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Tisagenlecleucel for relapsed/refractory acute lymphoblastic leukemia in the Irish healthcare setting: cost-effectiveness and value of information analysis

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Abstract

Objectives: This study evaluates the cost-effectiveness of tisagenlecleucel (a CAR T-cell therapy), versus blinatumomab, for the treatment of pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) in the Irish healthcare setting. The value of conducting further research, to investigate the value of uncertainty associated with the decision problem, is assessed by means of expected value of perfect information (EVPI) and partial EVPI (EVPPI) analyses.

Methods: A three-state partitioned survival model was developed. A short-term decision tree partitioned patients in the tisagenlecleucel arm according to infusion status. Survival was extrapolated to 60 months; general population mortality with a standardized mortality ratio was then applied. Estimated EVPI and EVPPI were scaled up to population according to the incidence of the decision.

Results: At list prices, the incremental cost-effectiveness ratio was EUR 73,086 per quality-adjusted life year (QALY) (incremental costs EUR 156,928; incremental QALYs 2.15). The probability of cost-effectiveness, at the willingness-to-pay threshold of EUR 45,000 per QALY, was 16 percent. At this threshold, population EVPI was EUR 314,455; population EVPPI was below EUR 100,000 for each parameter category.

Conclusions: Tisagenlecleucel is not cost effective, versus blinatumomab, for the treatment of pediatric and young adult patients with R/R ALL in Ireland (at list prices). Further research to decrease decision (parameter) uncertainty, at the defined willingness-to-pay threshold, may not be of value. However, there is a high degree of uncertainty underpinning the analysis, which may not be captured by EVPI analysis.

B-cell acute lymphoblastic leukemia (ALL) is one of the most common childhood cancers. Five-year survival in patients with newly diagnosed ALL has been reported to exceed 80 percent (1;2). However, the prognosis of patients with relapsed or refractory (R/R) disease is poor (3). Complete response rates in patients who experience a second, third, and fourth or later relapse have been reported to be 44, 27, and 12 percent, respectively (4). For these patients, allogeneic stem cell transplant (alloSCT) is a treatment option with potential long-term benefit. Successful alloSCT, however, is contingent on response to chemotherapy and availability of an appropriate donor. Treatment of these patients is a key challenge.

Tisagenlecleucel (a chimeric antigen receptor [CAR] T-cell therapy) received European Medicines Agency (EMA) conditional marketing authorization (2018) for the treatment of pediatric and young adult patients (up to 25 years of age) with ALL that is refractory, in relapse post-transplant, or in second or later relapse (5). The pivotal trials of tisagenlecleucel, ELIANA and ENSIGN, are single-arm with short duration of follow-up (6;7). The lack of randomized controlled trial evidence, and long-term follow-up data leads to much uncertainty regarding the expected benefits of this therapy, and its longevity. Patients and clinicians are at risk, should tisagenlecleucel not demonstrate long-term survival benefit. Payers are at financial risk due to the associated high upfront cost.

Aim

The aim of this study was to evaluate the cost-effectiveness of tisagenlecleucel, versus blinatumomab with or without alloSCT (henceforth "blinatumomab"), for R/R ALL in pediatric and young adult patients in the Irish healthcare setting. The value of conducting

further research to address uncertainties in the model was assessed by expected value of perfect information (EVPI) and partial EVPI (EVPPI) analyses.

Method

Model Structure

Short-Term Decision Tree

The model comprised a short-term decision tree (tisagenlecleucel) and a long-term partitioned survival model (tisagenlecleucel and blinatumomab). The decision tree represented the tisagenlecleucel pretreatment phase. During this phase, events may occur, which prevent patients proceeding to tisagenlecleucel infusion. All patients in the tisagenlecleucel arm entered the decision tree, underwent leukapheresis, and subsequently progressed to one of three outcomes, informed by pooled ELIANA and ENSIGN trial data (6;7) (Supplementary Figure 1):

- N1: proceed to infusion (83 percent of patients (6;7)).
- N2: do not proceed to infusion due to manufacturing failure or adverse event (AE) (9 percent of patients (6;7)). These patients were assumed to receive blinatumomab.
- N3: do not proceed to infusion due to death prior to infusion (8 percent of patients (6;7)). These patients did not receive any further active treatment.

For patients who did not proceed to infusion (i.e., N2 or N3), it was assumed that 50 percent received bridging chemotherapy and 50 percent received lymphodepleting chemotherapy (8).

Partitioned Survival Model

The partitioned survival model (Supplementary Figure 2) comprised three mutually exclusive health states: event-free survival, progressed disease, and death. Patients treated with blinatumomab entered the partitioned survival model directly. Patients in the tisagenlecleucel arm entered through the decision tree. Survival was measured from the time of treatment initiation in both arms. Most patients with R/R ALL are expected to relapse within 24 to 60 months post-treatment (9;10). It was assumed that patients who were alive after 60 months in either arm were long-term survivors. These were subject to age- and sex-matched general population mortality with a standardized mortality ratio (15.5) applied. This ratio was derived by Fidler et al., who examined mortality in pediatric and adolescent patients (less than 15 years) diagnosed (between 1940 and 2006) with ALL and survived 5 years postdiagnosis (n = 9,493; obtained from the British Childhood Cancer Survivor Study database) (11).

