EE361

Long-Term Remission (LTR) Assumptions in Bispecific Treatments: A Review of Recently Published Health Technology Assessments (HTAs) for Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Following Two or More Lines of Systemic Therapy (3L+)

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BACKGROUND

- Clinical trial follow-up for oncology treatments can be immature at early data read-outs, which poses challenges when predicting long-term survival for treatments with a new mechanism of action and immature data.
- This study focused on relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), an aggressive form of non-Hodgkin lymphoma (NHL) that accounts for approximately 30% of all NHL cases.[1]
- Bispecific antibodies (BsAbs i.e., glofitamab and epcoritamab), have introduced a novel mechanism of action in treating R/R DLBCL by targeting both CD20 on B-cells and CD3 on T-cells, engaging the immune system to eliminate malignant cells.[2]
- Clinical trials for BsAbs have shown significant promise in inducing durable response in patients with R/R DLBCL. For glofitamab, 39% (95% confidence interval [CI], 32–48) of patients achieved complete response (CR), with approximately 78% (95% CI, 64–91) maintaining response at 12 months.[3] Epcoritamab achieved a CR rate of 40% (95% CI, 32.4–48.2), with 64% (95% CI, 47.5–76.8) remaining in CR at 24 months.[4]
- To recognize the impact of anticipated durable remissions for BsAbs, economic models submitted for health technology assessment (HTA) included long-term remission (LTR) assumptions which substantially impacted survival extrapolations and cost-effectiveness results.

OBJECTIVE

- The primary objective of this study was to investigate the modeling approaches and acceptability of LTR assumptions in the context of the HTA submissions for glofitamab and epcoritamab in R/R DLBCL.

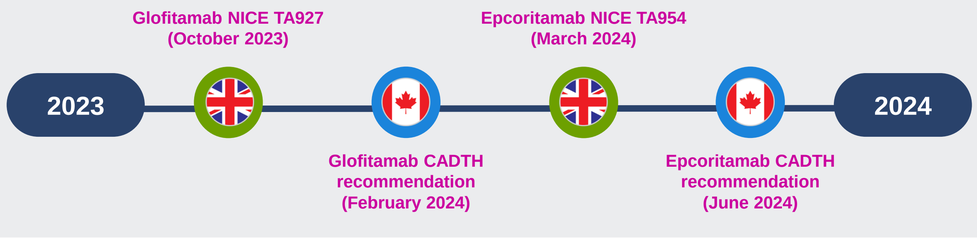
METHODS

- A targeted literature review (TLR) was conducted in June 2024 to review HTA submissions for glofitamab and epcoritamab in 3L+ R/R DLBCL.
- National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH) were targeted as at the time of this study as they were the only HTA agencies to review these therapies.

RESULTS

- **Figure 1** shows the timelines for HTA decision dates for NICE and CADTH submissions of glofitamab and epcoritamab.[5-8]

Figure 1: Timeline of HTA decision dates



- Key LTR assumptions and critiques for glofitamab and epcoritamab HTA submissions are summarized in **Table 1**.
- NICE assessed the BsAbs in 3L+ R/R DLBCL. The target population in the CADTH submissions further specified patients to be ineligible to receive or could not receive Chimeric Antigen Receptor T-cell (CAR T) or be CAR T-experienced. The assumptions underpinning LTR approach remained unaffected, regardless of prior treatment exposure.
- All submissions used a partitioned survival model (PSM) structure with three health states, i.e., progression-free survival (PFS), progressed disease (PD) and death, to compare BsAbs versus relevant comparators.

