CORE2 HEALTH

C2H
Evaluation Report

C2H1902

Tisagenlecleucel/B-ALL (Kymriah®)

March 2021

Center for Outcomes Research
and Economic Evaluation for Health

National Institute of Public Health

JAPAN

Cost-effectiveness evaluation of tisagenlecleucel (Kymria) by the academic group [Version 1.1]

Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia (B-ALL)

[November 11, 2020]

[Table of contents]

list of abbreviations

Abbreviations	Formal description
ALL	Acute Lymphoblastic Leukemia
alloHSCT	Allogeneic Hematopoietic Stem Cell Transplantation
ASMR	Amelioration du Service Médical Rendu
B-ALL	B-cell Acute Lymphoblastic Leukemia
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	Chimeric Antigen Receptor
CHRIs	Child Health Ratings Inventory
CI	Confidence interval
CR	Complete Remission
EFS	Event-Free Survival
DLBCL	Diffuse Large B-Cell Lymphoma
EQ-5D	EuroQol 5 Dimension
EQ-5D-3L	EuroQol 5 Dimension 3 Level
EQ-5D-5L	EuroQol 5 Dimension 5 Level
HAS	Haute Autorité de Santé
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
HUI2	Health Utilities Index Mark II
HSCT	Hematopoietic Stem Cell Transplantation
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MAIC	Matched Adjusted Indirect Comparison
MRD	Minimal Residual Disease
MSAC	Medical Services Advisory Committee
NA	Not Applicable
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient Access Schemes

PD	Progressive Disease
PROMIS	Patient-Reported Outcomes Measurement Information System
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RCT	Randomized Controlled Trial
SCT	Stem Cell Transplant
SF-36	36-Item Short Form Survey
SMC	Scottish Medicines Agency
SMR	Service Médical Rendu
TTO	Time Trade-Off

0. Framework of analysis

Table 0-1 The framework of analysis

Population	Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Patients aged 25 years or younger (at the time of treatment) who meet any of the following criteria (a) and (b) shall be included. ・Patients with primary disease who have not achieved remission after the standard chemotherapy was performed at least twice ・Patients with relapsed disease who have not achieved remission after the chemotherapy was performed at least once ・Patients who are not indicated for allogeneic hematopoietic stem cell transplantation or who have relapsed after allogeneic hematopoietic stem cell transplantation (a) Population aged <15 years (b) Population aged 15 to 25 years
comparator	(a) Blinatumomab ± allogeneic hematopoietic stem cell transplantation (alloHSCT) (b) Blinatumomab ± alloHSCT and inotuzumab ozogamicin ± alloHSCT
Reason for selection of comparator	For both populations, (post-relapse) secondary chemotherapy is standardly administered (± alloHSCT) according to the clinical practice in Japan or the NCCN (National Comprehensive Cancer Network) guidelines. "Guideline for Analysis of Cost-Effectiveness Evaluation by the Central Social Insurance Medical Council, 2nd Version" indicates that it is appropriate to use "blinatumomab (± alloHSCT)" as a comparator in the population aged <15 years, because blinatumomab have a high remission rate. For the population aged 15 to 25 years, both "blinatumomab

	(± alloHSCT)" and "inotuzumab ozogamicin (± alloHSCT)" can be selected as comparators, because both have a similar response rate. Use of inotuzumab ozogamicin is limited to people aged ≥15 years in Japan.
Other perspective in addition to public healthcare payer	Yes (Details: Analysis including productivity loss (manufacturer analysis only)) No
Outcome unit and the reason if QALY is not used.	Not applicable

1. Results by health technology assessment agency

Table 1-1 List of assessments (Including additional benefit)

Country	Organization	Results	
		Manufacturer	Academic analysis
UK	NICE	･Recommended/Not recommended/Conditionally recommended (Specify: Cancer Drugs Fund)/Other ( ) ･Status: Final Guidance/Draft/Other ( )	･Recommended/Not recommended/Conditionally recommended (Specify: Cancer Drugs Fund)/Other ( ) ･Status: Final Guidance/Draft/Other ( )
	SMC	･Recommended/Not recommended/Conditionally recommended (Specify: Patient Access Schemes)/Other ( )	･Recommended/Not recommended/Conditionally recommended (Specify: Patient Access Schemes)/Other ( )
France	HAS	· SMR: Important · ASMR: I/II/III/IV/V · Efficiency assessment: Yes (major ICER value:)/Under assessment/Not performed	· SMR: Important · ASMR: I/II/III/IV/V · Efficiency assessment: Yes (major ICER value:)/Under assessment/Not performed
Germany	IQWiG	· Major/Considerable/Minor/Unquantifiable/No additional benefit	· Major/Considerable/Minor/Unquantifiable/No additional benefit
Canada	CADTH	･Recommended/Not recommended/Conditionally recommended (Specify:)/Other ( )	･Recommended/Not recommended/Conditionally recommended (Specify: reduction in price)/ /Other

			( )
Australia	MSAC	·Recommended/Not recommended/Conditionally recommended (Specify:)/Other ( )	·Recommended/Not recommended/Conditionally recommended (Specify: risk share arrangement)/ Other ( )

Table 1-2 Implementation of cost-effectiveness analysis in each country

Country	Organization	Implementation	
		Manufacturer	Academic analysis
UK	NICE	Yes/ No/ Under assessment (with/without draft)/ Unknown	Yes/ No/ Under assessment (with/without draft)/ Unknown
	SMC	Yes/ No/ Under assessment/ Unknown	Yes/ No/ Under assessment/ Unknown
France	HAS	Yes/ No/ Under assessment/ Unknown	Yes/ No/ Under assessment/ Unknown
Canada	CADTH	Yes/ No/ Under assessment/ Unknown	Yes/ No/ Under assessment/ Unknown
Australia	MSAC	Yes/ No/ Under assessment/ Unknown	Yes/ No/ Under assessment/ Unknown

Table 1-3 Details of cost-effectiveness analysis in each country

Table 1-3-1 Details of cost-effectiveness analysis in UK (NICE)

Country	UK	
	Manufacturer	Academic analysis
Organization	NICE	
URLs	https://www.nice.org.uk/guidance/ta554/chapter/1-Recommendations	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Conditional recommendation	Same as in the left
If conditionally recommended, details of the condition	Cancer Drugs Fund	Same as in the left
Disease	Pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse	Same as in the left
Dosage	Treatment with tisagenlecleucel comprises a single-dose intravenous infusion of tisagenlecleucel. It is intended for autologous use only and at the following dosage: · For patients ≤50 kg: 0.2 to 5.0×10^6 CAR-positive	Same as in the left

	viable T cells per kg body weight · For patients >50 kg: 0.1 to 2.5×10^8 CAR-positive viable T cells (non-weight based)	
Comparator	Blinatumomab and salvage chemotherapy are both appropriate comparators and blinatumomab is the main comparator.	Same as in the left
Incremental cost-effectiveness ratio (ICER)	Company's probabilistic base-case ICER was £20,046 per QALY gained. The committee concluded the most plausible ICERs for tisagenlecleucel compared with blinatumomab when taking into account all the patient access scheme discounts were over £30,000 per QALY gained.	Same as in the left

