristine were dispensed in a double-blinded, double-dummy manner. Brentuximab vedotin, vincristine, and their placebo replacements were prepared by the pharmacist at each study site, and a pharmacy mask was enforced. The investigators, patients, Blinded Independent Central Review (BICR), and the sponsor were masked to treatment assignments. Randomisation was stratified by histological subtype according to local pathology assessment (ALK-positive systemic anaplastic large cell lymphoma *vs* all other histologies) and baseline IPI score (0–1 *vs* 2–3 *vs* 4–5).

Procedures

Patients received 21-day cycles of either A+CHP or CHOP. The number of cycles (six or eight) was decided at the investigator's discretion at registration. All patients received the CHP components of the CHOP regimen (cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² intravenously on day 1 of each cycle and prednisone 100 mg once daily orally on days 1 to 5 of each cycle). The study used a double-dummy design with brentuximab vedotin and a placebo form of vincristine (A+CHP group; brentuximab vedotin 1·8 mg/kg intravenously on day 1 of each cycle) or vincristine and a placebo form of brentuximab vedotin (CHOP group; vincristine 1·4 mg/m² [maximum 2·0 mg] intravenously on day 1 of each cycle) given after CHP to patients in a double-blind, active-controlled manner. Consolidative stem cell transplantation or radiotherapy after treatment was permitted at the investigator's discretion (stem cell transplantation intent was prespecified before the first cycle of chemotherapy). Details regarding concomitant therapy and permitted dose modifications are provided in the appendix.

Outcomes

The primary endpoint was progression-free survival according to BICR, defined as the time from the date of randomisation to the date of first documentation of relapse or progressive disease,[18] death due to any cause, or receipt of subsequent systemic chemotherapy to treat residual or progressive peripheral T-cell lymphoma as determined by the investigator, whichever came first. The receipt of subsequent systemic chemotherapy was considered an event because it represents a failure of front-line treatment to achieve a cure. In the absence of progressive disease, receipt of radiotherapy to consolidate response to initial treatment, chemotherapy for the purpose of mobilising haemopoietic stem cells, or consolidative autologous or allogeneic stem cell transplantation were not considered events. The key α-controlled secondary endpoints were progression-free survival according to BICR for patients with centrally confirmed systemic anaplastic large cell lymphoma, CR rate according to BICR after completion of study treatment, overall survival, and proportion of patients who achieved an objective response according to BICR. Other secondary and exploratory endpoints are described in the protocol.

Lymphoma response and progression were assessed with the 2007 Revised Response Criteria for Malignant Lymphoma.[18] Radiographical disease evaluations were submitted to BICR imaging facility for masked review. CT and PET scans were done at screening, after cycle 4 and at the end of treatment. In long-term follow-up, CT scans were required at 9, 12, 15, 18, 21, and 24 months after initiation of study treatment, and every 6 months thereafter until the patients had disease progression, death, or analysis of the primary endpoint, whichever came first. Patients were followed for survival. Safety outcomes included the surveillance for and recording of

