

Brentuximab Vedotin addition to Gemcitabine in Relapsed or Refractory Peripheral T-cell Lymphoma: a LYSA Phase II Study

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Abstract:

We aim to evaluate the efficacy of brentuximab vedotin (BV) combined with gemcitabine followed by BV maintenance in relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL). Patients (pts) with at least 5% CD30-positive cells by immunohistochemistry received 4 GBV induction (28d) cycles of gemcitabine 1000 mg/m² (d1;d15) plus BV 1.8 mg/kg (d8) followed in responding pts by up to 12 BV maintenance (21d) cycles. Primary end point was overall response rate (ORR) after 4 induction cycles by CT-scan-based Lugano criteria. Of the 71 enrolled pts (median age of 66 years), 80.3% had received 1 prior line, 60.6% were refractory. The diagnoses per pathology central review were TFHL (47.9%), ALCL, [ALK- (19.7%) and ALK+ (7%)], PTCL-NOS (12.7%) and other entities (12.7%). In the intention-to-treat analysis, ORR was 46.5% with 19.7% complete response. Twenty-eight pts received maintenance. Grade 3-4 adverse events reported in ≥10% of pts during induction comprised: of neutropenia (55%), thrombocytopenia (14%), anemia (21%), infection (14%); during maintenance comprised of neutropenia (39%), thrombocytopenia (21%) and peripheral neuropathy (14%). With a median follow-up of 32.6 months, the median duration of response (DOR), progression-free (PFS) and overall survival were 15.8, 4.5 and 12.9 months, respectively. Efficacy, higher in ALCL, was present in the TFHL and PTCL-NOS group with and ORR, CR, PFS and DOR of 37.2%, 18.6%, 4 and 12.5 months, respectively. A negative association of high baseline soluble CD30 on both response and survival was found, which in ad hoc analysis appeared highly relevant in TFHL and PTCL-NOS patients. EudraCT 2017-000409-1 and NCT03496779

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Abstract:

We aim to evaluate the efficacy of brentuximab vedotin (BV) combined with gemcitabine followed by BV maintenance in relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL). Patients (pts) with at least 5% CD30-positive cells by immunohistochemistry received 4 GBV induction (28d) cycles of gemcitabine 1000 mg/m² (d1;d15) plus BV 1.8 mg/kg (d8) followed in responding pts by up to 12 BV maintenance (21d) cycles. Primary end point was overall response rate (ORR) after 4 induction cycles by CT-scan-based Lugano criteria. Of the 71 enrolled pts (median age of 66 years), 80.3% had received 1 prior line, 60.6% were refractory. The diagnoses per pathology central review were TFHL (47.9%), ALCL, [ALK- (19.7%) and ALK+ (7%)], PTCL-NOS (12.7%) and other entities (12.7%). In the intention-to-treat analysis, ORR was 46.5% with 19.7% complete response. Twenty-eight pts received maintenance. Grade 3-4 adverse events reported in $\geq 10\%$ of pts during induction comprised: of neutropenia (55%), thrombocytopenia (14%), anemia (21%), infection (14%); during maintenance comprised of neutropenia (39%), thrombocytopenia (21%) and peripheral neuropathy (14%). With a median follow-up of 32.6 months, the median duration of response (DOR), progression-free (PFS) and overall survival were 15.8, 4.5 and 12.9 months, respectively. Efficacy, higher in ALCL, was present in the TFHL and PTCL-NOS group with and ORR, CR, PFS and DOR of 37.2%, 18.6%, 4 and 12.5 months, respectively. A negative association of high baseline soluble CD30 on both response and survival was found, which in *ad hoc* analysis appeared highly relevant in TFHL and PTCL-NOS patients. EudraCT 2017-000409-1 and NCT03496779

Key Points:

Brentuximab addition to Gemcitabine safely increases ORR to 46.5% with 19.7% CR with a and 15.8 months DOR in 71 pts with R/R PTCL.

ALCL had the best results. In TFHL and PTCL-NOS pts, soluble CD30 appears strongly predictive of outcome whereas CD30 expression is not.

