Supplementary Material

Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children and young adults

Contents

Supplementary Methods

Supplementary Methods (S1). PRISMA checklist

Section and Topic	Item no.	Checklist item	Reported on page no:
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	

Section and Topic	Item no.	Checklist item	Reported on page no:
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If	

Section and Topic	Item no.	Checklist item	Reported on page no:
		comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Methods (S2). Search strategy

We searched Medline (OvidSP) [1946-present], Embase (OvidSP), Cochrane Database of Systematic Reviews & Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)[Issue 8 of 12, August 2021], Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database (NHS–EED) & Health Technology Assessment Database (Centre for Reviews & Dissemination https://www.crd.york.ac.uk/CRDWeb/HomePage.asp) [inception to 31/03/2015], Science Citation Index & Social Citation Index (Web of Science Core Collection) [1900-present] and Cost Effectiveness Analysis Registry - Basic Search (http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx). The search strategy consisted of title/abstract keywords and subject headings to describe the key concepts of children, leukaemia and relapse. A methodological filter for economic studies was adapted from the NHS EED filter available at https://www.crd.york.ac.uk/crdweb/searchstrategies.asp. The search was restricted to English language; no publication limits were applied. Full strategies for all databases available in **Supplementary Methods (S3)**. Results were exported to Endnote X9 where duplicates were removed. Remaining references were exported into EXCEL for screening of articles.

Supplementary Methods (S3). Full electronic search strategy

S3.1. MEDLINE database

No.	Searches
1	adolescent/ or exp child/ or infant/
2	Pediatrics/
3	(infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric*).ti,ab,kw.
4	1 or 2 or 3
5	exp Leukemia/
6	leuk?emi*.ti,ab,kw.
7	5 or 6
8	Recurrence/ or Neoplasm Recurrence, Local/
9	exp treatment failure/
10	(recur* or relaps* or refractor*).ti,ab,kw.
11	((treatment or therap* or induction) adj5 (fail* or resistan*)).ti,ab,kw.
12	Disease Progression/ or Disease Resistance/
13	8 or 9 or 10 or 11 or 12
14	4 and 7 and 13
15	"Value of Life"/
16	quality-adjusted life years/
17	("Value of life" or "value for money" or "quality adjusted life year*" or qaly* or qald* or qale* or "disability adjusted life year*" or daly*).ti,ab.
18	Economics/
19	exp "costs and cost analysis"/
20	Economics, Dental/
21	exp economics, hospital/
22	Economics, Medical/
23	Economics, Nursing/
24	Economics, Pharmaceutical/
25	(economic$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab.
26	expenditure$.ti,ab.
27	"willingness to pay".ti,ab.
28	budget$.ti,ab.
29	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	((energy or oxygen) adj cost).ti,ab.
31	(metabolic adj cost).ti,ab.
32	((energy or oxygen) adj expenditure).ti,ab.

33	30 or 31 or 32
34	29 not 33
35	exp animals/ not humans/
36	34 not 35
37	14 and 36
38	limit 37 to english language

S3.2. EMBASE database

No.	**Searches**
1	exp adolescent/ or exp child/
2	Pediatrics/
3	(infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric*).ti,ab,kw.
4	1 or 2 or 3
5	exp Leukemia/
6	leuk?emi*.ti,ab,kw.
7	5 or 6
8	cancer growth/ or cancer recurrence/ or deterioration/ or recurrent disease/ or relapse/ or tumor growth/ or tumor recurrence/
9	(recur* or relaps* or refractor*).ti,ab,kw.
10	((treatment or therap* or induction) adj5 (fail* or resistan*)).ti,ab,kw.
11	8 or 9 or 10
12	4 and 7 and 11
13	leukemia relapse/
14	4 and 13
15	12 or 14
16	socioeconomics/
17	disability-adjusted life year/ or quality adjusted life year/
18	("Value of life" or "value for money" or "quality adjusted life year*" or qaly* or qald* or qale* or "disability adjusted life year*" or daly*).ti,ab.
19	Health Economics/
20	exp Economic Evaluation/
21	exp Health Care Cost/
22	Pharmacoeconomics/
23	(economic$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab.
24	expenditure$.ti,ab.
25	"willingness to pay".ti,ab.
26	budget$.ti,ab.
27	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28	((energy or oxygen) adj cost).ti,ab.
29	(metabolic adj cost).ti,ab.
30	((energy or oxygen) adj expenditure).ti,ab.
31	28 or 29 or 30
32	27 not 31
33	(animal/ or exp animal experiment/ or nonhuman/) not (exp human/ or human experiemnt/)
34	32 not 33
35	15 and 34
36	limit 35 to english language

S3.3. NHS–EED

No.	Searches
	((infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or under-age* or pubescen* or pediatric* or paediatric* or peadiatric*)) AND (leukemia* OR leukaemia*)

S3.4. Web of Science (WoS)