Cycle length was 1 month (30.4 days); a half-cycle correction was applied. A lifetime horizon of 88 years was employed. A discount rate of 4 percent was applied to costs and outcomes after the first year (12).

Population

The population was aligned with the EMA licensed population of tisagenlecleucel (Supplementary Material 1.2) (5). Starting age was 12 years, 44 percent were female, body surface area was 1.32 m^2, and weight was 42.2 kg (7;13–15).

Intervention

The intervention was tisagenlecleucel, administered at the EMA licensed dose and modeled as a single-dose intervention (5).

Comparator

Blinatumomab (routine care in Ireland) was the comparator. Blinatumomab may be administered to patients with the intent to receive subsequent alloSCT. It was assumed that 49 percent of patients receive alloSCT following blinatumomab, in line with clinical opinion (n = 5). Dosing was in line with the licensed indication (Supplementary Material 1.3) (16). Patients were assumed to receive up to two cycles (17;18).

Perspective

The perspective was that of the healthcare payer, the Health Service Executive (HSE) in Ireland (12). Direct medical costs were included.

Model Inputs

Efficacy Data

Treatment effectiveness was based on the effect on overall survival (OS) and event-free survival (EFS). Efficacy data, identified by systematic literature review, were derived from the pooled ELIANA (6) and ENSIGN (7) (tisagenlecleucel), and NCT01471782 (18;19) (blinatumomab) trials. ELIANA (n = 75) and ENSIGN (n = 64) were single-arm, phase II trials, which evaluated the efficacy of tisagenlecleucel in the population of interest here. Median duration of follow-up was 13.1 months (ELIANA) and 32 months (ENSIGN) (6;7). NCT01471782 (n = 70) was a single-arm, phase I/II trial, which evaluated the efficacy of blinatumomab in the population of interest. Median duration of follow-up was 24 months (18;19). Further detail is provided in Supplementary Material 1.2.

Individual patient-level data (IPD) from published Kaplan–Meier curves of OS and EFS were reconstructed by digitizing the published curves and applying the algorithm by Guyot et al. (20). Due to the single-arm nature of the trials, and lack of publicly available raw IPD, a naïve comparison was conducted.

Extrapolation of survival data was conducted in line with NICE Decision Support Unit Guidance (technical support document 14 (21)). Standard parametric (Gompertz, exponential, Weibull, log-logistic, log-normal, generalized gamma) extrapolation models were explored (21). Due to the innovative mechanism of tisagenlecleucel and the potential for complex hazard functions (10), flexible cubic spline models (one-, two-, and three-knot spline models across all scales), and mixture cure models were also explored. Survival models were fitted individually to the treatment arms. The best fitting model was selected based on AIC (Akaike information criterion) and BIC (Bayesian information criterion) statistics (Supplementary Material 1.4), visual fit, and clinical plausibility (21).

Overall Survival. The one-knot (odds) spline model was deemed the best fit to the OS data of tisagenlecleucel and blinatumomab. This model closely aligned with judgments, for both tisagenlecleucel and blinatumomab, elicited from clinical opinion (n = 5). Alternative models were explored in scenario analysis.

Event-Free Survival. EFS data for tisagenlecleucel were based on ELIANA only (6); the Kaplan–Meier curve of EFS was not publicly available for ENSIGN (7). The generalized gamma model was deemed the best fit. EFS data were not reported for blinatumomab. EFS was therefore, estimated from the OS curve of blinatumomab by assuming that the cumulative hazard function for EFS was proportional to the cumulative hazard function

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for OS. This approach has been accepted by National HTA agencies (13;22). The ratio between EFS and OS was based on the study by Kuhlen et al. (23). This overall cumulative hazard was applied to the OS data of NCT01471782 (blinatumomab) to generate EFS data.

After month 60, the cumulative survival probabilities for EFS were assumed to flatten up to the point at which EFS met OS. Death due to progression was assumed to only occur within the first 60 months in both arms, as patients alive after 60 months were assumed to be long-term survivors. EFS could not exceed OS at any point.

Utility Inputs

Utility data were derived through systematic literature review. Heath-state utility data comprised data collected using the EQ-5D-3L in ELIANA, with the UK valuation set applied (13). Patients alive after 60 months were assumed to have utility equivalent to that of the event-free survival state. Disutility associated with pretreatment procedures, intensive care unit (ICU) admission, febrile neutropenia and pancytopenia were also included. The proportion of patients experiencing AEs, and their duration, were informed by relevant trials (6;7;15;18;19). An age adjustment was applied, using the multiplicative approach (24). Time dependent post-alloSCT disutility was applied to reflect improvement in health over time (25). Further detail is provided in Table 1 and Supplementary Material 1.5.

Cost Inputs

Irish cost data were used, where available. Where necessary, costs were inflated to 2020 using the Consumer Price Index for health (36), and converted to Euro using purchasing power parities (37). See Table 1.

