Epcoritamab (Tepkinly®) as monotherapy for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

General information [1]

Drug description

The active substance of Tepkinly® is epcoritamab, an antineoplastic agent. By simultaneously binding to CD20 on the B-cell and CD3 on the T-cell, epcoritamab mediates the formation of an immunological synapse, with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins resulting in the lysis of CD20-expressing B-cells.

Indication

Epcoritamab (Tepkinly®) as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL after 2 or more lines of systemic therapy.

Incidence

The incidence of DLBCL is approx. 7 cases per 100,000 people per year; men are more often affected than women [2].

Current treatment [2]

- **<u>Treatment recommendations for patients who are eligible for high-dose therapy:</u>**
  - Among the last years, standard therapy for younger patients (≤60 years of age) with relapsed disease and elder patients without therapy-limiting comorbidities was conventional salvage therapy, followed by high-dose therapy with ASCT. However, satisfying results can only be expected when there is a response to the conventional dosed induction therapy, which is rare if there are less than 12 months between the primary diagnosis and the relapse.
  - For induction therapy, 3 cycles of R-DHAP or R-ICE were considered as equal.
  - Alternatively, R-GDP, which is considered as equal (but better tolerated) to R-DHAP provides an option.
  - For high-dose therapy, BEAM protocol is commonly used.
  - A maintenance therapy with rituximab is not indicated.
  - For younger high-dose-eligible patients with primary refractory disease or early relapse (within 12 months after completion of first-line therapy), 3 randomised phase 3 trial of standard-high-dose therapy followed by ASCT was compared directly to randomised anti-CD19 CAR T-cell therapy. ZUMA-7 trial showed a significant improvement of event-free survival for patients in the axicabtagene-ciloleucel arm. Also, among patients of TRANSFORM trial´s lisocabtagene-maraleucel arm, significant improvement of event-free survival was achieved. On the contrary, there was no significant difference between CAR T-cell therapy with tisagenlecleucel vs. standard therapy among patients of the BELINDA trial. Despite the negative results of the BELINDA trial, therapy with axicabtagene-ciloleucel or lisocabtagene-maraleucel can be considered – following approval and reimbursement – as new standard in patients with primary refractory disease or early relapse.
  - Currently, axicabtagene-ciloleucel and tisagenlecleucel are approved by the EMA in patients with at least 2 prior therapies, indicated (according to the approval studies) in patients with relapsed/refractory DLBCL, primary mediastinal B-cell lymphoma and transformed follicular lymphoma, respectively. Patients with chemo-refractory disease, a short interval between primary diagnosis and relapse or relapse following high-dose therapy are alternatively candidates for an allogenic transplantation. Currently, it remains unclear if a CAR-T-cell therapy is superior to an allogeneic transplantation.
- **<u>Treatment recommendations for patients who are NOT eligible for high-dose therapy:</u>**
  - Patients who are ineligible (because of their age or comorbidities) for an autologous or allogeneic stem cell therapy or a CAR T-cell therapy, treatment aims to be palliative.
  - Curative treatment seems to be possible if the interval between the primary diagnosis and the relapse is long and there is response to repeated immunochemotherapy.
  - Beside the R-GemOX regimen, more intense chemotherapy regimens (e.g., R-DHAP or R-ICE) can be applied.
  - Furthermore, the combination of rituximab, bendamustine and polatuzumab-vedotin (Pola-BR) is approved for patients with first relapse of DLBCL who are not candidates for a HSCT. The approval study for Pola-BR shows, as compared with rituximab and bendamustine, a significant improvement of response rate, PFS and OS. In August 2021, the EMA approved tafasitamab combined with lenalidomide for patients who are ineligible for high-diose therapy, providing an option without chemotherapeutical agents.
  - In patients with a second relapse, the option of CAR T-cell therapy should always be considered.