Table 1-3-2 Details of cost-effectiveness analysis in UK (SMC)

Country	UK	
	Manufacturer	Academic analysis
Organization	SMC	
URLs	https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-fullsubmission-smc2129	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Conditional recommendation	Same as in the left
If conditionally recommended, details of the condition	Patient Access Scheme	Same as in the left
Disease	pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse	Same as in the left
Dosage	Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion. A single dose of tisagenlecleucel contains: · for patients 50kg and below: 0.2 to 5 x 10^6 CAR [chimeric antigen receptor] positive viable T cells/kg body weight	Same as in the left

	· for patients above 50kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)	
Comparator	Salvage chemotherapy, blinatumomab or palliative therapies	Same as in the left
Incremental cost-effectiveness ratio (ICER)	ICER versus salvage chemotherapy (with PAS for tisagenlecleucel) Base case: £25,238	Results using PAS prices and list prices for both tisagenlecleucel and blinatumomab are not disclosed

Table 1-3-3 Details of cost-effectiveness analysis in France (HAS)

Country	France	
	Manufacturer	Academic analysis
Organization	HAS	
URLs	https://www.has-sante.fr/jcms/c_2891689/en/kymriah-tisagenlecleucel-anti-cd19-car-t	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Results SMR: Important / ASMR: III	Same as in the left
If conditionally recommended, details of the condition	NA	Same as in the left
Disease	pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse	Same as in the left
Dosage	Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion. A single dose of tisagenlecleucel contains: · for patients 50kg and below: 0.2 to 5 x 10^6 CAR [chimeric antigen receptor] positive viable T cells/kg	Same as in the left

	body weight. · for patients above 50kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based).	
Comparator	salvage chemotherapy, blinatumomab, inotuzumab, and palliative care	Salvage chemotherapy, Clofarabine, blinatumomab
Incremental cost-effectiveness ratio (ICER)	NA	€189,822/QALY for clofarabine as comparator when time horizon is limited to 10 years

Table 1-3-4 Details of cost-effectiveness analysis in Germany (IQWIG)

Country	Germany	
	Manufacturer	Academic analysis
Organization	IQWIG	
URLs	https://www.iqwig.de/en/projects28results/projects/health-economic/g18-11-tisagenlecleucel-b-cell-acute-lymphoblasticleukaemia-assessment-according-to-35a-para-1-sentence-11-social-code-book-v.10617.html	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Unquantifiable	Same as in the left
If conditionally recommended, details of the condition	NA	Same as in the left
Disease	pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse	Same as in the left
Dosage	Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion. A single dose of tisagenlecleucel contains: · for patients 50kg and below: 0.2 to 5 x 10^6 CAR	Same as in the left

	[chimeric antigen receptor] positive viable T cells/kg body weight. · for patients above 50kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based)	
Comparator	None (reason：orphan designation)	Same as in the left
Incremental cost-effectiveness ratio (ICER)	NA	Same as in the left

Table 1-3-5 Details of cost-effectiveness analysis in Canada (CADTH)

Country	Canada	
	Manufacturer	Academic analysis
Organization	CADTH	
URLs	https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma https://cadth.ca/sites/default/files/pdf/car-t/ct0001-op0538-in-brief-e.pdf	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Conditional recommendation	Same as in the left
If conditionally recommended, details of the condition	On the condition that there is a reduction in price	Same as in the left
Disease	Pediatric and young adult patients three to 25 years old with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogeneic stem cell transplant (SCT), or are otherwise ineligible for allogeneic SCT, or have experienced a second or later relapse	Same as in the left
Dosage	The recommended dose is 0.2-5.0 x 10^6 CAR-positive viable T cells/kg body weight for patients 50 kg and below and 0.1-2.5 x 10^8 CAR-positive viable T cells for patients	Same as in the left

	above 50 kg as a single one-time treatment.	
Comparator	salvage chemotherapy	Same as in the left
Incremental cost-effectiveness ratio (ICER)	For r/r ALL, tisagenlecleucel, compared with end-of-life chemotherapy, was associated with an incremental cost per quality-adjusted life-year (QALY — a measure of the quantity and quality of life for a patient, as well as value for money for medical interventions) of CAD$53,269.	Same as in the left

Table 1-3-6 Details of cost-effectiveness analysis in Australia (MSAC)

Country	Australia	
	Manufacturer	Academic analysis
Organization	MSAC	
URLs	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519-public	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Recommendation	Conditional recommendation
If conditionally recommended, details of the condition	NA	Risk share arrangement · A pay only on successful infusion* arrangement; · Treatment to be limited to a single dose of tisagenlecleucel, as there is no evidence currently available informing the effectiveness or safety of multiple doses; and · A full review of clinical effectiveness, cost-effectiveness and budget impact will be conducted by the MSAC no later than 2 years post the commencement of public subsidy (note: Novartis will provide a submission to

		initiate this review). * Successful infusion: patient is infused with Kymriah with a clinically acceptable cell dose which is consistent with the expected cell dose specified prior to apheresis
Disease	pediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse posttransplant, or in second or later relapse	Same as in the left
Dosage	· For patients 50 kg and below: 0.2 to 5.0 x 10^6 CAR-positive viable T cells/kg body weight. · For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based).	Same as in the left
Comparator	comparator: blinatumomab with the intention to proceed to allo-SCT (Main), salvage hemotherapy with the intention to proceed to allo-SCT (Supportive)	Same as in the left
Incremental cost-effectiveness	NA	Not disclosed

ratio (ICER)		

[Review on the submission by the manufacturer in Chapter 1]

Although generally appropriate, the following matters were inconsistent with the description in the reports by the health technology assessment agency.

・An ICER was reported for France (HAS). The comparator was clofarabine combination therapy, with an ICER of €189,822/QALY over a 10-year time horizon.
・For Australia (MSAC), conditionally recommended by multiple conditions for price reduction and reimbursement.

・There are no comparison data such as randomized controlled trials (RCTs) that evaluated the efficacy and safety of tisagenlecleucel. There are no efficacy or safety data based on direct comparison with the comparator. This has a significant impact on the uncertainty of results.
・In addition, because there is no strong evidence that the no recurrence is experienced after 3 or 5 years from the administration of tisagenlecleucel. The limitation about long-term prognosis is pointed by health technology assessment agency. For this reason, NICE recommends the use under the Cancer Drugs Fund (data collection arrangement), and the period of data collection is set to be until June 2023 when the follow-up of Study ELIANA is completed.

