Response to brentuximab vedotin versus physician’s choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis

Kim, Youn H ; Prince, H Miles ; Whittaker, Sean ; Horwitz, Steven M ; Duvic, Madeleine ; et al ; Dummer, Reinhard

Abstract: Introduction Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, can lead to disfiguring lesions, debilitating pruritus and frequent skin infections. This study assessed response to brentuximab vedotin in patients with MF in the phase III ALCANZA study. Methods Baseline CD30 levels and large-cell transformation (LCT) status were centrally reviewed in patients with previously-treated CD30-positive MF using 2 skin biopsies obtained at screening; eligible patients required 1 biopsy with 10% CD30 expression. Patients were categorised as CD30min < 10% (1 biopsy with <10% CD30 expression), or CD30min > 10% (all biopsies with 10% CD30 expression) and baseline LCT present or absent. Efficacy analyses were the proportion of patients with objective response lasting 4 months (ORR4) and progression-free survival (PFS). Results Clinical activity with brentuximab vedotin was observed across all CD30 expression levels in patients with 1 biopsy showing 10% CD30 expression. Superior ORR4 was observed with brentuximab vedotin versus physician’s choice in patients: with CD30min < 10% (40.9% versus 9.5%), with CD30min > 10% (57.1% versus 10.3%), with LCT (64.7% versus 17.6%) and without LCT (38.7% versus 6.5%). Brentuximab vedotin improved median PFS versus physician’s choice in patients: with CD30min < 10% (16.7 versus 2.3 months), with CD30min > 10% (15.5 versus 3.9 months), with LCT (15.5 versus 2.8 months) and without LCT (16.1 versus 3.5 months). Safety profiles were generally comparable across subgroups. Conclusion These exploratory analyses demonstrated that brentuximab vedotin improved rates of ORR4 and PFS versus physician’s choice in patients with CD30-positive MF and 1 biopsy showing 10% CD30 expression, regardless of LCT status.

DOI: https://doi.org/10.1016/j.ejca.2021.01.054
Kim, Youn H; Prince, H Miles; Whittaker, Sean; Horwitz, Steven M; Duvic, Madeleine; et al; Dum-mer, Reinhard (2021). Response to brentuximab vedotin versus physician’s choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis. European Journal of Cancer, 148:411-421.
DOI: https://doi.org/10.1016/j.ejca.2021.01.054
Response to brentuximab vedotin versus physician’s choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis

Youn H. Kim a,*, H. Miles Prince b, Sean Whittaker c, Steven M. Horwitz d, Madeleine Duvic e, Oliver Bechter f, Jose A. Sanches g, Rudolf Stadler h, Julia Scarisbrick i, Pietro Quaglino j, Pier Luigi Zinzani k, Pascal Wolter l, Herbert Eradat m, Lauren C. Pinter-Brown n, Pablo L. Ortiz-Romero o, Oleg E. Akilov p, Judith Trotman q, Kerry Taylor r, Michael Weichenthal s, Jan Walewski t, David Fisher u, Marie McNeeley v, Alejandro A. Gru w, Lisa Brown x, M. Corinna Palanca-Wessels x, Julie Lisano x, Matthew Onsum x, Veronica Bunn y, Meredith Little y, William L. Trepicchio y, Reinhard Dummer z

a Dermatology and Medicine, Stanford University School of Medicine and Cancer Institute, 780 Welch Road, CJ220D, 94305, Stanford, CA, USA
b Department of Haematology, University of Melbourne, 140 Clarendon Street, 3002, East Melbourne, Australia
c St Johns Institute of Dermatology, Guys and St Thomas NHS Foundation Trust, St Thomas Street, SE1 7EL, London, UK
d Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, 10065, New York, NY, USA
e Department of Dermatology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1452, 77030, Houston, TX, USA

* Corresponding author: Multidisciplinary Cutaneous Lymphoma Program, Stanford University School of Medicine and Cancer Institute, 780 Welch Road, CJ220D, 94305, Stanford, CA, USA.

E-mail address: younkim@stanford.edu (Y.H. Kim), Miles.prince@petermac.org (H.M. Prince), Sean.whittaker@kcl.ac.uk (S. Whittaker), horwitzs@mskcc.org (S.M. Horwitz), mdovic@mdanderson.org (M. Duvic), oliver.bechter@uzleuven.be (O. Bechter), jasanchesjr@gmail.com (J.A. Sanches), rudolf.stadler@t-online.de (R. Stadler), julia.scarisbrick@uhb.nhs.uk (J. Scarisbrick), pietro.quaglino@unito.it (P. Quaglino), pierluigi.zinzani@unibo.it (P.L. Zinzani), pascalwolter@hotmail.com (P. Wolter), heradat@mednet.ucla.edu (H. Eradat), lpinterb@uci.edu (L. C. Pinter-Brown), portiz.hdoc@salud.madrid.org (P.L. Ortiz-Romero), akilovoe@upmc.edu (O.E. Akilov), judith.trotman@sswahs.nsw.gov.au (J. Trotman), ktaylor@iconcancercentre.com.au (K. Taylor), MWeichenthal@dermatology.uni-kiel.de (M. Weichenthal), jan.walewski@coi.pl (J. Walewski), david_c_fisher@dfci.harvard.edu (D. Fisher), Marie.McNeeley@gmail.com (M. McNeeley), AAG4B@hscmail.mcc.virginia.edu (A.A. Gru), lisannnebr@gmail.com (L. Brown), cpalanca@seagen.com (M.C. Palanca-Wessels), jlisano@seagen.com (J. Lisano), monsum@seagen.com (M. Onsum), Veronica.Bunn@takeda.com (V. Bunn), meredith.little@takeda.com (M. Little), bill.trepicchio@takeda.com (W.L. Trepicchio), Reinhard.Dummer@us.ch (R. Dummer).

