Cost-Effectiveness of Tisagenlecleucel in Paediatric and Young Adults' Relapsed or Refractory B-Cell Acute Lymphobastic Leukaemia, from a Greek Social Security System Perspective

PCN85

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BACKGROUND

- Relapsed/refractory pediatric acute lymphoblastic leukemia (r/r pALL) is the leading cause of cancer-related childhood death.[1,2]
- The overall cure rate of ALL in children is as high as 80%-85% with frontline conventional chemotherapy.[1,3-5] However, approximately 20% of the patients experience relapse[2,4,6,] and 2-3 % of patients do not respond to frontline treatment.[1]
- The prognosis for r/r pALL patients is dismal and allogeneic stem cell transplant (AlloSCT) seems to be the only potentially curative option, but it is limited by eligibility requirements and sub-optimal outcomes in later lines of treatment.[6-9]
- Current treatments used to treat r/r pALL include clofarabine monotherapy, clofarabine combination therapy (CCT), blinatumomab (Blin), and salvage chemotherapy (SC). However, the outcomes with these treatments are sub-optimal and mainly used as bridging therapy for AlloSCT.[10-17]
- Tisagenlecleucel, a CD19-directed genetically modified autologous T-cell immuno-cellular therapy, is approved by European Medicines Agency for paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.[18] Tisagenlecleucel has demonstrated remarkable early, deep, and durable responses with greater than 80% remission rates, and 18-month relapse-free survival and overall survival (OS) rates of 66% and 70%, respectively.[19]

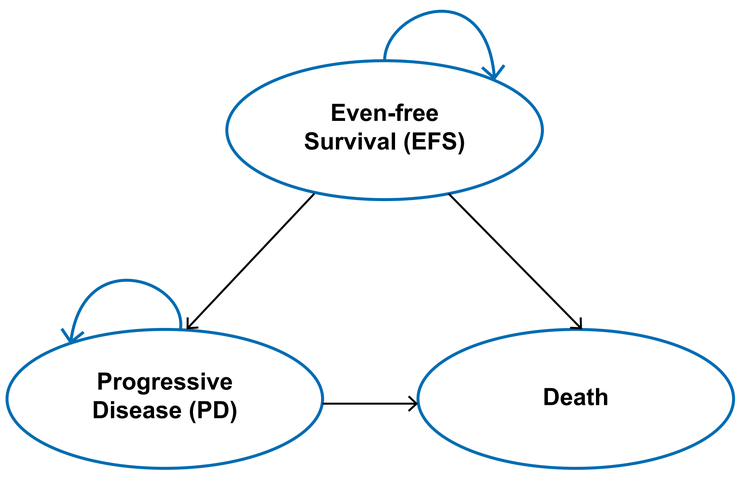
OBJECTIVE

- The current study aimed to assess the cost-utility of tisagenlecleucel in comparison with SC for the treatment of pediatric and young adult ALL patients with relapsed or refractory disease from a Greek social security system perspective.

METHODS

- A partitioned survival model with monthly cycles over a life time horizon (70 years) was developed to assess the cost-effectiveness of tisagenlecleucel in comparison with SC as a base case. CCT and Blin as comparators were briefly assessed in the additional sensitivity analyses.
- The model included 3 health states: event-free survival (EFS), progression and death (**Figure 1**). The estimation of patients occupying each health state was derived from the simulated OS and EFS curves.
- An intent-to-treat (ITT) approach was applied thereby including all enrolled patients (both tisagenlecleucel treated or not treated).
- Efficacy inputs for tisagenlecleucel were derived from the pooled data of three phase I/II single-arm trials (ELIANA: max follow-up of 31.7 months, ENSIGN: max follow-up of 36.5 months and B2101J: max follow-up of 57.5 months)[20-22], while published literature was used to derive efficacy inputs for comparators.[11-17] Subsequent AlloSCT was also considered in the model but not as a distinct health state.

Figure 1. Partitioned survival model structure



- The model conservatively assumed that the alive patients at 5-year will follow survival curve for ALL survivors regardless of treatment arms. OS for SC was derived from hazard ratio (HR) results from matching-adjusted indirect comparison using tisagenlecleucel as reference arm for the period until year 5. The OS derived was further used to estimate EFS for CCT.
- Pre-treatment, treatment costs, follow-up costs, adverse event (AE) costs, subsequent AlloSCT costs, and terminal care costs for each health state were obtained from Greek-specific databases.[23] Only direct costs were considered in the base case analysis (**Table 1**). Utility for each health state and dis-utilities associated with treatment related hospitalization, intensive care unit (ICU) stay, and subsequent AlloSCT were obtained from the literature (**Table 2**).[14,24,25]