RESULTS

NICE technology appraisals

- In both NICE submissions, LTR was defined as no disease progression after 2 years following treatment initiation.
- Mortality rates for patients who progressed before 3.5 years (glofitamab) or 2 years (epcoritamab) were informed by extrapolated OS data. After these time points, mortality was based on the age-matched general population adjusted using standardized mortality ratios (SMR) of 1.09 for glofitamab and 1.41 for epcoritamab.
- In NICE TA927, patients entering LTR saw health state utility values (HSUVs) revert to near general population levels, with a 10% utility decrement. This was not presented in the TA954 model, where HSUVs for patients in LTR continued to be based on the PFS state value from the EPCORE NHL-1 trial.
- Across both NICE appraisals, treatment durations differed. Glofitamab had a fixed treatment duration (12 cycles), while epcoritamab treatment continued to progression. The Evidence Assessment Group (EAG) critiqued the clinical plausibility of patients entering LTR and discontinuing follow-up while still receiving treatment with epcoritamab.
- Key evidence supporting LTR assumptions in NICE TA927 included precedents from previous 2L+ and 3L+ DLBCL non-BsAbs appraisals (e.g., TA649, TA559, TA567),[9-11] which were validated by clinical experts. Additionally, the NP30179 January 2023 data demonstrated prolonged OS and PFS with a sustained plateau around 18 months post-treatment initiation.
- EAG critiques in NICE TA927 highlighted uncertainty surrounding the cure definition and the timing of the LTR assumption. A UK clinical expert noted that the plateau observed in PFS, and duration of complete response curves had not been fully reached, highlighting the need for longer follow-up data to determine the proportion of patients cured with glofitamab.
- EAG critiques in NICE TA954 related to the company's assumptions regarding follow-up costs and survival. The assumption that patients entering LTR would no longer require follow-up was considered to underestimate costs.
- Despite concerns, NICE committees accepted the LTR assumptions from a 3-year time point but differences remained with respect to the SMRs (i.e., 1.09 for glofitamab and 1.41 for epcoritamab), as reflected in the final recommendation.
- In TA954 the NICE committee further suggested that the proportion of patients entering a LTR state should be based on the time-to-treatment discontinuation (TTD) curve especially in the absence of treatment stopping rule.

CADTH submissions

- In the CADTH submissions, the base-case analyses assumed that LTR occurred at 2 years (glofitamab) and 3 years (epcoritamab), with mortality rates set to be equivalent to or slightly higher than those of the general population. Future HSUVs were adjusted for age but no additional decrements were applied upon entering the LTR state in CADTH appraisals.
- Key evidence supporting the LTR assumptions was from clinical experts. For glofitamab, it was noted that the proportion of patients achieving CR in the NP30179 trial exceeded expectations, suggesting this could lead to better long-term survival outcomes. Similar expert insights were used to justify the LTR assumption in the CADTH epcoritamab submission.
- Key critiques from CADTH reviewers in the glofitamab submission related to the plausibility of the LTR assumption. They considered patients who were PF 2 years after treatment initiation could still experience disease progression, albeit at a slower rate, and that their mortality risk would likely remain higher than that of the general population. CADTH reviewers also indicated that once treatment is stopped, progression rates in the PF population would eventually converge between treatment arms.
- Key critiques from CADTH reviewers in the epcoritamab submission revolved around the uncertainty as to whether epcoritamab could have a curative effect for patients with R/R DLBCL, especially since treatment continues until disease progression or unacceptable toxicity. CADTH reviewers highlighted that the PSM did not fully capture the relationships between patient characteristics, probability of progression, and death, and overestimated survival post-progression for patients on epcoritamab compared to salvage chemotherapy without sufficient justification.
- Across both submissions, CADTH reviewers aligned in terms of removing the LTR assumption at 2 years (glofitamab) and 3 years (epcoritamab) and set the post-progression outcomes (QALY, cost) equal across treatment arms regardless of initial treatments, due to BsAbs being associated with longer post-progression survival versus salvage chemotherapy without a sufficient causal explanation.

