Title:

Brentuximab vedotin or physician's choice in CD30-positive CTCL (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

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Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

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Summary

Background Cutaneous T-cell lymphomas are rare, generally incurable, and associated with reduced quality of life. Present systemic therapies rarely provide reliable and durable responses. We aimed to assess efficacy and safety of brentuximab vedotin versus conventional therapy for previously treated patients with CD30-positive cutaneous T-cell lymphomas.

Methods In this international, open-label, randomised, phase 3, multicentre trial, we enrolled adult patients with CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma who had been previously treated. Patients were enrolled across 52 centres in 13 countries. Patients were randomly assigned (1:1) centrally by an interactive voice and web response system to receive intravenous brentuximab vedotin 1·8 mg/kg once every 3 weeks, for up to 16 3-week cycles, or physician's choice (oral methotrexate 5–50 mg once per week or oral bexarotene 300 mg/m² once per day) for up to 48 weeks. The primary endpoint was the proportion of patients in the intention-to-treat population achieving an objective global response lasting at least 4 months per independent review facility. Safety analyses were done in all patients who received at least one dose of study drug. This trial was registered with ClinicalTrials.gov, number NCT01578499.

Findings Between Aug 13, 2012, and July 31, 2015, 131 patients were enrolled and randomly assigned to a group (66 to brentuximab vedotin and 65 to physician's choice), with 128 analysed in the intention-to-treat population (64 in each group). At a median follow-up of 22·9 months (95% CI 18·4–26·1), the proportion of patients achieving an objective global response lasting at least 4 months was 56·3% (36 of 64 patients) with brentuximab vedotin versus 12·5% (eight of 64) with physician's choice, resulting in a between-group difference of 43·8% (95% CI 29·1–58·4; p<0·0001). Grade 3–4 adverse events were reported in 27 (41%) of 66 patients in the brentuximab vedotin group and 29 (47%) of 62 patients in the physician's choice group. Peripheral neuropathy was seen in 44 (67%) of 66 patients in the brentuximab vedotin group (n=21 grade 2, n=6 grade 3) and four (6%) of 62 patients in the physician's choice group. One of the four on-treatment deaths was deemed by the investigator to be treatment-related in the brentuximab vedotin group; no on-treatment deaths were reported in the physician's choice group.

Interpretation Significant improvement in objective response lasting at least 4 months was seen with brentuximab vedotin versus physician's choice of methotrexate or bexarotene.

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See Comment page 533

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Introduction

Cutaneous T-cell lymphomas are a rare group of non-Hodgkin lymphomas with heterogeneous characteristics, severe pruritus, and recurrent infectious complications. The most common forms are mycosis fungoides and Sézary syndrome.[1,2] Cutaneous T-cell lymphomas have an annual incidence in the USA of about 7·5 per million people.[2] Advanced stage mycosis fungoides or Sézary syndrome (IIB–IVB) manifests as cutaneous tumours, erythroderma, or extracutaneous disease, and is associated with inferior quality of life and shortened survival compared with early-stage disease (IA–IIA).[3,4] Uniform expression of the cell-surface antigen CD30 defines a subset of cutaneous T-cell lymphomas known as the CD30-positive T-cell lymphoproliferative disorders, including primary cutaneous anaplastic large-cell lymphoma (pcALCL).[1,5] Mycosis fungoides often expresses CD30, albeit heterogeneously.[6]

In early-stage disease, skin-directed therapy often controls symptoms.[7] For advanced-stage disease, no curative therapies exist. No randomised trials have established a preferred systemic therapy. Retinoids and methotrexate are consistently recommended for mycosis fungoides or pcALCL by standard of care

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Research in context

Evidence before this study

Cutaneous T-cell lymphoma is incurable and, unlike systemic lymphomas, multidrug systemic chemotherapy is ineffective, generally achieving responses lasting 3–6 months. Moreover, recently approved drugs such as bexarotene, vorinostat, romidepsin, and pralatrexate achieve a response in approximately 30% of patients and the associated phase 2 studies have shown that response duration is often short and progression-free survival is about 6–8 months. Methotrexate and bexarotene are the most frequently used systemic therapies worldwide for the treatment of cutaneous T-cell lymphoma.

CD30 is frequently expressed in cutaneous T-cell lymphoma subtypes, in particular mycosis fungoides and primary cutaneous anaplastic large-cell lymphoma (pcALCL). The safety and efficacy of brentuximab vedotin for the treatment of patients with other CD30-expressing haematological malignancies has been shown for Hodgkin's lymphoma and systemic ALCL.

We searched the scientific literature to identify reports of patients with cutaneous T-cell lymphoma, including mycosis fungoides and pcALCL, treated with brentuximab vedotin. We searched MEDLINE for studies published in English between database inception and Jan 16, 2017. Search terms included "CTCL", "cutaneous T-cell lymphoma", "mycosis fungoides", "primary cutaneous CD30-positive T-cell lymphoma", and "primary cutaneous anaplastic large cell lymphoma". We identified two phase 2 studies using single-drug brentuximab vedotin, one for the treatment of mycosis fungoides or Sézary syndrome, and the second in CD30-positive cutaneous T-cell lymphoma and lymphomatoid papulosis. We identified six case reports or series on the use of brentuximab vedotin in patients with mycosis fungoides and six case reports or series on the use of brentuximab vedotin in patients with pcALCL. These studies and reports showed single-drug activity of brentuximab vedotin in cutaneous T-cell lymphoma. We did not identify any phase 3 studies of brentuximab vedotin for cutaneous T-cell lymphoma.

Added value of this study

This is the first randomised study of a new systemic drug against standard therapy and the largest reported phase 3 trial in patients with cutaneous T-cell lymphoma, and unlike many previous studies, uses the present international consensus response criteria incorporating skin, nodal, visceral, and blood responses. The study shows impressive activity of brentuximab vedotin in patients with cutaneous T-cell lymphoma who require systemic therapy. The proportion of patients achieving an objective response lasting 4 months or longer was 56·3% with brentuximab vedotin versus 12·5% with physician's choice ($p<0·0001$). This endpoint captures the proportion of patients with a response and duration of response as a single measurement and reflects a more appropriate and stringent measure of treatment success than the proportion of patients with a response alone in a patient population for whom short clinical responses do not necessarily correspond with meaningful benefit. Improvement in progression-free survival was striking (16·7 months *vs* 3·5 months). Moreover, the proportions of patients achieving a complete response and improvement in symptom burden were all significantly improved in the brentuximab vedotin group and activity was consistent across key subgroups, including skin-only and extracutaneous disease subgroups. Treatment with brentuximab vedotin was not associated with any new or unexpected toxicities compared with the established safety profile.

Implications of all the available evidence

This study reports the first finding of benefit in a randomised phase 3 trial of a novel systemic drug versus an active standard comparator for the treatment of cutaneous T-cell lymphoma. We consider these results to be potentially practice changing and as a consequence approval is being sought from the US Food and Drug Administration and European Medicines Agency for the use of brentuximab vedotin in the treatment of patients with cutaneous T-cell lymphoma who require systemic therapy.

guidelines worldwide, including the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology,[8] the European Society for Medical Oncology,[7] and the European Organisation for Research and Treatment of Cancer.[5,9] Bexarotene is standard of care in all geographic areas participating in this trial[10] and the only treatment approved by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to treat skin manifestations of advanced stage cutaneous T-cell lymphoma in patients refractory to one or more systemic treatments. Histone deacetylase inhibitors (eg, vorinostat and romidepsin) are FDA-approved but not EMA-approved in cutaneous T-cell lymphoma, and are not available as standard of care options in cutaneous T-cell lymphoma (mycosis fungoides or pcALCL) in many non-US regions. The proportions of patients achieving an objective response for most monotherapies are 20–35%, lasting approximately 4–6 months.[11–14] Multidrug chemotherapy regimens have similarly short-lived responses and are reserved for patients who have not responded to single-drug systemic therapies or have substantial nodal or visceral disease.[7,11]

Brentuximab vedotin is an anti-CD30 antibody–drug conjugate that has received regulatory approval in more than 65 countries for the treatment of relapsed or refractory Hodgkin lymphoma[15] and systemic anaplastic large-cell lymphoma.[16]

In a phase 2 trial of 48 patients with CD30-positive relapsed or refractory cutaneous T-cell lymphomas, brentuximab vedotin showed notable activity, with

35 (73%) of 48 patients achieving an objective response, 17 (35%) of 48 achieving a complete response, and a median progression-free survival of 1 year. Activity was reported in 15 (54%) of 28 patients with mycosis fungoides who achieved an objective response irrespective of CD30 expression levels, and an objective response was achieved in 12 (100%) patients with CD30-positive pcALCL or lymphomatoid papulosis, or both.[17] Another phase 2 trial in 32 patients with relapsed or refractory mycosis fungoides or Sézary syndrome reported 21 (70%) of 30 patients achieving an objective response, with activity noted at all levels of CD30 expression.[18]

These results support the rationale for ALCANZA, which aims to investigate the efficacy and safety of brentuximab vedotin versus physician's choice of methotrexate or bexarotene in previously treated patients with CD30-positive cutaneous T-cell lymphoma. This is, to our knowledge, the largest reported phase 3 trial of a new systemic drug against standard therapy in patients with cutaneous T-cell lymphoma.

Methods

Study design and patients

This was an international, open-label, randomised, phase 3, multicentre study of brentuximab vedotin versus conventional therapy for previously treated patients with CD30-positive cutaneous T-cell lymphoma. The trial was done in 52 academic centres in 13 countries in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice, and appropriate regulatory requirements. Local ethics committees or institutional review boards approved the protocol.

Adult patients (aged ≥18 years) with CD30-positive mycosis fungoides who had received at least one previous systemic therapy, or adult patients with CD30-positive pcALCL who had received at least one previous systemic therapy or radiotherapy (Eastern Cooperative Oncology Group performance status 0 to 2), were enrolled. Patients were deemed CD30 positive if one or more biopsy samples had 10% or more CD30-positive malignant cells or lymphoid infiltrate by central review. Patients with mycosis fungoides had two or more skin biopsy samples taken from separate lesions, and patients with pcALCL had one or more samples taken. Patients who progressed on both previous methotrexate and bexarotene therapies were ineligible (full eligibility criteria in the appendix (p 4). All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) by an interactive voice and web response system to brentuximab vedotin or conventional therapy. The randomisation list was generated by the Takeda statistician who was not involved in the remainder of the trial. Treatments were administered open label. Randomisation was stratified by baseline disease diagnosis.