2. Systematic review (SR)

2.1 Clinical questions by the academic group

Table 2-1-1 Clinical question of SR

Item	Establishment of academic analysis
Population	B-cell acute lymphoblastic leukemia However, limited to patients aged ≤25 years after recurrence after hematopoietic stem cell transplantation or 2nd or subsequent chemotherapy
Intervention	The following therapies for the indication in the population: ・Tisagenlecleucel ・Blinatumomab ・Inotuzumab ozogamicin
Comparator	All comparators
Outcome	Any of the following outcomes: ・Survival (duration) Overall survival rate ・Morbidity Event-free survival Disease-free survival Progression-free survival Recurrence rate Duration of remission Frequency and timing of hematopoietic stem cell transplantation Adverse events ・Health-related quality of life (HRQL)
Study design	・RCT ・Controlled study ・Single arm study ・Observational study
Literature search period	From January 2019 to September 2020

2.2 Study design of SR

2.2.1 Inclusion and exclusion criteria for clinical study

Table 2-2-1 Eligibility criteria

Item	Inclusion criteria	Exclusion criteria
Population	・B-cell acute lymphoblastic leukemia However, limited to patients aged ≤25 years after recurrence after hematopoietic stem cell transplantation or 2nd or subsequent chemotherapy	・At least 20% patients with T-cell acute lymphoblastic leukemia ・Patients in complete remission (CR) ・Untreated patients ・At least 10 patients in clinical studies and at least 20 patients in observational studies
Intervention	Tisagenlecleucel Blinatumomab Inotuzumab ozogamicin	Therapies not clinically used
Comparator	No restrictions	
Outcome	At least one of the following outcomes: ・Survival (duration) Overall survival rate ・Morbidity Event-free survival Disease-free survival Progression-free survival Recurrence rate Duration of remission Frequency and timing of hematopoietic stem cell transplantation	

	Adverse events ・Health-related quality of life (HRQL)	
Study design	・RCT ・Controlled study ・Single arm study ・Observational study	
Type of literature	・Research report	・Abstract ・Note ・Editorial ・Letter
Language	English or Japanese	

2.2.2. Database

・PubMed
・Ichushi

2.2.3 Search formula

Table 2-2-3-1 Search formula for PubMed

Item	Serial number	Search formula	Number of results
Population	#1	"Precursor Cell Lymphoblastic Leukemia-Lymphoma"[MeSH] OR "acute lymphocytic leukemia" OR "acute lymphocytic leukaemia" OR "acute lymphoblastic leukemia" OR "acute lymphoblastic leukaemia" OR ((lymphocyt*[TIAB] OR lymphoblast*[TIAB] OR lymphat*[TIAB] OR lymphoid*[TIAB]) AND (leukemi*[TIAB] OR leukaemi*[TIAB]) AND acute[TIAB])	53,392

	#2	relapsed OR relapses OR relapsing OR refractory OR chemorefractory OR drugresistant OR "drug resistant" OR failed OR failure OR "transplant ineligible" OR "stem cell transplant ineligible" OR "SCT ineligible"	1,914,491
	#3	#1 AND #2	14,171
Study design	#4	"Clinical Trials as Topic"[MeSH] OR "Clinical Trial" [PT] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Randomized Controlled Trial" [PT] OR "Cross-Over Studies"[MeSH] OR "Prospective Studies"[MeSH] OR random* OR "random allocation" OR randomized OR randomised OR "double-blind" OR "singleblind" OR "single blind" OR "double blind" OR "clinical trial" "phase 1" OR "phase 2" OR "phase 1/2" OR "phase 1/phase 2" OR "phase 3" OR "phase 4" OR "Clinical Study"[PT] OR "Clinical Trial, Phase I"[PT] OR "Clinical Trial, Phase II"[PT] OR "Clinical Trial, Phase III"[PT] OR "Clinical Trial, Phase IV" [PT] OR "Controlled Clinical Trial"[PT] OR "Multicenter Study"[PT] OR placebo* OR "prospective study" OR singlearm OR "single arm" OR open-label OR "open label" OR trial OR "nonblinded" OR non-blinded OR non-randomized OR nonrandomized OR non-randomised OR nonrandomised OR parallel-group OR "parallel study" OR superiority OR non-inferiority OR change OR evaluat* OR prospectiv* OR retrospective* OR baseline OR cohort or consecutive* OR compare* OR compara* OR "case series" OR "comparative studies" OR "follow-up studies" OR registry OR observational OR nonrandomized OR nonrandomized	12,157,852
Limitation of integration	#5	#3 AND #4	8,523
	#6	#5 AND 2019:2020[DP]	877

and search period			

Table 2-2-3-2 Search formula for Ichushi

Item	Serial number	Search formula	Number of results
Population	#1	白血病-リンパ腫-前駆細胞リンパ芽球性/TH or 急性リンパ性白血病/AL or 前駆細胞リンパ芽球性白血病/AL or 急性リンパ芽球性白血病/AL or "Acute lymphoblastic leukemia"/AL or ((リンパ/AL or Lymphoma/AL) and (白血病/TH or 白血病/AL or Leukemia) and (急性/AL or acute/AL))	18,611
	#2	(再発/TH or 再発/AL or relapse/AL) or (難治性/AL or refractory/AL) or 化学抵抗性/AL or 薬物抵抗性/TH or 薬剤耐性/AL or 失敗/AL or 移植不適格/AL or ((幹細胞移植/TH or 幹細胞移植/AL or "stem cell transplantation"/AL) and (不適格/AL or 不適応/AL or ineligible/AL))	396,841
	#3	#1 AND #2	2,872
Study design	#4	ランダム化比較試験/TH or "randomized controlled trial"/AL or "randomized controlled trials"/AL or ランダム割付け/TH or ランダム化/AL or 無作為/AL or クロスオーバー研究/TH or クロスオーバー試験/AL "Cross-Over Studies"/AL or 二重盲検法/TH or 二重盲検/AL or 一重盲検法/TH or 単盲検/AL or 非盲検/AL or プラセボ/TH or プラセボ/AL or 臨床試験/TH or 臨床試験/AL or "Clinical trials"/AL or "Clinical trial"/AL or 比較試験/AL or 比較検討/AL or 対照試験/AL or 比較研究/AL or 対照研究/AL or "臨床研究・疫学研究"/TH or "Clinical study"/AL or "Clinical studies"/AL or "Comparative study"/AL or "Comparative studies"/AL or "Comparative research"/AL or "comparison study"/AL or "comparison research"/AL or 観察研究/TH or 観察研究/AL or "Observational study"/AL or "Observational studies"/AL or 非ランダム化/AL	523,560