Training. As per the EMA marketing authorization, healthcare professionals, who prescribe, dispense, or administer tisagenlecleucel, require training (15). An associated cost per patient was included in the tisagenlecleucel arm (Supplementary Material 1.6).

Tisagenlecleucel-Specific Pretreatment. In the tisagenlecleucel arm, all patients incurred the cost of leukapheresis and cryopreservation. Bridging chemotherapy (one cycle) and lymphodepleting chemotherapy (one cycle) were received by 88 and 95 percent of patients (who received infusion), respectively. This was informed by ELIANA and ENSIGN (6;7).

Drug Acquisition. Total drug acquisition costs for tisagenlecleucel and blinatumomab are presented in Table 1. It was assumed that 100 percent of patients received one cycle and 33 percent received a second cycle of blinatumomab, as per NCT01471782 (19).

Administration and Hospitalization. Costs were obtained from the Irish Healthcare Pricing Office DRG List (28), tertiary teaching hospitals, the Irish HSE DRG List (33), and the literature (30) (Table 1). The cost of outpatient administration of bridging chemotherapy was included (28). In the absence of severe AEs, the duration of hospitalization (including lymphodepleting chemotherapy) for patients receiving tisagenlecleucel is expected to be 3–4 weeks. This was informed by clinical opinion from one consultant hematologist in a Tertiary Teaching Hospital in Ireland. The hospitalization cost represented a mean length of stay of 24.5 days (28). Patients are required to remain within 2 hr of travel of the hospital for at least 4 weeks following infusion (15). It was arbitrarily assumed that 50 percent of patients required hospital-associated patient apartments for 4 days and that the remaining patients lived nearby. A cost was included for patients who received lymphodepleting chemotherapy but did not proceed to tisagenlecleucel (28).

In line with clinical opinion in Ireland ($n = 1$), patients receiving blinatumomab were assumed to be hospitalized for 7 days, after which they were discharged with an infusion pump (16). Infusion durations were assumed to alternate between 72- and 96-hr (38) (avoiding the need to change the infusion bag at weekends). This results in a 7-day inpatient stay (cycle one), seven outpatient visits (cycle one) and nine outpatient visits (cycle two).

Initiation and Monitoring. All tisagenlecleucel initiation and monitoring costs were assumed to be accounted for in the cost of hospitalization. Outpatient monitoring costs were included in the blinatumomab arm.

Health-state specific follow-up costs were applied for the event-free survival and progressed disease states. Follow-up requirements were sourced from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (3). Additional tisagenlecleucel-specific requirements were sourced from Yakoub-Agha et al (39).

Adverse Events. Tisagenlecleucel-specific AEs included cytokine release syndrome (CRS), B-cell aplasia, febrile neutropenia, pancytopenia, and non-CRS ICU admission. Data were obtained from pooled ELIANA and ENSIGN data (6;7). Other AEs, in the tisagenlecleucel arm, were assumed to be captured by the cost of hospitalization. Grade ≥ 3 AEs occurring in 5 percent or greater of the population in NCT01471782 were included for blinatumomab (18). CRS was also included in the blinatumomab arm. Supplementary Material 1.6 provides further detail.

Allogeneic Stem Cell Transplant. AlloSCT procedure (28) and follow-up costs, accounting for 365-days postdischarge (34), were included for the 49 percent of patients in the blinatumomab arm who received alloSCT.

Terminal Care. A once-off per patient terminal care cost was applied to patients upon entering the death state (35).

Key Input Parameters

Key input parameters are presented in Table 1.

Model Outputs

Deterministic ICER

The base case analysis considered the incremental cost-effectiveness ratio (ICER), calculated from deterministic costs and deterministic quality-adjusted life years (QALYs), using standard decision rules (12). In Ireland, most drugs that have been reimbursed to date have been considered under a willingness-to-pay threshold of EUR 45,000 per QALY (40;41). This threshold was considered here.

Probabilistic ICER and Scatterplot

Probabilistic sensitivity analysis (PSA) was conducted; parameters were varied according to appropriate distributions (Table 1). Results were generated using Monte Carlo Simulation (5,000 iterations).

A scatterplot of incremental costs and QALYs, generated from each iteration of the PSA, was constructed to illustrate the degree of

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Table 1. Key Input Parameters of Cost-Utility Model of Tisagenlecleucel Versus Blinatumomab in Pediatric and Young Adult Patients with R/R ALL