1 Current address: Department of Biometrics, Zymeworks, 1215 4th Avenue, 98101, Seattle, WA, USA.

https://doi.org/10.1016/j.ejca.2021.01.054
0959-8049/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Abstract  Introduction: Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, can lead to disfiguring lesions, debilitating pruritus and frequent skin infections. This study assessed response to brentuximab vedotin in patients with MF in the phase III AL-CANZA study.

Methods: Baseline CD30 levels and large-cell transformation (LCT) status were centrally reviewed in patients with previously-treated CD30-positive MF using ≥2 skin biopsies obtained at screening; eligible patients required ≥1 biopsy with >10% CD30 expression. Patients were categorised as CD30_{min} < 10% (≥1 biopsy with <10% CD30 expression), or CD30_{min} ≥ 10% (all biopsies with ≥10% CD30 expression) and baseline LCT present or absent. Efficacy analyses were the proportion of patients with objective response lasting ≥4 months (ORR4) and progression-free survival (PFS).

Results: Clinical activity with brentuximab vedotin was observed across all CD30 expression levels in patients with ≥1 biopsy showing >10% CD30 expression. Superior ORR4 was observed with brentuximab vedotin versus physician’s choice in patients: with CD30_{min} < 10% (40.9% versus 9.5%), with CD30_{min} ≥ 10% (57.1% versus 10.3%), with LCT (64.7% versus 17.6%) and without LCT (38.7% versus 6.5%). Brentuximab vedotin improved median PFS versus physician’s choice in patients: with CD30_{min} < 10% (16.7 versus 2.3 months), with CD30_{min} ≥ 10% (15.5 versus 3.9 months), with LCT (15.5 versus 2.8 months) and without LCT (16.1 versus 3.5 months). Safety profiles were generally comparable across subgroups.

Conclusion: These exploratory analyses demonstrated that brentuximab vedotin improved rates of ORR4 and PFS versus physician’s choice in patients with CD30-positive MF and ≥1 biopsy showing >10% CD30 expression, regardless of LCT status.
1. Introduction

Cutaneous T-cell lymphomas (CTCL) often have chronic courses and lead to disfiguring lesions, debilitating pruritus and frequent skin infections [1–3]. Mycosis fungoides (MF) is the most common CTCL subtype and patients frequently present with skin patches and/or plaques. Patients with advanced-stage MF may have skin tumours, erythroderma or extracutaneous disease [4]. Early-stage MF is primarily treated with skin-directed therapies, whereas in advanced-stage disease or refractory early-stage disease, systemic therapies are often used.

Diagnostic and clinical management of CTCL includes at least one skin biopsy assessed by expert dermatopathological evaluation, often utilising immunohistochemistry (IHC) staining. Both primary cutaneous anaplastic large cell lymphoma (pcALCL) and MF are characterised by expression of cell-surface CD30 antigen; pcALCL is characterised by a high level of CD30 expression (>75% of tumour cells) [4], whereas MF may express CD30 to a more variable degree (<1–100%) [5–8]. Technical limitations of detecting low levels of CD30 expression for patients with MF, along with inter-patient, intra-patient and inter-lesional variability between the skin and lymph node of CD30 expression, have been reported [6,8,9].

Large cell transformation (LCT) of MF is defined as the presence of ≥25% of aberrant T-cells with large cell morphology (and/or large cell nodules) and is often associated with aggressive clinical course and inferior prognosis [10–12]. Some reports suggest the presence of LCT is associated with higher levels of CD30 expression in MF patients; however, CD30 expression is not required for the determination of LCT [13]. Further, the presence of LCT has been reported in >50% of patients diagnosed with advanced-stage (IIb–IV) MF [11,12].

The phase III ALCANZA trial (NCT01578499) evaluated the efficacy and safety of brentuximab vedotin versus physician’s choice (PC) of methotrexate or bexarotene in patients with previously-treated CD30-positive MF or pcALCL who required systemic therapy [14]. Selection of methotrexate or bexarotene in the PC arm was made by the treating physician based upon the patient’s diagnosis (MF or pcALCL), comorbidities, prior use of either agent, and availability of treatment at the participating centre. In patients with MF, CD30 expression was evaluated by IHC assessment of ≥2 skin biopsies from separate lesions. ALCANZA primary results demonstrated the superiority of brentuximab vedotin over PC, with significant improvements in all primary and key secondary endpoints, including objective response rate lasting ≥4 months (ORR4 [56.3% versus 12.5%; p < 0.0001]), complete remission rate (16% versus 2%; p = 0.0046), median progression-free survival ([PFS] 16.7 versus 3.5 months; hazard ratio [HR]: 0.270 [95% CI: 0.169–0.430]; p < 0.0001) and mean maximum reduction in Skindex-29 score (−27.96 [standard deviation (SD): 26.877] versus −8.62 [SD: 17.013]; p < 0.0001) [14].

