Economic evaluations in relapsed or refractory follicular lymphoma: challenges for health technology assessment submissions

HTA83

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Introduction

- Treatment options for follicular lymphoma (FL) in the first-line and second-line settings are described in clinical guidelines.[1] However, third-line and later (3L+) standard of care has yet to be defined and effective treatments are lacking
- Chimeric antigen receptor (CAR) T cell[2–4] and T-cell bispecific antibody[5] therapies offer new opportunities but have faced access challenges in countries that focus on health technology assessment (HTA) for reimbursement decision-making[6–9]
- To better understand the challenges associated with HTA for new innovative treatment options in the 3L+ setting, a systematic literature review (SLR) of all published HTA evaluations in R/R FL was conducted

Methods

- The SLR was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting requirements
- Search strategies were developed to identify economic evaluations of treatments in patients with R/R FL published in English during the period
- Literature searches were conducted in September 2022 via Ovid SP in Embase, MEDLINE and MEDLINE In-Process, Cochrane Central Register of Controlled Trials (CENTRAL), National Health Service Economic Evaluation Database (NHS EED; discontinued in 2015), EconLit, International HTA Database, and Cost-Effectiveness Analysis (CEA) Registry
- Grey literature searches were performed across several HTA websites for data published since 2016 across several countries and conference proceedings published over the past 3 years. The reference lists of 2 recently published SLRs[10,11] were also cross-checked
- Updated searches of the National Institute for Health and Care Excellence (NICE) website were carried out in June 2023; these evaluations have also been included for completeness
- PICOS selection criteria are shown in **Table 1** and the quality of economic evaluations was assessed using the Drummond Checklist[12] by one reviewer and validated by a senior reviewer