1	TS=(leukaemia* OR leukemia*) AND TS=(infan* OR baby* OR babies OR toddler* OR preschooler* OR pre-schooler* OR kid OR kids OR child* OR schoolchild* OR boys OR girls OR adolescen* OR juvenil* OR youth* OR teen* OR minors OR underage* OR under-age* OR pubescen* OR pediatric* OR paediatric* OR peadiatric*) AND TS=(relaps* OR refract* OR recur* OR ((treatment OR therap* OR induction) NEAR/5 (fail* OR resistan*)))
2	TS=("Value of life" OR "value for money" OR "quality adjusted life year*" OR qaly* OR qald* OR qale* OR "disability adjusted life year*" OR daly*) OR TS=(economic* or cost or costs or costly or costing or pharmacoeconomic*) OR TS=(expenditure* OR "willingness to pay" OR budget*)
3	1 AND 2
4	1 AND 2 - limited to English

S3.5. Cochrane database

ID	Search
#1	MeSH descriptor: [Adolescent] explode all trees
#2	MeSH descriptor: [Child] explode all trees
#3	MeSH descriptor: [Infant] this term only
#4	MeSH descriptor: [Pediatrics] explode all trees
#5	(infan* or baby* or babies or toddler* or preschooler* or pre-schooler* or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric):ti,ab,kw
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Leukemia] explode all trees

#8	(leukemia* OR leukaemia*):ti,ab,kw
#9	#7 or #8
#10	MeSH descriptor: [Recurrence] this term only
#11	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#12	MeSH descriptor: [Treatment Failure] explode all trees
#13	(recur* or relaps* or refractor):ti,ab,kw OR (((treatment or therap* or induction) NEAR/5 (fail* or resistan*))):ti,ab,kw
#14	MeSH descriptor: [Disease Progression] this term only
#15	MeSH descriptor: [Disease Resistance] explode all trees
#16	#10 or #11 or #12 or #13 or #14 or #15
#17	#6 and #9 and #16
#18	MeSH descriptor: [Economics] this term only
#19	MeSH descriptor: [Economics, Hospital] explode all trees
#20	MeSH descriptor: [Economics, Medical] explode all trees
#21	MeSH descriptor: [Value of Life] explode all trees
#22	MeSH descriptor: [Health Care Costs] explode all trees
#23	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#24	(pharmacoeconomic* OR price* OR pricing):ti,ab,kw OR (((cost or economic) NEAR/2 (evaluation* or analy* or study or studies or effect* or benefit* or util* or consequence* or comparison* or identificat*))):ti,ab,kw OR (cost OR costs OR economic*):ti
#25	#18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#17 and #25

S3.6 CEA Registry

Basic search

1	leukemia	Methods	73
2	leukaemia	Methods	21

Supplementary Methods (S4). Data extraction form

Study ID:
Publication (Authors, Year):
Country
Main intervention
Comparator
Study perspective
Currency unit
Study design
Setting
Target population
Sample size
Model specification/assumptions
Time horizon
Measures of clinical effectiveness
Measures of cost-effectiveness
Price year
Costs categories
Main cost drivers
Opportunity cost
Excluded costs
Willingness-to-pay (Cost-effectiveness threshold)
Discount rate
Sensitivity analysis (uncertainty analysis)
Funding source
Conclusion/other comments

Supplementary Methods (S5). CHEERS checklist

Section/item	Item No.	Section/item	CHEERS Score
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as "cost-effectiveness" and describe the interventions compared **(1 point)**.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions **(1 point)**.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study **(0.5 point)**. Present the study question and its relevance for health policy or practice decisions **(0.5 point)**.	
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analysed including why they were chosen **(1 point).**	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made **(1 point)**.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated **(1 point)**.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen **(1 point)**.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate **(1 point)**.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate **(1 point)**.	
Choice of health Outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed **(1 point if reported or if not applicable. 0 points if applicable but not reported)**.	
Measurement of effectiveness	11a	Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data **(1 point)**.	
	11b	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data **(1**	

		point).	
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes **(1 point if reported or if not applicable. 0 points if applicable but not reported)**.	
Estimating resources and costs	13a	Single study–based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate opportunity costs **(1 point)**.	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate opportunity costs **(1 point)**.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary **(0.5 point)**. Describe methods for converting costs into a common currency base and the exchange rate **(0.5 point)**.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used **(0.5 point)**. Providing a figure to show model structure is strongly recommended **(0.5 point)**.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model **(1 point)**.	
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty **(1 point)**.	
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended **(1 point)**.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental	

		cost-effectiveness ratios **(1 point)**.	
Characterizing uncertainty	20a	Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective) **(1 point)**.	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions **(1 point)**.	
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information **(1 point if reported or if not applicable. 0 points if applicable but not reported)**.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge **(1 point)**.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support **(1 point)**.	
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations **(1 point).**	

