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REVIEW

Cost and cost-effectiveness of immunotherapy in childhood ALL: A systematic review

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Abstract

Survival rates for pediatric acute lymphoblastic leukemia (pALL) have improved dramatically; relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) remains challenging. Immunotherapies are rapidly evolving treatments for r/r ALL with limited cost-effectiveness data. This study identifies existing economic evaluations of immunotherapy in pALL and summarizes cost-effectiveness. Medline, Embase, and other databases were searched from inception to October 2022. Cost-effectiveness analyses evaluating immunotherapy in pALL were included. Costs reported in 2021 USD. Of 2960 studies, 11 met inclusion criteria. Tisagenlecleucel was compared to standard of care, clofarabine monotherapy, clofarabine combination therapy, or blinatumomab. No studies have evaluated blinatumomab or inotuzumab ozogamicin. Six studies found tisagenlecleucel to be cost-effective, five of which were supported by Novartis. Four found that it had the potential to be cost-effective, and one found that it was not cost-effective. The cost-effectiveness of tisagenlecleucel was highly dependent on list price and cure rates. This study can inform the use of tisagenlecleucel in pALL.

KEYWORDS
acute lymphoblastic leukemia, cancer, child, cost-effectiveness, immunotherapy, systematic review

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer [1–4]. Cure rates for pediatric ALL (pALL) have improved dramatically over the last 40 years, exceeding 85% in high-income countries [2, 3, 5–7]. Approximately 15%–20% of patients will, however, develop relapsed/refractory (r/r) ALL, with survival rates between 20% and 60% [2, 3, 7–9]. Hematopoietic stem cell transplant (HSCT), which entails significant risks and complications, remains the main treatment for high-risk r/r ALL and, until recently, the only curative option after salvage chemotherapy (SOC) [2 , 10–13].

Immunotherapy is a rapidly evolving category of novel treatments for childhood cancer and is an alternative in r/r ALL [5]. Blinatumomab, inotuzumab ozogamicin (InO), and tisagenlecleucel are immunotherapies approved for the treatment of r/r ALL by the US Food and Drug Administration [14]. Blinatumomab is a bispecific T-cell engager that targets CD19,with an approximate cost of $225,672 USD in adults [6 , 14–16]. InO is an antibody–drug conjugate that

Abbreviations: ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CHEC, Consensus Health Economic Criteria; Clo-C, clofarabine combination therapy; Clo-M, clofarabine monotherapy; DALY, disability-adjusted life-year; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost utility ratio; InO, inotuzumab ozogamicin; pALL, pediatric ALL; QALY, quality-adjusted life-year; r/r, relapsed/refractory; SOC, salvage chemotherapy; WTP, willingness-to-pay.

targets CD22, with an approximate cost of $177,463 USD in adults. While InO has been approved for adult use, trials involving pediatric participants are ongoing, with limited research into efficacy in the pediatric population based on compassionate use programs [14 , 17–20]. Tisagenlecleucel is a chimeric antigen receptor (CAR) T-cell therapy and is potentially curative, with a cost of $475,000 USD (2018) [9, 21].

Given the significant cost of these therapies, cost-effectiveness data are needed to guide decision making. While some cost-effectiveness studies have been conducted, they have not all been systematically synthesized and their results vary. Synthesis of these studies can inform decision making of policymakers, as well as help practitioners understand how cost-effectiveness analyses of immunotherapy have been approached. We therefore aimed to identify existing economic evaluations of immunotherapy in pALL and summarize their cost-effectiveness compared with other therapies.

2 | METHODS

2.1 | Search strategy and selection criteria

This study was conducted with a librarian scientist based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols recommendations. The protocol was not registered but is available upon request. All cost-effectiveness and cost-utility analyses that evaluated immunotherapies in pALL were included. Table 1 outlines inclusion and exclusion criteria.

The databases searched included Medline, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov for relevant articles published from inception to October 15, 2022 (Appendix A). The search strategy used four broad categories of terms related to ALL, pediatric, immunotherapy, and cost. For cost terms, filters developed by the McMaster Health Information Research Unit were used to maximize results [22, 23].

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria

Types of studies
• The following types of quantitative and qualitative economic evaluations were included:
  ○ Cost-effectiveness analyses (relates the cost to an outcome such as survival).
  ○ Cost-utility analyses (relates the cost to a utility measure such as QALYs gained or DALYs prevented.
• All analytic perspectives of economic evaluations such as society, payer, provider, healthcare system, or patient were included.
• No restrictions were placed on date of publication.
Types of participants
• Children and young adults (defined as less than 18 years of age) with acute lymphoblastic leukemia.
• Articles with a study population with both pediatric and adult participants (including young adults up to 25 years of age) were included if they contained a subgroup analysis with >75% of the patients in the pediatric age range (i.e., contained economic evaluation outcomes specific to a subgroup with >75% of the patients in the pediatric age range).
Types of interventions
• Generic terms:
  ○ Chimeric antigen receptor T cells
  ○ Immunotherapy/immunotherapies
• Specific immunotherapies:
  ○ Tisagenlecleucel
  ○ Blinatumomab
  ○ Inotuzumab ozogamicin
  ○ Yescarta (Axicabtagene ciloleucel)
Types of outcome measures
• Economic evaluation outcomes:
  ○ Monetary costs
  ○ Cost per life saved
  ○ Cost-effectiveness ratios
  ○ Cost per life-year or QALY gained
  ○ Cost per event (e.g., DALY) prevented

Exclusion criteria
• Review articles, guidelines, book chapters, conference abstracts, case reports, dissertations, commentaries, editorials, letters. • Studies focused on immunotherapy in ALL or other diseases but with no cost assessment.