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Procedures

Patients received either intravenous brentuximab vedotin 1·8 mg/kg once every 3 weeks, for up to 16 3-week cycles; or physician's choice of oral methotrexate 5–50 mg[19] once per week, for up to 48 weeks, or oral bexarotene 300 mg/m² (target dose) once per day, for up to 48 weeks. Investigators were permitted to make dose adjustments for toxicities using established dose-modification guidelines for each drug. Treatment continued until disease progression or unacceptable toxicity. Patients were assessed for safety, toxicity, response to treatment, and progression every 3 weeks before dosing on day 1 of each cycle and at the end of treatment.

Outcomes

The primary endpoint was the proportion of patients achieving an objective global response lasting (from first to last response) at least 4 months (ORR4). The intent of this endpoint was to capture durable response to the study drug that is minimally affected by other therapies. This endpoint was chosen because in patients with cutaneous T-cell lymphoma, short clinical responses might not equate to meaningful benefit. The interpretation of progression-free survival is confounded by patients who are symptomatic frequently proceeding to alternate therapies before meeting protocol criteria for progression. Assessment of response in cutaneous T-cell lymphoma should therefore reflect responses unaffected by subsequent treatments. Endpoints more appropriate for the assessment of response in cutaneous T-cell lymphoma than progression-free survival have been examined, including ORR4, an endpoint that captures the two clinically important aspects of treatment success, proportion of patients achieving a response and response duration, as a single measurement.[20] Key secondary endpoints were proportion of patients achieving a complete response, progression-free survival, and symptom burden measured by the symptom domain of health-related quality of life measure, Skindex-29.[21] Other secondary endpoints included duration of response, duration of skin response, event-free survival, Skindex-29 emotional and functional domains, Functional Assessment of Cancer Therapy-General (FACT-G), blood concentrations of brentuximab vedotin and monomethyl auristatin E, immunogenicity assessment, and safety.

To determine ORR4 and disease progression, an independent review facility reviewed global response scores using consensus guidelines by the International Society for Cutaneous Lymphomas and the European Organisation for Research and Treatment of Cancer.[5,22] The independent review facility was comprised of independent dermatologists (for review of photos from skin and modified severity weighted assessment tool [mSWAT] assessments), independent radiologists (for

See Online for appendix

review of CT, MRI, and PET for nodal and visceral involvement), and an independent pathologist (for review of Sézary cells for blood component in patients with mycosis fungoides). The global response score is a composite of several variables: skin evaluation (mSWAT; appendix p 9) per investigator; nodal and visceral radiographic assessment per independent review facility; and, for patients with mycosis fungoides, Sézary cell count per independent review facility. The independent review facility assessed global response score at the end of each cycle until end of treatment (appendix p 8). All treated patients without disease progression at end of treatment were to be followed up for assessment of the global response score and survival every 12 weeks for a minimum of 24 months, then every 6 months until disease progression, death, withdrawal from the study, or study closure. Overall response based on global response score was confirmed by sustained skin response per mSWAT assessment at the subsequent cycle. Investigators examined progression-free survival using two criteria: the prespecified criterion that counted all events despite two or more missed visits or starting of subsequent anticancer therapy (EMA criteria);[23] and a sensitivity analysis criterion that censored patients at last assessment before the missed visit or starting of subsequent anticancer therapy (FDA criteria).[24] Skindex-29 domain responses were scaled into 100-point scores by use of established scoring guidelines (higher scores indicate higher symptom burden and lower health-related quality of life).[25] FACT-G scores were calculated according to established scoring guidelines (version 4); for all FACT-G subscale scores and total score, a higher score indicates a better quality of life.

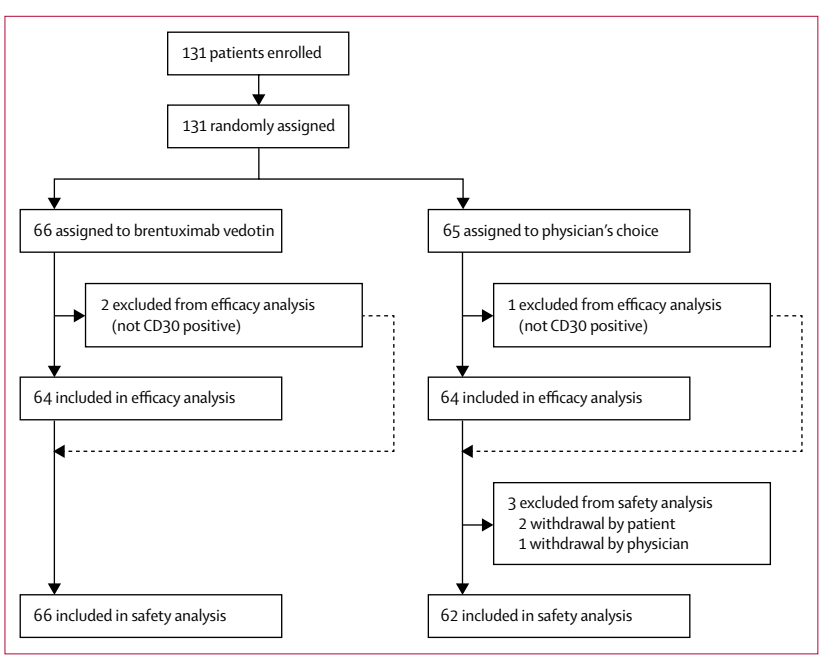

Figure 1: **Trial profile**

All health-related quality-of-life measures were collected before first dose, on all even-numbered cycles thereafter, at end of treatment, and during post-treatment follow-up. Serum and plasma were obtained from blood samples to measure blood concentrations of brentuximab vedotin, total antibody, and monomethyl auristatin E, and to assess immunogenicity. Blood samples were generally taken 1 h pre-dose and 30 min post-dose for all odd-numbered cycles and more extensively for cycles 1 and 3 (either 2 or 4 days post-dose or 3 and 5 days post-dose, depending on randomised pharmacokinetic group). Immunogenicity was assessed before dosing on all odd-numbered cycles and at end of treatment. Treatment-emergent adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

On the basis of a two-sided χ^2 test with a significance level of 0·05, and a 10% dropout rate, we calculated that a sample size of approximately 124 patients was needed to provide 90% power to detect a 30% improvement in ORR4 in the brentuximab vedotin group, assuming 70% of patients in the brentuximab vedotin treatment group and 40% in the physician's choice treatment group achieve an objective global response lasting at least 4 months.

To control the incidence of overall type I error for testing the hypotheses for the primary endpoint and three key secondary endpoints, we used a fixed-sequence testing procedure (ie, the key secondary endpoints can only be tested if the primary endpoint is statistically significant). A weighted Holm's procedure was further implemented for testing the three key secondary endpoints with weights 0·7 for complete response, 0·2 for progression-free survival, and 0·1 for the symptom domain of the Skindex-29. Adjusted p values, which adjust for multiplicity on the basis of the weighted Holm's procedure, were provided for each key secondary endpoint. Statistical significance was claimed at adjusted $p \leq 0{\cdot}05$ (two-sided).

We used a stratified Cochran-Mantel-Haenszel χ^2 test (by baseline disease diagnosis) to assess between-group differences in the proportion of patients achieving response endpoints. For time-to-event outcomes, we used Kaplan-Meier analyses to estimate distribution. We used stratified log-rank tests to generate p values and a stratified Cox regression model[26,27] to estimate the hazard ratio (HR) and associated 95% CI. For symptom domain per Skindex-29, we analysed the mean maximum symptom reductions from baseline with analysis of covariance modelling, controlling for baseline covariates (treatment, baseline score, disease diagnosis, and Eastern Cooperative Oncology Group performance status). We descriptively summarised FACT-G scores, total and subscale scores, for each treatment group over time. An Independent Data Monitoring Committee monitored

patient safety. Efficacy analyses were done in the intention-to-treat population and safety analyses were done in all patients who received at least one dose of study drug. Analyses were done with SAS version 9.3.

This study was registered with ClinicalTrials.gov, number NCT01578499.

Role of the funding source

The funders and ALCANZA steering committee members jointly designed the trial. The investigators and funders collected and interpreted the data, and the funders analysed the data. Medical writing support, provided by FireKite, was funded by the funders. All authors had access to all the data, contributed at all stages of manuscript development, approved the manuscript for submission, made the decision to submit the manuscript for publication, and vouch for its integrity. HMP and YHK had final authority over the manuscript and the decision to submit for publication.

Results

Between Aug 13, 2012, and July 31, 2015, we enrolled and randomly assigned 131 patients (66 to brentuximab vedotin and 65 to physician's choice; appendix p 12, figure 1). In total, 128 patients were included in the intention-to-treat population (64 in each group); three patients were excluded because of insufficient CD30 expression (appendix p 8).

Baseline characteristics were generally balanced between groups (table 1), with the exception of more patients with stage IVB mycosis fungoides and extracutaneous pcALCL in the brentuximab vedotin group. 97 patients had mycosis fungoides and 31 had pcALCL in the overall intention-to-treat population. Previous treatments (by region) are shown in the appendix (p 15).

