【キムリア点滴静注】に関する費用対効果評価 [第 1.1 版]

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【目次】

0．要旨

資料全体を通じて、公開することが困難な部分については黄色マーカーで示す。

分析対象技術名 [1.1 節]	キムリア点滴静注(tisagenlecleucel)
他国の医療技術評価機関における評価結果 [1.8 節]	NICE, SMC, HAS, IQWiG, CADTH, MSAC
対象とする疾患･集団 [2.1 節]（一部割愛）	1.再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病（B-ALL） • 15 歳未満の集団 • 15 歳以上 25 歳以下の集団 2.再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫（DLBCL） • 70 歳未満の患者及び 70 歳以上の患者のサブグループに分けて分析を実施する。
比較対照技術名 [2.2 節]	(B-ALL) • 15 歳未満の集団:ブリナツモマブ（同種 HSCT を含む）」、 • 15 歳以上 25 歳以下の集団:「ブリナツモマブ（同種 HSCT を含む）」、「イノツズマブ オゾガマイシン（同種 HSCT を含む）」 (DLBCL) • 70 歳未満の患者:サルベージ化学療法+/-同種 HSCT • 70 歳以上の患者:サルベージ化学療法
分析の立場と費用の範囲 [2.3 節]	基本分析では公的医療費支払者の立場から、公的医療費のみを含めた分析を行う。なお、生産性損失を含めた分析も補助的に実施する。
使用する効果指標 [2.4 節]	B-ALL, DLBCL 共に QALY を用いる
設定した分析期間 [2.5 節]	B-ALL, DLBCL 共に生涯を用いる
割引率 [2.6 節]	B-ALL, DLBCL の両方で、費用･効果ともに年率 2%で割引く。感度分析では費用･効果を同率で年率 0%から 4%の範囲で変化させる。
システマティックレビューのクリニカルクエスチョン [3.1/3.3 節]	(B-ALL)

	P: 再発または難治性の B 細胞性急性リンパ芽球性白血病（B-ALL）の患者。ただし、造血幹細胞移植後または 2 回目以降に再発後で 26 歳未満の患者に限る I: 対象集団の適応症に対する治療 C: 制限なし O: 生存（期間）、有効性、安全性、健康に関する QOL (DLBCL) P: 再発または難治性のびまん性大細胞型 B 細胞リンパ腫（DLBCL）の成人患者。ただし、以下のいずれかに当てはまる場合に限る ・ 自家造血幹細胞移植（ASCT）が不適格である患者 ・ 少なくとも過去 2 つ以上の治療に成功しなかった再発患者 I: 対象集団の適応症に対する治療 C: 制限なし O: 生存（期間）、有効性、安全性、健康に関する QOL
システマティックレビュー結果の概要 [3.2/3.4 節]	(B-ALL) PRISMA フローダイアグラムを 3.2 Figure 5.に示す。 抽出された 9 試験について 3.2 Table 5.に示す。 (DLBCL) PRISMA フローダイアグラムを 3.2 Figure 7.に示す。 抽出された 9 試験について 3.2 Table 8.に示す。
間接比較の結果 [3.7 節]	(B-ALL:<15 歳) チサゲンレクルユーセル試験の 15 歳未満集団とブリナツモマブの Gore 試験の内 15 歳未満集団を比較した。Pooled trial data(B2101J、ELIANA/B2202、ENSIGN/B2205)の 15 歳未満集団と Gore 2018 の 15 歳未満集団との間接比較（OS）において、conditional HR は[redacted](95% CI: [redacted]]）であった。 (B-ALL:>=15 歳) ブリナツモマブを比較対照とした場合、Pooled trial data（B2101J、ELIANA/B2202、ENSIGN/B220）の 15 歳以上集団と Gore 2018 の全体集団との MAIC 分析（OS）において、conditional HR は[redacted]（95%CI: [redacted]であっ

	た。 イノツズマブを比較対照とした場合、Pooled trial data（B2101J、ELIANA/B2202、ENSIGN/B2205）の 15 歳以上集団と Bhojwani 2019 の全体集団との MAIC 分析（OS）において、conditional HR は[redacted]（95%CI: [redacted]であった。 (DLBCL：<70 歳) JULIET 試験の 70 歳未満集団と CORAL extention studies（すべての患者が 70 歳未満）との MAIC 分析（OS）において、HR は[redacted] (95% CI; [redacted])であった。 (DLBCL：>=70 歳) JULIET 試験の 70 歳以上の患者数が[redacted] 例([redacted]%）と限られることから、CORAL 試験との OS 比較は実施不可能である。 JULIET 試験の全体集団と CORAL extention studies（すべての患者が 70 歳未満との MAIC 分析（OS）において、conditional HR は[redacted] (95% CI: [redacted]であった。
追加的有用性の有無　[3.8 節]	(B-ALL:<15 歳) ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (B-ALL：>=15 歳、対ブリナツモマブ) ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (B-ALL：>=15 歳、対イノツズマブ) ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (DLBCL：<70 歳) ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」

	(DLBCL：>＝70 歳) ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」
費用対効果の分析方法の概要 [4.1.1 項、4.2 節等]	**B-ALL:** The cost-effectiveness model was developed in Microsoft Excel®. The analysis used a decision tree approach to determine the proportion of patients initially assigned to tisagenlecleucel who continued to infusion. After the initial decision-tree partition, patients on tisagenlecleucel enter into the partitioned survival model. Patients on the comparators directly enter into the partitioned survival model. The model comprised of three mutually exclusive health states: (i) event-free survival (EFS), (ii) progressive disease (PD) and (iii) death. EFS was defined as the time from the date of treatment initiation to the earliest date of death, relapse, or treatment failure. All patients began in EFS at the model start. The proportion of patients in the EFS health state of the model was set to be equal to the EFS curve of each treatment. The PD state included alive patients who progressed or relapsed. The proportion of patients in the PD health state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of EFS patients. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. A monthly model cycle was used for estimating the proportion of patients in each heath state over time. Subsequent HSCT was considered in the model since subsequent HSCT is an important treatment option in the clinical pathway of r/r pALL patients. Subsequent HSCT was not modelled as a distinct health state, but the efficacy benefit of subsequent HSCT was captured in

	the OS and EFS estimates of each treatment arm, and the cost and disutility of subsequent HSCT was added separately for each treatment arm using age-group specific HSCT rate data if available. Half-cycle correction was applied, in order to account for the real-world in which patients transition to the subsequent health state continuously throughout a given cycle. Treatment costs before maintenance therapy initiation (if applicable) were applied as one-time costs in the model, which were not affected by the half-cycle correction. **DLBCL:** The cost-effectiveness model was developed in Microsoft Excel®. The analysis used a decision tree approach to determine the proportion of patients initially assigned to tisagenlecleucel who continued to infusion. After the initial decision-tree partition, patients on tisagenlecleucel enter into the partitioned survival model. Patients on salvage chemotherapy directly enter into the partitioned survival model. The model comprised of three mutually exclusive health states: (i) PFS, (ii) PD/RL and (iii) death. PFS was defined as the time from the date of tisagenlecleucel infusion or treatment initiation to the date of first documented progression or death due to any cause. All patients began in PFS at the model start. The proportion of patients in the PFS health state of the model was set to be equal to the PFS curve of each treatment. The PD/RL state included alive patients who progressed or relapsed. The proportion of patients in the PD/RL health state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of PFS

	patients. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. A monthly model cycle was used for estimating the proportion of patients in each heath state over time. Subsequent SCT, including both allo SCT and auto SCT, was considered only in the < 70 model. The efficacy benefit of subsequent SCT was captured in the OS and PFS estimates of each treatment arm. The cost and disutility of subsequent SCT were added separately for the proportion of patients who received the SCT treatment based on trial observation for tisagenlecleucel and literature for the comparator. Half-cycle correction was applied, in order to account for the real-world in which patients transition to the subsequent health state continuously throughout a given cycle. Treatment costs were applied as one-time costs in the model, which were not affected by the half-cycle correction.
結果の概要 [5.1 節]	**B-ALL:** (B-ALL:<15 歳) 本対象集団における ICER は¥2,087,581 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。 また、確率論的感度分析(PSA)においては、ICER が 750 万円以下となる確率は 100%であった。以上より、「750 万円以下」が ICER の所属する区間として妥当と判断する。 (B-ALL:>=15 歳) 【比較対照】ブリナツモマブ

	本対象集団における ICER は¥2,015,349 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 100％であった。 【比較対照】イノツズマブ 本対象集団における ICER は¥1,994,592 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 100％であった。 両比較対照群の分析結果から、「750 万円以下」が ICER の所属する区間として妥当と判断する。 DLBCL： (DLBCL：＜70 歳) 本対象集団における ICER は¥5,459,234 であり、これは価格調整の閾値である 750 万円を下回る。DSA においても、ほぼ全ての場合において ICER が 750 万円を下回っており、750 万円を超えるのは割引率を 4％に変更した場合、及び分析期間を [redacted] 年にした場合に限られる。その場合 ICER はそれぞれ¥7,789,845 と¥9,263,162 であった。分析期間については、『2.5 分析期間』で述べられている通り、「十分に長い分析期間」とすることから生涯、とすることが妥当と考える。他の DSA の結果を考慮し、 ICER の所属する区間は 750 万円以下が妥当であると考える。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 97.6％であることから、「750 万円以下」が ICER の所属する区間として妥当と判断する。 (DLBCL：＞＝70 歳)

	本報告においては、参考までに 70 歳以上の集団においても検証を行い、その結果は 5.1.2.2 に記載したとおり、基本分析の結果は¥5,231,584 であった。 「3.8 追加的有用性の有無に関する評価」に記載する通り、本分析対象集団においては、介入群（tisagenlecleucel）と比較対照群ともに有効性データのリミテーションが大きく、これらのデータに基づく分析結果の解釈には、十分に留意する必要がある。
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等（あるいは劣り）、かつ費用が高い

1．対象となる医薬品･医療機器の性質

1.1 名称

販売名:キムリア点滴静注

一般名:チサゲンレクルユーセル

1.2 保険償還価格

本品は、再生医療等製品であり、医薬品の区分にて保険償還価格が決定された。2019 年 5 月 22 日収載時保険償還価格は下記のとおりである。

算定	算定方式		原価計算方式
	原価計算	製品総原価	23,632,062 円
		営業利益	4,137,694 円
		流通経費	682,000 円
		消費税	2,276,140 円
	補正加算		有用性加算(I)(A=35%)、市場性加算(I)(A=10%) 加算係数=0.2 (加算前) ⇔ (加算後) 1 患者あたり 30,727,896 円 ⇔ 33,493,407 円
	外国平均価格調整		なし
算定薬価			1 患者あたり 33,493,407 円

消費税の増税により、2019 年 10 月 1 日に保険償還価格が下記に変更となった。

1 患者あたり 34,113,655 円

1.3 治療効果のメカニズム

本品は、患者末梢血由来の T 細胞に、遺伝子組換えレンチウイルスベクターを用いて CD19 を特異的に認識する CAR を導入し、培養・増殖させた T 細胞を構成細胞とし、医薬品と同様に薬理的作用による治療効果を期待して、点滴で静脈内に投与される再生医療等製品である。

本品に遺伝子導入される CAR は、CD19 を特異的に認識するマウス由来 scFv、ヒト CD8α ヒンジ及び膜貫通ドメイン、並びにシグナル伝達ドメインである CD3-ζ 及び 4-1BB から構成され、CD19 を発現した細胞を認識すると、導入 T 細胞に対して増殖、活性化、標的細胞に対する攻撃及び細胞の持続・残存に関する信号を伝達する。本品のこれらの作用により、CD19 陽性の B 細胞性の腫瘍に対し、腫瘍細胞を死滅させる効果が長期に持続することが期待される。

1.4 対象疾患

本品の効能、効果又は性能は下記のとおりである（添付文書より抜粋）。

1．再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病。ただし、以下のいずれかの場合に限る。

- 初発の患者では標準的な化学療法を 2 回以上施行したが寛解が得られない場合
- 再発の患者では化学療法を 1 回以上施行したが寛解が得られない場合
- 同種造血幹細胞移植の適応とならない又は同種造血幹細胞移植後に再発した場合

2．再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫。ただし、以下のいずれかの場合であって、自家造血幹細胞移植の適応とならない又は自家造血幹細胞移植後に再発した患者に限る。

- 初発の患者では化学療法を 2 回以上、再発の患者では再発後に化学療法を 1 回以上施行し、化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合
- 濾胞性リンパ腫が形質転換した患者では通算 2 回以上の化学療法を施行し、形質転換後には化学療法を 1 回以上施行したが、形質転換後の化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合