Regulatory status

EMA [1]	FDA [3, 4]
Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for **Tepkinly®**. **UPDATE**: Marketing authorisation issued on 22/09/2023 The full indication is: ❖ Tepkinly® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Tepkinly® is available as a 4 mg/0.8 ml concentrate for solution for injection and a 48 mg solution for injection. **Other indications**: none ✓ **Orphan status** ✓ **Medicine is under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	**Approval status for this indication**: On 19 May 2023, the FDA granted accelerated approval to epcoritamab-bysp (**Epkinly®**) for relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. ✓ This application was granted priority review. ✓ This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). **Other indications**: none

Manufacturer

Tepkinly® is manufactured by AbbVie Deutschland GmbH & Co. KG

Costs [5]

Tepkinly® solution for injection 48 mg/0.8 ml = 7,424.07 (ex-factory price)
Tepkinly® solution for injection 4 mg/0.8 ml = € 618.67 (ex-factory price)

Posology [3, 6]

- ❖ Administer Epkinly® to **well-hydrated** patients. Patients at an increased risk for clinical tumour lysis syndrome (CTLS) are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent.
- ❖ Administer **premedication** to reduce the risk of cytokine release syndrome (CRS):
  - Cycle 1 (all patients)
    - o Prednisolone (100 mg oral or IV) or dexamethasone (15 mg oral or IV) or equivalent: 30-120 minutes prior to each weekly administration of Epkinly® and for 3 consecutive days following each weekly administration of epcoritamab in Cycle 1.
    - o Diphenhydramine (50 mg oral or IV) or equivalent: 30-120 minutes prior to each weekly administration of epcoritamab.
    - o Acetaminophen (650 to 1,000 mg oral): 30-120 minutes prior to each weekly administration of epcoritamab
  - Cycle 2+ (patients who experienced grade 2 or 3 CRS with previous dose)
    - o Prednisolone (100 mg oral or IV) or dexamethasone (15 mg oral or IV) or equivalent: 30-120 minutes prior to next administration of epcoritamab after a Grade 2 or 3 CRS event and for 3 consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of grade 2 or higher.
- ❖ **Recommended prophylaxis**

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks, and the applicant should be in a position to provide the comprehensive clinical data in the future.

- Pneumocystis jirovecii pneumonia
    - Provide prophylaxis prior to starting treatment with epcoritamab.
- Herpes virus
    - Consider initiating prophylaxis against herpes virus prior to starting epcoritamab to prevent herpes zoster reactivation.

❖ Patients should be monitored for signs and symptoms of CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS and/or ICANS. Patients should be counselled on the signs and symptoms associated with CRS and ICANS and on seeking immediate medical attention should signs or symptoms occur at any time.

Warnings and precautions [3, 6]

❖ **Traceability**
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

❖ **CRS**
- CRS, including serious or life-threatening reactions, can occur in patients receiving Epkinly®.
- Initiate treatment with the Epkinly® step-up dosing schedule to reduce the incidence and severity of CRS.
- Withhold Epkinly® until CRS resolves or permanently discontinue based on severity.

❖ **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
- ICANS, including life-threatening and fatal reactions, can occur with Epkinly®.
- Monitor patients for neurological signs or symptoms of ICANS during treatment.
- Withhold Epkinly® until ICANS resolves or permanently discontinue based on severity.

❖ **Infections**
- Can cause serious or fatal infections.
- Monitor patients for signs or symptoms of infection, including opportunistic infections, and treat appropriately.

❖ **Cytopenia**
- Monitor complete blood cell counts during treatment.

❖ **Embryo-foetal toxicity**
- May cause foetal harm.
- Advise females of reproductive potential of the potential risk to the foetus and to use effective contraception.

❖ **Tumour lysis syndrome (TLS)**
- TLS has been reported in patients receiving epcoritamab. Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent.
- Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

❖ **Tumour flare**
- Tumour flare has been reported in patients treated with epcoritamab. Manifestations could include localised pain and swelling. Consistent with the mechanism of action of epcoritamab, tumour flare is likely due to the influx of T-cells into tumour sites following epcoritamab administration.
- There are no specific risk factors for tumour flare that have been identified; however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Patients treated with epcoritamab should be monitored and evaluated for tumour flare at critical anatomical sites.