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See Online for appendix

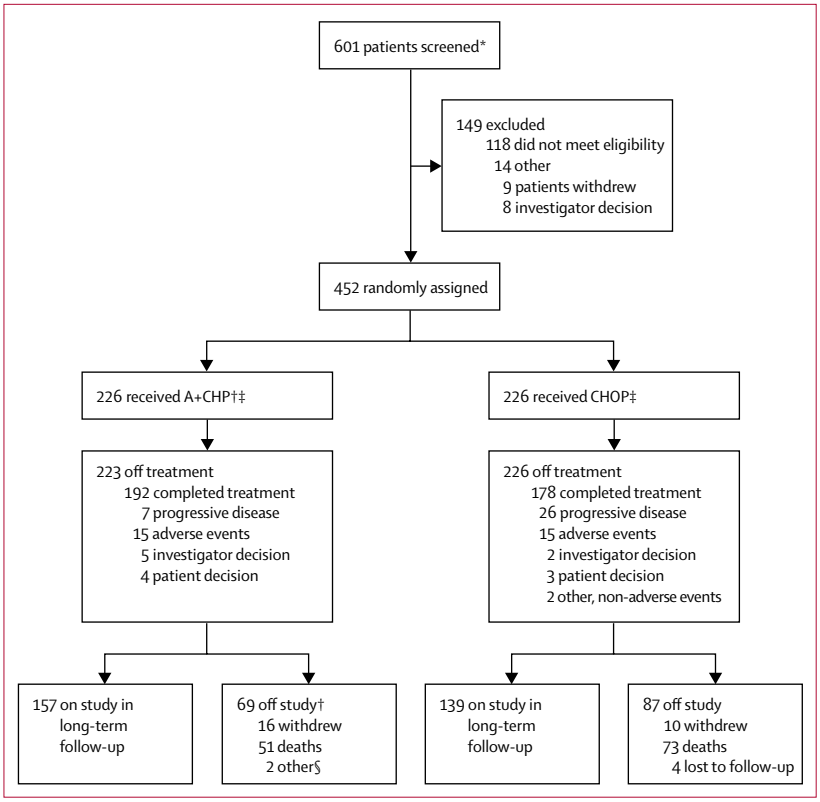


Figure 1: **Trial profile**
A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. *Screening informed consents were obtained for seven patients to allow sites to do screening activities that were not considered standard of care at their sites. The remaining 594 patients signed the full informed consent for the study. †Includes three patients who were randomly assigned to the A+CHP group but did not receive study treatment. ‡A total of 89 patients in the A+CHP group and 81 patients in the CHOP group were prespecified by the investigator at baseline to receive consolidative stem cell transplantation. §Other reasons for study discontinuation were change in diagnosis for one patient and one patient who was ineligible after randomisation, who did not receive any study treatment.

adverse events (defined according to the Medical Dictionary for Regulatory Activities [MedDRA], version 21.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03). Additional long-term follow-up and safety assessments are described in the protocol.

Statistical analysis

The trial was powered on the assumption of median progression-free survival of 23·9 months for the A+CHP group and 16·5 months for the CHOP group. An estimated 238 progression-free survival events would give the trial approximately 80% power to detect a hazard ratio (HR) for disease progression or death due to any cause of 0·6895 at a one-sided significance level of 0·025. We planned for enrolment of 450 patients, targeting 75% (±5%) of patients with a diagnosis of systemic anaplastic large cell lymphoma according to central pathology assessment to ensure the secondary endpoint of progression-free survival in systemic anaplastic large cell lymphoma could be appropriately assessed. Important changes to the targeted enrolment and primary analysis timing are described in the appendix.

We did formal statistical tests for progression-free survival according to BICR and for the key α-controlled secondary endpoints. After the significant test of the primary analysis of progression-free survival in favour of the A+CHP group, we did a fixed sequence testing procedure to ensure type 1 error control for the key secondary endpoints at an unadjusted α level until the preceding null hypothesis was not rejected. We carried out all testing in the order of progression-free survival according to BICR for patients with centrally confirmed systemic anaplastic large cell lymphoma, CR rate according to BICR, overall survival, and proportion of patients who achieved an objective response according to BICR. We did all statistical tests using a two-sided α of 0·05. We calculated confidence intervals at a two-sided 95% level. Results favouring the treatment group with $p<0·05$ are significant at the one-sided 0·025 level.

For the primary efficacy analysis, we used the stratified log-rank test (by the randomisation stratification factors) to compare the difference in progression-free survival between the treatment groups. We based the estimation of the HR upon the stratified Cox regression model. We also summarised progression-free survival using the Kaplan-Meier method. Similar methods were used for the key secondary efficacy endpoints of progression-free survival in patients with systemic anaplastic large cell lymphoma and overall survival. We calculated the progression-free survival and overall survival median follow-up using the reverse Kaplan-Meier method.[19] We tested the proportion of patients who achieved an objective response and CR rate between the A+CHP group and the CHOP group using the Cochran-Mantel-Haenszel test, stratified by the randomisation stratification factors.

An Independent Data Monitoring Committee monitored safety and assessed the results of an interim analysis for futility (appendix). We did all efficacy evaluations in the intention-to-treat (ITT) population, unless otherwise specified. We analysed safety in patients who received any amount of brentuximab vedotin or any component of CHOP (the safety population). Analyses were done with SAS version 9.4.

This study was registered with ClinicalTrials.gov, number NCT01777152.

Role of the funding source

The funders and ECHELON-2 steering committee members jointly designed the trial. The investigators and funders collected and interpreted the data, and the funders analysed the data. Medical writing assistance was funded by Seattle Genetics and was provided by Seattle Genetics and MMS Holdings. All authors had access to the data, contributed to the manuscript

development, approved the manuscript for submission, and vouch for its integrity. The corresponding author (SH) had final authority over the manuscript and the decision to submit for publication.

Results

Patients were enrolled between Jan 24, 2013, and Nov 7, 2016. The data cutoff date for this primary analysis was Aug 15, 2018. Of 601 patients assessed for eligibility, a total of 452 patients across 17 countries were recruited and randomly assigned to the A+CHP group (n=226) or the CHOP group (n=226; figure 1). Baseline characteristics were generally balanced between the two treatment groups (table 1; appendix). Overall, the median age was 58 years (IQR 45–67). The study enrolled patients with advanced disease (stage 3, 124 [27%] and stage 4, 240 [53%]; IPI ≥2, 351 [78%]) and 316 (70%) patients had systemic anaplastic large cell lymphoma (218 [48%] ALK-negative and 98 [22%] ALK-positive). Consolidative stem cell transplantation was delivered in 50 (22%) patients in the A+CHP group and 39 (17%) in the CHOP after the end of treatment at the discretion of the investigator (appendix).