This exploratory, post hoc analysis of patients with MF enrolled in ALCANZA evaluates whether baseline CD30 expression level impacted the efficacy and safety of brentuximab vedotin and retrospectively summarises the proportion and outcomes of patients with LCT at the time of enrollment.

2. Patients and methods

2.1. Patients

ALCANZA enrolled adult patients (aged ≥18 years) with CD30-positive MF (n = 100) or pcALCL (n = 31) who had received ≥1 previous systemic therapy (including radiotherapy for pcALCL), and had an Eastern Cooperative Oncology Group performance status of 0–2. This analysis was limited to patients with CD30-positive MF only.

For confirmation of eligibility, patients with MF were required to undergo ≥2 skin biopsies of patch, plaque or tumour lesions, selected at the investigator’s discretion, for central confirmation of CD30 expression by IHC. Each biopsy was ≥2 mm in diameter and obtained from separate skin lesions, where possible. Patients were eligible if they had at least one biopsy with ≥10% CD30-positive malignant cells or lymphoid infiltrate by central pathology review and were not limited to the number of total biopsies [14].

2.2. Study objectives

As reported previously [14], ALCANZA was an international, open-label, randomised, phase III, multi-centre study to assess the efficacy and safety of brentuximab vedotin compared with PC. Local ethics committees or institutional review boards approved the protocol, and all patients provided written informed consent.

The aims of these post hoc analyses were to determine the relationship between baseline CD30 expression and response to brentuximab vedotin and to summarise LCT status and outcomes.
2.3. Assessments

For CD30 assessment, patients with MF required two skin biopsies from separate lesions for eligibility, and additional biopsies were permitted at the investigator’s discretion. Eligibility required only one biopsy to be CD30-positive, defined as ≥10% of malignant cells or total lymphoid infiltrate demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining. Percent positivity was determined based on neoplastic cell staining first. If neoplastic cells could not be easily distinguished from non-neoplastic, then percent positivity was determined based on total lymphocyte staining. CD30

Fig. 1. Intra-patient, inter-patient and inter-lesional variability in baseline CD30 expression levels in patients with CD30-positive mycosis fungoides. Patients were allocated to two groups based on their biopsy with the CD30$_{\text{min}}$. Patients who had at least one biopsy with <10% CD30 expression (A) were allocated to the CD30$_{\text{min}}$ < 10% group, and those with both/all biopsies with ≥10% CD30 expression (B) allocated to CD30$_{\text{min}}$ ≥ 10% group. Baseline per patient CD30 expression levels are shown in (C). Each box represents an intra-patient range of CD30 expression for individual patients. Data were plotted from highest to lowest variability in CD30 expression. Horizontal bars within each box represent median CD30 expression among all biopsies tested. The top and bottom of each box represent maximum (CD30$_{\text{max}}$) and CD30$_{\text{min}}$ values for all biopsies from each patient. The horizontal dashed line at 10% represents the cut-off for enrollment. CD30$_{\text{max}}$, maximum CD30 levels; CD30$_{\text{min}}$, minimum CD30 levels.
expression levels were assessed by Marise McNeely (Central Pathology review) utilising the Ventana BerH2 assay. For descriptive purposes, patients’ baseline minimum and average CD30 expression results (CD30\textsubscript{min} and CD30\textsubscript{avg}) from their skin biopsies are reported. CD30\textsubscript{min} was derived by taking the average of the result of the biopsy with the lowest CD30 expression from each patient, and the CD30\textsubscript{avg} was calculated as the average CD30 expression for all biopsies from an individual patient. For the purposes of efficacy analyses, patients were categorised into one of two groups based on the lowest level of CD30 expression (CD30\textsubscript{min}): CD30\textsubscript{min} < 10% and CD30\textsubscript{min} ≥ 10% (Fig. 1). Patients categorised as CD30\textsubscript{min} < 10% had at least one biopsy with CD30 expression below 10% and at least one other biopsy with at least 10% CD30 expression, the threshold for eligibility (Fig. 1A). Patients categorised as CD30\textsubscript{min} ≥ 10% had ≥10% CD30 expression in both or all biopsies (Fig. 1B).

LCT status at study entry was retrospectively assessed using ≥2 biopsies obtained at the screening. Patients were deemed to have LCT if any single biopsy showed the presence of large cells with nuclei ≥4 times larger than those of normal lymphocytes present in >25% of total dermal infiltrate. LCT status was assessed via central pathologist review (Marise McNeely), and the LCT-assessment methodology was developed in collaboration with Alejandro Gru (University of Virginia).

Pathologists who provided a central review of CD30 expression and LCT status were blinded to patients' treatment assignment and clinical outcome.

Treatment-emergent adverse events (AEs) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Serious AEs were untoward medical occurrences that resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or capacity, a congenital anomaly/birth defect or an important medical event.

Statistical methods are described in the supplementary file.