Supplementary Table S1. Detailed CHEERS checklist scoring for included studies

Item no.	Section/item	Lin (2010)	Lin (2018)	Whittington (2018)	Sarkar (2019)	Santasusana (2020)	Thielen (2020)	Furzer (2020)	Yang (2020)	Maser (2020)	Schulthess (2021)	Wakase (2021)	Moradi-Lakeh (2021)	Item scores (out of 12)
1	Title	1	1	0.5	1	1	1	1	0.5	1	0.5	1	1	10.5
2	Abstract	1	1	1	1	1	1	1	1	1	0.5	1	0.5	11
3	Background and objectives	1	1	1	1	1	1	1	1	1	1	1	1	12
4	Target population & subgroups	1	0.5	1	1	1	0.5	0.5	0.5	1	0.5	0.5	1	9
5	Setting and location	1	1	1	0.5	1	1	1	1	1	1	1	1	11.5
6	Study perspective	1	1	1	1	1	1	1	1	1	0.5	1	1	11.5
7	Comparators	1	0.5	1	0.5	1	0.5	1	0	1	1	1	1	9.5
8	Time horizon	1	0.5	1	1	0.5	1	1	1	1	1	1	0.5	10.5
9	Discount rate	0	0.5	1	0.5	1	1	1	0	1	1	1	1	9
10	Choice of health outcomes	1	1	0.5	1	1	1	1	1	1	1	1	1	11.5
11	Measurement of effectiveness	0.5	1	1	0.5	1	1	1	1	1	1	1	1	11
12	Measurement and valuation of preference-based outcomes	1	1	0.5	1	1	1	1	0	1	1	0	1	9.5
13	Estimating resources and costs	1	1	1	1	1	1	0.5	1	0.5	0.5	1	1	10.5
14	Currency, price date and conversion	1	1	1	1	0	0.5	0.5	0.5	0	0	1	0.5	7
15	Choice of model	0	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	6.5
16	Assumptions	NA	1	1	1	1	1	1	1	1	0.5	1	1	10.5
17	Analytic methods	1	1	1	1	0.5	0.5	1	0	1	0	0	1	8
18	Study parameters	1	1	0.5	0.5	1	1	1	0.5	1	0.5	1	0.5	9.5
19	Incremental costs and outcomes	1	1	1	0.5	1	1	1	0.5	0.5	1	1	0.5	10
20	Characterizing uncertainty	1	1	1	1	1	1	1	0.5	1	1	1	1	11.5
21	Characterizing heterogeneity	1	1	0.5	0	1	0	0	0.5	0.5	1	0.5	1	7

22	Study findings, limitations, generalizability, and current knowledge (Discussion)	1	1	1	1	1	0.5	1	1	1	1	1	0.5	11
23	Source of funding	0.5	1	1	1	1	0.5	1	0	0	0.5	0.5	0.5	8.5
24	Conflicts of interest	1	0.5	1	0.5	1	0	1	0	0.5	0.5	0.5	1	7.5
Overall scoring (out of 24)		**19.5**	**21**	**21**	**19.5**	**21.5**	**19**	**21**	**15.5**	**19.5**	**17.5**	**19.5**	**19.5**	

Abbreviations: CHEERS: Consolidated Health Economic Evaluation Reporting Standards.

Supplementary Table S2. Key model input parameters, cost categories, and main cost drivers

Author (Year)	Key model input parameters			Cost categories	Main cost drivers
	Clinical evidence	Utilities (quality of life)	Drug(s) list price		
Lin *et al* (2010)	Clinical outcomes reported from real-world data analysis	NR	Retrospective micro-costing approach	• Cost categories: days in hospital, outpatient visits, IV treatments, nuclear medicine, laboratory and diagnostic services, radiotherapeutic and surgical procedures, blood products, medications, and emergency room visits. • PBSC costs: laboratory tests and donor collection fees but do not include costs of processing stem cell products in lab.	Room and board accounted for 50% of total costs, pharmacy accounted for ~28% of total costs. Other major cost items: blood products, lab and radiology services.
Maser *et al* (2020)	Literature review; Raetz 2008[1]; Gamis 2014[2]; Ammann 2015[3]; Gupta 2015[4].	0.81 (Kwon et al 2018)[5]	Drug Benefit Formulary[6]	Only included costs of Levofloxacin prophylaxis.	NR
Lin *et al* (2018) ***	• Tisa-cel: Maude et al[7], • Blina: von Stackelberg et al[8], • Clo-M: Jeha et al[9] • HSCT: von Stackelberg et al[8], Hijiya et al[10], Locatelli et al [11], Miano et al [12], Crotta et al[13]	• Tisa-cel: 0.78 (Tengs).[14] • Blina: 0.78 (Delea[15]; van Litsenburg[16]). • Clo-C and Clo-M: 0.71 (Furlong).[17].	Costs in US$ • Tisa-cel: $475,000 (Red Book[18]) • Blina: $44,000 (CMS[19]) • Clo-C: $67,000 (CMS[19]) • Clo-M: $47,000 (CMS[19])	• Direct health care costs: drugs (including tisa-cel), therapy administration, AE, HSCT, and follow-up. • Related costs: pre-infusion chemotherapy, administration, and complications. • Follow-up costs after tisa-cel assume 5 years of B-cell aplasia with monthly IV immunoglobulin infusions for patients in remission.	NR
Whittington *et al* (2018)	ICER[20], Jeha et al[9]	Kelly et al[21]	Acquisition cost (with markup) in $ • Tisa-cel: $575,000 • Clo-C: Clofarabine (264 per mg/mL), Cyclophosphamide (0.74 per mg/mL), Etoposide (0.09 per mg/mL) Red book[18]	• Cost categories: drugs, other chemotherapy, healthcare use costs (cost per hospital day, cost per ICU Day, office visits, IV administration, hematology panel, liver function tests).	NR
Sarkar *et al* (2019)	CAR–T cell transition probability: Maude et	Sung et al., 2003,[23] Furlong et al., 2012[24]	Costs in US$ • Tisa-cel: $475,000 (Bach et	• Cost of drug (tisa-cel), cost of toxicity, cost of end-of-life care (for 1 month for patients	NR