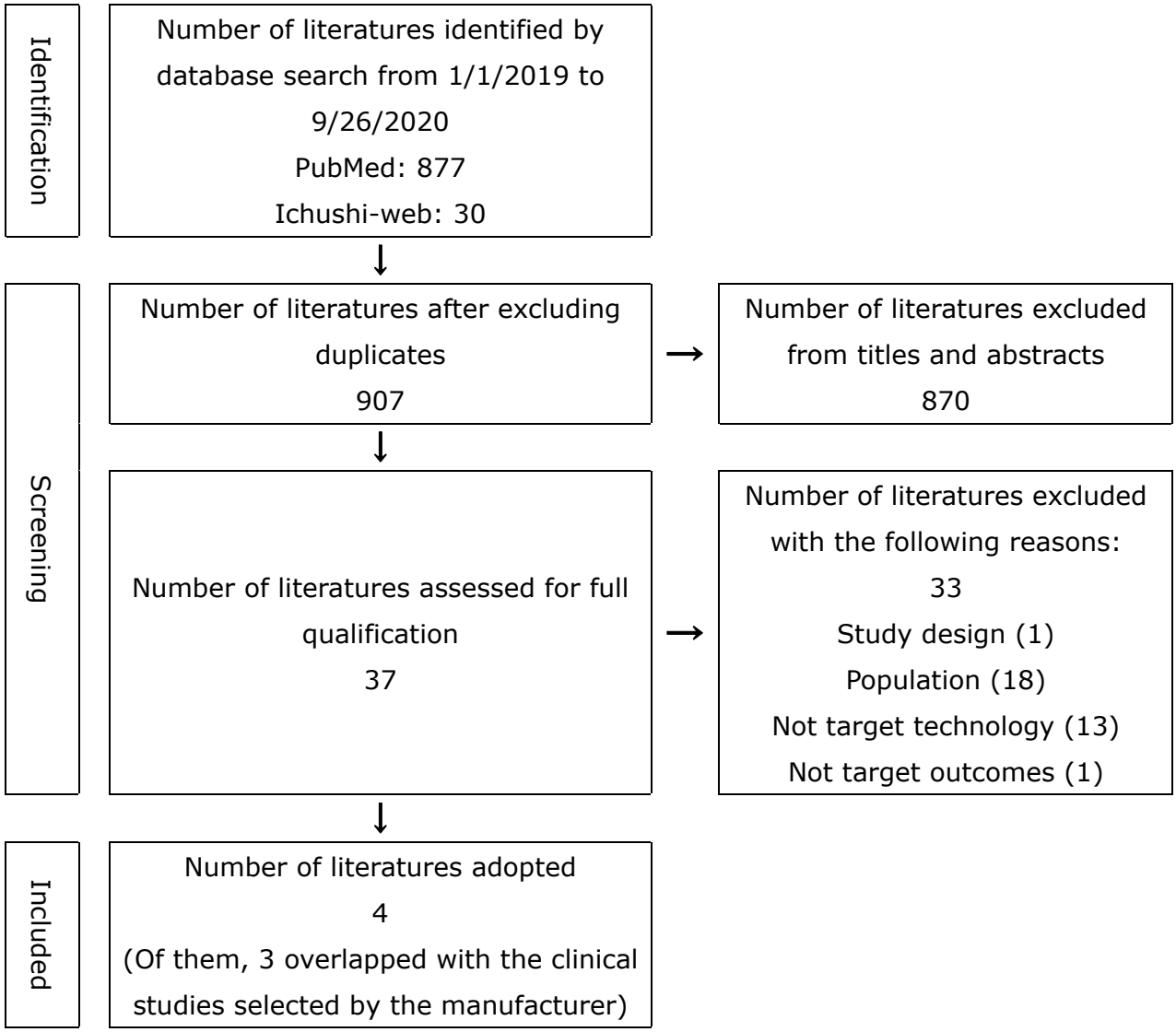
		or コホート/AL or 追跡研究/TH or フォローアップ研究/AL or 並行研究/AL	
Limitation of integration and search period	#5	#3 AND #4	351
	#6	#5 AND (DT=2019:2020)	30

2.2.4 Other

No special notes

2.3 Search results

Figure 2-3-1 Flow chart of SR



[Review on submission by the manufacturer in Chapter 2]

The results of the SR are:

☐ Completely consistent with submission by the manufacturer
☑ Overall consistent and contains all important literature to evaluate additional benefit
☐ There is a discrepancy in the results, and there is a lack of important literature to evaluate additional benefit.
☐ Other ( )

● Differences from the SR performed by the manufacturer (method).

The results of the SR conducted by the manufacturer are generally acceptable. On the other hand, since the existing literature search period is until [redacted] 2019, an additional search limited to Japanese literatures was performed until [redacted] 2019.

Since the additional search should not be confined to the Japanese population, the academic analysis also conducted both English and Japanese literature search from 2019 to the latest time point (September 26, 2020).

● Differences from the SR performed by the manufacturer (result).

One additional literature was selected as a result of a SR performed by the academic group [1]. The literature is shown in Table 2-3-1.

Table 2-3-1 List of literatures

Title of article	Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: results of the RIALTO trial, an expanded access study
Author name	Locatelli F et al.
Bibliographic information	Blood Cancer J. 2020;10(7):77
Test location	19 sites (7 countries)
Study enrollment period	2014-July 19, 2019
Population	Enrolled patients were aged >28 days to <18 years, with CD19-positive BCP-ALL in second or later relapse, any relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT), or refractory to other treatments
Key exclusion criteria	Patients with active acute (grade 2–4) or chronic graft-versus-host disease (GvHD) requiring systemic treatment, or active central nervous system or testicular involvement
Details of intervention method	Blinatumomab (5–15μg/m^2 per day) was administered as a 6-week induction cycle, comprising continuous infusion for 4 weeks, followed by a 2-week treatment-free period.
Details of comparator	NA
Study design	Single-arm study
Blinding method	Open-label
Primary endpoint	Incidence of treatment-emergent and treatment-related adverse events
Key secondary endpoints	Morphologic CR (<5% blasts) and MRD response (<10−4 leukemic blasts by flow cytometry) in the first two cycles, relapse-free survival, OS, alloHSCT rate after blinatumomab treatment, and 100-day mortality after alloHSCT
Statistical methods	Statistical reporting of this study is descriptive.

- Validity of the SR performed by the manufacturer.

The clinical study (RIALTO trial) of blinatumomab was detected. The article was published in July 2020 after submission of the manufacture’s report. The results of the SR the manufacturer are therefore valid.

2.4 Evaluation of additional benefit

Table 2-4-1 Evaluation of additional benefit

	Manufacturer	Academic analysis
Population	B-ALL patients aged <15 years	Same as in the left
Intervention	Tisagenlecleucel	Same as in the left
Comparator	Blinatumomab +/- alloHSCT	Same as in the left
Outcome	OS	Same as in the left
Additional benefit (Yes/No)	■ Additional benefit is not shown. ☐ "No additional benefit" or "Cannot be judged "	Same as in the left
Additional benefit (Study design)	☐ Meta-analysis of RCTs ☐ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ■ Comparison of single-arm studies ☐ No clinical study data	Same as in the left
Additional benefit (Reason)	In the indirect comparison (OS) between the population aged <15 years in the pooled trial data (B2101J, ELIANA/B2202, ENSIGN/B2205) and the population aged <15 years in Gore 2018, the	The point estimate of conditional HR showed the OS event is approximately [redacted]%, which is considerably smaller than 1. The upper limit of the 95% confidence interval of the HR does not cross

	conditional HR was [redacted](95% CI: [redacted]). Based on these results, it was judged that this product has additional benefit for the comparator.	1. It is indicated that this product has the number of events decreased to approximately [redacted]% even at the upper limit of confidence interval. Therefore the judgment of manufacturer on additional benefit is valid.

