



March 31, 2021

[C2H1902] Summary of cost-effectiveness evaluation of tisagenlecleucel (Kymriah)

1. Indications

Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia (B-ALL).
Relapsed or refractory CD19-positive diffuse large B-cell lymphoma (DLBCL).

2. Price of drug

Tisagenlecleucel was reimbursed from May 2019 for JPY 34,113,655 (as of March 2021). The price was calculated by a cost-calculation method with a usefulness premium of 35% (0.2 premium coefficient). This was designated as H3 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

This product is used for CAR-T therapy. Continual injection is not needed. Patients receive one dose of tisagenlecleucel. The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described hereafter. Inotuzumab is not indicated for patients younger than 15 years of age, and allogeneic hematopoietic stem cell transplantation (HSCT) is generally not performed on elderly people. Based on these factors, the whole patient population was categorized according to the age of the individuals.

(a) B-ALL

Population	Patients up to 25 years of age with relapsed or refractory CD19-positive B-ALL. Analyses should be performed for the following populations: (a) Patients up to 15 years of age (b) Patients from 15 to 25 years of age
Comparators	(a) Blinatumomab ± allogeneic HSCT

	(b) Blinatumomab ± allogeneic HSCT and Inotuzumab ± allogeneic HSCT
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(b) DLBCL

Population	Patients with relapsed or refractory CD19-positive DLBCL. Analyses should be performed for the following populations: (a) Patients up to 70 years of age (b) Patients aged 70 years and above
Comparators	(a) Salvage chemotherapy ± allogeneic HSCT (b) Salvage chemotherapy

4. Evaluation of additional benefits

According to the results of a systematic review, there are no randomized controlled trials (RCTs) on the use of tisagenlecleucel in patients with B-ALL. Indirect comparison was performed using pooled data from clinical trials (B2101J, ELIANA/B2202, and ENSIGN/B220). Based on these results, the ECCEE judged that tisagenlecleucel has additional benefits over the comparators for B-ALL.

Similarly, the results of systematic review revealed that there are no RCTs on the use of tisagenlecleucel in patients with DLBCL. Indirect comparison was performed using the data from the single-arm JULIET trial. Based on the results of indirect comparison, the ECCEE also agreed that tisagenlecleucel has additional benefits over the comparators for DLBCL.

5. Result of cost-effectiveness analysis

The manufacturer calculated the cost-effectiveness using a partitioned survival model based on the data obtained from clinical trials. On the contrary, the academic technology assessment group identified the following issues:

- There were certain methodological issues with the approach that was used for extrapolating the survival curve, and it caused an overestimation of the prognosis of tisagenlecleucel.
- During the analysis for DLBCL, the starting age in the model used by the manufacturer was decided by the age of the patients in the clinical trial. However, the age was found to be lower than the actual age of the patient population.
- The QOL score of the patients with remission was found to be high during analyses for DLBCL.
- Estimating the effectiveness of tisagenlecleucel in the population (b) with DLBCL

using the very small sample data of the JULIET trial was inappropriate, as patients less than 70 years had been excluded, and the uncertainty was high.

The academic group revised the economic model based on the aforementioned issues, and re-calculated the results. The results were submitted to the third session of the ECCEE and were approved. The final results obtained for each population are provided hereafter.

Population		Comparators	ICER (JPY/QALY)
B-ALL	aged < 15 years	Blinatumomab ± allogeneic HSCT	2,184,285
	aged ≥15 and < 25 years	Blinatumomab ± allogeneic HSCT	2,571,736
		Inotuzumab ± allogeneic HSCT	2,747,550
DLBCL	aged < 70 years	Salvage chemotherapy ± allogeneic HSCT	8,084,464
	aged ≥ 70 years	Salvage chemotherapy	12,538,653

USD 1 = JPY 105, and EUR 1=JPY 126 (as of March 2021)