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## Model Structure



**Supplementary Figure 1 Decision tree depicting outcomes in patients assigned to the tisagenlecleucel arm in cost-utility analysis of tisagenlecleucel for relapsed/refractory acute lymphoblastic leukaemia\***

**AlloSCT:** Allogeneic stem cell transplant; **QALY:** Quality-adjusted life year.



**Supplementary Figure 2 Partitioned survival model depicting outcomes (all treatments) in the cost-utility analysis of tisagenlecleucel for relapsed/refractory acute lymphoblastic leukaemia**

The partitioned survival model simulated the progression of patients through three, mutually exclusive health states: event-free survival, progressed disease, and death. The proportion of patients occupying each health state was determined by the area under the curve of the extrapolated event-free survival (EFS) and overall survival (OS) curves, capturing the main outcomes of the relevant trials. The area under the extrapolated OS curve provides an estimate of mean simulated survival. Health state membership of the event-free survival state is provided by the area under the EFS curve. Health state membership of the death state is estimated by subtracting the area under the OS curve, at each time point, from 1. The proportion of patients in the progressed disease state is derived as the difference between the OS and EFS curve at each time point. Differences between interventions were modelled by using different EFS and OS curves for each treatment (1).

## Clinical Trials Informing Cost-Utility Model

**Supplementary Table 1 Summary of trials informing the cost-utility model**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Title  | Trial Design | Key Eligibility Criteria | Intervention (sample size) | Key Outcomes |
| ELIANA (2, 3) | Phase II, single-arm, open-label, multi-centre  | Age: 3-21 yrs inclusiveCD19+, Primary refractory\*, chemorefractory†, or relapsed disease‡Karnofsky (≥16 yrs) or Lansky (<16 yrs) status ≥50%BM ≥5% lymphoblasts | Tisagenlecleucel; once-off single IV infusion (mITT n=75)Patients ≤50kg: 2.0 - 5.0 x 106 /kg Patients >50kg: 1.0 - 2.5 x 108  | **Primary:** ORR**Key Secondary:** EFS, OS |
| ENSIGN (4) | Phase II, single-arm, open-label, multi-centre  | Aged 3-21 yrs inclusivePrimary refractory\*, chemorefractory†, or relapsed disease§,Karnofsky (≥16 yrs) or Lansky (<16 yrs) status ≥50%BM ≥5% lymphoblasts | Tisagenlecleucel; once-off single IV infusion (mITT n=64)Patients ≤50kg: 2.0 to 5.0 x 106 /kg for Patients >50kg: 1.0 - 2.5 x 108  | **Primary:** ORR**Key Secondary:** RFS, OS |
| NCT01471782  (5, 6) | Phase I dose-finding Phase II: single-arm, open-label, multi-centre  | <18 years* + Relapsed| or refractory¶ disease

Karnofsky or Lansky (age <16 years) performance status ≥50%BM >25% lymphoblasts  | Blinatumomab IV infusion (n=70) Phase I: doses ranged between 5mcg/m2/day and 30mcg/m2/day.Phase II: stepwise 5/15 mcg/m2/day; 4-week continuous IV infusion, followed by a 2-week treatment-free intervalPatients achieving CR within the first 2 cycles could receive up to 3 more or be withdrawn from treatment to receive chemotherapy or alloSCT | **Phase I:** max. tolerated dose**Phase II:** **Primary -**CR within the first two cycles. **Secondary-** RFS, OS |

**ALL:** Acute lymphoblastic leukaemia; **AlloSCT:** Allogeneic stem-cell transplant**; BM:** Bone marrow**; CR:** Complete response; **EFS:** Event-free survival; **IV**: Intravenous; **mITT:** Modified intention-to-treat; **ORR:** Overall remission rate; **OS:** Overall survival; **RFS:** Relapse-free survival; **R/R:** Relapsed/refractory.

\*Defined as not achieving CR after 2 cycles of a standard chemotherapy regimen.

†Defined as not achieving CR after 1 cycle of standard chemotherapy for relapsed leukaemia.

‡Defined as second or greater bone marrow relapse, or any bone marrow relapse after alloSCT and ≥6 months from SCT at the time of tisagenlecleucel infusion.

§Defined as second or greater bone marrow relapse, or any bone marrow relapse after alloSCT and >6 months from SCT at the time of tisagenlecleucel infusion.

|Defined as second or later bone marrow relapse, or any bone marrow relapse after alloSCT and >3 months from SCT at the time of blinatumomab infusion.

¶Patients in first relapse must have failed to achieve a CR following full standard reinduction chemotherapy regimen of at least 4 weeks duration. Patients who have not achieved a first remission must have failed a full standard induction regimen.

## Blinatumomab Dosing Schedule

**Supplementary Table 2 Dosing regimen of blinatumomab, as per the National Cancer Control Programme Chemotherapy Regimen (7, 8)**

|  |  |  |
| --- | --- | --- |
| Patient Weight | Cycle 1 | Subsequent Cycles |
| Days 1-7 | Days 8-28 | Days 29-42 | Days 1-28 | Days 29-42 |
| <45kg (BSA-based dose)\* | 5 mcg/m2/day (not to exceed 9 mcg/day) | 15 mcg/m2/day (not to exceed 28 mcg/day) | 14 day treatment free interval | 15 mcg/m2/day (not to exceed 28 mcg/day) | 14 day treatment free interval |
| ≥45kg (fixed-dose) | 9 mcg/day | 28 mcg/day | 28 mcg/day |

**BSA:** Body surface area

## Efficacy Data

Mixture cure models were examined; however, they were not considered for inclusion in the model. The fitting of mixture cure models relies on a number of assumptions, mainly that the data are sufficiently mature and robust to reliably estimate a cure fraction. A mixture cure model is also only appropriate in cases where a true cure fraction exists and ‘cure’ is a reasonable assumption at a given time point. The NICE Decision Support Unit Technical Support Document 21 indicates that in order to reliably estimate the cure fraction, sufficient numbers at risk are required in the tail of the distribution (9). This is a particular concern with the ELIANA trial data, whereby eight patients were at risk at 18 months and zero were at risk at 22 months (2). These data are highly censored. The same concern arises with the blinatumomab trial data, with 14 patients at risk at 22 months, reducing to 6 at 24 months (5). As such, it is not reasonable to impose a statistical assumption of cure based on such limited data. The follow-up period of the ELIANA and ENSIGN trial data is not sufficiently long to determine whether a true ‘cure’ fraction exists.