The data cutoff for the primary analysis was done after a total of 219 progression-free survival events had occurred (appendix). The progression-free survival HR was 0·71 ([95% CI 0·54–0·93]; p=0·0110), equating to a 29% reduction in the risk of a progression-free survival event for the A+CHP group versus the CHOP group (figure 2A). After a median follow-up of 36·2 months (95% CI 35·9–41·8), the median progression-free survival in the A+CHP group was longer than that of the CHOP group (48·2 months [35·2–not evaluable] *vs* 20·8 months [12·7–47·6]). The 3-year progression-free survival was 57·1% (49·9–63·7) for the A+CHP group compared with 44·4% (37·6–50·9) for the CHOP group (appendix).

Prespecified analyses of progression-free survival were similar to the primary analysis of progression-free survival: investigator-assessed progression-free survival (HR 0·70 [95% CI 0·53–0·92]; appendix), BICR-assessed progression-free survival, for which events were limited to progression and death (0·75 [0·56–1·00]; appendix), and BICR-assessed progression-free survival, for which consolidative stem cell transplantation or consolidative radiotherapy were censored (0·71 [0·53–0·94]).

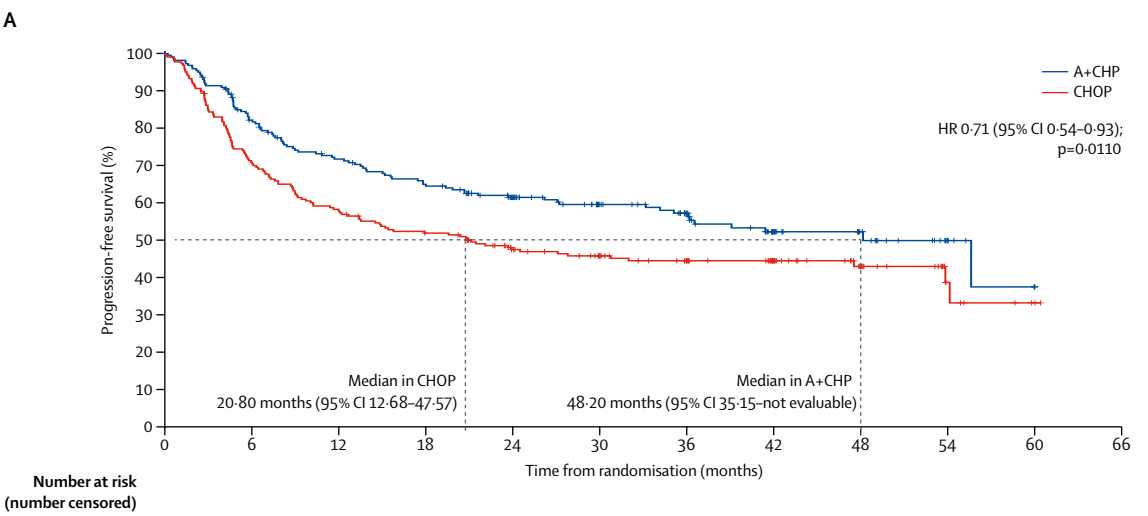
The progression-free survival analyses for important subgroups were generally consistent with the overall study results. Among the different histological subtypes, ALK-positive systemic anaplastic large cell lymphoma had the lowest HR, ALK-negative systemic anaplastic large cell lymphoma, and peripheral T-cell lymphoma not otherwise specified were similar to the ITT population, and the angioimmunoblastic T-cell lymphoma HR for progression-free survival was above unity. Importantly, this study was not powered to compare efficacy between individual histological subtypes (figure 2B).

	A+CHP group (n=226)	CHOP group (n=226)
Sex		
Men	133 (59%)	151 (67%)
Women	93 (41%)	75 (33%)
Median age, years (IQR)	58·0 (45–67)	58·0 (44–67)
Race		
Asian	45 (20%)	54 (24%)
Black or African American	12 (5%)	6 (3%)
White	139 (62%)	142 (63%)
Native Hawaiian or other Pacific Islander	1 (0%)	0
Other or unknown	29 (13%)	24 (11%)
ECOG performance†		
0	84 (37%)	93 (41%)
1	90 (40%)	86 (38%)
2	51 (23%)	47 (21%)
Diagnosis‡		
sALCL	162 (72%)	154 (68%)
ALK positive	49 (22%)	49 (22%)
ALK negative	113 (50%)	105 (46%)
PTCL-NOS	29 (13%)	43 (19%)
AITL	30 (13%)	24 (11%)
ATLL	4 (2%)	3 (1%)
EATL	1 (0%)	2 (1%)
Disease stage at diagnosis§		
1	12 (5%)	9 (4%)
2	30 (13%)	37 (16%)
3	57 (25%)	67 (30%)
4	127 (56%)	113 (50%)
Baseline IPI score¶		
0	8 (4%)	16 (7%)
1	45 (20%)	32 (14%)
2	74 (33%)	78 (35%)
3	66 (29%)	66 (29%)
4	29 (13%)	25 (11%)
5	4 (2%)	9 (4%)

