CORE2 HEALTH

C2H
Evaluation Report

C2H1902

Tisagenlecleucel/DLBCL (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 diffuse large B-cell lymphoma (DLBCL)

[November 11, 2020]

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list of abbreviations

Abbreviations	Formal description
AIC	Akaike's Information Criterion
ALL	Acute Lymphoblastic Leukemia
ASCT	Autologous hematopoietic Stem Cell Transplant
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
C2H	Center for Outcomes Research and Economic Evaluation for Health
CI	Confidence Interval
DLBCL	Diffuse Large B-Cell Lymphoma
EQ-5D	EuroQol 5 Dimension
EQ-5D-5L	EuroQol 5 Dimension 5 Level
HAS	Haute Autorité de Santé
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
HSCT	Hematopoietic Stem Cell Transplantation
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MAIC	Matched Adjusted Indirect Comparison
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
PFS	Progression Free Survival
QALY	Quality-Adjusted Life Year
QOL	Quality of Life

R-CHOP	Rituximab with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
R-DHAP	Rituximab with Dexamethasone, Cisplatin, and Cytarabine
R-GEMOX	Rituximab with Gemcitabine and Oxaliplatin
R-ICE	Rituximab with Ifosfamide, Carboplatin, and Etoposide
RCT	Randomized Controlled Trial
RL	Relapse
SCT	Stem Cell Transplant
SMC	Scottish Medicines Agency
SMR	Service Médical Rendu

0. Framework of analysis

Table 0-1 The framework of analysis

Population	Patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma (DLBCL) who are divided into the following age groups: (a) <70 years (b) ≥70 years
comparator	Population (a): Salvage chemotherapy +/- allogeneic hematopoietic stem cell transplantation (HSCT) Population (b): Salvage chemotherapy
Reason for selection of comparator	Salvage chemotherapy +/- allogeneic HSCT is the standard and effective for these DLBCL patients. For the population (b), allogeneic HSCT is generally not performed considering their age. Therefore comparators are determined as above.
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

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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:)/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: 294,381 €/QALY over 10 years)/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: On the condition that there is a substantial reduction in price)/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 sharing 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/ta567	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	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	Same as in the left
Dosage	Treatment with tisagenlecleucel comprises a single-dose intravenous infusion. It is intended for autologous use only and the dosage for adults with diffuse large B-cell lymphoma is 0.6 to 6.0x10^8 CAR-positive viable T cells.	Same as in the left
Comparator	Salvage chemotherapy excluding pixantrone	Same as in the left
Incremental cost-effectiveness ratio (ICER)	Company's base case: (ICER): £46,325 The committee: ranged between £42,991 and £55,403	Same as in the left

	per QALY gained	

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-resubmission-smc2200/	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	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	Same as in the left
Dosage	Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion. The recommended single dose of tisagenlecleucel for DLBCL patients is 0.6 to 6.0 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells (non-weight based).	Same as in the left
Comparator	Salvage chemotherapy	Same as in the left
Incremental cost-effectiveness	Base-case results – with PAS	Same as in the left

ratio (ICER)	Vs [R-]Gem-Ox ICER: £44,330 Vs [R-]GDP ICER: £44,151	

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/pprd_2982962/en/kymriah	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	SMR: Important / ASMR: IV	Same as in the left
If conditionally recommended, details of the condition	NA	Same as in the left
Disease	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	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 the dosage for adults with diffuse large B-cell lymphoma is 0.6 to $6.0x10^8$ CAR-positive viable T cells.	Same as in the left
Comparator	Salvage chemotherapy, Yescarta, palliative care, and alloSCT if patient eligible	Salvage chemotherapies · R-DHAP · R-ICE · R-GEMOX

Incremental cost-effectiveness ratio (ICER)	NA	294 381 €/QALY over 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/projects-results/projects/health-economic/g18-10-tisagenlecleucel-diffuse-large-b-cell-lymphoma-assessment-according-to-35a-para-1-sentence-11-social-code-book-v.10620.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	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	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 the dosage for adults with diffuse large B-cell lymphoma is 0.6 to 6.0x10^8 CAR-positive viable T cells.	Same as in the left
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	Manufacturer
Organization	CADTH	
URLs	https://cadth.ca/sites/default/files/pdf/car-t/ct0001-op0538-in-brief-e.pdf	https://cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-economic-report-DLBCL-jan2019.pdf
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	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma 33 (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma	Same as in the left
Dosage	Tisagenlecleucel is recommended as a single, onetime treatment (0.6 to 6.0 x 10^8 CAR-positive viable T cells).	Same as in the left
Comparator	salvage chemotherapy	Same as in the left
Incremental cost-effectiveness	For r/r DLBCL, tisagenlecleucel, compared with palliative	Same as in the left

ratio (ICER)	chemotherapy, was associated with an incremental cost per QALY of CAD$211,870.	

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/1519.1-public	Same as in the left
Target technology	Tisagenlecleucel	Same as in the left
Results	Support	Conditional recommendation
If conditionally recommended, details of the condition	An initial progress review at Year 1 to assess appropriateneness of patient eligibility criteria and patient numbers, with a full review of clinical effectiveness, costeffectiveness and budget impact to be conducted by the MSAC no later than 2 years post the commencement of public subsidy	Risk-sharing arrangement · Treatment must be delivered by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy; · Treatment must be delivered in a tertiary public hospital with appropriate credentials; · Governance and prescribing rules to ensure treatment is directed to patients most likely to benefit; · No payment for tisagenlecleucel for an unsuccessful infusion;

		· No payment for tisagenlecleucel if a patient is apheresed but does not receive the infusion of engineered lymphocytes; · A limit to one successful CAR-T infusion per lifetime; · Data on the use of tisagenlecleucel for B cell lymphoma's in Australia should be recorded by the Australian Bone Marrow Transplant Recipient Registry, with the cost of data collection met by the applicant · An initial progress review at Year 1 to assess appropriateneness of patient eligibility criteria and patient numbers, with a full review of clinical effectiveness, costeffectiveness and budget impact to 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)
Disease	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	Same as in the left

Dosage	0.6 to 6.0 x 10^8 CAR-positive viable T cells (non-weight based)	Same as in the left
Comparator	Salvage chemotherapy with the intention to proceed to allo- or auto-SCT	Salvage chemotherapy regimen
Incremental cost-effectiveness ratio (ICER)	NA	Not disclosed

[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.