### Overall Survival AIC and BIC Statistics

**Supplementary Table 3 AIC and BIC statistics of standard parametric models used in the extrapolation of overall survival in bespoke cost-utility model for R/R ALL in paediatric and young adult patients\***

|  |
| --- |
| Overall Survival |
|  | **ELIANA\_ENSIGN Pooled (tisagenlecleucel)** | **NCT01471782** **(blinatumomab ± alloSCT)** |
|  | **AIC** | **BIC** | **AIC** | **BIC** |
| Gompertz | 451.8 | 457.7 | 342.2 | 346.7 |
| Exponential | **449.8** | **452.8** | 345.3 | 347.5 |
| Weibull | 451.8 | 457.7 | 346.2 | 350.7 |
| Log-logistic | 452.3 | 458.1 | 340.9 | 345.4 |
| Log-normal | 453.7 | 459.6 | **339.3** | **343.8** |
| Generalised gamma | 453.7 | 462.5 | 340.4 | 347.1 |

**ALL:** Acute lymphoblastic leukaemia; **AlloSCT:** Allogeneic stem cell transplant; **R/R:** Relapsed/refractory.

\*The lowest AIC and BIC statistics for each data set are highlighted in Bold.

**Supplementary Table 4 AIC and BIC statistics of spline models used in extrapolation of overall survival in bespoke cost-utility model for R/R ALL in paediatric and young adult patients\***

|  |
| --- |
| Overall Survival |
|  | **ELIANA\_ENSIGN pooled (tisagenlecleucel)** | **NCT01471782****(blinatumomab ± alloSCT)** |
|  | **AIC** | **BIC** | **AIC** | **BIC** |
| 1 Knot Spline (Hazard) | 453.7 | **462.5** | 340.7 | 347.4 |
| 1 Knot Spline (Odds) | 454.9 | 462.7 | 340.6 | 347.3 |
| 1 Knot Spline (Normal) | **453.2** | 463.0 | **340.4** | **347.1** |
| 2 Knot Spline (Hazard) | 455.6 | 467.4 | 342.7 | 351.7 |
| 2 Knot Spline (Odds) | 456.2 | 468.0 | 342.5 | 351.5 |
| 2 Knot Spline (Normal) | 455.9 | 467.6 | 342.4 | 351.4 |
| 3 Knot Spline (Hazard) | 457.7 | 472.3 | 344.4 | 355.6 |
| 3 Knot Spline (Odds) | 458.2 | 472.9 | 344.0 | 355.2 |
| 3 Knot Spline (Normal) | 457.9 | 472.5 | 343.9 | 355.1 |

**ALL:** Acute lymphoblastic leukaemia; **AlloSCT:** Allogeneic stem cell transplant; **R/R:** Relapsed/refractory.

\* The lowest AIC and BIC statistics for each data set are highlighted in Bold.

### Event-Free Survival AIC and BIC Statistics

**Supplementary Table 5 AIC and BIC statistics of standard parametric models used in extrapolation of event-free survival in bespoke cost-utility model for R/R ALL in paediatric and young adult patients**†

|  |
| --- |
| Event-Free Survival\* |
|  | **ELIANA (tisagenlecleucel)** |
|  | **AIC** | **BIC** |
| Gompertz | 217.3 | 222.0 |
| Exponential | 217.0 | 219.3 |
| Weibull | 204.2 | 208.9 |
| Log-logistic | 206.2 | 210.8 |
| Log-normal | 208.0 | 212.6 |
| Generalised gamma | **200.8** | **208.7** |

**ALL:** Acute lymphoblastic leukaemia; **R/R:** Relapsed/refractory.

\*EFS of blinatumomab was derived by assuming that the cumulative hazard function for EFS is proportional to the cumulative hazard function for OS. The ratio between EFS and OS (0.88) was estimated based on the Kuhlen et al. (FLA-IDA) study (10).

†The lowest AIC and BIC statistics for each data set are highlighted in Bold.

**Supplementary Table 6 AIC and BIC statistics of spline models used in extrapolation of event-free survival in bespoke cost-utility model for R/R ALL in paediatric and young adult patients**†‡

|  |
| --- |
| ELIANA (tisagenlecleucel)\* |
|  | **AIC** | **BIC** |
| 1Knot Spline (Hazard) | 202.6 | **209.5** |
| 1 Knot Spline (Odds) | 203.6 | 210.2 |
| 2 Knot Spline (Hazard) | 201.6 | 210.9 |
| 2 Knot Spline (Odds) | **200.6** | 209.8 |

**ALL:** Acute lymphoblastic leukaemia; **R/R:** Relapsed/refractory.

\*EFS of blinatumomab was derived by assuming that the cumulative hazard function for EFS is proportional to the cumulative hazard function for OS. The ratio between EFS and OS was estimated based on the Kuhlen et al. study (10).

†The lowest AIC and BIC statistics for each data set are highlighted in Bold.

‡Three-knot spline models and normal scale spline models not included due to overfitting.

### Survival Model Extrapolations

**Tisagenlecleucel:** Of the standard parametric models, the log-normal and log-logistic were deemed most appropriate, to extrapolate the pooled ELIANA and EINSIGN trial data, based on AIC and BIC statistics, visual fit and clinical plausibility. The one-knot spline models were considered to be the most appropriate of the spline models, based on marginally more favourable AIC and BIC statistics and visual fit (when compared to the two- and three-knot spline models). The long-term OS outcomes predicted by the spline models were closely aligned across all scales and number of knots. The predicted OS outcomes (up to month 60) and Kaplan-Meier curve of the pooled ELIANA and ENSIGN trial data are presented in Supplementary Figure 3.