Data are n (%), unless stated otherwise. Data shown are for the intention-to-treat population. A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. AITL=angioimmunoblastic T-cell lymphoma. ALK=anaplastic lymphoma kinase. ATLL=adult T-cell leukaemia or lymphoma. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. EATL=enteropathy-associated T-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. IPI=international prognostic index. PTCL-NOS=peripheral T-cell lymphoma not otherwise specified. sALCL=systemic anaplastic large cell lymphoma. *A full description of baseline characteristics can be found in the appendix. †Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability. ‡Diagnosis per local assessment. §The Ann Arbor staging system ranges from 1 to 4, with higher stages indicating more widespread disease. ¶The IPI score is calculated based on a patient's disease characteristics and represents increasing degrees of risk.

Table 1: **Baseline patients' demographic and disease characteristics***

Treatment with A+CHP reduced the risk of death by 34% compared with CHOP (HR 0·66 [95% CI 0·46–0·95], p=0·0244; figure 3A; appendix). As of the data cutoff date, 124 deaths occurred: 51 (23%) deaths in



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	Event/N		HR (95% CI)
	A+CHP	CHOP	
Overall	95/226	124/226	0·71 (0·54–0·93)
IPI Score			
0–1	18/52	27/48	0·53 (0·29–0·97)
2–3	56/141	77/145	0·71 (0·50–1·00
4–5	21/33	20/33	1·03 (0·55–1·92)
Age			
<65 years	54/157	75/156	0·67 (0·47–0·95)
≥65 years	41/69	49/70	0·70 (0·46–1·08)
Sex			
Male	59/133	80/151	0·80 (0·57–1·13)
Female	36/93	44/75	0·49 (0·31–0·78)
Baseline ECOG status			
0–1	76/174	105/179	0·66 (0·49–0·89)
2	19/51	19/47	0·98 (0·51–1·87)
Disease stage			
1–2	15/42	19/46	0·95 (0·48–1·88)
3	29/57	35/67	0·69 (0·42–1·14)
4	51/127	70/113	0·64 (0·45–0·93)
Disease indication			
ALK-positive sALCL	5/49	16/49	0·29 (0·11–0·79)
ALK-negative sALCL	50/113	60/105	0·65 (0·44–0·95)
AITL	18/30	13/24	1·40 (0·64–3·07)
PTCL-NOS	19/29	31/43	0·75 (0·41–1·37)

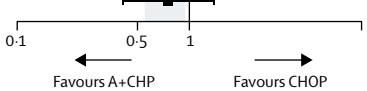

Figure 2: **Progression-free survival according to Blinded Independent Central Review in ITT population**
(A) The HR for treatment with A+CHP *vs* CHOP and the 95% CIs were computed from a log-rank test using stratification factors (ALK-positive sALCL: yes or no and IPI scores of 0–1, 2–3, 4–5) at randomisation. (B) Progression-free survival according to the Blinded Independent Central Review in key prespecified subgroups. The HR for treatment with A+CHP *vs* CHOP and the 95% CIs were based on the Cox regression model considering stratification factors at randomisation. The IPI subgroup was changed after randomisation in one patient in the A+CHP group (from 0–1 to 2–3) and one patient in the CHOP group (from 4–5 to 2–3). A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. AITL=angioimmunoblastic T-cell lymphoma. ALK=anaplastic lymphoma kinase. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. IPI=international prognostic index. ITT=intention-to-treat. PTCL-NOS=peripheral T-cell lymphomanot otherwise specified. sALCL=systemic anaplastic large cell lymphoma.