Abbreviations: ALL, acute lymphoblastic leukemia; DALY, disability-adjusted life-year; QALY, quality-adjusted life-year.

2.2 | Data collection and analysis

One reviewer (Y.S.L.) screened all abstracts. Three reviewers independently reviewed the full text of studies meeting inclusion criteria. Y.S.L. reviewed all eligible articles; S.G. and P.P. each reviewed half. Discrepancies were resolved through discussion within the group. The kappa measure of agreement between reviewers was calculated. One reviewer (Y.S.L.) extracted data from all included studies using a standardized template (Appendix B). All costs were converted to 2021 USD using the International Monetary Fund Consumer Price indices and exchange rates available through the International Revenue Service.

Outcomes measured included healthcare costs, life-years and quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness (ICER) and utility (ICUR) ratios. Cost-effectiveness was based on whether the ICER/ICUR was below the willingness-to-pay (WTP) threshold. Given the anticipated heterogeneity in studies and outcomes, meta-analysis was not likely to be feasible. We a priori decided to conduct a subgroup analysis based on whether studies were funded by pharmaceutical companies.

2.3 | Assessment of risk of bias

The methodological quality of studies was appraised using the Consensus Health Economic Criteria (CHEC) (Appendix C) [24]. Research Ethics Board approval was not required.

3 | RESULTS

3.1 | Data abstraction and study selection

The search strategy identified 2960 studies. After removing duplicates, 1777 studies remained. Sixteen (0.9%) met criteria for full text review, 10 of which met full inclusion criteria (Figure 1). The kappa measure of agreement between reviewers was 1.0, indicating perfect agreement. One additional study [25] was identified for inclusion during full text review. This study was not captured in the original search as it was a review article. Upon further inspection however, it was found to include a new cost-effectiveness analysis.

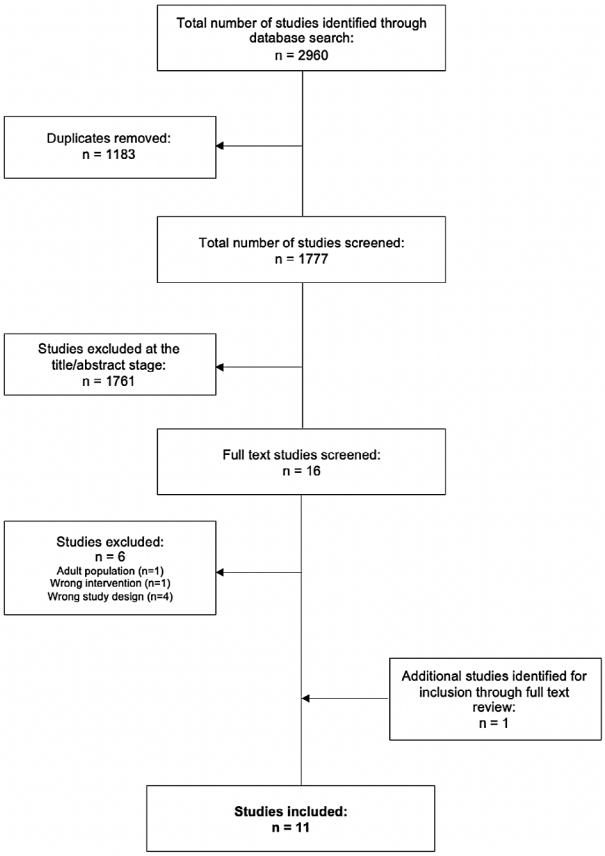

FIGURE 1 Flow diagram for study selection.

3.2 | Study characteristics

The study characteristics are summarized in Table 2. Studies were published between 2018 and 2022 and were conducted in nine countries: Canada, US, Spain, Japan, Netherlands, Ireland, Singapore, Switzerland, and England. The populations in the studies varied from only pediatric patients to young adult patients up to 25 years of age. All studies focused on tisagenlecleucel, compared to an alternative treatment: SOC, clofarabine monotherapy (Clo-M), clofarabine combination therapy (Clo-C), or blinatumomab. No study has focused on blinatumomab (except as a comparator) or InO. Five studies were supported by Novartis, the company that produces tisagenlecleucel [3, 26–29]. Study perspectives included public payer, healthcare system, and societal.