・For the UK (SMC), there is a discrepancy between Table 1-1 and Table 1-3-2 in the manufacturer's report. Table 1-3-2 referred to conditional recommendation.
・An ICER was reported for France (HAS). The comparator at this time was salvage chemotherapy with an ICER of 294,381 €/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.

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	Adult patients with relapsed or refractory DLBCL However, limited to patients who meet any of the following criteria and are not indicated for autologous hematopoietic stem cell transplantation (ASCT) or relapsed after ASCT: ・ Failure to achieve a complete response with chemotherapy or recurrence with chemotherapy after at least two chemotherapies in patients with initial disease and at least one chemotherapy after recurrence in patients with relapsed disease
Intervention	The following therapies for the indication in the population: ・ Tisagenlecleucel
Comparator	Clinically used salvage chemotherapy
Outcome	Any of the following outcomes: ・ Survival (duration) Overall survival rate ・ Efficacy Event-free survival Disease-free survival Progression-free survival (PFS) Response rate Remission rate Recurrence rate ・ Safety Adverse events ・ Health-related quality of life (HRQL)

Study design	・RCT ・Controlled study ・Single arm study ・Observational studies in some cohorts of RCTs
Literature search period	From January 1, 2019 to September 24, 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	・ Adult patients with relapsed or refractory DLBCL treated with ≥2 lines of chemotherapy who have failed, are ineligible for, or do not consent to ASCT ・ Non-specified DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma ・ ≥80% patients with DLBCL arising from DLBCL or follicular lymphoma if other histology is included and results for the DLBCL subgroup are not reported	・ Patients with low-grade non-Hodgkin's lymphoma ・ Population in which <80% patients underwent R-CHOP therapy ・ Patients who meet the following criteria Patients with active hepatitis B infection Patients with active hepatitis C infection Patients with active human immunodeficiency virus infection Patients with central nervous system lesion caused by malignant tumor
Intervention	Available therapies	Therapies not clinically used CAR-T therapy other than tisagenlecleucel
Comparator	No restrictions	
Outcome	At least one of the following outcomes: ・ Survival (duration) OS	

	・Efficacy Event-free survival Disease-free survival PFS Response rate Remission rate Recurrence rate ・Frequency and timing of stem cell transplantation ・Safety Adverse events ・Health-related quality of life (HRQL)	
Study design	・RCT ・Controlled study ・Single arm study ・Observational studies in some cohorts of RCTs	・Sample size less than 5
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
Population	#1	"lymphoma, large b-cell, diffuse"[MeSH] OR "lymphoma, primary cutaneous anaplastic large cell"[MeSH] OR DLBCL OR "Diffuse large B-cell lymphoma" OR ((Lymphoma*[TIAB]) AND (diffuse[TIAB] OR "B-Cell"[TIAB] OR "Large Cell"[TIAB] OR Anaplastic[tiab] OR Primary[TIAB] OR "Aggressive NHL"[TIAB] OR "non-Hodgkin*"[TIAB]))
	#2	Recurrence[TIAB] OR recurrent[TIAB] OR recurring[TIAB] OR refractory[TIAB] OR relaps*[TIAB] OR "R/R"[TIAB] OR fail*[TIAB]
	#3	#1 AND #2
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
Limitation of integration and search period	#5	#3 AND #4
	#6	#5 AND 2019:2020[DP]

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

Item	Serial number	Search formula
Population	#1	リンパ腫-びまん性大細胞型 B 細胞性/TH or びまん性大細胞型 B 細胞性リンパ腫/AL or "Diffuse large B-cell lymphoma"/AL or ((リンパ/AL or Lymphoma/AL) and (原発性/AL or primary/AL or 未分化/AL or anaplastic/AL or 攻撃性/TH or 攻撃性/AL or aggressive/AL or びまん性/AL or diffuse/AL or B 細胞/TH or B 細胞/AL or B-Cell/AL or "B cell"/AL or 大細胞/AL or "Large Cell"/AL or リンパ腫-非 Hodgkin/TH or 非ホジキン/AL or non-Hodgkin/AL or "non Hodgkin"/AL)
	#2	(再発/TH or 再発/AL or relapse/AL) or (難治性/AL or refractory/AL) or 失敗/AL
	#3	#1 AND #2
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 非ランダム化/AL 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
	#6	#5 AND (DT=2019:2020)

