Lisocabtagene maraleucel (Breyanzi®) for the treatment of diffuse large B-cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B)

General information

Drug description [1]	Indication [2]
Lisocabtagene maraleucel (Breyanzi®, liso-cel, JCAR017) is an autologous, CD19-directed, defined composition, 4–1BB chimeric antigen receptor (CAR) T-cell product administered at equal target doses of CD8+ and CD4+ CAR+ T cells.	Lisocabtagene maraleucel (Breyanzi®) is indicated for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

Incidence

The incidence of DLBCL is 3 to 7 cases per 100,000 persons; the disease is more common in men. The median age of disease onset is approximately 70 years [3].
About 5% of DLBCLs have rearrangements of the MYC and BCL2/BCL6 genes and are thus called HGBCL [4].
The annual incidence of PMBCL is 0.4/million [5].
The rate of new cases of FL was 2.5/100,000 persons per year[1] [6]; FL3B accounts for 5-10% of cases of FL [7].

Current treatment

- According to the Onkopedia guideline for DLBCL, the following is recommended [3]:
  - For patients with refractory disease or early relapse (within 12 months from completion of first-line therapy) who are eligible for high-dose therapy, treatment with axicabtagene ciloleucel or lisocabtagene maraleucel can be considered – following approval and cost assumption - as new standard of care.
  - This is based on the results of the ZUMA-7 trial, showing a significant improvement of event-free survival (EFS) in patients who received axicabtagene ciloleucel. Patients of the TRANSFORM trial receiving lisocabtagene maraleucel also achieved significant improvement of EFS.
  - However, there was no significant difference between CAR T-cell therapy as compared with standard salvage therapy among patients of the BELINDA trial.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 30 March 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Breyanzi®. The CHMP adopted a new indication: ❖ Breyanzi® is indicated for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. **Other indications**: ❖ Breyanzi® is indicated for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy. ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 24 June 2022, the FDA granted supplemental approval to Breyanzi® for the treatment of adult patients with large B-cell lymphoma (LBCL), including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL3B who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy [8]. **Other indications**: Breyanzi® is indicated [9]: ❖ For the treatment of adult patients with LBCL, including DLBC not otherwise specified (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL3B, who have: • Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or • Relapsed or refractory disease after two or more lines of systemic therapy. ❖ Limitations of use: Breyanzi® is not indicated for the treatment of patients with primary central nervous system lymphoma.

Manufacturer [9]

The manufacturer of Breyanzi® is Juno Therapeutics, Inc., a Bristol-Myers Squibb Company.

Costs

1 Based on 2016–2020 cases, age-adjusted.

Currently, for Austria, there is no cost information for Breyanzi® available.
According to an IQWiG assessment, the costs for Breyanzi® therapy are € 346,212.51 per patient and year; additionally, costs for the in-patient stay (e.g. lymphocyte depletion and premedication) occur [10].

Posology [11]

- Breyanzi® must be administered in a qualified treatment centre. Treatment should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Breyanzi®.
- At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available per patient prior to infusion of Breyanzi®. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- Breyanzi® is intended for autologous use only.
- Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR+ viable T cells in one or more vials. The target dose is 100 × 106 CAR+ viable T cells (consisting of a target 1:1 ratio of CD_4+ and CD8+ cell components) within a range of 44-120 × 106 CAR+ viable T cells (please see the release for infusion certificate for additional information pertaining to dose).
- The availability of Breyanzi® must be confirmed before starting lymphodepleting chemotherapy regimen.
- Patients should be clinically re-assessed prior to administration of lymphodepleting chemotherapy and Breyanzi® to ensure no reasons to delay therapy.
- **Pre-treatment** (lymphodepleting chemotherapy)
  - Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m²/day and fludarabine 30 mg/m²/day, administered IV for 3 days. Please see the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.
  - Breyanzi® is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy. If there is a delay of more than 2 weeks between completing lymphodepleting chemotherapy and the infusion of Breyanzi®, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving the infusion.
- **Pre-medication**
  - To minimise the risk of infusion reactions, the patient is to be pre-medicated with paracetamol and diphenhydramine (25-50 mg, IV or orally) or another H1-antihistamine, approximately 30 to 60 minutes before infusion of Breyanzi®.
  - Prophylactic use of systemic corticosteroids should be avoided, as the use may interfere with the activity of Breyanzi®.
- **Monitoring after infusion**
  - Patients should be monitored 2-3 times during the first week following infusion, for signs and symptoms of potential CRS, neurologic events and other toxicities.
  - Physicians should consider hospitalisation at the first signs or symptoms of CRS and/or neurologic events.
  - Frequency of monitoring after the first week should be carried out at the physician's discretion and should be continued for a least 4 weeks after infusion.
  - Patients should be instructed to remain within proximity of a qualified treatment centre for at least 4 weeks following infusion.