Parameter	Value	Source	Probabilistic sensitivity analysis distribution
Tisagenlecleucel arm			
Decision tree probability inputs			
N1: Infusion with tisagenlecleucel	0.83	(6;7)	Dirichlet
N2: Receive blinatumomab	0.09		
N3: Death state	0.08		
Efficacy inputs			
EFS distribution	Generalized gamma		Multivariate normal
Disutility values			
Apheresis/Bridging/Lymphodepleting chemotherapy	−0.20	(26)	Normal
Intensive care unit (Noncytokine release syndrome)	−0.80	Assumption	
Pancytopenia	−0.15	(27)	
Pretreatment costs (EUR, 2020)			
Leukapheresis	1,249.00	(28)	Gamma
Cryopreservation	5,544.68	Tertiary teaching hospital	
Bridging chemotherapy	159.56	See Supplementary Material 1.6	Not varied
Lymphodepleting chemotherapy	414.44		
Drug acquisition costs (EUR, 2020)			
Tisagenlecleucel	301,762.13	(29)	Not varied
Administration and hospitalization costs (EUR, 2020)			
Bridging chemotherapy administration	692.00	Tertiary teaching hospital	Gamma
Hospitalization: Tisagenlecleucel	37,944.00	(28)	
Lymphodepleting chemotherapy administration	5,100.00	(28)	
Patient apartment (per night)	63.90	(30)	
Training	1,595.55	See Supplementary Material 1.6	
Per cycle EFS follow-up costs (EUR, 2020)			
Months 1–12	115.94	See Supplementary Material 1.6	
Months 13–24	54.85		Gamma
Months 25–60	36.57		
Month 61 onwards[a]	18.28		
Total adverse event costs (EUR, 2020)			
Total tisagenlecleucel[b] (EUR)	18,864.79	See Supplementary Material 1.6	Gamma
Intravenous immunoglobulin (per dose) (EUR)	1,365.00		Not varied
Proportion intravenous immunoglobulin (%)	47		Beta
Blinatumomab arm			
Efficacy inputs			
EFS:OS cumulative hazard ratio	0.88	(23)	Log-normal
Disutility values			
AlloSCT (0–3 months)	−0.20	(30;31)	Normal
AlloSCT (4–12 months)	−0.13	(25)	
Drug acquisition costs (EUR, 2020)			
Blinatumomab: Dosing based on body surface area[c]	89,213.55	(32)	Not varied
Blinatumomab: Fixed-dosing regimen[c]	125,381.20	(32)	

(*Continued*)

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Table 1. (*Continued*)

Parameter	Value	Source	Probabilistic sensitivity analysis distribution
Administration and hospitalization costs (EUR, 2020)			
Hospitalization: Blinatumomab	11,826.00	(28)	Gamma
Infusion pump	118.67	Rockford Healthcare	
Outpatient appointment	136.76	(33)	
Per cycle initiation and EFS follow-up costs (EUR, 2020)			
Monitoring	198.30	See Supplementary Material 1.6	Gamma
Months 1–12	78.74		
Months 13–24	36.25		
Months 25–60	24.17		
Month 61 onwards[a]	12.08		
Total adverse event costs (EUR, 2020)			
Total blinatumomab (EUR)	3,347.16		Gamma
AlloSCT			
AlloSCT procedure (EUR)	202,698.00	(28)	Gamma
Follow-up first 100 days postdischarge[d] (EUR)	64,618.28	(34)	
Follow-up 101–200 days postdischarge[d] (EUR)	36,524.17	(34)	
Follow-up 201–365 days postdischarge[d] (EUR)	40,957.86	(34)	
Proportion AlloSCT blinatumomab (%)	49	Clinical opinion	Beta
Both tisagenlecleucel and blinatumomab arms			
Efficacy inputs			
OS distribution	One-knot (odds) spline		Multivariate normal
Standardized mortality ratio	15.5	(11)	Log-normal
Health-state utility values			
EFS	0.80	(13)	Beta
PD	0.63	(13)	
All patients alive after 60 months	0.80	Assumption	
Disutility values			
Cytokine release syndrome	−0.80	Assumption	Normal
Febrile neutropenia	−0.15	(27)	
Follow-up costs (EUR, 2020)			
PD[e]	78.74	See Supplementary Material 1.6	Gamma
Terminal care (once-off cost)	7,732.48	(35)	

[a]Patients who were alive at 61 months incurred the cost of EFS from month 61 onwards, regardless of health state (22).
[b]Excluding the cost of intravenous immunoglobulin for the treatment of B-cell aplasia.
[c]50 percent of patients receive dosing based on body surface area (used for patients weighing < 45 kg) and 50 percent of patients receive fixed-dosing regimen (used for patients weighing ≥ 45 kg). Dosing regimen presented in Supplementary Material 1.3.
[d]In the cost-utility model, these were converted to a per cycle cost and applied to the proportion of patients experiencing the event.
[e]Assumed equal to the EFS follow-up costs of blinatumomab in months 1–12 (13;22).
ALL, acute lymphoblastic leukemia; AlloSCT, allogeneic stem cell transplant; EFS, event-free survival; OS, overall survival; PD, progressed disease; R/R, relapsed/refractory.

uncertainty surrounding the estimates. The mean probabilistic ICER was estimated.

Cost-Effectiveness Acceptability Curve

For each iteration of the PSA, the expected net monetary benefit (NMB) for tisagenlecleucel and blinatumomab was estimated. From the NMB values, the probabilities of each treatment being cost effective over a range of thresholds (EUR 0.00 per QALY to EUR 350,000 per QALY) were plotted to produce the cost-effectiveness acceptability curve.