Article :

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group representing 6.3% of non-cutaneous lymphomas, including: angioimmunoblastic T-cell lymphoma (AITL) (the major subtype of the follicular helper T-cell lymphomas (TFHL) subgroup), PTCL not otherwise specified (PTCL, NOS), and anaplastic large cell lymphomas (ALCL), ALK+ or ALK-.¹

Patients with relapsed or refractory (R/R) PTCL have a poor prognosis, with a median progression-free survival (PFS) of around 3 months and a median overall survival (OS) of 5 to 11 months in patients unable to reach transplant consolidation.²⁻⁶ The most consistent curative approach remains allogeneic hematopoietic cell transplantation (allo-HCT).^{7,8} Only a small proportion of patients are eligible, and allo-HCT should at best be offered to patients with controlled disease. Treatment options after failing first line therapy are limited, stressing the need for novel therapeutic agents. Numerous regimens are currently being used, with no evidence that multidrug combinations are more effective than monotherapies.^{9,10}

Brentuximab vedotin (BV), an anti-CD30 chimeric monoclonal antibody coupled to the microtubule-disrupting monomethyl auristatin E, has shown spectacular efficacy in the treatment of R/R ALCL (both ALK- and ALK+), with an ORR of 86%, including 57% CR, and 25.6 months median duration of response (DOR).^{11,12} Data pertaining to BV monotherapy in relapse treatment of non-ALCL entities that may express CD30 were reported in prospective phase 2 studies with lower ORR and CR rates of 25-45% and 10-25% respectively.¹³⁻¹⁵ In non-ALCL entities, the factors predictive of response are not determined and appear unrelated to the level of CD30 expression in the tumor.^{13,14,16}

The LYSA group designed a prospective phase II study to assess the efficacy and tolerability of an induction treatment associating BV to gemcitabine a chemotherapy usually used as reference arm in controlled trial¹⁷ followed in responders by BV maintenance in CD30-positive R/R PTCL patients.

PATIENTS AND METHODS

Study Design and Participants

This LYSA prospective open-label Phase II study was conducted in 31 centers in France and in 8 centers in Belgium (ClinicalTrials.gov identifier NCT03496779). Patients' recruitment took place between April 10, 2018 and October 8, 2019, with the last patient visit on August 25, 2022 and a cut-off date of October 2022. The protocol was approved by an independent Ethics Committee (30/01/2018 and 08/05/2018 for France and Belgium), and informed consent was obtained from each patient before any study-related procedure, in accordance with the Helsinki declaration.

Patients aged 18 to 80 years with histologically proven PTCL, CD30 positive (at least 5% of cells according to local examination of the most recent available biopsy), relapsing after or refractory to ≥ 1 line but no more than 3 prior lines of therapy, and at least one ≥ 1.5 cm nodal or extra-nodal target lesion were eligible.

Main exclusion criteria were central nervous system involvement, neutrophil count $< 1500/\text{mm}^3$, platelet count $< 75000/\text{mm}^3$, hemoglobin < 8 g/dL, creatinine > 2.0 mg/dL or creatinine clearance < 40 ml/minute. All criteria are listed in the online version of the protocol.

Study Treatment

Patients were to receive 4 GBV induction cycles every 28 days comprising gemcitabine 1000 mg/m² intravenously at Day 1 and Day 15 combined with BV 1.8 mg/kg intravenously at Day 8. Patients achieving CR or partial remission (PR) after 4 induction cycles were started on maintenance with BV 1.8 mg/kg once every 21 days, up to a maximum of 12 cycles. After the end of induction (EOI), eligible patients could also stop BV maintenance and proceed to consolidation by autologous HCT (auto-HCT) or allo-HCT at their physician's discretion (Supplemental figure 1). Administration of granulocyte colony-stimulating factor and antibiotic prophylaxis were left to the physicians' discretion. In the event of peripheral neuropathy, as soon as National Cancer Institute's Common Terminology Criteria for Adverse

events (AEs) (NCI CTCAE) grade 2 or more (v4.03) was observed, rules for treatment suspension, dose adjustment or even discontinuation were applied.

Study Assessments

Pre-therapeutic evaluation included collection of disease-related symptoms, clinical examination, blood sampling, bone marrow trephine biopsy, cervical, thoracic abdominal and pelvic CT and PET-scan. The primary endpoint was overall response rate (ORR) after the 4th induction cycle in application of the revised Lugano 2014 criteria based on investigators' assessment of clinical and CT-scan response.¹⁸ PET-CT assessment at 4th cycles was a secondary objective. Additional assessments were scheduled after the 2nd induction cycle, after every 3 maintenance cycles, and at the end of maintenance whether complete (12 cycles) or prematurely interrupted. Follow-up was then performed every 3 months for the first 2 years, then every 6 months until at least 3 years after the last inclusion. The safety assessment consisted of collecting and grading AEs using the criteria of NCI CTCAE version 4.03.