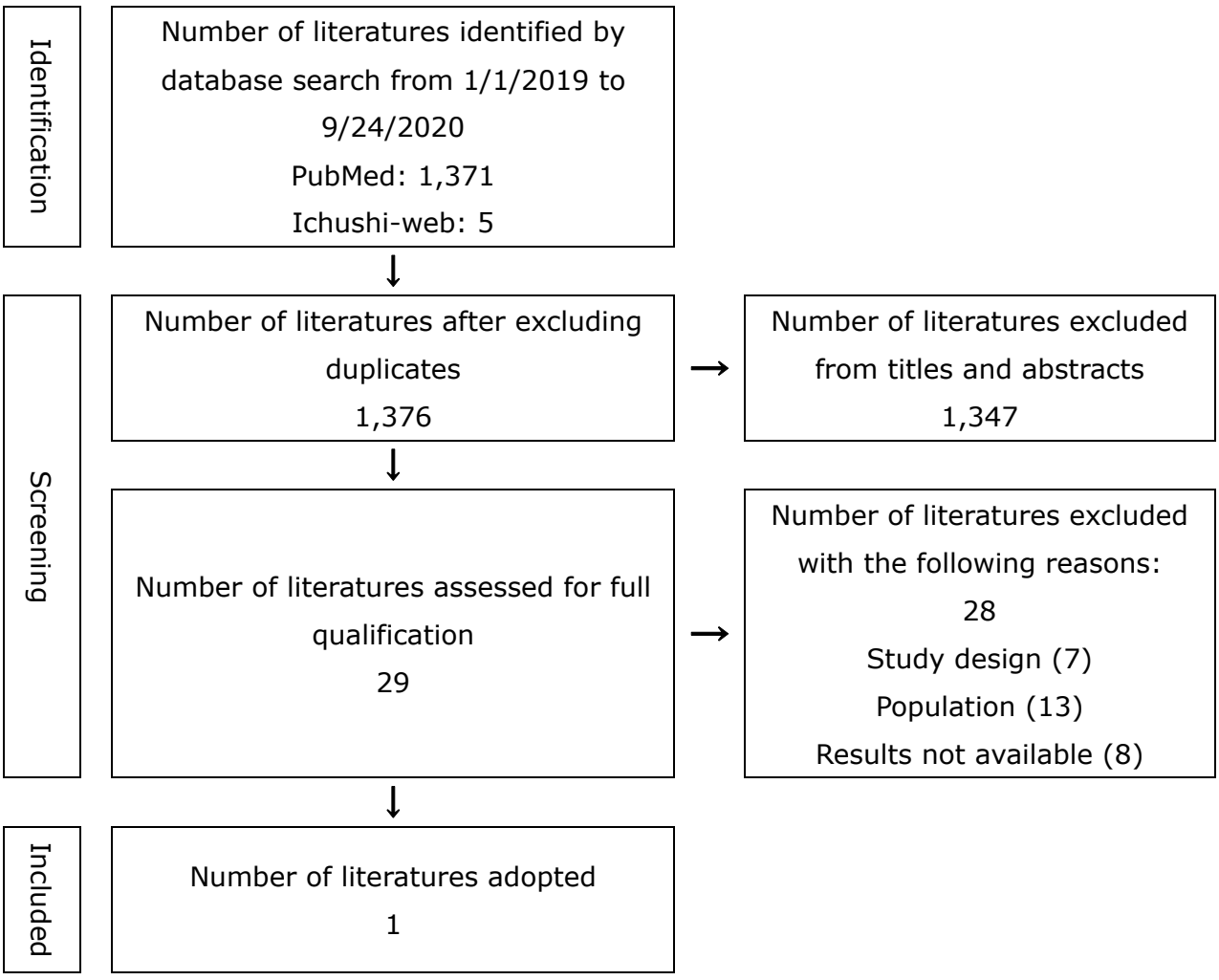
2.2.4 Other

No special notes

2.3 Search results

As a result of a SR, JULIET study, a clinical trial of tisagenlecleucel, was obtained. This literature was also considered in the evaluation of the additional benefit of manufacturers, and no new qualified literature was obtained to evaluate the additional benefit.

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 those 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 from [redacted], [redacted] to [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 24, 2020).

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

The number of literatures included in the screening differed because the search period was different. However there was no difference in the literatures critical to the evaluation of additional benefit.

- Validity of the SR performed by the manufacturer.

It is not appropriate to limit the scope of SR to the Japanese population. However, the review included all the literatures critical to the evaluation of additional benefit.

2.4 Evaluation of additional benefit

The manufacturer's explanation about the presence or absence of additional benefit is reasonable for population aged <70 years and that aged ≥70 years, with additional benefit for the comparator.

Table 2-4-1 Evaluation of additional benefit [Population aged <70 years]

	Manufacturer	Academic analysis
Population	DLBCL patients aged <70 years	Same as in the left
Intervention	Tisagenlecleucel	Same as in the left
Comparator	Rescue chemotherapy +/- allogeneic HSCT	Same as in the left
Outcome	OS	Same as in the left
Additional benefit (Yes/No)	■ additional benefit is 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)	The conditional HR (OS) was [redacted] (95% CI: [redacted]) in the MAIC analysis of the population aged <70 years in JULIET Study versus CORAL extension studies (all patients were aged ≤70 years). Based on these results, it was judged that this product has additional benefit for the comparator.	The point estimate of conditional HR assumes the OS event is to approximately [redacted], which is considerably smaller than 1. 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.

Table 2-4-2 Evaluation of additional benefit [Population aged ≥70 years]

	Manufacturer	Academic analysis
Population	DLBCL patients aged ≥70 years	Same as in the left
Intervention	Tisagenlecleucel	Same as in the left
Comparator	Rescue chemotherapy	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	Same as in the left

	☐ Indirect comparison of RCT ■ Comparison of single-arm studies ☐ No clinical study data	
Additional benefit (Reason)	As for the efficacy data in the intervention group (tisagenlecleucel), the number of patients aged ≥70 years who correspond to this population is limited to [redacted] among patients who received this product in the JULIET study. In addition, the amount of information for analysis of OS and progression-free survival (number of events by the survival time analysis method) is [redacted] patients. Originally, the JULIET study was designed without assuming analysis by age, resulting in a very small sample size and reduced statistical power when stratified by age. Therefore, it is difficult to examine the comparability in indirect comparison and to adjust the data using statistical methods. Based on the above, it is extremely difficult to judge only the additional benefit based on the results of extraction of patients aged ≥70 years in the JULIET Study. In C2H of the 3rd meeting of the Expert Committee of Cost-Effectiveness Evaluation held on [redacted] 2019, a comment was obtained that if it becomes difficult to	Since the number of patients aged ≥70 years is very limited and the number of events is [redacted], the academic analysis also supports the use of data from the entire population to evaluate additional benefit in the population aged ≥70 years. The point estimate of conditional HR assumes the OS event is approximately [redacted], which is considerably smaller than 1. 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.

	show the additional benefit by constructing a subpopulation that was not originally assumed, it is acceptable to refer to the results of the entire population before segmentation, and in this case, the entire population without age division. The conditional HR was [redacted] (95% CI: [redacted]) in the MAIC analysis (OS) between the entire population in the JULIET Study and the CORAL extension studies (all patients were aged ≤70 years). Since the additional benefit was confirmed by indirect comparison of the entire population, it was judged that this product has additional benefit for the comparator also for this patient population.	

