COST-EFFECTIVENESS STUDIES OF THE BREXU-CEL IN RELAPSED/REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND MANTLE CELL LYMPHOMA: A SYSTEMATIC REVIEW

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BACKGROUND

Brexucabtagene autoleucel (Brexu-cel), one of the recent Chimeric antigen receptor T cell (CART-cell) therapies was approved by the US-FDA for refractory/ relapsed B-cell acute lymphoblastic leukemia (R/R ALL) in adults and refractory/relapsed mantle cell lymphoma (R/R MCL).[1] Brexu-cel is costly and various cost-effectiveness analysis (CEA) studies exist.

OBJECTIVE

To examine the CEA studies of brexu-cel in patients with R/R ALL and R/R MCL across different jurisdictions

METHODS

Inclusion criteria

- Original studies published until 25 November 2023 and health technology assessment (HTA) reports in English exploring CEA of brexu-cel to treat R/R ALL and R/R MCL
- Studies with outcomes such as cost per life year gained (LYG) or quality-adjusted life year (QALY) gained, or any other measures of economic evaluations without any restrictions on countries

Exclusion criteria

- Qualitative studies, conference proceedings, editorials, commentaries, reviews, or methodological articles
- Studies that reported only patient-reported outcomes, quality of life, survival outcomes, or utilities without any cost analysis

Quality assessment

- Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022)[2] was used to assess the quality of the included studies.

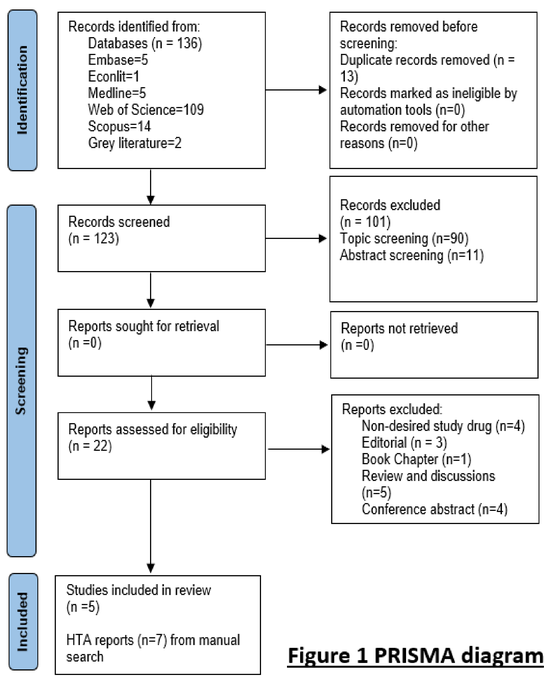

Figure 1 PRISMA diagram

RESULTS

Table 1: Evidence from included studies

Author, Country, Year	Study Perspective	Population	Comparator	Model structure	Cycle length	Time horizon	Discount rate/year	Reported ICER	ICER (2023 US dollars)	Conclusion	CHEERS score (%)
Shah B et al., US, 2022[3]	A payer	R/R B-ALL patients in line with ZUMA-3 mITT population	SoC (BLIN, INO, CHEMO)	Decision tree and PSM	1 week	Lifetime	3% cost and benefits	BLIN: $20,843/QALY INO: $77,271/QALY CHEMO: $93,768 /QALY	BLIN: $23,464/QALY INO: $86,762/QALY CHEMO:$105,381/QALY	Cost-effective (CE WTP: $150,000/QALY)	23 (82.14%)
Ball G et al., Canada, 2022[4]	Healthcare system	Post-BTKi R/R MCL patients in line with ZUMA-2 ITT population	BSC*	3-state PSM	1 month	Lifetime	1.5% cost and benefits	CAD 88,503/QALY	$80,632/QALY	Cost-effective (CE WTP: CAD 100,000/QALY)	24 (85.71%)
Marchetti M et al., Italy, 2023[5]	Healthcare system	Post-BTKi R/R MCL patients in line with ZUMA-2 safety population	R-BAC (Rituximab, bendamustine, cytarabine)	3-state PS-MCM	1 month	Lifetime	3% cost and benefits	€64,798/QALY	$98,903/QALY	Cost-effective (CE WTP: €87,330/QALY)	23 (82.14%)
Petersohn S et al., UK, 2022[6]	Healthcare system	Post-BTKi R/R MCL patients in line with ZUMA-2 safety population	SoC**	3-state PSM	1 month	Lifetime	3.5% cost and benefits	£67,713/QALY	$108,978/QALY	Cost-effective (CE WTP = NR)	24 (85.71%)
Simons C et al., US, 2021[7]	A payer	Post-BKTi R/R MCL patients in line with ZUMA-2 safety population	SoC#	3-state PS-MCM	1 month	Lifetime	3% cost and benefits	$31,985/ QALY	$37,639/QALY	Cost-effective (CE WTP: $150,000/QALY)	24 (85.71%)