Pathological review and exploratory analysis of CD30 associated parameters

Patients' biopsies were collected at the LYSA-Pathology laboratory, Henri Mondor University Hospital, Créteil, France. Review of diagnoses according to the 2017 WHO classification¹⁹ and assessment of CD30 expression by immunohistochemistry (IHC) (BerH2 clone ; Dako ; Agilent technologies) on the most recent tumor samples available before inclusion were performed by two expert pathologists (LdeL and PG). The percentages of CD30-positive cells in neoplastic cells and among all tumor cells (neoplastic cells and reactive microenvironment), were evaluated and recorded with 5% increments based on an adaptation of a previous work.²⁰ Soluble serum CD30 (sCD30) was measured by enzyme-linked immunosorbent assay (CD30 Human ELISA Kit (ThermoFisher, Asnieres France) from frozen (-80°C) collected at baseline, according to product instruction). An initial screening dose was carried out by diluting the sera to 1/4, then dilutions to 1/10 or 1/100 were carried out, if necessary, to remain within the calibration range. Both central IHC assessment of CD30 expression and sCD30 and assays were performed blinded to the study investigators.

Statistical Procedures

Sample size calculation was based on the primary endpoint ORR at the end of 4 induction cycles on the full analysis set corresponding to all patients receiving at least 1 dose of study treatment. To provide a 80% power to detect an increase of 15% of the ORR with one-sided alpha of 0.05, a total of 70 patients was required. The null hypothesis (H0) was $ORR \leq 35\%$ according to the gemcitabine monotherapy arm of the Lumiere study (NCT01482962)²¹. Patients without response assessment (due to whatever reason) are considered as non-responders. Response rates are expressed with 90% confidence interval according to Pearson-Clopper method. Logistic regression models were used to estimate the odd ratios (with 90% CIs) of prognostic factors. Time to event analysis were performed using Kaplan-Meier method and are defined as the time from inclusion to event. Patients without event are censored at the time of last visit with adequate assessment (or last contact for OS). For patients who underwent allo-HCT or auto-HCT consolidation, follow-up was censored at the date of transplantation. Time to event endpoints in the different groups were compared with the use of two-sided log rank tests and Cox proportional-hazards regression. Two different approaches, X-Tile²² and ROC analysis were used to define the optimal cutoff with minimal p-value of CD30 associated parameters for prediction. Cut-off for survival data were determinate with the X-Tile software, allowing to divide the population into subsets for the marker analyzed and to calculate log-rank p-value at each cut-point. The minimal p-value is then selected as the optimal cut-off. Cut-off for response rate were determinate with ROC curves to optimize the sensibility and specificity with the use of the Youden index. Analyses were done with SAS software (version 9.3 or higher), and X-Tile (version 3.6.1).

Considering the analysis of sCD30 and CD30 expression association with response and outcome, we used an approach adjusted for multiple comparisons according to Miller and Siegmund method.^{23,24}

RESULTS

Patients Characteristics

The baseline characteristics of the 71 patients enrolled and treated are shown in Table 1. Median age was 66 years, 66% were male and most had stage III-IV lymphoma (91.6%). Median time from PTCL diagnosis to inclusion was 9.4 months. Centrally reviewed histology according 2017 WHO classification was TFHL (47.9%), [including AITL (38%) and nodal TFHL (9.9%)], followed by ALCL [including ALK+ (19.7%) or ALK- (7%)], PTCL-NOS (12.7%) and all other entities (12.7%). All patients had been exposed to CHOP/CHOP-like, 15.5% to autologous HCT, 80.3% were on 2nd line therapy, and 60.6% were refractory to their previous line.

Consort diagram is on Figure 1. Forty-five patients completed the 4 GBV induction cycle, 28 patients started the BV maintenance and 8 of those reached 12 maintenance cycles. Premature discontinuation was recorded in 63 patients, substantially from lymphoma progression (n = 36) followed by death or AEs (n = 15). There were 3 study withdrawals related to study deviation or patient's request. Finally, 9 eligible patients were withdrawn to enable entry into a transplantation program as permitted by protocol after initial evaluation, either before (n = 4) or during maintenance (n = 5). Eventually 5 underwent allo-HCT (including 1 after relapse and a short course of further treatment) and 1 auto-HCT followed by BV maintenance (Supplemental Figure 2).

Efficacy

We ran intention-to-treat response evaluation of the full analysis set (n = 71) at EOI. ORR was of 46.5% (90%CI, 36.30% to 56.89%) with a CR and PR rate of 19.7% (90%CI, 12.33% to 29.10%) and 26.7% (90%CI, 18.29% to 36.75%) respectively. Hence, the lower limit of the 90%CI being above the 35% (null hypothesis), this phase 2 study provides a positive result according to our statistical plan. At 2 GBV cycles (n = 33), ORR was 49.3% [90%CI, 39.00% - 59.63%] and CR rate was 12.7% [90%CI, 6.78% - 21.08%]. The best ORR was 55% with CR and PR of 26.8% [90%CI, 18.29% - 36.75%] and 28.2% [90%CI, 19.51% - 38.24%] respectively and in the 66 evaluated patients for this criterion, the median time to best response was 3.5 (0.7 - 12) months.