All studies were model-based with lifetime horizons. Discount rates for costs and effects varied from 1.5% to 4%. Costs were reported in local currency with reference years ranging from 2017 to 2020. Collected costs varied, including direct healthcare costs and societal costs.

Resource use for treatments was determined from clinical trials (tisagenlecleucel—ELIANA, ENSIGN, B2101J; blinatumomab—NCT01471782), scientific literature, and expert opinion. Unit costs were obtained from clinical trials for tisagenlecleucel, the literature for comparators, and local economic or government resources for healthcare and related costs.

3.3 | Model summary and comparison

Studies used partitioned survival modeling ($n = 8$) [3, 21, 25–30], state-transition microsimulation ($n = 2$) [2, 9], and cohort modeling ($n = 1$) [31]. The partitioned survival models included three health states: event-free survival (EFS), progressive/relapsed disease, and death. In six studies [21, 25, 26, 28–30], a decision tree was used to determine the proportion of patients who received tisagenlecleucel infusion. In Whittington et al., the decision tree included a second event node that assessed a patient's response to treatment and a third event

TABLE 2 Study and economic evaluation characteristics.

Author (year)	Ribera Santasusana et al. (2020)	Wakase et al. (2021)	Furzer et al. (2020)	Whittington et al. (2018)	Sarkar et al. (2019)	Thielen et al. (2020)	Lin et al. (2018)	Carey et al. (2022)	Wang et al. (2022)	Moradi-Lakeh et al. (2021)	Walton et al. (2019)
Country	Spain	Japan	Canada	US	US	Netherlands	US	Ireland	Singapore	Switzerland	England
Population	Pediatric and young adult patients up to 25 years of age with B-ALL that is refractory, in relapse post-transplant or in second or later relapse	Pediatric and young adult patients with r/r B-ALL	Patients with two or more relapses, older than 2 years and younger than 21 years	Patients younger than 25 years with B-ALL that was refractory or in second or later relapse	Simulated pediatric patients with r/r B-ALL	Pediatric patients with r/r pALL, 12 years of age	US children with r/r B-ALL	EMA licensed population for tisagenlecleucel, starting age 12 years	Young patients with r/r ALL in Singapore	pALL patients who were primary refractory, chemo-refractory, relapsed after HSCT, chemo-resistant, or otherwise ineligible for HSCT	Patients with r/r B-ALL in patients aged up to 25 years
Study perspective	Healthcare perspective (NHS in Spain)	Public healthcare payer's perspective	Public payer perspective	Payer perspective	Third party payer perspective (primary base case analysis) Societal perspective (secondary analysis)	Healthcare perspective Societal perspective	US health payer perspective	Healthcare perspective	Healthcare perspective	Swiss mandatory healthcare system	Not stated
Source	Novartis	Novartis	POGO Seed Grant, MOHLTC, Institute of Cancer Research	Institute for Clinical and Economic Review (support by dues from Novartis, among others)	National Institutes of Health	Novartis	Veterans Affairs Office of Academic Affiliations and National Center for Advancing Translational Science (one author with Novartis consulting role)	Not stated	Novartis	Novartis	National Institute of Health Research

(Continues)

TABLE 2 (Continued)

Author (year)	Ribera Santasusana et al. (2020)	Wakase et al. (2021)	Furzer et al. (2020)	Whittington et al. (2018)	Sarkar et al. (2019)	Thielen et al. (2020)	Lin et al. (2018)	Carey et al. (2022)	Wang et al. (2022)	Moradi-Lakeh et al. (2021)	Walton et al. (2019)
Immunotherapy	TIS	TIS	TIS	TIS	TIS	TIS	TIS	TIS	TIS	TIS	TIS
Control	FLA-IDA salvage chemotherapy[a]	BLN Clo-C[b] therapy	Standard of care including intensive combination chemotherapy and HSCT	Clo-M	Standard of care, modeled after a phase II trial by Hijiya et al.[c]	Clo-C Clo-M BLN	BLN Clo-C[b] Clo-M	BLN	BLN FLA-IDAG chemotherapy	BLN Clo-C FLA-IDA	BLN Salvage chemotherapy
Type of EE	CEA, CUA	CEA	CUA	CEA	CEA	CEA	CEA	CEA	CEA	CUA	CEA
Analytic approach	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based	Model-based
Model structure and type	Partitioned survival model with monthly cycles	Decision tree and partitioned survival model with monthly cycles	State-transition microsimulation model	Decision tree and partitioned survival model	Individual-based state-transition microsimulation model	Partitioned survival model	Markov model	Decision tree and partitioned survival model	Decision tree and partitioned survival model	Decision tree and partitioned survival model	Decision tree and partitioned survival model
Time frame of analysis	Lifetime horizon	Lifetime horizon	Lifetime horizon (up to max age of 60 years)	Lifetime horizon	Lifetime horizon	Lifetime horizon (88 years)	Lifetime horizon	Lifetime horizon (88 years)	Lifetime horizon (88 years)	Lifetime horizon	Lifetime horizon (88 years)
Discount rate per year (costs/effects)	3%/3%	2%/2%	1.5%/1.5%	3%/3%	3%/3%	4%/1.5%	3%/3%	4%/4%	3%	3.5%/3.5%	3.5%/3.5%
Currency and year	2018 EUR	2018 YEN	2018 CAD	2017 USD	2017 USD	2018 EUR	2017 USD	2020 EUR	2020 Singapore	2019 CHF	2017 GBP