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) Mean age in the target patient population [only in the population aged <70]
b) Extrapolation of survival curves (PFS and OS) [only in the population aged <70 years]
c) Data source of survival curves (PFS and OS) for tisagenlecleucel [only in the population aged ≥70 years]
d) QOL scores for PFS

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

a) Cost parameters (drug prices)
b) Cost parameters (salvage chemotherapy)
c) Cost of PFS (Excel model)

3.3 Analysis by the academic group for major points

3.3.1 Mean age in the patient population [only in the population aged <70 years]

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)
5.1.4	176	5

[Description of report]
Change in starting age (DLBCL only)
The starting age for the bace case analysis was set at [redacted] years for the population to be analyzed aged <70 years and [redacted] years at that aged ≥70 years (Section 5.2). These are the mean age of patients included in the tisagenlecleucel efficacy data by population to be analyzed. In general, the age representative of the patients included in the efficacy data will be used as the starting age for the analysis in the cost-effectiveness analysis. For the population to be analyzed aged ≥70 years, we received a comment from C2H that the starting age for analysis was 70 years in the discussion with C2H held on [redacted] 2019, and it can be said that the age of [redacted] years is a more conservative setting.
In addition, according to an Internet survey conducted on clinicians by us (for details, see 5.1.5), the intention to prescribe CAR-T therapy including tisagenlecleucel varies greatly by age group, and it is therefore considered inappropriate to use age composition such as cancer registration data and epidemiological data as the starting age for analysis. As a scenario analysis, ICER was analyzed when the starting age for analysis was changed (Section 5.1.2).
The mean age of DLBCL patients aged <70 years was calculated from the data of [redacted] which was considered in the scenario analysis. When the starting age was set at [redacted] years, there was no major difference in the results from the base-case. For patients aged

≥70 years, no scenario analysis has been set because the intention of prescription is markedly limited, and since the basic analysis was a conservative analysis compared with the patients aged 70 years for which comments were given by C2H, scenario analysis regarding the starting age has not been performed.

[Details of academic analysis (revision)]

The mean age of the population in the base-case analysis was changed to 57 years instead of [redacted] years. It was higher than that used by the manufacturer (early 50s).

The manufacturer used the mean age of the population enrolled in the clinical studies. However the characteristics of patients enrolled in the clinical studies are not consistent with those of patients treated with tisagenlecleucel in the actual clinical practice. Therefore, the mean age of the patient with DLBCL aged <70 who underwent autologous transplantation was estimated by the following procedures, usingNDB；National Database of Health Insurance Claims and Specific Health Checkups of Japan. In principle, the patients treated with tisagenlecleucel have undergone autologous transplantation. Therefore, the age of patients estimated from the claim database is more appropriate. This value is also consistent with the mean age based on data from [redacted] submitted by the manufacturer.

Table 3-3-1-2 Changes of the starting age

	Manufacturer's submission	Academic analysis
Starting age	[redacted]	57

[Estimation method and results based on the claims database]

Patients aged <70 years with DLBCL-related disease name (International Classification of Diseases-10 code: C833) between October 2018 and September 2019 were included. The month when the autologous transplant-related claim code (hematopoietic stem cell transplantation [bone marrow transplantation] [autologous transplantation]: 150266410, hematopoietic stem cell transplantation [peripheral blood stem cell transplantation] [autologous

transplantation]: 150266310) is included in the patients was defined as the month when the stem cell transplantation was performed in the DLBCL patient. The age was estimated from the age class recorded in this month (5-year increments). The mean age was calculated by multiplying the frequency for each class by the class value and dividing by the number of patients. The median was also calculated.

As a result, 380 patients were included (the table below). Mean and median age were 56.8 and 57.0 years, respectively.

Table 3-3-1-3 Number of patients by age class

Age class	n	%
0 to 39 years old*	24	6.3%
40-44	15	3.9%
45-49	28	7.4%
50-54	56	14.7%
55-59	67	17.6%
60-64	114	30.0%
65-69	76	20.0%
Total	380	100.0%

*For the age of 0 to 39 years, a total value is shown because there are cells in which the number of patients is less than 10.

3.3.2 Extrapolation of survival curves (PFS and OS) [only in the population aged <70 years]

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

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.1.2	101-103	Figure 27, 28

[Description of report]
Estimation of survival curve (OS)
The OS associated with tisagenlecleucel infusion was based on the data from the JULIET trial among patients <70 years (data cut-off: [redacted]). It was defined as starting from the time of infusion per JULIET trial protocol. The OS for patients in the tisagenlecleucel arm but not infused was the same as that of the salvage chemotherapy. The OS associated with salvage chemotherapy was derived from the published Kaplan-Meier (KM) curves in the CORAL extension studies, and was defined from the time of last relapse.[11], [12] CORAL is considered to be more appropriate for this age-specific population group since all patients are less than 70 years old. Pseudo-patient level data were then derived based on the KM data using the algorithm outlined in Guyot et al. 2012.[35] The number of event information was incorporated into the reconstruction of individual patient data (IPD).
For both tisagenlecleucel infused patients and salvage chemotherapy, the observed OS were used during the trial period until year 3. Afterwards, those who remained alive were assumed long-term survivors of DLBCL. Maurer et al., 2014 identified "patients with DLBCL who achieve event-free status at 24 months (EFS24) have a subsequent overall survival equivalent to that of the age- and sex-matched general population", based on prospective patient data. The assumption of 3 years as a cure point is considered more conservative.[42] The long-term DLBCL survival was modelled using the 2018 Japan life table, with a mortality adjustment using the standardized mortality ratio (SMR) of DLBCL longterm survivors published in literature.[38], [42]

The same mortality risk was applied to all patients who remained alive from year 3 onwards in the model. This assumption reduced some of the long-term uncertainties arising from data extrapolation beyond the maximum reported follow-up. A targeted literature review was conducted to identify publications to inform long-term survival for the study population (registry or SMR studies). Maurer et al., 2014 was identified as the most relevant input source and used to inform the mortality of long-term DLBCL survivors.[42]
The predicted OS curves for tisagenlecleucel and salvage chemotherapy in the base-case analysis are reported in Figure 27.