❖ **CD20-negative disease**
- There are limited data available on patients with CD20-negative DLBCL treated with epcoritamab, and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with epcoritamab should be considered.

- **Patient card**
  - The doctor must inform the patient of the risk of CRS and ICANS and any signs and symptoms of CRS and ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS and/or ICANS. Patients should be provided with a patient card and instructed to carry the card at all times. This card describes symptoms of CRS and ICANS which, if experienced, should prompt the patient to seek immediate medical attention.
- **Immunisation**
  - Live and/or live-attenuated vaccines should not be given during epcoritamab therapy. Studies have not been conducted in patients who received live vaccines.
- **Excipients with known effect**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.
  - This medicinal product contains 21.9 mg of sorbitol per vial, which is equivalent to 27.33 mg/ml.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PEs	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
EPCORE NHL-1 NCT03625037	68[2]	Patients received priming and intermediate doses followed by full doses of subcutaneous epcoritamab administered in 28-day cycles; each subsequent cohort involved escalation of the priming, intermediate, or full dose (0.0128–60 mg)[3]	-	to determine the maximum tolerated dose and the recommended phase 2 dose of epcoritamab	6.6 - 13.6 months	**ongoing**[4], multicentre, open-label, phase 1/2 trial	CD3, CD20	Genmab and AbbVie	EPCORE NHL-1 [8]

Inclusion criteria [5]	Exclusion criteria	Patient characteristics at baseline (patients with relapsed or refractory DLBCL, n=46)
❖ Patients ≥18 years and ECOG PS 0, 1, or 2 with documented CD20+ mature B-cell neoplasm according to WHO classification: • DLBCL – de novo or transformed, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, marginal zone lymphoma (nodal, extranodal, or mucosa-associated). ❖ Relapsed, progressive, and/or refractory disease following treatment with an anti-CD20 monoclonal antibody (potentially in combination with chemotherapy and/or relapsed after ASCT rescue). ❖ Patients must have exhausted or been ineligible for all standard therapeutic options. ❖ Patients with indolent lymphoma (follicular, marginal zone, or small lymphocytic lymphoma) must have a need for treatment initiation based on symptoms and/or disease burden.	❖ Primary CNS lymphoma or known CNS involvement by lymphoma at screening as confirmed by MRI/CT (brain) and, if clinically indicated, by lumbar puncture. ❖ Known past or current malignancy other than inclusion diagnosis, except for cervical carcinoma of stage 1B or less, non-invasive basal cell or squamous cell skin carcinoma, non-invasive, superficial bladder cancer, prostate cancer with a current PSA level <0.1 ng/mL or any curable cancer with a CR duration of >2 years. ❖ Known clinically significant cardiac disease.	❖ Age, years: 68 (range, 55–74) ❖ Male sex: 65% ❖ ECOG performance status: • 0: 50% • 1: 46% • 2: 3: 0% ❖ Ann Arbor stage: • I: 7% • II: 11% • III: 26% • IV: 57% ❖ Extranodal disease: 63% ❖ Time since diagnosis, months: 25.4 (11.0–54.6)

[2] 73 patients were enrolled in the dose-escalation part and 68 received epcoritamab at full doses of 24 mg or less (n=53), 48 mg (n=12), or 60 mg (n=3).
[3] Patients received the priming dose of subcutaneous epcoritamab on day 1 of cycle 1 and an intermediate dose (introduced at the 1.5 mg full dose level to bridge the widening gap between the priming dose and the full dose) on day 8 of cycle 1. Subcutaneous epcoritamab (1 mL) was administered in 28-day cycles until disease progression or unacceptable toxicity, according to the following schedule: weekly dosing in cycles 1 and 2 (days 1, 8, 15, 22), dosing every 2 weeks in cycles 3–6 (days 1, 15), and dosing every 4 weeks from cycle 7 onward (day 1).
[4] The EPCORE NHL-1 trial is currently ongoing; estimated study completion date is 04/2029.
[5] For detailed in- and exclusion criteria, please see supplementary appendix.

