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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1. ABSTRACT

Full Study Title: Effectiveness and Safety for Re-treatment with Brentuximab-vedotin (BV) in Patients with Relapsed/Refractory (R/R) CD30+ malignancies: a retrospective medical chart review study in Spain. The BELIEVE Study			
Phase:	Non-interventional	**Type:**	Retrospective, Voluntary Post-Authorisation Safety Study (PASS)
Number of Patients: 43		**Number of Study Centers**: 30	

Background and Rationale:

Classical Hodgkin neoplasm of lymphoid tissue, histopathological defined by the presence of malignant mononuclear Hodgkin cells and Reed-Sternberg (RS) cells in a background of inflammatory cells. RS cells are typically CD30 positive, with membranous and Golgi patterns.

In the European Union, the incidence rate of cHL is 2.3, with an annual death rate of 0.4 cases per 100,000. In Spain, the number of cHLcases in 2019 was 1,486 (2019 REDECAN Report) 1, with a crude rate of 3.2, a world standard population-adjusted crude rate of 3.0 and a European standard population-adjusted crude rate of 3.2 lymphoma. The five-year prevalence is approximately 3,883 cases, predominantly affecting young adults between 20 and 40 years old, with a higher incidence in women.

Patients with advanced cHL have a less favorable prognosis. However, overall cHL remains highly curable. The Ann Arbor system is used to stage cHL, ranging from Stage I to IV. The standard first-line treatment for early-stage disease (primarily Stages I and II) is the ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine), followed by targeted radiotherapy. In Spain, the ABVD regimen is the most common treatment for patients with newly diagnosed Stage IV HL, used in 80-90% of cases, but it can cause severe or even life-threatening complications, such as pulmonary toxicity.

Non-Hodgkin lymphomas (NHL) are a diverse group of cancers with varying biology and prognosis. NHL originates in B cells, T cells, or natural killer (NK) cells. T cells and are further divided into peripheral T cell lymphomas (PTCL) and cutaneous T cell lymphomas (CTCL). Systemic anaplastic large cell lymphoma (sALCL) is an aggressive type of non-Hodgkin lymphoma that originates from T cells. It is classified based on the presence (ALK-positive) or absence (ALK-negative) of ALK protein

expression. The incidence of sALCL is estimated to be between 1.5 and 2.0% of all malignant lymphomas.

According to GLOBOCAN data from 2018, Central and Eastern Europe reported 23,807 new NHL cases, with 11,628 in men and 12,179 in women. The mortality figures were 12,148 for men and 5,999 for women. A five-year prevalence of 25% was estimated across Europe.

Brentuximab-vedotin

The Brentuximab vedotin(BV) is an antibody-drug conjugate, administered intravenously. It combines a humanized IgG monoclonal antibody targeting CD30 with the antimitotic compound monomethylauristatin E (MMAE). Clinical studies have demonstrated its effectiveness in various subtypes of T-cell lymphoma and its potential long-term benefits for patients who previously achieved complete response (CR) or partial response (PR) with BV.

Rationale:

Currently, there are only two published studies evaluating the efficacy and safety of BV as a retreatment in cHL and sALCL patients, and only a small number of clinical cases published in CTCL patients. Given the limited real-world data available on the effectiveness and safety of BV retreatment in patients with R/R cHL/ cutaneous T cell lymphoma (CTCL; mycosis fungoides [MF] and primary cutaneous anaplastic large cell lymphoma [pcALCL]) and sALCL, it would be desirable to improve the knowledge around the administration of BV in this clinical setting. As BV may become established as a preferred first-line therapeutic option in both untreated cHL and sALCL cases, future research efforts could be aimed at further exploring the efficacy and safety of BV retreatment in patients who progress or relapse after receiving front-line BV treatment.

Objectives:

Primary objectives

- Assess the effectiveness of re-treatment with BV in Patients with R/R cHL/ CTCL; MF and pcALCL and sALCL)
- Assess the safety (peripheral neuropathy / myelosuppression / infection etc.) of re-treatment with BV in in the studied population.

Secondary objectives

- Describe the patterns of use related to BV as retreatment.

- Describe patient characteristics just prior to the BV retreatment (Just before the initiation of BV retreatment.)
- Describe the duration of tumor control after BV as retreatment.

Exploratory objectives (if applicable)

- Describe further treatment patterns after completion of BV retreatment.
- Explore predictors of response to BV as retreatment therapy.
- Describe disease evolution since the diagnosis of cHL, CTCL or sALCL.