3. Results

3.1. Patients and disposition

Baseline demographics and disease characteristics for the intention to treat population and patient dispositions have been previously reported [14]. Of the 131 patients randomised, 100 had CD30-positive MF (n = 50 in each arm). After randomisation, biopsies from the 100 patients with MF were reassessed for CD30 expression levels using the Ventana IUO assay; baseline biopsy CD30 expression ranged from 0.0% (undetectable) to 100.0%. Three patients (two in the brentuximab vedotin arm and one in the PC arm) had biopsies that were not confirmed as CD30-positive. All three received study treatment, and consequently, they were included in safety analyses but were excluded from the ITT analyses reported in the primary publication. The median CD30\textsubscript{min} was 10.0% (range: 0.0–100.0%). CD30 levels exhibited high inter-patient and intra-patient variability with several patients exhibiting >60% difference in CD30 expression between biopsies (range: 0–72%) (Fig. 1C). When patients were categorised per baseline, CD30 expression level (CD30\textsubscript{min} < 10% and CD30\textsubscript{min} ≥ 10%), 43 patients (43.0%; 22 in the brentuximab vedotin arm and 21 in the PC arm) had ≥1 biopsy with <10% CD30 expression (CD30\textsubscript{min} < 10%) and 57 patients (57.0%; 28 in the brentuximab vedotin arm and 29 in the PC arm) had all biopsies with ≥10% CD30 expression (CD30\textsubscript{min} ≥ 10%).

Of the 100 patients with CD30-positive MF, 96 were evaluated for LCT status (n = 48 in each arm) and were included in the response-by-LCT analyses, 4 patients had biopsies that could not be assessed due to crushing artefacts and were therefore classified as having unknown LCT status. Baseline characteristics were well balanced between subgroups (Table 1). In both arms, patients with LCT had a wide range of baseline CD30 levels per patient (Table S1). In general, patients with LCT had higher median value of average CD30 (CD30\textsubscript{avg}) positivity (brentuximab vedotin: 50%; PC:...

| Table 1 | Baseline characteristics of patients with LCT-evaluable CD30-positive mycosis fungoides. |
|---------|-----------------------------------------------------------|
|          | Brentuximab vedotin (n = 48) | Physician's choice (n = 48) |
| Male, n (%) | 27 (56) | 26 (54) |
| Median age, years (range) | 56 (22–83) | 59 (22–81) |
| LCT present, n (%) | 17 (35) | 17 (35) |
| LCT absent, n (%) | 31 (65) | 31 (65) |
| Overall staging, n (%) | 15 (31) | 19 (40) |
| IA–IIA | 19 (40) | 18 (38) |
| III | 4 (8) | 2 (4) |
| IV | 9 (19) | 9 (19) |
| Unknown | 1 (2) | — |
| LCT present (n = 17) | (n = 17) |
| Median CD30\textsubscript{avg}\% (range) | 50.00 (3.0–95.0) | 35.00 (6.3–97.5) |
| Median CD30\textsubscript{min}\% (range) | 30.00 (0.0–95.0) | 20.00 (0.0–95.0) |
| LCT absent (n = 31) | (n = 31) |
| Median CD30\textsubscript{avg}\% (range) | 15.00 (3.8–70.0) | 15.00 (1.0–71.7) |
| Median CD30\textsubscript{min}\% (range) | 5.00 (0.0–60.0) | 8.00 (0.0–50.0) |

CD30\textsubscript{avg}, CD30 average levels; CD30\textsubscript{min}, minimum CD30 levels; LCT, large cell transformation.
35%) compared with those without LCT (brentuximab vedotin: 15%; PC: 15%) (Table 1).

3.2. Efficacy

3.2.1. Efficacy of brentuximab vedotin by CD30 expression level

Recognising the high inter-patient and intra-patient variability of CD30 expression levels at baseline, the relationship between baseline CD30 levels and ORR4 was assessed on a per-patient basis. Among the 50 patients with CD30-positive MF treated with brentuximab vedotin, 25 patients (50.0%) achieved ORR4 criteria independent of baseline CD30 expression levels (Fig. 2). Brentuximab vedotin was superior to PC in the CD30$_\text{min}$ < 10% subgroup (ORR4 40.9% versus 9.5%; $\Delta$ 31.4% [95% CI: 2.8–58.1]) and CD30$_\text{min}$ ≥ 10% subgroup (ORR4 57.1% versus 10.3%; $\Delta$ 46.8% [95% CI: 20.6–67.0]) (Table 2).

![Fig. 2. Overall response rate lasting ≥4 months in patients with CD30-positive mycosis fungoides treated with brentuximab vedotin. Per patient objective response rate lasting ≥4 months and minimum baseline (CD30$_\text{min}$) levels. Each box represents an intra-patient range of CD30 expression for individual patients; individual dots represent CD30 expression from individual biopsies at baseline. Data were plotted from highest to lowest variability in CD30 expression. Horizontal bars within each box represent median CD30 expression among all biopsies tested. The top and bottom of each box represent 75th and 25th percentiles; upper and lower ends of vertical dashed lines represent maximum and minimum values (for patients with two biopsies 75th and 25th percentiles overlapped maximum and minimum values). The horizontal dashed line at 10% represents the cut-off for enrollment.](image-url)
Median PFS in the brentuximab vedotin arm was higher than that in the PC arm, regardless of baseline CD30 expression. For patients with CD30 min < 10% median PFS with brentuximab vedotin was 16.7 months (95% CI: 8.6–27.0) versus 2.3 months (95% CI: 1.6–3.5) with PC (HR: 0.189; 95% CI: 0.087–0.414). For patients with CD30 min/C21 ≥ 10%, median PFS was 15.5 months (95% CI: 9.8–22.8) versus 3.9 months with PC (95% CI: 2.2–6.3) with HR: 0.340 (95% CI: 0.172–0.674) (Fig. 3). The CD30 min and CD30 max levels at baseline had no discernible effect on whether patients achieved an ORR4 or not (Fig. S1).