	al[7]; FDA Drug Advisory Meeting[22]	Hettle et al., 2017,[25] Aristides et al., 2015,[26] Beauchemin et al., 2016[27] Cuthbertson et al., 2005[28]	al.[29]) • Standard of care: (Clo-C): 51,286 (AWP[8,12,22,30,31,32]; followed by HSCT: successful: 299,987; failed: 459,682 (Lin et al., [33])	who died after relapse).	
Santasusana *et al* (2020)	• Tisa-cel: ELIANA, ENSIGN, and B2101J trials.[7,34,35,36,37] • FLA-IDA: Von Stackelberg et al.[8]	• Utility in the EFS state: 0.91; utility in the PD/RL state: 0.75 (Kelly et al[21]). • Disutility associated with tisa-cel or FLA-IDA: − 0.42 (Sung et al,).[23]	• Tisa-cel: € 320,000 (discounted € 307,200). • FLA-IDA: Fludarabine 25 mg/mL, 1 vial, 2 mL (€ 49.77); Cytarabine 1 g, 1 vial, 10 mL (€ 14.380); and Idarubicin 5 mg, 1 vial, 5 mL) (€ 40.90).	• Cost categories: pharmacological treatments and costs derived from health resource use. • In infused patients, based on the clinical trial results, costs of the use of the following resources were considered: bridging chemotherapy, lymphodepleting chemotherapy (96% of patients), tisa-cel infusion, hospitalization, management of AE, HSCT, follow-up and terminal care. • In non-infused patients, costs of salvage chemotherapy (one FLA-IDA cycle), hospitalization, AE management, follow-up and terminal care were considered. • For the comparator, the pharmacological costs of salvage chemotherapy (FLA-IDA), hospitalization costs, costs of the management of AE, costs of HSCT, follow-up and terminal care costs were considered.	In the case of tisa-cel, the main cost determinant was the pharmacological cost while, in the case of FLA-IDA, it was the cost derived from HSCT.
Thielen *et al* (2020) ****	• Tisa-cel: duration of benefit in months: 60 • EFS vs OS ratio for all Comparators: 0.69 (Van den Berg et al, 2011).[38]	• Utility for EFS: 0.83 and for PD: 0.68 (ELINA trial). [34] • Disutility for tisa-cel, Clo-M, Clo-C, Blina: -0.20 (Kwon et al (utility value)[5]; Gaynon (duration Clo-M)[39]; Hijiya (duration (Clo-C)[40]; von Stackelberg (duration Blina).[8]	• Pretreatment cost for lymphodepleting regimen: €521 (ELIANA trial) [34] • Tisa-cel €320,000 • Clo-M: €71 020 • Clo-C: €35 453 • Blina: €117 934 (Dutch Z-index public list price, Jeha 2006, Hijiya 2011, von Stackelberg 2016). [8,9,40]	• Costs of pretreatment, treatment, AE, follow-up period, subsequent HSCT, and future medical costs. • Tisa-cel included costs for drug acquisition and administration, outpatient and inpatient days.	Main cost driver was the much higher drug acquisition costs for tisa-cel, compared to other drugs.
Furzer *et al* (2020)	Clinical outcomes reported from Canadian population-based registry.	• Tisa-cel: 0.80 (Short-term utility assumed equivalent to HSCT without GVHD).[41]	• Tisa-cel: CaD $625,000 (Bach et al, 2018). [29] • HSCT: CAD $112,582 (Ontario Ministry of Health	• Costs associated with in-hospital treatment and follow-up care for both treatment strategies. • For patients infused with tisa-cel,, additional	For those who received tisa-cel, the most significant cost component

