Epcoritamab (Tepkinly®) as monotherapy for the treatment of relapsed or refractory follicular lymphoma (FL)

General information

Drug description [1]

Epcoritamab (Tepkinly®) is a subcutaneously administered CD3xCD20 T-cell–engaging, bispecific antibody that activates T cells, directing them to kill malignant CD201 B cells.

Indication [2]

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

Incidence [3]

FL is the most common indolent non-Hodgkin lymphoma in Western Europe and in the U.S.; in Asia, it is very rare. In Europe, FL accounts for 20–35% of newly diagnosed non-Hodgkin lymphomas.

Current treatment [3]

The Onkopedia treatment recommendation for the treatment of relapsed or refractory FL is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [4, 5]
Approval status for this indication: On June 27 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for **Tepkinly®**. The CHMP adopted a new indication as follows: ❖ Tepkinly® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. **Other indications**: ❖ Tepkinly® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	**Approval status for this indication**: On June 26 2024, the FDA granted accelerated approval to epcoritamab-bysp (**Epkinly™**), a bispecific CD20-directed CD3 T-cell engager, for adult patients with relapsed or refractory FL after two or more lines of systemic therapy. ✓ Accelerated approval ✓ Priority review ✓ Breakthrough designation **Other indications**: Epkinly™ is indicated for the treatment of: ❖ Adult patients with 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.

Manufacturer

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

Costs [6]

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

[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.

Posology[2] [5]

- **Pre- and Post-Administration Medications**
  - Cycle 1 (all patients)
    - Dexamethasone[3] (15 mg oral or IV) or prednisolone (100 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 Epkinly™ in Cycle 1
    - Diphenhydramine (50 mg oral or IV) or equivalent
    - Acetaminophen (650 mg to 1,000 mg oral)
  - Cycle 2+ (Patients who experienced Grade 2 or 3[4] CRS with previous dose)
    - Dexamethasone (15 mg oral or IV) or Prednisolone (100 mg oral or IV) or equivalent
      - 30-120 minutes prior to the next administration of Epkinly™ after a Grade 2 or 3b CRS event.
      - And for 3 consecutive days following the next administration of Epkinly™ until Epkinly™ is given without subsequent CRS of Grade 2 or higher.
- **Recommended Prophylaxis**
  - Provide Pneumocystis jirovecii pneumonia prophylaxis prior to starting treatment with Epkinly™.
  - Consider initiating prophylaxis against herpes virus prior to starting Epkinly™ to prevent herpes zoster reactivation.

Warnings and precautions [5]

- **Cytokine release syndrome (CRS)**
  - CRS, including serious or life-threatening reactions, can occur in patients receiving Epkinly®.
  - Initiate treatment with the Epkinly® step-up dosage 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 them appropriately.
- **Cytopenias**
  - 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.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
EPCORE NHL-1 NCT03625037	128[5]	subcutaneous epcoritamab 48 mg in 28-day cycles: weekly in cycles 1–3, biweekly in cycles 4–9, and	-	ORR by IRC	17.4 months (IQR 9.1–20.9),	**ongoing[6]**, single-arm, open-label,	CD20	Genmab A/S and AbbVie	EPCORE NHL-1 [8]

[2] Since there is currently no EMA EPAR available, chapters "Posology" and "Warnings and precautions" refer to FDA Label Information.
[3] Dexamethasone is the preferred corticosteroid when available.
[4] Patients will be permanently discontinued from EPKINLY after Grade 4 CRS.
[5] Follicular Lymphoma Dose-Expansion Cohort: 128 patients with relapsed/refractory FL G1-3.
[6] Estimated study completion date is 01/2029.

		every 4 weeks until disease progression or unacceptable toxicity				multicohort, multicenter, phase 1-2 trial			