Applying PET-CT, the overall metabolic response rate after 4 GBV was (n = 32) 45.1% (90%CI, 34.96% to 55.50%), including 23.9% complete metabolic response (Table 2).

After a median follow-up of 32.6 months (range, 0.5 – 45), the median DOR, PFS, time to next treatment and OS were 15.8 months (95%CI, 10.4 to NA), 4.5 months (95%CI, 3.5 to 10), 9.4 months (95%CI 6.0 to 13.4 and 12.9 months (95%CI, 9.0 to 29.6) respectively (Figure 2 A-D). The description of 14 long-term responding PTCL patients with at least 12 months without disease progression is reported in Figure 2 E.

The analysis of efficacy according to PTCL entities is reported in supplemental table 1A and 1B and supplemental figure 4.

CD30 associated parameters evaluation

Secondary endpoint included the analysis of CD30 associated parameters. CD30 expression by IHC was centrally evaluated in 63 patients on biopsies taken either at relapse prior to inclusion (n = 25), at diagnosis (n = 35) or at a previous relapse (n = 3). In ALCL, CD30 expression in neoplastic cells was constant, with a median of 92.5% positive cells. In the non-ALCL entities, the percentage of CD30-positive neoplastic cells was lower, with a median of 10.0% in TFHL, 25.0% in PTCL-NOS and 52.5% in other entities (Supplemental Table 2). In 3 TFHL patients with less than 5% CD30-positive neoplastic cells, CD30 was found expressed at 5% within the tumor including non-neoplastic cells.

For 65 patients with sCD30 available at baseline the median level was 308 (21-9136) ng/mL. (Supplemental Table 3). We examined the potential interactions between the levels of sCD30 or CD30 expression with other covariates. Applying the cutoff of 10% (see below) the percentage CD30 expression on neoplastic cells was not associated with any clinical variable, except unsurprisingly with histology, as this percentage is much higher in ALCL than in the other subtypes. Applying the cutoff of 120 ng/mL (see

below) high sCD30 was associated with stage III-IV and intermediate or high IPI but not with histology, although sCD30 levels were higher in ALCL patients. (Supplemental Table 4A and B) We failed to demonstrate any correlation between baseline sCD30 and the percentage of CD30-positive neoplastic cells either in the ALCL ($P = 0,27$) or in the non-ALCL ($P = 0,48$) groups.

Prognostic parameters

According to a pre-specified univariate analysis we explored the prognostic value of baseline characteristics including CD30-related parameters. Baseline sCD30 was predictive of ORR with an optimal cut-off level of 120 ng/mL (Supplemental Figure 3). Conversely, no relevant cut-off was found for the percentage of CD30-positive neoplastic cells by IHC. Therefore, based on previous reports¹⁶ and on Echelon-2 trial inclusion criteria²⁵ we applied the 10% cut-off of CD30-positive neoplastic cells for further analysis.

This univariate analysis included 11 variables. An increased LDH level was associated with a lower ORR ($P = 0.008$) and a CR rate ($P = 0.044$). Refractory status was associated with shorter PFS ($P = 0.031$) and OS ($P = 0.007$). Non-ALCL histology was associated with both shorter PFS ($P = 0.049$) and OS ($P = 0.041$). Strikingly while CD30 expression $\geq 10\%$ had no impact, a high sCD30 above 120 ng/mL negatively influenced ORR ($P = 0.0004$), CR ($P = 0.0057$), PFS ($P = 0.0114$) and OS ($P = 0.0196$) (Supplemental Table 5).

We performed an exploratory *ad hoc* multivariate model including variables found to have significant impact in pre-specified univariate analysis and one additional variable of clinical relevance (ECOG ≥ 2). ALCL histology and a low sCD30 level appeared in this model to have an independent positive impact on OS, PFS and ORR. For CRR, only sCD30 had an impact in this analysis (Table 3).

We finally performed another exploratory *ad hoc* analysis focusing on TFHL and PTCL-NOS patients, having shorter PFS and OS and spanning a wide range of both percentage of CD30-positive and baseline sCD30. We confirmed in this group the very high negative impact of baseline sCD30 above 120 ng/mL and the absence of impact of CD30 expression on neoplastic cells $\geq 10\%$ on ORR, PFS and OS (Figure 3). As a continuous variable, the percentage of CD30-positive neoplastic cells also had no impact, while baseline sCD30 remained significantly associated with ORR ($P = 0.012$), CR ($P = 0.038$), PFS ($P = 0.043$), but less with OS ($P = 0.052$) and not with DOR ($P = 0.10$).