At a median follow-up of 22·9 months (95% CI 18·4–26·1), ORR4 strongly favoured the brentuximab vedotin group versus the physician's choice group, with an ORR4 of 56·3% (36 of 64 patients) versus 12·5% (eight of 64 patients), resulting in a between-group difference of 43·8% (95% CI 29·1–58·4; p<0·0001; table 2, figure 2); this favouring of the brentuximab vedotin group was seen in both mycosis fungoides (50% [24 of 48 patients] *vs* 10% [five of 49]) and pcALCL (75% [12 of 16] *vs* 20% [three of 15]) subgroups. Improvement of ORR4 in the brentuximab vedotin group compared with the physician's choice group was consistent across all key subgroups, including subgroups with skin-only and extracutaneous disease (figure 2). Average baseline CD30 expression of all biopsy samples for each patient was between 3% and 100%, and ORR4 to brentuximab vedotin was seen across the range of CD30 expression levels (appendix p 13). The proportion of patients achieving an objective response (lasting any duration) was higher in the brentuximab vedotin group (67% [43 of 64 patients]) than in the physician's choice group (20% [13 of 64]; p<0·0001; table 2). The proportion of patients achieving a complete response was also higher in the brentuximab vedotin group (16% [ten of 64]) than in the

	Brentuximab vedotin (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Age (years)	62 (51–70)	59 (48–67)	60 (48–69)
Sex			
Male	33 (52%)	37 (58%)	70 (55%)
Female	31 (48%)	27 (42%)	58 (45%)
Race			
White	56 (88%)	53 (83%)	109 (85%)
Other	5 (8%)	10 (16%)	15 (12%)
Not reported	3 (5%)	1 (2%)	4 (3%)
ECOG PS			
0	43 (67%)	46 (72%)	89 (70%)
1	18 (28%)	16 (25%)	34 (27%)
2	3 (5%)	2 (3%)	5 (4%)
Median CD30 expression*	32·5% (12·5–67·5)	31·3% (12·0–47·5)	31·3% (12·5–60·0)
Time since initial diagnosis (months)	42·2 (12·8–87·4)	37·0 (12·3–102·7)	40·9 (12·7–96·8)
Time since progression on last therapy† (months)	2·4 (1·4–7·9)	1·3 (0·9–3·7)	1·9 (1·1–3·8)
Lines of previous therapy			
Total	4·0 (2·0–7·0)	3·5 (2·0–5·5)	4·0 (2·0–6·0)
Skin-directed	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Systemic	2·0 (1·0–4·0)	2·0 (1·0–3·0)	2·0 (1·0–4·0)
Mycosis fungoides	48 (75%)	49 (77%)	97 (76%)
Disease stage‡§			
IA–IIA	15/48 (31%)	18/49 (37%)	33/97 (34%)
IIB	19/48 (40%)	19/49 (39%)	38/97 (39%)
IIIA–IIIB	4/48 (8%)	2/49 (4%)	6/97 (6%)
IVA1	0	1/49 (2%)	1/97 (1%)
IVA2	2/48 (4%)	8/49 (16%)	10/97 (10%)
IVB	7/48 (15%)	0	7/97 (7%)
pcALCL	16 (25%)	15 (23%)	31 (24%)
Disease stage‡			
Skin			
T_1	1/16 (6%)	4/15 (27%)	5/31 (16%)
T_2	3/16 (19%)	5/15(33%)	8/31 (26%)
T_3	12/16 (75%)	6/15 (40%)	18/31 (58%)
Node			
N_0	10/16 (63%)	11/15 (73%)	21/31 (68%)
N_1	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_2	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_3	2/16 (13%)	2/15 (13%)	4/31 (13%)
Visceral			
M_0	12/16 (75%)	14/15 (93%)	26/31 (84%)
M_1	4/16 (25%)	1/15 (7%)	5/31 (16%)

Data are median (IQR) or n (%), unless stated otherwise. Data shown are for the intention-to-treat population. ECOG PS=Eastern Cooperative Oncology Group performance status. pcALCL=primary cutaneous anaplastic large-cell lymphoma. T=tumour. N=node. M=metastasis. *Based on average CD30 expression among all biopsies for each patient's baseline visit. †Excluding radiotherapy. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table.

Table 1: **Baseline characteristics**

	Brentuximab vedotin				Physician's choice of methotrexate or bexarotene			
	Total (n=64)	ORR4	ORR	CR	Total (n=64)	ORR4	ORR	CR
ITT population	64 (100%)	36 (56%)*	43 (67%)	10 (16%)	64 (100%)	8 (13%)†	13 (20%)	1 (2%)
Mycosis fungoides	48 (75%)	24 (50%)	31 (65%)	5 (10%)	49 (77%)	5 (10%)	8 (16%)	0
Stage‡§								
IA–IIA	15 (31%)	6 (40%)	8 (53%)	1 (7%)	18 (37%)	4 (22%)	5 (28%)	0
IIB	19 (40%)	12 (63%)	13 (68%)	3 (16%)	19 (39%)	1 (5%)	3 (16%)	0
IIIA–IIIB	4 (8%)	2 (50%)	3 (75%)	0	2 (4%)	0	0	0
IVA	2 (4%)	2 (100%)	2 (100%)	1 (50%)	9 (18%)	0	0	0
IVB	7 (15%)	2 (29%)	4 (57%)	0	0	NA	NA	NA
pcALCL	16 (25%)	12 (75%)	12 (75%)	5 (31%)	15 (23%)	3 (20%)	5 (33%)	1 (7%)
Disease involvement‡								
Skin only	9 (56%)	8 (89%)	8 (89%)	4 (44%)	11 (73%)	3 (27%)	5 (45%)	1 (9%)
Extracutaneous disease	7 (44%)	4 (57%)	4 (57%)	1 (14%)	4 (27%)	0	0	0

Data are n (%). ORR4, ORR, and CR percentages are based on the number of patients in the total column. ORR4=achieved an objective response lasting at least 4 months. ORR=achieved an objective response. CR=achieved a complete response. ITT=intent to treat. NA=not applicable. pcALCL=primary cutaneous anaplastic large-cell lymphoma. *One patient with mycosis fungoides in the brentuximab vedotin group achieved a partial response after C1, C2, and C3, and discontinued because of an adverse event. About 4·3 months later the patient received chemotherapy (gemcitabine) before end-of-treatment visit. Total duration of response, including after receipt of gemcitabine, was 4·8 months. †One patient with pcALCL in the bexarotene group who achieved partial response after C2 and sustained it at C5 chose to withdraw from treatment. The patient received subsequent therapy (methotrexate) about 3·5 months into the response to bexarotene but before end-of-treatment visit. Total duration of response, including after receipt of methotrexate, was 4·4 months. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table: one patient in the brentuximab vedotin group had partial response and one patient in the physician's choice group had no response.

Table 2: **Patient responses by clinical stage at baseline**

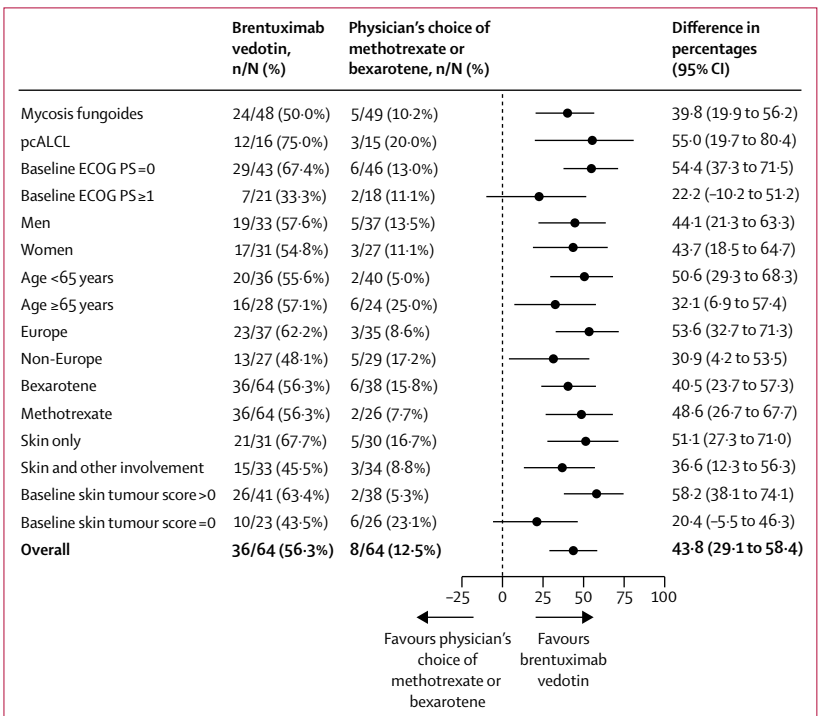

Figure 2: **Proportion of patients achieving an objective global response lasting at least 4 months**
pcALCL=primary cutaneous anaplastic large-cell lymphoma. ECOG PS=Eastern Cooperative Oncology Group performance status.

physician's choice group (2% [one of 64]; p=0·0046; adjusted p=0·0046; table 2). 20 (41%) of 49 patients with mycosis fungoides in the physician's choice group compared with 37 (77%) of 48 patients in the brentuximab vedotin group had a 50% or higher reduction in mSWAT (figure 3). Notably, ten (63%) of 16 patients with pcALCL in the brentuximab vedotin group had 100% reduction in skin disease.

Benefit with brentuximab vedotin was shown for all key secondary endpoints. Median progression-free survival per EMA criteria was 16·7 months in the brentuximab vedotin group versus 3·5 months in the physician's choice group (HR 0·270, 95% CI 0·169–0·430; p<0·0001; adjusted p<0·0001; figure 4), and median progression-free survival as per FDA criteria was 17·2 months versus 3·5 months (HR 0·181, 0·101–0·324; p<0·0001; appendix p 14). The proportional hazards assumption was verified. 38 patients in the brentuximab vedotin group and 47 patients in the physician's choice group received one or more subsequent anticancer therapies (appendix p 17).

Patient-reported burden of symptoms, measured by the Skindex-29, showed significantly greater symptom reduction in the brentuximab vedotin group, compared with the physician's choice group, with a mean maximum reduction of –27·96 (SD 26·877) versus –8·62 (17·013; p<0·0001; adjusted p<0·0001), representing a difference in mean maximum reduction of –18·9 (95% CI –26·6 to –11·2).