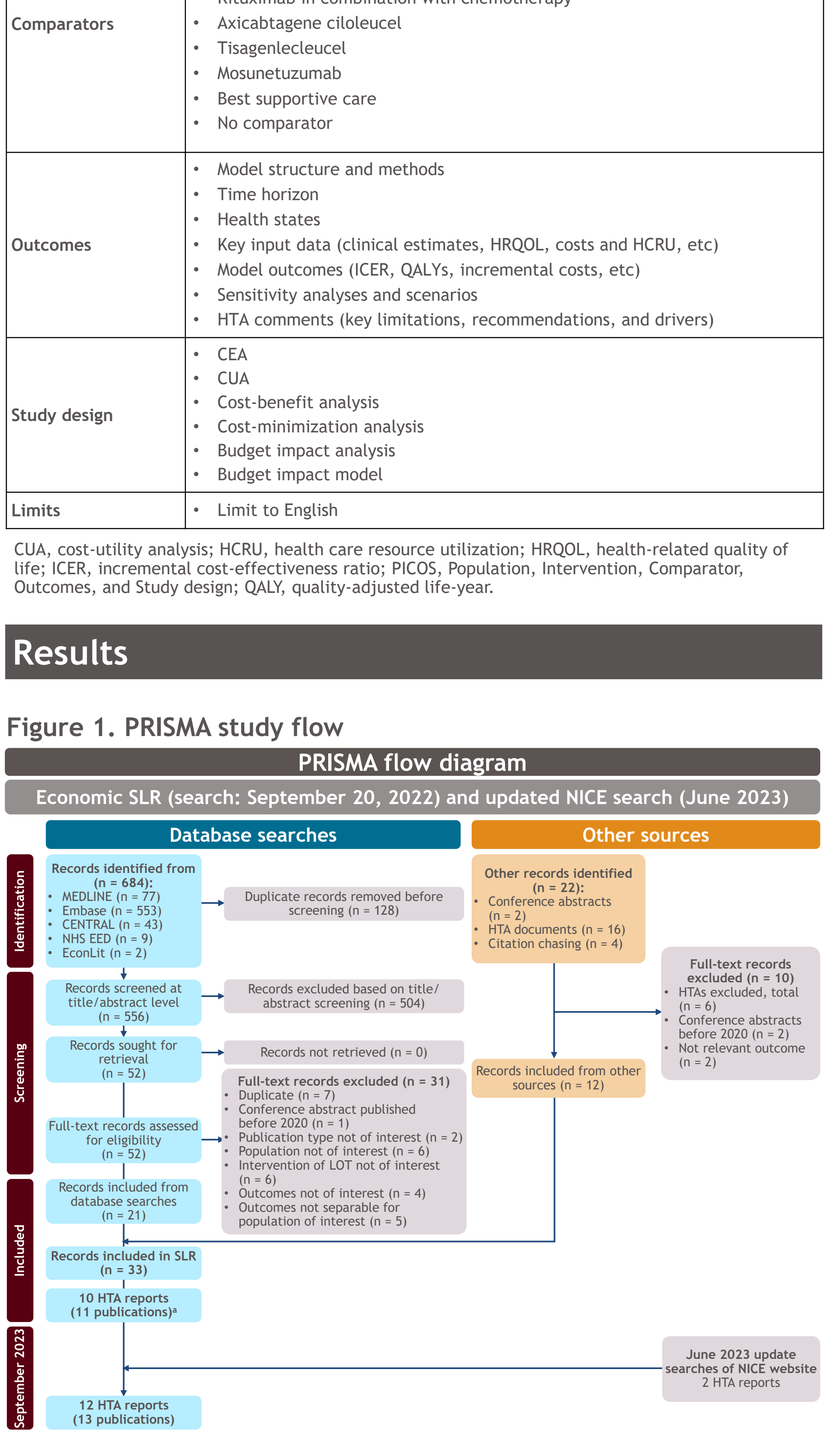
Table 1. PICOS study selection criteria

Criterion	Inclusion criteria
Population	• Adults (≥ 18 years) diagnosed with R/R FL • Where studies include mixed populations of patients, separate data must be available for patients with FL or ≥ 80% of included patients should have FL
Interventions	• Any interventions for treatment of R/R FL
Comparators	Any comparator, including but not limited to: • Obinutuzumab with bendamustine followed by obinutuzumab maintenance • Lenalidomide with rituximab • Rituximab in combination with chemotherapy • Axicabtagene ciloleucel • Tisagenlecleucel • Mosunetuzumab • Best supportive care • No comparator
Outcomes	• Model structure and methods • Time horizon • Health states • Key input data (clinical estimates, HRQOL, costs and HCRU, etc) • Model outcomes (ICER, QALYs, incremental costs, etc) • Sensitivity analyses and scenarios • HTA comments (key limitations, recommendations, and drivers)
Study design	• CEA • CUA • Cost-benefit analysis • Cost-minimization analysis • Budget impact analysis • Budget impact model
Limits	• Limit to English

CUA, cost-utility analysis; HCRU, health care resource utilization; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PICOS, Population, Intervention, Comparator, Outcomes, and Study design; QALY, quality-adjusted life-year.

Results

Figure 1. PRISMA study flow



[a]Ten unique reports and 1 ERG review.
ERG, Evidence Review Group; LOT, line of therapy.

Search results

- After screening at full text, a total of 13 records were ultimately included in the SLR reporting on 12 unique economic models (**Figure 1**)