Safety

During induction, patients were exposed to 236 cycles of GBV (mean 3.3 (+/-1.01) cycles/patient) delivered over a mean of 2.7 (+/- 1.01) months. A dose reduction of BV and gemcitabine was applied for 28 (39.4%) and 26 (36.6%) patients respectively and treatment was discontinued due to AEs in 2 patients. During maintenance, 28 patients were exposed to 219 cycles of BV, mean 7.8 (+/- 4.07) cycles/patient (range 1 to 12) delivered over a mean of 5.0 (+/- 2.98) months. BV dose reduction was applied in 16 (57.1%) patients and treatment was discontinued due to AEs in 10 patients.

At least one grade ≥ 3 AE was reported in 13 patients during induction and in 17 patients during maintenance. Grade III and IV AEs are reported in Table 4.

Peripheral neuropathy of any grade, assessed as an AE of clinical interest, was reported in 22 patients during induction (n=9; 12.6%) or during maintenance (n = 13; 46.4%), including grade 1 (n = 2), 2 (n = 13) or 3 (n = 7). In 7 patients, grade 3 (n = 5) or 2 (n = 2) peripheral neuropathies led to treatment discontinuation.

During the study 44 deaths were reported, including 31 related to lymphoma with a median time from inclusion to death of 7.7 (0.53-40.87) and 5.6 (1.31-39.26) months respectively. In 13 cases, death resulted from concurrent illness [n=9, including sepsis (5), sudden death (1), pneumonitis (1), respiratory distress (1), altered general condition (1), Covid-19 (1)], toxicity of subsequent re-induction therapy (n=1), or unknown (n=3). (Supplemental Table 6) Five of the deaths from concurrent illness were reported as AEs occurring during induction, no $\geq$ grade 3 neutropenia were recorded during the GBV cycles in these patients and the investigator's narrative did not describe that death resulted from neutropenia.

DISCUSSION

In R/R PTCLs the development of new strategies is imperative and following this aim the LYSA group tested a regimen comprising GBV induction followed by BV maintenance. We obtained an ORR of 46.5%, significantly higher compared to a published experience of gemcitabine alone²⁶, with almost 20% CR and a DOR exceeding 15 months which is achieved according to statistical plan, in comparison with gemcitabine alone. The cohort was well characterized based on central pathological review according to the WHO 2017 classification. In univariate analysis, the treatment had more efficacy in patients with relapsed than in those with refractory disease and with ALCL, consistent with the knowledge that BV-based therapy is most beneficial in ALCL either in the R/R setting^{12,13,27,28} or in front line²⁵.

Despite being in line with our hypothesis, the benefit of combining BV to gemcitabine in comparison to gemcitabine alone remains modest. This study does not address the comparison of combining gemcitabine with BV compared to BV alone and does not provide statistically backed result for each PTCL entity, a frequent pitfall in PTCL studies.

The inclusion of ALCL may have led to an upward bias in the results. At time of study conception, BV was registered in R/R ALCL, based on the compelling results of a single pivotal phase 2 monotherapy study.^{11,12} Additional prospective data seemed useful. Moreover, given the possible inaccuracies of histopathological diagnosis²⁹, the probability of including CD30-positive PTCL that would have turned out to be ALCL after review was significant. We finally based our statistical hypothesis on the gemcitabine arm of the Lumiere trial in which ALCL could be included.^{21,26} Surprisingly in ALCL compared to the pivotal phase 2, ORR and CR rate appear lower with a shorter PFS which however was censored in the event of transplantation. The changes in BV administration related to AEs were identical. The use of a combination at the expense of a reduction in the dose intensity of BV therefore does not appear to explain this difference. In addition real life data of BV in ALCL³⁰⁻³³ have not always replicated the results of the pivotal phase 2 study and in the Echelon-2 trial update²⁷, ALCL patients who experienced progression after CHOP arm and received BV alone or in combination had an 51% ORR and 39% CR rate.

For the non-ALCL entities, experience on BV monotherapy had been initially collected in 3 prospective studies^{13,15,14} of 35, 21 and 16 patients, the first being before the official classification identifying the major TFHL entity. This study brings additional data in 34 TFHL and 9 PTCL-NOS patients. In this group as whole, the ORR, and CR are 37.2 and 18.6%, the PFS and DOR are of 4 (2.9-6.4) and 12.5 (120.1-25.2) months respectively and 7 patients remained free of progression for at least 12 months. Compared to gemcitabine monotherapy, ORR and CR rate at 4 cycles of the GBV combination appear in the same range than in 2 prospective studies (ORR of 55 and 30% ; CR of 35 and 22%)^{21,34}. Likewise, if we consider the prospective results on BV monotherapy^{13,15,14}, our study does not show that combining Gemcitabine with BV brings better results but confirms the level of activity of a BV-based strategy in PTCL-NOS and TFLH patients. Most recent data are going in the same direction. In the real-life 81 R/R PTCL patients treated with BV and bendamustine (BBV) combination,²⁸ the ORR and CR rate were 68 and 49% respectively with response lasting more than one year suggesting that may be bendamustine is a better choice for a combo. The Ro-CHOP phase 3 study exploratory analysis also suggest the benefit of BV-based therapy in the treatment of PTCL relapses³⁵. Finally in the 33 patients of the PTCL cohort (excluding ALCL) of the CheckMate phase II, a combination of BV and nivolumab gives³⁶ an ORR and CR rate of 45.5 and 33.3% respectively with a DOR of 4.6 months.³⁷