No substantial difference in Skindex-29 emotional or functioning domains was seen over time; however, skin disease at end of treatment had less of an effect in patients in the brentuximab vedotin group for both domains. The mean change from baseline to end of

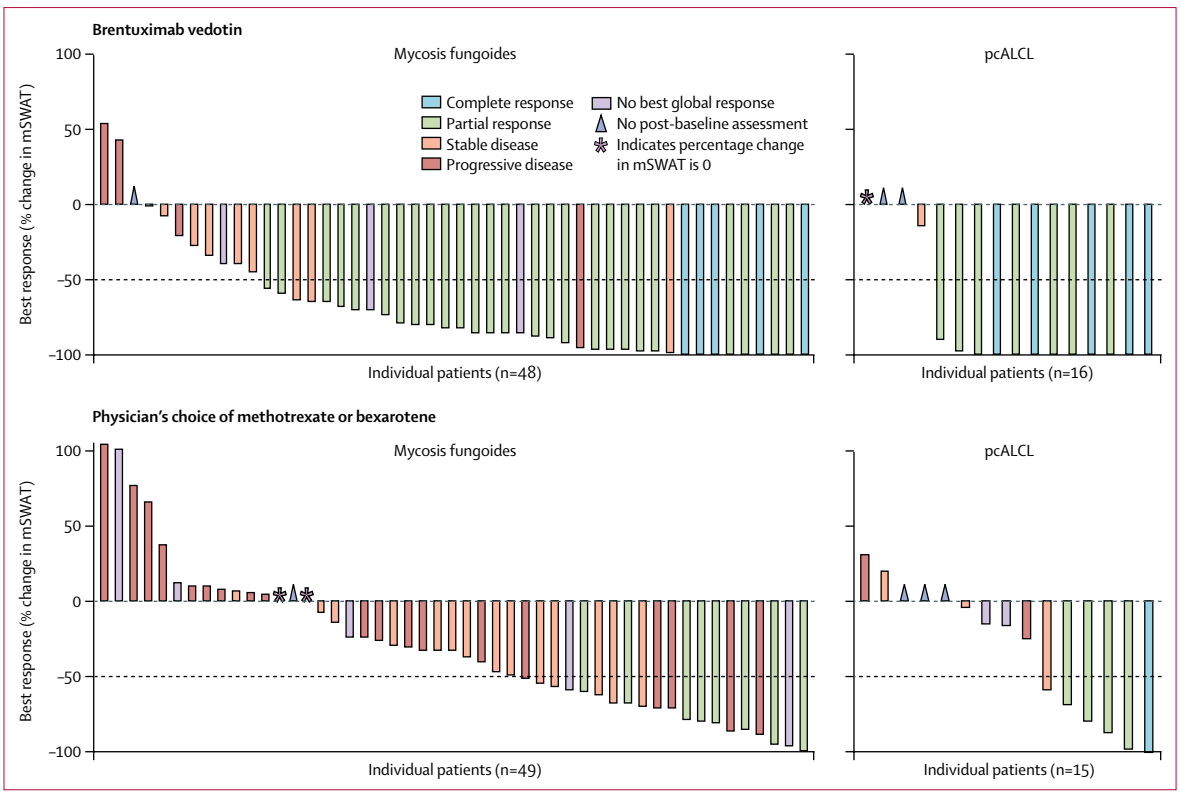

Figure 3: **Maximum percent change in skin mSWAT score**
mSWAT=modified severity weighted assessment tool. pcALCL=primary cutaneous anaplastic large-cell lymphoma.

treatment for the emotions domain was –14·43 (SD 20·901) for the brentuximab vedotin group and –1·84 (18·555) for the physician's choice group. The mean change from baseline to end of treatment for the functioning domain was –11·10 (25·312) for the brentuximab vedotin group and –1·22 (22·448) for the physician's choice group. Results from the FACT-G questionnaire showed no significant differences between the two treatment groups for total score or any subscale score.

Median event-free survival was 9·4 months in the brentuximab vedotin group versus 2·3 months in the physician's choice group (HR 0·285, 95% CI 0·189–0·429; p<0·0001). Median duration of response for the 43 responders to brentuximab vedotin was 15·1 months (95% CI 9·7–25·5) versus 18·3 months (3·5–18·4) for the 13 responders to physician's choice treatment. Median duration of skin response among the 47 patients in the brentuximab vedotin group who had skin response was 20·6 months (14·1–25·7) versus 18·3 months (3·5–18·9) for the 19 patients with skin response in the physician's choice group.

Additional secondary endpoints included assessment of blood concentrations of brentuximab vedotin and monomethyl auristatin E, and immunogenicity. The pharmacokinetic results were consistent with the known pharmacokinetic properties of brentuximab vedotin and did not suggest differences in pharmacokinetics between patients with pcALCL and mycosis fungoides, and did not indicate changes in the pharmacokinetics of the antibody–drug conjugate, total antibody, or monomethyl auristatin E with time upon multiple dosing. Assessment of the immunogenicity of brentuximab vedotin showed no discernible effect of anti-therapeutic antibodies on efficacy and safety (data not shown, but planned for future publication).

Overall, 128 patients received study treatment and were included in the safety population (brentuximab vedotin n=66, physician's choice n=62). The population for analysis is described in more detail in the appendix (p 8). The median duration of treatment was 269 days (12 [IQR 5–16] 3-week cycles) of brentuximab vedotin versus 114 days of bexarotene (equivalent to 5·5 [IQR 3–11] 3-week cycles) and 77 days of methotrexate (equivalent to 3 [IQR 2–6] 3-week cycles). Median relative dose intensity was 99·6% (IQR 92·7–100·0) for brentuximab vedotin and 94·3% (IQR 73·6–100·0) for bexarotene. Treating physicians determined the methotrexate dose (5–50 mg once per week); the median dose was 21·7 mg/week (IQR 16·7–30·6). Three patients remained on treatment (all in the brentuximab vedotin group) at the time of data analysis. The most frequent reasons for treatment discontinuation were completion of 16 cycles in the brentuximab vedotin group (23 [35%] of 66 patients) and

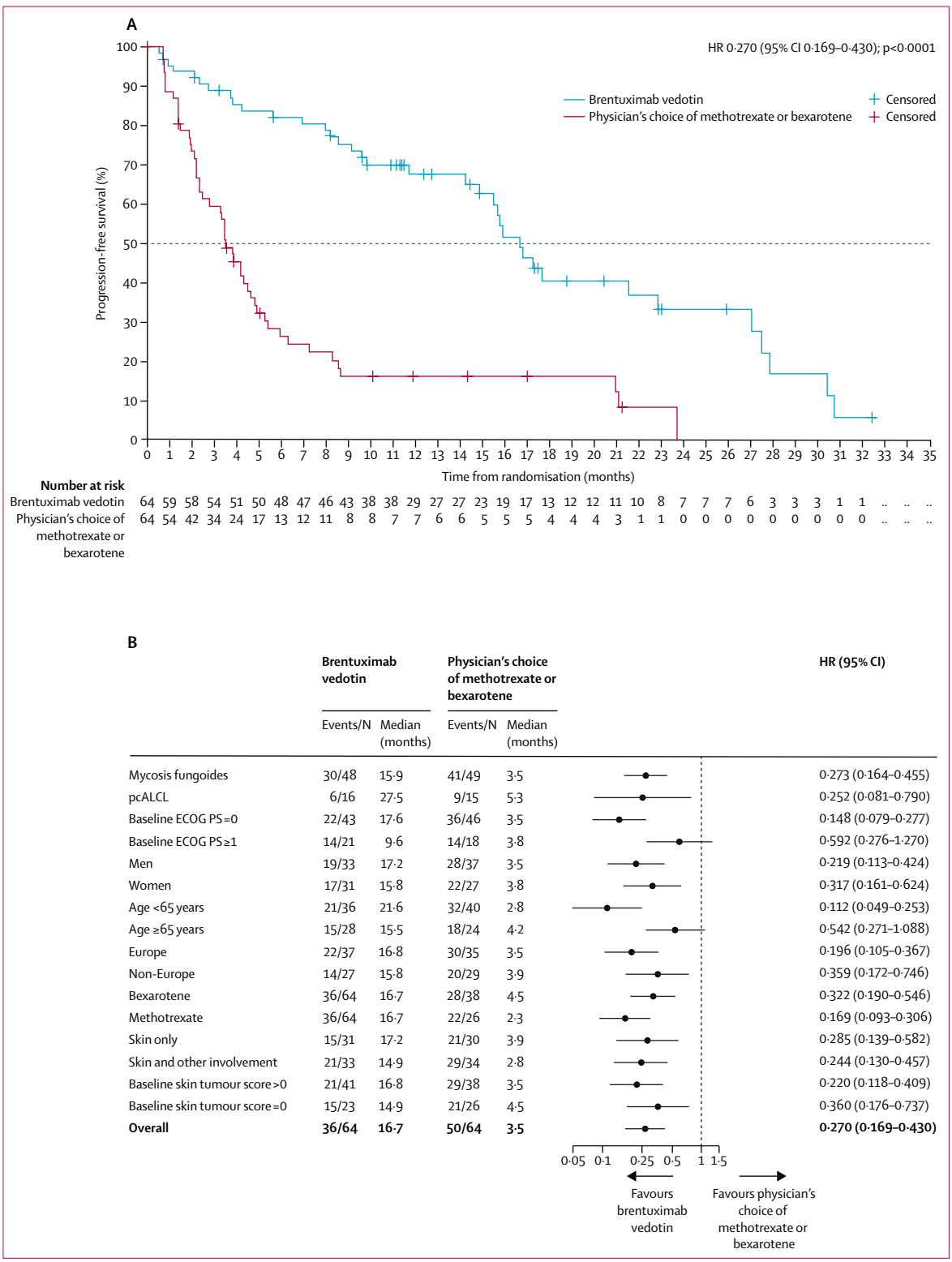

Figure 4: **Progression-free survival**
Progression-free survival was assessed in the intention-to-treat population overall (A) and in subgroups (B) by independent review using European Medicines Agency censoring guidelines,[23] which count all events despite missed visits or starting of new anticancer therapies before an event. Assessment using US Food and Drug Administration criteria is presented in the appendix (p 14). pcALCL=primary cutaneous anaplastic large-cell lymphoma. ECOG PS=Eastern Cooperative Oncology Group performance status.

	Brentuximab vedotin (n=66)			Methotrexate (n=25)			Bexarotene (n=37)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Peripheral sensory neuropathy SMQ	30 (45%)*	3 (5%)	0	1 (4%)	0	0	0	0	0
Nausea	24 (36%)	1 (2%)	0	4 (16%)	0	0	4 (11%)	0	0
Diarrhoea	19 (29%)	2 (3%)	0	1 (4%)	0	0	3 (8%)	0	0
Fatigue	19 (29%)	3 (5%)	0	5 (20%)	1 (4%)	0	12 (32%)	0	0
Vomiting	11 (17%)	1 (2%)	0	2 (8%)	0	0	1 (3%)	0	0
Alopecia	10 (15%)	0	0	1 (4%)	0	0	1 (3%)	0	0
Pruritus	11 (17%)	1 (2%)	0	2 (8%)	0	0	6 (16%)	2 (5%)	0
Pyrexia	11 (17%)	0	0	7 (28%)	1 (4%)	0	4 (11%)	0	0
Decreased appetite	10 (15%)	0	0	1 (4%)	0	0	2 (5%)	0	0
Asthenia	7 (11%)	1 (2%)	0	3 (12%)	0	0	2 (5%)	0	1 (3%)
Dyspnoea	7 (11%)	0	0	0	0	0	0	0	0
Maculopapular rash	7 (11%)	1 (2%)	0	1 (4%)	0	0	2 (5%)	0	0
Peripheral oedema	7 (11%)	0	0	4 (16%)	0	0	2 (5%)	0	0
Pruritus (generalised)	7 (11%)	1 (2%)	0	0	0	0	1 (3%)	0	0
Arthralgia	8 (12%)	0	0	2 (8%)	0	0	2 (5%)	0	0
Myalgia	8 (12%)	0	0	0	0	0	2 (5%)	0	0
Headache	5 (8%)	0	0	1 (4%)	0	0	5 (14%)	0	0
Anaemia	3 (5%)	0	0	0	0	0	6 (16%)	3 (8%)	0
Skin infection	2 (3%)	2 (3%)	0	3 (12%)	1 (4%)	0	4 (11%)	0	0
Hypertriglyceridaemia	1 (2%)	0	0	0	0	0	11 (30%)	5 (14%)	3 (8%)

Shown are commonly reported (≥10% of patients) treatment-emergent adverse events in the safety population. SMQ=standardised Medical Dictionary for Regulatory Activities query. *Overall, events reported by investigators as peripheral neuropathy or peripheral sensory neuropathy (including events additional to those reported in ≥10% of patients) were reported as grade 1 in 17 patients, grade 2 in 21 patients, and grade 3 in six patients.