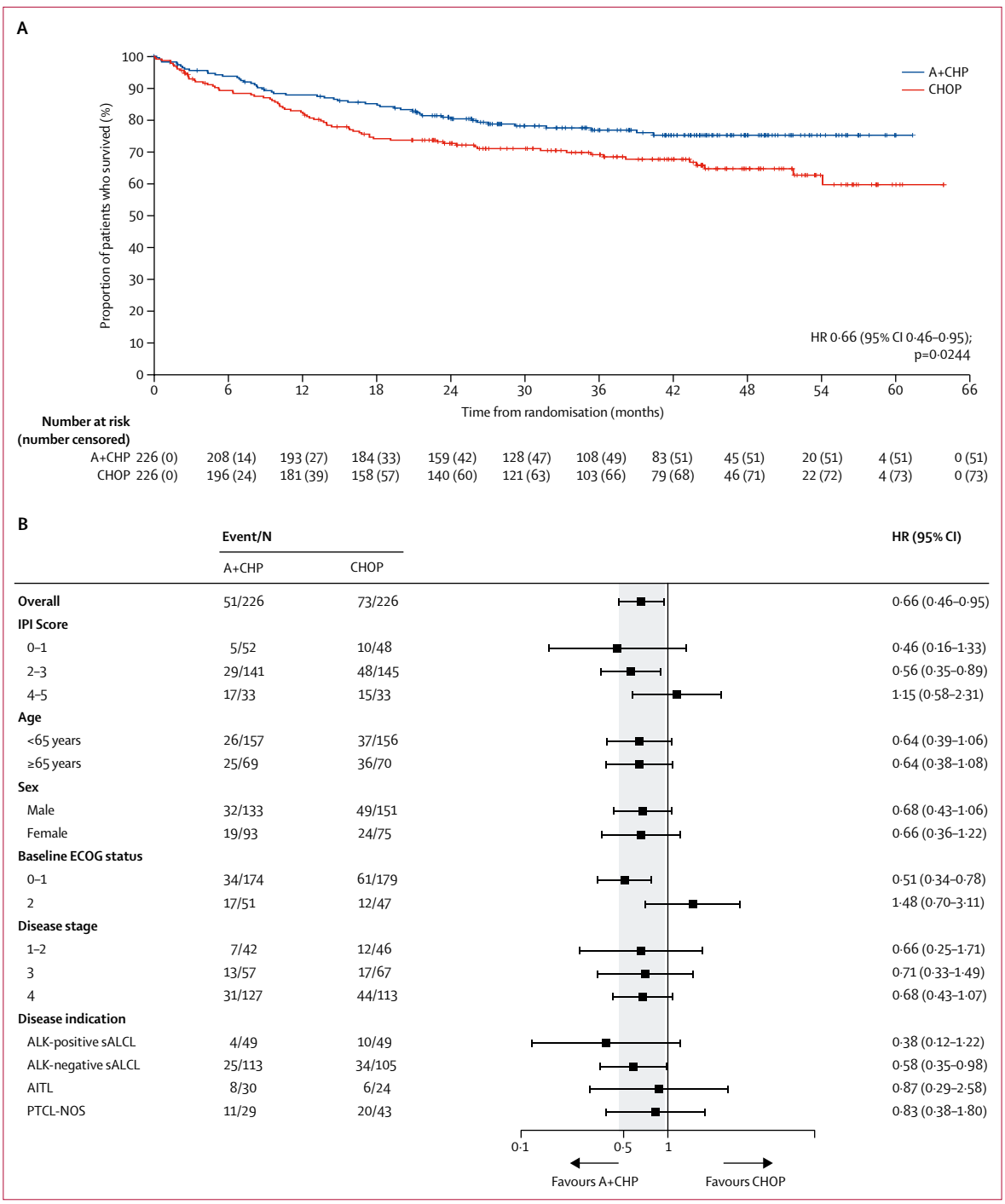

Figure 3: **Overall survival for the ITT population**

(A) The HR for treatment with A+CHP *vs* CHOP and the 95% CIs were computed from log-rank test using stratification factors (ALK-positive sALCL: yes or no and IPI score: 0–1, 2–3, 4–5) at randomisation. (B) Overall survival in key prespecified subgroups. The HR for treatment with A+CHP *vs* CHOP and the 95% CIs were based on the Cox regression model considering stratification factors at randomisation. The IPI subgroup was changed after randomisation in one patient in the A+CHP group (from 0–1 to 2–3) and one patient in the CHOP group (from 4–5 to 2–3). A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. AITL=angioimmunoblastic T-cell lymphoma. ALK=anaplastic lymphoma kinase. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. IPI=international prognostic index. ITT=intention-to-treat. PTCL-NOS=peripheral T-cell lymphomanot otherwise specified. sALCL=systemic anaplastic large cell lymphoma.