One-Way Sensitivity Analysis

One-way sensitivity analysis (OWSA) of all parameters was performed to determine the impact on the deterministic ICER of

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changes to individual parameters. Upper and lower bounds of the 95 percent confidence interval (CI) for point estimates were used where available. Otherwise, point estimates were varied ± 25 percent. A tornado plot was constructed, illustrating the impact of the ten most influential parameters.

Scenario Analysis

A number of scenario analyses were conducted to assess the impact on the deterministic ICER of employing alternative, plausible assumptions.

Price Analysis

An analysis was conducted (using the "Goal Seek" function in Microsoft Excel) to determine the decrease in the list price of tisagenlecleucel that would be required for the ICER to meet the EUR 45,000 per QALY threshold.

Expected Value of Perfect Information and Partial Expected Value of Perfect Information

EVPI represents the estimated value of eliminating uncertainty in the model. EVPPI identifies the parameters whose uncertainty drives decision uncertainty, allowing further research to be prioritized (42). EVPI and EVPPI were calculated on 5,000 iterations of the PSA and over a range of thresholds. EVPPI was estimated using the Gaussian process regression approach (43;44). EVPPI was calculated for the parameter categories: utility values, survival analysis, hospitalization and monitoring costs, AE costs, and alloSCT. Estimates of EVPI and EVPPI were scaled up to population according to the incidence of the decision (six patients per year, as per clinical opinion [$n = 1$] in Ireland; total 51 patients over 10 years when discounting is applied) (12). A technology time horizon of 10 years was assumed (10). A discount rate of 4 percent was applied. Population EVPI estimates were plotted over the range of thresholds.

Results

Deterministic Results

Deterministic model outcomes are presented in Table 2. At list prices, tisagenlecleucel was not cost effective, versus blinatumomab, at the EUR 45,000 per QALY threshold.

Probabilistic Results

Expected incremental costs and incremental QALYs are presented in a scatterplot in Figure 1. Mean expected costs and QALYs are presented in Table 2.

The cost-effectiveness acceptability curve is presented in Supplementary Material 1.7. At the EUR 45,000 per QALY threshold, there was a 16 percent probability that tisagenlecleucel was cost effective.

One-Way Sensitivity Analysis

Outcomes of OWSA are presented in Supplementary Figure 8. The main drivers in the model were the rate of alloSCT in the blinatumomab arm, discount rate on outcomes, and tisagenlecleucel infusion cost.

Scenario Analysis

Results of scenario analyses are presented in Table 2 and Supplementary Material 1.9.

Price Analysis

A 28 percent decrease (including 5.5 percent rebate) on the tisagenlecleucel list price was required to reduce the deterministic ICER to the EUR 45,000 per QALY threshold. The probability of cost-effectiveness here was 44 percent.

Expected Value of Perfect Information

At the EUR 45,000 per QALY threshold, the 10-year population EVPI was EUR 314,455. Population EVPI, over a range of thresholds, is depicted in Figure 2.

The population EVPI analysis was rerun at the price that reduced the ICER to EUR 45,000 per QALY (EUR 229,105; representing a 28 percent price decrease). At this threshold, the 10-year population EVPI was EUR 1,149,810 (Figure 3).

Partial EVPI

At the EUR 45,000 per QALY threshold, 10-year population EVPPI was below EUR 100,000 for each parameter category. Survival analysis had the highest population EVPPI (EUR 67,189), followed by alloSCT parameters (EUR 29,338), utility values (EUR 25,255), AE costs (EUR 18,649) and hospitalization and monitoring costs (EUR 1,215).

The population EVPPI analysis was rerun at the price of tisagenlecleucel that reduced the ICER to EUR 45,000 per QALY. At the EUR 45,000 per QALY threshold, population EVPPI was below EUR 500,000 for each category. Similar to the EVPPI at list price, survival analysis had the highest population EVPPI. Here, it was valued at EUR 371,813. This was followed by alloSCT (EUR 272,459), hospitalization and monitoring costs (EUR 211,894), utility values (EUR 133,375) and AE costs (EUR 50,222).

Supplementary Material 1.10 depicts the value of uncertainty associated with each parameter category.

Discussion

Deterministic and Probabilistic Results

At list prices, tisagenlecleucel is not cost effective, versus blinatumomab, at a EUR 45,000 per QALY willingness-to-pay threshold.

The high degree of uncertainty in the clinical evidence base of tisagenlecleucel translates to uncertainty in cost-effectiveness. Uncertainty associated with the naïve comparison is difficult to quantify. For immature survival data, such as that used in this analysis, the true uncertainty lies in extrapolation of the data and the appropriate choice of survival model. Such uncertainty is generally not captured in the PSA. Caution is therefore, warranted in the interpretation of results. The cost-effectiveness acceptability curve indicated that the probability of cost-effectiveness of tisagenlecleucel exceeds that of blinatumomab at thresholds of approximately EUR 80,000 per QALY and over. As some PSA iterations lie in the north-west quadrant (more costly, less effective), the probability of cost-effectiveness of tisagenlecleucel will not reach 100 percent at any threshold.