Study Design:

A multicenter, non-interventional, medical chart review study conducted in public and private Spanish sites was designed to describe the efficacy and safety of BV retreatment in the Spanish population in real clinical practice. Each patient chart was reviewed from the time of cHL, CTCL or sALCL diagnosis until his/her study inclusion, progression, or death, whichever was earliest.

Patient data from medical records were extracted in the following periods (see Figure 2 for periods description of the study):

- **Pre-index period:** since diagnosis to start BV retreatment initiation.
- **Index date:** The date that patient initiates BV retreatment was considered.
- **Post-index period**: data since start BV retreatment to date progression or death, whatever came first (or treatment discontinuation due to toxicities or any cause).

All study data was collected retrospectively from the medical records of patients and covered the period from initiation of BV treatment until patient´s inclusion date or until treatment discontinuation due to toxicities or any cause.

Study Population:

The target population consisted of patients with a confirmed diagnosed of cHL, CTCL; MF and pcALCL and sALCL with CD30 positive, and who have previously achieved a CR or PR with BV treatment and subsequently experienced disease progression/relapse and were administered BV retreatment. If they

met the specified inclusion criteria, they were considered included. The Ethics Commitee approves a waiver for the informed consent.

Inclusion criteria

1. Patients greater than or equal to 18 years at the time of the first treatment with BV
2. Histologically confirmed cHL, CTCL (MF and pcALCL) or sALCL with CD30 positive.
3. Patients previously treated with BV containing regimen, with evidence of objective response (determined by having achieved CR or PR), and subsequent disease progression or relapse after discontinuing treatment BV retreatment*
4. Patients with data of disease relapse or progression ≥6 months since the last dose of the first treatment with BV
5. Patient with data available at the participating site since diagnosis of cHL, CTCL (MF and pcALCL) or sALCL.
6. Patients having received at least, two doses of BV as retreatment and having follow up information available at the site for a minimum period of six months or until death.

Exclusion criteria

1. Patients judged by the investigator or sub-investigator to be ineligible for enrollment in the study.

Data Collection and Assessments:

In the present study, data was collected using retrospective period data.

Variables obtained retrospectively were based on and limited to the information available in the medical records of the selected patients, following standard clinical practices. All the variables collected in this study were obtained by reviewing patient's medical chart available at the study site. Some derived variables and endpoints will be calculated afterwards based on the variables collected.

<u>Patient characteristics at diagnosis:</u>

- Age
- Sex
- Ethnicity
- Occupational status and occupation,
- Civil status,

- Living conditions
- Virus test (Tests for common viral diseases such as HBV, HCV and HIV)

Comorbidities (Complications, symptoms and other cHL, CTCL (MF or pcALCL) OR sALCL associated disorders and concomitant treatment present before the initiation of first treatment with BV)

Adverse Events

The following specific AEs were be collected in the Ecrf or Safety analysis: Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy, Neutropenia, Febrile Neutropenia, Renal dysfunction, Liver dysfunction, Pulmonary disorder, Others with clinical relevance, in the following study periods:

- AE due to first treatment with BV
- AE after the end of the first treatment with BV and prior to the retreatment with BV.
- AE related to the retreatment with BV.
- AE after the retreatment with BV and during the follow-up period (≥ 6 months), until death or until loss of follow up)

- Disease characteristics:

- At the diagnosis of cHL, CTCL (MF and pcALCL) or sALCL and before first BV treatment
- After first BV treatment and prior to BV retreatment
- At BV retreatment Initiation
- After discontinuation or BV retreatment termination

- Treatment regimen for cHL, CTCL (MF and pcALCL) or sALCL during the 6-month follow-up period from the termination of BV retreatment at the time just before BV first treatment.

Statistical Methods:

Statistical analyses were performed by IQVIA Information S.A. with SAS® statistical software version 9.4 . Given the descriptive nature of the study, most of the analyses centered around presenting the means, standard deviations, counts, and proportions. Descriptive statistics were presented as absolute and relative frequencies for discrete variables and mean, standard deviation, median, quartiles, minimum and maximum will be reported for quantitative variables. Unless otherwise specified in the description of the analyses, a two-sided 95% confidence interval (CI) was considered as a default (alpha = 5%).

All data were analyzed for overall sample and for different subgroups: cHL, CTCL and sALCL.