*BSC= A blended comparator including chemoimmunotherapy, such as bendamustine + rituximab, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP), and R-DHAP with other therapies including lenalidomide (+/− rituximab), bortezomib (+/− rituximab), and allogeneic transplant; **SoC = A basket comparator including cytotoxic chemotherapy (bendamustine, cytarabine, and doxorubicin-hydrochloride), proteasome inhibitors (bortezomib), immunomodulatory drugs (lenalidomide, rituximab) and Bcl-2 protein inhibitors (venetoclax); #SoC= A basket comparator including cytotoxic chemotherapy (bendamustine), proteasome inhibitors (bortezomib), immunomodulatory drugs (lenalidomide), Bcl-2 protein inhibitors (venetoclax), and BTK inhibitors (acalabrutinib, ibrutinib, zanubrutinib); PSM=Partitioned survival model; PS-MCM=Partitioned survival mixture cue model; QALY=Quality Adjusted Life-years; SoC= Standard of Care; BSC= Best Supportive care; , INO= Inotuzumab ozmogamicin, BLIN= Blinatumomab, CHEMO= salvage chemotherapy; CAD= Canadian dollars; USD= US dollars, WTP = Willingness to pay; ICER=Incremental cost-effectiveness ratio; mITT= modified intent-to-treat; BKTi= Bruton's tyrosine kinase inhibitors.

Table 2: Evidence from HTA reports

Agency, Country, Year	Study Perspective	Population	Comparator	Model structure	Cycle length	Time horizon	Discount rate/year	Reported ICER	Conclusion
CADTH, Canada, 2022[8]	Healthcare system	R/R ALL patients in line with the ZUMA-3 population	BLIN±TKIs INO±TKIs Salvage chemotherapy (FLAG-IDA or hyper CVAD)	Decision tree and PSM	1 week	Lifetime	1.5% costs and benefits	CHEMO:$59,987/QALY*	Likely biased estimates of cost-effectiveness towards brexu-cel (CE WTP = $50,000/QALY)
NICE, England, 2021[9]	Healthcare system	R/R ALL population in line with ZUMA-3 mITT population and two subgroups (Ph- and Ph+) for whom SCT is not indicated.	*Overall population:* INO *Ph-subgroup:* INO, BLIN *Ph+ subgroup:* INO, Ponatinib	3-state PSM	1 week	Lifetime	3.5% costs and benefits	*Overall population* INO: £23,690/QALY *Ph- ; Ph+ subgroup* BLIN: £53,540/QALY INO: £40,447;40,772/QALY Ponatinib: £62,242/QALY	Considerable uncertainty around the cost-effectiveness of brexu-cel (CE WTP = £50,000/QALY)
MSAC, Australia, 2023[10]	Healthcare system	R/R ALL patients post standard R/R chemotherapy or hematopoietic stem cell transplantation in line with ZUMA-3 population	BLIN	Decision tree and PSM	1 week	Lifetime	5% costs and benefits	$90,636/QALY	High ICER but most likely underestimated due to overestimated incremental QALY (CE WTP = NR)
SMC, Scotland, 2023[11]	NR	R/R ALL patients in line with ZUMA-3 population	*Overall population* INO, FLAG-IDA *Ph- subgroup* INO, FLAG-IDA, BLIN *Ph+ subgroup* INO, FLAG-IDA, Ponatinib	Decision tree and 3-state PSM	1 week	Lifetime	NR	*Overall population* INO:£43,424/QALY FLAG-IDA:£53,006/QALY *Ph- ;Ph+ subgroups* INO:£49,568;£42,950/QALY FLAG-IDA:£58,072;£52,747/QALY BLIN:£52,599/QALY Ponatinib:£50,803/QALY	Cost-effective (CE WTP = NR)
CADTH, Canada, 2021[12]	Healthcare system	Post-BTK inhibitor R/R MCL patients in line with the ZUMA-2 population	BSC**	3-state PSM	1 month	Lifetime	1.5% costs and benefits	$91,559/QALY***	Considerable uncertainty around the cost-effectiveness of brexu-cel (CE WTP = $50,000/QALY)
NICE, England, 2020[13,14]	Healthcare system	Post-BTK inhibitor R/R MCL patients in line with the ZUMA-2 population	SoC#	3-state PSM	1 month	Lifetime	3.5% costs and benefits	£46,898-£72,920/QALY$	Considerable uncertainty around the cost-effectiveness of brexu-cel (CE WTP = £50,000/QALY)
MSAC, Australia, 2023[15]	Healthcare system	Post-BTK inhibitor R/R MCL patients in line with the ZUMA-2 population	Salvage therapy##	Decision tree and PSM	NR	Lifetime	5% costs and benefits	Redacted	Redacted (CE WTP = NR)