なお、本品の指定から分析結果の提出時までの間に、保険適用となる疾患が追加される予定はない。

分析対象とする疾患の疫学的性質

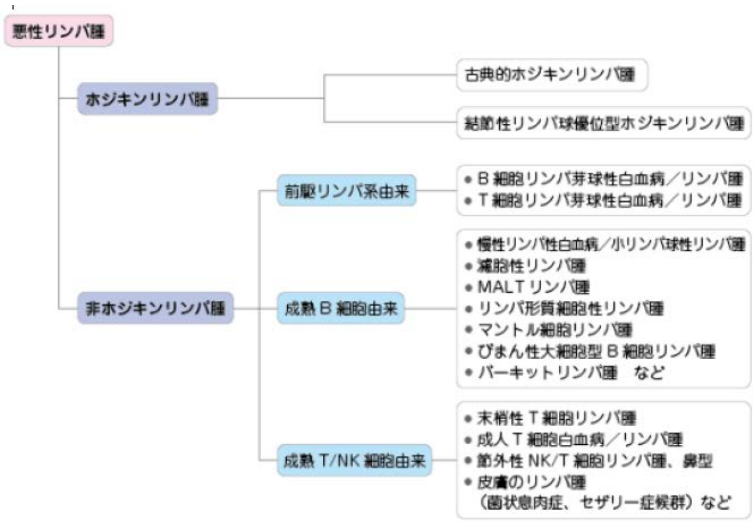
（B-ALL）

- ALL は骨髄のリンパ系前駆細胞が腫瘍化により過剰に増殖し，急速に進行する疾患であり，B-ALL が ALL の約 80％を占める。[1]ALL では正常な造血機能が阻害され、白血球減少、貧血、血小板減少に伴う症状（全身倦怠感，出血等）や腫瘍増殖による局所症状（リンパ節腫脹や肝脾腫等）が生じる。ALL は年齢にかかわらず発症するが、好発年齢は 2～5 歳で、診断時の年齢は全体の 60％が 20 歳未満である。
- ALL の総患者数は約 5,000 人と報告されている（厚生労働省平成 26 年患者調査）。小児の ALL 患者では一次治療により 80％以上の患者で治癒が得られるが、約 20％の小児の ALL 患者は再発し、再発した場合ほとんどの患者は最終的にこの疾患により死亡に至る。小児の ALL は小児がんの死因の第 1 位であり、特に再発又は難治性の小児の ALL は生存期間（中央値）が 3～6 ヵ月と予後不良の疾患である。[2]–[5]

（DLBCL）

- 「再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫」は、Figure 1 に示すとおり、成熟 B 細胞由来の悪性リンパ腫であり、非ホジキンリンパ腫の 30％～35％を占める。[6]

Figure 1　悪性リンパ腫の分類



- DLBCL は全身に広がるリンパ組織から発生するため病変の部位によって症状は異なるが、リンパ節腫大、節外病変、全身症状（発熱、体重減少、寝汗）等が認められる。また、DLBCL は女性に比べやや男性で多く発症する。DLBCL はあらゆる年齢層で発症するが、発症率は年齢とともに増加し、半数以上の患者は 60 歳以上で診断される。悪性リンパ腫の総患者数は 2014 年時点で 64,000 人と推計され、約 33%が DLBCL であることから総患者数は約 21,000 人と推計される。[7], [8]

<u>分析対象とする疾患における当該医薬品･医療機器の使用(見込)者数</u>

保険償還時の使用見込み数は、ピーク時市場規模予測で 216 名である。

<u>当該医薬品･医療機器を使用する患者の主な年齢(層)や性別等</u>

本品の 2 つの適応症は共に希少疾病を対象としており、対象患者数は非常に限られている。また、本品は、原材料として用いる非動員末梢血単核球を患者さんから採取後に製品製造を行うことから、投与までに一定の期間を要する。適格性の判断においては、適正使用ガイド等を用いて実施されている。日本の実臨床における症例数が限られることから、臨床試験における年齢区分を下記のとおり示す。

(B-ALL)

Table 1. 人口統計学的特性（B2202 試験, FAS）

Demographic variable Statistics	N=75 n (%)
Age (years)	
Mean (SD)	12.0 (5.28)
Median	11.0
Min-Max	3-23
Age category (years) - n (%)	
<10	31 (41.3)
≥ 10 to <18	31 (41.3)
≥ 18	13 (17.3)

(DLBCL)

Table 2.人口統計学的特性（C2201 試験, FAS）

Demographic variable Statistics	N[redacted]
Age (years)	
Mean (SD)	[redacted] ([redacted])
Median	56.0
Min-Max	22.0 - 76.0
Age category (years) - n (%)	
<65	[redacted]
≥ 65	[redacted]

1.5 使用方法等

本品使用時の概要は下記のとおりである。

製品名	キムリア点滴静注
製品特性	ヒト体細胞加工製品
投与経路	静注
投与量	疾患および体重ごとに異なる
投与頻度	単回投与

＜医療機関での白血球アフェレーシス～製造施設への輸送＞

1．白血球アフェレーシス

十分量のＴリンパ球を含む非動員抹消血単核球を採取する。

2．白血球アフェレーシス産物の凍結保存

採取後速やかに白血球アフェレーシス産物を調製し、液体窒素気相下で凍結保存する。

3．白血球アフェレーシス産物の輸送

凍結保存した白血球アフェレーシス産物を、梱包して本品製造施設へ輸送する。

＜医療機関での受入れ～投与＞

4．本品の受領及び保存

凍結した状態で本品を受領し、使用直前まで液体窒素気相下で凍結保存する。

5．投与前の前処置

本品の投与予定日前の 1 週間以内の末梢血白血球数が 1,000/μL を超える場合、本品投与の 2 日前までに以下のリンパ球除去化学療法を前処置として行う。前処置の化学療法の特性や患者の状態を考慮の上、前処置から本品投与までに必要な間隔を設定する。

1．再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病に用いる場合のリンパ球除去化学療法

1．シクロホスファミド水和物 500mg/m^2を 1 日 1 回 2 日間点滴静注及びフルダラビンリン酸エステル 30 mg/m^2を 1 日 1 回 4 日間点滴静注する。なお、患者の状態により適宜減量する。

2．シクロホスファミド水和物による Grade 4 の出血性膀胱炎の既往がある、又はシクロホスファミド水和物に抵抗性を示した患者には、シタラビン 500 mg/m^2を 1 日 1 回 2 日間点滴静注及びエトポシド 150 mg /m^2を 1 日 1 回 3 日間点滴静注する。なお、患者の状態により適宜減量する。

2．再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫に用いる場合のリンパ球除去化学療法

1．シクロホスファミド水和物 250 mg /m^2を 1 日 1 回 3 日間点滴静注及びフルダラビンリン酸エステル 25 mg/m^2を 1 日 1 回 3 日間点滴静注する。なお、患者の状態により適宜減量する。

2．シクロホスファミド水和物による Grade 4 注）の出血性膀胱炎の既往がある、又はシクロホスファミド水和物に抵抗性を示した患者には、ベンダムスチン塩酸塩 90 mg/m^2を 1 日 1 回 2 日間点滴静注する。なお、患者の状態により適宜減量する。

6．本品の投与

投与直前に本品を解凍し、適応症に応じて下記のとおり単回静脈内投与する。

1. 再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病に用いる場合
   通常、25 歳以下（投与時）の患者には、体重に応じて以下の投与量を単回静脈内投与する。
   • 体重 50 kg以下の場合には、CAR 発現生 T 細胞として 0.2×10^6～5.0×10^6 個/kg
   • 体重 50 kg超の場合には、CAR 発現生 T 細胞として 0.1×10^8～2.5×10^8 個（体重問わず）
2. 再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫に用いる場合
   通常、成人には、CAR 発現生 T 細胞として 0.6×10^8～6.0×10^8 個（体重問わず）を単回静脈内投与する。

本品の製造に先立ち白血球アフェレーシスを、本品の投与予定日前の1週間以内の末梢血白血球数が1,000/μLを超える場合には移植細胞の生着促進等を目的としたリンパ球除去化学療法（以下、「LD化学療法」という）を行う必要があり、さらに本品の投与によりサイトカイン放出症候群（以下、「CRS」という）等の重篤な又は死亡に至る可能性がある副作用が認められる可能性がある。したがって、アフェレーシスの実施中、LD化学療法の実施中、本品の投与中及び投与後には、患者の観察を十分に行い、異常が認められた場合には、発現した事象に応じた専門的な知識と経験を持つ医師により、必要に応じてICU等において集学的な全身管理を含む適切な措置を行う必要がある。使用にあたっては、最適使用推進ガイドラインにあるとおり、下記施設での使用のみとなる。

ア　日本造血細胞移植学会が定める移植施設認定基準の全ての項目を満たす診療科（認定カテゴリー1）を有する施設

イ 認定カテゴリー1 に準ずる診療科（認定基準のうち、移植コーディネーターの配置に係る基準以外を満たす診療科）を有する施設

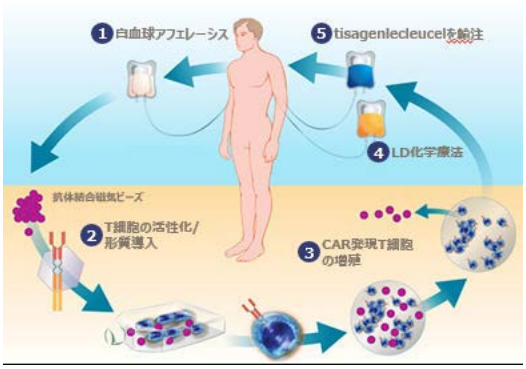
1.6 対象疾患の治療における当該医薬品･医療機器の位置づけ

【本品の革新性】

本品による治療の概略を Figure 2 に示す。白血球アフェレーシスにより患者から採取した T 細胞は採取施設で凍結され，米国の製造施設に送られ[1]，レンチウイルスベクターを用い遺伝子導入が行われる[2]。次に CAR 発現 T 細胞を ex vivo で培養増殖させ[3]，リンパ球除去化学療法を行った後[4]，CTL019 を患者へ投与する[5]。投与された CAR 発現生 T 細胞が B 細胞性腫瘍に対し抗腫瘍効果を発揮する。

本品は，臨床上有用な新規作用機序を有し，希少疾病用医薬品の指定を受けて開発・承認された薬剤であり，国内で初めて承認される細胞遺伝子改変細胞療法である。

Figure 2 本品の治療概略



【B-ALL】

<u>B-ALL の既存治療およびアンメットニーズ</u>

現在，再発又は難治性の小児 ALL に対する治療選択肢としては大量化学療法に続く同種 HSCT，救援化学療法，免疫療法，支持療法等があり，このうち唯一治癒が期待できるのは同種 HSCT である。しかしながら同種 HSCT であっても効果は限定的であり，移植に関連した致死的な移植片対宿主病（GVHD），長期の免疫抑制に伴う侵襲性の全身性感染症や晩期障害（成長障害等）といった合併症も問題となる。再発又は難治性の小児 ALL 患者に対する「第三寛解期（CR3）以降の同種 HSCT」，「寛解が得られていない状態での同種 HSCT」，又は「同種 HSCT 施行後の再発に対する 2 回目の同種 HSCT」の 1 年生存率は 25％～55％，5 年生存率は 20％～45％と報告されている。

再発・難治性 ALL に対する治療選択肢は，同種造血幹細胞移植，クロファラビン，イノツズマブオゾガマイシン，ブリナツモマブなどが国内で承認されているが，治療後に深い寛解を維持できずに再発する患者も多い。同種造血幹細胞移植は，再発・難治性 ALL に対する治癒可能な治療選択肢の一つだが，適応患者が限定的である上，合併症を発現する場合は重症となる場合がある。ALL に対する超大量化学療法や全身放射線照射治療などによる，晩期障害が発現する場合は入院が長期に及ぶ場合も多く，就学年齢の学童児が通学できない等により小児の成長に影響を及ぼす。

ALL の治療目標は治癒を目指すことであり，特に長期予後と関連があるとされている残存病変（MRD）が陰性となる深い寛解の持続を目指すことである。再発又は難治性の小児 ALL 患者に対して長期に深い寛解をもたらし，同種造血幹細胞移植を実施しなくても良好な治療効果をもたらすことが期待でき，かつ忍容性の高い安全性プロファイルを有する新たな治療が望まれていた。