(Continues)

TABLE 2 (Continued)

Author (year)	Ribera Santasusana et al. (2020)	Wakase et al. (2021)	Furzer et al. (2020)	Whittington et al. (2018)	Sarkar et al. (2019)	Thielen et al. (2020)	Lin et al. (2018)	Carey et al. (2022)	Wang et al. (2022)	Moradi-Lakeh et al. (2021)	Walton et al. (2019)
Types of costs	Direct healthcare	Direct healthcare, societal (sensitivity analyses)	Direct healthcare	Direct healthcare	Direct healthcare, societal	Direct healthcare, societal	Direct healthcare	Direct healthcare	Direct healthcare	Direct healthcare	Direct healthcare

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL; BLN, Blinatumomab; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; Clo-C, clofarabine combination therapy; Clo-M, clofarabine monotherapy; EE, economic evaluation; EMA, European Medicines Agency; FLA-IDA, fludarabine, cytarabine, idarubicin; FLA-IDAG, fludarabine, cytarabine, idarubicin with granulocyte colony stimulating factor; HSCT, hematopoietic stem cell transplant; pALL, pediatric acute lymphoblastic leukemia; r/r, relapsed/refractory; NHS, National Health System; TIS, tisagenlecleucel.

[a]Combination of fludarabine, cytarabine, and idarubicin.

[b]Clofarabine + cyclophosphamide + etoposide.

[c]Patients received upfront clofarabine, etoposide, and cyclophosphamide, followed by HSCT.

node of HSCT. The second part of the model was a long-term semi-Markov partitioned survival model with three health states: alive and responding to treatment, alive and not responding to treatment, and dead [21].

Two studies [2, 9] used state-transition microsimulation models estimating mean costs and QALYs over a patient's lifetime. Furzer et al. simulated 100,000 patients with second relapse ALL and followed them as they transitioned through health states: relapse, HSCT, tisagenlecleucel, death, and cure. Patients could transition between health and treatment states in monthly cycles up to a maximum age of 60 years. A multistate model estimated transition likelihood for each treatment. Their SOC strategy also involved a three-state model starting at second relapse, predicting health trajectories based on treatment [2]. Sarkar et al. simulated 100,000 pediatric patients with r/r B-ALL who received tisagenlecleucel or SOC. This model incorporated healthcare costs, toxicity, quality of life, disease progression, and survival with a 1-month cycle length and lifetime horizon. For each therapy, health states included remission, recurrence/progression, toxicity, and death [9].

Lin et al. used a Markov model that followed a hypothetical cohort of children with r/r B-ALL, comparing tisagenlecleucel to blinatumomab, Clo-C, and Clo-M. After receiving initial therapy, outcomes included remission, HSCT, cure, or refractory disease and death. Blinatumomab and clofarabine therapies were modeled as bridges to HSCT. For patients in the tisagenlecleucel arm who failed to receive the infusion, outcomes were dependent on whether this was due to a major adverse event, thus unable to tolerate additional therapy, or due to a manufacturing failure, after which they received blinatumomab. After achieving remission with tisagenlecleucel, only a minority received HSCT or alternative treatment [31].

3.4 | Cost summary and comparison

Table 3 summarizes all standardized costs in 2021 USD. The total cost for tisagenlecleucel therapy ranged from $385,084 [28] to $1,044,616 [9]. Costs varied depending on components of treatment included (e.g., pre-treatment, adverse events, hospital stay, and drug administration). The cost of tisagenlecleucel itself ranged from $312,969 [3] to $512,172 [9, 31]. The total cost for comparators varied based on the treatment (Figure 2). For SOC: $92,797 [2] to $475,080 [9], depending on the inclusion of HSCT. For blinatumomab: $153,603 [29] to $332,740 [27]. For Clo-C: $143,285 [28] to $403,268 [31]. For Clo-M: $200,201 [27] to $363,648 [21]. The lowest incremental cost was compared with blinatumomab ($165,407 USD) [28]. The highest incremental cost was compared with SOC ($569,535 USD) [9].

3.5 | Cost-effectiveness

Table 3 shows the ICER/ICUR per QALY for tisagenlecleucel and the WTP threshold for each study. Compared with SOC, the ICUR ranged from $35,879 [3] to $228,746 [2] USD/QALY gained, and

TABLE 3 Cost and cost-effectiveness of tisagenlecleucel versus comparator treatments.