	A+CHP group (n=226)	CHOP group (n=226)	Response rate difference (95% CI), p value
Proportion of patients who achieved an objective response [95% CI]	188 (83% [77·7–87·8])	163 (72% [65·8–77·9])	11·1 (3·4–18·7), 0·0032
Complete remission rate	153 (68% [61·2–73·7])	126 (56% [49·0–62·3])	11·9 (3·1–20·8), 0·0066
Response*			
Complete remission	153 (68%)	126 (56%)	..
Partial remission	35 (15%)	37 (16%)	..
Stable disease	5 (2%)	11 (5%)	..
Progressive disease	15 (7%)	31 (14%)	..
Not evaluable†	18 (8%)	21 (9%)	..

Data are n (%), unless otherwise specified. Data shown are for the intention-to-treat population. A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. *Best response at end of treatment was assessed in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007).[18] Complete remission, partial remission, stable disease, progressive disease, and not evaluable are mutually exclusive. †Patients with no post-baseline response assessments were not evaluable.

Table 2: **Summary of response at end of treatment according to the Blinded Independent Central Review**

	A+CHP group (n=223)	CHOP group (n=226)
Any adverse events	221 (99%)	221 (98%)
Grade ≥3 adverse events	147 (66%)	146 (65%)
Serious adverse events	87 (39%)	87 (38%)
Discontinued treatment due to adverse events	14 (6%)	15 (7%)
Death due to adverse events	7 (3%)	9 (4%)

Data are n (%). A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. *Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of A+CHP and CHOP.

Table 3: **Summary of adverse events***

	A+CHP group (n=223)		CHOP group (n=226)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	103 (46%)	5 (2%)	87 (38%)	4 (2%)
Peripheral sensory neuropathy	100 (45%)	8 (4%)	92 (41%)	6 (3%)
Neutropenia	85 (38%)	77 (35%)	85 (38%)	76 (34%)
Diarrhoea	85 (38%)	13 (6%)	46 (20%)	2 (1%)
Constipation	64 (29%)	2 (1%)	67 (30%)	3 (1%)
Alopecia	58 (26%)	0	56 (25%)	3 (1%)
Pyrexia	58 (26%)	4 (2%)	42 (19%)	0
Vomiting	57 (26%)	2 (1%)	39 (17%)	4 (2%)
Fatigue	54 (24%)	2 (1%)	46 (20%)	4 (2%)
Anaemia	46 (21%)	30 (13%)	36 (16%)	23 (10%)

Data are n (%). Common adverse events are shown for those occurring in ≥20% of patients in the safety population. A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. *Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of A+CHP and CHOP.

Table 4: **Summary of common adverse events**

the A+CHP group and 73 (32%) deaths in the CHOP group. After a median follow-up of 42·1 months (95% CI 40·4–43·8), the median overall survival was not reached for either group. Furthermore, the 75th percentile overall survival was not reached for the A+CHP group but was 17·5 months for the CHOP group. Overall survival was numerically in favour of A+CHP for key subgroups, including both non-systemic anaplastic large cell lymphoma histological subtypes, peripheral T-cell lymphoma not otherwise specified, and angioimmunoblastic T-cell lymphoma (figure 3B). The confidence intervals for all histological subtypes and the ITT population overlapped (figure 3B).

Analysis of progression-free survival according to BICR for the subset of patients with centrally confirmed systemic anaplastic large cell lymphoma was consistent with the results of the primary analysis. Risk of progression-free survival events according to BICR reduced by 41% for the subset of patients with systemic anaplastic large cell lymphoma in the A+CHP group compared with the CHOP group (HR 0·59 [95% CI 0·42–0·84], p=0·0031). The CR rate and proportion of patients who achieved an objective response were significantly higher in the A+CHP group than in the CHOP group (CR rate, p=0·0066; objective response, p=0·0032; table 2). Similar results were obtained when the CR rate and proportion of patients who achieved an objective response were assessed by the investigators (CR rate, p=0·0043; objective response, p=0·0018).

Excluding stem cell transplantation or radiotherapy for consolidation of response to initial therapy, 59 (26%) patients in the A+CHP group and 94 (42%) patients in the CHOP group received subsequent anticancer therapies for residual or progressive disease (appendix); 23 (10%) in the A+CHP group and 49 (22%) in the CHOP group received brentuximab vedotin-containing subsequent therapy.

Most patients completed treatment as intended, with 198 (89%) patients in the A+CHP group and 184 (81%) patients in the CHOP group receiving six or more cycles (appendix). The proportion of patients receiving more than six cycles of treatment was 19% in both the A+CHP (n=42) and CHOP groups (n=44; appendix). The median relative dose intensity was 99·2% (IQR 93·6–100·0) for brentuximab vedotin in the A+CHP group and 99·1% (IQR 95·9–102·3) for vincristine in the CHOP group.