**Supplementary Figure 3 Tisagenlecleucel overall survival extrapolation predictions of 'best fitting' standard parametric and spline models**

**Blinatumomab:** Examining the extrapolations of the NCT01471782 data, all models exhibited long tails in the long-term OS extrapolations (Supplementary Figure 4). The log-normal and log-logistic models appear to underestimate OS slightly towards the end of the observed follow-up period. Due to the small number of patients left at risk from month 14 onwards (n=5), judgements based on model fit to the tail of the blinatumomab Kaplan-Meier data are unreliable. The one-knot (odds) spline model had the most favourable OS extrapolation to month 60.



**Supplementary Figure 4 Blinatumomab overall survival extrapolation predictions of 'best fitting' standard parametric and spline models**

For the base case analysis, the one-knot (odds) spline model was chosen to extrapolate the tisagenlecleucel and blinatumomab OS trial data. Although this model appeared to overestimate OS of tisagenlecleucel, the model predictions at 60 months were slightly lower than those judged by the experts consulted in the expert elicitation exercise; 28% and 33%, respectively. The one-knot (odds) spline model provided a reasonable fit to the blinatumomab data and the 60-month OS predictions were aligned with those judged by the experts.



**Supplementary Figure 5 60-month event-free survival and overall survival predictions for tisagenlecleucel**



**Supplementary Figure 6 60-month event-free survival and overall survival predictions for blinatumomab**

## Utility Inputs

**Supplementary Table 7 Systematic literature review of utility data for relapsed/refractory acute lymphoblastic leukaemia) search strategy**

|  |
| --- |
| **EMBASE 09 January 2021** |
| #1 'acute lymphoblastic leukemia'/exp OR 'acute lymphoblastic leukemia' OR 'acute lymphoblastic leukaemia'/exp OR 'acute lymphoblastic leukaemia' OR 'acute lymphoblast\*'#2 relapsed OR relapses OR relapsing OR refractory OR failed OR failure#3 infan\*:ab,ti OR newborn\*:ab,ti OR 'new born':ab,ti OR 'new borns':ab,ti OR baby\*:ab,ti OR babies:ab,ti OR neonat\*:ab,ti OR child\*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler\*:ab,ti OR adoles\*:ab,ti OR teen\*:ab,ti OR minors\*:ab,ti OR underag\*:ab,ti OR 'under age':ab,ti OR 'under aged':ab,ti OR juvenil\*:ab,ti OR youth\*:ab,ti OR puber\*:ab,ti OR pubescen\*:ab,ti OR prepubescen\*:ab,ti OR pediatric\*:ab,ti OR paediatric\*:ab,ti OR peadiatric\*:ab,ti OR 'young adult'#4 #1 AND #2 AND #3#5 'european quality of life 5 dimensions questionnaire' OR 'eq-5d' OR 'eq 5d' OR 'eq5d' OR 'euroqol' OR 'eq5d\*'#6 'standard gamble' OR 'sg' OR 'time trade off' OR 'time trade-off' OR 'time tradeoff' OR 'tto#7 utilit\* OR "health utilit$" OR "health state$ utilit$" OR "health state$ utilit$ value$" OR 'hsu' OR 'hsuv'#8 exp AND quality AND of AND life#9 'quality-adjusted life year' OR 'quality adjusted life year'#10 'health-related quality of life' OR 'health-related quality-of-life' OR 'health related quality of life' OR 'health related quality-of-life' OR 'hrqol'#11 (((((((((((sf36 OR sf) AND 36 OR short) AND form AND 36 OR shortform) AND 36 OR short) AND form36 OR shortform36 OR sf) AND thirtysix OR sfthirtysix OR sfthirty) AND six OR sf) AND thirty AND six OR shortform) AND thirtysix OR shortform) AND thirty AND six OR short) AND form AND thirtysix OR short) AND form AND thirty AND six#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11#13 #4 AND #12#14 #4 AND #12 AND [humans]/lim AND [english]/lim AND [embase]/lim AND [2000-2021]/py |
| **MEDLINE (via EBSCO)** |
| S1 'acute lymphoblastic leukemia'/exp OR 'acute lymphoblastic leukemia' OR 'acute lymphoblastic leukaemia'/exp OR 'acute lymphoblastic leukaemia' OR 'acute lymphoblast\*' S2 relapsed OR relapses OR relapsing OR refractory OR failed OR failure S3 ( paediatrics or pediatrics or children or child or young person ) OR ( infants or baby or newborn or neonate ) OR ( minors or youth or children or adolescent or young adult ) S4 S1 AND S2 AND S3 S5 'european quality of life 5 dimensions questionnaire' OR 'eq-5d' OR 'eq 5d' OR 'eq5d' OR 'euroqol' OR 'eq5d\*'S6 'standard gamble' OR 'sg' OR 'time trade off' OR 'time trade-off' OR 'time tradeoff' OR 'tto'S7 ( "European organization for research and treatment of cancer" ) OR eortc qlq-c30S8 "The pediatric quality of life inventory" OR PedsQLS9 functional assessment of cancer therapy - general OR fact-gS10 ((((((((((sf36 OR sf) AND 36 OR short) AND form AND 36 OR shortform) AND 36 OR short) AND form36 OR shortform36 OR sf) AND thirtysix OR sfthirtysix OR sfthirty) AND six OR sf) AND thirty AND six OR shortform) AND thirtysix OR shortform) AND thirty AND six OR short) AND form AND thirtysix OR short) AND form AND thirty AND sixS11 quality of life OR ( quality of life or well being or well-being or health-related quality of life ) OR qol OR ( hrqol or health-related quality of life )S12 quality adjusted life years OR qaly OR qaly analysisS13 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12S14 S4 AND S13S15 S14 Limit to articles on human subjects. S16 S15 Limit to articles published in EnglishS17 S16 Limit to articles published from January 01 2000 |
| **CENTRAL (via Cochrane Library)** |
| #1 MeSH descriptor: [Leukemia] explode all trees#2 acute lymphoblastic leukaemia OR ACUTE LYMPHOBLASTIC LEUKEMIA OR LYMPHOBLAST#3 relapsed OR relapses OR relapsing OR refractory OR failed OR failure#4 #1 AND #2 and #3#5 'european quality of life 5 dimensions questionnaire' OR 'eq-5d' OR 'eq 5d' OR 'eq5d' OR 'euroqol'#6 "standard gamble" OR 'sg' OR 'time trade off' OR 'time trade-off' OR 'time tradeoff' OR 'tto'#7 "European organization for research and treatment of cancer" OR eortc qlq-c30#8 "The pediatric quality of life inventory" OR PedsQL#9 "functional assessment of cancer therapy general" OR "fact g"#10 "SF36" OR "short form 36"#11 quality of life OR ( quality of life or well being or wellbeing or health-related quality of life ) OR qol OR ( hrqol or health-related quality of life )#12 quality adjusted life years OR qaly OR qaly analysis#13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12#14 #13 AND #4#15 #14 with Cochrane Library publication date Between Jan 2000 and Jan 2021 |