Table 2-4-2 Evaluation of additional benefit

	Manufacturer	Academic analysis
Population	B-ALL patients aged 15 to <25 years	Same as in the left
Intervention	Tisagenlecleucel	Same as in the left
Comparator	Blinatumomab +/- alloHSCT Inotuzumab +/- alloHSCT	Same as in the left
Outcome	OS	Same as in the left
Additional benefit (Yes/No)	■ Additional benefit is not shown. ☐ "No additional benefit" or "Cannot be judged "	Same as in the left
Additional benefit (Study design)	☐ Meta-analysis of RCTs ☐ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ■ Comparison of single-arm studies ☐ No clinical study data	Same as in the left
Additional benefit (Reason)	In the MAIC analysis (OS) between the population aged ≥15 years in the pooled trial data (B2101J, ELIANA/B2202, ENSIGN/B220) and the overall population in Gore 2018 when blinatumomab was	Compared with inotuzumab or blinatumomab, the upper limit of the 95% confidence interval of the conditional HR does not exceed 1 in either case. Point estimate of HR suggested that this product may decrease the OS events to approximately [redacted]

	used as a comparator, the conditional HR was [redacted](95%CI: [redacted]). In the MAIC analysis (OS) between the population aged ≥15 years in the pooled trial data (B2101J, ELIANA/B2202, ENSIGN/B2205) and the overall population in Bhojwani 2019 when inotuzumab was used as a comparator, the conditional HR was [redacted](95%CI: [redacted]). Based on these results, it was judged that this product has additional benefit for the comparator.	to [redacted]. It is indicated that this product has the number of events decreased by approximately [redacted]% even at the upper limit of confidence interval. Therefore the judgment of manufacturer on additional benefit is valid.

3. Cost-effectiveness analysis by the academic group

3.1 Should the cost-effectiveness analysis submitted by the manufacturer be reconsidered?

☐ Nothing special	→	Terminated in this section
☑ Yes	→	Continued below

3.2 Summary of analysis (revise) by the academic group

3.2.1 Major points that need to be reconsidered (significant impact on results)

a) Parameters (estimation of EFS and OS)
b) QOL scores (QOL scores for EFS and PD)

3.2.2 Minor points that need to be reconsidered (other than 3.2.1)

a) Cost parameters (drug prices)
b) QOL scores (for Age-related utility)
c) Estimation of EFS in the blinatumomab group
d) QOL scores (Treatment disutility)
e) QOL scores (Subsequent HSCT disutility)

3.3 Analysis (revision) by the academic group for major points

3.3.1 Parameters (estimation of EFS and OS)

Table 3-3-1-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.1.1	96	3

[Description of report]
The assumption of 5 years as a cure point is considered more conservative. The long-term ALL survival was modelled using the 2018 Japan life table, with a mortality adjustment using the SMR of 5-year ALL survivors published in the literature (Table 13).[30],[38] The same mortality risk was applied to all treatments. This assumption reduced some of the long-term uncertainties arising from the extrapolation of data beyond the maximum reported follow-up. The estimated SMR-adjusted survival rate was applied to all patients who remain alive from year 5 onwards in the model. A targeted literature review was conducted to identify publications to inform long-term survival for the study population (registry or SMR studies). MacArthur et al., 2007 was identified as the most relevant input source and used to inform the mortality of 5-year ALL survivors.

[Details of academic analysis (revision)]

According to the manufacture's analysis, the OS function was extrapolated using mortality rate which was estimated by multiplying SMR (standardized mortality ratio) of the long survivor by mortality rate of general people. However, this extrapolation can not consider excess mortality in PD patients, and the OS was overestimated. Therefore, this cannot be regarded as an appropriate OS extrapolation. For example, in the population aged 15 to 25 years, the life expectancy of patients who had relapsed after the treatment with Kymriah at 3 years was approximately 10 years or longer.

In addition, the EFS function was extrapolated by a horizontal line (y=C; C is

a constant) assuming that no event occurs. However, even the patients with EFS should experience events such as death due to other causes. Death events that are reflected in OS should be handled as events in EFS. Such extrapolation of EFS function is not appropriate.

Therefore, the OS function was extrapolated using the parametric function estimated by the manufacturer after the 5th year when the Kaplan-Meier curve was interrupted. The EFS function was extrapolated after the 5th year using the standardized mortality ratio used by the manufacturer to account for the deaths other than other disease. However, if the OS and EFS functions crossed, the OS function was also extrapolated using the EFS function estimation method.

In the manufacturer's response to our inquiry (dated [redacted] 2019), it was described "After 5 years of treatment with Kymriah, long-term survival (cure) was assumed, and the subsequent OS was extrapolated using the SMR of MacArthur et al.". The fact that long-term survival (cure) can be achieved by tisagenlecleucel is acceptable. This can be achieved by the "absence of recurrence (after the 5th year)". It does not justify the extrapolation of the EFS curve after the 5th year (cure point) by the horizontal line. It is not also appropriate that the OS curve extrapolation method is changed when the 5th year started.

In the population aged <15 years, OS and EFS were reversed within 5 years in the tisagenlecleucel group. In that case, it is not appropriate to estimate the OS in the blinatumomab group using the OS of tisagenlecleucel group. Thus, the estimation of OS in the blinatumomab group was performed using the parametric function in the tisagenlecleucel group and the adjusted hazard ratios from time 0.

As the academic analysis, the estimated life years in the tisagenlecleucel group and blinatumomab group in the population aged <15 years were as described in Table 3-3-1-2. Additionally, the results of academic analysis of estimated survival curves were shown in Figures 3-3-1-1 to 3-3-1-4.

Similarly, the academic analysis in the population aged 15 to 25 years were shown in Table 3-3-1-3 and Figures 3-3-1-5 to 3-3-1-10.

