NCPE Assessment

Technical Summary

Tisagenlecleucel (Kymriah®)

HTA ID: 22044

12 August 2024

Applicant: Novartis Ireland Ltd

Tisagenlecleucel for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tisagenlecleucel (Kymriah®).*

Following assessment of the Applicant's submission, the NCPE recommends that tisagenlecleucel (Kymriah®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Novartis Ireland Ltd) Health Technology Assessment of tisagenlecleucel (Kymriah®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In July 2023, Novartis Ireland Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tisagenlecleucel (Kymriah®) for the treatment of relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. Novartis Ireland Ltd is seeking reimbursement of tisagenlecleucel on the Oncology Drugs Management System.

Tisagenlecleucel is a CD19-targeted CAR T-cell therapy. It is administered as a once-off, single-dose intravenous infusion in a qualified treatment centre. Prior to infusion, a patient may undergo a number of steps: apheresis, bridging therapy, and lymphodepleting therapy. Post-infusion monitoring should occur daily for the first 10 days after infusion, in a qualified treatment centre. Patients should remain within proximity of a qualified treatment centre for up to four weeks post-infusion.

The Applicant anticipates that tisagenlecleucel will be used in line with its licensed indication (as stated above). The treatment pathway at this line of therapy is heterogeneous. There is no universal standard of care. For the licensed population, chemotherapy was the chosen comparator. The chemotherapy arm comprised a weighted average of several chemotherapy regimens, which were informed by clinical opinion in Ireland. The Applicant also evaluated the cost-effectiveness of tisagenlecleucel in a subgroup of the licensed population, known as the double-refractory population. For the double-refractory population, chemotherapy, idelalisib, and rituximab in combination with lenalidomide (herein R^2) were the chosen comparators.

Of note, clinical opinion, obtained by the Review Group, indicated that at this line of therapy, stem cell transplant (SCT) is provided to eligible patients to consolidate the response achieved from systemic therapy (e.g. chemotherapy). Consolidative SCT was not explicitly considered by the Applicant in the comparator regimens. This is a limitation. Additionally, the Review Group highlight that R^2 is also a relevant comparator in the licensed population. Due to lack of data to inform efficacy of R^2 in the licensed population, an analysis of comparative effectiveness in the licensed population was not provided.

1. Comparative effectiveness of tisagenlecleucel

ELARA trial

The efficacy and safety of tisagenlecleucel was evaluated in the ELARA trial. This is a phase II, single-arm, open-label multicentre study. Patients were required to have Grade 1, 2 or 3a follicular lymphoma that was refractory to second- or later-line systemic therapy (including an anti-CD20 antibody and an alkylating agent), or relapsed within 6 months after completion of a second- or later-line systemic therapy. Patients whose disease relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion, or that relapsed after autologous SCT were also included. The intention-to-treat (ITT) population was defined as all patients enrolled in the study (n=98). Of these patients, 97 proceeded to infusion with tisagenlecleucel (the 'mITT population'). The efficacy analysis set (EAS) population (n=94) comprised all patients who received tisagenlecleucel and had measurable disease at baseline per independent review committee. Tisagenlecleucel was administered as a single intravenous infusion at a target dose of $0.6x10^8$ to $6.0x10^8$ CAR-positive viable T-cells. Bridging therapy and lymphodepleting therapy were permitted prior to tisagenlecleucel infusion.

Results were presented for the 36-month analysis (29 March 2023 data cut). The primary endpoint was independent review committee-assessed complete response rate, defined as the proportion of patients with a best overall response of complete response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever came first. Complete response rate was 67.3% (95% CI 57.1 to 76.5) in the ITT population and 68.0% (95% CI 57.7 to 77.3) in the EAS population. Progression-free survival (PFS) and overall survival (OS) were secondary endpoints. Median PFS was 38.4 months (95% CI 19.5 to not estimable) in the ITT population and 36.6 months (95% CI 18.2 to not estimable) in the EAS population. Median OS was not reached in the ITT or EAS populations.

Indirect Treatment Comparison

Due to the lack of direct comparative evidence, indirect treatment comparisons (ITCs) were conducted to generate estimates of relative effectiveness versus the comparators of

relevance. In the ITC, the March 2023 data cut of ELARA was used to inform the efficacy of tisagenlecleucel in the licensed population (i.e. versus chemotherapy using the ReCORD-FL data). As outlined, this is the population of most relevance to the assessment. The ITC in the double-refractory populations (versus chemotherapy, idelalisib and R^2, respectively) was not updated to reflect the most recent data cut of ELARA (March 2023). Instead, the March 2022 data cut was used to inform efficacy of tisagenlecleucel in the double-refractory population.