**Supplementary Table 8 Utility values used in the bespoke cost-utility model of tisagenlecleucel for R/R ALL in paediatric and young adult patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Value (SE) | Source  | Duration (days) | Proportion |
| Event-Free Survival  | 0.80 (0.23) | EQ-5D-3L collected in ELIANA trial with the UK valuation set applied, identified through HTA appraisal published by NoMA (11) | Duration spent in health state | 100% of patients in state |
| Progressed Disease  | 0.63 (0.36) |
| All Patients Alive after 60 Months | 0.80 (0.23) | Assumption. HTA submission appraisals (11-13), Hettle et al. (14), HTA evaluation (15) | Duration of survival | 100% of patients |
| Apheresis | -0.202 (0.006) | Kwon et al. (16) | 0.5 | 100% of patients in tisagenlecleucel arm |
| Bridging Chemotherapy | 21 | 88% of patients who received tisagenlecleucel (2, 4), and 50% of those who did not proceed to infusion\* |
| Lymphodepleting Chemotherapy | 4 | 95% of patients who received tisagenlecleucel (2), and 50% of those who did not proceed to infusion\* |
| CRS ICU Admission Tisagenlecleucel | -0.80 (0.23) | Assumption. HTA submission appraisals (11, 12, 17), Hettle et al. (14), HTA evaluation (15) | 8 (3) | 47% of patients who received tisagenlecleucel (3) |
| CRS ICU Admission Blinatumomab | Assumption | 5 (6) | 5.7% of patients who received blinatumomab (6) |
| Non-CRS ICU Admission Tisagenlecleucel | Assumption. HTA submission appraisal CADTH (17) | 1.78 (17) | 90% of patients who received tisagenlecleucel (3, 4, 17) |
| Febrile Neutropenia  | -0.15 (0.04†) | Assumption | 7‡ | 36% of patients who received tisagenlecleucel (2, 4)17% of patients who received blinatumomab (5) |
| Pancytopenia | 182.4§ | 3% of patients who received tisagenlecleucel (3) |
| AlloSCT (0- 3 months)  | -0.20 (0.05†) | Forsythe et al. (18)  | 91.2 (12) | 49%‡ of patients who received blinatumomab |
| AlloSCT (4-12 months post-alloSCT) | -0.13 (0.16) | Felder-Puig et el. (19) | 273.6 (12) |

**ALL:** Acute lymphoblastic leukaemia; **AlloSCT:** Allogeneic stem cell transplant;; **CRS:** Cytokine release syndrome; **ICU:** Intensive care unit; **N/A:** Not applicable; **R/R:** Relapsed/refractory; **SE:** Standard error,

\*83% of patients in the tisagenlecleucel arm proceeded to infusion.

†Assumed 25% of mean point estimate.

‡Based on clinical opinion.

§Assumption.

## Cost Inputs

### Training

Staff costs were estimated as per the National Guidelines for the Economic Evaluation of Health Technologies in Ireland (20). The formula used to estimate the per patient cost of training, presented below, was derived from the HTA submission appraisal of axicabtagene ciloleucel published by NICE (21). The expected number of patients to be treated per centre per year was estimated to be six. The expected number of years before healthcare professionals require retraining was assumed to be two (21).

**Supplementary Table 9 Estimated staff training requirements for implementation of tisagenlecleucel for R/R ALL in paediatric and young adult patients**

|  |  |  |
| --- | --- | --- |
| Role | Number Trained  | Source |
| Consultant haematologist (Attending) | 4 | Assumption |
| Non-consultant hospital doctor (Fellow) | 1 | Assumption |
| Consultant intensivist (Attending) | 1 | Assumption\* based on adverse event profile of tisagenlecleucel |
| Consultant neurologist (Attending) | 1 | Assumption\*based on adverse event profile of tisagenlecleucel |
| Advanced practice registered nurse | 2 | Assumed that advanced practice registered nurse, specialising in the treatment of leukaemia, at Children’s Health Ireland at Crumlin will receive training. Also includes the CAR T-cell therapy co-ordinator.  |
| Nurses | 10 | Assumption nursing staff will be providing monitoring of patient |
| Pharmacist | 3 | Assumption based on need for pharmacy to be involved in bridging chemotherapy, lymphodepleting chemotherapy, receipt and adverse event management of tisagenlecleucel (22) |
| Laboratory | 2 | Assumption\* based on need for laboratory staff to be involved in receipt and storage of tisagenlecleucel (22) |

\*Assumed that these staff members receive 8 hours training (instead of 16) as they are involved only in specific aspects of the CAR T-cell therapy process.