Warnings and precautions [12]

- **CRS**
  - CRS, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi®.
  - Do not administer Breyanzi® to patients with active infection or inflammatory disorders.
  - Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- **Neurologic toxicities**
  - Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi®, including concurrently with CRS, after CRS resolution, or in the absence of CRS.
  - Monitor for neurologic events after treatment with Breyanzi®.
  - Provide supportive care and/or corticosteroids as needed.
- **Hypersensitivity reactions**
  - Monitor for hypersensitivity reactions during infusion.
  - Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged cytopenias**
  - Patients may exhibit Grade 3 or higher cytopenias for several weeks following Breyanzi® infusion. Monitor complete blood counts.
- **Hypogammaglobulinemia**
  - Monitor and consider immunoglobulin replacement therapy.
- **Secondary malignancies**

- In the event that a secondary malignancy occurs after treatment with Breyanzi®, contact the manufacturer.

❖ **Effects on ability to drive and use machines**

- Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks after Breyanzi® administration.

❖ According to the FDA, Breyanzi® is available only through a restricted program under a **Risk Evaluation and Mitigation Strategy**.

Study characteristics [1, 13-18]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
TRANSFORM NCT03575351	184[2] (1:1)	**Liso-cel** (100 × 106 CAR–positive T cells)	**SOC**[3] (3 cycles of platinum-based immunochemotherapy[4] followed by high-dose chemotherapy and ASCT in responders)	Event-free survival (EFS)	17.5 months (data cutoff date: 13 May 2022)	Global, randomised, open-label, phase 3 study	-	Celgene, a Bristol-Myers Squibb Company	[1, 17]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Adults (18-75 years of age) having PET–positive LBCL per Lugano 2014 criteria ❖ Refractory (stable disease, progressive disease, PR or CR with relapse ≤3 months) or relapsed (CR with relapse ≤12 months) disease after CD20 antibody and anthracycline-containing first-line therapy ❖ ECOG PS ≤1 ❖ Adequate organ function ❖ Eligible for high-dose chemotherapy and ASCT	❖ Ineligibility for HSCT ❖ Planning to undergo ASCT ❖ Primary cutaneous large B-cell lymphoma, EBV-positive diffuse LBCL, Burkitt lymphoma, or transformation from chronic lymphocytic leukaemia/small lymphocytic lymphoma (Richter transformation) ❖ Patients with prior history of malignancies ❖ Treatment with any prior gene therapy product ❖ Receipt of previous CD19-targeted therapy ❖ Active hepatitis B or active hepatitis C ❖ Uncontrolled systemic fungal, bacterial, viral, or other infection (including tuberculosis) ❖ Active autoimmune disease requiring immunosuppressive therapy ❖ History of any one of the following cardiovascular conditions within the past 6 months before signing the ICF: class III or IV heart failure as defined by the NYHA, cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease	❖ Male sex: 48% vs. 66% ❖ Median age: 60 vs. 58 years ❖ Age ≥65 to <75 years: 39% vs. 25% ❖ DLBCL not otherwise specified: 58% vs. 54% ❖ HGBCL with gene rearrangements in MYC and BCL2, BCL6, or both: 24% vs. 23% ❖ ECOG PS 0: 52% vs. 62% ❖ ECOG PS 1: 48% vs. 38% ❖ Prior response status refractory: 73% vs. 76% ❖ Prior response status relapsed: 27% vs. 24%

[2] A total of 184 patients were randomly assigned, with 92 patients in each arm. In the SOC arm, n= 91 were treated with second-line immunochemotherapy (1 withdrew consent), n=43 (47%) received high-dose chemotherapy and ASCT, and n=61 (66%) were **approved for crossover to receive liso-cel**, and of them, n=58 were infused (**57 with liso-cel** and 1 with nonconforming product). In the liso-cel arm, n=89 received liso-cel infusion (1 withdrew consent, 1 had a manufacturing failure, and 1 received a nonconforming CAR T-cell product).

[3] If requested by the investigator, patients in the SOC group were allowed to cross over to receive liso-cel as thirdline treatment upon approval of the sponsor based on IRC confirmation of one of the following criteria: CR or PR not achieved after 3 cycles of immunochemotherapy, progressive disease at any time, or need to start a new antineoplastic therapy due to absence of complete response after 18 weeks post-randomisation.