<u>標準的な治療フローと当該医薬品の位置づけ</u>

B-ALL における治療の概要を下記(Figure 3)に示す。当該医薬品の治療対象患者を緑色で示す。

Figure 3. B-ALL における治療の概要

また診療ガイドラインにおける本品の位置づけは下記のとおりである。

＜診療ガイドライン＞

□NCCN ガイドライン（Pediatric Acute Lymphoblastic leukemia, ver.2.2020）[9]：本品は，再発又は難治性の ALL 患者（26 歳未満，かつ難治性又は 2 回目の再発以降，かつフィラデルフィア染色体陽性の ALL の場合には 2 種類以上の TKI の治療歴がある）に対し，治療選択肢の一つであり，その後に同種 HSCT を検討する（Category 2A））。ただし，本品投与後の同種 HSCT の意義は不明である。

【DLBCL】

<u>DLBCL の既存治療およびアンメットメディカルニーズ</u>

- DLBCL 患者では一次治療により約 60%の患者で治癒が得られるが，再発又は難治性の DLBCL 患者では，自家幹細胞移植（自家 HSCT）を実施できなかった場合あるいは自家 HSCT 実施後 1 年以内に再発した場合の予後は不良である。
- 再発・難治性 DLBCL に対する二次治療は，自家造血幹細胞移植併用大量化学療法が標準治療であるが，制約が多い[10]
    - 一次治療に対し r/r であった患者の約 50%は，年齢や感染症の問題等で自家造血幹細胞移植併用大量化学療法の適応とはならない
    - 移植適応である患者の約 50%は，救援化学療法によって十分な奏効が得られず，自家造血幹細胞移植併用大量化学療法を施行できない

- 自家造血幹細胞移植併用大量化学療法を施行した患者の約 60%は，移植後に再発する

- 自家造血幹細胞移植の適応とならない患者や自家造血幹細胞移植後に再発した　患者は，予後不良であり，新たな治療選択肢が求められている。
  - 自家造血幹細胞移植の適応とならない患者では，OS 中央値は 4.4 ヵ月，1 年及び 2 年 OS はそれぞれ 23%，16%である[11]
  - 自家造血幹細胞移植後に再発し，三次治療を受けた患者では，OS 中央値は 10 ヵ月で，1 年 OS は 39%である[12]
  - 自家造血幹細胞移植後 1 年以内に再発した患者の OS 中央値は 6.2 ヵ月である[13]

- 国内でも上記に示したエビデンスを主な根拠として外国と同様の治療戦略が造血器腫瘍診療ガイドラインで推奨されており（日本血液学会 2018），再発又は難治性で自家 HSCT に適応がないか，又は自家 HSCT 後に再発した DLBCL 患者では現時点で治癒をもたらす標準的な治療法はないため，持続的な奏効を得て長期予後の改善につなげることができる新規の治療法が早急に求められていた。

診療ガイドラインにおける本品の位置づけは下記のとおりである。

＜診療ガイドライン＞

□NCCN ガイドライン（B-Cell Lymphomas, ver.1.2020）[14]：本品は，DLBCL に組織学的形質転換した FL 患者に対する選択肢の一つである（Preferred）。

<u>標準的な治療フローと当該医薬品の位置づけ</u>

当該医薬品の治療対象患者を赤枠でしめす(Figure 4)。

Figure 4 DLBCL における治療の概要

1.7 主な有害事象

リスク管理計画書に示された重篤な有害事象は下記のとおりである。

1. サイトカイニン放出症候群

   サイトカイン放出症候群があらわれることがあるので、患者の状態を十分に観察し、適宜、血液検査等を実施すること。高熱、悪寒、筋肉痛、関節痛、悪心、嘔吐、下痢、発汗、発疹、食欲不振、疲労、頭痛、低血圧、脳症、呼吸困難、頻呼吸、低酸素症、臓器障害（一過性の心不全及び不整脈、腎不全、AST 増加、ALT 増加、ビリルビン増加を含む）等の異常が認められた場合には、製造販売業者が提供するサイトカイン放出症候群管理アルゴリズム等に従い、適切な処置を行うこと。また、サイトカイン放出症候群を発現した患者で播種性血管内凝固症候群、毛細血管漏出症候群、血球貪食症候群、マクロファージ活性化症候群が報告されている。

2. 神経系事象

   脳症等の神経系事象があらわれることがあるので、頭痛、せん妄、不安、浮動性めまい、振戦等の症状があらわれた場合は、患者の状態を十分に観察し、異常が認められた場合には、適切な処置を行うこと。

3. 感染症

   細菌、真菌、あるいはウイルス等による重度の感染症（敗血症、肺炎等）があらわれることがあり、死亡に至った例が報告されている。また、発熱性好中球減少症があらわれることがある。

さらに、B 型又は C 型肝炎ウイルスキャリアの患者又は既往感染者、HIV 感染者において、ウイルスの再活性化又は増加による悪化があらわれる可能性がある。患者の状態を十分に観察し、異常が認められた場合には、抗生物質の投与等の適切な処置を行うこと。

4. 低 γ グロブリン血症

低 γ グロブリン血症又は無 γ グロブリン血症があらわれることがある。患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

（参考：本品の投与による副作用の治療に用いる薬剤について）

○トシリズマブ（遺伝子組換え）注の効能又は効果、用法及び用量

効能又は効果：腫瘍特異的 T 細胞輸注療法に伴うサイトカイン放出症候群

用法及び用量：通常、トシリズマブ（遺伝子組換え）として体重 30 kg 以上は 1 回 8 mg/kg、体重 30 kg 未満は 1 回 12 mg/kg を点滴静注する。

○低 γ グロブリン血症があらわれることがあるので、本品の投与前及び投与後は定期的に血液検査を行い、患者の状態を十分に観察し、必要に応じて免疫グロブリン製剤の投与を行うこと。

1.8 他国の医療技術評価機関における評価結果

【主要国における評価の一覧表】

・B-ALL

国名	機関名	評価結果（記載例）	リスト価格（現地通貨建）
イギリス	NICE	・ 推奨/非推奨/[条件つき推奨](具体的に: Cancer Drugs Fund)/その他（　　） ・ 評価ステータス: [最終ガイダンス]/ドラフト/その他（　　）	£282,000
	SMC	・ 推奨/非推奨/[条件つき推奨](具体的に: Patient Access Schemes)/その他(　　)	
フランス	HAS	・ SMR: important ・ ASMR: I/II/[III]/IV/V ・ 効率性評価: あり(主な ICER の値:　　)/[評価中]/未実施	€ [redacted]
ドイツ	IQWiG	・Major/Considerable/Minor/[Unquantifiable]/No additional benefit	€ [redacted]
カナダ	CADTH	・ 推奨/非推奨/[条件つき推奨](具体的に: On the condition that there is a reduction in price)/その	CAD [redacted]

		他(　　)	
オーストラリア	MSAC	・ 推奨/非推奨/条件つき推奨(具体的に:　　)/その他(　　)	NA

・DLBCL

国名	機関名	評価結果 (記載例)	リスト価格(現地通貨建)
イギリス	NICE	・ 推奨/非推奨/条件つき推奨(具体的に: Cancer Drug Fund)/その他 (　　) ・ 評価ステータス: 最終ガイダンス/ドラフト/その他(　　)	£282,000
	SMC	・ 推奨/非推奨/条件つき推奨(具体的に:　　)/その他()	
フランス	HAS	・ SMR: important ・ ASMR: I/II/III/IV/V ・ 効率性評価: あり(主な ICER の値:　　)/評価中/未実施	€ [redacted]
ドイツ	IQWiG	・Major/Considerable/Minor/Unquantifiable/No additional benefit	€ [redacted]
カナダ	CADTH	・ 推奨/非推奨/条件つき推奨(具体的に: On the condition that there is a substantial reduction in price)/その他(　　)	CAD [redacted]
オーストラリア	MSAC	・ 推奨/非推奨/条件つき推奨(具体的に:　　)/その他(　　)	NA

【各国における費用対効果評価の詳細】

1. 評価の有無の一覧

2020 年 [redacted] 月 [redacted] 日現在の結果を下記に示す。

B-ALL

国名	機関名	評価結果の有無
イギリス	NICE	あり/ なし/ 評価中(ドラフトあり/なし)/不明

	SMC	あり/ なし/ 評価中/不明
フランス	HAS	あり/ なし/ 評価中/不明
カナダ	CADTH	あり/ なし/ 評価中/不明
オーストラリア	PBAC	あり/ なし/ 評価中/不明

DLBCL

国名	機関名	評価結果の有無
イギリス	NICE	あり/ なし/ 評価中(ドラフトあり/なし)/不明
	SMC	あり/ なし/ 評価中/不明
フランス	HAS	あり/ なし/ 評価中/不明
カナダ	CADTH	あり/ なし/ 評価中/不明
オーストラリア	PBAC	あり/ なし/ 評価中/不明

2．評価結果の詳細

2020 年 [redacted] 月 [redacted] 日現在の結果を下記に示す。

【B-ALL】

国名	イギリス
機関名	NICE
評価結果の URL など	https://www.nice.org.uk/guidance/ta554/chapter/1-Recommendations
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	Cancer Drugs Fund
評価対象疾患	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
使用方法 (※)	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 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).
比較対照	Blinatumomab and salvage chemotherapy are both appropriate comparators and blinatumomab is the main comparator
主要な増分費用効果比の値	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.

国名	イギリス
機関名	SMC
評価結果の URL など	https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-fullsubmission-smc2129/
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	Patient Access Scheme
評価対象疾患	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
使用方法 (※)	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. • for patients above 50kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based).

比較対照	Salvage chemotherapy, blinatumomab or palliative therapies
主要な増分費用効果比の値	ICER versus salvage chemotherapy (with PAS for tisagenlecleucel) Base case： £25,238

国名	フランス
機関名	HAS
評価結果の URL など	https://www.has-sante.fr/jcms/pprd_2982962/en/kymriah
評価対象技術	キムリア点滴静注
評価結果	SMR: Important / ASMR: III
条件付き推奨の場合は、その条件の詳細	NA
評価対象疾患	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
使用方法 (※)	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. • for patients above 50kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based).
比較対照	salvage chemotherapy, blinatumomab, inotuzumab, and palliative care
主要な増分費用効果比の値	NA

国名	ドイツ
機関名	IQWIG
評価結果の URL など	https://www.iqwig.de/en/projects-

	results/projects/health-economic/g18-11-tisagenlecleucel-b-cell-acute-lymphoblastic-leukaemia-assessment-according-to-35a-para-1-sentence-11-social-code-book-v.10617.html
評価対象技術	キムリア点滴静注
評価結果	Unquantifiable
条件付き推奨の場合は、その条件の詳細	NA
評価対象疾患	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
使用方法 (※)	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. • for patients above 50kg: 0.1 to 2.5 x 10^8 CAR positive viable T cells (non-weight based).
比較対照	なし（理由：orphan designation）
主要な増分費用効果比の値	NA

国名	カナダ
機関名	CADTH
評価結果の URL など	https://cadth.ca/sites/default/files/pdf/car-t/ct0001-op0538-in-brief-e.pdf
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	On the condition that there is a reduction in price
評価対象疾患	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.
使用方法 (※)	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 above 50 kg as a single one-time treatment.
比較対照	salvage chemotherapy
主要な増分費用効果比の値	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

国名	オーストラリア
機関名	MSAC
評価結果の URL など	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519-public
評価対象技術	キムリア点滴静注
評価結果	推奨
条件付き推奨の場合は、その条件の詳細	NA
評価対象疾患	pediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse
使用方法 (※)	• 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).
比較対照	comparator: blinatumomab with the intention to

	proceed to allo-SCT (Main), salvage chemotherapy with the intention to proceed to allo-SCT (Supportive)
主要な増分費用効果比の値	NA

【DLBCL】

国名	イギリス
機関名	NICE
評価結果の URL など	https://www.nice.org.uk/guidance/ta567
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	Cancer Drugs Fund
評価対象疾患	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
使用方法 (※)	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.
比較対照	Salvage chemotherapy excluding pixantrone
主要な増分費用効果比の値	Company's base case: (ICER): £46,325 The committee: ranged between £42,991 and £55,403 per QALY gained

国名	イギリス
機関名	SMC
評価結果の URL など	https://www.scottishmedicines.org.uk/medicines-advice/tisagenlecleucel-kymriah-resubmission-smc2200/
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	Patient Access Scheme

評価対象疾患	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
使用方法 (※)	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).
比較対照	Salvage chemotherapy
主要な増分費用効果比の値	Base-case results – with PAS Vs [R-]Gem-Ox ICER: £44,330 Vs [R-]GDP ICER: £44,151

国名	フランス
機関名	HAS
評価結果の URL など	https://www.has-sante.fr/jcms/pprd_2982962/en/kymriah
評価対象技術	キムリア点滴静注
評価結果	SMR: Important / ASMR: IV
条件付き推奨の場合は、その条件の詳細	NA
評価対象疾患	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
使用方法 (※)	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.
比較対照	Salvage chemotherapy, Yescarta, palliative care, and alloSCT if patient eligible
主要な増分費用効果比の値	NA

国名	ドイツ
機関名	IQWIG
評価結果の URL など	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
評価対象技術	キムリア点滴静注
評価結果	Unquantifiable
条件付き推奨の場合は、その条件の詳細	NA
評価対象疾患	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
使用方法 (※)	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.
比較対照	なし（理由：orphan designation）
主要な増分費用効果比の値	NA

国名	カナダ
機関名	CADTH
評価結果の URL など	https://cadth.ca/sites/default/files/pdf/car-t/ct0001-op0538-in-brief-e.pdf
評価対象技術	キムリア点滴静注
評価結果	条件つき推奨
条件付き推奨の場合は、その条件の詳細	On the condition that there is a reduction in price
評価対象疾患	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma

	(DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
使用方法 (※)	Tisagenlecleucel is recommended as a single, one-time treatment (0.6 to 6.0 x 10^8 CAR-positive viable T cells).
比較対照	salvage chemotherapy
主要な増分費用効果比の値	For r/r DLBCL, tisagenlecleucel, compared with palliative chemotherapy, was associated with an incremental cost per QALY of CAD$211,870.