Table 3-3-1-2 Life years by academic analysis (population aged <15 years)

	Manufacturer's submission		Academic analysis	
	Tisagenlecleucel group	Blinatumomab group	Tisagenlecleucel group	Blinatumomab group
Life years (LYs)	[redacted]	[redacted]	[redacted]	[redacted]
EFS	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3-3-1-1 Estimated survival time curve by manufacturer for the tisagenlecleucel group (population aged <15 years)

Figure 3-3-1-2 Estimatioed survival time curve by academic analysis for the tisagenlecleucel group (population aged <15 years)

Figure 3-3-1-3 Estimated survival time curve by manufacturer for the blinatumomab group (population aged <15 years)

Figure 3-3-1-4 Estimated of survival time curve by academic analysis

for the blinatumomab group (population aged <15 years)

Table 3-3-1-3 Life years by the academic analysis (population aged 15 to 25 years)

	Manufacturer's submission			Academic analysis		
	Tisagenlecleucel group	Blinatumomab group	Inotuzumab ozogamicin group	Tisagenlecleucel group	Blinatumomab group	Inotuzumab ozogamicin group
Life years (LYs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3-3-1-5 Estimated survival time curve by manufacturer for the tisagenlecleucel group (population aged 15 to 25 years)

Figure 3-3-1-6 Estimated survival time curve by academic analysis for the tisagenlecleucel group (population aged 15 to 25 years)

Figure 3-3-1-7 Estimated survival time curve by manufacturer for the blinatumomab group (population aged 15 to 25 years)

Figure 3-3-1-8 Estimated survival time curve by academic analysis for the blinatumomab group (population aged 15 to 25 years)

Figure 3-3-1-9 Estimated survival time curve by manufacturer for the

inotuzumab ozogamicin group (population aged 15 to 25 years)

Figure 3-3-1-10 Estimated of survival time curve by academic analysis for the inotuzumab ozogamicin group (population aged 15 to 25 years)

3.3.2 QOL scores (QOL scores for EFS and PD)

Table 3-3-2-1 Corresponding part of report by manufacturer

In the reports. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2.1	80, 83, 105	-

[Description of report]
Because a trial-based utility score was only available for [redacted] patients aged 15 years and above in the ELIANA alone, the base-case utility inputs were based on published studies and trial-based utility inputs were used in the sensitivity analysis. Kelly et al., 2015 used a decision analysis to evaluate cranial radiation therapy for pediatric T-cell ALL patients and performed a systematic literature review (SLR) of utility studies as part of the analysis.[30] While the study focused on T-cell ALL, the SLR of utilities included all forms of ALL. The study used existing mapping functions to convert generic quality-of-life measure (i.e. SF36 and CHRIs) to preference-based utility estimates (i.e. HUI2 and EQ-5D). The utility inputs for health states in the state of relapse and cured after relapse were considered relevant for the CEA model and was used to inform the utility value for the PD and EFS states respectively in the base-case model.

[Details of academic analysis (revision)]

The analysis by manufacturer used the QOL scores of 0.91 for EFS and 0.75 for PD. The EFS value of 0.91 was determined by assigning the value of SF-36 obtained from Essig et al. [2] to the formula by Nichol et al. [3], which could convert SF-36 to HUI2. Essig et al. used SF-36 for data collection of survivors in Switzerland, who were diagnosed as <16 years of age between 1976 and 2003. They survived for at least 5 years and ≥16 years of age at the survey. Based on the analysis of from 457 survivors, it reported they have a higher QOL than the general population.

For the PD value of 0.75, the global HRQOL measured using Child Health

Ratings Inventories (CHRIs) in patients undergoing HSCT were measured by Rodday et al.[4]. They were converted using mapping PROMIS to EQ-5D by Revicki et al.[5]. Aristides M et al.[6] performed in the UK, reported a PD QOL score of 0.30 using TTO. Thus, the analysis submitted by the manufacturer used the conversion of generic quality-of-life measure (SF36 or CHRIs) to preference-based measure (HUI2 or EQ-5D), which had problems such as a mixture of scales.

On the other hand, ELIANA measured QOL scores using EQ-5D-3L at baseline, at 1 month, at 3 months and thereafter every 3 months for 2 years. The results have been reported by Laetsch et al.[7]. In the academic analysis, QOL scores reported by Laetsch et al. (Table 3-3-2-2) was used as the base case analysis.

Table 3-3-2-2 QOL score

	Manufacturer's submission	Academic analysis
Progressive disease	0.75	0.69
Event-free survival	0.91	0.81

3.4 Analysis (revision) by the academic group other than 3.3

3.4.1 Cost parameters (drug prices)

Table 3-4-1-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.3	108	22

[Description of report]
For both B-ALL and DLBCL diseases, the costs for the target technology to be analyzed and the comparator technology were estimated by the accumulation method based on the medical fee schedule and the National Health Insurance Drug Price Standard as of October 2019 in principle.

[Details of academic analysis (revision)]

The prices of some medicines used by the manufacturer for analysis was not consistent with the latest drug price.

In the "Guideline for Analysis of Cost-Effectiveness Evaluation by the Central Social Insurance Medical Council 2nd Version", it is stated that " Unit costs should be derived from the latest medical fee schedule, the National Health Insurance Drug Price Standard, or similar resources. It is particularly essential to use the latest unit costs for the selected technology or comparator(s).". Academic analysis was performed using the latest drug price (as of April 2020) for the tisagenlecleucel and the comparators (blinatumomab, inotuzumab ozogamicin).

Table 3-4-1-2 Drug prices of comparators

	Manufacturer's submission	Academic analysis

Blincyto (blinatumomab)	JPY 281,345	JPY 286,336
Besponsa (inotuzumab ozogamicin)	JPY 1,307,092	JPY 1,331,297

3.4.2 QOL scores (for Age-related utility)

Table 3-4-2-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2	107	8

[Description of report]

Age-related utility

Because the utility inputs for the model were estimated based on a pediatric and adolescent population, the model considered additional age-related decrements as the modelled population became older over the modelled time horizon. The decrements were calculated based on Janssen 2014, which described the health utilities of healthy populations by different age groups using the EQ-5D index population norms based on the Japan time-trade-off value sets.[32] Age-related utility decrements were estimated based on the absolute utility values reported for each age group (e.g. adjustment for age 25-34 was calculated as 0.96/0.97) and were applied to all alive patients over the modelled time horizon.

[Details of academic analysis (revision)]

In the manufacture's analysis, population norms measured by EQ-5D-3L based on Tsuchiya et al. was used as the QOL score after cure. However, the most recent population norms in Japan was measured by Shiroiwa et al.[8] using EQ-5D-5L. The academic analysis was performed using the most recent data in Japan. The population norms by Shiroiwa et al. were shown in Table 3-4-2-2.

Table 3-4-2-2 Population norms of EQ-5D-5L

	Manufacturer's submission	Academic analysis
Age <25	0.97	0.9475
Age 25-34	0.96	0.9475
Age 35-44	0.97	0.9435
Age 45-54	0.94	0.9275
Age 55-64	0.91	0.932
Age 65-74	0.88	0.905
Age 75+	0.77	0.847

3.4.3 Estimation of EFS in the blinatumomab group

Table 3-4-3-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.1.1	99	10

[Description of report]
As such, up to year 5, EFS for blinatumomab was estimated based on its OS data assuming a constant cumulative HR between OS and EFS over time. The ratios were estimated based on inotuzumab per Bhojwani 2019.[16] To estimate an overall cumulative HR between OS and EFS, the ratio was first estimated as the natural log of OS probability divided by the natural log of EFS probability at monthly intervals until the end of the observed period. The overall cumulative HR between OS and EFS was then calculated as the average of cumulative HRs at all monthly intervals. This assumption is justifiable on the basis that EFS is highly correlated with OS.[40]

[Details of academic analysis (revision)]

The manufacturer's submission used the assumption that OS and EFS are also highly correlated in the blinatumomab group, but this assumption is not always clinically validated. Therefore, in the analysis by the academic group, the robustness of the analytical was investigated by conducting a sensitivity analysis assuming that the ratio of EFS to OS is 1.00 as the most extreme assumption.