Estimation of survival curve (PFS)
The PFS of tisagenlecleucel infused patients was based on the data from the JULIET trial (data cut-off: [redacted]) among patients <70 years. To be consistent with the approach used for the OS estimation, observed data were used during the trial period until year 3. After year 3, the cumulative survival probabilities of PFS were assumed to flatten up until they reached OS. PFS was assumed to be less than or equal to OS at all time points. The PFS for patients in the tisagenlecleucel arm but not infused was the same as that of the salvage chemotherapy.
PFS data for salvage chemotherapy were not available in the literature. In the absence of data, the PFS curve was derived from the OS curve assuming a constant cumulative HR over time, i.e., the cumulative hazard function for PFS would be proportional to cumulative hazard function for OS. The ratio was based on the (R)-ICE and (R)-DHAP arms from Gisselbrecht et al. 2010.[43] To estimate an overall cumulative HR between OS and PFS, the ratio was first estimated as the natural log of OS probability divided by the natural log of PFS probability at yearly intervals until the end of the observed period. The overall cumulative HR between OS and PFS was then calculated as the average of cumulative HRs at all yearly intervals. This assumption is justifiable on the basis that PFS is highly correlated with OS.[44] The predicted PFS curves for tisagenlecleucel and salvage chemotherapy in the base-case analysis are reported in Figure 28.

[Details of academic analysis (revision)]

According to the manufacture's analysis, after three years (cure point) 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 cannot consider excess mortality in PD/RL patients, and the OS was overestimated. Therefore, this cannot be regarded as an appropriate OS extrapolation. For example, the life expectancy of the PD/RL patient after 3 years was approximately 10 years or more in the population aged <70 years.

In addition, the PFS function was extrapolated by a horizontal line (y=C; C is a constant) assuming that no event occurs. However, even the patients with PFS should experience events such as death due to other causes. Death events that are reflected in OS should be handled as events in PFS. Such extrapolation of EFS function is not appropriate.

In the manufacturer's response to our inquiry (dated [redacted] 2020), it was described "After 3 years of treatment with Kymriah, long-term survival (cure) was assumed, and the subsequent OS was extrapolated using the SMR of Maurer et al. in 2014.". The fact that long-term survival (cure) can be achieved by tisagenlecleucel was acceptable. This could be achieved by the "absence of recurrence (after the 3rd year)". It did not justify the extrapolation of the EFS curve after the 3rd 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.

The OS function was extrapolated using the parametric function estimated by the manufacturer when the Kaplan-Meier curve is interrupted (the Cycle 37 after the 3rd year (Cycle 36)). The manufacturer did not use a parametric function to estimate survival time curves for DLBCL population. Therefore, by extrapolating the integrated function by weighting each parametric function based on the weighted AIC, we estimate OS curve.

It does not actually occur that the mortality rate estimated by the parametric OS function is smaller than the SMR-based mortality rate by the manufacturer. If such case occurs, the OS function was extrapolated by switching the curve to the mortality rate based on the SMR at the time point.

The PFS function was extrapolated after the Cycle 37 year using the standardized mortality ratio used by the manufacturer to account for the deaths other than other disease. However, if the OS and PFS functions crossed, the OS function was also extrapolated using the PFS function estimation method.

Table 3-3-2-2 Estimated life years

	Manufacturer's submission (starting age: [redacted] years)		Academic analysis (starting age: 57 years)	
	Tisagenlecleucel group	Salvage chemotherapy +/- allogeneic HSCT group	Tisagenlecleucel group	Salvage chemotherapy +/- allogeneic HSCT group
Life years	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PD/RL	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3-3-2-1 Estimated survival curve by manufacturer for the tisagenlecleucel group

Figure 3-3-2-2 Estimated survival curve by academic analysis for the tisagenlecleucel group

Figure 3-3-2-3 Estimated survival curve by manufacturer for salvage chemotherapy +/- allogeneic HSCT group

Figure 3-3-2-4 Estimated survival curve by academic analysis for salvage chemotherapy +/- allogeneic HSCT group

3.3.3 Data source of survival curves (PFS and OS) for tisagenlecleucel [only in the population aged ≥70 years]

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

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.1.3	103-105	Figure 29, 30

[Description of report]
Estimation of survival curve (OS)
The OS associated with tisagenlecleucel infusion was based on the data from the JULIET trial among patients ≥70 years (data cut-off: [redacted]).[29] It was defined as starting from the time of infusion per JULIET trial protocol. The OS for patients in the tisagenlecleucel arm but not infused was the same as that of the salvage chemotherapy. The OS associated with salvage chemotherapy was derived from the published Kaplan-Meier (KM) curves for patients without subsequent SCT in the CORAL extension studies, and was defined from the time of last relapse.[11], [12] Pseudo-patient level data were then derived based on the KM data using the algorithm outlined in Guyot et al. 2012.[35] The number of event information was incorporated into the reconstruction of individual patient data (IPD). For both tisagenlecleucel infused patients and salvage chemotherapy, the [redacted] observed OS were used during the trial period until year 3. Afterwards, those who remained alive were assumed long-term survivors of DLBCL. Maurer et al., 2014 identified "patients with DLBCL who achieve event-free status at 24 months (EFS24) have a subsequent overall survival equivalent to that of the age- and sex-matched general population", based on prospective patient data. The assumption of 3 years as a cure point is considered more conservative. The longterm DLBCL survival was modelled using the 2018 Japan life table, with a mortality adjustment using the standardized mortality ratio (SMR) of DLBCL longterm survivors published in literature.[38], [42] The same mortality risk was applied to all patients who remained alive from

year 3 onwards in the model. This assumption reduced some of the long-term uncertainties arising from data extrapolation beyond the maximum reported follow-up. A targeted literature review was conducted to identify publications to inform long-term survival for the study population (registry or SMR studies). Maurer et al., 2014 was identified as the most relevant input source and used to inform the mortality of long-term DLBCL survivors.[42] The predicted OS curves for tisagenlecleucel and salvage chemotherapy in the base-case analysis are reported in Figure 29.