国名	オーストラリア
機関名	MSAC
評価結果の URL など	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public
評価対象技術	キムリア点滴静注
評価結果	Support
条件付き推奨の場合は、その条件の詳細	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
評価対象疾患	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
使用方法 (※)	0.6 to 6.0 x 10^8 CAR-positive viable T cells (non-weight based)
比較対照	Salvage chemotherapy with the intention to proceed to allo- or auto-SCT
主要な増分費用効果比の値	NA

2．費用効果分析における分析条件の設定

2019 年[redacted] 月[redacted] 日に実施された費用対効果評価専門組織において、決定された分析対象集団およびは比較対照は、Section 2.1 および 2.2.に示したとおりである。分析枠組の決定にあたっては、当初より弊社意見は、全体集団を 1 つの集団としてみなして分析をするものであった。参考までに、2019 年[redacted] 月[redacted] 日第一回分析前協議において提出した弊社意見における分析案は下記のとおりであった。

- B-ALL：サブグループの設定は行わず、対照技術は[redacted]。
- DLBCL：サブグループの設定は行わず、対照技術は、[redacted]

2.1 分析対象とする集団

2019 年[redacted] 月[redacted] 日に実施された費用対効果評価専門組織において、決定された分析対象は下記のとおりである。以下、分析枠組みに関する厚生労働省からの通知資料の抜粋。

【B-ALL】

対象とする疾患	再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病。ただし、25 歳以下（治療時）の、以下のいずれかの場合に限る。 • 初発の患者では標準的な化学療法を 2 回以上施行したが寛解が得られない場合 • 再発の患者では化学療法を 1 回以上施行したが寛解が得られない場合 • 同種造血幹細胞移植の適応とならない又は同種造血幹細胞移植後に再発した場合
サブグループ解析	• 15 歳未満の集団 • 15 歳以上 25 歳以下の集団

【DLBCL】

対象とする疾患	再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫。ただし、以下のいずれかの場合であって、自家造血幹細胞移植の適応とならない又は自家造血幹細胞移植後に再発した患者に限る。 • 初発の患者では化学療法を 2 回以上、再発の患者では再発後に化学療法を 1 回以上施行し、化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合

	• 濾胞性リンパ腫が形質転換した患者では通算 2 回以上の化学療法を施行し、形質転換後には化学療法を 1 回以上施行したが、形質転換後の化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合
サブグループ解析	70 歳未満の患者及び 70 歳以上の患者のサブグループに分けて分析を実施する。

2.2 比較対照

2019 年[redacted]月[redacted]日に実施された費用対効果評価専門組織において、決定された比較対照技術は下記のとおりである。以下、分析枠組みに関する厚生労働省からの通知資料の抜粋。

【B-ALL】

比較対照技術名	15 歳未満の集団においては「ブリナツモマブ（同種 HSCT を含む）」、15 歳以上 25 歳以下の集団においては効果が同程度と考えられる「ブリナツモマブ（同種 HSCT を含む）」、「イノツズマブ オゾガマイシン（同種 HSCT を含む）」の両者を比較対照とする。
比較対照技術を選定した理由	いずれの集団においても、日本における診療実態、あるいは米国 NCCN ガイドラインを参照すると、現在実施されている標準治療は（再発後）2 次化学療法（同種 HSCT を含む）である。 化学療法としては、「中央社会保険医療協議会における費用対効果評価の分析ガイドライン第 2 版」に従い、候補となり得るものの中で、寛解率が高いと考えられる 15 歳未満の集団においては「ブリナツモマブ（同種 HSCT を含む）」、15 歳以上 25 歳以下の集団においては効果が同程度と考えられる「ブリナツモマブ（同種 HSCT を含む）」、「イノツズマブ オゾガマイシン（同種 HSCT を含む）」の両者を比較対照とすることが適当である。なお、イノツズマブ イゾガマイシンは添付文書上で、「低出生体重児、新生児、乳児、幼児又は小児に対する安全性及び有効性は確立していない」とされることから、成人（15 歳以上）のみ比較対照技術として含めることとした。
比較対照技術の使用方法 （添付文書より一部抜粋）	ブリナツモマブ（ビーリンサイト 点滴静注用 35μg） **効能・効果**：再発又は難治性の B 細胞性急性リンパ性白血病 **用法及び用量**：通常、ブリナツモマブ（遺伝子組換え）として以下の投与量を 28 日間持続点滴静注した後、14 日間休薬する。これを 1 サイクルとし、最大 5 サイクル繰り返す。その後、ブリナツモマブ（遺伝子

	組換え)として以下の投与量を 28 日間持続点滴静注した後、56 日間休薬する。これを 1 サイクルとし、最大 4 サイクル繰り返す。なお、患者の状態により適宜減量する。 ○ 体重が 45 kg 以上の場合:1 サイクル目の 1～7 日目は 1 日 9 μg、それ以降は 1 日 28 μg とする。 ○ 体重が 45 kg 未満の場合:1 サイクル目の 1～7 日目は 1 日 5 μg/m2(体表面積)、それ以降は 1 日 15 μg/m^2(体表面積)とする。ただし、体重が 45 kg 以上の場合の投与量を超えないこと。 ＜用法・用量に関連する使用上の注意＞ (1) 本品投与によりサイトカイン放出症候群が発現する可能性があるため、本品投与前及び増量前はデキサメタゾンを投与すること。 <u>イノツズマブ オゾガマイシン</u> **効能・効果**:再発又は難治性の CD22 陽性の急性リンパ性白血病 [効能・効果に関連する使用上の注意] 1. フローサイトメトリー法等の検査によって、CD22 抗原が陽性であることが確認された患者に使用すること **用法及び用量**:通常、成人にはイノツズマブ オゾガマイシン(遺伝子組換え)として 1 日目は 0.8mg/m^2(体表面積)、8 及び 15 日目は 0.5mg/m^2(体表面積)を 1 日 1 回、1 時間以上かけて点滴静脈内投与した後、休薬する。1 サイクル目は 21～28 日間、2 サイクル目以降は 28 日間を 1 サイクルとし、投与を繰り返す。投与サイクル数は造血幹細胞移植の施行予定を考慮して決定する。なお、患者の状態により適宜減量する。 [用法・用量に関連する使用上の注意] 1. 1 サイクル目の期間は原則 21 日間とするが、寛解(血球数の回復の有無を問わない)が得られた場合は、28 日間まで延長できる。また、寛解(血球数の回復の有無を問わない)が得られた場合、2 サイクル目以降の 1 日目の投与量は、イノツズマブ オゾガマイシン(遺伝子組換え)として 0.5mg/m^2(体表面積)とすること。なお、骨髄中の芽球が 5%未満で、末梢血中の白血病芽球及び髄外病変が消失した場合に、寛解(血球数の回復の有無を問わない)が得られたと判断すること。 2.本品の投与サイクル数は、以下のとおりとする。 ⑴HSCT の施行を予定している場合

	投与サイクル数の増加に応じて HSCT 施行後の VOD/SOS の発現リスクが高まるおそれがあるので、本品の効果が得られる最小限のサイクル数とすること。治療上やむを得ないと判断される場合を除き、3 サイクル終了までに投与を中止すること。[「警告」、「効能・効果に関連する使用上の注意」、「慎重投与」、「重要な基本的注意」、「副作用」、「高齢者への投与」及び「その他の注意」の項参照] ⑵HSCT の施行を予定していない場合 6 サイクルまで投与を繰り返すことができる。ただし、3 サイクル終了までに本品の効果が得られない場合には、投与を中止すること。 3．本品を 7 サイクル以上投与した際の有効性及び安全性は確立していない。 [小児等への投与] 低出生体重児、新生児、乳児、幼児又は小児に対する安全性及び有効性は確立していない。[使用経験がない。]

【DLBCL】

比較対照技術名	• 70 歳未満の患者:サルベージ化学療法+/-同種 HSCT • 70 歳以上の患者:サルベージ化学療法
比較対照技術を選定した理由	治療効果の大きい治療法はサルベージ化学療法+/-同種 HSCT であるが、70 歳以上のサブグループについては、同種 HSCT が積極的には実施されないことから、上記の集団ごとに、比較対照技術を設定し、それぞれ分析する。
比較対照技術の使用方法	造血器腫瘍診療ガイドライン(2018 年版日本血液学会ガイドライン)に示された salvage chemotherapy のレジメンは下記のとおりである。その中で本邦の実臨床における使用度合い、保険償還された医薬品を使用したレジメンを考慮して比較対照技術に含めるレジメンを決定した。[15] <u>救援化学療法</u> DHAP 療法(DEX, CDDP, AraC)(＋R) (R-)ESHAP 療法(mPSL, ETP, AraC, CDDP) (R-)ICE 療法(IFM, CBDCA, ETP) CHASE(R)療法(CPA, AraC, DEX, ETP) Dose adjusted(DA)-EPOCH(-R)療法(ETP, PSL, VCR, CPA, DXR)

	MINE 療法（MIT, IFM,メスナ, ETP） GDP 療法（Gem, DEX, CDDP）

2.3 分析の立場と費用の範囲

【B-ALL】

基本分析では公的医療費支払者の立場から、公的医療費のみを含めた分析を行う。ただし、本品が長期間のベネフィットを患者にもたらす可能性があること、対象疾患が小児および若年性であること等を考慮し、生産性損失を含めた分析も補助的に実施する。

【DLBCL】

基本分析では公的医療費支払者の立場から、公的医療費のみを含めた分析を行う。ただし本品は既存の治療方法と異なり、持続的な有効性と Social functioning ability の改善が期待できる。そのため本治療法による患者の生産性への影響は大きいと考えられることから、生産性損失を含めた分析も補助的に実施する。

2.4 効果指標

【B-ALL&DLBCL】

両疾患ともに効果の指標として質調整生存年（QALYs）を用いる。また参考値として、生存年（LYs）の推計結果も表示する。

2.5 分析期間

【B-ALL&DLBCL】

両疾患ともに分析期間は生涯に設定する。これは、中央社会保険医療協議会における費用対効果評価の分析ガイドライン第 2 版（以降、分析ガイドライン）7.1 の記載、「評価対象技術の費用や効果におよぼす影響を評価するのに十分に長い分析期間を用いる」とも合致する。

第一回分析前協議でも弊社意見として生涯の分析期間を提示しており、2019 年 [redacted] 月 [redacted] 日に実施した分析の進め方に関する会議においても、C2H 側から生涯の分析期間を提示されている。