Table 1: Review of the LTR assumptions in BsAbs across NICE and CADTH submissions

Characteristic	Glofitamab (NICE TA927)	Glofitamab (CADTH PC0320-000)	Epcoritamab (NICE TA954)	Epcoritamab (CADTH PC0334-000)
Recommended population	Adults with R/R DLBCL who have had two or more systemic treatments.[a]	Adults with R/R DLBCL after at least two prior lines of therapy and are ineligible to receive or cannot receive CAR T therapy or have previously received CAR T therapy.	Adults with relapsed or refractory large B-cell lymphoma who have had two or more systemic therapies but only if received pola, or if pola is contraindicated or not tolerated.[b]	Adult patients with R/R DLBCL, not otherwise specified, DLBCL after two or more lines of systemic therapy and who have previously received or are unable to receive CAR T therapy.
Intervention and comparators (including key trials	• Intervention: Glofitamab (NP30179) • Comparators: Axi-cel (ZUMA-1); pola-BR (GO29365); BR (Hong 2018)	• Intervention: Glofitamab (NP30179) • Comparators: Salvage chemotherapy (rituximab-based regimens represented by R-GDP [SCHOLAR-1]); pola-BR (GO29365)	• Intervention: Epcoritamab (EPCORE NHL-1) • Comparators: R-based CIT (SCHOLAR-1); axi-cel (ZUMA-1); pola + BR (scenario: EUnetHTA submission for pola + BR, Sehn et al. 2019 and Sehn et al. 2022 extension study)	• Intervention: Epcoritamab (EPCORE NHL-1) • Comparators: Pola-BR (GO29365); scenario analyses: R-CIT (SCHOLAR-1); CAR T therapies including liso-cel, axi-cel, and tisa-cel
Model structure	• PSM comprising of three health states: PFS, PD, and death.	• PSM comprising of three health states: PFS (on/off treatment), PD, and death.	• PSM comprising of three health states: PFS, PD, and death.	• PSM comprising of three health states: PFS, PD, and death.
LTR assumptions (company submission)	• Assumed patients who are alive and PF at 2 years after treatment initiation are in LTR. Upon entering LTR, patients do not progress and revert to near general population utility (assumed 10% lower versus general population). • Patients in LTR assumed to incur no further costs. • To maintain consistency, LTR was assumed to be treatment independent, with the same assumptions applied to all treatment arms in the model.	• If a patient's disease does not progress within the first 2 years after treatment initiation, it will not progress after that time point. • Company assumed a continued treatment benefit long after treatment discontinuation, and that mortality is independent of treatment and disease status.	• Company submission assumed that patients who are alive and PF at 2 years after treatment initiation enter LTR. • Patients in LTR receive the PFS utility value based on EPCORE NHL-1 study. • Patients in LTR assumed to use no healthcare resources beyond treatment. • LTR assumption applied to all treatments in the model.	• Company assumed that patients in this population who remained PF 3 years after initiating treatment were considered functionally cured and no longer at risk of progression for the remainder of the model time horizon.
Excess mortality (company submission)	• Assumed that 3.5 years after treatment initiation, patients experienced a 9% increased risk of mortality (Maurer et al. 2014),[12] relative to the age-matched general population, reflective of prior treatment related toxicity.	• Assumed the mortality rate after 2 years for patients with progressed disease to only be slightly higher than that of the general population.	• Assumed PF patients after 2 years who are in LTR experience an increased relative risk of mortality of 1.41 compared with the general population.	• Not reported
HTA critiques	Concerns raised by the EAG (CRD and CHE Technology Assessment Group) included: • Although accepted for axi-cel, there is no clinical plausibility of cure for other treatments in R/R DLBCL and limited data exists that support this assumption. • There is no accepted clinical definition of cure and substantial uncertainty exists around the time-point at which cure can be assumed. • If cure is assumed, there is uncertainty around which utility decrement and which excess mortality estimate if any, should be used. • EAG stated that excess mortality was too optimistic, citing another study (Howlader et al. 2017)[13] which showed 41% excess mortality in people whose DLBCL had been in remission and progression-free 2 years after treatment.	• Clinical experts noted that LTR assumptions lack clinical plausibility and patients who are PF 2 year after treatment initiation still experience progression, though at a slower rate. Patients who are PF also have a higher rate of mortality than the general population. • Clinical experts also suggested that once treatment is stopped, event rates when PF will eventually become equivalent between treatment arms – this is challenging to model in a PSM. • Given limitations of PSM structure for not modelling PF patients with on and off treatment, CADTH assumed the probability of progression after 30 months was the same for glofitamab and salvage chemotherapy and the probability began to converge after 18 months through linear interpolation. • CADTH assumed the outcomes (costs and QALYs) post-progression would be the same (30 months) regardless of initial treatment for PD patients.	Concerns raised by the EAG (BMJ-TAG) included: • Suggested it was clinically implausible that patients would enter LTR and be discharged from follow-up while still on treatment with epcoritamab (no stopping rule). • EAG noted that company's approach mainly effects follow-up costs in the model and survival, as patients in LTR are assumed to not be followed up anymore (i.e., underestimating costs as well as overestimating the probability of survival).	• CADTH considered there was significant uncertainty as to whether epcoritamab has a curative effect on patients with R/R DLBCL, given epcoritamab is an ongoing treatment until disease progression or unacceptable toxicity. • CADTH considered the model to inadequately capture the causal relationships between patient characteristics, the probability of progression, and death, as it predicted that epcoritamab is associated with longer survival after disease progression compared with current treatment.
Final HTA recommendations	• The committee concluded that there is uncertainty about the exact point of a cure but assumed a cure point of 3 years with a 9% increased risk of background mortality was reasonable.	• CADTH removed the LTR assumption after 2 years PF arm assumed no difference in outcomes for patients who experience disease progression for the comparison of salvage chemotherapy and glofitamab.	• The committee concluded that it is appropriate to apply the LTR assumption 3 years after starting epcoritamab or its comparators, as in TA927. • The committee concluded that there is limited evidence on the proportion of patients who stop epcoritamab when entering LTR, noting this proportion should be based on the TTD curve from EPCORE NHL-1 trial.	• CADTH removed the 3-year assumed equal efficacy between epcoritamab versus pola-BR and revised long-term disease progression and mortality for glofitamab and salvage chemotherapy.