Table 3: **Treatment-emergent adverse events**

disease progression in the physician's choice group (40 [62%] of 65; appendix p 12).

Safety profiles for both groups are summarised in the appendix (p 18). Serious adverse events were similar between groups, occurring in 19 (29%) of 66 patients in the brentuximab vedotin group versus 18 (29%) of 62 patients in the physician's choice group. Discontinuation due to adverse events occurred in 16 (24%) patients in the brentuximab vedotin group versus five (8%) in the physician's choice group. Four on-treatment deaths in the brentuximab vedotin group (three unrelated to study drug [one each of disease progression, sepsis, and pulmonary embolism], and one multiple organ dysfunction syndrome in a patient with $T_{3b}N_0M_1$ pcALCL, attributed by the investigator to tumour lysis caused by brentuximab vedotin on sites of visceral lymphoma involvement) occurred within 30 days of the last dose. Overall, 16 (24%) deaths occurred in the brentuximab vedotin group and 14 (23%) in the physician's choice group after a median follow-up of 22·9 months. Grade 3–4 adverse events were reported in 27 (41%) of 66 patients in the brentuximab vedotin group and 29 (47%) of 62 patients in the physician's choice group.

Among frequently reported (≥10% of patients) treatment-emergent adverse events, peripheral sensory neuropathy was the most frequently described in the brentuximab vedotin group, and is a subcategory of peripheral neuropathy (table 3). Considering all adverse events, peripheral neuropathy, a known toxicity with brentuximab vedotin, was reported in 44 (67%) of 66 patients in the brentuximab vedotin group (n=17 grade 1, n=21 grade 2, n=6 grade 3) and four (6%) of 62 patients in the physician's choice group (n=1 grade 1, n=3 grade 2). Nine patients discontinued assigned treatment due to peripheral neuropathy in the brentuximab vedotin group (none in the physician's choice group). At the last follow-up (median 22·9 months), 36 (82%) of 44 patients in the brentuximab vedotin group had improvement (≥1 grade) or resolution of peripheral neuropathy. Elevated serum transaminase concentrations, a known toxicity for methotrexate, were not frequently seen in either group. Elevated triglycerides, a known toxicity with bexarotene, were reported in one (2%) of 66 patients receiving brentuximab vedotin (grade 1) versus 11 (30%) of 37 patients receiving bexarotene (n=1 grade 1, n=2 grade 2, n=5 grade 3, n=3 grade 4; table 3). Other treatment-emergent adverse events were consistent with reported safety profiles for the individual drugs.

Discussion

This international, open-label, randomised, phase 3, multicentre trial met its primary endpoint, showing significant improvement in the proportion of previously treated patients with mycosis fungoides or pcALCL

achieving an objective global response lasting at least 4 months with brentuximab vedotin than with physician's choice of methotrexate or bexarotene. Specifically, treatment with brentuximab vedotin showed a 43·8% (95% CI 29·1–58·4) absolute improvement in ORR4 (56·3% [36 of 64 patients] *vs* 12·5% [eight of 64]) compared with physician's choice of methotrexate or bexarotene. Kaplan-Meier analysis of progression-free survival showed early and widening separation of the study groups, with 3·7 times improvement in the risk of progression and a 13·2 month median progression-free survival benefit (16·7 months *vs* 3·5 months) with brentuximab vedotin versus physician's choice. Activity of the brentuximab vedotin group was further shown through improvements in all other key secondary endpoints, including proportion of patients achieving a complete response and symptom burden assessed by the health-related quality of life measure Skindex-29. Among the responders, duration of response was similar in the two groups, recognising that there were only 13 responders in the physician's choice group compared with 43 in the brentuximab vedotin group; this finding is consistent with previous observations that a subgroup of patients has prolonged remissions with methotrexate or bexarotene.[11]

The clinical benefit reported in this Article builds on the previous positive reports of brentuximab vedotin for the treatment of CD30-positive cutaneous T-cell lymphoma in the relapsed or refractory setting.[17,18] This study represents the first demonstration of benefit in a randomised phase 3 trial with a novel systemic drug versus an active standard comparator for the treatment of cutaneous T-cell lymphoma. The proportions of patients achieving an objective response in the physician's choice group were 16% (n=8) for mycosis fungoides and 33% (n=5) for pcALCL, which are similar to values seen with the approved systemic drugs in cutaneous T-cell lymphoma, romidepsin[13] and vorinostat,[14] which were typically around 30–35%. However, the proportion of patients with an objective response in our trial was assessed by the consensus global assessment criteria, whereas vorinostat was largely assessed by skin response and romidepsin by a non-traditional method of global assessment. In the present study, a lower proportion of patients achieved response in the physician's choice group than in previously reported trials of methotrexate or bexarotene; previous studies of bexarotene, the only treatment approved by both the EMA and FDA to treat skin manifestations of cutaneous T-cell lymphoma, reported 45% of patients with advanced stage lymphoma[28] and 54% of patients with early stage lymphoma[29] achieving an objective response. 33% of patients with an objective response have been reported for methotrexate,[19] which is widely recommended for pcALCL treatment.[5,8] These differences are probably due to previous studies having less stringent and standardised assessment tools for response or different dose schedules than the present study.[28,29] Moreover, these previous studies focused on assessment of the skin compartment only, without detailed nodal, visceral, or blood assessment. By comparison, in the present study, 50% or more reduction in the skin compartment, as measured by mSWAT, was seen in 41% (n=20) of patients with mycosis fungoides in the physician's choice group compared with 77% (n=37) in the brentuximab vedotin group.

Limitations of this international randomised controlled trial included the restricted number of drugs available in the physician's choice group. In view of the absence of a single-drug standard of care therapeutic option for mycosis fungoides and pcALCL worldwide, and the fact that these are the most commonly used drugs in cutaneous T-cell lymphoma,[10] we identified methotrexate and bexarotene as acceptable comparators to brentuximab vedotin in this study. Although drugs such as vorinostat, romidepsin, or pralatrexate are available in the USA, these options are not consistently approved or available for patients with cutaneous T-cell lymphoma in most other participating countries. Moreover, considering that bexarotene is readily available in the USA, this might have been a contributing factor for the higher proportion of non-US patients in this study who would have gained access to this treatment by participation on this trial. Similarly, the size of the study limited the ability to analyse specific subsets within the heterogeneous population of patients with cutaneous T-cell lymphoma; these subsets include various patient characteristics such as ethnic and racial groups, and disease characteristics such as folliculotropic mycosis fungoides and large-cell transformation. However, because none of these subgroups were formally excluded, this should not affect the comparative interpretation of brentuximab vedotin tested against the physician's choice groups in this randomised study population. Additionally, this study population would not be regarded as very high risk; about a third had early-stage disease, and median lines of previous systemic therapy was two. Finally, some patient groups with mycosis fungoides or Sézary syndrome were not included in this trial. Patients with high blood Sézary cell count were excluded and the eligibility cutoff for CD30 positivity was somewhat arbitrarily chosen as 10% or more CD30-positive malignant cells or lymphoid infiltrate. While this trial was ongoing, both patients with high Sézary cell counts and patients with lesions with low CD30 expression were shown to respond to brentuximab vedotin;[17,18] as such, this trial might not have enrolled all patients with mycosis fungoides or Sézary syndrome capable of responding to brentuximab vedotin.

Importantly, treatment with brentuximab vedotin, compared with methotrexate or bexarotene, was not associated with any new or unexpected toxicities. The safety profiles of the brentuximab vedotin and comparator groups showed similar proportions of patients with serious adverse events, although more adverse events and discontinuations due to adverse

events were reported in the brentuximab vedotin group. However, duration of exposure to brentuximab vedotin was substantially longer than in the control group. No on-treatment deaths were reported in the physician's choice group; one of the four on-treatment deaths was deemed by the investigator to be treatment-related in the brentuximab vedotin group. The only grade 3 or higher adverse events with 5% or higher difference between groups were peripheral neuropathy, a known toxicity with brentuximab vedotin,[15,16] which resolved or improved in most patients after cessation or completion of treatment, and elevated triglycerides, which were more frequent in patients receiving bexarotene. Hypertriglyceridaemia of all grades has previously been recorded in 46 (79%) of 58 patients receiving bexarotene in a study in early-stage cutaneous T-cell lymphoma.[29] Although preventive strategies and dose titrations are suggested to manage these toxicities,[30] the similar dose intensities between study groups reported here highlight the efforts made by the treating physicians to optimise side-effect management and the dose of bexarotene in these patients.

In conclusion, brentuximab vedotin was associated with substantially improved proportions of patients achieving an objective global response lasting at least 4 months or a complete response, increased progression-free survival, and a reduction in patient-reported symptom burden compared with physician's choice of present standard therapies of methotrexate or bexarotene. These data provide compelling evidence favouring brentuximab vedotin over methotrexate or bexarotene for the treatment of relapsed or refractory CD30-positive cutaneous T-cell lymphoma.

Contributors

HMP, YHK, SMH, RD, SW, and MD formed the ALCANZA steering committee, collected and analysed data, drafted the report, revised it critically, and gave final approval to submit for publication. JS, PQ, PLZ, PW, JAS, PLO-R, OEA, LG, JT, KT, SD, MW, JW, DF, BD, RS, TF, and TMK collected and analysed data in this study, drafted the report, revised it critically, and gave final approval to submit for publication. YW, MCP-W, EZ, WLT, WZ, H-ML, YL, DH, and ML analysed data in this study, drafted the report, revised it critically, and gave final approval to submit for publication.