In prospective studies evaluating BV-based therapy in PTCL and CTCL, CD30 expression by IHC on tumor samples was an inclusion criterion, with different levels depending upon the studies obtained by local^{13,15,25,38} or central^{11,39} assessment. Other than the ALCL entity combining constant and strong CD30 expression and the best BV results, the correlation between CD30 expression and BV efficacy in mature T-cell lymphomas remains unclear¹⁶. Analysis of parameters associated with CD30 was an essential secondary objective of our study. Following inclusion, among 63 centrally evaluated patients, 59 (93.6%) had at least 5% CD30-positive neoplastic cells by IHC. Applying the $\geq 10\%$ cut-off of positivity we did not

find any correlation with efficacy, as previously described¹⁶. Conversely, we found a significant negative impact of a high level of baseline sCD30 on both response and survival.

Focusing on TFHL and PTCL-NOS patients, having less benefit of study treatment, and spanning a wide range of both percentages of CD30-positive and of baseline levels of sCD30, an exploratory *ad hoc* analysis did not find any impact of CD30 expression while the level of baseline sCD30 kept a strong predictive impact on outcome. This finding on TFHL and PTCL-NOS patients has yet to be confirmed by a validation cohort, and the impact of sCD30 should ideally be examined across the main PTCL entities and for other BV-based therapy, including BV monotherapy.

We should note that in our cohort, the correlation between sCD30, response, and survival was not found for ALCL, potentially due to the small sample size. Two other studies also found no correlation between sCD30 and BV efficacy in a series of 25 B-cell and T-cell lymphomas including 10 cases of AITL and 5 cases of EBV-positive PTCL⁴⁰ and in a series of 32 cases of CTCL⁴¹.

While remaining cautious, this sCD30 assay could become a useful predictive marker of BV-based therapy efficacy in the tight timeframe of an aggressive disease and should also be tested in front line and in the context of emerging CD30 targeting therapies including CAR-T and bispecific antibodies. CD30 is cleaved by the metalloproteases ADAM10 or ADAM17 from normal and neoplastic cells^{42,43} and its ectodomain sCD30 is released. We speculate that the prognostic impact of high baseline sCD30, could be explained by *in vivo* neutralization of BV. sCD30 level which in our study was also associated advanced stage as well as an intermediate or high IPI could also indicates particular lymphoma aggressiveness as demonstrated in Hodgkin lymphoma⁴⁴.

The side effects of this study treatment were dominated by hematological AEs. Grade ≥ 3 neutropenia related to the GBV combination was found in 55%, higher compared to gemcitabine monotherapy (31%)²⁶ and BV monotherapy in ALCL (21%)¹¹. The occurrence of Peripheral neuropathy of all grades was also found (21%) but at a level not exceeding that of BV monotherapy in ALCL¹¹. Of the 44 deaths which occurred during the study, 13 were considered unrelated to the lymphoma, 5 during GBV induction including respiratory distress, sudden death, septic shock, sepsis and or alteration of general condition. In the context of R/R PTCL, the occurrence of this type of complication is not unexpected.

In the difficult task of treating R/R PTCL^{2,4}, conventional multidrug therapy has produced disappointing results, with no evidence of superiority over limited combinations.^{9,10} Pralatrexate⁴⁵ is not registered worldwide. Histone deacetylase inhibitors alone or in combination have an efficacy seemingly linked to the TFH phenotype.⁴⁶ This includes belinostat⁴⁷ and romidepsin the latter withdrawn from the United States market despite positive results^{48,49}. The oral form of azacytidine in TFHL in the ORACLE phase 3 has an impact on OS but paradoxically no superiority in response.⁵⁰ Drugs targeting EZH2⁵¹ and phosphatidylinositol 3-kinase^{52,53} are in development. However for eligible patients, the best curative approach remains allo-HCT, as we reported in the AATT long-term analysis.⁸ It is essential to bridge patients to transplant using an effective and tolerable approach. In this study, out of the 49 patients deemed of eligibility for their age was under 70 years and who achieved a response to induction, 9 patients were withdrawn from study with the aim to proceed to HCT.