Author (year)	Ribera Santasusana et al. (2020)	Wakase et al. (2021)	Furzer et al. (2020)	Whittington et al. (2018)	Sarkar et al. (2019)	Thielen et al. (2020)	Lin et al. (2018)	Carey et al. (2022)	Wang et al. (2022)	Moradi-Lakeh et al. (2021)	Walton et al. (2019)
Original cost	2018 EUR	2018 YEN	2018 CAD	2017 USD	2017 USD	2018 EUR	2017 USD	2020 EUR	2020 Singapore	2019 CHF	2017 GBP
Tisagenlecleucel											
Total cost	444,998.35	35,084.26	475,381.32	718,932.65	1,044,616.08	688,091.76	645,876.37	435,021.21	439,659.73	530,800.72	Not reported
Cost of drug	312,969.56	326,162.50	501,490.67	437,222.72	512,172.42	398,403.71	512,172.42	348,316.77	367,041.33	394,025.36	Not reported
Comparators											
Total cost	SOC: 123,314.25	BLN: 219,677.25 Clo-C: 143,286.48	SOC: 92,797.04	Clo-M: 363,648.89	SOC: 475,080.35	BLN: 332,740.55 Clo-C: 241,432.65 Clo-M: 200,201.60	BLN: 304,068.68 Clo-C: 403,268.39 Clo-M: 338,572.92	BLN: 253,882.99	BLN: 153,603.13 SOC: 107,621.66	BLN: 296,117.37 Clo-C: 292,792.22 SOC: 269,128.33	Not reported
Incremental cost	SOC: 321,684.10	BLN: 165,407.01 Clo-C: 241,797.78	SOC: 382,594.87	Clo-M: 355,283.76	SOC: 569,535.73	BLN: 355,351.21 Clo-C: 446,659.11 Clo-M: 487,890.16	BLN: 341,807.70 Clo-C: 242,607.99 Clo-M: 307,303.45	BLN: 181,138.21	BLN: 286,056.60 SOC: 332,038.07	BLN: 242,122.70 Clo-C: 289,696.20 SOC: 339,709.39	Not reported
WTP threshold (USD/QALY)[a]	62,250.58	71,707.90	40,700.46 81,400.91	107,825.77	107,825.77	99,600.93	53,912.89 107,825.77 161,738.66	51,942.42	67,240.57	103,684.37	66,723.87
Determination of WTP threshold	Not stated	Threshold used for rare diseases with unmet needs in Japan	Described as a commonly cited threshold. Multiple thresholds used	Described as a commonly cited threshold	Based on literature	Not stated	Not stated. Multiple thresholds used	Based on Irish standards	Based on WHO recommended thresholds (no published WTP for Singapore)	Based on a recent analysis of the willingness to pay within the Swiss population	Described as a commonly used threshold

(Continues)

TABLE 3 (Continued)

Author (year)	Ribera Santasusana et al. (2020)	Wakase et al. (2021)	Furzer et al. (2020)	Whittington et al. (2018)	Sarkar et al. (2019)	Thielen et al. (2020)	Lin et al. (2018)	Carey et al. (2022)	Wang et al. (2022)	Moradi-Lakeh et al. (2021)	Walton et al. (2019)
ICER/ICUR (USD/QALY)	35,879.39	BLN: 19,457.42 Clo-C: 25,286.14	40% cure rate: 57,794.65 20% cure rate: 114,775.29 10% cure rate: 228,736.56	49,460.76	Payer perspective: 69,655.45 Societal perspective: 74,938.91	Healthcare perspective: BLN: 39,444.46 Clo-C: 46,726.53 Clo-M: 45,291.03	BLN: 40% 5-year relapse-free survival rate: 65,773.72 20% 5-year relapse-free survival rate: 162,816.92 Bridge to HSCT: 198,399.42	BLN: 84,361.41	BLN: 38,156.15 SOC: 33,650.35	BLN: 37,760.81 Clo-C: 35,802.21 SOC: 33,138.56	BLN: 37,007.73 SOC: 60,581.27
ICER/ICUR range[b]	19,761.07 to 48,154.47	BLN: (–) to 27,588.28 Clo-C: (–) to 35,913.72	40% cure rate: 46,398.52 to 197,804.21 20% cure rate: 76,516.86 to 634,927.11 10% cure rate: (–) to 2,991,483.5	39,895.54 to 83,564.97	55,422.45 to 250,155.79	BLN: 36,377.99 to 66,854.63 Clo-C: 41,883.43 to 78,860.28 Clo-M: 39,588.88 to 75,770.16	40% 5-year relapse-free survival rate: 54,991.14 to 97,043.19 20% 5-year relapse-free survival rate: 99,199.71 to dominated Bridge to HSCT: 133,703.96 to 1,053,457.79	BLN: 58,013.91 to 426,644.63	BLN: 20,714.34 to 62,418.32 SOC: 18,592.85 to 54,959.30	BLN: (–) to 62,210.62 Clo-C: (–) to 77,763.28 SOC: (–) to 46,657.97	BLN: 23,653.61 to 61,563.44 SOC: 35,268.90 to 99,181.03

Note: All costs are in 2021 USD.