Estimation of survival curve (PFS)

The PFS of tisagenlecleucel infused patients was based on the data from the JULIET trial (data cut-off: July 1, 2019) among patients ≥70 years.[29] To be consistent with the approach used for the OS estimation, observed data were used during the trial period until year 3. After year 3, the cumulative survival probabilities of PFS were assumed to flatten up until they reached OS. PFS was [redacted] assumed to be less than or equal to OS at all time points. The PFS for patients in the tisagenlecleucel arm but not infused was the same as that of the salvage chemotherapy. PFS data for salvage chemotherapy were not available in the literature.[11], [12] In the absence of data, the PFS curve was derived from the OS curve assuming a constant cumulative HR over time, i.e., the cumulative hazard function for PFS would be proportional to cumulative hazard function for OS. The ratio was based on the (R)-ICE and (R)-DHAP arms from Gisselbrecht et al. 2010.[43] To estimate an overall cumulative HR between OS and PFS, the ratio was first estimated as the natural log of OS probability divided by the natural log of PFS probability at yearly intervals until the end of the observed period. The overall cumulative HR between OS and PFS was then calculated as the average of cumulative HRs at all yearly intervals. This assumption is justifiable on the basis that PFS is highly correlated with OS.[44] The predicted PFS curves for tisagenlecleucel and salvage chemotherapy in the base-case analysis are reported in Figure 30.

[Details of academic analysis (revision)]

In analyzing the population aged ≥70 years, the manufacturer estimated OS and PFS functions using the data of patients aged ≥70 years in the JULIET

Study. However, the proportion of the population aged ≥70 years in the JULIET Study was only [redacted]% ([redacted]), which was [redacted] [redacted]% of the entire population.

As a result, the OS in the population aged ≥70 years was [redacted]% at 3 years, which is more than [redacted]% higher than the OS in the population aged <70 years ([redacted]%) and the OS in the entire population ([redacted]%). In addition, the PFS in the population aged ≥70 years was [redacted]% at 3 years, which is more than [redacted]% different from the PFS in the population aged <70 years ([redacted]%) and the PFS in the entire population ([redacted]%).

However, it is not appropriate to use the data of small population that is sensitive to random error, unless there is evidence to support that older patient is associated with a greater effect of tisagenlecleucel. Therefore, it is more appropriate to analyze the population aged ≥70 years using the data of the entire population by assuming that there is no heterogeneity with the treatment effect in the entire population. The manufacturer uses the entire population to show additional benefit of population aged ≥70 years as follows;

"Among patients who received this product in the JULIET Study, only [redacted] patients aged ≥70 years correspond to this population. In addition, the amount of information for analysis of OS and progression-free survival (number of events by the survival time analysis method) is [redacted] patients. (...) For the above reasons, it is extremely difficult to judge only the additional benefit based on the results of extracting only the patients aged ≥70 years in the JULIET study." Only in the estimation of cost-effectiveness, it is inconsistent that limited data of patients aged ≥70 years is used..

For the OS and PFS functions through the 3rd year (Cycle 36), the parameters used by the manufacturer in each population shall be weighted by the sample size for each population (aged <70 years, [redacted]; aged ≥70 years, [redacted]) and pooled, as we don't have the data of entire population.

Thereafter, the OS and PFS functions were extrapolated in the same manner as Section 3.3.2. However, in and after Cycle 37, the parametric function of OS based on the entire population results in the JULIET Study is not included in the documents/data submitted by the manufacturer. Therefore, the OS function to be used for extrapolation shall be estimated by weighting the function

estimated from the population aged <70 years (weighted AIC) and the function estimated from the population aged ≥70 years (weighted AIC), respectively. This shall be extrapolated in and after Cycle 37 of the OS function.

Table 3-3-3-2 Estimated life years

	Manufacturer's submission		Academic analysis	
	Tisagenlecleucel group	Salvage chemotherapy group	Tisagenlecleucel group	Salvage chemotherapy group
Life years	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PD/RL	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3-3-3-1 Estimation of survival time curve by manufacturer for the tisagenlecleucel group

Figure 3-3-3-2 Estimation of survival time curve by academic analysis for the tisagenlecleucel group

Figure 3-3-3-3 Estimation of survival time curve by manufacturer for salvage chemotherapy group

Figure 3-3-3-4 Estimation of survival time curve by academic analysis for salvage chemotherapy group

3.3.4 QOL scores for PFS

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

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2.2	107	Table 4.2.2.2

[Description of report]
Health states utility
Because JULIET data did not collect EQ-5D data directly, a targeted literature review was conducted to identify publications that report quality-of-life measures for the population. The utility inputs used in the base-case were obtained from Chen et al. 2017, where micro-simulation models were developed to study the cost-effectiveness of precision treatment strategies for DLBCL patients.[33]
These inputs were also used in the most recent CEA model of CAR-T therapies for the adult lymphoma population developed by the Institute for Clinical and Economic Review. In the DSA, an alternative set of utility values were considered based on SF-36 data collected from the JULIET data. A mapping algorithm was used to convert the SF-36 data to derive the utility measures.

[Details of academic analysis (revision)]

The manufacturer used 0.83 as a QOL score for PFS. However, this PFS value is almost the same as the population norms of EQ-5D-5L in patients aged ≥70 years (male: 0.866, female: 0.828) shown by Shiroiwa et al.[1]. It is possible that QOL scores after the age of 70 may be overestimated.

For this reason, the academic analysis used 0.70, which reflects the actual status more based on Lin JK et al.[2] for the patients with PFS and age of 70 years or older. Therefore, for the population aged <70 years, the QOL score of PFS was set as 0.70 when they reach to 70 years old (if the starting age was set at 57 years, Cycle 156). For the population aged ≥70 years, the QOL score of PFS was set as 0.70 from Cycle 0 because the starting age was [redacted] years.

Table 3-3-4-2 QOL scores in PFS

	Manufacturer's submission	Academic analysis
Population aged <70 years	0.83 (total time horizon)	0.83 (time horizon up to age of <70 years) 0.70 (time horizon after age of 70 years)
Population aged ≥70 years	0.83 (total time horizon)	0.70 (total time horizon)

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, etc. 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 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's analysis, particularly the price of medicines for the salvage chemotherapy, is not consistent with the latest drug prices.

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, 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)." Analysis by the academic group shall be performed using the latest drug price (as of April 2020) [3]. For dexamethasone (oral) and prednisone (oral), the cited product is also inappropriate (originally, injection shall be used), so the revision was shown in Section 3.4.2.