### 3.2.2. Efficacy of brentuximab vedotin by LCT status

ORR4 was consistently higher with brentuximab vedotin versus PC in patients with LCT (n = 11 [64.7%] versus n = 3 [17.6%]) and those without LCT (n = 12 [38.7%] versus n = 2 [6.5%]) (Table 2). Within the brentuximab vedotin arm, a higher proportion of patients with LCT achieved an ORR4 than those without LCT (64.7% [n = 11] versus 38.7% [n = 12]) (Table S1), although the difference was not significant (p = 0.155). Median PFS was improved with brentuximab vedotin versus PC in patients with LCT (15.5 months [95% CI: 9.1–22.8] versus 2.8 months [95% CI: 1.4–7.3];

![Fig. 3. Comparison of PFS with brentuximab vedotin versus physician’s choice by baseline CD30 expression level in patients with CD30-positive mycosis fungoides. CD30 min, minimum CD30; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.](image-url)

Table 3

Overall summary of treatment-emergent AEs by CD30 expression level.

| Treatment | Brentuximab vedotin (n = 50) | Physician’s choice (n = 49) |
|-----------|------------------------------|----------------------------|
| CD30 min subgroup | CD30 min < 10% (n = 22) | CD30 min ≥ 10% (n = 28) | CD30 min < 10% (n = 21) | CD30 min ≥ 10% (n = 28) |
| Any treatment-emergent AE, n (%) | 22 (100.0) | 28 (100.0) | 20 (95.2) | 23 (82.1) |
| Grade ≥3 AE, n (%) | 11 (50.0) | 10 (35.7) | 12 (57.1) | 9 (32.1) |
| Serious AE, n (%) | 7 (31.8) | 8 (28.6) | 9 (42.9) | 5 (17.9) |
| Peripheral neuropathy, n (%) | 15 (68.2) | 19 (67.9) | 0 | 2 (7.1) |

AE, adverse event; CD30 min, minimum CD30 levels.
p = 0.002) and without LCT (16.1 months [95% CI: 8.6–21.6] versus 3.5 months [95% CI: 2.2–4.3]; p < 0.001) (Table 2).

Among patients with LCT, the median CD30<sub>avg</sub> expression was 65% in patients who achieved ORR4 versus 20% in those who did not (Table S1). Of the patients with LCT who achieved ORR4, 9/11 patients in the brentuximab vedotin arm had CD30<sub>avg</sub> ≥ 40.0%, but responses were also noted in the 2 patients with low CD30<sub>avg</sub> (10.0% and 17.5%) (Fig. S2A). In the PC arm 3 patients with a range of CD30<sub>avg</sub> values achieved OR lasting ≥4 months (Fig. S2B).

### 3.3. Safety analyses

In the primary analysis of the ALCANZA safety population, any grade adverse events (AEs) occurred in 95% of 66 patients in the brentuximab vedotin arm and 90% of the 62 patients in the PC arm; grade 3–4 AE rates were 41% and 47% in the brentuximab vedotin and PC arms, respectively [14]. In the brentuximab vedotin arm, peripheral neuropathy was the most frequent any grade AE, occurring in 67% of patients in the brentuximab vedotin group versus 6% in the PC arm. In the PC arm, the AE profiles were different between patients treated with methotrexate and bexarotene. The most frequent any grade AE in methotrexate-treated patients was pyrexia (28% [4% grade 3]), whereas the most frequent AE in bexarotene-treated patients was hypertriglyceridaemia (30% [14% grade 3, 8% grade 4]) [14].

Table 3 presents a summary of treatment-emergent AEs occurring in patients with MF categorised by CD30 expression levels per the current analysis. Overall, AE incidences were similar in the brentuximab vedotin and PC treatment arms regardless of CD30 expression levels. Peripheral neuropathy occurred more often in brentuximab vedotin-treated patients with similar rates between CD30<sub>min</sub> < 10% and CD30<sub>min</sub> ≥ 10% (68.2% and 67.9%, respectively). Rates of grade ≥3 AEs were not significantly different in patients with CD30<sub>min</sub> < 10% compared with those with CD30<sub>min</sub> ≥ 10% in the brentuximab vedotin arm (50.0% versus 35.7%; p = 0.4670) and the PC arm (57.1% versus 32.1%; p = 0.1447). The incidence of serious AEs exhibited a similar pattern with numerically higher incidences in patients with CD30<sub>min</sub> < 10% compared with those with CD30<sub>min</sub> ≥ 10% in the brentuximab vedotin arm (31.8% versus 28.6%) and the PC arm (42.9% versus 17.9%). There was no difference in safety with respect to LCT status.

### 4. Discussion

Previous studies have demonstrated responses to brentuximab vedotin in patients with MF across a range of CD30 expression levels, including 0% [7,8]. The current analyses found that despite high inter-patient and intra-patient variability in baseline CD30 expression levels of patients with MF, a higher proportion of patients treated with brentuximab vedotin patients achieved ORR4 compared with those who received PC, and median PFS values were higher with brentuximab vedotin, regardless of baseline CD30 expression levels as assessed by CD30<sub>min</sub>. Clinical responses lasting at least 4 months (ORR4 criteria) were observed across all CD30 expression levels. In addition, AE profiles were generally comparable, irrespective of baseline CD30 expression levels.