補助的な分析として、分析期間を短縮 (ALL:[redacted] 年[redacted] 年、DLBCL[redacted] 年)した結果も表示する。

2.6 割引率

【B-ALL&DLBCL】

両疾患ともに分析ガイドラインに従い、費用･効果ともに年率 2%で割引を行うこととする。感度分析では費用･効果を同率で年率 0%から 4%の範囲で変化させる。

2.7 分析条件の設定の要約

【B-ALL】

分析対象とする集団	再発又は難治性の CD19 陽性の B 細胞性急性リンパ芽球性白血病。ただし、25 歳以下（治療時）の、以下のいずれかの場合に限る。 ・ 初発の患者では標準的な化学療法を 2 回以上施行したが寛解が得られない場合 ・ 再発の患者では化学療法を 1 回以上施行したが寛解が得られない場合 ・ 同種造血幹細胞移植の適応とならない又は同種造血幹細胞移植後に再発した場合
比較対照	15 歳未満の集団においては「ブリナツモマブ（同種 HSCT を含む）」、15 歳以上 25 歳以下の集団においては効果が同程度と考えられる「ブリナツモマブ（同種 HSCT を含む）」、「イノツズマブ オゾガマイシン（同種 HSCT を含む）」の両者を比較対照とする。
比較対照を選定した理由	いずれの集団においても、日本における診療実態、あるいは米国 NCCN ガイドラインを参照すると、現在実施されている標準治療は（再発後）2 次化学療法（同種 HSCT を含む）である。 化学療法としては、「中央社会保険医療協議会における費用対効果評価の分析ガイドライン第 2 版」に従い、候補となり得るものの中で、寛解率が高いと考えられる 15 歳未満の集団においては「ブリナツモマブ（同種 HSCT を含む）」、15 歳以上 25 歳以下の集団においては効果が同程度と考えられる「ブリナツモマブ（同種 HSCT を含む）」、「イノツズマブ オゾガマイシン（同種 HSCT を含む）」の両者を比較対照とすることが適当である。なお、イノツズマブ イゾガマイシンは添付文書上で、「低出生体重児、新生児、乳児、幼児又は小児に対する安全性及び有効性は確立していない」とされることから、成人（15 歳以上）のみ比較対照技術として含めることとした。
分析の立場と費用の範囲	ベースケースは公的医療費支払者の立場（公的医療費のみ） 追加的な分析において生産性損失を考慮する
効果指標	QALY、参考値：生存年
分析期間	生涯
割引率	費用・効果ともに年率 2%

	感度分析 0%-4%

【DLBCL】

分析対象とする集団	再発又は難治性の CD19 陽性のびまん性大細胞型 B 細胞リンパ腫。ただし、以下のいずれかの場合であって、自家造血幹細胞移植の適応とならない又は自家造血幹細胞移植後に再発した患者に限る。 ・ 初発の患者では化学療法を 2 回以上、再発の患者では再発後に化学療法を 1 回以上施行し、化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合 ・ 濾胞性リンパ腫が形質転換した患者では通算 2 回以上の化学療法を施行し、形質転換後には化学療法を 1 回以上施行したが、形質転換後の化学療法により完全奏効が得られなかった又は完全奏効が得られたが再発した場合
比較対照	・ 70 歳未満の患者:サルベージ化学療法+/-同種 HSCT ・ 70 歳以上の患者:サルベージ化学療法
比較対照を選定した理由	治療効果の大きい治療法はサルベージ化学療法+/-同種 HSCT であるが、70 歳以上のサブグループについては、同種 HSCT が積極的には実施されないことから、上記の集団ごとに、比較対照技術を設定し、それぞれ分析する。
分析の立場と費用の範囲	ベースケースは公的医療費支払者の立場(公的医療費のみ) 追加的な分析において生産性損失を考慮する
効果指標	QALY、参考値:生存年
分析期間	生涯
割引率	費用・効果ともに年率 2% 感度分析 0%-4%

3．追加的有用性

3.1 クリニカルクエスチョン

B-ALL 及び DLBCL の両疾患について、クリニカルクエスチョンを下記の通り PICO の形式で設定した。

3.1.1 B-ALL

海外文献 SLR における CQ:

対象集団	Children and young adults (patients under 26 years of age) with r/r ALL after transplantation or second or further relapses Share of the relevant patient population in the study population at least 80% B-cell ALL[a]
介入	Tisagenlecleucel, single infusion, as approved. Previously available treatment options licensed or recommended for ALL or related oncology indications (e.g., stem cell transplantation, chemotherapy)
比較対照	Any comparator therapy
アウトカム	Mortality: • Overall survival Morbidity: • Event-free survival • Disease-free survival • Progression-free survival • Response rate • Remission duration • Recurrence rate • Frequency and timing of stem cell transplants • Adverse events Health-related quality of life: • Disease-specific or general validated survey instruments
研究デザイン	Randomized controlled trials Controlled clinical trials Uncontrolled single-arm clinical studies Observational studies

	All studies include in the EMA historical comparison
文献検索期間	From January 1, 1946 to July 30, 2019

a. Studies in which B-cell lineage was not reported were assumed to have a majority of patients with B-cell ALL since that is the most common immunophenotype in the population

国内文献 SLR における CQ:

対象集団	再発または難治性の B 細胞性急性リンパ芽球性白血病（B-ALL）の患者 ただし、造血幹細胞移植後または 2 回目以降に再発後で 26 歳未満の患者に限る
介入	対象集団の適応症に対する以下の療法 • チサゲンレクルユーセル
比較対照	制限なし
アウトカム	以下のいずれかのアウトカム： 生存（期間）、有効性、安全性、健康に関する QOL
研究デザイン	ランダム化比較試験（RCT）、比較臨床試験(CCT)
文献検索期間	[redacted] 年 [redacted] 月 [redacted] 日から [redacted] 年 [redacted] 月 [redacted] 日まで

3.1.2 DLBCL

海外文献 SLR における CQ:

対象集団	• Adult patients with relapsed or refractory disease after ≥2 lines of therapies, and either having failed autologous hematopoietic stem cell transplantation (ASCT), or being ineligible for or not consenting to ASCT • Histology of interest included DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma • If other histologies were included, and the DLBCL subgroup results were not reported, share of the relevant patient population in the study population had

	to be at least 80% for DLBCL and transformed follicular lymphoma (tFL)
介入・比較対照	Available treatment options (e.g., stem cell transplantation, chemotherapy), no limitation on comparators
アウトカム	At least one of the following outcomes available: Survival • Overall survival (OS) Response • Event-free survival • Disease-free survival • Progression-free survival (PFS) • Response rate • Remission rate • Recurrence rate Frequency and timing of stem cell transplants Safety • Adverse events Health-related quality of life • Disease-specific or general validated survey instruments
研究デザイン	Randomized control trial (RCT) Controlled clinical trials Uncontrolled single-armed clinical studies
文献検索期間	[redacted]

[redacted]

国内文献 SLR における CQ:

対象集団	再発または難治性のびまん性大細胞型 B 細胞リンパ腫（DLBCL）の成人患者 ただし、以下のいずれかに当てはまる場合に限る

	・ 自家造血幹細胞移植（ASCT）が不適格である患者 ・ 少なくとも過去 2 つ以上の治療に成功しなかった再発患者
介入	対象集団の適応症に対する以下の療法 • チサゲンレクルユーセル
比較対照	制限なし
アウトカム	以下のいずれかのアウトカム： 生存（期間）、有効性、安全性、健康に関する QOL
研究デザイン	ランダム化比較試験（RCT）、比較臨床試験(CCT)
文献検索期間	[redacted] 年 [redacted] 月 [redacted] 日から [redacted] 年 [redacted] 月 [redacted] 日まで

B-ALL と DLBCL の両疾患について、患者数が限られるなどの理由からこれまで臨床試験として本品のランダム化比較試験（RCT）は実施されておらず、いずれも単群試験である。本製品と比較対照技術の RCT が抽出される可能性は極めて低いため、クリニカルクエスチョンの「研究デザイン」に単群試験を含めることにした。

国内外で公開されているエビデンスを網羅するため、両疾患について英語及び日本語によるシステマティックレビューを実施した。

分析ガイドラインには、文献検索終了時点について「分析枠組みが決定された後から製造販売業者による分析提出までの一時点に決める」と規定されている。しかし分析枠組みの合意に時間を要し、製造販売業者による分析提出までの期間が限られていたことから、既に一定以上の質を有するエビデンスが検出されていることを鑑み、英語によるシステマティックレビューについては文献検索終了時点を分析枠組みの決定以前に設定した（具体的な文献検索終了時点については上述の表を参照）。これらについて 2019 年 [redacted] 月 [redacted] 日に実施された C2H 及び厚生労働省との協議の中で提案したところ、特に反対意見は出なかった。なお国内の文献を対象としたシステマティックレビューについては、対象となるデータベースが比較的少数であるなどの理由から、分析ガイドラインの規定に従い、文献検索終了時点を分析枠組みの決定後に設定した。以上より、今回の文献検索時点の設定は分析ガイドラインと照らし合わせて適切であると考える。

3.2 システマティックレビュー

3.2.1 B-ALL

海外文献 SLR：

Data Source and Search Terms

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify English-language studies published from the start of database indexing (since [redacted]. Searches were conducted using a combination of search

terms and keywords for relapsed/refractory ALL and the validated algorithms to identify study designs of interest.

The search terms and strategies were developed and adapted to the idiosyncrasies of each database using the appropriate indexing terms. The search strategies for each search interface (EMBASE.com, PubMed, and the Cochrane Library) included a combination of free-text search terms and controlled vocabulary terms (MeSH terms in MEDLINE via PubMed and the Cochrane Library and EMTREE terms in EMBASE.com), as recommended by the Cochrane Collaboration. As multiple literature databases were searched, duplicate citations were removed, and related publications were identified and grouped accordingly. The search algorithms used are outlined in Appendix B.

Supplementary searches of grey literature were conducted to complement the database searches and to provide supplemental data from recent or ongoing trials. The databases and information resources searched in the SLR are shown in Table 3, below. In addition, references from relevant published SLRs were reviewed to ensure comprehensive literature retrieval.

Table 3. Information sources searched in the clinical SLR

Information source	Interface / URL
Databases and registries (searched with no lower limit to publication date)	
MEDLINE and MEDLINE In-process	https://www.ncbi.nlm.nih.gov/pubmed
Embase	https://www.embase.com
Cochrane Collaboration Central Register of Clinical Trials (CENTRAL)	Cochrane Library
ClinicalTrials.gov	https://www.clinicaltrials.gov/
European Union Clinical trials register (EU-CTR)	https://www.clinicaltrialsregister.eu/
WHO International Clinical Trials Registry Platform (WHO ICTRP)	http://apps.who.int/trialsearch/
Conference proceedings (searched from [redacted] through [redacted]	
American Society for Blood and Marrow Transplantation (ASBMT)	https://www.asco.org/

Information source	Interface / URL
American Society of Clinical Oncology (ASCO)	http://www.esmo.org/
American Society of Hematology (ASH)	http://www.hematology.org/
European Hematology Association (EHA)	https://ehaweb.org/
European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/
European Society of Medical Oncology (ESMO)	http://www.esmo.org/

Screening (Inclusion/Exclusion Criteria)

The SLR included clinical trials (both randomized controlled trials [RCTs] and single-arm trials) and observational studies that evaluated treatment of relapsed/refractory ALL in pediatric patients and young adults, from birth to 25 years of age (inclusive), and that reported efficacy, safety, and health-related quality of life (HRQoL) outcomes related to treatment. The SLR included a broad range of study designs since RCT evidence was limited for this population as the majority of trials were single-arm studies. Observational evidence was included since there were a limited number of clinical trials available on this population. Study selection was accomplished based on the participants, interventions, comparisons, outcomes, and study design (PICOS) criteria shown in Table 4.

Once the literature searches were conducted and all duplicates across databases were removed, the identification of articles was accomplished through a two-level selection and evaluation process. In the first level of review, the pre-defined inclusion and exclusion criteria were used to evaluate the titles/abstracts of records identified from the searches. Full-text articles were then retrieved and reviewed for abstracts deemed relevant during the first level of review. All the exclusion and inclusion criteria were required to be met for a study to be included at this stage. During both levels of the review process, records were screened by two independent reviewers and a third, senior reviewer reconciled any discrepancies between the screening results. All accepted studies met all of the inclusion criteria and none of the exclusion criteria.

Table 4. PICOS Screening/eligibility Criteria

項目	組み入れ基準	除外基準
Patient Population	Children and young adults (patients under 26 years of age) with r/r ALL after transplantation or second or further relapses Share of the relevant patient population in the study population at least 80% B-cell ALL[a]	Patients who do not conform to the approved indication of Tisagenlecleucel: •Studies of patients over 26 years of age where the data are not reported separately for patients aged 25 years and under •Studies of indications other than ALL •Studies in which the majority of patients have T-cell ALL (>20%) •Studies of patients in complete remission •Studies of patients with ALL who are treatment-naïve •At least 10 ALL patients evaluated per treatment arm for trials and 20 ALL patients for observational studies
Intervention	Tisagenlecleucel, single infusion, as approved. Previously available treatment options licensed or recommended for ALL or related oncology indications (e.g., stem cell transplantation, chemotherapy)	Interventions that are not used in practice in the relevant field of application.
Comparator therapy	Any comparator therapy	None

項目	組み入れ基準	除外基準
Endpoints	Mortality: • Overall survival Morbidity: • Event-free survival • Disease-free survival • Progression-free survival • response rate • Remission duration • recurrence rate • Frequency and timing of stem cell transplants • Adverse events Health-related quality of life: • Disease-specific or general validated survey instruments	Studies without results available for at least one of the endpoints of interest in the inclusion criteria.
Study type	Randomized controlled trials Controlled clinical trials Uncontrolled single-arm clinical studies Observational studies All studies include in the EMA historical comparison	Dose finding studies Case reports Narrative reviews Systematic reviews Opinions Animal /In vitro studies
Publication type	Study report Full Text Publication All publications that were part of the historical comparison presented to the EMA in the regulatory process	Conference abstracts, editorials, notes, letters to the editor (with the exception of the studies of the historical comparison presented to the EMA)
Language	English	Non-English languages

a. Studies in which B-cell lineage was not reported were assumed to have a majority of patients with B-cell ALL since that is the most common immunophenotype in the population

Extraction

Data from the included studies were captured into an extraction template created in Microsoft Excel®. Each article was extracted by one researcher familiar with the subject area and validated by a second, independent researcher.