Inclusion criteria for expansion part relapsed/refractory aNHL cohort[7]	Expansion exclusion criteria	Patient characteristics at baseline (n=128)
❖ Documented CD20+ mature B-cell neoplasm according to WHO classification Swerdlow et al., 2016 or WHO classification 2008 based on representative pathology report. ❖ DLBCL (de novo or transformed from all indolent subtypes including Richter's transformation), including: • Patients with "double-hit" or "triple-hit" DLBCL • Other aggressive B-NHL (beginning in Stage 2): o Primary mediastinal (thymic) large B-cell lymphoma o High-grade B-cell lymphoma o Follicular lymphoma grade 3B (FL 3B). ❖ Relapsed or refractory disease and previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody-containing therapy. ❖ Either failed prior autologous hematopoietic stem cell transplantation (HSCT), or ineligible for autologous HSCT due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment.	❖ Primary CNS lymphoma or CNS involvement by lymphoma at screening as confirmed by mandatory MRI/CT scan (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. • Any curable cancer with a CR of >2 years duration ❖ AST and/or ALT >3x ULN. ❖ Total bilirubin >1.5x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin. ❖ Estimated GFR <45 mL/min/1.73m^2 ❖ Known clinically significant cardiac disease, including: • Onset of unstable angina pectoris within 6 months of signing ICF • Acute myocardial infarction within 6 months of signing ICF • Congestive heart failure (grade III or IV as classified by the NYHA and/or known decrease ejection fraction of <45%. ❖ Chronic ongoing infectious diseases requiring treatment (excluding prophylactic treatment) at the time of enrolment or within the previous 2 weeks prior to the first dose of GEN3013. ❖ Confirmed history 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.	❖ Age: 65 (range, 55–72) years ❖ Female sex: 38% ❖ ECOG PS: • 0: 55% • 1: 40% • 2: 5% ❖ Creatinine clearance by Cockcroft–Gault method, mL/min: • ≥90: 41% • ≥60 to <90: 42% • ≥45 to <60: 17% ❖ Ann Arbor stage: • I: 4% • II: 11% • III: 25% • IV: 60% ❖ FL International Prognostic Index at inclusion: • 0 or 1: 13% • 2: 24% • 3–5: 61% ❖ β2 microgloblulin: • High: 62% • Normal: 35% ❖ Bulky disease • ≤6 cm: 74% • >6 cm: 26% ❖ Bone marrow involvement per investigator's assessment: 30% ❖ Time from diagnosis to first dose of epcoritamab: 6 years (range, 3–11) ❖ Time from end of previous line of therapy to first dose of ❖ Epcoritamab: 5 months (range, 2–17) ❖ Time from end of last anti-CD20 therapy to first dose of epcoritamab: 10 months (3–22) ❖ Number of previous lines of therapy: 3 (2–4) • Two: 37% • Three: 32%

[7] For detailed in- and exclusion criteria, please see trial protocol.

	❖ Prior treatment with chimeric antigen receptor T-cell (CAR-T) therapy within 30 days prior to first GEN3013 administration. ❖ Eligible for curative intensive salvage therapy followed by high dose chemotherapy with HSCT rescue. ❖ Autologous HSCT within 100 days prior to first GEN3013 administration, or any prior allogeneic HSCT or solid organ transplantation. ❖ Active hepatitis B or ongoing hepatitis C infection that has not been cured. ❖ Known human immunodeficiency virus (HIV) infection ❖ Exposed to live or live attenuated vaccine within 4 weeks prior to signing ICF. ❖ Pregnancy or breast feeding. ❖ Patient has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient or that could prevent, limit, or confound the protocol-specified assessments. ❖ Contraindication to all uric acid lowering agents.	• Four or more: 31% ❖ Progression within 24 months of initiating first-line Chemoimmunotherapy: 42% ❖ Progression within 24 months of initiating any first-line therapy: 52% ❖ Double refractory disease: 70% ❖ Primary refractory disease: 54% ❖ Refractory to previous anti-CD20 therapy: 79% ❖ Refractory to last previous systemic therapy: 69% ❖ Previous chimeric antigen receptor T-cell therapy: 5%