One-Way Sensitivity and Scenario Analyses

The model was sensitive to the discount rate on outcomes. Altering the discount rate on costs had less impact. Reducing the discount rate on outcomes to 0 percent (whilst maintaining a 4 percent

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Table 2. Deterministic, Probabilistic, and Scenario Analysis Results of the Incremental Analysis of Cost-Effectiveness of Tisagenlecleucel versus Blinatumomab in Pediatric and Young Adult Patients with R/R ALL

Technology	Total costs (EUR)	Total QALYs	Incremental costs (EUR)	Incremental QALYs	ICER (EUR per QALY)
Deterministic results					
Blinatumomab	219,950	2.18			
Tisagenlecleucel	376,878	4.33	156,928	2.15	73,086
Mean probabilistic results					
Blinatumomab	219,064	2.31			
Tisagenlecleucel	383,035	4.50	163,971	2.18	75,119
Scenario Analysis[a]					
Parameter/ Assumption	*Base case*	*Scenario*	*Justification*	*Scenario ICER (EUR per QALY) (base case ICER EUR 73,086/QALY)*	
Extrapolation of pooled ELIANA and ENSIGN (Tisagenlecleucel) OS Data	One-knot (odds) spline	Log-normal	60-month OS predicted by log-normal closely aligned with clinical opinion	56,570	
Extrapolation of NCT01471782 (Blinatumomab) OS Data	One-knot (odds) spline	Log-normal	Log-normal model was best fit (AIC and BIC) of standard parametric models	58,262	
Time-point of long-term survival	After 60 months	After 24 months	Majority of patients expected to relapse within 24– 60 months post-treatment (9;10)	60,090	
		No time-point assumed. Long-term survival is based upon full extrapolation of OS and EFS data	Assumption regarding long-term survival is uncertain	129,379	
Standardized mortality ratio	15.5	9.05 (45)	Excess mortality may decrease over time	69,658	
		0.00		63,144	
		15.5 from month 61(11). 4.2 from month 121 (46)		67,407	
Discount rate	4% on costs and outcomes	1.5% (costs and outcomes)	Potential for benefits to be sustained over a long period	55,630	
		4% (costs); 1.5% (outcomes)	Gravelle and Smith propose that the discount rate on health outcomes should be 1– 3.5% lower than that on costs (47)	50,260	
		Hyperbolic (costs and outcomes): 4% (0–30 yr), 3.5% (31–60 yr), 3% (61–100 yr)	Hyperbolic discounting may be applicable when the time horizon exceeds 30 yr (48)	71,887	

[a]Scenario analyses were conducted on deterministic outcomes. Thus, they should be considered indicative only.
ALL, acute lymphoblastic leukemia; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; R/R, relapsed/refractory.

discount on costs), decreased the ICER to less than EUR 45,000 per QALY. This sensitivity to the discount rate on outcomes is expected due to the time divergence between high upfront costs and long-term health outcomes.

Scenario analysis highlighted the impact of changing the time-point (post-treatment) at which patients are considered long-term survivors. A "worst case" (conservative) scenario, which removed the structural assumptions regarding the time-point of long-term survival, had a sizeable impact on the deterministic ICER (approximately EUR 56,000 per QALY increase). The associated probability of cost-effectiveness, at the EUR 45,000 per QALY threshold, was 3 percent. Although simple price reductions on tisagenlecleucel may reduce the ICER to a payer threshold, they do not address the decision uncertainty faced by clinicians, patients, and payers. Performance-linked reimbursement agreements may be valuable in managing the associated financial risk.

The paucity of long-term data was also reflected in uncertainty in the most appropriate survival model. Spline models were chosen (for OS), over standard parametric models, due to their enhanced flexibility. However, the log-normal model was also a reasonable option. Employing this model to extrapolate the OS data of

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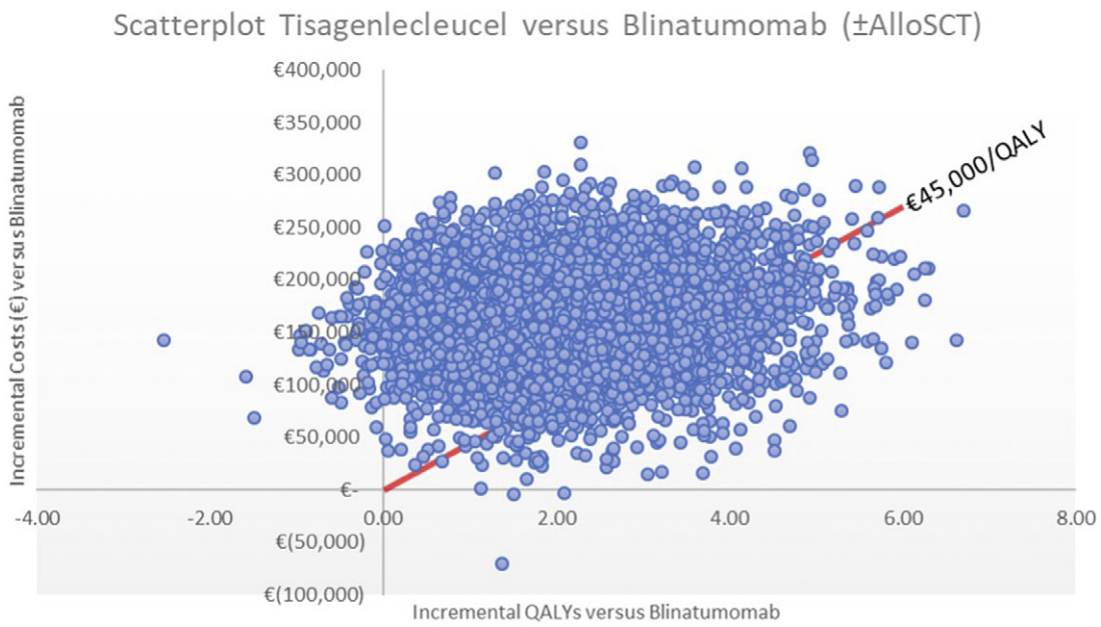