Trial quality and a risk of bias assessments were assessed at extraction for each study considered similar to the ELIANA trial. To assess risk of bias/quality, we applied the following questions to each trial:

1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Was knowledge of the allocated interventions adequately prevented during the trial (blinded)?
4. Was a power calculation conducted?
5. Were the groups similar at baseline in terms of prognostic factors?
6. Were there fewer than [redacted] withdrawals?
7. Was there a balanced percentage of dropouts between groups?
8. Was intention to treat (ITT) analysis conducted?
9. Were subgroup analyses defined a priori?

Result

The electronic database searches yielded 12,935 titles and abstracts. After removing duplicate references across the databases, 9,595 unique studies remained for screening. Of these, 8,697 abstracts were excluded and 898 references remained for further full-text review. Following full-text screening, 714 of the 89 studies were excluded and 184 studies were included. Exclusions were primarily because studies did not report outcomes separately for patients of interest (206 studies). In addition 17 conference abstracts identified EMA submission for tisagenlecleucel. The PRISMA flow diagram for the SLR is presented in Figure 5. Ultimately, 14 of the included studies had populations that were similar to the ELIANA trial and 9 of those were deemed eligible for inclusion in statistical analysis. Details on the 9 studies are presented in Table 5.

Figure 5. PRISMA flow diagram for the Systematic Review

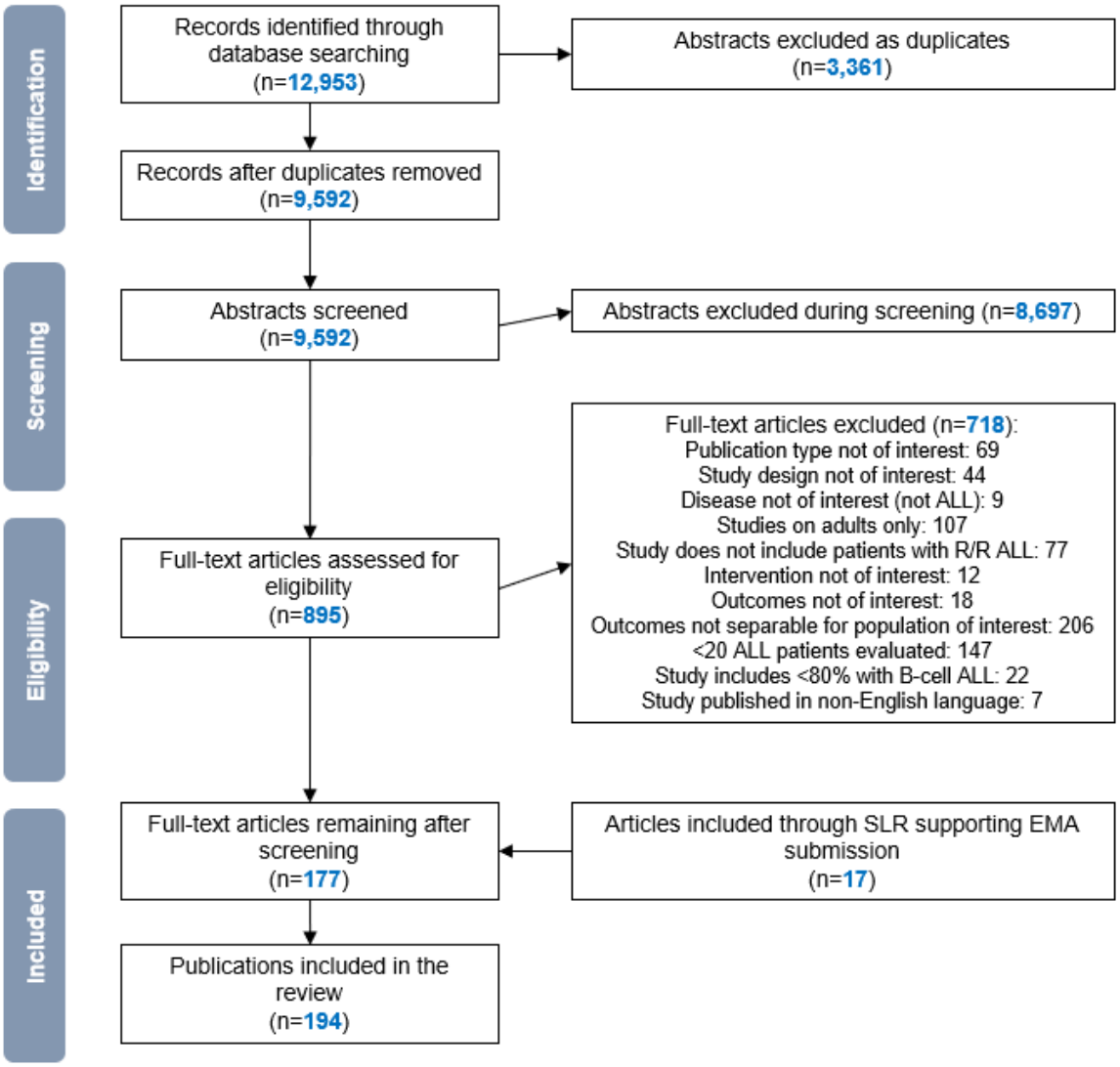


Table 5. List of clinical studies (papers) identified

Name of clinical trial	Intervention	Comparisons	Sample size	Statistic	Reference
NR, Retrospective cohort	inotuzumab ozogamicin	None	51	Univariable and multivariable logistic regression was used to examine associations between patient and disease characteristics and the probability of achieving CR. Univariable and multivariable Cox regression analysis was used to assess the associations between EFS/OS and patient/disease characteristics. Estimates of EFS or OS probability were based on the product limit estimator with Greenwood SE. Reported p-values are all two-sided.	Bhojwani et al. 2019 [16]
MT103-205 NCT01471782	blinatumomab	None	70	A minimum of 40 patients (first stage, n = 21; second stage, n = 19) was estimated to be needed to provide 80% power to test the null hypothesis, with two-sided p=0.05, that achievement of CR within the first two cycles was 10% versus the alternative hypothesis of 27.5%. The proportion of responders with exact 95% CIs was calculated. RFS and OS (time from enrollment to first relapse or death, respectively) were estimated using the Kaplan-Meier method.	von Stackelberg et al. 2016 [17]
RIALTO NCT02187354	blinatumomab	None	40	NR	Locatelli et al. 2018 [18]
NR, Phase II trial	Clofarabine monotherapy	None	61	The study's primary objective was to estimate the overall remission rate, which was defined as patients who achieved CR or CR without platelet recovery divided by the number of treated patients. Kaplan-Meier methods were used to summarize duration of remission and overall survival. Patients who were in remission or alive at last follow-up were censored at that point. In addition, patient performance	Jeha et al. 2006 [19]

Name of clinical trial	Intervention	Comparisons	Sample size	Statistic	Reference
				status on study as well as transplantations that occurred after clofarabine were analyzed.	
NR, NCT00315705	Clofarabine, cyclophosphamide, and etoposide	None	25	The primary efficacy analysis included all patients who received at least one dose of clofarabine. All patients who received any amount of study drug were included in the safety analysis. Descriptive statistics were used to describe response rates. Time-to-event outcomes, such as DOR and OS, were described using Kaplan-Meier estimates. DOR was calculated censoring patients known to be in remission at last follow-up, and separately with censoring at the time of alternative therapy or HSCT.	Hijiya et al. 2011 [20]
NR, Prospective cohort	Clofarabine, cyclophosphamide, and etoposide	None	24	Qualitative data were reported in terms of absolute frequencies and percentages, and quantitative data in terms of medians with minimum and maximum values. The probability of OS was estimated using the Kaplan–Meier method. The log-rank test was used to compare survival curves. A p-value less than 0.05 was considered statistically significant.	Miano et al. 2012 [21]
NR, Phase II trial	Clofarabine, cyclophosphamide, and etoposide	None	25	Quantitative variables were reported as median and range. Patient- and disease-related variables were analysed for their prognostic value on probability of obtaining CR or CRp. The probability of OS was estimated by the Kaplan–Meier method, and expressed as 18-month probability, with the corresponding 95% CI. P-values < 0.05 were considered significant.	Locatelli et al. 2009 [22]
NR, Retrospective cohor	Salvage chemotherapy	Palliative care or Supportive care (no antileukemic therapy)	93	Differences in the distribution of variables among subgroups were assessed by the Mann–Whitney U- or Kruskal–Wallis test for continuous variables. Exact Fischer-test was used to analyze the independency of two, Pearson-test of more than two qualitative variables. Kaplan–Meier life-table-analysis was performed to present	von Stackelberg et al. 2011

Name of clinical trial	Intervention	Comparisons	Sample size	Statistic	Reference
t				survival data of the total cohort and subgroups only considering disease- or treatment-related deaths as subsequent events. Subgroups were compared by the two-sided log-rank-test. In all tests, two-sided p≥0.05 or higher was regarded as not significant. Multivariate Cox stepwise- forward-conditional–regression-analysis was done to determine statistically significant independent indicators of outcome	[23]
NR, Prospective cohort	Salvage chemotherapy	Salvage chemotherapy + SCT	242	The OS and EFS probabilities were calculated using the Kaplan–Meier method and groups were compared using the log-rank test. The median follow-up time was estimated using the reverse Kaplan–Meier method. The impact of prognostic factors on EFS and OS was evaluated in a univariate and multivariate manner by using the Cox proportional hazards model.	Kuhlen 2018 [24]

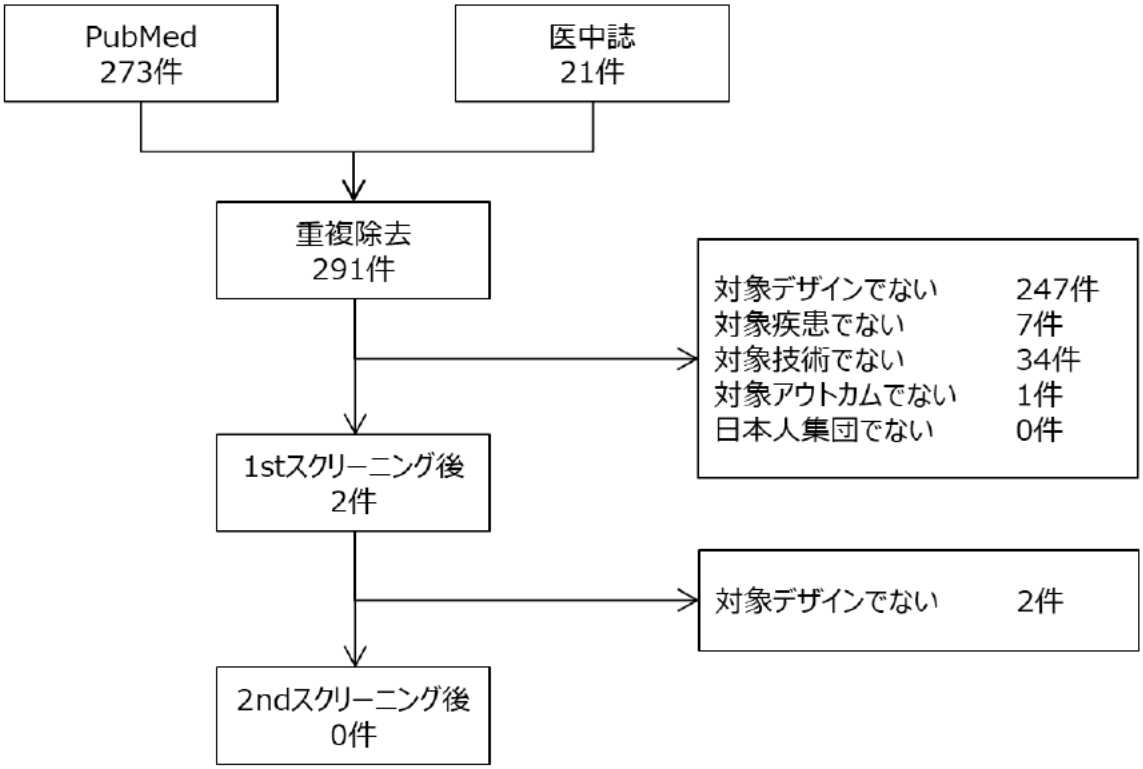
国内文献 SLR:
日本人を対象としたエビデンスの有無を検証するため、日本語及び英語での文献検索を実施した。データソースとして PubMed、医中誌を選定した。Table 6 に各データソースの詳細を示す。分析ガイドラインの規定に則り、文献検索期間を[redacted]年[redacted]月から分析枠組み決定後の[redacted]年[redacted]月に設定した。PubMed 及び医中誌において文献抽出のため作成した検索式については、Appendix B を参照。海外文献の SLR と条件を揃えるため、原則として国内文献の SLR においても Table 4 と同一の組み入れ基準及び排除基準を設定し海外文献 SLR と重複するものは除外した。