Table 1: Summary of average direct costs per patient

Cost	Tisagenlecleucel	SC	CCT	Blin
Pre-treatment	4,088.21 €	0.00 €	0.00 €	0.00 €
Treatment	284,799.90 €	5,684.96 €	29,878.22 €	93,714.36 €
Adverse events	17,294.22 €	3,133.52 €	4,357.92 €	1,439.06 €
Follow-up	2,464.92 €	300.16 €	890.71 €	1,105.83 €
Subsequent AlloSCT	4,626.17 €	12,035.99 €	10,557.37 €	9,566.27 €
Terminal care	473.77 €	704.32 €	674.94 €	664.34 €
Total	313,747.18 €	21,858.96 €	46,359.16 €	106,489.86 €

Blin: Blinatumomab; CCT: Clofarabine combination therapy; AlloSCT: allogeneic stem cell transplant; SC: Salvage chemotherapy

Table 2: Utility values (various published sources)[14,24,25]

Parameter	Utility/Disutility
Health State Utilities (Base-case)	
EFS	0.91
PD	0.75
Treatment Disutilities	
Tisagenlecleucel	-0.42
Salvage chemotherapy	-0.42
Clofarabine combination	-0.42
Blinatumomab	-0.42
Subsequent AlloSCT	-0.57
Other Disutilities (based on assumption)[a]	
ICU stay due to CRS (Tisagenlecleucel)	-0.91
ICU stay not due to CRS (Tisagenlecleucel)	-0.91

CRS: Cytokine Release Syndrome; EFS: event-free survival; ICU: intensive care unit; PD: progressive disease; AlloSCT: allogeneic stem cell transplant; SC: Salvage chemotherapy

[a]The patients are assumed to have 0 utility when they are in ICU. A disutility of -0.91 is estimated based on the complete remission utility. The same disutility is considered for ICU stay due to CRS and ICU stay not due to CRS.

- Incremental life year (LY) and incremental quality-adjusted life year (QALY) gains, and incremental cost-effectiveness ratio (ICER) were estimated comparing tisagenlecleucel with the comparators. The tisagenlecleucel price was explored at the willingness to pay (WTP) threshold of 20,000 €, 30,000 € and 50,000 € per QALY.

RESULTS

- Under an assumption of prolonged EFS with tisagenlecleucel, tisagenlecleucel vs. SC was associated with incremental LY gain of 9.50 years, incremental QALY gain of 8.36 years and ICER of 34,917 € per QALY in the base-case analysis over the lifetime horizon. The results were consistent when tisagenlecleucel was compared with the other two comparators (CCT and Blin) (**Table 3**).

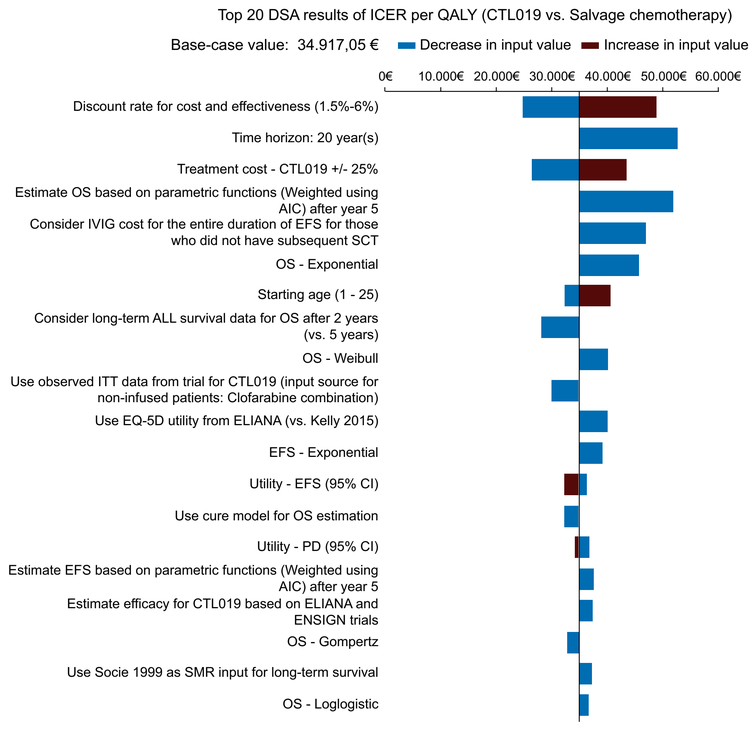
Table 3: Incremental outcomes (tisagenlecleucel vs. comparators)

Incremental Outcomes	Base case	Sensitivity analyses	
	vs. SC	vs. CCT	vs. Blin
Incremental QALY	8.36	7.29	6.91
Incremental costs per QALY gained, ICER	34,917.05 €	36,682.84 €	29,979.92 €

Blin: Blinatumomab; CCT: Clofarabine combination therapy; ICER: Incremental cost-effectiveness ratio QALY: quality-adjusted life year; SC: Salvage chemotherapy

- Further, deterministic sensitivity analyses showed greatest sensitivity to discount rate, time horizon and tisagenlecleucel cost (**Figure 2**).