❖ Documentation of CD20+ mature B-cell neoplasm based on any representative pathology report. ❖ At least one measurable site of disease based on CT (or MRI) with involvement of two or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm or one clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm and baseline fluorodeoxyglucose PET scans demonstrating positive lesion compatible with CT- or MRI-defined anatomical tumour sites. ❖ Lymphocyte counts <5 × 109/L; platelet counts ≥75 × 109/L; absolute neutrophil counts ≥1.0 × 109/L; growth factor support allowed in case of bone marrow involvement. ❖ Haemoglobin level ≥9 g/dL (≥5.6 mmol/L) with or without transfusion. ❖ At least 4 weeks from last dose of unconjugated anti-CD20 targeting therapy until first dose of epcoritamab. ❖ At least 12 weeks from last dose of radio-conjugated or toxin-conjugated compound until first dose of epcoritamab. ❖ At least 4 weeks from last dose of investigational monoclonal antibodies, investigational chemotherapy, or another investigational anticancer agent until first dose of epcoritamab. ❖ Resolution of toxicities from prior therapy to a grade that does not contraindicate trial participation in the opinion of the investigator. ❖ Before the first dose of epcoritamab, during the trial and for 12 months after last administration of epcoritamab, a woman must be either: • not of childbearing potential, of childbearing potential and practicing a highly effective method of birth control. ❖ A man who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control during the trial and for 12 months after receiving the last dose of epcoritamab.	❖ AST and/or ALT >3×ULN; total bilirubin >1.5× ULN; creatinine clearance <45 mL/min. ❖ Chronic ongoing infectious diseases requiring treatment at the time of enrolment or within the previous 2 weeks prior to the first dose of epcoritamab. ❖ Confirmed history of or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy. ❖ Seizure disorder requiring therapy. ❖ Any prior therapy with an investigational bispecific antibody targeting CD3 and CD20. ❖ Prior treatment with chimeric antigen receptor T-cell therapy within 30 days prior to first administration of epcoritamab. ❖ Patients eligible for curative intensive salvage therapy followed by high-dose chemotherapy with HSCT rescue. ❖ Autologous HSCT within 100 days prior to first administration of epcoritamab, or any prior allogeneic HSCT or solid organ transplantation. ❖ Active HBV or HCV (if laboratory evidence for a chronic infection with hepatitis B, close monitoring and prophylactic therapy is required), or known human immunodeficiency virus infection. ❖ Pregnancy or breastfeeding.	❖ Time since relapse or progression, months: 1.5 (1.1–2.3) ❖ Number of lines of previous therapy: 3.0 (2.0–4.0) ❖ Previous therapies: • Anti-CD20 monoclonal antibody: 100% • Anthracyclines: 100% • Alkylating agents: 100% • Autologous stem-cell transplantation: 15% • CAR-T therapy: 11% ❖ Treatment-refractory patients by therapy: • Last line of systemic therapy: 89% • Alkylating agents: 87% • Last anti-CD20 monoclonal antibody: 89%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Data cutoff date 31 January 2021:</u> ❖ Mean half-life of epcoritamab: 8.8 days following administration of the first full dose ❖ Mean time to reach maximum plasma concentration: 2.8 days ❖ Response rates started to plateau at the 48 mg epcoritamab dose for patients with DLBCL and those with follicular lymphoma ❖ Increasing the dose beyond 48 mg did not provide any substantial increase in the predicted response rate ❖ 48 mg was identified as the recommended phase 2 dose as well as the lowest biologically effective dose, which was associated with optimal trimer formation and improved clinically relevant response rates, while potentially minimising safety risks **Antitumour responses in patients with relapsed or refractory DLBCL:** ❖ 0.76 mg to <12 mg: ORR 13% (95% CI, 2–38), CR 13% (2–38) ❖ 12 mg to 60 mg: ORR 68% (45–86), CR 45% (24–68) ❖ 48 mg: ORR 88% (47–100), CR 38% (9–76)	**<u>Data cutoff date 31 January 2021:</u>** ❖ No patients discontinued due to treatment-related AEs ❖ No dose-limiting toxic effects or dose reductions occurred during the dose-limiting toxicity evaluation period and the maximum tolerated dose was not reached up to the highest dose of 60 mg ❖ SAEs: 68% ❖ CRS grade 2: 29% ❖ Neurological symptoms grade 3: 3%