**Supplementary Table 10 Cost breakdown of staff training costs (23), calculated in line with the National Guidelines for the Economic Evaluation of Health Technologies in Ireland (20).**



$$\frac{Cost per centre}{Number of patients per centre per year × Number of years before retraining}$$

### Drug Acquisition Costs

All drug acquisition costs were calculated in line with National Centre for Pharmacoeconomics Ireland guidelines (23).

**Supplementary Table 11 Total, per patient, cost of bridging chemotherapy.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (12, 25) | PTW (€) | Mark-Up 8% (€) | Reimbursement Price\* (€) | Pharmacy Fees (€) | Strength (mg) | Cost/Unit | Cost/Cycle† | Cost Source |
| Mercaptopurine | CDS | 72mg/m2 orally daily for 3 weeks | 57.39 | 4.59 | 61.98 | 5.48 | 1,250 | 0.05 | 107.71 | IPHA Price Realignment 2019 (26) |
| Dexamethasone | CDS | 6mg/m2 orally daily for 5 days | 12.71 | 1.02 | 13.73 | 5.48 | 200 | 0.10 | 3.81 | PCRS List of Reimbursable Items (27) |
| Oral Methotrexate | CDS | 20mg/m2 orally once weekly for 2 weeks | 12.14 | 0.97 | 13.11 | 5.48 | 250 | 0.07 | 3.93 | PCRS List of Reimbursable Items (27) |
| Vincristine | Hospital | 1.5mg/m2 IV weekly for 1 week | 85.04 | 0 | 85.04 | 0 | 10 | 0.85 | 17.01‡ | IPHA Price Realignment 2018 (28) |
| Intrathecal Methotrexate | CDS | 12mg on day 1 of week 3 administered intrathecally | 17.96 | 1.44 | 19.40 | 5.48 | 12.5 | 0.78 | 24.88§ | IPHA Price Realignment October 2020 (29) |
| Co-trimoxazole | CDS | 480mg orally twice weekly for 3 weeks | 12.17 | 0.97 | 13.14 | 5.48 | 48,000 | 0.01 | 2.23 | PCRS List of Reimbursable Items (27) |
| Total | 159.56 |

**CDS:** Community Drug Scheme; **IPHA:** Irish PharmaceuticalHealthcare Association; **IV:** Intravenous; **PCRS:** Primary Care Reimbursement Service; **PTW:** Price-to-wholesaler.

\*Rebate at 5.5% not applicable as all agents off-patent.

†Assuming mean body surface area of 1.32m2, where applicable.

‡Available in pack size of 5x2mg vial. One vial required per cycle (€85.04/5=€17.01).

**Supplementary Table 12 Total, per patient, cost of lymphodepleting chemotherapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (30) | PTW (€) | Reimbursement Price\* (€) | Strength/ Vial (mg) | Number of Vials Required/Cycle*†* | Cost/Cycle | Cost Source |
| Fludarabine | Hospital | 30mg/m2 IV once daily for 4 days | 77.15 | 77.15 | 50 | 4 | 308.60 | NCPE Internal Cost Database |
| Cyclophosphamide | Hospital | 500mg/m2 IV once daily for 2 days | 26.46 | 26.46 | 500 | 4 | 105.84 | NCPE Internal Cost Database |
| Total | 414.44 |

**IV:** Intravenous; **NCPE:** National Centre for Pharmacoeconomics; **PTW:** Price-to-wholesaler.

\*Mark-up (8%) and pharmacy fees not applicable as both agents are hospital products. Rebate (5.5%) not applicable as both agents off-patent.

† Assuming mean body surface area of 1.32m2.

**Supplementary Table 13 Total, per patient, cost per treatment course of blinatumomab based on body surface area dosing regimen\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (7, 8) | PTW (€)(29) | Rebate 5.5% (€) | Reimbursement Price | Number of vials required (8) | Total Cost | Total Cost per treatment course |
| Cycle 1 |
| Blinatumomab Days 1-7 | Hospital | 5mcg/m2/day | 2,551.51 | 140.33 | 2,411.18 | 2 | 4,822.35 | 40,990.01 |
| Blinatumomab Days 8-28  | 15mcg/m2/day | 2,551.51 | 140.33 | 2,411.18 | 15 | 36,167.65 |
| Cycle 2 |
| Blinatumomab Days 1-28 | Hospital | 15mcg/m2/day | 2,551.51 | 140.33 | 2,411.18 | 20 | 48,223.54 | 48,223.54 |
| Total |  |  |  |  |  |  |  | 89,213.55 |

**PTW:** Price to wholesaler.

\*Assumes alternate infusion durations of 72- and 96-hours over the cycle period (31)

**Supplementary Table 14 Total, per patient, cost per treatment course of blinatumomab based on fixed-dose regimen\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (7, 8) | PTW (€)(29) | Rebate 5.5% (€) | Reimbursement Price | Number of vials required (8) | Total Cost | Total Cost per Treatment Course |
| Cycle 1 |
| Blinatumomab Days 1-7 | Hospital | 9mcg/day | 2,551.51 | 140.33 | 2,411.18 | 3 | 7,233.53 | 57,868.25 |
| Blinatumomab Days 8-28  | 28mcg/day | 2,551.51 | 140.33 | 2,411.18 | 21 | 50,634.72 |
| Cycle 2 |
| Blinatumomab Days 1-28 | Hospital | 28mcg/day | 2,551.51 | 140.33 | 2,411.18 | 28 | 67,512.95 | 67,512.95 |
| Total |  |  |  |  |  |  |  | 125,381.20 |