[4] Investigators could switch a patient's regimen within one of the three protocol-defined salvage regimens (i.e., R-DHAP, R-ICE, or R-GDP) in case of toxicity or unsatisfactory response.

[5] For detailed in- and exclusion criteria, please see study protocol.

	❖ History or presence of clinically relevant central nervous system pathology ❖ Progressive vascular tumour invasion, thrombosis, or embolism ❖ Pregnant or nursing (lactating) women	

Efficacy (I vs. C)	**Safety** (I vs. C)
Median EFS: NR (95% CI, 9.5-NR) vs. 2.4 months (95% CI, 2.2-4.9); HR 0.356; 95% CI, 0.243-0.522 **EFS rates at 18 months**: 52.6% (95% CI, 42.3-62.9) vs. 20.8% (95% CI, 12.2-29.5) **CR rate per IRC**: 74% (95% CI, 63.7-82.5) vs. 43% (95% CI, 33.2-54.2); stratified 1-sided p-value <.0001 **Median PFS per IRC**: NR (95% CI,12.6-NR) vs. 6.2 months (95% CI, 4.3-8.6); stratified HR 0.400 (95% CI, 0.261-0.615); p<.0001 **12-month PFS rate per IRC**: 63.1% (95% CI, 53.0-73.3) vs. 31.2% (95%CI, 20.2-42.3) **18-month PFS rate per IRC**: 58.2% (95% CI, 47.7-68.7) vs. 28.8% (95% CI,17.7-40.0) **Median OS**: NR (95% CI, 29.5-NR) vs. 29.9 months (95% CI, 17.9-NR); HR 0.724; 95% CI, 0.443-1.183; p=0.0987 **12-month OS rate**: 83.4 % (95% CI, 75.7-91.1) vs. 72.0% (95% CI, 62.7-81.3) **18-month OS rate:** 73.1% (95% CI, 63.9-82.3) vs. 60.6% (95% CI, 50.2-71.1) **ORR:** 87% (95% CI, 78.3-93.1) vs. 49% (95% CI, 38.3-59.6) **Median duration of CR**: NR (95% CI, NR-NR) vs. 9.3 months (95% CI, 5.1-NR) **Median DOR**: NR (13.4-NR) vs. 9.1 months (5.1-NR); HR 0.579 (95% CI, 0.340-0.984) **Subsequent therapies in I:** 33% received systemic anticancer therapy, 11% received SCT, 4% received radiation therapy **Subsequent therapies in C**: **63% crossed over and received CAR+ T cells[6],** 25% received systemic anticancer therapy, 2% received allogeneic SCT **Crossover patients (n=57[7]):** ❖ ORR: 61% ❖ CR rate: 53% ❖ Median EFS: 5.9 months (95% CI, 3.1-15.1) **Cellular kinetics:** ❖ Median time to maximum expansion: 10 days (range, 6-22) ❖ Median maximum expansion was 33,285 copies per µg ❖ Median area under the curve from 0 to 28 days after infusion was 268,911 day × copies per µg ❖ Cellular kinetics for the crossover subgroup were similar to those of the liso-cel arm ❖ Persistence of the liso-cel transgene was observed up to 23 months after infusion	**Patients experiencing TEAE (any grade)**: n=92/92 (100%) vs. n=90/91 (99%) **Patients experiencing TEAE grade ≥3**: n=85/92 (92%) vs. n=81/91 (89%) **Patients experiencing serious TEAE**: n=44/92 (48%) vs. n=45/91 (49%) **Deaths[8]:** n=28/92 (30%) vs. n=9/91 (10%) **Deaths in crossover subgroup[9]:** n=29/58 (50%) Deaths in SOC + crossover subgroup: n=38/91 (42%) **Deaths due to TEAEs**: n=2/92 (2%) vs. n=2/91 (2%) **Rates of any-grade CRS and neurological events of any grade in I**: 49% and 11%, respectively **Rates of any-grade CRS and neurological events of grade 3 in I**: 1% and 4%, respectively **Severe infections:** n=14/92 (15%) vs. n=19/91 (21%)

Patient-reported outcomes [16]

- ❖ Data cutoff: 8 March 2021
- ❖ N=47 (51%) vs. n=43 (47%) patients were eligible for inclusion in the EORTC QLQ-C30 analysis set; n=45 (49%) vs. n=40 (43%) patients were included in the FACT-LymS analysis set
- ❖ EORTC QLQ-C30 completion rates at baseline and at month 6: 52% and 39% vs. 54% and 43%, respectively
- ❖ **Baseline domain scores for the EORTC QLQC30 and FACT-LymS (both arms, mean, SD):**
  - Global health status/QoL: 68.0 (21.7)

[6] Timing of crossover: 8% after completion of SOC cycle 1 and before completion of SOC cycle 2; 21% after completion of SOC cycle 2 and before completion of SOC cycle 3; 36% after completion of SOC cycle 3 and before HDCT/ASCT; 34% after HDCT/ASCT.