Abbreviations: BLN, Blinatumomab; Clo-C, clofarabine combination therapy; Clo-M, clofarabine monotherapy; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost utility ratio; QALY, quality-adjusted life-year; SOC, salvage chemotherapy; WTP, willingness-to-pay.

[a]WTP thresholds based on values identified in each study.

[b]ICER/ICUR ranges based on sensitivity analyses conducted and values reported in each study.

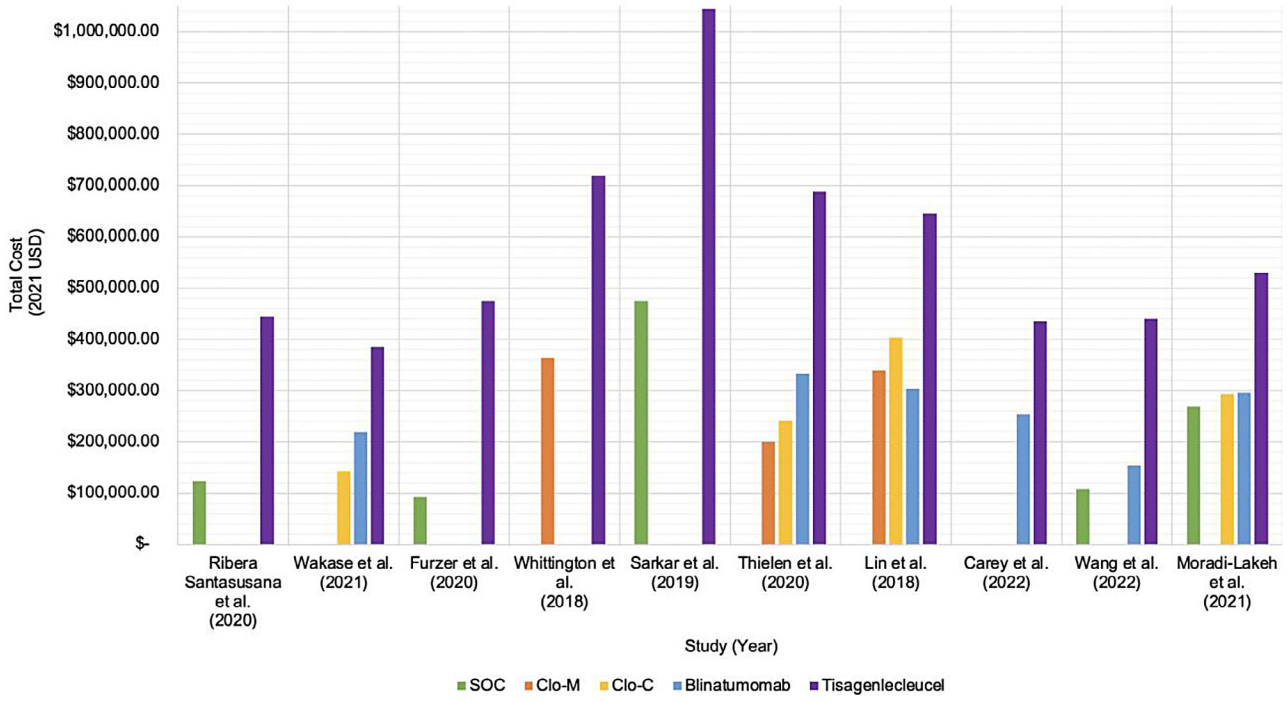

FIGURE 2 Total cost comparison of tisagenlecleucel and comparators. Walton et al. [25] did not report total costs.