		• HSCT: 0.73 (Ontario Ministry of Health and Long Term Care13; Kurosawa et al[41])	and Long Term Care13; Kurosawa et al) [41]	nonproduct costs applied for cell infusion, monitoring and management of adverse events, and associated hospitalizations.	was the product itself. .
Yang *et al* (2020)	NR	NR	• Tisa-cel: $475,000 (RED BOOK.[18] CMS Physician Fee Schedule).[42] Pre-treatment regimens: • Regimen A: Fludarabine $281.23; Cyclophosphamide $817.47 (RED BOOK) [18] • Regimen B: Cytarabine $11.40; Etoposide $42.40 (RED BOOK) [18]	• Cost components included leukapheresis, lymphodepleting chemotherapy, tisa-cel infusion and hospital administration, inpatient and ICU admissions, medical professional visits, laboratory tests and procedures, for medical professional visits and management of major AE (resource estimates based on ELIANA trial).	Top 3 drivers of "additional cost" were AE management (51.6%), inpatient and ICU admissions not attributed to AE (42.1%), and laboratory tests and procedures (3.8%).
Schulthess *et al* (2021)	Clinical evidence from RWD from EHR	NR	• Tisa-cel: US$475 000 • HCT: US$303,065	• Internal costs within the hospital, the cost of CAR-T infusion and follow-up (excluding price cost of CAR-T cell therapy).	80% of the cost is due to the purchase price of the drug itself.
Wakase *et al* (2021)	• Tisa-cel: ELIANA, ENSIGN, and B2101J trials.[34,35,36] • Blina: von Stackelberg,[8] Gore et al[43] • Clo-C: Miano et al, Hijiya et al, Locatelli et al.[11,12,40]	• Tisa-cel (infused patients): -0.42; 32 d • Blina: -0.42; 61 d • Clo-C: 0.42; 47 d (Sung et al.;[23] (disutility) ELIANA study;[34] (duration for Tisa-cel) von Stackelberg et al. (duration for Blina); [8] Hijiya et al.(duration for Clo-C). [40]	Costs including drug and administration costs: • Tisa-cel: JPY 40,276,340 • Blina: JPY 11,872,596 • Clo-C: JPY 2,984,104 596	• Costs categories: pretreatment costs, treatment costs, AE costs, follow-up costs, subsequent HSCT costs, and terminal care costs.	NR
Moradi-Lakeh *et al* (2021)	• Tisa-cel: ELIANA, ENSIGN, and B2101J trials. [34,35,36] • Comparators: Hijiya 2011; Jeha 2006; Kuhlen 2018; Locatelli 2009; Miano 2012;	• Utility for EFS (0.91) and for PD (0.75) Treatment disutility • Tisa-cel: (infused patients): -0.03 • Clo-C: -0.03 • Blina: -0.02	• Tisa-cel: CHF 329,367 • Blina: CHF 127,816 • Clo-C: CHF 51,284 • FLA-IDA: CHF 3,600	• Costs categories: pre-treatment leukapheresis, bridging chemotherapy and lymphodepleting costs for tisa-cel arm, drug and procedure acquisition costs for tisa-cel and comparators, associated drug administration costs, associated hospitalization and ICU costs, adverse event	NR

	von Stackelberg 2016, von Stackelberg 2011.[40,9, 44,11,12, 8, 45]	•Salvage chemo: -0.04		costs, sub- sequent SCT costs, other follow-up and monitoring costs, and terminal care costs.	

Abbreviations: CCG: Children's Cancer Group; **NR:** Not reported; **PBSC:** Peripheral blood stem cell; **HSCT:** haematopoietic stem cell transplantation; **tisa-cel:** tisagenlecleucel; AE: adverse events; **Blina:** Blinatumomab; **Clo-C:** Clofarabine combination therapy; **Clo-M:** Clofarabine monotherapy; **ICER:** Institute for Clinical and Economic Review; **PD:** progressive disease; **RL:** relapse. **NR:** Not reported; **RWD:** Real-world data. Clofarabine combination therapy includes clofarabine, cyclophosphamide, and etoposide. FLA-IDA salvage chemotherapy includes combination of fludarabine, cytarabine and idarubicin. Reference list is included in Additional References (below in this document).

Supplementary Table S3. Sensitivity (uncertainty) analysis

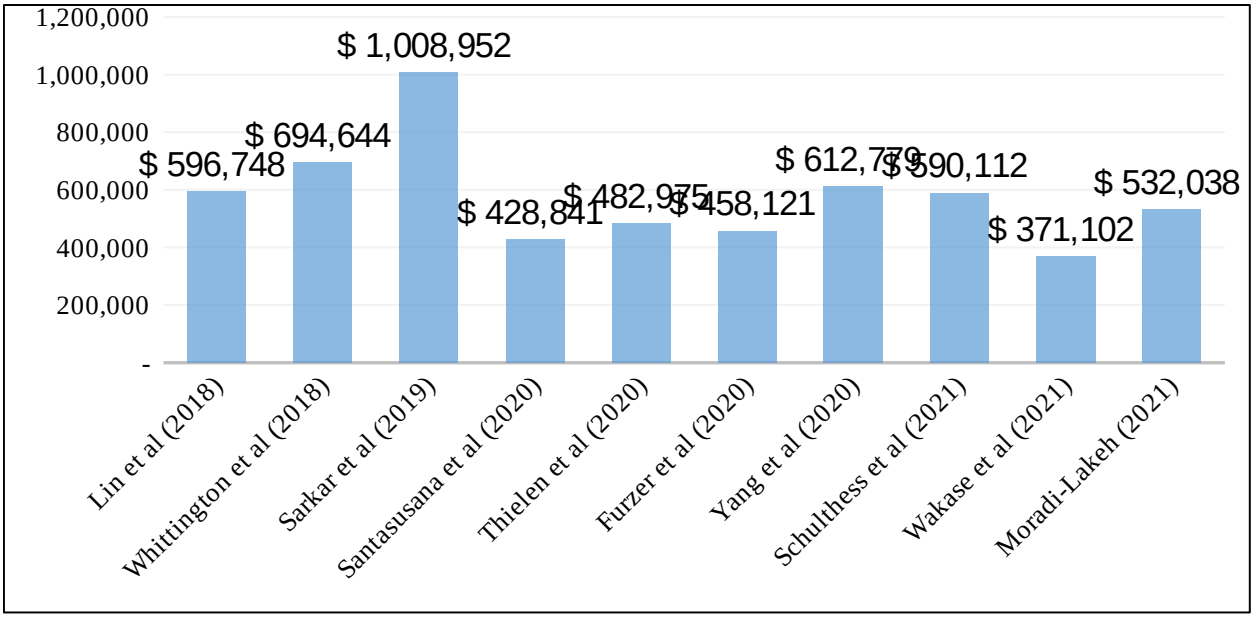
Author (Year)	Method of sensitivity (uncertainty) analysis	Results of sensitivity (uncertainty) analysis
Lin *et al* (2010)	One-way and probabilistic sensitivity	• There was a higher probability that PBSCT was less effective and more costly, and 19% probability for PBSCT being less costly, but also less effective.