Table 3-4-3-2 Ratio of EFS to OS

	Manufacturer's submission	Academic analysis
EFS vs OS ratio	[redacted]	1.00

3.4.4 QOL scores (Treatment disutility)

Table 3-4-4-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2	106	16

[Description of report]
Treatment disutility
Inputs for treatment disutility in the treatment phase were based on the estimates from Sung et al., 2003.[31] A decrement of 0.42 was used for all comparators (i.e., blinatumomab and inotuzumab) and tisagenlecleucel. The treatment disutility estimates are assumed to capture the utility decrements for all short-term AEs associated with the treatment, with the exception for the cytokine release syndrome (CRS).

[Details of academic analysis (revision)]

The manufacture's analysis used the assumption that the decrease in QOL score (disutility) was the same between the tisagenlecleucel and the comparator group. On the other hand, the committee paper of NICE in the UK pointed out that the disutility (-0.42) during treatment did not apply to the blinatumomab group. Therefore, in the academic analysis, the robustness was investigated by a sensitivity analysis assuming that the decrease in QOL for blinatumomab is 0 as the most extreme assumption.

3.4.5 QOL scores (Subsequent HSCT disutility)

Table 3-4-5-1 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2	106	34

[Description of report]

Subsequent HSCT disutility

The model assumed patients could receive subsequent HSCT after initial treatment. Patients receiving subsequent HSCT were assumed to have additional HSCT disutility (a decrement of 0.57), derived from Sung et al., 2003.[31] The disutility associated with HSCT was assumed to last for 1. The rates of subsequent HSCT were obtained from the same clinical trial study used for the efficacy estimation. Similar to the efficacy inputs, age-group specific data was used for the rate of subsequent HSCT where feasible. The subsequent HSCT disutility considered in the model are summarized in Section 4.2.

[Details of academic analysis (revision)]

In the manufacturer's analysis, this decrease in QOL score (0.57) was applied for 1 year using Sun et al.. However, in Roddy et al.[4], which was used as a QOL score of PD in the manufacturer's analysis, changes in QOL scores after HSCT were shown. The decrease was smaller than 0.57. In addition, Felder-Puig et al.[9] reported QOL scores after HSCT in children. The decrease was in QOL score was 0.13 per year on average measured by HUI. According to Kurosawa et al.[10] surveyed in Japan, the QOL score within 1 year after HSCT was 0.59. That is, the manufacturer's analysis may have overestimated decreases in QOL scores after HSCT.

Therefore, in the academic analysis, robustness was investigated by a sensitivity analysis in which 0.13, a decrease in QOL score (disutility), was applied for 1 year after HSCT, and the period when 0.57 is used, was limited to

3 months.

4. Results of cost-effectiveness analysis

4.1 Results of academic analysis

・The following analysis should be performed

☑ Cost-effectiveness analysis (calculate the ICER)
☐ Cost-minimization analysis (compare costs with each other)

4.1.1 Results of base case analysis by the academic group

(a) Population aged <15 years

The base case analysis by the manufacturer and the academic group are shown in Tables 4-1-1-1 and 4-1-1-2, respectively. The academic group estimated the ICER to be JPY 2,184,285/QALY compared with blinatumomab, which was less than JPY 7.5 million/QALY.

Table 4-1-1-1 Base case analysis by the analysis by manufacturer

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	11.11	9.05	40,448,386	18,882,649	2,087,581
Comparator	2.07		21,565,737		

Table 4-1-1-2 Base case analysis by the academic group

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.86	8.57	40,475,633	18,722,085	2,184,285
Comparator	1.29		21,753,548		

(b) Population aged 15 to 25 years

Compared with blinatumomab, the base case analysis by the manufacturer and the academic group are shown in Tables 4-1-1-3 and 4-1-1-4, respectively. The base case results compared with inotuzumab ozogamicin are shown in Tables 4-1-1-5 and 4-1-1-6. The academic group estimated the ICER to be JPY 2,571,736 /QALY compared with blinatumomab, and JPY 2,747,550/QALY compared with inotuzumab ozogamicin, which were less than 7.5 million yen/QALY as with the results by the manufacturer.

Table 4-1-1-3 Base case analysis by the manufacturer (comparator: blinatumomab)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (yen)	Incremental cost (yen)	ICER (yen/QALY)
Tisagenlecleucel	11.58	8.56	40,245,192	17,256,268	2,015,349
Comparator	3.01		22,988,924		

Table 4-1-1-4 Base case analysis by the academic group (comparator: blinatumomab)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.55	6.64	40,258,162	17,084,078	2,571,736
Comparator	1.91		23,174,084		

Table 4-1-1-5 Base case results by the analysis by manufacturer (comparator: inotuzumab ozogamicin)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	11.58	9.55	40,245,192	19,049,180	1,994,592
Comparator	2.03		21,196,012		

Table 4-1-1-6 Base case analysis by the academic group (comparator: inotuzumab ozogamicin)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.55	6.88	40,258,162	18,906,157	2,747,550
Comparator	1.67		21,352,005		

4.1.2 Factors that are not reflected in the academic analysis but can influence the ICER

[Factors increasing ICER]

a) Duration of effect of tisagenlecleucel: This analysis assumes the effect of tisagenlecleucel continues for life time. However, the empirical data do not support the duration. The ICER is assumed to be worse than the current value if the effect of tisagenlecleucel does not continue for life time.

b) Retreatment with tisagenlecleucel: Retreatment with tisagenlecleucel is not considered in the current analysis. The ICER is assumed to be worse if the retreatment by tisagenlecleucel is needed for some patients.

4.2 Sensitivity analysis

(a) Population aged <15 years

The one-way sensitivity analysis was performed mainly for the parameters having a large impact on ICER in the manufacturer's submission. In addition, the academic group performed scenario analysis by changing the setting described in 3.4. The results are shown in Tables 4-2-1 to 4-2-6.

Even in the scenario analysis with the most extreme assumption, the ICER of tisagenlecleucel was less than JPY 7.5 million/QALY as compared with blinatumomab.