Figure 1. Scatterplot of incremental costs and incremental QALYs from probabilistic analysis of tisagenlecleucel versus blinatumomab (with or without allogeneic stem cell transplant).

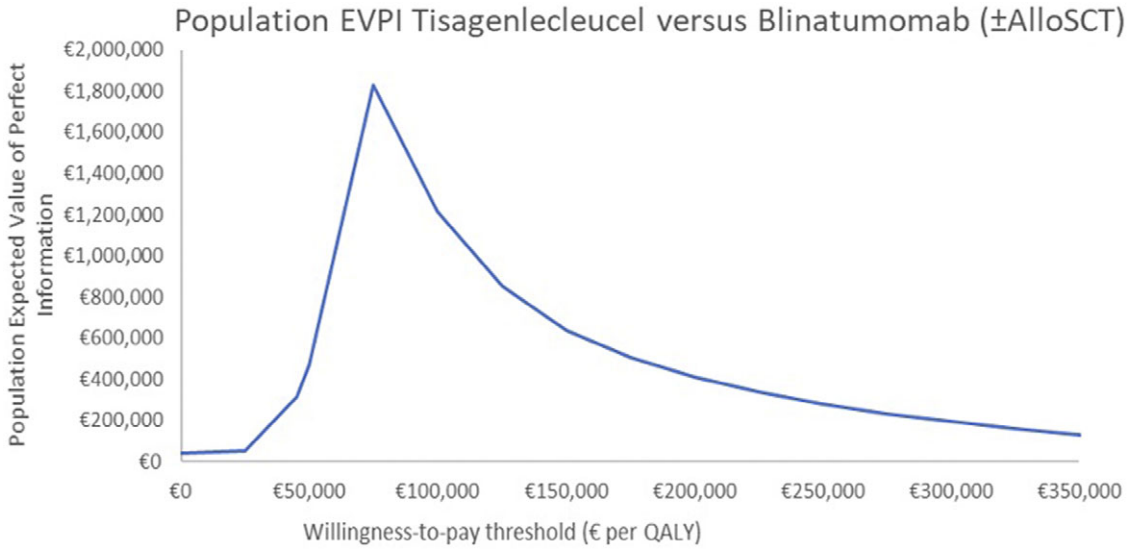

Figure 2. Population expected value of perfect information, over various willingness-to-pay thresholds, of tisagenlecleucel versus blinatumomab (with or without allogeneic stem cell transplant).

tisagenlecleucel decreased the deterministic ICER by approximately EUR 16,500 per QALY. The associated probability of cost-effectiveness, at the EUR 45,000 per QALY threshold, was 27 percent.

EVPI and EVPPI

At list prices, EVPI indicated that the cost of further research should not exceed EUR 314,455. At the population EVPI peak (a threshold of approximately EUR 75,000 per QALY), the probability of cost-effectiveness of tisagenlecleucel was 48 percent. At higher thresholds, the corresponding consequences of decision uncertainty reduce, resulting in a reduction in population EVPI (10). At list prices, parameters associated with survival analysis had the highest population EVPPI. Thus, if further research is conducted, this area should be prioritized.

Population EVPI and EVPPI analyses were rerun at the price of tisagenlecleucel that reduced the ICER to EUR 45,000 per QALY. The 10-year population EVPI, at a EUR 45,000 per QALY threshold, increased considerably. Parameters associated with survival analysis also had the highest population EVPPI in this scenario. There were some changes in the ranking of parameter categories compared to those described at the list price of tisagenlecleucel. Uncertainty associated with the model decision is driven by different categories depending on the cost of tisagenlecleucel and subsequent estimates of cost-effectiveness. The reasons for this change in ranking are not clear. Notably, the top two categories for research prioritization were consistent between the two analyses.