Table 6. Information sources searched in the clinical SLR

Information source	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
医中誌	https://search.jamas.or.jp/

検索式による文献検索を実行したところ、PubMed で 273 件、医中誌で 21 件を抽出した。重複する文献を除外した結果、291 件の文献を特定した。291 件の文献に対して、エキスパートによる 2 段階のスクリーニングを実施した。1 次スクリーニングの結果、本品に関するグローバル治験 2 件が抽出されたものの、いずれも単群試験であったことから 2 次スクリーニングの結果 0 件となった。Figure 6 に本 SLR の PRISMA フローダイアグラムを示す。

Figure 6. PRISMA flow diagram for the Systematic Review



3.2.2 DLBCL

海外文献 SLR:

Data Sources and Search Terms

The SLR to identify studies of treatments for adult patients with r/r DLBCL was

conducted for the time span of [redacted] to [redacted] The time frame covered studies published over a decade, since rituximab's approval for DLBCL by both the European Medicines Agency (EMA) (approved in 2002) and the US Food and Drug Administration (FDA) (approved in 2006). The following databases were searched:

- EMBASE (https://www.embase.com)
- MEDLINE (inclusive "in-process & other non-indexed citations") (https://www.ncbi.nlm.nih.gov/pubmed)
- Cochrane Controlled Trials Register (CCTR) (Cochrane Library)

To capture results from the most recent trials that might not have been published as a full text, additional searches were performed for clinical trials in trial registries. The registry search was conducted on [redacted] without any limit to the time frame of the trials. Publications or other data associated with included trials specified in the registries were also leveraged to capture additional results, including full text articles, conference abstracts, and regulatory documents. The following trial registries were included in the search:

- Clinicaltrials.gov (https://www.clinicaltrials.gov/)
- European Union Clinical Trials Register (EU-CTR) (https://www.clinicaltrialsregister.eu/)
- World Health Organization (WHO) and International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)

The search strategies for databases via Ovid were developed in accordance with the best practices for systematic literature search including those published by the Cochrane Collaboration, and health technology assessment (HTA) agencies, and incorporated the PICOS elements to identify publications relevant to the research questions. Search terms comprised of combinations of keywords (free text), subject headings (e.g., Medical Subject Headings [MeSH]) and the relationship between the search terms (e.g., Boolean logic). Additional criteria were added (where appropriate/possible depending on the search interface used) to restrict the search results to English publications in human studies published in [redacted] or later. The search strategies for studies on three databases are provided in Appendix B. Duplicate citations within databases were excluded.

Manual searches were performed on trial registries' websites to identify relevant records. The search strategies for clinical trials in registries are delineated in Appendix B. All records identified from the database and registry searches were electronically downloaded from the database for screening.

Screening (Inclusion/Exclusion Criteria)

A two-level screening was conducted on all records from the database search. The detailed inclusion/exclusion criteria provided in Table 7 were used as a guideline for the study selection to ensure that all decisions regarding the inclusion and exclusion of studies were consistent.

For all records identified from the database search, two-level screening (level I and level II screening) were conducted by two reviewers independently as follows:

- Level I screening based on title and abstract

Studies identified from the databases were screened initially based on the title and abstract exported from the databases. Studies that did not meet the inclusion criteria or met the exclusion criteria were excluded at level I. When decisions to include or exclude studies could not be made based on title and abstract alone, full-text articles were obtained and assessed at level II.

- Level II screening based on full text publication

In this step, the full-text articles for studies included after level I screening were reviewed. The same inclusion/exclusion criteria as used in the level I screening were applied to all full-text articles.
Any discrepancies between the two reviewers regarding the inclusion/exclusion decisions were reconciled by a third reviewer.
Trials identified from the trial registry search were only screened at one level utilizing all information available (including study reports, conference abstracts/posters, and full-text articles). Two reviewers independently screened all information, with any discrepancies on the inclusion/exclusion decisions reconciled by a third reviewer.

Table 7. PICOS Screening/eligibility Criteria

項目	組み入れ基準	除外基準
Documentation type	Full text articles and conference papers from Ovid All publications (including study reports, conference abstracts/posters, and full-text articles) for trials identified from registry search	Other document types (e.g., conference abstracts, editorials, notes, letters to the editor)
Year restriction	[redacted]	N/A
Study type	Randomized control trial (RCT) Controlled clinical trials Uncontrolled single-armed clinical studies	Case reportsb Dose finding studies Narrative reviews Observational studies (except for those including RCT cohorts)
Patient population	Adult patients with relapsed or refractory disease after ≥2 lines of therapies, and either having failed autologous hematopoietic stem cell transplantation (ASCT), or being ineligible for or not consenting to ASCT Histology of interest included DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL	Newly diagnosed patients, or treatment-naïve patients Indolent NHL or other histology not covered in the inclusion list Patients with active hepatitis B virus, active hepatitis C virus, active HIV or active CNS involvement by malignancy Sample size too small (less than 5)

項目	組み入れ基準	除外基準
	arising from follicular lymphoma If other histologies were included, and the DLBCL subgroup results were not reported, share of the relevant patient population in the study population had to be at least 80% DLBCL and tFL	
Intervention	Available treatment options (e.g., salvage chemotherapy)	Interventions that are not used in practice in the relevant field of application No previous treatment with R-CHOP or less than 80% treated with R-CHOP
Comparator therapy	No limitation	No limitation
Endpoints	At least one of the following outcomes available: Survival • Overall survival (OS) Response • Event-free survival • Disease-free survival • Progression-free survival (PFS) • Response rate • Remission rate • Recurrence rate Frequency and timing of stem cell transplants Safety • Adverse events Health-related quality of life • Disease-specific or general validated survey instruments	Studies without results on at least one of the mentioned relevant endpoints
Language	Publications published in English	Publications not published in English
Duplicate	Unique articles	Duplicated study

Extraction

After two-level screening, studies related to a regimen or combination of regimens of salvage chemotherapy, which represent the standard of care for r/r DLBCL in clinical practice of Japan were further selected for detailed data extraction. Those regimens or combinations of regimens will be considered as potential comparators in the ITC of tisagenlecleucel. Based on input from the Center for Outcomes Research and Economic Evaluation for Health (C2H) and Ministry of Health, Labour, and Welfare (MHLW), clinical practice on how salvage chemotherapy can be used differs by patient age groups. While patients < 70 years have the option to receive subsequent stem cell transplantation (SCT) after salvage chemotherapy, patients ≥ 70 years will be managed with salvage chemotherapy alone without SCT. To account for the heterogeneity in the comparator, data available for the two age groups were extracted, separately.

For each study, the following information was extracted:

- Study design
    - Intervention model (e.g., randomized/single-arm trial or observational study)
    - Masking (blinded or open-label)
    - Trial phase
    - Geographic location
- Patient population
    - Inclusion/exclusion criteria
    - Sample size for patient population of interest
    - Key baseline characteristics (definition and data availability)
        - Demographics (e.g., age, gender, and race)
        - Clinical characteristics including critical prognostic factors (e.g., histology, International Prognostic Index [IPI], Eastern Cooperative Oncology Group [ECOG] performance status)
        - Treatment history (e.g., prior treatments, response to prior treatment)
- Efficacy outcomes
    - Definitions and data availability
    - Methods of assessment (e.g., response assessment)

To ensure accuracy, data extraction were conducted by one researcher and audited by another independent researcher. A third researcher was consulted if there were any unresolved differences between the two researchers. If multiple publications were available for the same study, the publication reporting most recent data was used as the primary data source for data extraction, while the other publications were used as supplementary sources.

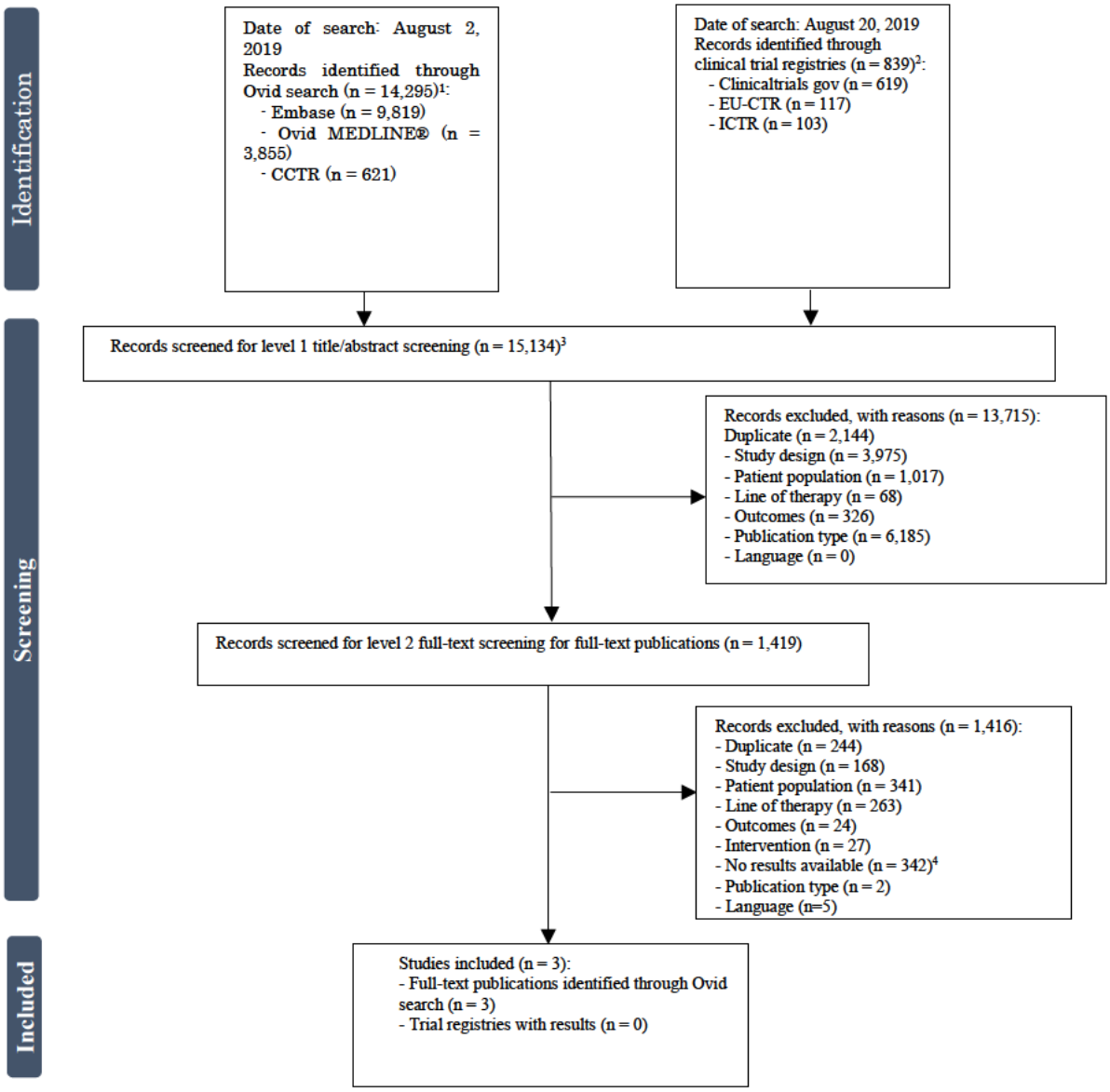
Result

A total of 15,134 records were identified from the search for studies with the search timeframe of [redacted] to [redacted] Of these, 14,295 records were identified from the database search, and 839 from the registry search.

In the level I screening, abstracts for 14,295 records identified from database search were screened, and 580 of those records were included after level I screening. In the level II screening, 1,419 records (including 580 database records from the level I screening and 839 records from the registry search) were screened. After level II screening, three records (from the database search) met

all inclusion criteria and were included. The PRISMA diagram illustrating the study selection process is presented in Figure 7. Details on the 9 studies are presented in Table 8.