In conclusion, we show that a widely available combination of GBV followed by BV maintenance, is beneficial in R/R PTCL not only in ALCL but also in the major entity TFHL and in PTCL-NOS. This study adds to the limited available prospective data advocating the addition of BV in relapse protocols, in all PTCL entities expressing the target of this drug conjugate. In addition, in TFHL and PTCL-NOS patients we found that blood baseline sCD30 levels could be a useful biomarker of response and survival.

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Contributions

O.T., G.D designed, performed research in particular patients' inclusion and treatment, analyzed data and wrote the report. R.D. designed and performed research, in particular patients' inclusion and treatment. K.B., Se.B., M.M., L.Y., S.G., S.L.G., C.B., M.A., J.D., C.T., E.B., F.M., S.T., C.M., A.B., R.H., A.C., E.G., G.C., H.F., V.C., B.D., H.Z., D.S., E.N.-V., C.D., S.C., in particular patients' inclusion and treatment. S.L., T.B. and M.-H. D. performed research, in particular sCD30 analysis P.G., A. L.-P., M.P. and L.d.L. performed research, in pathology review and CD30 expression assessments. S.G. did statistical analysis K.B. (second author) and S.L. (third author) provided an equal contribution to the work.

Conflicts of Interest

O.T. Takeda : Travel grant, honorarium and research support. Abbvie : Travel grant, honorarium. BeiGene : Travel grant, honorarium. Astra-Zeneca : Travel grant, honorarium. P.G. Takeda : Travel grant, honorarium and research support.

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Figure's legend

Figure 1. CONSORT diagram.

Explanatory notes to be placed below the figure:

Protocol deviations were in one patient the administration of a 5th BV induction cycle before a consolidation with auto-HCT and one patient the absence of a 12th cycle of maintenance.

“Other reason” means patients withdrawn for transplantation program as permitted by protocol after initial evaluation, either before (n=4) or during maintenance (n=5).

Figure 2: (A) Kaplan-Meier estimates of duration of response of patients achieving either CR or PR after 4 cycles of GBV induction, (B-D) Kaplan-Meier estimates of (B) time to treatment failure, (C) progression free survival and (D) overall survival for the entire cohort. (E) Course of patients with confirmed PTCL and at least 12 months without progression from inclusion.

Figure 3: ORR (A, B) and Kaplan-Meier estimate, with number of subjects at risk and 95% confidence limit of DOR (C, D), PFS (E, F) and OS (G, H) with relative impact of IHC CD30 expression on neoplastic cells (<10% versus ≥10%; left panels) and of ELISA baseline sCD30 level (≤120 ng/mL versus >120 ng/mL; right panels) and in the exploratory analysis of TFHL and PTCL-NOS patients.

Tables

Table 1. Characteristics of included patients.

Parameters

Patients, No.	71	
Age (years)		
Median	66	
Range	20-79	
Age group, years		
≤ 60	23	(32.4)
60 to ≤ 70	26	(36.6)
> 70	22	(31.0)
Sex, n (%)		
Male	47	(66.0)
Female	24	(36.0)
ECOG performance status, n (%)		
0	22	(31.0)
1	33	(46.5)
2	16	(22.5)
LDH, n (%)		
normal	33	(46.5)
> upper limit	38	(53.5)
Ann Arbor stage, n (%)		
I	1	(1.4)
II	5	(7.0)
III	8	(11.3)
IV	57	(80.3)
Extranodal involvement		
0-1 sites	55	(67.6)
≥ 2 sites	16	(32.4)
IPI score		
Low risk	8	(11.3)
Intermediate-low risk	18	(25.4)
Intermediate-high risk	25	(35.2)
High risk	20	(28.2)
Diagnoses according to WHO 2017*, n (%)		
TFH lymphoma (TFHL)	34	(47.9)
<i>AITL</i>	27	(38.0)
<i>Nodal TFHL</i>	7	(9.9)
PTCL-NOS	9	(12.7)
ALCL ALK-	14	(19.7)
ALCL ALK+	5	(7.0)

Other entities ⁽¹⁾	12	(12.6)
CD30 expression on neoplastic cells ⁽²⁾ (%)		
Median	27.5	
Range	(0-100)	
Soluble CD30 ⁽³⁾ (ng/mL)		
Median	308	
Range	(21-9136)	
Disease status, n (%)		
Relapsed ⁽⁴⁾	28	(39.4)
Refractory ⁽⁵⁾	43	(60.6)
Prior lines		
1 line	57	(80.3)
2 lines	11	(15.5)
3 lines	3	(4.2)
Prior therapy		
CHOP/CHOP like regimens	71	(100.0)
ASCT transplantation	11	(15.5)
Bendamustine	2	(2.8)
Epigenetic modifiers	5	(7.0)
Romidepsine	4	(5.6)
Azacytidine	1	(1.4)
Rituximab	4	(5.6)
Radiotherapy	2	(2.8)
Time from diagnosis to enrollment (months)		
Median	9.4	
Range	(2-131)	