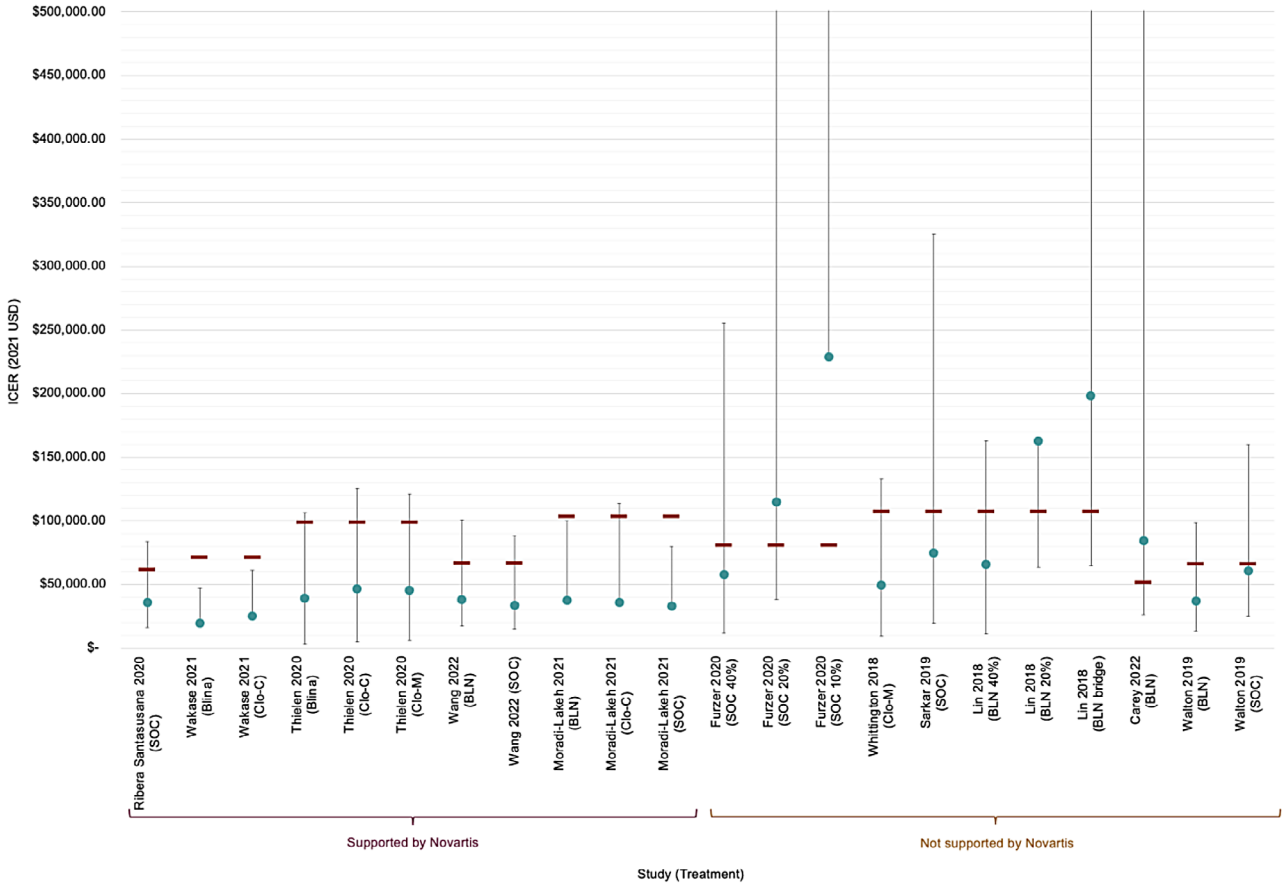

FIGURE 3 Cost-effectiveness comparison by study and treatment type. Specific comparator treatments are listed on the *x*-axis. Error bars indicate the range of incremental cost-effectiveness ratio (ICER) based on analyses of uncertainty. The willingness-to-pay (WTP) thresholds used in each study are delineated by red horizontal lines. Values for ICERs, WTP thresholds, and ranges delineated by error bars can be found in Table S1.

was highly dependent on the assumed cure rate. Compared with Clo-M, the ICER ranged from $45,291 [27] to $49,460 [21] USD/QALY gained. Compared with Clo-C, the ICER ranged from $25,286 [28] to $45,726 [27] USD/QALY gained. Compared with blinatumomab, the ICER ranged widely from $19,457 [28] to $198,399 [31] USD/QALY gained, depending on assumed cure rate. The WTP thresholds ranged substantially from $40,700 [2] to $161,738 [31] USD/QALY.

Six studies concluded that tisagenlecleucel was cost-effective [3, 21, 26–29]. Four studies concluded that tisagenlecleucel has the potential to be cost-effective, depending on long-term cure rates and list prices [2, 9, 25, 31]. One study concluded that tisagenlecleucel was not cost-effective [30]. Cost-effectiveness varied depending on whether the study was supported by Novartis. The range of ICERs for the five studies [3, 26–29] supported by Novartis was narrower: $19,457 [28] to $46,726 [27]. The range of ICERs for the six studies [2, 9, 21, 25, 30, 31] not supported by Novartis was wider: $37,007 [25] to $228,736 [2]. All studies supported by Novartis concluded that tisagenlecleucel was cost-effective, while only one of six independent studies concluded the same (Figure 3).

3.6 | Analyses of uncertainty

All studies included analyses of uncertainty. Deterministic sensitivity analyses demonstrated that assumed long-term cure rates determined whether a model would remain robust to alternative assumptions/inputs [2, 3, 9, 25–31]. Additional factors that impacted the ICER were discount rate for costs/effects, cost of tisagenlecleucel, earlier age at therapy, and consideration of productivity gains. In Sarkar et al., if a pessimistic survival model was assumed, tisagenlecleucel was no longer cost-effective [9].

Probabilistic sensitivity analyses were used to estimate the probability of tisagenlecleucel being cost-effective at different thresholds, influenced by long-term cure rate and price discount [2, 9, 21, 25–30]. In Lin et al., tisagenlecleucel was cost-effective assuming a 5-year EFS of 40% with WTP of $150,000. However, the probability of tisagenlecleucel remaining cost-effective decreased to 53% with a long-term survival rate of 20% [31]. Furzer et al. determined that at its current cost, tisagenlecleucel's cost-effectiveness would fall below $50,000/QALY only with a cure rate over 40%. The ICER rose to $114,775 USD/QALY if the cure rate decreased to 20% [2]. Scenario analyses found that other factors that impacted the ICER included modification of time horizon, decrease in price of tisagenlecleucel, and longer duration of treatment with intravenous immunoglobulin for B-cell aplasia [3, 21, 25–28, 30, 31].