Table 2. Summary of included HTA economic evaluations

HTA submission ID	Type of CUA	Time horizon	Perspective	Recommended for reimbursement?
3L+ setting (no separate data by LOT)				
NICE TA604 idelalisib, 2019—2022[14]	Markov model and partitioned survival	NR	Health care and personal and social services	No
CADTH pCODR idelalisib, 2016[20]	Partitioned survival	30 years	Health care system	No
NICE ID3931 mosunetuzumab, 2023[25]	Partitioned survival	40 years	Health care system	No
4L+ setting (no separate data by LOT)				
NICE ID1685 axicabtagene ciloleucel, 2023[24]	Partitioned survival	40 years	Health care system	No
R/R disease (no separate data by LOT)				
SMC No. (1219/17) obinutuzumab + bendamustine, 2017[19]	Markov model	NR	Health care system	Yes
SMC2281 lenalidomide + rituximab, 2020[18]	Partitioned survival	40 years	Health care system	Yes
PBAC obinutuzumab + bendamustine, 2016[22]	Markov model	15 years	Health care system	No
PBAC obinutuzumab + bendamustine, 2018[23]	Markov model	NR	Health care system	Deferred
CADTH pCODR obinutuzumab + bendamustine, 2017[21]	Markov model	25 years (reanalysis 10 years)	Health care system	Yes, with clinical criteria and/or conditions
NICE TA629 obinutuzumab + bendamustine, 2020[15]	Partitioned survival	Lifetime (25 years)	Health care and personal and social services	Yes
NICE TA472 obinutuzumab + bendamustine, 2020[16] NICE Rafia, 2018 - ERG comments on TA472 obinutuzumab + bendamustine, 2020[17]	Partitioned survival	Lifetime	Health care and personal and social services	Yes
NICE TA627 lenalidomide + rituximab, 2020[13]	Partitioned survival	40 years	Health care and personal and social services	Yes

CADTH, Canadian Agency for Drugs and Technologies in Health; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drug Review; SMC, Scottish Medicines Consortium; TA, technology assessment.

Overview of included HTA economic evaluations

- Twelve economic evaluations were submitted to HTA bodies over an 8-year period (2016—2023) and applied either a Markov model or partitioned survival model to simulate cost utility in 3L+ settings,[14,20,25] fourth-line or later (4L+) settings,[24] or in previously treated R/R patients[14,15–19, 21–23] with FL (**Table 2**)
- Idelalisib and the 2 most recently evaluated treatments (axicabtagene ciloleucel,[24] and mosunetuzumab[25]) failed to be approved by NICE
- Quality of the economic evaluations using the Drummond Checklist[12] was judged to be acceptable, though no evaluation fulfilled all the assessment criteria. Poor reporting of the justification for model selection and inputs, and the failure to report details of statistical tests were the main areas of concern

HTA assessment group criticisms and concerns

- Issues raised by HTA assessment groups focused on choice of treatment comparator (n = 8), model structure, inputs, and time horizon (n = 8), uncertainly in model outputs (eg, ICER estimation) (n = 8), and lack of scenarios to investigate uncertainties in the model (n = 8)
- Issues with the choice of comparators for the treatment of R/R FL were highlighted as problematic across several HTA assessments[13,14,16,17,20–23] due to the lack of clear guidance and consensus in treatment guidelines
- The choice of model inputs was challenging for several evaluations[13,14,16–18,21,23,24] that lacked appropriate clinical data from mature direct head-to-head clinical trials of relevant comparators. Alternative indirect comparison and extrapolation methods were frequently criticized by HTA assessment groups
- Uncertainly in the outputs from economic models was a commonly raised concern across several evaluations[13,14,18,19,22,23–25]
- Failure to fully investigate the impact on the final ICER values in alternative scenarios has led to further criticism from HTA assessment groups[13,14,18,19,22,23]
- However, HTA assessment groups admit that uncertainty in some cases cannot be resolved without more robust clinical data becoming available
- Issues that newer CAR T cell therapies face based on evidence from the recent NICE evaluation of axicabtagene ciloleucel include:
  - Long-term survivor assumptions remain uncertain given the immaturity of the PFS and overall survival (OS) data
  - There is unresolvable uncertainty around comparative effectiveness given the lack of comparative data from a clinical trial and issues around using data from observational studies (not relevant to the UK population)
  - Utility values are not available for the 3L+ patient population
- **Table 3** summarizes key considerations and expected feedback from HTA agencies for submission of a CAR T cell therapy versus conventional therapies (eg, chemoimmunotherapies, phosphatidylinositol 3-kinase inhibitors, anti-CD20 monoclonal antibody, and lenalidomide)