Table 3-4-1-2 Drug prices that need to be changed

Drug name	Name of product considered to be quoted by the manufacturer	Drug price (before change)	Drug price (after change)
Etoposide	VePesid Injection 100 mg 5 mL	4,172.0 yen	3,680.0 yen
Ifosfamide	Ifomide for Injection 1 g	2,997.0 yen	2,865.0 yen
Carboplatin	Paraplatin Injection 450 mg 45 mL	24,464.0 yen	21,155 yen
Rituximab	Rituxan Intravenous Infusion 500 mg 50 mL	157,855.0 yen	148,996 yen
Gemcitabine	Gemcitabine for I.V. Infusion 1 g/25 mL "Sandoz" etc.	8,495.0 yen	7,180 yen
Dexamethasone (oral)	Decadron Injection 6.6 mg 2 mL	314.0 yen	NA
Cisplatin	Cisplatin Intravenous Drip Infusion 50 mg “Pfizer” 100 mL	7,099.0 yen	3,874.0 yen
Methylprednisolone	Methylprednisolone Sodium Succinate for Injection 100 mg AFP 1 g	1,769.0 yen	1,732.0 yen
Cytarabine	Cytarabine for I.V. Infusion 1 g "TEVA"	5,156.0 yen	4,715.0 yen
Dexamethasone	Decadron Injection 6.6 mg 2 mL	314.0 yen	299.0 yen
Cyclophosphamide	Endoxan for Injection 500 mg	1,254.0 yen	1,277.0 yen
Doxorubicin	Doxorubicin Hydrochloride Injection 50 mg "Sandoz" 25 mL etc.	4,351.0 yen	3,957.0 yen
Vincristine	Oncovin for Injection 1 mg	2,638.0 yen	2,521.0 yen
Prednisone (oral)	Prednisolone Sodium Succinate	167.0 yen	NA

	for Injection 20 mg “F” etc.		

3.4.2 Cost parameters (salvage chemotherapy)

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

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.3.2	127-132	Table 28

[Description of report]
Salvage chemotherapy cost
Because there is no consensus on a standard regimen for salvage chemotherapy in r/r DLBCL and CORAL extension studies did not report specific regimens, the treatment cost of salvage chemotherapy was estimated as the average of five different chemotherapy regimens suggested by key opinion leaders in Japan, including (R)-ICE, (R)-GDP, (R)-ESHAP, (R)-DHAP, and (R)-EPOCH. In the basecase, it was assumed that all patients received the treatments in combination with rituximab. Drug acquisition costs were calculated as a function of unit drug costs, dosing, administration cost, and treatment duration. The treatment cost and administration cost of salvage chemotherapy were obtained from the official gazette released by MHLW. For (R)-ICE dosing schedules and cycles were from Kewalramani 2004.[55] For (R)-GDP dosing schedules and cycles were from Crump 2004.[56] For (R)-ESHAP dosing schedule was from Martin 2008, and dosing cycles were from National Guideline Alliance 2016.[22], [57] For (R)-DHAP dosing schedules and cycles were from Oki 2008.[58] For (R)-EPOCH dosing schedule and cycles were from Jermann 2004.[59]

[Details of academic analysis (revision)]

Although dexamethasone used in (R)-GDP therapy and prednisone used in (R)-EPOCH therapy are both oral drugs, the prices of injections were referred to in the manufacturer's submission. It is necessary to re-calculate with the prices of oral drugs using the latest one (April 2020) [3]. The daily dose was calculated based on body surface area of [redacted] for the population aged <70

years and [redacted] for the population aged ≥70 years, and the corresponding number of tablets required per day was calculated.

Table 3-4-2-2 Drug prices need to be changed

Drug name	Brand name in the manufacturer's submission	Drug price	Replacing brand name	Drug price
Dexamethasone (oral)	Decadron Phosphate Injection 6.6 mg 2 mL	JPY 314.0	LenaDex Tablets 4mg	JPY 172.1 /tablet
Prednisone (Oral)	Prednisolone Sodium Succinate for Injection 20 mg "F", etc.	JPY 167.0	Rrednisolone Tablets 5 mg	JPY 9.8 /tablet

Table 3-4-2-3 Number of tablets in the population aged <70 years

Drug name	Replacing brand name	Dose per tablet	Daily dose (calculated based on body surface area of [redacted])	Number of tablets per day
Dexamethasone (oral)	LenaDex Tablets 4mg	4 mg/tablet	40 mg	40/4 = 10
Prednisone (Oral)	Rrednisolone Tablets 5 mg	5 mg/tablet	60×[redacted] = [redacted] ≒ 120 mg	120/5 = 24

Table 3-4-2-4 Number of tablets in the population aged ≥70 years

Drug name	Replacing brand name	Dose per tablet	Daily dose (calculated based on body surface area of [redacted])	Number of tablets per day
Dexamethasone	LenaDex	4 mg/tablet	40 mg	40/4 = 10

(oral)	Tablets 4mg			
Prednisone (Oral)	Rrednisolone Tablets 5 mg	5 mg/tablet	60× [redacted] = [redacted] ≒ 110 mg	110/5 = 22

3.4.3 Cost of PFS (Excel model)

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

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
Excel model	Trace sheet	NA

[Description of report] NA

[Details of academic analysis (revision)]

As the monthly cost for PFS, different values have to be used for (a) the first year, (b) the second year, (c) the third to fifth years, and (d) the sixth year and thereafter. However, in the Excel file submitted by the manufacturer, the monthly cost for the third year was referred to as the costs for the second year. Accordingly, the monthly cost to be used for the second year was JPY 1,036 for the tisagenlecleucel group and JPY 383 for the comparator group .

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 <70 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 8,084,464/QALY compared with salvage chemotherapy +/- allogeneic HSCT, 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	5.70	3.23	37,362,788	17,649,143	5,459,234
Comparator	2.46		19,713,646		

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	4.16	2.60	33,423,970	20,991,305	8,084,464
Comparator	1.56		12,432,665		

(b) Population aged ≥70 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 12,538,653/QALY compared with salvage chemotherapy.