Declaration of interests

HMP reports research funding from and is an advisory board member for Millennium Pharmaceuticals Inc (a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd) and Celgene Corporation, and is an advisory board member for Eisai. YHK is a member of a steering committee and advisory board for Eisai; has received research funding from and is an advisory board member for Forty Seven and Seattle Genetics Inc; is a member of a steering committee and has received research funding from Kyowa Hakko Kirin and Millennium Pharmaceuticals Inc; has acted as a consultant to Portola and Horizon; and has participated as a principal investigator on current trials by miRagen, Merck, Soligenix, Tetralogic, Neumedicine, Innate, KHK, Eisai, Millennium Pharmaceuticals Inc, and Forty Seven. SMH has received consulting fees from or is on an advisory board for Celgene, Infinity Pharmaceuticals, Kyowa Hakka Kirin, Seattle Genetics Inc, Spectrum Pharmaceuticals, Millennium Pharmaceuticals Inc, HUYA Bioscience, and Forty Seven; and has received research funding from Celgene, Infinity Pharmaceuticals, Kyowa Hakko Kirin, Seattle Genetics Inc, Spectrum Pharmaceuticals, Millennium Pharmaceuticals Inc, and ADC Therapeutics. RD has received consulting fees and honoraria from Bristol-Myers Squibb, Roche, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, and Millennium Pharmaceuticals Inc; and has received research funding from Bristol-Myers Squibb, Roche, GlaxoSmithKline, Merck Sharp and Dohme, and Novartis. JS has received consulting fees from 4SC, Millennium Pharmaceuticals Inc, and Therakos. PLZ has received consulting fees from, and is an advisory board member for, Roche, Gilead, Janssen, Millennium Pharmaceuticals Inc, Pfizer, Bayer, Amgen, Infinity, and TG Pharmaceuticals. JAS is an advisory board member for Leo Pharma. PLO-R has received travel expenses from Janssen; travel expenses and consulting fees from Almirall; research funding from MEDA; and has a patent of *PLG1* mutation for diagnostic or treatment of cutaneous lymphomas. OEA has received consulting fees from Actelion Pharmaceuticals, Celgene Corporation, and TetraLogic Pharmaceuticals; and has received research grant support from Trillium Therapeutics and Actelion Pharmaceuticals. SD has received research funding from Kyowa Hakko Kirin Pharmaceutical. MW reports receiving consulting fees and travel expenses from Millennium Pharmaceuticals Inc, Takeda Oncology, and TEVA Pharmaceuticals. JW has received honoraria from Roche, Millennium Pharmaceuticals Inc, Celgene, Servier, and Gilead Sciences; is an advisory board member for Roche, Millennium Pharmaceuticals Inc, Janssen-Cilag, Boehringer Ingelheim, Celgene, Mundipharma, and Amgen; has received research funding from Roche, Mundipharma, Celgene, GlaxoSmithKline, Genentech, Seattle Genetics Inc, Gilead Sciences, Bayer, Pfizer, Boehringer Ingelheim, Celltrion, and Novartis; and has received travel expenses from Roche, Celgene, Millennium Pharmaceuticals Inc, Sanofi, and Servier. DF is an advisory board member for Seattle Genetics Inc. BD has participated as a principal investigator on current trials by Millennium Pharmaceuticals Inc. RS has received consulting fees from Millennium Pharmaceuticals Inc, Seattle Genetics Inc, and 4SC. TF has received consulting fees and travel expenses from Seattle Genetics Inc, Celgene, AbbVie, and Pharmacyclics/Janssen. TMK has received honoraria from Celgene, Medivation, Astellas, Sanofi, Bristol-Myer Squibb, and Genentech; is an advisory board member for Genentech, Pfizer, Seattle Genetics Inc, AbbVie, Eisai, Exelexis, and Bayer; and has received data monitoring committee honoraria from Amgen, Merck, and Argos. YW and MCP-W are employees of Seattle Genetics Inc. EZ, WLT, WZ, H-ML, YL, DH, and ML are employees of Millennium Pharmaceuticals Inc. SW has received a research grant from Galderma and an honoraria from Celgene. MD has received research funding from, and is a member of an advisory board and safety committee for, Millennium Pharmaceuticals Inc and Seattle Genetics Inc. PQ, PW, LG, JT, and KT declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Prince HM, Kim YH, Horwitz SM, et al, on behalf of the ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017; published online June 6. http://dx.doi.org/10.1016/S0140-6736(17)31266-7.

SUPPLEMENTARY APPENDIX

Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma

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‡Listed in Part I

This appendix has been provided by the authors to give readers additional information about their work.

Contents

Part I – ALCANZA investigators

Patients were recruited from 52 centrers across 13 countries. The following investigators (listed by country) participated:

Australia: Judith Trotman, David Joske, H. Miles Prince, Kerry Taylor, Ian D. Lewis; **Austria:** Constanze Jonak, Franz Trautinger; **Belgium:** Oliver Bechter (Pascal Wolter), Dominique Bron; **Brazil:** Vladmir Claudio C. de Lima, Jose Antonio Sanches Junior; **Canada:** Richard Klasa; **France:** Martine Bagot, Marie Beylot-Barry, Stephane Dalle, Michel D'Incan, Brigitte Dreno, Florent Grange; **Germany:** Jan Nicolay, Rudolf Stadler, Michael Weichenthal, Marion Wobser, Chalid Assaf, Carmen Loquai; **Italy:** Pietro Quaglino, Michele Spina, Pier Luigi Zinzani, Alberto Bosi, Pier Paolo Fattori, **Poland:** Aleksandra Grzanka, Jan Walewski; **Spain:** Andres Lopez-Hernandez, Pablo L. Ortiz-Romero, Jose Juan Rifon Roca, Silvana Novelli Canales; **Switzerland:** Reinhard Dummer; **United Kingdom:** Timothy Illidge, Rod Johnson, Sean Whittaker (Stephen Morris), Pam McKay, Julia Scarisbrick; **United States:** Madeleine Duvic, Tatyana Feldman, Oleg Akilov (Larisa Geskin), Steve Horwitz, Youn H. Kim, Barbara Pro (Timothy Kuzel), Adam Lerner, Herbert Eradat, Lubomir Sokol, David C. Fisher, Sarah Hughey

Part II – Additional methodology

Inclusion criteria

- Male or female patients 18 years or older with diagnosis of mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL).
- Histologically confirmed CD30+ disease by central laboratory assessment and pathology review. Tissue from at least two lesion biopsies for MF and one lesion biopsy for pcALCL performed at screening must be available for confirmation of CD30 positivity, defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. (A minimum of 10% staining in at least one sample is required. Per cent positivity should be determined using per cent neoplastic cells staining first. If neoplastic cells cannot be easily distinguished from non-neoplastic, then per cent positivity should be determined using per cent total lymphocytes staining).
- Patients with pcALCL who have received prior radiation therapy or at least one prior systemic therapy; patients with MF who have received at least one prior systemic therapy.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2.
- Female patients who:
    a. Are postmenopausal for at least 1 year before the screening visit, OR
    b. Are surgically sterile, OR
    c. If they are of childbearing potential, agree to practice two effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, OR
    d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation,

symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception).

- Male patients, even if surgically sterilised (ie, status post vasectomy), who:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception).
- Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
- Suitable venous access for the study-required blood sampling, including pharmacokinetic sampling.
- Clinical laboratory values as specified below within 4 days before randomisation (laboratory values may be performed locally):
    a. Total bilirubin must be <1.5× the upper limit of normal (ULN).
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be <3× the upper limit of the normal range. AST and ALT may be elevated up to five times the ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in liver.
    c. Creatinine clearance or calculated creatinine clearance >40 mL/minute.
- Patients must have radiographically or clinically measurable or evaluable disease.
- A 3-week washout period is required from previous treatments (with the exception of a 12-week washout for antibody-directed or immunoglobulin-based immune therapy, or other monoclonal antibody therapies), unless it is not in the best interest of the

patient in the opinion of the investigator. Individual cases should be discussed with the project clinician before enrolment.

- Recovered (ie, ≤ grade 1 toxicity) from the reversible effects of prior antineoplastic therapy.

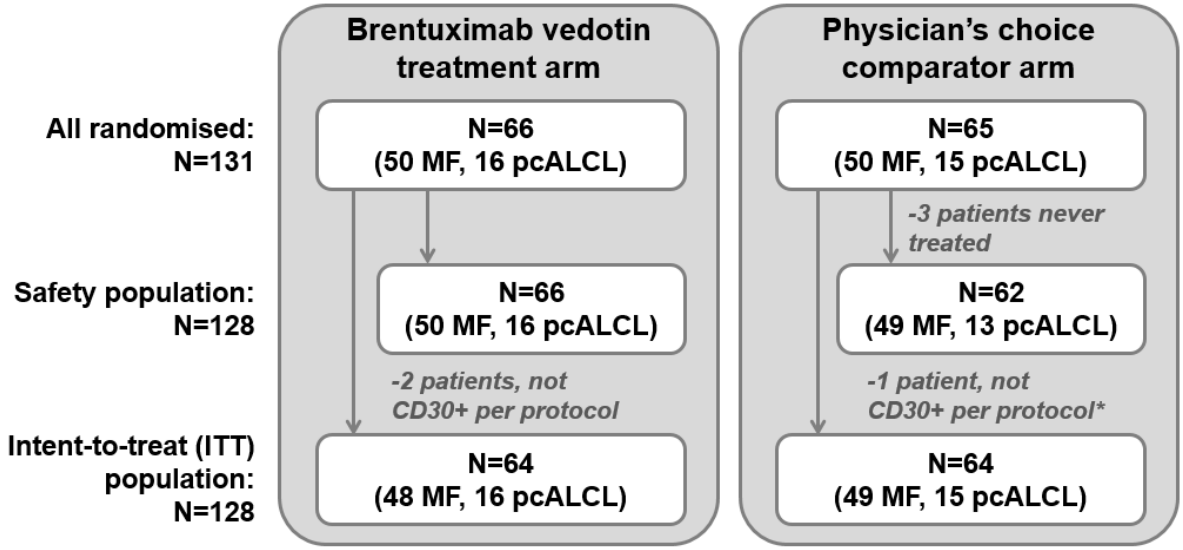
Exclusion criteria

- A concurrent diagnosis of systemic anaplastic large cell lymphoma, or other non-Hodgkin lymphoma (concurrent lymphomatoid papulosis was permitted).
- A concurrent diagnosis of Sézary syndrome or B_2 disease.
- Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
    a. Myocardial infarction within 6 months of enrolment.
    b. New York Heart Association Class III or IV heart failure.
- Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or electrocardiographic evidence of acute ischaemia or clinically significant conduction system abnormalities.
- History of another primary malignancy not in remission for at least 3 years. The following are exempt from the 3-year limit: completely resected in situ carcinoma, such as non-melanoma skin cancer and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear.
- Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy.
- Known HIV infection.
- Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
- Any severe active systemic viral, bacterial, or fungal infection within 1 week prior to first study drug dose requiring systemic antimicrobial therapy. (Oral antibiotics for prophylaxis are allowed).