	analysis	• There is a 36.8% probability that PBSCT would be less costly but also less effective compared with BMT. • PBSCT has an equivalent opportunity (24%) of being the dominant option or being the dominated choice over BMT. • Overall, there is no clear preference for either treatment method, because of the large degree of uncertainty in the results. • The ICER was reduced to $1.41 million in the analysis of high-risk patients, with BMT more expensive and more effective than PBSCT.
Maser *et al* (2020)	One-way deterministic, probabilistic (Monte Carlo simulation), and threshold analysis.	• Levofloxacin prophylaxis remained cost-effective within the predetermined range of values for all parameters. • Levofloxacin prophylaxis became a nondominant alternative at daily levofloxacin costs of ≥$21.55 but remained cost effective throughout the range tested, using a willingness-to-pay threshold of $50 000/QALY.
Lin *et al* (2018) ***	One-way deterministic and probabilistic sensitivity analysis	• In one-way sensitivity analyses, two model parameters rendered tis-cel cost-effective by assuming modest long-term outcomes: reductions in price and a low discount rate. • In a bridge- to-transplantation scenario, increasing the proportion of patients who receive a transplantation (and achieve remission) from 0.55 to 0.75 improved tis-cel's economic value, but it would not make it cost-effective. • Tis-cel's economic value was substantially worse if costs and benefits were over 15 years rather than lifespan. • Several parameters moderately worsened tis-cel's economic value: standardized mortality ratio after long-term remission, cost of care after long-term remission, and cost of care for grade 4 cytokine release syndrome. • In probabilistic sensitivity analyses, tis-cel at a 5-year RFS rate of 40% was cost-effective in 99.3%, 98.7%, and 6.0% of simulations at WTP thresholds of $150,000, $100,000, and $50,000, respectively. • Tis-cel at a 5-year RFS rate of 20% was cost-effective in 53.1%, 6.5%; at a 5-year RFS rate of 0% and in the absence of transplantation, Tis-cel consistently produced inferior outcomes to Blinatumomab at a higher cost.
Whittington *et al* (2018)[5]	Probabilistic sensitivity analysis and scenario analyses.	• Study results were robust to probabilistic sensitivity analyses. • Across scenario analyses that included more conservative assumptions regarding long-term relapse and survival, the incremental cost-effectiveness ratio ranged from $37,000 to $78,000 per QALY gained.
Sarkar *et al* (2019)	One-way deterministic and probabilistic sensitivity analyses	• CAR-T was cost-effective in 94.8% of iterations at a WTP of $100,000/QALY. • CAR-T therapy would be cost effective 94.8% of the time at a WTP threshold of $100,000 per QALY. • Base-model assumed a 76.0% 1-year survival, if this decreased to 57.8%, then CAR-T is no longer cost-effective. • If the complete remission rate of CAR-T recipients decreased from 81% to 56.2%, or if the health utility of disease-free survivors decreased from 0.94 to 0.66, then CAR-T was no longer cost-effective.
Santasusana *et al* (2020)	Deterministic sensitivity analyses and scenario analysis	• Sensitivity analysis showed that model results were robust, since all variations result in an ICUR below €50,000/QALY. • Changes in parameters that most affected the results were those made in the discount rate for costs and benefits (0–5%; 3% base case), the pharmacological cost of tis-cel (± 25%) and age of onset (1–25 years; 12 years base case). • All modifications resulted in an ICUR below € 40,000/QALY. • In scenario analysis, the modification of the time horizon (20 years; vs lifetime in the base-case) and different OS parametric functions are the most influential variations in results, resulting in an ICUR below € 50,000/QALY.
Thielen *et al* (2020)****	Deterministic and probabilistic sensitivity analyses	• Results showed that 98% of the iterations in the probabilistic sensitivity analysis were cost-effective. • None of the scenarios of choosing different survival parameters exceeded the WTP threshold of 80,000 EURO/QALY. • Variation of starting age of the simulated cohort was the most influential factor for the ICER in all three comparators. • Scenario analyses, assuming a time horizon of 20 years had the highest impact on the ICER. In this scenario, the ICERs per QALY gained increased to 60 859 EUR, 63 341 EUR, and 53 698 EUR for Clo-M, Clo-C, and Blina, respectively. This implies that tisa-cel is less cost-effective with a shorter time-horizon.