*BLIN ± TKIs and INO ± TKIs were extendedly dominated by brexu-cel in the sponsor-corrected base case;**BSC = A blended comparator –rituximab, bendamustine, bortezomib, and anthracycline.;***Sponsor-corrected base-case ICER;#SoC= R-bendamustine, R-CHOP(Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), R-BAC(Rituximab, bendamustine, cytarabine), R-CVP (Rituximab, cyclophosphamide, vincristine sulfate, and prednisone), FCR(Fludarabine, cyclophosphamide, and rituximab); $Base case analysis of the Evidence Review Group (ERG)'s produced ICERs ranging from £58,223 to £72,920/ QALY accounting for the lower and upper mortality range of the excess mortality adjustment (2.36 to 4.37). NICE concluded that the ICER (with the discount agreed in the commercial arrangement) ranged between £46,898 and £72,920/ QALY based on the existing evidence which favored the lower ERG mortality adjustment with an ICER of £58,223/QALY. ##Salvage therapy = various chemoimmunotherapy regimens (platinum/lenalidomide/bortezomib, R-CHOP/R-DHAP); BSC=Best supportive care; SoC= Standard of care; mITT = modified intent-to-treat; NR= Not reported; INO= Inotuzumab ozmogamicin; BLIN= Blinatumomab; TKIs= Tyrosine kinase inhibitors; CHEMO= salvage chemotherapy; FLAG-IDA= Fludarabine + Cytarabine + Granulocyte stimulating factor + Idarubicin; CE= Cost-effectiveness; WTP=Willingness to pay; Ph+ = Philadelphia chromosome-positive, Ph- = Philadelphia chromosome-negative; PSM=Partitioned Survival Model; CAD= Canadian dollars; USD= US dollars; ICER=Incremental cost-effectiveness ratio; CVAD=Cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone.

- Most of the CEA studies evaluated brexu-cel in R/R MCL patients.
- For each disease, the model structures were similar across the CEA studies and HTA reports.
- Only Canada and the UK have the CEA studies and HTA reports of brexu-cel in R/R MCL patients. The ICERs in the HTA reports tended to be higher.
- All CEA studies and HTA reports included only direct costs and conducted one-way, probabilistic, and scenario sensitivity analyses.
- ICERs of brexu-cel for R/R ALL patients from the US study varied from $23,464 to $105,381/QALY, depending upon the comparators, whereas for R/R MCL patients, the ICERs of brexu-cel were CAD 88,503, €64,798, £67,713, and $31,985/QALY in Canada, Italy, UK, and the US, respectively.
- All reports, except from Scotland for R/R ALL patients, concluded that the ICERs were inconclusive due to either bias or uncertainty, and the ICER was redacted from Australia for R/R MCL.
- There is a lack of subgroup analysis in the CEA studies of brexu-cel. In other words, heterogeneity of the results was not examined.

CONCLUSIONS

- Overall, the comparators, model structures, inputs, and analyses of the CEA studies and HTA reports of brexu-cel for both R/R ALL and R/R MCL patients were almost consistent across different jurisdictions.
- All CEA studies and HTA reports showed that brexu-cel had higher QALYs and costs, compared to standard treatment and salvage therapy. While the CEA studies and HTA reports concluded that brexu-cel was cost-effective, the HTA reports indicated the uncertainty of the results.