- Receiving antibody-directed or immunoglobulin-based immune therapy (eg, immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose.
- Corticosteroid therapy for the treatment of cutaneous T-cell lymphoma within 3 weeks of first dose of study drug.
- Known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.
- Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 of any cycle.
- Treatment with radiotherapy or other skin-directed therapy or any investigational products within 3 weeks before the first dose of study drug.
- Progressed on prior therapy with both bexarotene and methotrexate.
- Oral retinoid therapy for any indication within 3 weeks of the first dose of study drug.
- Systemic therapy with Vitamin A in doses of greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately three times recommended dietary allowance) within 3 weeks before the first dose of study drug.
- History of pancreatitis or significant risk factors for developing pancreatitis (eg, prior pancreatitis, uncontrolled hyperlipidaemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity), or elevated lipase value ≥3× ULN with an amylase level >ULN at screening.
- Any other condition that, in the opinion of the investigator or project clinician, would interfere with a patient’s ability to receive or complete the study.
- Previous receipt of brentuximab vedotin.

Populations for analysis

The intent-to-treat (ITT) population included all patients identified as CD30-positive by the Ventana CD30 (Ber-H2) assay and randomised to treatment, and was used for all primary and secondary efficacy analyses. The safety population included all randomised patients who received at least one dose of study drug, and was used for all safety analyses.



*Study enrolment began before availability of the Ventana CD30 (Ber-H2) assay, using an assay by Quest Diagnostics to assess CD30 status for eligibility. When the Ventana assay became available, it was adopted for use in the study and the biopsies previously tested at Quest Diagnostics were re-assayed. Biopsies from three patients were not confirmed positive (ie, were not ≥10% positive via the Ventana assay). These three patients (two in the brentuximab vedotin arm and one in the physician's choice arm) were included in safety analyses, but were excluded from the ITT population (N=128).

Independent review facility (IRF)

Use of the Global Response Score (GRS) was in accordance with ISCL/USCL/EORTC consensus recommendations for trials conducted in patients with cutaneous T-cell lymphoma (CTCL).[1] Efficacy responses were based on the GRS as determined by IRF. GRS consisted of skin assessment (mSWAT) by the investigator, nodal and visceral radiographic assessment by IRF, and for the patients with MF only, enumeration of circulating Sézary

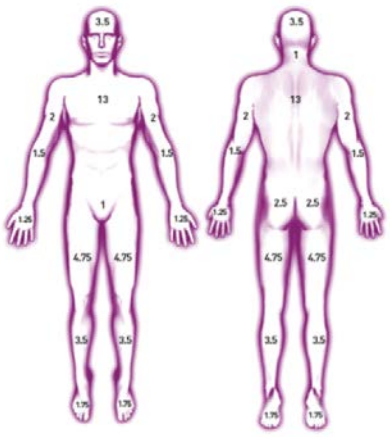
cells by IRF. Imaging results, laboratory values and photographs of lesions were provided for IRF review.

	Evaluation	Source	Evaluator(s)	GRS
T – Tumour (Skin)	mSWAT	Physical examination (data in eCRF)	Principal investigator	GRS determined by IRF for primary endpoint (ORR4)
N – Node	Node measurements	CT scan	Independent radiologist	
M – Metastases	Visceral evaluation	CT scan		
B – Blood	Sézary cell count	Central pathology lab	Independent pathologist	

CT=computed tomography. eCRF=electronic case report form. ORR4=overall response rate lasting ≥4 months.

TNM staging for pcALCL per Kim et al.[2]

Modified Severity Weighted Assessment Tool (mSWAT)



- The body is divided into 12 regions with pre-assigned percentages of total body surface area (BSA).
- The extent of skin disease is assessed for each region and weighted for more severe lesion per the assessment table below.
- The patient's palm (including four fingers and thumb), measured from wrist to fingertips is approximately 1% of total BSA.
- The mSWAT provides a numerical score of skin involvement between 0–400.

		Assessment of involvement in patient's skin		
Body region	**% BSA in Body region**	**Patch[a]**	**Plaque[b]**	**Tumour[c]**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA weighting factor		**×1**	**×2**	**×4**

mSWAT score equals summation of each column line.
BSA=body surface area. mSWAT=modified Severity Weighted Assessment Tool.
[a]Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
[b]Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
[c]Any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
Figure reprinted from Dis Mon, Oct;3, Levenson SM and Lund CC, Thermal Burns, 1–47, Copyright (1957), with permission from Elsevier.

The mSWAT score is calculated as:
Sum of %BSA from all body regions affected by patches × severity-weighting factor of 1
+ Sum of %BSA from all body regions affected by plaques × severity-weighting factor of 2
+ Sum of %BSA from all body regions affected by tumours × severity-weighting factor of 4
= Total mSWAT (maximum score=400)

Endpoint definitions

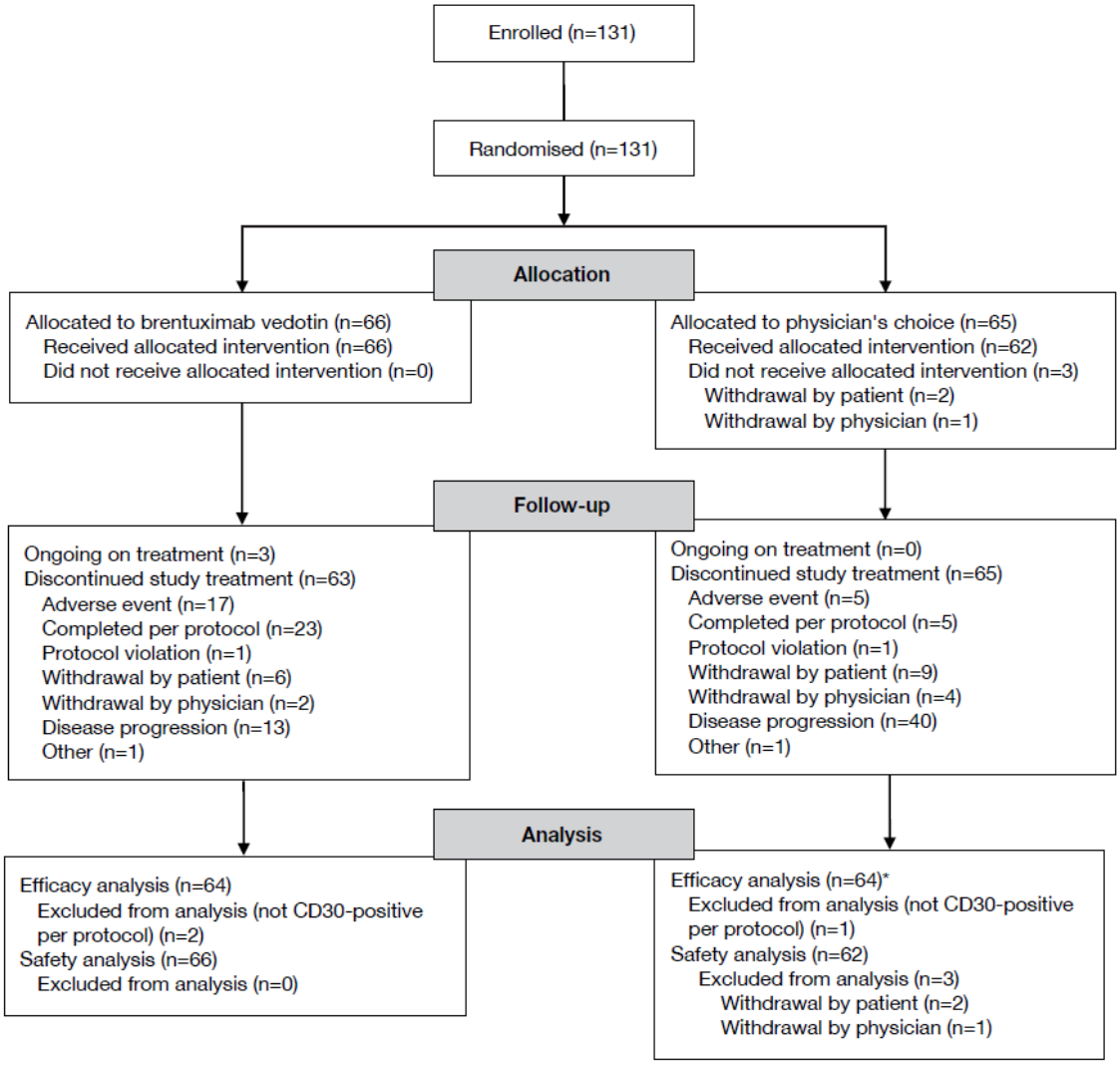
Progression-free survival was defined as the time from randomisation until disease progression or death due to any cause, whichever occurs first.

Duration of response in subjects with a confirmed response is the time between first documentation of response and disease progression.

Event-free survival was defined as the time from randomisation until any cause of treatment failure: disease progression, early discontinuation of treatment for any reason (other than completed maximum number of cycles), start of subsequent anticancer therapy or death due to any cause, whichever occurs first.