Results:

Study population:

Disposition

In total 51 patients were included in the full analysis set, 43 of them fulfilled all inclusion and none of the exclusion criteria and thus were eventually included in the study. The dataset included 16 patients in cHL group, 14 patients in CTCL group, and 13 patients in sALCL group. All 43 patients were included in the safety analysis set and efficacy analysis set for safety and effectiveness evaluation.

Demographic and other baseline characteristics

Patients included in the study had a mean age of 46.2 years; this was higher in patients in the CTCL group (52.9 [13.5] years and sALCL group (51.3 [10.8] years) and was lower in patients in the cHL group (36.2 [13.3] years). The majority of patients in the study were males (58.1%). The number and percentage of male patients in cHL, CTCL, and sALCL groups was 9 (56.2%), 8 (57.1%), and 8 (61.5%), respectively. Among patients enrolled in the study, the majority (37 patients [88.1%]) were Caucasians (13 patients [86.7%] in HL, 12 patients [85.7%] in CTCL and 12 patients [92.3%] in sALCL groups). This was followed by 4 patients (9.5%) of Hispanic origin (2 patients [13.3%] in cHL, 1 patient [7.1%] in CTCL and 1 patient [7.7%] in sALCL groups). One patient (7.1%) in the CTCL group belonged to 'other' ethnic group. A total of 27 patients (62.8%) were alive at the time of data collection from medical records (7 patients (43.8%) in HL, 10 patients (71.4%) in CTCL and 10 patients (76.9%) in sALCL groups). No alive patient was lost to follow-up at the time of data collection from medical records.

Primary *analysis* results

Primary Effectiveness Evaluation (Overall Response Rate)

A total of 33 patients (76.7%) in the study achieved ORR. The percentage of patients achieving ORR was higher in sALCL group (12 patients [92.3%]) compared to patients in cHL group (12 patients [75%]) and CTCL group (9 patients [64.3%]). Overall, the median (min-max) time to achieve ORR in patients was 4.1 (0.6 - 24.3) months (2.9 [1.7 - 24.3], 6.2 [2.2 - 21.7] and 5.1 [0.6 - 15.4] months in cHL, CTCL and sALCL groups, respectively.)

Safety Evaluation

Adverse events during period P1

Overall, 19 patients (46.3%) had AEs related to first BV treatment (6 patients [42.9%] in cHL, 5 patients [35.7%] in CTCL and 8 patients [61.5%] in sALCL group). At the end of P1 period, AEs reported in 2 patients (4.7%) were ongoing (1 patient each in CTCL and sALCL groups). Overall, 6 patients (14%) reported severe AEs (1 patient [6.2%] in cHL group, 2 patients [14.3%] in CTCL group and 3 patients [23.1%] in sALCL group), see table 17 and 18. Commonly reported AEs in the overall group were peripheral sensory neuropathy (10 patients [23.3%], other events with clinical relevance (9 patients [20.9%]), neutropenia (4 patients [9.3%]) and febrile neutropenia (1 patient [2.3%]). Note that each patient could have more than 1 AE. Percentages are always given respect to the overall patients for each cohort.

No Grade 5 and Grade 2 events were reported in the study. Grade 3 and 4 events were reported in 2 patients (neutropenia and febrile neutropenia reported in 1 patient [2.3%] each). There were 2 patients (4.7%) reported with Grade 1 event of peripheral sensory neuropathy.

Adverse events during period P2

A total of 11 patients (26.2%) experienced AEs related to BV treatment (5 patients [33.3%] in cHL, 1 patient [7.1%] in CTCL and 5 patients [38.5%] in sALCL group). At the end of P2 period, AEs reported in 4 patients (9.3%) were ongoing (1 patient each in cHL and CTCL groups, and 2 patients in sALCL group). In total, 4 patients (9.3%) had severe AEs (2 patients [12.5%] in cHL group, 1 patient [7.1%] in CTCL group and 1 patient [7.7%] in sALCL group). The AEs of common occurrence were other events with clinical relevance (10 patients [23.3%]), peripheral sensory neuropathy and febrile neutropenia (2 patients [4.3%] each, respectively.

Only Grade 3 events of febrile neutropenia were reported in 2 patients (4.7%).