3.7 | Methodological quality of the studies

Studies were of high methodological quality based on CHEC criteria (Appendix C). All studies disclosed conflicts of interest, with five studies disclosing funding by Novartis. Walton et al. conducted an alternative base case analysis on the company's proposed model; therefore, information regarding the study perspective and detailed costs was not provided [25]. The results did not vary based on the methodological quality of the studies.

4 | DISCUSSION

Our findings summarize the existing evidence on cost-effectiveness of immunotherapy in r/r pALL. Many studies have evaluated the cost-effectiveness of tisagenlecleucel; however, none have evaluated blinatumomab or InO, which are less expensive than tisagenlecleucel but still represent significant costs. Future studies evaluating the cost-effectiveness of these immunotherapies are needed, as they are increasingly being used in r/r ALL.

Significant variability existed between the results of the studies. Unsurprisingly, cost-effectiveness was highly dependent on the assumed long-term cure rate of tisagenlecleucel, which is uncertain given the short-term follow-up of trials. Two studies demonstrated that below a long-term cure rate of 40%, the chance of cost-effectiveness was very low [2, 31]. A recent study followed patients for 4.8 years after receipt of tisagenlecleucel followed by alloHSCT [32]. These patients had a 5-year EFS of 61.9%; however, these results are not generalizable to patients receiving tisagenlecleucel alone [32]. In the 3-year update of the ELIANA trial, patients were followed for 38.8 months from the date of infusion with a 3-year EFS of 44% [33]. Our findings suggest that investigators should be strongly encouraged to publish long-term outcomes of seminal CAR-T trials to help inform decision makers.

The price of tisagenlecleucel also varied across studies. The list price for tisagenlecleucel as of 2018 was $475,000 USD [9, 21]. While some studies used available list prices, other studies reported different values. In addition, an outcome-based pricing strategy was used in some studies such that payment for tisagenlecleucel was only applied if a patient achieved initial remission. While this can mitigate some financial risk, the high rates of initial remission with tisagenlecleucel make its impact less significant [31]. A recent study by Heine et al. estimated the budget impact of tisagenlecleucel for pALL in Europe and concluded that while tisagenlecleucel has a promising role, it still represents a significant financial burden [34]. Our findings build upon this recent systematic review, incorporating results from CEAs completed since its publication, and thus providing policymakers with the most up-to-date information regarding cost-effectiveness of immunotherapies in pALL.

The choice of WTP threshold also impacted cost-effectiveness. In some studies, the WTP threshold was based on country-specific predefined standards [26, 28, 30]. However, in others, the WTP was justified as a "commonly used threshold" or no rationale was provided. In some studies, multiple hypothetical WTP thresholds were used [2, 31]. Although the choice of a WTP threshold is in some ways itself a value-based judgment, this variability presents a major challenge in interpreting and comparing results.

Finally, it is worth noting that the above sources of variability were treated differently based on funding source. The studies supported by Novartis tended to have lower base case ICERs with less variability

in sensitivity analyses; all found tisagenlecleucel to be cost-effective. The remainder of the studies tended to have higher base case ICERs with substantial variability in sensitivity analyses. Most of these studies concluded that tisagenlecleucel was either not cost-effective or had the potential to be cost-effective depending on different factors, including price reductions or optimistic cure rates. When assessing cost-effectiveness studies of novel agents, decision makers should take the funding source into account.

Study strengths include a robust search strategy and comprehensive analysis of the studies. Several limitations also merit mention. As noted above, we could not identify any literature regarding blinatumomab or InO, which limits the ability of policymakers to make funding decisions. Second, significant heterogeneity existed between studies based on costs included, the cost of tisagenlecleucel acquisition, and cost of total treatment. Third, all studies were conducted in high-income countries, limiting generalizability to other settings.

In conclusion, studies identified in this systematic review focused on the cost-effectiveness of tisagenlecleucel in pediatric r/r ALL. While some included blinatumomab as a comparator, none studied blinatumomab or InO as the intervention. Most studies found that the cost-effectiveness of tisagenlecleucel was highly dependent on list price and long-term cure rates, which are currently unclear. Other important factors to consider include potential conflicts of interest, as studies supported by Novartis generally showed more favorable results. While additional economic evaluations are needed to explore cost-effectiveness of immunotherapies in pALL with longer-term follow-up, this study can help inform the decisions of policymakers with respect to the use of tisagenlecleucel in r/r pALL based on current literature.

AUTHOR CONTRIBUTIONS

Conceptualization and design, data analysis and interpretation, and manuscript writing (original draft, review, and editing): Yolanda Scoleri-Longo, Petros Pechlivanoglou, and Sumit Gupta.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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DATA AVAILABILITY STATEMENT

Systematic review data are available upon request.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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