**PTW:** Price to wholesaler.

**\***Assumes alternate infusion durations of 72- and 96-hours over the cycle period (31)

### Monitoring and Follow-Up

**Supplementary Table 15 Total, per patient, monitoring costs associated with blinatumomab**

|  |
| --- |
| Drug Monitoring Costs |
| Item | **Reference** | **Resource Use** | **Frequency (per cycle)** | **Unit Cost (€)** | **Total Cost****(€; 2020)** | **Cost Reference (currency; year)** |
| Blinatumomab |
| Coagulation Screen | NCCP (7) | 1 | 8 | 7.85 | 62.80 | Murphy et al. (£; 2014) (32) |
| Complete Blood Count | 1 | 4 | 8.43 | 33.72 | O’Brien et al. (€; 2013) (33) |
| Liver Profile | 1 | 4 | 12.42 | 49.68 | NCPE Internal Cost Database(€; 2018) |
| Neurological Observation | 4 | 168 | 0 | 0 | Assumed to be accounted for in cost of consultant visit and parent-assessed |
| Renal Profile | 1 | 4 | 7.79 | 31.16 | O’Brien et al. (€; 2013) (33) |
| Uric Acid | 1 | 1 | 20.94 | 20.94 | NCPE Internal Cost Database(€; 2020) |
| Total (per 42 day cycle) | 198.30 |

**NCCP:** National Cancer Control Programme; **NCPE:** National Centre for Pharmacoeconomics.

**Supplementary Table 16 Per patient health-state monitoring costs**

|  |
| --- |
| Event-Free Survival Health State |
| Requirement | **Reference** | **Resource Use** | **Frequency (per year)** | **Unit Cost (€)** | **Total Cost** **(€; 2020)** | **Cost Reference (currency; year)** |
| Month 1-12 Inclusive (Every 2 Months) |
| Consultant Appointment | NCCN (34) | 1 | 6 | 136.76  | 820.56  | Irish HSE DRG List (€; 2013) (35) |
| Complete Blood Count | 1 | 6 | 8.43 | 50.58  | O’Brien et al. (€; 2013) (33) |
| Liver Profile | 1 | 6 | 12.42 | 74.52  | NCPE Internal Cost Database(€; 2018) |
| Quantitative Immunoglobulin (tisagenlecleucel only) | Yakoub-Agha et al. (22) | 1 | 6 | 55.87 | 335.23 |
| Serum Protein Electrophoresis (tisagenlecleucel only) | 1 | 6 | 18.62 | 111.74 |
| Month 13-24 Inclusive (Every 4 Months) |
| Consultant Appointment | NCCN (34) | 1 | 3 | 136.76  | 410.28  | Irish HSE DRG List(€; 2013) (35) |
| Complete Blood Count | 1 | 3 | 8.43  | 25.29  | O’Brien et al. (€; 2013) (33) |
| Quantitative Immunoglobulin (tisagenlecleucel only) | Yakoub-Agha et al. (22) | 1 | 3 | 55.87 | 167.61 | NCPE Internal Cost Database(€; 2018) |
| Serum Protein Electrophoresis (tisagenlecleucel only) | 1 | 3 | 18.62 | 55.87 |
| Month 25-60 Inclusive (Every 6 Months) |
| Consultant Appointment | NCCN (34) | 1 | 2 | 136.76  | 273.52  | Irish HSE DRG List(€; 2013) (35) |
| Complete Blood Count | 1 | 2 | 8.43  | 16.86  | O’Brien et al. (€; 2013) (33) |
| Quantitative Immunoglobulin (tisagenlecleucel only) | Yakoub-Agha et al. (22) | 1 | 2 | 55.87 | 111.74 | NCPE Internal Cost Database(€; 2018) |
| Serum Protein Electrophoresis (tisagenlecleucel only) | 1 | 2 | 18.62 | 37.25 |
| Month 61 Onwards |
| Consultant Appointment | NCCN (34) | 1 | 1 | 136.76 | 136.76 | Irish HSE DRG List (€; 2013 (35) |
| Complete Blood Count | 1 | 1 | 8.43 | 8.43 | O’Brien et al. (€; 2013) (33) |
| Quantitative Immunoglobulin (tisagenlecleucel only) | Yakoub-Agha et al. (22) | 1 | 1 | 55.87 | 55.87 | NCPE Internal Cost Database(€; 2018) |
| Serum Protein Electrophoresis (tisagenlecleucel only) | 1 | 1 | 18.62 | 18.62 |

**DRG:** Diagnosis-related group; **EFS:** Event-free survival; **HSE:** Health Service Executive; **NCCN:** National Comprehensive Cancer Network; **NCPE:** National Centre for Pharmacoeconomics.

### Adverse Events

#### Tisagenlecleucel

**Supplementary Table 17 Cost breakdown of tocilizumab for the treatment of cytokine release syndrome in patients receiving tisagenlecleucel**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (36) | PTW (€) (37) | Rebate 5.5% (€) | Reimbursement Price\* (€) | Strength/Vial (mg) | Number of Vials Required/Dose*†* | Cost/ Dose | Cost Source |
| Tocilizumab | Hospital | 8mg/kg | 712 | 39.16 | 672.84 | 400 | 1 | 672.84 | MIMS 2020 (37) |

**MIMS:** Monthly Index of Medical Specialities Ireland; **PTW:** Price-to-wholesaler.

\*Mark-up (8%) pharmacy fees not applicable as agent is a hospital product.

†Assuming mean weight of 42.4kg

**Supplementary Table 18 Total, per patient, cost of treating cytokine release syndrome in patients receiving tisagenlecleucel**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Tisagenlecleucel CRS Cost | Cost (€; 2020) | Proportion of patients (%) | Duration (days)/Number of doses | Total Cost (€) |
| ICU Admission | 2797.76(33) | 47 (3) | 8 (3) | 10,519.58  |
| Tocilizumab | 672.84 (37) | 28 (2, 4) | 1.24 (38) | 376.79† |
| Total |  |  |  | 10,896.37 |

**CRS:** Cytokine release syndrome; **ICU:** Intensive care unit.

†Assuming mean weight of 42.4kg. Vial sharing not assumed.