Notes: a) *In company submission (TA927), it was proposed by the company that glofitamab may be used a treatment line ahead of CAR T therapy, in patients who are ineligible for CAR T therapy, or patients who have failed CAR T therapy in prior treatment lines. b) In company submission (TA954) following patient population were considered: Base case population A, vs. R-based CIT (no prior CAR T population from EPCORE NHL-1); Base case population B, vs. axi-cel (no prior CAR T, CAR T eligible population from EPCORE NHL-1).* ***Abbreviations:*** *Axi-cel, axicabtagene ciloleucel; BMJ-TAG, British Medical Journal Technology Assessment Group; BR, bendamustine and rituximab; BsAb, bispecific antibody; CADTH, Canadian Agency for Drugs and Technologies in Health; CAR T, chimeric antigen receptor T-cell; CHE, Centre for Health Economics; CR, complete response; CRD, Centre for Reviews and Dissemination; EAG, evidence assessment group; EUnetHTA, European Network for Health Technology Assessment; HTA, health technology assessment; Liso-cel, lisocabtagene maraleucel; LTR, long-term remission; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; PSM, partitioned survival model; QALY, quality-adjusted life year; R-CIT, rituximab-based chemoimmunotherapy; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R/R DLBCL, relapsed or refractory diffuse large B cell lymphoma; SMR, standardized mortality ratio; TA, technology appraisal; Tisa-cel, tisagenlecleucel; TTD, time to treatment discontinuation.*

CONCLUSIONS

- NICE and CADTH demonstrated different approaches in evaluating LTR assumptions. Heterogeneity exists in the application and justification of LTR assumptions, posing risks of inconsistent decision-making across HTA submissions.
- Approaches to modelling LTR need to be evidence-driven, clinically plausible, and validated utilizing mature follow-up data (where available) and external evidence from treatments with similar mechanism of actions, especially when associated with clinical benefits post-progression or after treatment discontinuation.
- Where evidence is not available, plausibility should be supported by input from clinical experts.

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