Efficacy (n=128)	Safety (n=128)
Data cutoff: April 21 2023; median follow-up: 17.4 months **ORR:** 82.0% (95% CI, 74.3–88.3) **CR**: 62.5% (95% CI, 53.5–70.9; 80 of 128) **Median time to response**: 1.4 months (IQR 1.3–1.5) **Median time to CR**: 1.5 months (1.4–2.8) **Patients with a response who remained in response at 18 months after first response**: 58.4% (95% CI 46.4–68.7) **Patients with a CR who remained in CR at 18 months after first response:** 72.2% (57.6–82.5) **PFS at 18 months from initiation of therapy (all patients):** 49.4% **PFS at 18 months from initiation of therapy (patient with CR):** 73.8% **MRD:** evaluable in 71%; of these 67% were MRD **negative** **Estimated number of patients who were alive at 18 months**: 70.2% (60.4–78.0) **Estimated number of all patients who had not initiated another line of antilymphoma therapy at 18 months**: 63.3% (53.7–71.4)	**CRS:** 66% **Injection-site reaction**: 57% **COVID-19 (including COVID-19 pneumonia):** 40% **Fatigue:** 30% **TEAEs leading to treatment discontinuation:** 19% **Immune effector cell-associated neurotoxicity syndrome**: 6% **Neutropenia:** 28% (excluding febrile neutropenia) **Febrile neutropenia**: 3% **Fatal TEAEs**: n=13 patients[8] and included Deaths that were considered by the investigator to be related to treatment: 0

Patient-reported outcomes [10]
According to the Appendix, changes in lymphoma symptoms are planned to be measured by the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym). Currently, results are not available.

ESMO-MCBS version 1.1 [11]

[8] COVID-19, pneumonia, sepsis from Pseudomonas aeruginosa, lymphoma transformation, myelodysplastic syndrome (pre-existing condition), interstitial lung disease, organising pneumonia, and cardiopulmonary failure in one patient each.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 82%	-	ORR ≥60%	3	-	NA	-	3

Risk of bias - study level (case series) [12]

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	no[9]	yes	yes	unclear[10]	no
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	unclear[11]	yes	yes	yes	yes	yes	unclear[12]	yes

Overall risk of bias: moderate

Ongoing trials

NCT number/trial name	Description	Estimated study completion date
NCT03625037 / EPCORE NHL-1	Please see above.	01/2029
NCT05409066 / EPCORE FL-1	A phase 3, open-label study to evaluate the safety and efficacy of epcoritamab in combination with rituximab and lenalidomide compared to lenalidomide in subjects with relapsed or refractory FL.	06/2023

Available assessments

- A Health Technology Briefing "Epcoritamab for treating relapsed or refractory follicular lymphoma" [13].
- G-BA conducted an efficacy assessment for epcoritamab in January 2024 [14].
- CADTH published a Reimbursement Recommendation for Epkinly® in June 2024 [15].
- No further assessments were identified via NICE and ICER.

Other aspects and conclusions: wichtige Informationen **fett**gedruckt**!**

- In June 2024, the **CHMP adopted a new indication** for Tepkinly® as monotherapy for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. In June 2024, the **FDA granted accelerated approval** to epcoritamab-bysp (Epkinly™) for adult patients with relapsed or refractory FL after two or more lines of systemic therapy.
- **EPCORE NHL-1** (NCT03625037) is an ongoing, multicohort, single-arm, phase 1–2 trial assessing epcoritamab monotherapy in patients with relapsed or refractory FL.
- Primary endpoint for the pivotal cohort was independently reviewed **ORR**. ORR was 82.0% (95% CI, 74.3–88.3), with a CR of 62.5% (95% CI, 53.5–70.9).

[9] Different characteristics at baseline.
[10] Trial protocol not available.
[11] Trial protocol not available.
[12] Trial is currently ongoing.