Table 4-2-1 Results of one-way sensitivity analysis

Parameter	Range of parameters		Rationale for setting	ICER range (JPY/QALY)	
	Lower limit	Upper limit		Lower limit	Upper limit
Discount rate	0%	4%	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	1,361,145	3,167,566

Table 4-2-2 Scenario analysis: the ratio of EFS to OS in the blinatumomab group is 1.00 (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.96	7.98	40,473,327	18,739,516	2,349,241
Comparator	1.98		21,733,811		

Table 4-2-3 Scenario analysis: the disutility of treatment with blinatumomab is 0 (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.88	8.52	40,475,633	18,722,085	2,197,215
Comparator	1.36		21,753,548		

Table 4-2-4 Scenario analysis: the disutility by HSCT is 0.13

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.94	8.52	40,475,633	18,722,085	2,197,066
Comparator	1.42		21,753,548		

Table 4-2-5 Scenario analysis: the period of disutility by HSCT is limited to 90 days

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.96	8.51	40,475,633	18,722,085	2,199,842
Comparator	1.45		21,753,548		

Table 4-2-6 Scenario analysis: the HSCT implementation rate in the tisagenlecleucel treatment group is the same with the comparator group (30.65%) (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	9.79	8.51	43,651,272	21,897,724	2,574,183
Comparator	1.29		21,753,548		

(b) Population aged 15 to 25 years

The one-way sensitivity analysis was performed mainly for the parameters having a large impact on ICER in the manufacture's submission. In addition, scenario analysis was performed by changing the setting described in 3.4. The results compared with blinatumomab are shown in Tables 4-2-7 to 4-2-12, and the results compared with inotuzumab ozogamicin are shown in Tables 4-2-13 to 4-2-16.

Even in the scenario analysis with the most extreme assumption, the ICER of tisagenlecleucel was less than JPY 7.5 million/QALY as compared with both blinatumomab and inotuzumab ozogamicin.

Table 4-2-7 Results of one-way sensitivity analysis (comparator: blinatumomab)

Parameter	Range of parameters		Rationale for setting	ICER range (JPY/QALY)	
	Lower limit	Upper limit		Lower limit	Upper limit
Discount rate	0%	4%	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	1,747,541	3,496,074

Table 4-2-8 Scenario analysis: the ratio of EFS to OS in the blinatumomab group is 1.00 (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.73	5.88	40,253,838	17,106,019	2,907,616
Comparator	2.85		23,147,819		

Table 4-2-9 Scenario analysis: the disutility of treatment with blinatumomab is 0 (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.58	6.60	40,258,162	17,084,078	2,588,772
Comparator	1.98		23,174,084		

Table 4-2-10 Scenario analysis: the disutility by HSCT is 0.13

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.65	6.58	40,258,162	17,084,078	2,596,894
Comparator	2.07		23,174,084		

Table 4-2-11 Scenario analysis: the period of disutility by HSCT is limited to 90 days

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.67	6.56	40,258,162	17,084,078	2,602,382

Comparator	2.10		23,174,084		

Table 4-2-12 Scenario analysis: Assuming that the HSCT implementation rate in the tisagenlecleucel treatment group is the same as the comparator group (35.71%) (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.47	6.56	44,355,564	21,181,480	3,229,059
Comparator	1.91		23,174,084		

Table 4-2-13 Results of one-way sensitivity analysis (comparator: inotuzumab ozogamicin)

Parameter	Range of parameters		Rationale for setting	ICER range (yen/QALY)	
	Lower limit	Upper limit		Lower limit	Upper limit
Discount rate	0%	4%	Because the influence on ICER is large among the factors of the one-way sensitivity analysis performed by the manufacturer	1,882,060	3,703,46

Table 4-2-14 Scenario analysis: the disutility by HSCT is -0.13

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.65	6.79	40,258,162	18,906,157	2,783,302
Comparator	1.85		21,352,005		

Table 4-2-15 Scenario analysis: the period of disutility by HSCT is set as 90 days

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.67	6.77	40,258,162	18,906,157	2,791,132
Comparator	1.89		21,352,005		

Table 4-2-16 Scenario analysis: the HSCT implementation rate in the tisagenlecleucel treatment group is same with the comparator group (41.18%) (most extreme assumption)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	8.45	6.77	45,594,314	24,242,308	3,579,509
Comparator	1.67		21,352,005		

4.3 Interpretation of cost-effectiveness analysis

(a) Population aged <15 years

Population	Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia.

	Patients aged 25 years or younger (at the time of treatment) who meet any of the following criteria (a) and (b) shall be included. ・ Patients with primary disease who have not achieved remission after the standard chemotherapy was performed at least twice ・ Patients with relapsed disease who have not achieved remission after the chemotherapy was performed at least once ・ Patients who are not indicated for allogeneic hematopoietic stem cell transplantation or who have relapsed after allogeneic hematopoietic stem cell transplantation
Comparator	Blinatumomab ± alloHSCT
Type of the threshold	☐ Regular product ☑ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☑ JPY 5 million or less (JPY 7.5 million or less) ☐ More than JPY 5 million (more than JPY 7.5 million) and not more than JPY 7.5 million (not more than JPY 11.25 million) ☐ More than JPY 7.5 million (more than JPY 11.25 million) and not more than JPY 10 million (not more than JPY 15 million) ☐ More than JPY 10 million (more than JPY 15 million) ☐ Equivalent (or inferior) in effectiveness and expensive
Reason for such judgment	The base case analysis showed the ICER of JPY 2,184,285/QALY. In addition, sensitivity analyses of the parameters resulted in the ICER of less than JPY 7.5 million/QALY in all cases. Based on the above, the ICER in the this population is most likely to belong to the interval of "JPY 7.5 million or less".

(b) Population aged 15 to 25 years

Population	Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Patients aged 25 years or younger (at the time of treatment) who meet any of the following criteria (a) and (b) shall be included. ・ Patients with primary disease who have not achieved remission after the standard chemotherapy was performed at least twice ・ Patients with relapsed disease who have not achieved remission after the chemotherapy was performed at least once ・ Patients who are not indicated for allogeneic hematopoietic stem cell transplantation or who have relapsed after allogeneic hematopoietic stem cell transplantation
Comparator	Blinatumomab ± alloHSCT and inotuzumab ozogamicin ± alloHSCT
Type of the threshold	☐ Regular product ☑ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☑ JPY 5 million or less (JPY 7.5 million or less) ☐ More than JPY 5 million (more than JPY 7.5 million) and not more than JPY 7.5 million (not more than JPY 11.25 million) ☐ More than JPY 7.5 million (more than JPY 11.25 million) and not more than JPY 10 million (not more than JPY 15 million) ☐ More than JPY 10 million (more than JPY 15 million) ☐ Equivalent (or inferior) in effectiveness and expensive
Reason for such judgment	The base case analysis showed that the ICER compared with blinatumomab is JPY 2,571.73/QALY. The ICER compared with inotuzumab ozogamicin is JPY 2,745,550 /QALY. In addition, sensitivity analyses of the parameters

	resulted in the ICER of less than 7.5 million yen/QALY in all cases. Based on the above, the ICER in the this population is most likely to belong to the interval of "7.5 million yen or less".

4.4 Price adjustment rate

4.4.1 Proportion of patients with ALL and DLBCL

For the proportions of patients with ALL and DLBCL, the manufacturer has estimated [redacted] patients ([redacted]%) with ALL and [redacted] patients ([redacted]%) with DLBCL based on a peak predicted exposure of 216 patients. The manufacturer explained that estimates were made based on [redacted] rather than actual clinical data because of not enough time since the recent launch of tisagenlecleucel. This estimate by the manufacturer is acceptable to the academic group. Therefore [redacted]% is used as the proportion of patients with ALL.

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