* Centrally reviewed

(1) Other entities included : Enteropathy associated T-cell lymphoma (n=2), Subcutaneous panniculitis-like T-cell lymphoma (n=1); Intestinal T-cell lymphoma NOS (n=1); Mycosis fungoides uncertain (n=1); Primary cutaneous CD30+ T-cell lymphoproliferative disorder (n=1), T-cell lymphoma unclassified (n=1); unclassifiable lymphoma (n=1); uncertain diagnosis of lymphoma (n=1).

(2) Semi-quantitative evaluation of expression by immunohistochemistry (on available biopsies in 63 patients).

(3) By ELISA on serum at baseline (available in 65 patients).

(4) At least PR or CR before progression following last prior line.

(5) No PR or CR following last prior line.

Table 2. Response at 4 GBV induction cycles

<i>Lugano CT-Scan based*</i>	Nb	%	90% IC
Overall response	33	46.5	36.30 to 56.89
CR,	14	19.7	12.33 to 29.1
PR	19	26.7	18.29 to 36.75
Stable disease	4	5.6	1.95 to 12.43
Progressive disease	27	38.0	28.37 to 48.46
Death,	3	4.2	1.16 to 10.56
Non evaluable**	4	5.6	1.95 to 12.43

*Primary endpoint

**Related to premature withdrawal for early PD (n=3) or for adverse event after one cycle (n=1)

<i>Lugano PET-Scan based</i>	Nb	%	90% IC
Overall metabolic response	32	45.1	34.96 to 55.50
Complete metabolic response	17	23.9	15.87 to 33.72
Partial metabolic response	15	21.1	13.50 to 30.65
Progressive metabolic disease	11	15.5	8.94 to 24.34
Missing***	28	39.4	29.68 to 49.88

***Related to overt (clinically and/or on CT-scan) disease progression (no PET-CT done) (n=21), deaths (n=3), premature withdrawal after 4 cycles for adverse event (n=2) or other reason (n=2)

Table 3. Multivariate model of response and outcome

Characteristics	ORR		CR		PFS		OS	
	Odd ratio	P	Odd ratio	P	Hazard ratio	P	Hazard ratio	P
LDH Normal (n=33) > upper limit (n=38)	NS	NS	NS	NS	NS	NS	NS	NS
ECOG PS 0 or 1 (n=55) ≥2 (n=16)	NS	NS	NS	NS	NS	NS	NS	NS
Status Relapse (n=43) Refractory (n=28)	NS	NS	NS	NS	NS	NS	NS	NS
Histology ALCL (n=19) Non ALCL (n=52)	0.043	<0.001	NS	NS	3.33	0.002	4.76	0.002
sCD30 ≤ 120 ng/mL (n=20) > 120 ng/mL (n=45)	0.099	0.002	0.15	0.006	3.34	<0.001	4.13	<0.001

Table 4. Grade ≥3 adverse events in patients with relapsed or refractory T-Cell Lymphoma exposed to GBV induction phase (n=71) and maintenance phase (n=28)

Adverse Event	Induction phase (n=71)			Maintenance phase (n=28)		
	No. of patients	% of patients	No. of events	No. of patients	% of patients	No. of events
Total	58	81.7	189	11	39.3	
Neutropenia	39	54.9	74	6	21.4	6
Thrombocytopenia	10	14.1	15	0	0.0	0
Anemia	15	21.1	24	0	0.0	0
Febrile neutropenia	2	3.1	2	0	0.0	0
Infection	10*	14.1	13	2**	7.1	2
Peripheral neuropathy	3	4.2	3	4	14.3	4
Cardiovascular	5	7.0	5	0	0.0	0
Gastrointestinal	4	5.6	4	0	0.0	0
Liver	4	5.6	4	0	0.0	
Skin	3	4.2	3	1	3.6	1
Ionogram abnormalities	2	2.8	2	0	0.0	0
Respiratory	2	2.8	1	1	3.6	1
Tumor lysis syndrome	1	1.7	1	0	0.0	0
Lipase increased	1	1.7	1	0	0.0	0
Arthritis	1	1.7	1	0	0.0	0
Sudden death	1	1.7	1	0	0.0	0

*Including Pneumonia (3), Sepsis or septic shock (3), *Campylobacter* infection (1), *Clostridium difficile* colitis (1), Device related infection (1), *Pneumocystis jiroveci* pneumonia (1), *Pseudomonas* infection (1)

**Including Bronchitis (1) and Cytomegalovirus chorioretinitis (1)

Figure 1