Furzer *et al* (2020)	One-way and probabilistic sensitivity analyses	• Results were robust across 1-way and structural sensitivity analyses • Increasing proportion of patients receiving IV immunoglobulin treatment, removing the value-based pricing structure and increasing standardized mortality ratio or decreasing estimated time horizon all increased the estimated ICUR. • While lowering the assumed treatment age and assuming all patients reach infusion lowered the ICUR. • The probabilistic sensitivity analysis demonstrated some overlap on expected QALYs between tisa-cel and standard care, although the incremental effect was largely in favor of tisa-cel (95%CI, 0.37-4.73QALYs gained). • Across all Monte Carlo iterations, incremental tisa-cel cost was more than standard care (95% CI, 422000-530000). • Cost-effectiveness acceptability curve indicated a 32% probability of tisa-cel being cost-effective at 150000 per QALY
Yang *et al* (2020)	Scenario analyses	• In the scenario analyses, the total costs ranged from $483,169 (tisa-cel treatment in the outpatient setting without adverse events) to $672,373 (tisa-cel treatment in inpatient setting with grade 3/4 cytokine release syndrome and B-cell aplasia). • Under the scenario that all patients received tisa-cel treatment in the outpatient setting and did not experience any AEs during follow-up, the model calculated a cost of $8,026 aside from the tisa-cel procedure and administration. Under the scenario that all patients received tisa-cel in the inpatient setting and experienced grade ¾ CRS and B-cell aplasia, the model calculated a cost of $197,230 aside from the t tisa-cel procedure and administration
Schulthess *et al* (2021)	Not done.	Not done.
Wakase *et al* (2021)	Deterministic and probabilistic sensitivity analyses	• Model results remained robust to alternative model assumptions and inputs. • Across all scenarios, the incremental costs per QALY gained ranged from tisa-cel being dominant to <2,885,485 compared with a blinatumomab, and from tisa-cel being dominant to <3,756,251 compared with a Clo-C.
Moradi-Lakeh *et al* (2021)	Deterministic and probabilistic sensitivity analyses	• Tisa-cel had a 100% probability of being cost-effective versus all comparators using a WTP threshold of CHF 100,000. • Highest impact was including productivity gains which ended up with dominancy of tisa-cel over competitors. • Tisa-cel was more effective and cheaper than all standard treatments, cost-effective under all scenarios and assumptions.

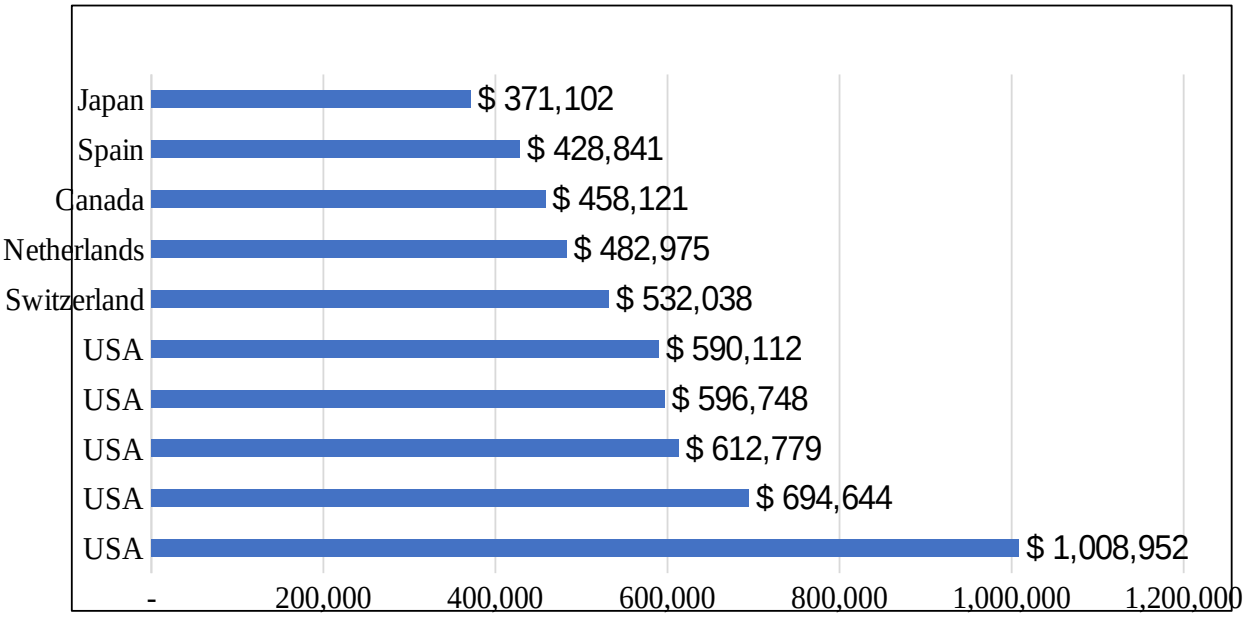
Abbreviations: PBSCT: Peripheral stem cell transplantation**; BMT:** bone marrow transplant; **NA:** Not applicable; **tisa-cel:** tisagenlecleucel; **RFS:** relapse-free survival; **WTP:** willingness-to-pay; **OS**: overall survival; **ICER:** incremental cost-effectiveness ratio; **ICUR:** Incremental cost-utility ratio; **DSA:** Deterministic sensitivity analysis.