The results observed in the ALCANZA study were consistent with previously reported investigator-initiated studies [6–8] where significant clinical activity was observed in patients with low-levels (<10%) of skin CD30 expression. In ALCANZA, demonstration of the effectiveness of brentuximab vedotin in patients who have low (<10%) or visually undetectable levels of CD30 by IHC in one biopsy may be due to lack of sensitivity of the assay used to detect cell-surface CD30 expression. In another CTCL study, the use of a more sensitive detection methodology (e.g. multispectral imaging) suggests that appreciable CD30 expression may be present in up to 95% of IHC-negative biopsies [8]. A post-marketing commitment for the approval of brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisolone (CHP) in front-line sALCL or other CD30-expressing peripheral T-cell lymphomas is to develop a clinically validated in vitro diagnostic for CD30 expression to inform patient selection. In the meantime, standard IHC detection remains an appropriate tool for characterising CD30-expressing malignancies, though guidelines may be helpful.

In ALCANZA, the presence of highly variable CD30 expression between different lesions within the same patient (intra-patient variability) may also contribute to why patients identified as “CD30-negative” in a single biopsy may benefit from brentuximab vedotin. With 43% of MF patients enrolled having at least one baseline biopsy with <10% CD30 expression, multiple biopsies may be considered for testing; however, assessment of CD30 expression levels in an investigator-initiated trial utilising multiple skin biopsies demonstrated similar intra-patient variability in the CD30 expression levels [6,8]. Other studies have postulated that alternative, CD30-independent tumour killing mechanisms may contribute to the antitumour activity of brentuximab vedotin. These include antibody-dependent cellular phagocytosis, immunogenic cell death, the bystander effect and depletion of CD30-positive T regulatory cells [15–20]. In the ALCANZA study, there does not appear to be a level of CD30 expression that is predictive of
response to brentuximab vedotin for patients with MF making the determination of a threshold level uncertain. Interpretation of these findings may be limited as the ALCANZA study excluded patients with <10% CD30 expression per central review, and patients may have been selected for screening based upon the local evaluation of CD30 expression.

LCT in patients with MF is largely seen as an independent prognostic factor for a less favourable outcome in patients with MF, being associated with aggressive disease and inferior prognosis [10–13,21]. Contrary to this, the current sub-analysis of patients with MF in the ALCANZA study found that the superior efficacy of brentuximab vedotin compared with PC was largely unaffected by the presence or absence of LCT. In terms of the ALCANZA primary endpoint, ORR4, patients with MF and baseline LCT achieved higher ORR4 than those without LCT in both the brentuximab vedotin and the PC arms. Within each arm, median PFS was comparable between LCT subgroups, suggesting no clinically meaningful impact of LCT status on PFS. Interpretation of results per LCT status may, however, be limited by low sample size and intra-patient heterogeneity of detectable LCT in individual biopsies. In other words, patients without LCT may actually have false-negative biopsies based on selection bias relating to the biopsy site. Within each arm, median PFS was comparable between LCT subgroups, suggesting no clinically meaningful impact of LCT status on PFS.

Finally, the safety profiles of brentuximab vedotin and PC in patients with MF were similar and largely unaffected by baseline CD30 status; rates of serious AEs were similar between the CD30 subgroups. Peripheral neuropathy is a known effect of brentuximab vedotin treatment and is generally reversible [14]. There was no meaningful difference in rates of peripheral neuropathy in each of the CD30 subgroups evaluated.

In conclusion, these results indicate that in the ALCANZA study population, CD30 expression is present in most of the patients with MF, both with and without LCT. Given that treatment responses were observed across the entire range of CD30 expression, study outcomes demonstrate a consistently favourable benefit/risk profile for brentuximab vedotin in patients, irrespective of baseline CD30 expression levels and LCT status.

**Author contributions**

**Study concepts:** Alejandro A. Gru, Steven M. Horwitz, Youn H. Kim, Julie Lisano, Meredith Little, Lauren C. Pinter-Brown, H. Miles Prince, Jose A. Sanches, Julia Scarisbrick, Rudolf Stadler, William L. Trepicchio.

**Study design:** David Fisher, Alejandro A. Gru, Steven M. Horwitz, Youn H. Kim, Julie Lisano, Meredith Little, Lauren C. Pinter-Brown, H. Miles Prince, Pietro Quaglino, Julia Scarisbrick, Rudolf Stadler, William L. Trepicchio.

**Data acquisition:** Oliver Bechter, Reinhard Dummer, Madeleine Duvic, Herbert Eradat, David Fisher, Alejandro A. Gru, Steven M. Horwitz, Youn H. Kim, Julie Lisano, Meredith Little, Marise McNeely, Pablo L. Ortiz-Romero, Lauren C. Pinter-Brown, H. Miles Prince, Pietro Quaglino, Jose A. Sanches, Julia Scarisbrick, Rudolf Stadler, Kerry Taylor, William L. Trepicchio, Judith Trotman, Jan Walewski, Michael Weichenthal, Pascal Wolter, Pier L. Zinzanni.