Adverse events during period P3

Nearly half of the patients (18 [45%]) had AEs related to BV retreatment (7 patients [53.8%] in cHL, 4 patients [28.6%] in CTCL and 7 patients [53.8%] in sALCL groups) At the end of P3 period, AEs reported in 9 patients (20.9%) were ongoing (2 patients [12.5%] in cHL group, 2 patients [14.3%] in CTCL group and 5 patients [38.5%] in ALCL group). Overall, severe AEs was reported in 8 patients (18.6%); 2 patients (12.5%) in HL group, 3 patients (21.4%) in CTCL group and 3 patients (23.1%) in

sALCL group. Commonly reported AEs in the overall patients during P3 were: other events with clinical relevance (4 patients [25%]), peripheral sensory neuropathy (9 patients [20.9%]), neutropenia (5 patients [11.6%]), peripheral motor neuropathy (2 patients [4.7%]) and pulmonary disorder (1 patient [2.3%]).

No Grade 5 and Grade 1 events were reported during the P3 period. Grade 4 event of peripheral motor neuropathy was reported in 1 patient ([2.3%]). There were 4 Grade 3 events reported in 3 patients (peripheral motor and peripheral sensory neuropathy in 1 patient each [2.3%] and neutropenia in 2 patients [4.7%]). A total of 3 Grade 2 events occurred in 3 patients (peripheral sensory neuropathy in 2 patients [4.7%] and neutropenia in 1 patient [2.3%]).

Adverse events during period P4

Overall, 11 patients (28.9%) experienced AEs after second retreatment with BV (4 patients [30.8%] in cHL, 3 patients [23.1%] in CTCL and 4 patients [33.3%] in ALCL group). At the end of P4 period, AEs reported in 5 patients (11.6%) were ongoing (1 patient each in HL and CTCL group and 3 patients in sALCL group). Overall, severe AEs was reported in 7 patients (16.3%; 3 patients (18.8%) in cHL group, 2 patients (14.3%) in CTCL group and 2 patients (15.4%) in sALCL group. The AEs of common occurrence in overall patients were: other events with clinical relevance (10 patients [23.3%]), peripheral sensory neuropathy (3 patients [7.1%]) and febrile neutropenia (2 patients [4.7%]).

Two Grade 1 events were reported in 1 patient (2.3%; peripheral motor and sensory neuropathy).

Secondary analysis results

Best overall response:

Complete response (CR) was achieved for 26 patients (60.5%). The percentage of patients who achieved CR was higher in sALCL group (11 patients [84.6%]) and cHL group (11 [68.8%]) compared to patients in CTCL group (4 [28.6%]). Overall, the median (min-max) time to CR in 26 patients was 4.0 (0.6-24.3) months. The median (min-max) time to achieve CR in patients was 3.0 (2.6 - 24.3) in cHL group, 7.8 (2.3 - 21.7) in CTCL group, and 5.4 (0.6 - 15.4) months in sALCL group.

Seven patients (16.3%) achieved PR (1 patient [6.2%] in cHL group, 5 (35.7%) in CTCL group and 1 patient (7.7%) in sALCL group). The progression of disease was observed in 6 patients (14%); 2 patients (12.5%) in cHL group, 3 patients (21.4%) in CTCL group and 1 patient (7.7%) in ALCL group. However, stable disease was observed in 4 patients (9.3%); 2 (12.5%) in cHL and 2 (14.3%) in CTCL groups.

Overall, the median (min-max) time to best response (TBR) in patients was 4.1 (0.5 – 43.9) months. The median (min-max) time to achieve TBR in patients was 3.1 (0.5 – 24.3) in cHL group, 6.6(2.2 – 43.9) in CTCL group and 5.4 (0.6 -15.4) months in ALCL group.

Time to treatment failure

Sixteen patients (37.2%) had treatment failure in the study (4 patients [25%] in cHL, 7 patients [50%] in CTCL and 5 patients [38.5%] in sALCL groups). Overall, the median (min-max) TTF was 7.0 (0.4-34.5) months. The median (min-max) TTF in patients was 2.3 (0.4 – 5.5) in cHL group, 8.0 (4.1 - 12.1) in CTCL group, and 10.6 (4.7 - 34.5) months in sALCL group.

Overall survival:

The OS was reported for 16 patients (37.2%) which includes 9 patients (56.2%) in cHL group, 4 patients (28.6%) in CTCL group and 3 patients (23.1%) in sALCL group. Overall, the median (min-max) OS observed in patients was 9.5 (0.5 – 77.5) months; this was 9.6 (0.5 – 77.5) in cHL group, 6.4 (2.3 – 25.4) in CTCL group and 11.7 (4.9 -31.6) months in sALCL group.