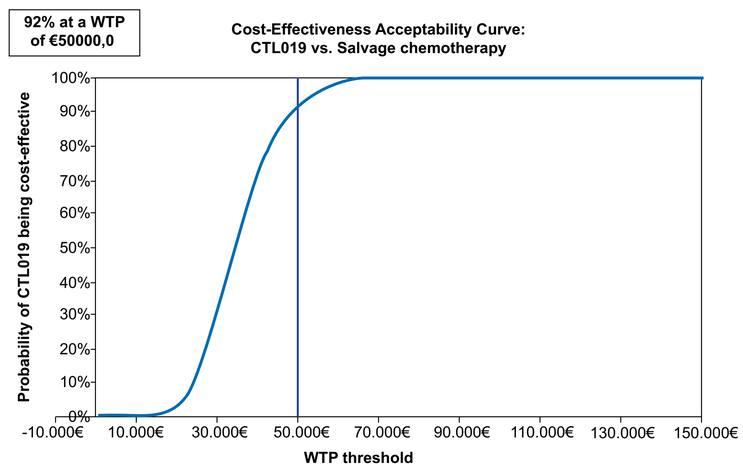
Figure 2: Deterministic sensitivity analysis results (cost per QALY) (Tisagenlecleucel vs. SC)



Key: Mild = Background retinopathy; Moderate = pre-proliferative retinopathy; Severe = maculopathy or proliferative retinopathy; PCS = physical component score; MCS = mental component score; SF 12 = short form -12 score; VI = visual impairment

- The probabilistic sensitivity analyses showed that tisagenlecleucel had a 92% probability of being cost-effective at a WTP threshold of 50,000 € per QALY (**Figure 3**).

Figure 3: Cost-effectiveness plane



LIMITATIONS

- There are inherent differences in the patient populations across different tisagenlecleucel trials which have been pooled together to derive the efficacy and safety data. Furthermore, the tisagenlecleucel studies being single-arm trials, the baseline patient differences are inherent in comparison with baseline patient characteristics from the comparator studies.
- The clinical trial studies for tisagenlecleucel used for the efficacy estimation had limited follow-up. Therefore, results based on extrapolation of efficacy data beyond the trial period in the model should be interpreted with caution.
- EFS data are not reported for comparator arms in their respective publications; EFS for comparators are estimated based on OS assuming a constant cumulative hazard ratio.
- Detailed hospitalization data is observed for tisagenlecleucel from the ELIANA trial, whereas such information is not available for other treatments. Therefore, it is likely the hospitalization duration for other treatments might be underestimated.
- The follow-up cost for tisagenlecleucel patients in remission is estimated based on the clinical trial protocol due to lack of real-world evidence.
- The CRS management cost is estimated based on observed resource utilization among tisagenlecleucel patients with Grade 3/4 CRS. The same cost is assumed for patients treated with Blin who experienced Grade 3/4 CRS. Furthermore, the cost of CRS management could be over-estimated since recently publised real-world evidence reports a much lower rate of grade 3/4 CRS with tisagenlecleucel.[26]

CONCLUSIONS

- Tisagenlecleucel is associated with an ICER of 34,917 € per QALY gained when compared with SC, indicating it is a potentially acceptable cost-effective treatment option for the pediatric and young adult ALL patients with relapsed or refractory disease in Greece. Sensitivity analyses support the findings and contribute to the robustness of the economic case.

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Acknowledgments

The authors acknowledge Nishkarsh Likhar and Mohd Tariq Roomi (Novartis, Hyderabad) for creating the poster content. The final responsibility for the content lies with the authors.

Disclosures

AK is the Director of First Department of Pediatrics, National and Kapodistrian University of Athens, 'Aghia Sophia' Children's Hospital, Athens, Greece, engaged by Novartis (Hellas) S.A.C.I., Greece as a clinical expert for the development of this work; AGA, SAC and PS are employees of HealThink PC, Thessaloniki, Greece, they were contracted by Novartis (Hellas) S.A.C.I., Greece for the development of this work; AM and SF are employees of Novartis (Hellas) S.A.C.I., Greece.

Funding

This research was sponsored by funds from Novartis (Hellas) S.A.C.I., Greece.

Poster presented at ISPOR European Congress; 2–6 November 2019, Copenhagen, Denmark