**Quality control of data and algorithms:** Oliver Bechter, David Fisher, Youn H. Kim, Meredith Little, Jose A. Sanches, William L. Trepicchio.

**Data analysis and interpretation:** Oliver Bechter, Lisa Brown, Veronica Bunn, Reinhard Dummer, Madeleine Duvic, David Fisher, Alejandro A. Gru, Steven M. Horwitz, Youn H. Kim, Julie Lisano, Meredith Little, Matthew Onsum, Pablo L. Ortiz-Romero, M. Corinna Palanca-Wessels, Lauren C. Pinter-Brown, H. Miles Prince, Jose A. Sanches, Julia Scarisbrick, Rudolf Stadler, William L. Trepicchio, Jan Walewski, Michael Weichenthal, Pascal Wolter, Pier L. Zinzanni.

**Statistical analysis:** Lisa Brown, Veronica Bunn, Meredith Little.

**Manuscript preparation:** Oleg E. Akilov, Oliver Bechter, Reinhard Dummer, Alejandro A. Gru, Steven M. Horwitz, Youn H. Kim, Julie Lisano, Meredith Little, Matthew Onsum, M. Corinna Palanca-Wessels, Lauren C. Pinter-Brown, H. Miles Prince, Julia Scarisbrick, Rudolf Stadler, Kerry Taylor, Pascal Wolter.

**Manuscript editing:** All authors.

**Manuscript review:** All authors.

**Funding**

This research was co-funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and Seagen, Inc., Bothell, WA, USA, and was also funded in part through the NIH/NCI Cancer Center Support Grant [grant number P30 CA008748]. Medical writing assistance was funded by Millennium Pharmaceuticals, Inc.

**Data sharing statement**

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual participants data supporting the results reported in this article, will be made available within three months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification in compliance with applicable privacy laws, data protection and requirements for consent and anonymisation.
Conflict of interest statement

Y.H.K. reports advisory roles for Seagen and Takeda. H.M.P. reports advisory board for and grants or funds from Takeda. D.F. reports advisory roles for Kyowa Kirin. S.M.H. reports consulting fees from ADC Therapeutics, C4 Therapeutics, Celgene, Janssen, Kura Oncology, Kyowa Hakko Kirin, Myeloid Therapeutics, Seagen, Takeda, Verastem and Vividion Therapeutics, and research grants or funds from ADC Therapeutics, Aileron, Celgene, Daiichi Sankyo, Forty Seven, Inc., Kyowa Hakko Kirin, Millennium/Takeda, Portola Pharmaceuticals, Seagen, Trillium Pharmaceuticals and Verastem. M.D. reports research funding from Takeda and Millennium for this study, Seagen for a physician IST, and institutional funding from Solenginex, miragene, Rhizen and Eisai. O.B. reports consulting fees from Novartis, BMS, Sanofi, Pierre, Fabre and MSD. J.A.S. reports speaker’s bureau, and consultancy/advisory roles for Takeda (Brazil). J.S. reports consulting fees from/Clinical Expert for Takeda. P.Q. reports advisory boards and speaker fee for Takeda, Kiowa, Therakos, Miragen, Helsinn-Recordati, Innate Pharma, 4SC and Actelion. P.L.Z reports advisory roles for and honoraria from Merck, BMS, Servier, Takeda, TG Therapeutics, ADC Therapeutics, Abbvie, Incyte, Janssen, Gilead, Eusapharma, Roche, Debiopharm and Novartis. H.E. reports advisory roles for Abbvie and Genentech, honoraria from Abbvie, Genentech, Takeda and Pharmacysc, grants or funds from Abbvie, Genentech, Pharmacysc, Acerta, Celgene and Astrazeneca. L.C.P-B. reports advisory roles for and honoraria from Seagen. P.L.O-R. reports advisory roles for Takeda, Helsinn, 4SC, Actelion, Innate Pharma, Recordati Rare Diseases, Kyowa and miRagen, grants or funds from MEDA, and PLCG1 mutation patent. O.E.A. reports advisory roles for Trillum Therapeutics, Bioniz, Kyowa Kirin and Meivir, and research grants or funds from Actelion, Adaptive Biotechnology, Trillum Therapeutics, Pfizer and Kyowa Kirin. J.T. reports research funding from Takeda, Celgene, Roche, Beigene, Janssen and PCYC. M.W. reports honoraria from Takeda and Kyowa Kirin, and research grants or funds from Millennium. J.W. reports advisory roles for Roche, Celgene, Takeda, Janssen-Cilag, Servier, Amgen, BMS, Abbvie, Novartis and Gilead, honoraria from Roche, Celgene, Takeda, Janssen-Cilag, Servier, Amgen, Abbvie, Gilead and Novartis, grants or funds from Roche, GSK/ Novartis, Takeda and Janssen-Cilag, and conference travel support from Roche. A.A.G. reports advisory roles for Seagen, Innate Pharma and StemLine Therapeutics, honoraria and grants or funds from StemLine Therapeutics, and consultancy fees from Innate Pharma and StemLine. L.B. reports employment for Zymeworks. M.C.P-W., J.L. and M.O. report employment for and ownership of stocks/shares from Seagen. V.B. reports employment for Takeda Pharmaceuticals. M.L. reports employment for and ownership of stocks/shares from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd. W.L.T. reports employment for and ownership of stocks/shares from Takeda Pharmaceuticals. R.D. reports intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron and Alligator. S.W., R.S., P.W., K.T., and M.M. have no conflicts of interest to disclose.