- 48 mg to 60 mg: ORR 91% (59–100), CR 55% (23–83)
- In patients with relapsed or refractory DLBCL who received doses of ≥12 mg, the median time to response was 1.4 months (IQR, 1.3–2.6); median time to reach CR was 2.7 months (1.3–2.8)
- Longest duration of ongoing CR was more than 11.2 months.

Median PFS for patients with relapsed or refractory DLBCL who received doses of epcoritamab of at least 12 mg was 9.1 months (IQR, 1.6–not estimable); median PFS for patients who received doses of at least 48 mg has not been reached.

Median time to response in patients with relapsed or refractory follicular lymphoma treated with doses of ≥0.76 mg: 1.9 months (IQR, 1.5–3.5)

Median time to response in patients with relapsed or refractory diffuse large B-cell lymphoma who received doses of ≥12 mg: 1.4 months (IQR, 1.3–1.5)

A **transient decrease in circulating peripheral CD4+ T-cells and CD56− and CD8+ T-cells** was observed within 6h of the first subcutaneous dose of epcoritamab; subsequent dosing elicited expansion of CD4+ and CD8+ T-cells after 6–8 weeks of treatment.

Results as of 18 November 2022 (median follow-up: 20 months, range 0.3 - 28.2):

- Patients received a mean of 9.1 cycles
- LBCL overall response and CR rates were 63.1% and 39.5%, respectively, and were consistent for DLBCL (61.9% and 39.6%)
- The median duration of response: 20.8 months
- Median time to CR: 2.7 months
- 8 patients converted from partial response to CR at week 36
- **Median OS:** 18.5 months (95% CI, 11.7–NR), with an estimated 58% of patients alive at 12 months
- Median OS was not reached in patients who achieved CR
- Clinical tumour lysis syndrome grade 3: 1%
- Overall deaths: 56%[6]

Results as of 18 November 2022 (median follow-up: 20 months, range 0.3 - 28.2):

- Most common TEAEs of any grade were: CRS 51%, neutropenia 24%, pyrexia 24%, fatigue 23%, nausea 22%, and diarrhoea 21%
- Grade 1 ICANS: 6%
- Fatal TEAEs: n=15 (2 were considered related: COVID-19, ICANS)
- CRS was predominantly low grade (48% grade 1–2; 3% grade 3) and occurred following the first full dose (C1D15)
- 1 patient discontinued due to grade 1 CRS

Patient-reported outcomes

The evaluation of patient-reported outcomes is not provided by the EPCORE NHL-1 trial.

ESMO-MCBS for Haematological Malignancies [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS for Haematological Malignancies was not applicable because the primary endpoints "maximum tolerated dose and the recommended phase 2 dose of epcoritamab" could not be assessed.											

Risk of bias - study level (case series) [11]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[7]	yes	yes	yes	no[8]

[6] Disease progression was the most common cause of death (49%). Other causes of death, all post treatment, were COVID-19 (n=1), lymphoma (n=1), graft-versus-host disease (n=1), and septic shock (n=1); the cause of death was unknown in 1 patient. No deaths occurred due to treatment-related AEs.

[7] Heterogenous baseline characteristics.

[8] Open-label trial.