- ❖ According to the Appendix, changes in lymphoma symptoms are planned to be measured by the FACT-Lym. Currently, results are not available.
- ❖ The original **ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of **3**.
- ❖ The **risk of bias** was considered **moderate**; it is increased by the open-label trial design.
- ❖ Besides EPCORE NHL-1, one further phase 3 trial evaluating the safety and efficacy of epcoritamab in combination with rituximab and lenalidomide compared to lenalidomide in subjects with relapsed or refractory FL, was identified via ClinicalTrials.gov.
- ❖ To eventually assess the efficacy and safety of epcoritamab monotherapy in patients with relapsed and refractory FL, final analysis data and quality-of-life data are required.

First published: 07/2024

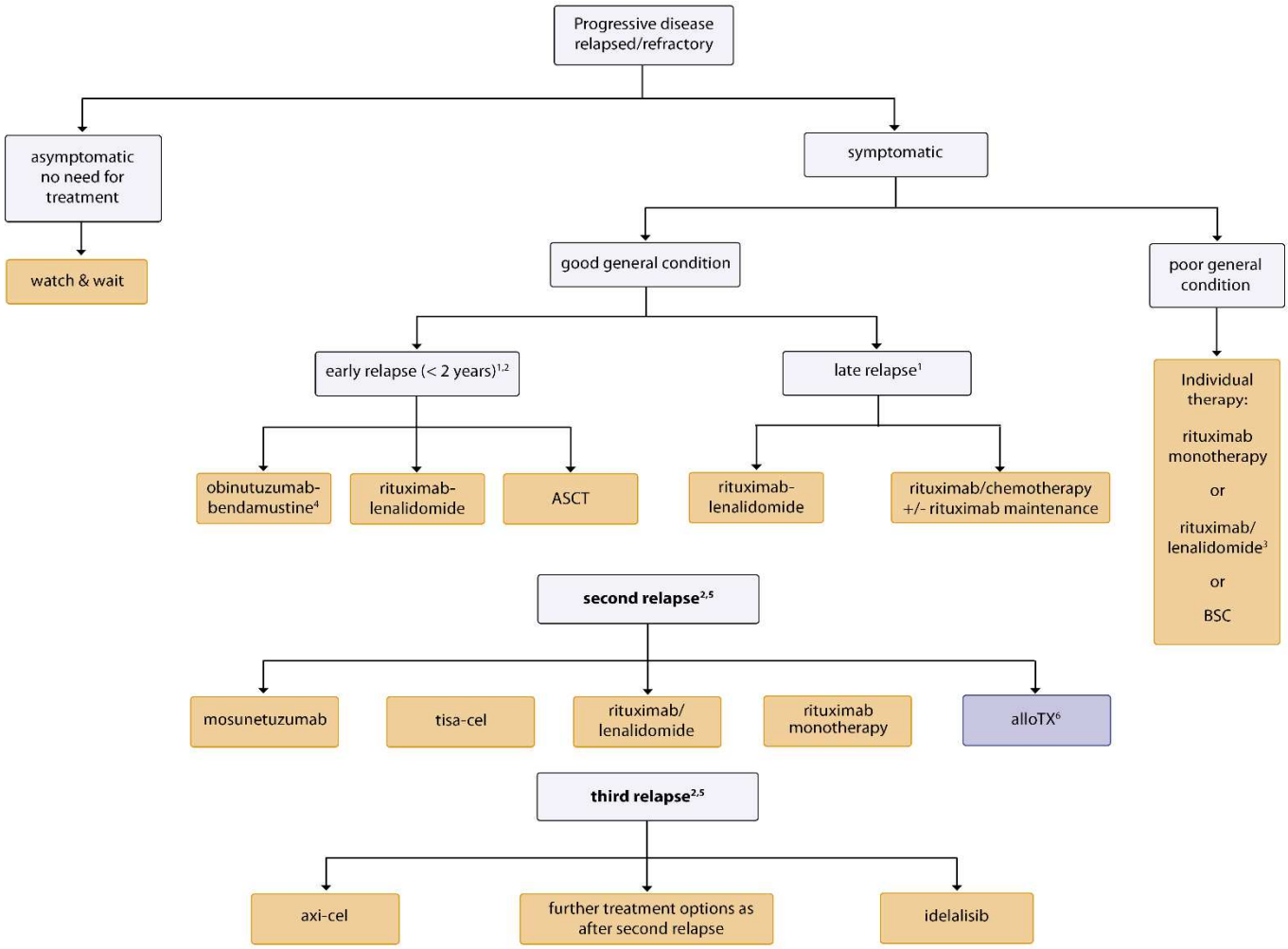
Abbreviations: AE=adverse event, AJ=adjustment, aNHL=aggressive B-cell non-Hodgkin lymphoma, ALT=alanine transaminase, AST=aspartate aminotransferase, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CRS=cytokine release syndrome, CT=computed tomography, DLBCL=diffuse large B-cell lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance status EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FL=follicular lymphoma, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GFR=glomerular filtration rate, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, ICANS=Immune effector cell-associated neurotoxicity syndrome, ICER=Institute for Clinical and Economic Review, ICF=informed consent form, Int.=intention, IRC=independent review committee, IV=intravenous, MG=median gain, MRD=measurable residual disease, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, NYHA=New York Heart Association, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, ULN=upper limit of normal, WHO=World Health Organization