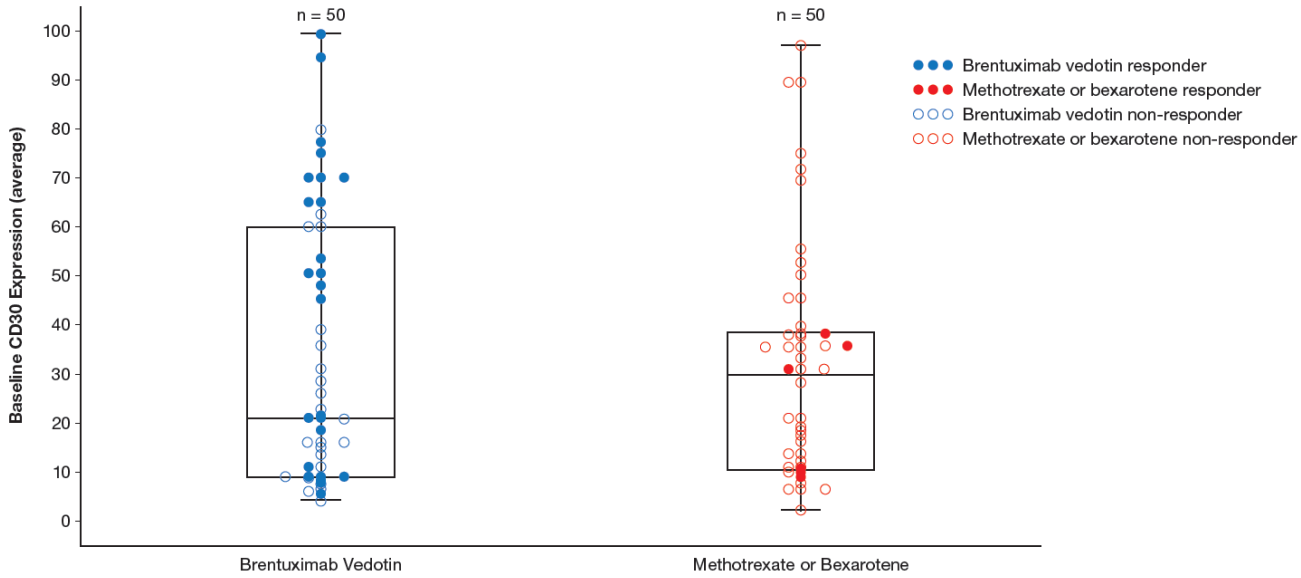
Part III – Supplementary Figures

Supplementary Figure S1: CONSORT diagram



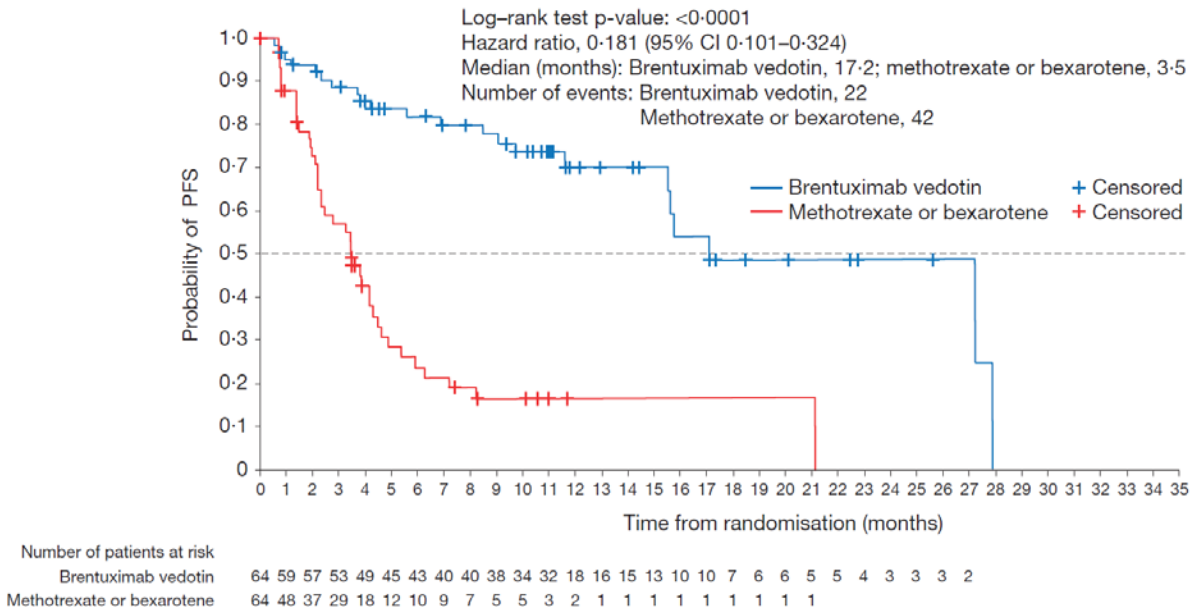
*Three patients randomised to the physician's choice arm did not receive any study drug: 2 patients with MF (who had been assigned to receive methotrexate) withdrew consent, and the third, a patient with pcALCL (who had been assigned to receive bexarotene), had spontaneous regression of CTCL lesions, so the investigator chose to withdraw this patient. These 3 patients were excluded from safety analyses, but were included in the ITT population.

Supplementary Figure S2: **Boxplot of average baseline CD30 expression with subject level ORR4 status by treatment group for MF patients in all-enrolled population**



Responders are defined as patients who achieve ORR4 (global response lasting ≥4 months on study as determined by an independent review facility). Average baseline CD30 expression is defined as the average CD30 expression of all biopsies for each patient's baseline visit. All-enrolled population includes all patients randomised to treatment (ie, ITT population plus three patients excluded for insufficient CD30 expression).

Supplementary Figure S3: **Progression-free survival sensitivity analysis – FDA criteria – assessed by independent review (ITT population)**



EMA=European Medicines Agency. FDA=Food and Drug Administration. ITT=intent-to-treat. PFS=progression-free survival.

FDA[3] guidance differs from EMA[4] guidance in that the EMA criteria do not censor patients for subsequent antineoplastic therapy started prior to disease progression/death, whereas the FDA guidance censors such patients at the date of the last adequate assessment prior to starting the subsequent antineoplastic therapy. The FDA guidance also censor patients for disease progression/death after more than one missed visit at the date of the last assessment before the missed visit.[3]

Part IV – Supplementary Tables

Supplementary Table S1: **Prior therapy, by region (ITT population)**

	Brentuximab vedotin			Methotrexate or bexarotene		
	EU n=37	NA n=13	RoW n=14	EU n=35	NA n=19	RoW n=10
Type of prior therapy — n (%)*						
Skin-directed therapy	29 (81)	11 (85)	12 (86)	28 (80)	16 (84)	7 (70)
Topical steroids	2 (6)	2 (15)	3 (21)	4 (11)	9 (47)	1 (10)
Topical retinoids	0	1 (8)	0	0	0	0
Topical chemotherapy	2 (6)	1 (8)	0	0	1 (5)	1 (10)
Radiotherapy	23 (64)	6 (46)	11 (79)	22 (63)	13 (68)	6 (60)
Phototherapy	20 (56)	6 (46)	6 (43)	21 (60)	6 (32)	2 (20)
Other	1 (3)	1 (8)	0	0	0	0
Systemic therapy	36 (100)	13 (100)	14 (100)	35 (100)	19 (100)	10 (100)
Bexarotene	18 (50)	8 (62)	0	17 (49)	5 (26)	0
Chemotherapy	27 (75)	6 (46)	12 (86)	22 (63)	15 (79)	8 (80)
Methotrexate	11 (31)	4 (31)	11 (79)	11 (31)	7 (37)	7 (70)
Other chemotherapy	19 (53)	4 (31)	7 (50)	20 (57)	8 (42)	4 (40)
Oral retinoids	3 (8)	1 (8)	1 (7)	2 (6)	1 (5)	1 (10)

	Brentuximab vedotin			Methotrexate or bexarotene		
	EU n=37	NA n=13	RoW n=14	EU n=35	NA n=19	RoW n=10
Photopheresis	1 (3)	1 (8)	1 (7)	2 (6)	1 (5)	1 (10)
Denileukin diftitox	0	0	0	0	1 (5)	0
Immunotherapy[†]	18 (50)	2 (15)	6 (43)	20 (57)	4 (21)	5 (50)
HDACi	4 (11)	5 (38)	4 (29)	3 (9)	6 (32)	4 (40)
Steroids	10 (28)	2 (15)	6 (43)	7 (20)	3 (16)	3 (30)
Other/Unknown	6 (17)	1 (8)	3 (21)	3 (9)	2 (11)	0

EU=Europe. HDACi=histone deacetylase inhibitor. ITT=intent-to-treat. NA=North America. RoW=rest of world. (including: South America, Australia).

*Percentages are based on the number of patients with non-missing values in the ITT population with prior therapy/prior radiation/prior transplant procedure.

[†]Immunotherapy included: interferon, interferon alpha, interferon alpha-2a, interferon gamma, alemtuzumab, monoclonal antibodies, and mogamulizumab.

Supplementary Table S2: **Subsequent anticancer therapies (ITT population)**

	Brentuximab vedotin (n=64)	Methotrexate or bexarotene (n=64)
≥1 subsequent anticancer therapy — n (%)*	38 (59)	47 (73)
Type of therapy — n (%)†		
Skin-directed therapy	17 (45)	22 (47)
Radiotherapy	12 (32)	16 (34)
Phototherapy	6 (16)	6 (13)
Topical steroids	1 (3)	5 (11)
Systemic therapy	34 (89)	44 (94)
Chemotherapy	23 (61)	22 (47)
Other chemotherapy	19 (50)	19 (40)
Methotrexate	8 (21)	6 (13)
Immunotherapy	9 (24)	5 (11)
Bexarotene	6 (16)	4 (9)
Brentuximab vedotin	5 (13)	29 (62)
Steroids	5 (13)	3 (6)
HDACi	4 (11)	3 (6)
Photopheresis	0	1 (2)
Other/unknown	1 (3)	4 (9)

HDACi=histone deacetylase inhibitor. ITT=intent-to-treat.

*Percentages are based on the number of patients in the ITT population.

†Percentages are based on the number of patients in the ITT population who have received ≥1 subsequent anticancer therapy.

Supplementary Table S3: **Overall safety profile (safety population)**

	Brentuximab vedotin (n=66)	**Methotrexate or bexarotene (n=62)**	**Total (N=128)**
Any AE — n (%)	63 (95)	56 (90)	119 (93)
Any grade ≥3 AE — n (%)	27 (41)	29 (47)	56 (44)
Drug-related AE — n (%)	57 (86)	44 (71)	101 (79)
Drug-related grade ≥3 AE — n (%)	19 (29)	18 (29)	37 (29)
Serious AE — n (%)	19 (29)	18 (29)	37 (29)
Drug-related serious AE — n (%)	9 (14)	3 (5)	12 (9)
AE resulting in study drug discontinuation — n (%)	16 (24)	5 (8)	21 (16)
On-treatment deaths — n (%)*	4 (6)	0	4 (3)

AE=adverse event.

*On-treatment deaths are defined as deaths that occur within 30 days after the last dose of study drug. Causes of deaths in the four patients in the brentuximab vedotin arm were: lymphoma, sepsis, multiple organ dysfunction syndrome, and pulmonary embolism. Multiple organ dysfunction syndrome was considered by the investigator to be related to brentuximab vedotin treatment.

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