[7] 3 patients approved for crossover did not receive liso-cel and 1 patient received nonconforming product and were not included in the efficacy analyses.

[8] The most frequent cause of death was disease progression.

[9] Includes deaths that occurred after approval to receive liso-cel in patients randomised to the SOC arm who crossed over to receive liso-cel.

- Physical functioning: 85.5 (16.2)
- Cognitive functioning: 87.8 (17.3)
- Fatigue: 30.9 (22.9)
- Pain: 28.2 (28.6)
- FACT-LymS: 47.5 (8.1)

❖ **Changes from baseline**

- In the **SOC arm**, observed mean change scores showed **clinically meaningful worsening in global health status/QoL** at month 6, **fatigue** at day 29 and month 6, and **pain** at month 6; mean scores for the other primary domains of interest were generally maintained or meaningfully improved over time in both treatment arms.
- Results from the MMRM analyses, which considered all data points through day 126 and controlled for relevant baseline covariates, showed that the **overall least squares mean changes from baseline to day 126 with the liso-cel arm were clinically meaningfully improved** compared with those with the SOC arm **in cognitive functioning** (2.2 vs. −2.1) and **fatigue** (−2.0 vs. 3.8) domains.
- Differences in the remaining primary and secondary domains of interest between arms were small and fell within the between-group MIDs, except for the emotional **functioning domain**, where it **favoured the SOC arm**.

❖ **Proportion of patients with clinically meaningful changes**

- The proportion of patients with meaningful improvement in global health status/QoL, cognitive functioning, and fatigue was higher, whereas a lower proportion deteriorated in the liso-cel arm than in the SOC arm from day 126 to month 6.
- Results for pain scores trended toward improvement in the liso-cel arm and deterioration in the SOC arm at month 6.
- For other primary domains of interest (physical functioning and FACT-LymS), the proportions of patients with meaningful improvement or deterioration were generally similar between the liso-cel arm and the SOC arm across visits through month 6.

❖ **Time to confirmed deterioration**

- **Time to confirmed deterioration favoured the liso-cel arm** vs. the SOC arm **in global health status/QoL** (median: not yet reached by the time of data cutoff vs. 19.0 weeks; HR, 0.47; 95% CI, 0.24-0.94). However, there was a trend toward greater risk of deterioration in emotional functioning for liso-cel vs. SOC (median in both arms not reached; HR 1.30; 95% CI, 0.61-2.78).
- Time to confirmed deterioration in other primary domains of interest was generally comparable between both arms.

❖ **Sensitivity analyses**

- Based on MMRM, overall least squares mean changes estimated using a "while on treatment" strategy, the liso-cel arm showed clinically meaningful improvement relative to the SOC arm in global health status/QOL (4.88; 95% CI, −1.97-11.73), cognitive functioning (3.73; 95% CI, −1.45-8.91), and fatigue (−5.01; 95% CI, −12.75-2.74), while showing no clinically meaningful worsening relative to the SOC arm in any domain.

ESMO-MCBS version 1.1 [19]

Disclaimer: Though not finally validated, but feasibility tested in [20], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS is not applicable because the primary endpoint "EFS" has not yet been met.											

Risk of bias (RCT) [21]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Free from other sources of bias	**Risk of bias**
yes (low risk)	yes (low risk)	no[10] (high risk)	unclear[11,12] (uncertain risk)	no[13,14] (high risk)	high

Ongoing trials [22]

[10] The TRANSFORM trial was conducted as an open-label trial.
[11] Since the TRANSFORM trial is ongoing, there is no final analysis data available.
[12] Deviation from the intended intervention: high crossover rate
[13] Industry-funded trial. The funder had a role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit.
[14] The small sample size of the trial, combined with the existence of heterogenous LBCL subtypes and the possibility of variable use of salvage regimens affect the comparability of the results.