Tisagenlecleucel versus Chemotherapy

An unanchored ITC was used to evaluate the efficacy of tisagenlecleucel (ELARA) versus chemotherapy (ReCORD-FL) in the licensed population and the double-refractory population. ReCORD-FL was a non-interventional retrospective medical chart review multi-centre study, which was conducted specifically to generate comparative effectiveness evidence versus tisagenlecleucel. At the December 31 2020 data cut of ReCORD-FL, a total of 187 patients received at least three lines of treatment and matched the eligibility criteria of ELARA. The Applicant used propensity scores to try to adjust for differences between patient populations. One eligible line of therapy per patient was selected from ReCORD-FL based on highest propensity score. Only patients whose selected line of therapy was chemotherapy were included in the ITC analyses for the licensed population (n=78 for ReCORD-FL). For the double-refractory population, a subgroup analysis of patients with double-refractory disease, defined as being refractory to rituximab and an alkylating agent, was conducted to compare this subgroup in ELARA (n=66) with this subgroup in ReCORD-FL (n=98). In this analysis, the selected line of therapy from ReCORD-FL was not restricted to chemotherapy and therefore, the full sample size of ReCORD-FL was utilised. Both adjusted and unadjusted results indicated that tisagenlecleucel is associated with improved PFS and OS versus chemotherapy in the licensed and double-refractory populations.

Tisagenlecleucel versus Idelalisib

The DELTA trial was used to inform efficacy of idelalisib. DELTA is a phase II, multicentre, single-arm, open-label study investigating the efficacy of idelalisib monotherapy in patients with relapsed or refractory indolent non-Hodgkin's lymphoma. To evaluate the efficacy of idelalisib in patients with follicular lymphoma (n=72), a post-hoc subgroup analysis was performed. An unanchored matching-adjusted indirect comparison (MAIC) was used. Both

adjusted and unadjusted results indicated that tisagenlecleucel is associated with improved PFS and OS versus idelalisib in the double-refractory population.

Tisagenlecleucel versus R^2

The MAGNIFY study was used to inform efficacy of R^2. MAGNIFY is a phase IIIb, open-label, randomised study of patients with Grades 1-3b or transformed follicular lymphoma, marginal zone lymphoma, or mantle cell lymphoma who received at least one prior therapy. For the purpose of this analysis, a subgroup analysis of patients with double-refractory follicular lymphoma (n=50) was presented. Inclusion criteria differed between the ELARA and MAGNIFY trials in several respects. An unanchored MAIC was used. Both adjusted and unadjusted results indicated that tisagenlecleucel is associated with improved PFS versus R^2 in the double-refractory population. OS data were not available from the MAGNIFY trial. Thus, this outcome was not assessed in the MAIC.

For all comparisons, across all populations, the relative treatment effects are highly uncertain due to observed and non-observed differences between the studies, which could not be adjusted for.

2. Safety of tisagenlecleucel

The adverse event profile of tisagenlecleucel, observed in ELARA, was aligned with that seen in other indications of tisagenlecleucel. No new safety signals were identified. Cytokine release syndrome, cytopenias, infections and neurotoxicity are the most common adverse events and most frequently reported in the first eight weeks following tisagenlecleucel infusion. A number of risk minimisation measures are outlined in the summary of product characteristics.

3. Cost effectiveness of tisagenlecleucel

Methods

A de novo partitioned survival model was used to evaluate the cost effectiveness of tisagenlecleucel. The partitioned survival model included three mutually exclusive health states; progression-free, post-progression and death. For the licensed population, efficacy of tisagenlecleucel was informed by the ITT population of the ELARA trial. The most recent data

cut of ELARA (March 2023) was used in the cost-effectiveness model. However, parameters derived from the ITC, for the double-refractory population, were based on the March 2022 data cut. The ReCORD-FL data (ITT population) were used to generate comparative effectiveness estimates versus chemotherapy. The key efficacy inputs, OS and PFS, were modelled using a dependent model approach, with parametric distributions fitted to time-to-event data from ELARA and ReCORD-FL until month 60. Under this approach, a constant relative treatment effect is assumed over time, and the PFS and OS curves fitted to each arm have a similar shape. After month 60, the PFS and OS rates were informed by the ReCORD-FL data. For the double-refractory population, the double-refractory population of the ELARA trial was also examined using the relevant subgroup from ELARA. Efficacy of chemotherapy was informed by the double-refractory subgroup of ReCORD-FL. Relative treatment effects for PFS of idelalisib and R^2 were informed by the Applicant's MAIC. OS of idelalisib was informed by parametric extrapolation of the OS data. As OS was not published for R^2, OS inputs for R^2 were estimated based on the PFS data of R^2 and assuming a constant cumulative hazard ratio between OS and PFS. The model was highly sensitive to changes in the OS extrapolation curve for tisagenlecleucel. Overall, the Review Group considered the survival estimates in both the Applicant and NCPE-adjusted base case to be highly uncertain, due to the lack of data. Results should therefore be interpreted with caution.

Utility data were derived from EQ-5D-3L data collected during the ELARA trial. The small sample size is a notable limitation of the values. The limited utility data identified in the literature, relating to the population of relevance to this assessment, is a key limitation. The model included drug acquisition, administration, monitoring, subsequent treatment, and adverse event costs.

The Review Group identified a number of limitations in the Applicant's base case, which were explored in the NCPE-adjusted base case. The most notable of these included employing an independent survival modelling approach instead of a dependent. This approach was employed given violation of the proportionality assumption.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are

presented in Table 1 for the licensed population, and Table 2 for the double-refractory population.