Distribution of Treatment and Transplantation

Treatments

Before the start of BV retreatment, the mean (standard deviation [SD]) number of lines of therapy received by patients was 6.2 (4.8) while it was 1.1 (1.8) after BV retreatment. The mean (SD) number of lines of therapy received by CTCL patients (8.8 [6.9]) was higher compared to HL and sALCL patients (5.8 [3.1] and 3.9 [2.1], respectively). The mean (SD) number of lines of therapy received by patients after retreatment with BV were reduced and was 1.1 (1.8); this was similar in all the study groups.

For period of follow up see table 6 and 8.

Transplantation

Autologous transplants

A total of 7 patients (16.3%) underwent an autologous transplantation before starting first treatment with BV while after starting first treatment with BV, a total of 10 patients (23.3%) received an autologous transplantation. In the study, the mean (SD) number of BV retreatment cycles were 7.6 (4.8) and this was similar between cHL, CTCL and sALCL groups.

Allogenic transplants

Before the start of retreatment with BV, 6 patients (14%) had an allogeneic transplantation and after starting retreatment a total of 9 patients (20.9%) underwent an allogeneic transplantation.

Duration of periods

The median (min - max) duration of all periods from diagnosis to end of follow-up was 75.1 (21.3 - 244.9) months; (ie, 6.26 [1.78 – 20.41] years). This was higher in patients in CTCL group (81.7 [26.7 - 169.1] months; ie, 6.81 [2.23 -14.09] years)) and cHL group (77.1es [21.3 - 186.5] months; ie, 6.43 [1.78 – 15.54] years) and lower in patients in sALCL group (66.0 [26.0 - 244.9]; ie, 5.50 [2.17 – 20.41] years).

Disease characteristics (See table 9)

Disease characteristics during period P0

In the cHL group, according to the Ann Arbor classification system, 7 patients (50%) had Stage II cHL at diagnosis, 3 (21.4%) had IVb, 2 (14.3%) each had Stage III and IVa.

In the sALCL group, 4 patients [30.8%] had Stage III, 3 patients (23.1%) each had Stage II and IVb, 2 (15.4%) had Stage I, and 1 patient [7.7%] had Stage IVa sALCL and 2 patients were missing.

According to European Organisation for Research and Treatment of Cancer (EORTC) classification for CTCL patients; 5 patients (35.7%) had Stage IA, 3 patients (21.4%) had Stage IVA, 2 patients (14.3%) each had Stage IB and IIB, and 1 patient (7.1%) each had Stage IIA and Stage IVB CL.

Disease characteristics during Period P2

According to Ann Arbor classification, among 12 patients with cHL group, 6 patients [50%] had Stage II cHL at diagnosis, 2 patients (16.7%) each had Stage III and Stage IVa and 1 patient (8.3%) each had Stage I and Stage IVb HL. (4 patients data missing)

Of 13 patients in the sALCL group with available data for Ann Arbor clinical stage, 4 patients (30.8%) had Stage IVb, 3 patients (23.1%) had Stage I and 2 patients (15.4%) each had Stage II, Stage III and Stage IVa ALCL.

As per EORTC classification for CTCL patients; 4 patients (36.4%) had Stage IVB CL, 3 patients (27.3%) had Stage IIB, 2 patients (18.2%) had Stage IVA and 1 patient each (9.1%) had Stage IA and Stage IB.

Disease characteristics during Period P3

As per Ann Arbor classification, among 16 patients with HL, 5 patients (38.5%) had Stage II, 3 patients (23.1%) had Stage IVa, 2 patients (15.4%) each had Stage III and Stage IVb and 1 patient (7.7%) had Stage I and 3 patients were missing.

Out of 13 patients in the sALCL group, 3 patients (25%) each had Stage II and Stage IVb and 2 patients (16.7%) each had Stage I, Stage III and Stage IVa and 1 patient was missing.

According to EORTC classification for CTCL patients; 1 patient (9.1%) had Stage IB, 3 patients (27.3%) had Stage IIB, 4 patients (36.4%) had Stage IVA and 3 patients (27.3%) had Stage IVB CL.

Disease characteristics during period P4

Data on the Ann Arbor staging system was available for 6 patients in the HL group but missing for remaining 10 patients. In total, 3 patients [50%] each had Stage I and Stage IVa HL.

Out of 13 patients in sALCL group, data for Ann Arbor classification on clinical staging was missing for 9 patients.

Among 4 patients in the sALCL group, 2 patients (50%) had Stage IVb and 1 patient (25%) each had Stage II and Stage III.