Table 3. Key considerations and expected feedback from HTA agencies for HTA submissions of CAR T cell versus conventional therapies

Key considerations	CAR T cell therapy (NICE ID1685 axicabtagene ciloleucel, 2023[24])	Conventional therapies
Model structure	• Partitioned survival model approach, or decision tree combined with partitioned survival model to differentiate between infused versus not infused patients • Those who do not receive CAR T cell therapy but are not dead (due to experiencing adverse events [AE] or manufacturing defect) incur outcomes for the comparator arm	Partitioned survival analysis model
	Well accepted by NICE ERG	Well accepted by NICE ERG
Comparator arm	• Control arm constructed using real-world data with or without matching the patient characteristics across the 2 cohorts	• Usually informed by the control arm of the randomized controlled trial
	ERG critique: Real-world evidence data not generalizable to the UK	Well accepted by NICE ERG
Efficacy outcomes	• Differentiation made between long-term survivors and non—long-term survivors • Some proportion of patients assumed to be long-term survivors after 5 years. The proportion used is based on assumption or parametric models • General population mortality risk adjusted for the excess mortality from disease (hazard ratio = 1.09) applied for long-term survivors, and hazards from the parametric models used for non—long-term survivors • Utility and HCRU for long-term survivors assumed to be the same as that for the general population	• Use of Kaplan-Meier data and parametric models fitted to trial data • Treatment effect assumed to last up to specific duration after which hazard for deaths were considered equal in control and intervention arm
	ERG critique: uncertainty around the proportion of patients who would be long-term responders and what time point would be considered "long-term" The ERG suggested that other methods are explored, including alternative OS modeling approaches like mixture cure models, splines, and piecewise	**ERG critique:** clinical plausibility of long-term OS and PFS extrapolations is uncertain Usually unclear how long treatment effects will last
Cost outcomes	• Additional cost components for CAR T cell therapies included leukapheresis, bridging therapy, conditioning chemotherapy, and infusion-related monitoring and hospitalization	• Included usual costs like drug acquisition and administration, HCRU, subsequent therapy cost, end of life cost, and AE costs
	NICE ERG note that CAR T cell therapies include additional cost components	Well accepted by NICE ERG

Discussion

- Due to frequent lack of comparative evidence from head-to-head clinical trials, data gaps have to be filled by either indirect evidence or estimates combining observational data across several therapy lines, which may not be representative of the target population of interest
- Lack of mature long-term clinical data points necessitate estimation from other data
- Due to the nonreimbursement of new innovative treatment options, the pool of comparator treatments remains unchanged, resulting in ongoing challenges associated with access of innovative options in HTA-focused markets

Strengths and limitations

- The SLR applied robust methods and conducted searches across several relevant electronic databases and grey literature sources to ensure clinical relevance of the captured evidence
- Assessment of the economic evaluations in some cases was hampered by poor reporting, especially with respect to the modeling methods and input data
- The redaction of commercially sensitive information within the HTA assessment reports led to a further lack of detail and clarity
- Only a limited number of newer therapies such as CAR T cell therapies and T-cell engagers have presently been evaluated

Conclusions

- Mature clinical data from relevant comparative clinical trials were lacking. Future submissions need to carefully consider methodologies and model inputs, as well as testing different assumptions
- The lack of consensus on treatment algorithms and of direct head-to-head data from clinical trials leads to uncertainty in clinical inputs and ICER values
- In comparison to conventional therapies, novel and emerging treatment options like CAR T cell and T-cell bispecific antibody therapies could potentially provide extra clinical advantages to patients with R/R FL in later LOTs. However, the HTA evaluation of these therapies seems to face additional challenges compared with those faced by conventional therapies

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