Table 4-1-1-3 Base case analysis by the analysis by manufacturer

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	3.64	2.47	21,450,349	12,934,205	5,231,584
Comparator	1.16		8,516,144		

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

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	2.16	1.24	24,112,176	15,548,531	12,538,653
Comparator	0.92		8,563,645		

4.1.2 F 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 <70 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 QOL of PFS, assuming the value 0.70 continued from the starting age (57 years). Next, the best-case and worst-case fitting to OS curve was applied. As a result, ICER was lower than JPY 7.5 million JPY/QALY when QOL score of PFS was increased by 10%. This parameter was associated with large uncertainty.

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
QOL scores in PFS	<70 years: 0.747 ≥70 years: 0.63 (-10%)	<70 years: 0.913 ≥70 years: 0.77 (+10%)	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	7,336,913	9,001,632
QOL scores in PD/RL	0.351 (-10%)	0.429 (+10%)	The life years of PD/RL varied in analysis by the academic group.	8,052,054	8,117,135
Salvage chemotherapy price	897,490 (-25%)	1,495,816 (+25%)	The value of salvage chemotherapy varied in analysis by the academic group.	8,024,502	8,144,426
Discount rate	0%	4%	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	6,021,582	10,344,761

Table 4-2-2 Scenario analysis: 0.70 continues as QOL score of PFS from the starting age (57 years)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	3.79	2.36	33,423,970	20,991,305	8,880,499
Comparator	1.42		12,432,665		

Table 4-2-3 Scenario analysis: Exponential curve was fitted OS function in both groups (the prognosis of PD/RL was assumed to be the most pessimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	4.08	2.76	32,140,264	23,598,799	8,555,809
Comparator	1.32		8,541,465		

Table 4-2-4 Scenario analysis: Exponential curve was fitted to OS function only in the tisagenlecleucel group (when the prognosis of PD/RL was assumed to be the most pessimistic)

	Effect (QALY)	Incremental effect (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	4.15	2.59	33,252,035	20,819,370	8,051,277
Comparator	1.56		12,432,665		

Table 4-2-5 Scenario analysis: Gompertz curve was fitted to in both groups (when the prognosis of PD/RL was assumed to be the most pessimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	4.42	2.66	37,594,880	22,077,347	8,287,742
Comparator	1.75		15,517,533		

Table 4-2-6 Scenario analysis: Gompertz curve was fitted to OS function only in the tisagenlecleucel group (when the prognosis of PD/RL was assumed to be the most optimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	4.36	2.80	36,713,489	24,280,824	8,670,069
Comparator	1.56		12,432,665		

(b) Population aged ≥70 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 best-case and worst-case fitting to OS curve was applied. As a result, there was no parameters which ICER was decreased to less than JPY 11.25 million.

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Table 4-2-7 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
QOL scores in PFS	0.63 (-10%)	0.77 (+10%)	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	11,336,812	14,025,531
QOL scores in PD/RL	0.351 (-10%)	0.429 (+10%)	The life years of PD/RL varied in analysis by the academic group.	12,456,644	12,621,749
Salvage chemotherapy price	895,309 (-25%)	1,492,181 (+25%)	The value of salvage chemotherapy varied in analysis by the academic group.	12,450,980	12,626,326
Discount rate	0%	4%	The influence on ICER is large among the parameters of the one-way sensitivity analysis performed by the manufacturer	10,321,473	14,858,393

Table 4-2-8 Scenario analysis: Exponential curve was fitted OS function in both groups (the prognosis of PD/RL was assumed to be the most pessimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	2.02	1.36	21,875,005	17,561,781	12,866,493
Comparator	0.66		4,313,224		

Table 4-2-9 Scenario analysis: Exponential curve was fitted to OS function only in the tisagenlecleucel group (when the prognosis of PD/RL was assumed to be the most pessimistic)

	Effect (QALY)	Incremental effect (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	2.16	1.23	24,000,216	15,436,571	12,518,404
Comparator	0.92		8,563,645		

Table 4-2-10 Scenario analysis: Gompertz curve was fitted to in both groups (when the prognosis of PD/RL was assumed to be the most pessimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	2.28	1.30	26,079,232	16,528,684	12,706,111
Comparator	0.98		9,550,548		

Table 4-2-11 Scenario analysis: Gompertz curve was fitted to OS function only in the tisagenlecleucel group (when the prognosis of PD/RL was assumed to be the most optimistic)

	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
Tisagenlecleucel	2.25	1.33	25,585,780	17,022,135	12,784,609
Comparator	0.92		8,563,645		

4.3 Interpretation of analytical results

(a) Population aged <70 years

Population	Among the patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma, the population aged <70 years
Comparator	Salvage chemotherapy +/- allogeneic HSCT
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 results of base csae analysis showed the ICER of JPY 8,084,464 /QALY. Since the results of the one-way sensitivity analysis showed similar tendency, it is most likely that the ICER belongs to the interval of "more than JPY 7.5 million and not more than JPY 11.25 million".

(b) Population aged ≥70 years

Population to be analyzed	Among the patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma, the population aged ≥70 years
Comparator	Salvage chemotherapy
Reference value for ICER	☐ 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 results of base case analysis showed the ICER of 12,538,653 JPY/QALY. Since the results of the one-way sensitivity analysis showed similar tendency, it is most likely that the ICER belongs to the interval of "more than 11.25 million JPY and not more than 15 million JPY".

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 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.

4.4.2 Proportion of patients with DLBCL

The populations include two patient groups with <70 years of age and ≥ 70 years of age. It is necessary to calculate the weight for each price adjustment rate. The manufacturer has submitted survey data from [redacted] for the proportion of age groups (every 5 years of age) considering administration of CAR-T therapy. This estimation shows that the proportion of patients decreased as age increased, and the proportion of patients aged <70 years versus ≥70 years is [redacted]% and [redacted]%, respectively. This estimate by the manufacturer is acceptable to the academic group. Therefore it is appropriate to use [redacted]% and [redacted]% as the proportion of patients with DLBCL in each population.

5. References

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[3] Ministry of Health, Labour and Welfare, "List of Products Included in the NHI Price List and Information on Generic Drugs (applied on August 26, 2020)"[Online] Available: https://www.mhlw.go.jp/topics/2020/04/tp20200401-01.html. [Accessed: 2020 Sep 30].