**Supplementary Table 19 Total, per patient, cost of non-CRS ICU admission in patients receiving tisagenlecleucel\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Non-CRS ICU Cost | Cost (€; 2020) | Proportion (%) | Duration (days) | Total Cost (€) |
| Tisagenlecleucel | 2,797.76 (33) | 90 (3, 4) | 1.78 (17) | 4,482.01 |

**CRS:** Cytokine release syndrome; **ICU:** Intensive care unit.

\*Represents the mean ICU length of stay for non-CRS adverse events in the ELIANA trial (17). Assumption aligned with HTA submission appraisals published by NICE (12) and CADTH (17).

**Supplementary Table 20 Total, per patient, cost of treating febrile neutropenia in patients receiving tisagenlecleucel**

|  |  |  |  |
| --- | --- | --- | --- |
| Febrile Neutropenia Cost | Cost (€; 2020) | Proportion (%) | Total Cost (€) |
| Tisagenlecleucel | 9,451.31(33) | 36 (2, 4) | 3,416.75 |

**Supplementary Table 21 Total, per patient, cost of treating pancytopenia in patients receiving tisagenlecleucel\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Pancytopenia Cost | Cost (€; 2020) | Proportion (%) | Duration | Total Cost (€) |
| Tisagenlecleucel | 387(39) | 3(3) | Once/month for 6 months | 69.66 |

\*It was assumed that patients are treated as a one-day daycase, once per month, for the duration of pancytopenia (i.e. 6 months)

**Supplementary Table 22 Total, per patient, adverse event costs associated with tisagenlecleucel (excluding cost of B-cell aplasia)**

|  |  |
| --- | --- |
| Adverse Event | Cost (€; 2020) |
| Cytokine Release Syndrome | 10,896.37 |
| Non-CRS ICU | 4,482.01 |
| Febrile Neutropenia | 3,416.75 |
| Pancytopenia | 69.66 |
| Total | 18,864.79 |

**CRS:** Cytokine release syndrome; **ICU:** Intensive care unit.

**Supplementary Table 23 Total cost per dose, per patient, of intravenous immunoglobulin for the treatment of B-cell aplasia¶**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Reimbursement Scheme (24) | Dose (14) | PTW (€) | Reimbursement Price\* (€) | Strength/Vial (mg) | Number of Vials Required/Dose*†* | Cost/Dose | Cost Source |
| Immunoglobulin | Hospital | 500mg/kg | 65 | 65 | 1,000 | 21‡ | 1,365 | Tertiary Teaching Hospital |

**PTW:** Price-to-wholesaler.

\*Mark-up (8%) pharmacy fees not applicable as agent is a hospital product. Rebate (5.5%) not applicable.

†Assuming mean weight of 42.4kg.

‡Round down to nearest vial as per the General Medical Council (40) and Hettle et al. (14).

**¶**It was assumed that all patients, who received infusion with tisagenlecleucel, in the EFS health state had B-cell aplasia and that 47.1% of these required treatment with intravenous immunoglobulin (11). This may be a reasonable approach considering B-cell aplasia, being a marker for tisagenlecleucel persistence, is correlated to duration of remission.

#### Blinatumomab

**Supplementary Table 24 Total, per patient, cost of treating cytokine release syndrome in patients receiving blinatumomab\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Blinatumomab CRS Cost | Cost (€; 2020) | Proportion of patients (%) | Duration (days) | Total Cost (€) |
| ICU Admission | 2797.76(33) | 5.7 (6) | 5 (6) |  797.36  |

**CRS:** Cytokine release syndrome; **ICU:** Intensive care unit.

\*It was assumed that 5.7% of patients on blinatumomab were admitted to the ICU for a period of five days. This assumption were based on the proportion of patients in NCT01471782 who experienced ‘serious’ CRS (5.7%) and median time to resolution of CRS (five days) (6). As tocilizumab is only licensed for the treatment of CRS associated with CAR T-cell therapy (36), no tocilizumab-associated costs were applied to patients in the blinatumomab arm.

**Supplementary Table 25 Total, per patient, adverse event costs associated with blinatumomab**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Adverse Event | ResourceUse | Cost (€; 2020) | Proportion of Patients (%) (6) | Total Cost (€; 2020) | Cost Source (currency; year) | Justification |
| Anaemia | DRG Q61B (daycase) (Red Blood Cell Disorder INTC)  |  743 | 36 | 267.48 | HPO DRG List (€; 2020) (39) | Hgb<8.0 g/dL; <4.9 mmol/L;<80 g/L; transfusion indicated (41) |
| Thrombocytopenia | Outpatient appointment |  136.76  | 21 | 28.72 | Irish HSE DRG List (R99 OncologyRepeat Attendance) (€; 2013) (35) | Assumed outpatient appointment required. No specific management costs included |
| Hypokalaemia | DRG K64B (Endocrine Disorders MINC) |  2,722 | 17 | 462.74 | HPO DRG List (€; 2020) (39) | <3.0-2.5 mmol/L; hospitalisation indicated (41) |
| Neutropenia | DRG R62B (daycase) (Other Neoplastic Disorder INTC) |  387 | 17 | 65.79 | HPO DRG List (€; 2020) (39) | Assumption |
| Febrile Neutropenia | O’Brien et al.  | 9,451.31(33) | 17(5) | 1,606.72 | O’Brien et al. (33) | O’Brien et al. conducted a microcosting study to evaluate the resource use and cost of hospitalisation for febrile neutropenia from the health-payer's perspective |
| Alanine aminotransferase increased | None |  -  | 16 | 0.00 | N/A | Asymptomatic, detected during drug monitoring and managed through dose reduction/interruption; no additional costs incurred (41) |
| Platelet Count Decreased | Outpatient appointment |  136.76  | 14 | 19.15 | Irish HSE DRG List (R99 OncologyRepeat Attendance) (€; 2013) (35) | Assumed outpatient appointment required. No specific management costs included |
| Neutrophil Count Decreased | Outpatient appointment |  136.76  | 13 | 17.78 | Irish HSE DRG List (R99 OncologyRepeat Attendance) (€; 2013) (35) | Assumed outpatient appointment required. No specific management costs included |
| Aspartate aminotransferase increased  | None |  -  | 11 | 0.00 | N/A | Asymptomatic, detected during drug monitoring and managed through dose reduction/interruption; no additional costs incurred (41) |
| Leukopenia | DRG R62B (daycase) (Other Neoplastic Disorder INTC) |  387  | 10 | 38.70 | HPO DRG List (€; 2020) (39) | Assumption  |
| White blood cell count decreased | Outpatient appointment |  136.76  | 10 | 13.68 | Irish HSE DRG List (R99 ‘OncologyRepeat Attendance’) (€; 2013) (35) | Assumed OPD visit required. No specific management costs included |
| Hypertension | DRG F67A (daycase) (Hypertension) |  484 | 6 | 29.04 | HPO DRG List (€; 2020) (39) | Medical intervention indicated (41)  |
| Total | 2,549.80 |
| Plus cytokine release syndrome (Table 22) | 797.36 |
| Total (EUR) | 3,347.16 |