10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear[9]	yes	yes	yes	yes
Overall risk of bias: moderate								

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT03625037/ EPCORE NHL-1	Please see above.	04/2029
NCT04628494/ EPCORE DLBCL-1	A randomised, open-label, phase 3 trial of epcoritamab vs. investigator's choice chemotherapy in relapsed/refractory DLBCL	04/2028

Available assessments

- A Health Technology Briefing "Epcoritamab for diffuse large B-cell lymphoma after two previous treatments" was published by NIHR in November 2021 [13].
- No further assessment was identified.

Other aspects and conclusions

- In July 2023, the **CHMP adopted a positive opinion**, recommending the granting of a conditional marketing authorisation for **Tepkinly®** as monotherapy for the treatment of adult patients with relapsed or refractory DLBCL after ≥2 lines of systemic therapy. Marketing authorisation was issued on 22 September 2023. In May 2023, the **FDA granted accelerated approval to Epkinly®** for relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.
- EPCORE NHL-1 (NCT03625037) is an **ongoing**, first-in-human, multicentre, open-label, **phase 1/2 trial**. Eligible patients were ≥18 years and had relapsed, progressive, or refractory CD20+ mature B-cell non-Hodgkin lymphoma, were required to have received previous treatment with an anti-CD20 monoclonal antibody-containing regimen and be ineligible to receive all standard therapeutic options. Patients were required to have measurable disease, an ECOG PS of 0–2, and adequate renal and hepatic function. Patients were excluded if they had CNS lymphoma (or known CNS involvement), received CAR-T therapy within 30 days before the first dose of epcoritamab, had chronic or ongoing infections, or required immunosuppressive therapy. Patients who received previous allogeneic stem cell transplantation (SCT) or solid organ transplantation.
- The **primary endpoints** were to determine the maximum tolerated dose and the recommended phase 2 dose. No dose-limiting toxic effects were observed, and the maximum tolerated dose was not reached; the full dose of 48 mg was identified as the recommended phase 2 dose.
- The evaluation of **patient-reported outcomes was not provided** by the EPCORE NHL-1 trial.
- The **ESMO-MCBS for Haematological Malignancies was not applied**, because the primary endpoints "maximum tolerated dose and the recommended phase 2 dose of epcoritamab" could not be assessed.
- The **risk of bias** of NCT03625037 was considered **moderate;** it **increased** due to the ongoing status and the open-label-design of the trial, as well as the heterogeneous characteristics at baseline.
- Beside the phase 1/2 EPCORE NHL-1 trial, **one ongoing phase 3 trial**, evaluating epcoritamab vs. investigator's choice chemotherapy in relapsed/refractory DLBCL, was identified.
- In conclusion, it must be stated that the available evidence for the assessed indication is rare. Robust phase 3 data, including patient-reported outcomes are required.

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine transaminase, ASCT=autologous stem cell transplantation, AST=aspartate aminotransferase, BEAM=carmustine, etoposide, cytarabine, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CRS=cytokine release syndrome, CT=computed tomography, DLBCL=Diffuse large B-cell lymphoma, ECOG=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EPAR=European public assessment report, ESMO-MCBS= European Society of Medical

[9] The EPCORE NHL-1 trial is currently ongoing.

Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HBV=hepatitis b virus, HCV= hepatitis C virus, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, ICANS=Immune effector cell-associated neurotoxicity syndrome, Int.=intention, IQR=interquartile range, IV=intravenous, LBCL=large B-cell lymphoma, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NR=not reached, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PM=preliminary grade, Pola-BR=polatuzumab vedotin, bendamustine and rituximab, PSA=prostate specific antigen, QoL=quality of life, R-DHAP=rituximab, dexamethasone, high-dose cytarabine, R-GDP= rituximab, gemcitabine, dexamethasone, platinum, R-GemOX=rituximab, gemcitabine, oxaliplatin, R-ICE=rituximab, ifosfamide, carboplatin, and etoposide phosphate, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, ULN=upper limit of normal, WHO=World Health Organization

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