Supplementary Figure S1. Costs of CAR–T cell therapy (USD 2019) for relapsed/refractory ALL



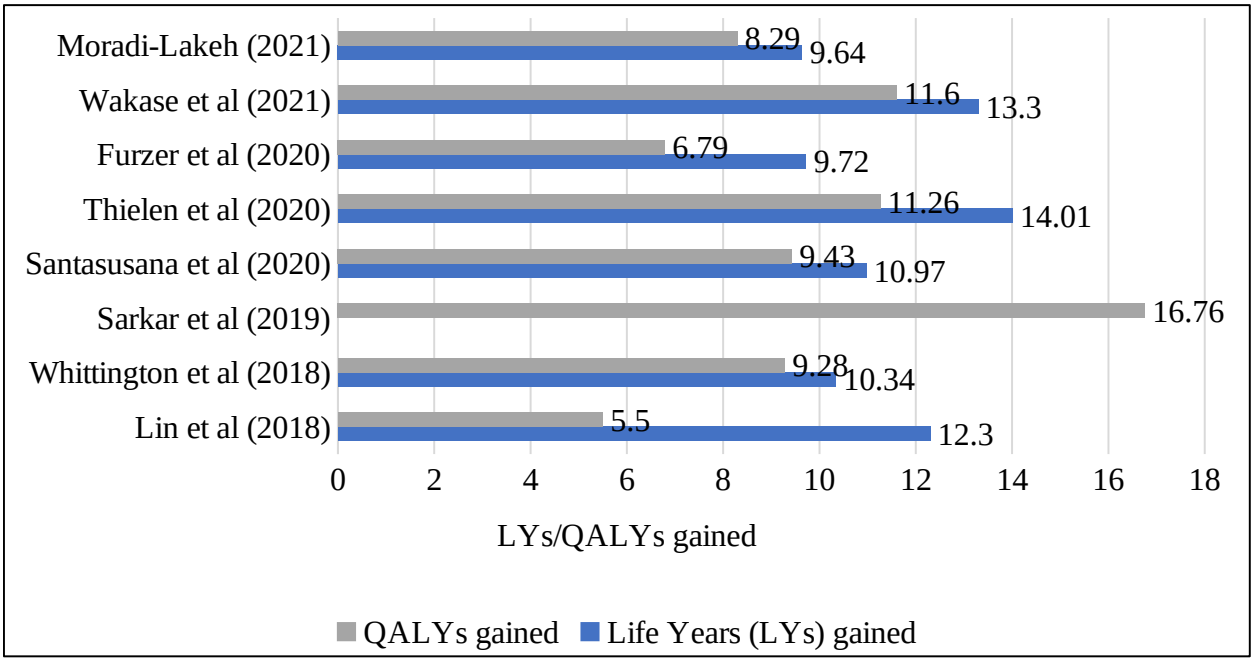
* Costs were discounted at 3% annually for all studies, except for Thielen et (2020) at 4%; Furzer et al (2020) at 1.5%; Wakase et al (2021) at 2%; Moradi-Lakeh et al (2021) at 3.5%; and no discounting for Yang et al (2020). All studies estimated lifetime horizon. Study perspectives were as follows: Lin *et al* (2018): US health payer perspective; Whittington *et al* (2018) and Sarkar *et al* (2019): payer perspective; Santasusana *et al* (2020): Spanish NHS perspective; Thielen *et al* (2020): Netherlands Healthcare perspective; Furzer *et al* (2020): Public insurer perspective; Yang *et al* (2020) and Schulthess *et al* (2021): U.S. healthcare (hospital) perspective; Wakase *et al* (2021): Japanese public healthcare payer's perspective; Moradi-Lakeh *et al* (2021): Switzerland healthcare system.

Supplementary Figure S2. Costs of CAR-T cell therapy in USD (2019), by country



* Costs were discounted at 3% annually for all studies, except for Thielen et (2020) at 4%; Furzer et al (2020) at 1.5%; Wakase et al (2021) at 2%; Moradi-Lakeh et al (2021) at 3.5%; and no discounting for Yang et al (2020). All studies estimated lifetime horizon. Study perspectives were as follows: Lin *et al* (2018): US health payer perspective; Whittington *et al* (2018) and Sarkar *et al* (2019): payer perspective; Santasusana *et al* (2020): Spanish NHS perspective; Thielen *et al* (2020): Netherlands Healthcare perspective; Furzer *et al* (2020): Public insurer perspective; Yang *et al* (2020) and Schulthess *et al* (2021): U.S. healthcare (hospital) perspective; Wakase *et al* (2021): Japanese public healthcare payer's perspective; Moradi-Lakeh *et al* (2021): Switzerland healthcare system.

Supplementary Figure 3. Effects/outcomes of CAR-T cell therapy: LYs gained and QALYs gained*



Abbreviations: LYs: Life years; QALYs: Quality adjusted life years. * LYs gained and QALYs gained were included as absolute effects/outcome of CAR–T cell therapy, not incremental values compared to other treatment interventions.

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