**DRG:** Diagnosis-related group; **HPO:** Healthcare Pricing Office; **HSE:** Health Service Executive; **OPD:** Outpatient department.

## Cost-Effectiveness Acceptability Curve



**Supplementary Figure 7 Cost-effectiveness acceptability curve of tisagenlecleucel versus blinatumomab in paediatric and young adult patients with R/R ALL**

## One-Way Sensitivity Analysis



**Supplementary Figure 8 Tornado diagram of one-way sensitivity analysis of tisagenlecleucel versus blinatumomab in paediatric and young adult patients with R/R ALL (base case ICER EUR 73,086 per QALY)**

**AlloSCT:** Allogeneic stem cell transplant; **BSA:** Body surface area; **EFS:** Event-free survival; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.

## Scenario Analysis

Scenarios which have the greatest impact on the ICER are highlighted in Bold.

**Supplementary Table 26 Impact of scenario analysis, examining alternative model assumptions, on deterministic ICER of tisagenlecleucel versus blinatumomab in paediatric and young adult patients with R/R ALL\***†

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter/Assumption | Base Case  | Scenario | Justification | Scenario ICER (EUR per QALY)(base case ICER EUR 73,086/QALY) |
| Time Horizon | 88 years | 2 years | Median follow up was 13.1 months in ELIANA (3) & 31.7 months in ENSIGN (4) | **369,621** |
| Proportion of Patients Who Receive Infusion in the Tisagenlecleucel Arm | 83%  | 100%  | Efficacy data in ELIANA & ENSIGN is based on patients who received infusion (i.e. mITT) (2, 4) | 69,253 |
| Extrapolation of ELIANA (Tisagenlecleucel) Event-Free Survival Data | Generalised gamma model | Two-knot (odds) spline model | Two-knot (odds) spline model also have reasonable AIC and BIC statistics, visual fit, and clinical plausibility  | 73,290 |
| Utility of Long-Term Survivors | All patients alive after 60 months assumed utility equivalent to event-free survival health state (0.80) | All patients alive after 60 months assumed utility derived from Kwon et al. (0.90)  | Alternative published utility value (16) | 71,817 |
| Disutility Values Associated with Select Adverse Events | Included | Excluded | Potential for disutility due to adverse events to be captured by health-state utility values | 72,490 |
| Duration of Intravenous Immunoglobulin Treatment | Duration of event-free survival | 11.4 months | Median time to B-cell recovery in ELIANA was 11.4 months (11) | 60,010 |
| Dosing Regimen of Blinatumomab | 50% of patients receive dosing based on body surface area and 50% receive fixed-dosing regimen | 100% receive dosing based on body surface area  | Lack of published data on weight distribution of patients in ELIANA, ENSIGN (tisagenlecleucel), and NCT01471782 (blinatumomab) | 78,012 |
| 100% receive fixed-dosing regimen  | 68,161 |
| Cycles of Blinatumomab Received | 100% of patients receive one cycle, 33% receive a second cycle | 100% of patients receive one cycle, 33% receive a second cycle, 11.4% receive a third cycle, 4.3% receive a fourth cycle, and 4.3% receive a fifth cycle (6) | Up to five cycles permitted in NCT01471782 (6) | 68,037 |
| Tisagenlecleucel Hospitalisation | All patients hospitalised for 24.5 days. 50% of these are subsequently discharged to hospital-associated patient apartments for 4 nights | All patients hospitalised for 29 days | Patients may be hospitalised for a long period considering the innovative nature of tisagenlecleucel | 74,999 |
| Proportion of Patients Receiving AlloSCT in the Blinatumomab Arm | 49% based on expert clinical opinion | 35.7%  | 35.7% of patients received alloSCT in NCT01471782 (6) | 88,443 |
| Proportion of Patients Receiving AlloSCT in the Tisagenlecleucel Arm | 0% based on expert clinical opinion | 12%  | 12% of patients received alloSCT in the pooled ELIANA & ENSIGN data (2, 4) | 85,705 |

**ALL:** Acute lymphoblastic leukaemia; **AlloSCT:** Allogeneic stem cell transplant; **ICER:** Incremental cost-effectiveness ratio; **mITT:** Modified intention-to-treat; **NICE:** National Institute of Health and Care Excellence; **QALY:** Quality-adjusted life year; **R/R:** Relapsed/refractory.

\*Scenarios that have the greatest impact on the ICER are highlighted in Bold.

†Scenario analyses were conducted on deterministic outcomes. Thus, they should be considered indicative only.

## Population Partial Expected Value of Perfect Information



**Supplementary Figure 9 Population partial expected value of perfect information of parameter categories – tisagenlecleucel versus blinatumomab**

**AlloSCT:** Allogeneic stem cell transplant.



**Supplementary Figure 10 Population partial expected value of perfect information of parameter categories – tisagenlecleucel (price that reduced the ICER to €45,000 per QALY) versus blinatumomab**

**AlloSCT:** Allogeneic stem cell transplant.

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