The incidence and severity of treatment-emergent adverse events were similar between groups (table 3; table 4). A higher incidence of diarrhoea (any grade)

was reported in the A+CHP group (85 [38%] patients) than in the CHOP group (46 [20%]). Most (49 [58%] of 85) cases of diarrhoea in the A+CHP group were grade 1; the remaining cases were grade 2 (23 [27%]) and grade 3 (13[15%]). Other treatment-emergent adverse events of any grade reported in 20% or more of patients in the A+CHP group (*vs* the CHOP group) were nausea (103 [46%] *vs* 87 [38%]), peripheral sensory neuropathy (100 [45%] *vs* 92 [41%]), neutropenia (85 [38%] in both), constipation (64 [29%] *vs* 67 [30%]), alopecia (58 [26%] *vs* 56 [25%]), pyrexia (58 [26%] *vs* 42 [19%]), vomiting (57 [26%] *vs* 39 [17%]), fatigue (54 [24%] *vs* 46 [20%]), and anaemia (46 [21%] *vs* 36 [16%]; table 4). Grade 3 or higher events were generally similar between groups. Treatment discontinuations due to adverse events occurred in 14 (6%) patients in the A+CHP group and 15 (7%) patients in the CHOP group. Adverse events leading to death occurred in seven (3%) patients in the A+CHP group and nine (4%) patients in the CHOP group; causes of deaths are summarised in the appendix.

The incidence and severity of neutropenia were similar between groups and were lower in the subset of patients receiving primary prophylaxis with granulocyte-colony stimulating factor (appendix). Febrile neutropenia was reported in 41 (18%) patients in the A+CHP group versus 33 (15%) patients in the CHOP group, including one grade 5 event in the CHOP group. Grade 3 or worse infections occurred in 42 (19%) patients in the A+CHP group and 31 (14%) patients in the CHOP group.

Peripheral neuropathy events were identified on the basis of a standardised MedDRA query and are summarised by event in the appendix. Treatment-emergent peripheral neuropathy events occurred in 117 (52%) patients in the A+CHP group and 124 (55%) patients in the CHOP group; most had a maximum severity of grade 1 (75 [64%] of 117 in the A+CHP group and 88 [71%] of 124 in the CHOP group). Peripheral neuropathy events returned to baseline or lower in 58 (50%) patients in the A+CHP group, with a median time to resolution of 17·0 weeks, and in 79 (64%) patients in the CHOP group, with a median time to resolution of 11·4 weeks (appendix). Of the patients with ongoing events at last follow-up, most were grade 1 (44 [72%] of 61 patients in the A+CHP group and 32 [71%] of 45 patients in the CHOP group). Two patients in the A+CHP group and one patient in the CHOP group had ongoing grade 3 peripheral neuropathy events.

Discussion

ECHELON-2 is the first prospective trial in peripheral T-cell lymphoma to show an overall survival benefit over an established standard therapy, CHOP. In this double-blind, double-dummy, randomised, placebo-controlled, active-comparator phase 3 study, enrolling 452 patients with previously untreated CD30-positive peripheral T-cell lymphoma, A+CHP showed superior progression-free survival and significantly longer overall survival than CHOP. Treatment with A+CHP led to a 29% reduction in the risk of a progression-free survival event and a 34% lower risk of death, with a 77% probability of survival at 36 months. Importantly, these improvements in survival came without an observed increase in toxicity. A+CHP was well tolerated, with a manageable safety profile compared with CHOP, although the median time to resolution of peripheral neuropathy was longer with A+CHP (17·0 weeks) than with CHOP and (11·4 weeks). The rates of neutropenia, febrile neutropenia, and neuropathy were similar between the two groups.

For decades, CHOP has remained the most commonly used front-line regimen for previously untreated patients with peripheral T-cell lymphoma.[4,20,21] With the exception of low IPI score (<2) ALK-positive systemic anaplastic large cell lymphoma, peripheral T-cell lymphomas are aggressive neoplasms with poor prognosis. Attempts to improve upon CHOP, primarily in single-arm or phase 2 studies, have been largely unsuccessful. Single drugs, such as alemtuzumab, pralatrexate, and denileukin diftitox, have been added to CHOP or to a CHOP-like backbone without any clear benefit and often excess toxicity.[22–24] Romidepsin plus CHOP has been assessed in a phase 1b–2 trial,[25] but with a higher rate of toxicity than would be anticipated with CHOP alone. A phase 3 randomised trial comparing this regimen to CHOP is ongoing. Similarly, alternate or more intensive combination chemotherapy regimens have failed to show superiority over CHOP alone.[5,26,27]

The main front-line therapy thought to offer a potential benefit over CHOP is CHOP plus etoposide (CHOEP).[9,20] This assessment is based on a retrospective subset analysis of completed prospective studies, which found a 3-year event-free survival advantage with CHOEP (75·4%) versus CHOP (51·0%) for a subset of younger (≤60 years), more favourable patients with the greatest benefit seen in patients with ALK-positive systemic anaplastic large cell lymphoma. However, CHOEP provided no improvement in overall survival and older patients had greater toxicity, with more pronounced rates of grades 3–4 leucocytopenia, thrombocytopenia, and anaemia than with CHOP.[20,28] To date, the superiority of CHOEP remains untested in a prospective randomised trial.