References:

1. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol 41:2238-2247.
2. European Medicines Agency (EMA). Tepkinly - opinion on variation to marketing authorisation [Available from: https://www.ema.europa.eu/en/medicines/human/variation/tepkinly].
3. Onkopedia, Buske C, et. al. Onkopedia Leitlinien. Follikuläres Lymphom. [Available from: https://www.onkopedia.com/de/onkopedia/guidelines/follikulaeres-lymphom/@@guideline/html/index.html#ID0ETMAE].
4. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to epcoritamab-bysp for relapsed or refractory follicular lymphoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-epcoritamab-bysp-relapsed-or-refractory-follicular-lymphoma#:~:text=On%20June%2026%2C%202024%2C%20the,more%20lines%20of%20systemic%20therapy].
5. U.S. Food and Drug Administration (FDA). Epkinly. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761324s003lbl.pdf].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Supplement to: Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol. 2024 Aug;11(8):e593-e605.
8. Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol. 2024 Aug;11(8):e593-e605.
9. U.S. National Library of Medicine, ClinicalTrials.gov. First-in-Human (FIH) Trial in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma (EPCORE™ NHL-1). [Available from: https://clinicaltrials.gov/study/NCT03625037].

10. Phillips T, Lugtenburg P, Kalsekar A, et al. Improvements in Patient-Reported Outcomes in Relapsed or Refractory Large B-Cell Lymphoma Patients Treated With Epcoritamab. Clinical Lymphoma, Myeloma and Leukemia. 2024 Mar;24(3):e78-e87.e2.
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology. 2017;28: 2340–2366.
12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about
13. National Institute for Health Research (NIHR). Epcoritamab for treating relapsed or refractory follicular lymphoma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2023/07/31063-Epcoritamab-for-B-Cell-Lymphoma-V1.0-JUN2023-NON-CONF.pdf].
14. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertung. Epcoritamab. [Available from: https://www.g-ba.de/downloads/92-975-7056/2023-10-15_Nutzenbewertung-G-BA_Epcoritamab_D-980.pdf].
15. CADTH. CADTH Reimbursement Recommendation. Epcoritamab (Epkinly). [Available from: https://www.cadth.ca/sites/default/files/DRR/2024/PC0334_Epkinly-Final_Rec.pdf].

Appendix – Figure 1:



Legend:

curative therapy intention; palliative therapy intention;

BSC – Best Supportive Care;
ASCT – autologous stem cell transplantation
tisa-cel, axi-cel - CAR-T-cell therapy
[1]after initial immunochemotherapy
[2]participation in clinical trials recommended
[3]dose reduction as appropriate, reduced number of cycles
[4]if refractory to rituximab
[5]depending on prior therapy and duration of remission
[6]preferably after ASCT failure and as part of clinical trials