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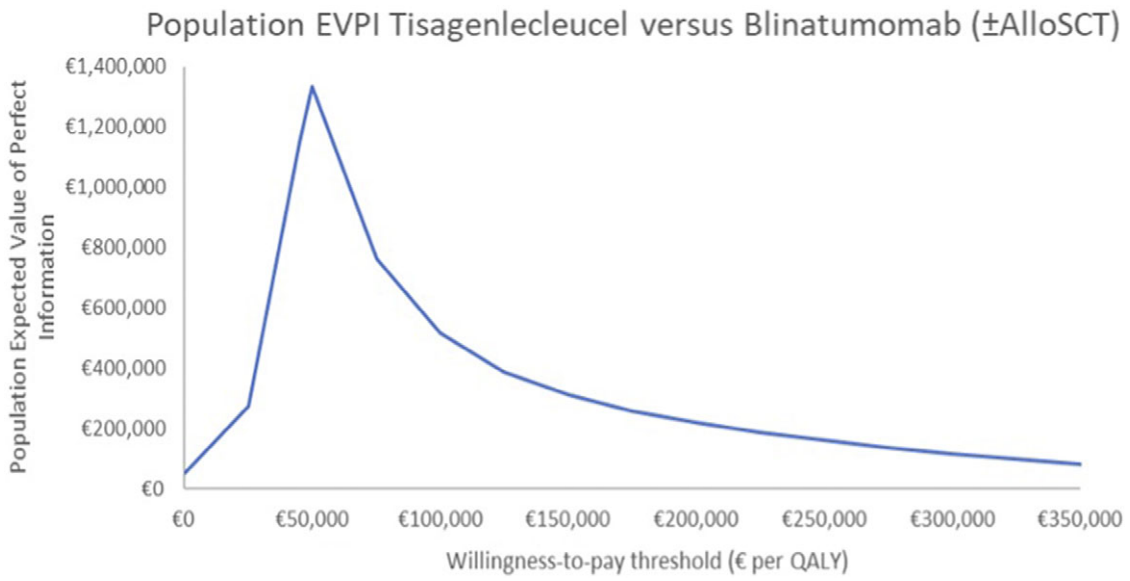

Figure 3. Population expected value of perfect information, over various willingness-to-pay thresholds, of tisagenlecleucel (price that reduced the ICER to EUR 45,000 per QALY) versus blinatumomab (with or without allogeneic stem cell transplant).

Modeled alloSCT costs, in the blinatumomab arm, were based on a higher rate of alloSCT than that observed in NCT01471782 (18); efficacy was derived from the trial. This approach favors tisagenlecleucel. In NCT01471782, data were not presented separately for patients who did and did not proceed to alloSCT, precluding an analysis of survival benefit associated with alloSCT. In the absence of a structural link between alloSCT and survival benefit, it is likely that the EVPPI analysis overstates the impact of uncertainty on alloSCT. This is because stochastic variability on this parameter impacts costs only. Of note, the rate of alloSCT employed in the model is based on clinical opinion and is therefore, subject to uncertainty.

EVPI and EVPPI investigate parameter uncertainty. Structural uncertainties, such as that associated with the naïve comparison, are not investigated. The low EVPI and EVPPI estimates are likely a reflection, to some degree, of the low estimated incidence of the decision (six patients per year).

Comparison with the Literature

The National Centre for Pharmacoeconomics (NCPE Ireland) evaluated a Pharma-Applicant HTA of tisagenlecleucel for this indication (from the perspective of the HSE). Similar to our findings, tisagenlecleucel was not cost effective (vs. blinatumomab); ICERs ranged from EUR 75,748 per QALY (incremental costs EUR 321,755; incremental QALYs 4.25) to EUR 116,506 per QALY (incremental costs EUR 457,033; incremental QALYs 3.92) (29). Thielen et al. evaluated the cost-effectiveness of tisagenlecleucel (vs. blinatumomab) from a Dutch societal perspective, generating an ICER of EUR 31,682 per QALY. Of note, Thielen et al. employed a discount rate of 1.5 percent on outcomes (30). No EVPI analyses were identified in the literature.

Limitations

Patients in the progressed disease state after 60 months were assumed to survive long-term. This was based on clinical opinion. This approach has been accepted by the National Institute for Health and Care Excellence (NICE UK) for reimbursement decision making (8) and has been employed in the literature (14). Mixture cure models are an alternative approach to model long-term survival; this approach was not used here due to the high degree of censoring towards the end of the trial follow-up periods. Mixture cure models cannot reliably estimate a cure fraction under such conditions (49).

Due to model complexity, PSA was conducted only for the base case analyses and key scenarios. Thus, results of OWSA and scenario analyses should be considered indicative only.

No population subgroups were considered due to paucity of published data. Without these data, it is not possible to predict how results might differ between patient subgroups.

Conclusion

At list prices, tisagenlecleucel is not cost effective, versus blinatumomab, for the treatment of pediatric and young adult patients with R/R ALL in Ireland. Although tisagenlecleucel was associated with an incremental QALY gain, the clinical evidence supporting the model was highly uncertain. Population EVPI and EVPPI analyses indicated that further research to decrease decision uncertainty (in parameters), at the defined willingness-to-pay threshold, may not be of value. However, uncertainty in the model may not be adequately captured by OWSA, PSA, and EVPI. Performance-linked reimbursement agreements may be a valuable approach to managing the financial risk associated with this uncertainty.

Medical Subject Headings. Hematologic Neoplasms; Leukemia; and Health Care Economics and Organizations.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S0266462322000356.

Conflicts of Interest. The authors have no conflicts of interest to declare.

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