Table 1 Applicant base case incremental cost-effectiveness results for the licensed population[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Tisagenlecleucel[b]	345,080	9.03	--	--	--
Chemotherapy	42,169	5.82	302,911	3.21	94,344

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a]Corresponding probabilistic ICER using 1,000 iterations =€95,704 per QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]A commercial in confidence PAS is in place for tisagenlecleucel; not included in this table.

Table 2 Applicant base case incremental cost-effectiveness results for the double-refractory population[a,b,d]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Tisagenlecleucel[c]	349,799	9.00	--	--	--
Chemotherapy	46,031	5.40	303,768	3.59	84,535
Idelalisib[c]	85,627	5.96	264,172	3.04	87,003
R^2	62,136	5.07	287,662	3.93	73,225

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **R^2**: Rituximab in combination with lenalidomide.
[a]Corresponding probabilistic ICER using 1,000 iterations:= €94,572 per QALY versus chemotherapy, €90,083 per QALY versus idelalisib, €80,439 per QALY versus R^2.
Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]This is a subgroup of the licensed indication. The licensed population is that of most relevance to the assessment.
[c]A commercial in confidence PAS is in place for tisagenlecleucel and idelalisib; not included in this table.
[d]The probabilistic ICER is more relevant to decision making, than the deterministic ICER, as it incorporates uncertainty. Where the deterministic and probabilistic output are similar, the deterministic can be considered a proxy for the probabilistic.

Results of the NCPE-adjusted base case deterministic cost-effectiveness analysis are presented in Table 3 for the licensed population, and Table 4 for the double-refractory population.

Table 3 NCPE-adjusted base case incremental cost-effectiveness results in the licensed population[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Tisagenlecleucel[b]	346,422	8.46	--	--	--
Chemotherapy	39,531	5.90	306,892	2.56	119,924

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a]Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]A commercial in confidence PAS is in place for tisagenlecleucel; not included in this table.

Table 4 NCPE-adjusted base case incremental cost-effectiveness results in the double-refractory population[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Tisagenlecleucel[c]	341,825	7.80	--	--	--
Chemotherapy	42,669	5.43	299,156	2.37	126,172
Idelalisib[c]	83,617	5.92	258,207	1.89	136,865
R^2	61,490	5.54	280,335	2.27	123,706

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **R^2**: Rituximab in combination with lenalidomide.
[a]Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]This is a subgroup of the licensed indication. The licensed population is that of most relevance to the assessment.
[c]A commercial in confidence PAS is in place for tisagenlecleucel and idelalisib; not included in this table.

Sensitivity analysis

Deterministic one-way sensitivity analysis indicated that the most influential parameters in the NCPE-adjusted base case were tisagenlecleucel treatment costs and the discount rate on costs and outcomes. In the double-refractory population, for all comparisons, the most influential parameters were aligned with the licensed population. Additionally, for the comparison versus R^2, the PFS:OS hazard ratio used to estimate OS was a key driver. Scenario analyses indicate that results are sensitive to extrapolations of OS.

A price-ICER analysis, using the NCPE-adjusted base case for the licensed population, indicated that a 92.6% and 71.5% reduction in the price-to-wholesaler of tisagenlecleucel was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. A commercial-in-confidence patient access scheme is currently in place for tisagenlecleucel. This is not considered in these estimates.

4. Budget impact of tisagenlecleucel

The price-to-wholesaler per single-dose intravenous infusion of tisagenlecleucel is €307,353.21. The total cost to the HSE, inclusive of rebate and VAT, is €351,919.43.

The eligible population is defined as patients with relapsed or refractory follicular lymphoma after two or more prior lines of systemic therapy (i.e. the licensed population). This reflects the licensed population. Based on population estimates obtained from the National Cancer Registry Ireland and clinical opinion, the Applicant estimated that there will be 182 patients eligible for treatment in year one, increasing to 195 by year five. Based on clinical opinion in Ireland, tisagenlecleucel was expected to have a 53% market share in years one to five,

inclusive. However, the Applicant considered this to be an overestimate, due to national capacity limitations. The Applicant therefore arbitrarily assumed that 10% of the estimated 53% (i.e. 5.3%) will receive tisagenlecleucel in years one (n=10) to five (n=10), inclusive. Based on clinical opinion to the Review Group, the Review Group assumed that 15 patients per year will receive treatment with tisagenlecleucel. Using these NCPE estimates, the five-year cumulative gross drug budget impact was €26.5 million (€21.2 million excluding VAT). This estimate includes tisagenlecleucel drug acquisition costs, bridging therapy costs, and lymphodepleting therapy costs. The five-year cumulative net drug budget impact was €24.8 million (€19.6 million excluding VAT). Based on the Applicant base case assumptions, the cumulative five-year gross and net drug budget impacts, inclusive of VAT, were €17.6 million (€14.1 million excluding VAT) and €16.5 million (€13.0 million excluding VAT), respectively.

The population of eligible patients and the proportion expected to receive treatment, are very uncertain. Therefore, there is considerable uncertainty associated with budget impact estimates.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that tisagenlecleucel not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.