Acknowledgements

The authors would like to thank the patients who participated in this study and their families, as well as other investigators and staff at all ALCANZA clinical sites. They would also like to thank the members of the Independent Data Monitoring Committee and Independent Review Committee and Marise McNeely (CD30 and LCT) and Alejandro Gru (LCT) for the pathological review of biopsies. Additionally, the authors would like to acknowledge Hedley Coppock of Ashfield MedComms, an Ashfield Health company, part of UDG Healthcare plc, for writing support during the development of this manuscript, which was funded by Millennium Pharmaceuticals, Inc., and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. Ann Intern Med 2015;163:461—4).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.01.054.

References

[1] Rangwala S, Duvic M, Zhang C. Trends in the treatment of cutaneous T-cell lymphoma — critical evaluation and perspectives on vorinostat. Blood Lymphat Canc 2012;2:17–27. https://doi.org/10.2147/BLCTT.S15564.
[2] Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol 2019;180: 496–526. https://doi.org/10.1111/bjd.17240.
[3] Li JY, Horwitz S, Moskowitz A, Myskowski PL, Pulitzer M, Querfeld C. Management of cutaneous T cell lymphoma: new and emerging targets and treatment options. Canc Manag Res 2012;4: 75–89. https://doi.org/10.2147/CMAR.S9660.
[4] Willems R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019; 133: 1703–14. https://doi.org/10.1182/blood-2018-11-881268.
Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, Mehra T, Ikenberg K, Moos RM, Benz R, Nair G, Schanz U, Kim YH, Tavallaee M, Sundram U, Salva KA, Wood GS, Li S, Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015;33:3750–5.

Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015;33:1204–6.

Rahbar Z, Li S, Tavallaee M, Novoa RA, Kim J, Kim YH. Variability in the expression of immunohistochemical markers: implications for biomarker interpretation in cutaneous T-cell lymphoma. J Invest Dermatol 2018;138:1204–6. https://doi.org/10.1016/j.jid.2017.11.035.

Variability in the expression of immunohistochemical markers: implications for biomarker interpretation in cutaneous T-cell lymphoma. J Invest Dermatol 2018;138:1204–6. https://doi.org/10.1016/j.jid.2017.11.035.

Ferreira S, et al. Brentuximab as a treatment for CD30+ cutaneous T-cell lymphoma and sezary syndrome. JAMA Dermatol 2015;151:73–7. https://doi.org/10.1001/jamadermatol.2014.1629.

Mehra T, Ikenberg K, Moos RM, Benz R, Nair G, Schanz U, et al. Brentuximab as a treatment for CD30+ mycosis fungoides and sezary syndrome. JAMA Dermatol 2015;151:73–7. https://doi.org/10.1001/jamadermatol.2014.1629.

Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730–9. https://doi.org/10.1200/JCO.2009.27.7665.

Santen RJ, Spitz A. A survey of patients with advanced-stage cutaneous T-cell lymphoma. J Clin Oncol 2015;33:3766–73. https://doi.org/10.1001/jco.2015.61.7142.

Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 2008;112:3082–7. https://doi.org/10.1182/blood-2008-05-154609.

Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 2012;119:1643–9. https://doi.org/10.1182/blood-2011-08-376319.

Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. 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;390:555–66. https://doi.org/10.1016/S0140-6736(17)31266-7.

Cao A, Heiser R, Law C-L, Gardai SJ. Auristatin-based antibody drug conjugates activate multiple ER stress response pathways resulting in immunogenic cell death and amplified T-cell responses [abstract]. Canc Res 2016;76(Suppl 14):4914. https://doi.org/10.1158/1538-7445.AM2016-4914.

Gardai SJ, Epp A, Law C-L. Brentuximab vedotin-mediated immunogenic cell death [abstract]. Canc Res 2015;75(Suppl 15):2469. https://doi.org/10.1158/1538-7445.AM2015-2469.

Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 2018;131:1183–94. https://doi.org/10.1182/blood-2017-10-811224.

Li F, Zhang X, Emmerton K, Jonas M, Setter J, Arthur B, et al. Relationship between in vivo antitumor activity of ADC and payload release in preclinical models [abstract]. Canc Res 2014;74(Suppl 19):3604. https://doi.org/10.1158/1538-7445.AM2014-3604.

Olfazoglu E, Kessler KM, Sievers EL, Grewal IS, Gerber HP. Combination of the anti-CD30-auristatin-E antibody-drug conjugate (SGN-35) with chemotherapy improves antitumour activity in hodgkin lymphoma. Br J Haematol 2008;142:69–73. https://doi.org/10.1111/j.1365-2141.2008.07146.x.

Sutherland MS, Sanderson RJ, Gordon KA, Andreyka J, Cerveny CG, Yu C, et al. Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-auristatin conjugates. J Biol Chem 2006;281:10540–7. https://doi.org/10.1074/jbc.M510026200.

Benton EC, Crichton S, Talpur R, Agar NS, Fields PA, Wedgeworth E, et al. A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and sezary syndrome. Eur J Canc 2013;49:2859–68. https://doi.org/10.1016/j.ejca.2013.04.018.