As detailed above, previous attempts to improve upon CHOP have generally followed a one-size-fits-all approach, applying non-targeted therapy to heterogeneous peripheral T-cell lymphoma subtypes. ECHELON-2 capitalises on the documented single-drug activity of brentuximab vedotin in CD30-positive relapsed or refractory systemic anaplastic large cell lymphoma[29,30] and other CD30-positive peripheral T-cell lymphoma subtypes, to improve efficacy in a patient population most

likely to benefit. To ensure the key secondary endpoint of progression-free survival in the systemic anaplastic large cell lymphoma subtype could be appropriately assessed, the trial was designed to enrol a target of 75% (±5%) patients with systemic anaplastic large cell lymphoma. As such, most (70%) of the ITT population was made up of patients with systemic anaplastic large cell lymphoma. A limitation of this study was that it was not powered to compare efficacy between individual histological subtypes and small subgroup sizes preclude definitive determination of the treatment effect in the non-systemic anaplastic large cell lymphoma population. In patients with peripheral T-cell lymphoma not otherwise specified, the HRs for progression-free survival and overall survival were both less than 1, while angioimmunoblastic T-cell lymphoma showed wide confidence intervals and the HR for progression-free survival was 1·4 and for overall survival was 0·87. A future study with a larger number of patients with angioimmunoblastic T-cell lymphoma or non-systemic anaplastic large cell lymphoma could increase the precision by which benefits can be assessed. Nevertheless, the progression-free survival and overall survival benefits for the study, most clearly shown with systemic anaplastic large cell lymphoma, are generally consistent across all evaluable histological subtypes with overlapping confidence intervals.

In addition to superior survival, this trial represents an elevation in the quality of data for studies in peripheral T-cell lymphoma. Our knowledge of the expected outcomes for patients with peripheral T-cell lymphoma is largely based on single-arm phase 2 studies or retrospective analyses.[4,6,8,20,28,31] In the prospective, randomised ECHELON-2 trial, the CHOP group did better than the historical controls with a median progression-free survival of 20·8 months and a median overall survival not reached. Possible explanations for these superior outcomes might be attributed to the greater number of patients with systemic anaplastic large cell lymphoma, including those with ALK-positive systemic anaplastic large cell lymphoma (albeit with an IPI requirement ≥2), enrolment on a clinical trial, and the young age of the patients (median age 58 years). Additionally, whether CD30 is prognostic among peripheral T-cell lymphoma subtypes, such as peripheral T-cell lymphoma not otherwise specified and angioimmunoblastic T-cell lymphoma, remains unknown.[7] Despite the higher than expected efficacy in the CHOP group, A+CHP was statistically superior for all primary and secondary endpoints.

The high rate of subsequent disease progression in previously untreated peripheral T-cell lymphoma has led to the use of consolidation with autologous stem cell transplantation as a means of improving long-term outcomes. Although phase 2 studies have suggested higher rates of progression-free survival with front-line consolidation with high-dose chemotherapy and autologous stem cell transplantation,[32] no randomised studies have been done. Consolidation after treatment with autologous stem cell transplantation has nevertheless become part of the standard treatment plan at many centres, particularly for patients with high-risk disease and histological subtypes other than ALK-positive systemic anaplastic large cell lymphoma. In ECHELON-2, consolidative therapy was permitted, but did not affect the results of the primary or secondary endpoints of progression-free survival and overall survival as the benefits of A+CHP were seen both with and without censoring the patients in both groups who received consolidative therapy.

In conclusion, the ECHELON-2 trial has shown that the addition of brentuximab vedotin to CHP resulted in higher rates of progression-free and overall survival without added toxicity and supports the potential for A+CHP to become a new standard of care for many patients with CD30-positive peripheral T-cell lymphoma.

Contributors

OAO'C, BP, TI, and LT formed the ECHELON-2 steering committee and contributed equally to the oversight of the study, including study design and maintaining the quality of study conduct. SH, OAO'C, BP, TI, MF, RA, NLB, JHC, FM, ED-D, GR, WSK, TF, AL, DB, AI, KTo, KTs, S-PY, AS, AH, KJS, SY, SI, PLZ, LT, ZH, ML, SR, JW, and TM analysed the data, drafted the report, revised it critically, and gave final approval to submit for publication. ZH, ML, SR, JW, and TM collected the data.

Declaration of interests

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