NCT number/trial name	Description	Estimated study completion date
NCT03575351/TRANSFORM	Please see above.	10/2023
NCT03744676	A safety trial of lisocabtagene maraleucel (JCAR017) for relapsed and refractory B-cell non-Hodgkin lymphoma in the outpatient setting.	09/2023
NCT03484702	A phase 2, single-arm, multi-center trial to determine the efficacy and safety of JCAR017 in subjects with relapsed or refractory DLBCL or with other aggressive B-cell malignancies.	12/2023
NCT05633615	A randomised phase II trial of consolidation therapy following CD19 CAR T-cell treatment for relapsed/refractory DLBCL or grade 3BFL.	12/2029
NCT05583149	A phase 2 study of acalabrutinib in combination with lisocabtagene maraleucel in relapsed/refractory aggressive B-cell lymphomas.	09/2029

Available assessments

- In 2020, a Health Technology Briefing "Lisocabtagene maraleucel for relapsed or refractory, aggressive B-cell non-Hodgkin Lymphoma – second line" was published by **NIHR** [23].
- **CADTH** published a reimbursement review for lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in October 2022 [24].
- An assessment evaluating the efficacy of lisocabtagene maraleucel in patients with DLBCL, PMBCL and FL3B was published by the **G-BA/IQWiG** in January 2023 [7].
- The **NICE** appraisal to evaluate the clinical and cost effectiveness of lisocabtagene maraleucel within its marketing authorisation for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma was suspended in November 2021 following information received from the company [25].

Other aspects and conclusions

- In March 2023, the **CHMP adopted a new indication** for Breyanzi® for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. This indication is **approved by the FDA** since June 2022.
- NCT03575351, the **TRANSFORM trial**, aims to compare lisocabtagene maraleucel with a SOC as second-line therapy for primary refractory or early relapsed (≤12 months) LBCL. **Eligible patients** (18-75 years of age) had PET–positive LBCL per Lugano 2014 criteria, refractory or relapsed disease after CD20 antibody and anthracycline-containing first-line therapy, an ECOG PS ≤1, adequate organ function, and were eligible for high-dose chemotherapy and ASCT. The wide range of **exclusion criteria** included i.a. an ineligibility for HSCT, a planned ASCT, primary cutaneous large B-cell lymphoma, EBV-positive diffuse LBCL, Burkitt lymphoma, or transformation from chronic lymphocytic leukaemia/small lymphocytic lymphoma (Richter transformation), patients with prior history of malignancies, treatment with any prior gene therapy product and the receipt of previous CD19-targeted therapy.
- The majority of TRANSFORM trial patients had an ECOG PS of 0 which is defined as fully active, able to carry on all pre-disease performance without restriction [26]. The median age of DLBCL disease onset is approximately 70 years; of note, the median age of trial patients was 60 and 58 years, respectively. These facts indicate that most TRANSFORM trial patients were younger and might have been at a better performance status than the average DLBCL patient.
- **Limitations** of the TRANSFORM trial are the small sample size of 92 patients per group, the heterogeneous LBCL subtypes and the open-label design.
- Efficacy analysis might be affected by the **variable use of salvage regimens** (the investigators could switch a patient's regimen within one of the 3 protocol-defined salvage regimens in case of toxicity or unsatisfactory response); as well as by the **high (63%) crossover rate** of the trial.
- The **risk of bias** of the TRANSFORM trial was considered as **high**, based on the mentioned limitations and the substantial role of the funding source.
- Final analysis data from the TRANSFORM trial, and **additional, robust phase 3 data** (no further ongoing phase 3 trial was identified) is required to determine the role of lisocabtagene maraleucel for the treatment of patients with DLBCL, HGBCL, PMBCL and FL3B.

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Abbreviations: AE=adverse event, AJ=adjustment, ASCT=autologous stem cell transplantation, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CRS=cytokine release syndrome, DLBCL=diffuse large B-cell lymphoma, DOR=duration of response, EBV=Epstein-Barr virus, ECOG PS=Eastern Cooperative Oncology Group performance status, EFS=event-free survival, EMA=European Medicines Agency, EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 items, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-LymS=Functional Assessment of Cancer Therapy-Lymphoma subscale, FDA=Food and Drug Administration, FL3B=follicular lymphoma grade 3B, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HGBCL=high grade B cell lymphoma, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, ICF=informed consent form, Int.=intention, IQWIG=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, LBCL=large B-cell lymphoma, MG=median gain, MID= minimally important differences, MMRM=mixed-effects regression model for repeated measures, n=number of patients, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, NR=not reached, NYHA=New York Heart Association, ORR=Overall response rate, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, PR=partial response, QoL=quality of life, R-DHAP=rituximab, dexamethasone, cytarabine, cisplatin, R-GDP=rituximab, dexamethasone, gemcitabine, cisplatin, R-ICE=rituximab, ifosfamide, etoposide, carboplatin, SAE=serious adverse event, SD=standard deviation, SOC=standard of care, ST=standard treatment, TEAE=treatment-emergent adverse event

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