Data on the EORTC staging system was available for 7 patients in the CTCL group but missing for the remaining 7 patients. A total of 2 patients (28.6%) had Stage IA, 1 patient (14.3%) had Stage IB, 2 patients (28.6%) had Stage IIB and 1 patient (14.3%) each had Stage IVA and IVB CTCL.

<u>Treatment characteristics during period P3</u>

Overall, premedication for infusion reaction was received by 16 patients (37.2%; 5 patients [31.2%] in cHL group, 7 patients [50%] in CTCL group and 4 patients [30.8%] in sALCL group) and majority of them (10 patients [62.5%]) received corticosteroids. Other medications were received by 13 patients (81.2%) including antihistaminics, dexchlorpheniramine, ondansetron, other antiemetics, paracetamol and polaramine. Thirteen patients (30.2%) received supportive therapies (6 patients [37.5%] in HL

group, 2 patients [14.3%] in CTCL group and 5 patients [38.5%] in sALCL group) which included G-CSFs, combination of supportive therapies, antibiotics, antiviral and other drugs.
During P3 period, after antitumor effect of BV retreatment, the disease was presented by more than half of the patients (21 patients (51.2%); 4 patients (28.6%) in HL group, 10 patients (71.4%) in CTCL group and 7 patients (53.8%) in sALCL group. Commonly used methods for the disease assessment were: PET/CT (19 patients [54.3%] overall; 9 patients [69.2%] in cHL group, 1 patient [9.1%] in CTCL group and 9 patients in sALCL), followed by CT alone (9 patients [25.7%] overall; 3 patients [23.1%] in cHL group, 5 patients [45.5%] in CTCL and 1 patient in sALCL group). (8 missing data)

In half of patients (19 patients [50%]), the disease was localised in body parts other than neck, chest, abdomen and pelvis. The mean (SD) number of BV cycles administered to study patients was 8.1 (5.4); this was higher in cHL group (10.4 [6.5]) compared to sALCL group (5.2 [1.5]). After completion of all expected BV administration cycles, CR was achieved for 6 patients (60%); 4 patients (80%) in HL group and 2 patients (40%) in sALCL group. One patient (20%) in sALCL group achieved a PR and a total of 3 patients (30%) had progressive disease (PD) (1 patient [20%] in HL group and 2 patients [40%] in sALCL group).

There were a total of 5 patients in the study who have been retreated with BV more than once, 4 of them were retreated in two occasions and 1 on them were retreated in 3 occasions. One of the patients that was retreated in two occasions, the second retreatment was off label.

Discussion and Conclusions: The BELIEVE study is the first real word evidence study in Spain that assessed the role of BV monotherapy as retreatment. BV retreatment was found to be effective and generally well-tolerated in Spanish patients with R/R cHL, CTCL, and sALCL. This results are aligned with the previous results of BV showed in the pivotal studies. The study results showed BV's antitumor activity in cHL, CTCL and sALCL patients. Patients with sALCL responded better than those with cHL and both sALCL and cHL responded better than CTCL. Safety profiles were manageable, with most AEs being mild to moderate and consistent with known BV toxicities. BV retreatment is a promising and safe treatment alternative for cHL, sALCL, and CTCL patients. However, the relatively small study sample size and the presence of missing data in some variables warrant caution in interpreting these

results. Further studies with larger cohorts are necessary to validate these findings and optimize BV retreatment strategies.

Ethical and Regulatory Considerations:

This study was conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology (ISPE) GPP guideline, and the Spanish Royal Decree 957/2020 of November 3rd, which publishes guidelines on observational post-authorisation studies for medicinal products for human use, as well as local laws and regulations. Special attention was paid to data protection law: Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. The study was read and approved by the ethics committee at the Hospital Universitari de Bellvitge. Once approved, this committee notified the additional centres aiding with participant recruitment. An exception for the collection of informed consent was approved by the Ethics Committee based on the retrospective design of the study, due to the fact that the patients were not interviewed at any time during the study development, that the study did not affect to the usual clinical practice of the sites and the participating patients and because all documentation related to the study, and the participating patients were treated with strict confidentiality, ensuring compliance with the regulations at all times. For patients who were deceased at study inclusion, the consent from the relatives will be obtained as applicable per local regulations, if applicable.

Marketing Authorization Holder

Takeda Pharma A/S
Delta Park 45, 2665 Vallensbaek Strand, Danmark
medinfoEMEA@takeda.com