Figure 7. PRISMA diagram of included and excluded studies



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CCTR: Cochrane Controlled Trials Register; EU: European Union; EU-CTR: EU Clinical Trials Register; ICTR: International Clinical Trials Registry.
Notes:
[1] Ovid search was conducted by database.
[2] Clinical trial registry search was conducted in three registries.
[3] Registry records were directly screened at level 2 with all available information.
[4] This screening criterion was only applicable for registry records.

Table 8. List of clinical studies (papers) identified from Ovid search (N=3)

Name of clinical trial	Intervention	Comparisons	Sample size	Statistic	Reference
CORAL extension study 1	Salvage therapy	N/A	• Full analysis set (baseline characteristics reported): N = 75 • Patients evaluated for response: N = 75 • Patients evaluated for survival: N = 73	• Number of patients (%) achieving ORR, CR, PR • Median OS	Van Den Neste et al. 2017[12]
CORAL extension study 2	Salvage therapy	N/A	• Full analysis set (baseline characteristics reported): N = 203 • Patients evaluated for response: N = 203 • Patients evaluated for survival: N = 193	• Number of patients (%) achieving ORR, CR, PR • Median OS	Van Den Neste et al. 2016[11]
SCHOLAR-1	Salvage therapy	N/A	• Primary abstraction: N=861 • Analysis set (baseline characteristics reported): N=636 • Patients evaluated for response: N=523 • Patients evaluated for survival: N=603	• Number of patients (%) achieving ORR, CR, PR • Median OS	Crump et al 2017[13]

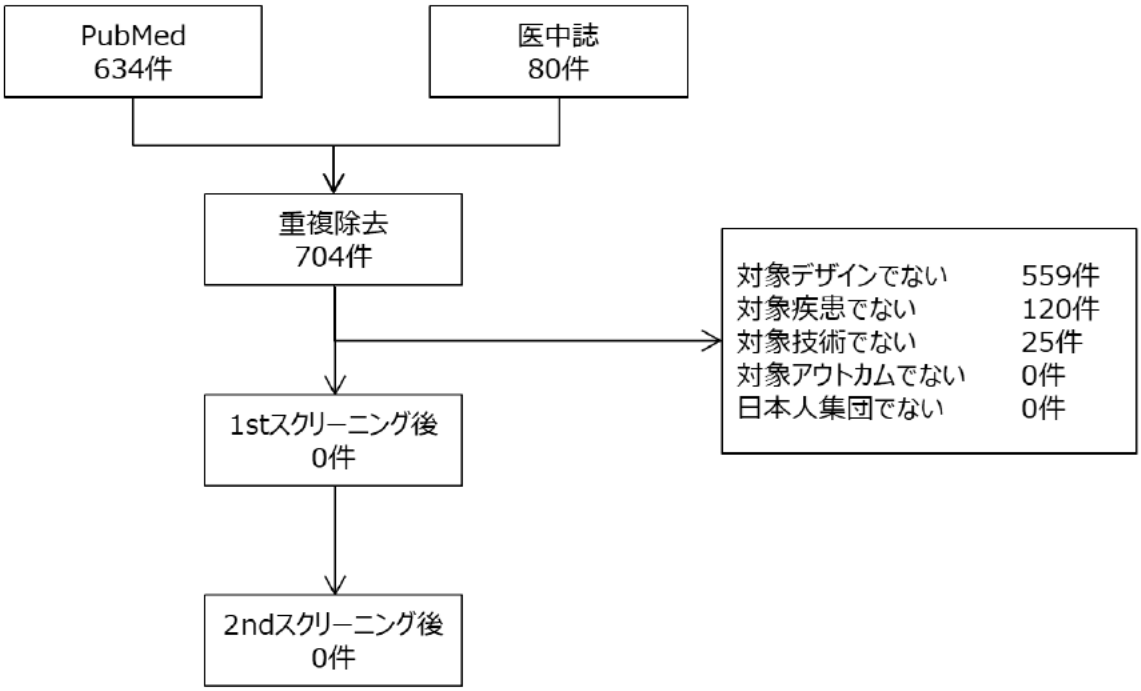
国内文献 SLR:
日本人を対象としたエビデンスの有無を検証するため、日本語及び英語での文献検索を実施した。データソースとして PubMed、医中誌を用いた。Table 9 に各データソースの詳細を示す。分析ガイドラインの規定に則り、文献検索期間を [redacted] 年 [redacted] 月から分析枠組み決定後の [redacted] 年 [redacted] 月に設定した。PubMed 及び医中誌において文献抽出のため作成した検索式については、Appendix B を参照。海外文献の SLR と条件を揃えるため、原則として国内文献の SLR においても Table 7 と同一の組み入れ基準及び排除基準を設定した。

Table 9. Information sources searched in the clinical SLR

Information source	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
医中誌	https://search.jamas.or.jp/

検索式による文献検索を実行したところ、PubMed で 634 件、医中誌で 80 件を抽出した。重複する文献を除外した結果、704 件の文献を特定した。704 件の文献に対して、エキスパートによる 1 次スクリーニングを実施したところ、該当する文献は抽出されなかった。Figure 8 に本 SLR について PRISMA フローダイアグラムを示す。

Figure 8. PRISMA flow diagram for the Systematic Review



3.3 クリニカルクエスチョン(異なる比較対照あるいは単群試験) [該当する場合のみ]
該当せず

3.4 システマティックレビュー (異なる比較対照あるいは単群試験) [該当する場合のみ]
該当せず

3.5 既存データの再解析
該当せず

3.6 メタアナリシスの詳細　[該当する場合のみ]
該当せず

3.7 間接比較やネットワークメタアナリシスの結果 [該当する場合のみ]
B-ALL 及び DLBCL の両疾患について、システマティックレビュー（Section 3.2）において tisagenlecleucel と比較対照技術を直接比較した試験は確認されなかった。そのため、個別の研究から臨床成績を取り出し、間接比較を実施した。両疾患ともに患者数が極めて限られており、比較対照技術も含めて、入手可能なエビデンスは単群試験に限定されている。それゆえ、ネットワークメタアナリシスのような手法による間接比較は不可能である。患者特性を揃えるために[redacted]でマッチングした上で比較を行った。

3.7.1 B-ALL: Kymriah(tisagenlecleucel) vs. Blinatumomab
Data Sources
Patient-level data from three tisagenlecleucel trials (B2202, B2205J, and B2101J)
Patient-level data on patient characteristics and OS for patients treated with tisagenlecleucel from the B2202 (ELIANA; NCT02435849), B2205J (ENSIGN; NCT02228096), and B2101J (NCT01626495) trials were pooled and used in the analyses.[25]–[27] All three trials are single-armed studies without randomization, and the patient characteristics are similar across all three trials. Pooling of the data from all available evidence increased the overall sample size and allowed the use of the long-term follow-up data to limit uncertainties from efficacy extrapolation.
Study B2202 is a single-arm, multicenter phase II trial to determine the efficacy and safety of tisagenlecleucel in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia (ALL). The data cutoff date was [redacted] Among the [redacted] patients enrolled, [redacted] patients [redacted]%) were infused and were included in the full analysis set (FAS)/modified intention-to-treat [mITT] population. Of the infused patients, [redacted] patients were aged <15, while [redacted] patients were aged ≥15 years. The median age of the mITT patient population was [redacted] years (range: [redacted] years). Among the [redacted] patients who received tisagenlecleucel infusion, the median time from infusion to data cutoff was [redacted] months.
Study B2205J is a single-arm, multicenter phase II trial to determine the efficacy and safety of tisagenlecleucel in pediatric patients with relapsed and refractory B-cell ALL or B-cell lymphoblastic lymphoma. The data cutoff date was [redacted] Up to the last patient visit ([redacted]), no lymphoblastic lymphoma patients were enrolled. Hence, all the results presented here are for ALL patients. A total of [redacted] patients were enrolled, with [redacted] patients treated with tisagenlecleucel and included in the mITT. Of the infused patients, [redacted] patients were aged <15, while [redacted] patients were aged ≥15 years. The median age of the mITT patient population was [redacted] years (range: [redacted] years). Among the [redacted] patients who received tisagenlecleucel infusion, the median time from infusion to last patient visit was [redacted] months.
Study B2101J is a single-arm, phase I/IIA trial to determine the efficacy and safety of tisagenlecleucel in pediatric patients with resistant or refractory CD19+ leukemia and lymphoma. The data cutoff date was [redacted] For the B2101J

trial, a total of [redacted] patients with non-CNS3 ALL were infused with tisagenlecleucel in the latest data cut and were included in the analyses (patients with CNS3 ALL or patients with lymphoma were excluded to make the populations comparable with ELIANA and ENSIGN populations). Of the [redacted] included patients, [redacted] patients were aged <15, while [redacted] patients were aged ≥15 years. The median age of the analytical patient population was [redacted] years (range: [redacted] years). Among the [redacted] patients included for analysis, the maximum OS follow-up time was [redacted] months.

Patient-level data from a blinatumomab trial (Gore 2018 study)

Because all clinical trials of tisagenlecleucel were designed as single-arm trials due to the nature of the rare disease and ethical considerations, indirect treatment comparison of tisagenlecleucel with comparator blinatumomab was warranted. Patient-level data for patients treated with blinatumomab was extracted from the Gore 2018 publication and used to inform the OS of blinatumomab for these analyses.[28] The Gore 2018 study (NCT01471782) reported data from a phase I/II trial of blinatumomab treatment in pediatric patients with relapsed or refractory B-cell precursor ALL. The primary results of this phase I/II trial have been reported in a prior publication (Stackelberg 2016).[17] In the Gore 2018 study, the final results for remission, survival after blinatumomab treatment, and patient-level data were reported. Thus, in the current comparison, we used the data reported in the Gore 2018 study. The date of study completion was May 24, 2016. By then, all patients had either completed the 2-year follow-up, withdrawn from study, or died. In total, 70 patients who received the recommended phase II dose in either phase were included. Of the 70 included patients, 62 patients were aged <15, while 8 patients were aged ≥15 years. The median age of the analytical patient population was 8.0 years (range: 0 - 17.0 years). The median OS follow-up time was 7.5 months and the maximum OS follow-up time was 24.4 months.Specifically, patient-level data on age, disease status (i.e., prior allogeneic hematopoietic stem cell transplantation [alloHSCT], number of relapses, refractory disease status), outcomes, and other treatments (e.g., OS) after blinatumomab treatment were available.

Methods

Patients who were infused with tisagenlecleucel (mITT population) from the tisagenlecleucel trials (B2202, B2205J, and B2101J) and patients treated with blinatumomab from the Gore 2018 study were included. OS was compared between two treatments in the two age groups: (a) patients aged under 15 years old and (b) patients aged 15 years or above. Given the small number of patients aged 15 years or above (8 out of 70) in the Gore 2018 study, the analysis in the group of patients aged 15 years or above included all blinatumomab-treated patients.

Specifically, the following analyses comparing OS between two treatments were performed:

(a) Patients aged under 15 years old: Tisagenlecleucel patients (age < 15) from pooled three trials vs. blinatumomab patients (age < 15) from Gore 2018 study

(b) Patients aged 15 years old or above: Tisagenlecleucel patients (age ≥ 15) from pooled three trials vs. all blinatumomab patients from Gore 2018 study

In the tisagenlecleucel trials (B2202, B2205J, and B2101J), OS was defined as time from infusion to death. In the Gore 2018 study, OS was defined as time from initiation of blinatumomab treatment to death.

A multivariable Cox regression model adjusting for cross-trial differences in patient characteristics was used to compare OS. Patient characteristics that were consistently reported in tisagenlecleucel and blinatumomab trials were adjusted including:

- Age (years)
- AlloHSCT and number of prior relapses
  - With prior alloHSCT
  - Without prior alloHSCT and 0 or 1 relapse
  - Without prior alloHSCT and 2 or more relapses

The multivariable Cox regression model provided an estimated conditional HR comparing tisagenlecleucel vs. blinatumomab, accounting for cross-trial heterogeneities in patient characteristics. The conditional HR contrasted the hazards of death in patients with a given set of patient characteristics (i.e., at individual patient level) if treated with tisagenlecleucel vs. blinatumomab.

Results

(a) Patients aged under 15 years old

The analysis included [redacted] tisagenlecleucel patients aged <15 from the three tisagenlecleucel trials and 62 blinatumomab patients aged <15 from the Gore 2018 study. The unadjusted HR of death between two treatments was [redacted] (95% CI: [redacted] In the adjusting for patient characteristics using a multivariable Cox regression model, tisagenlecleucel was associated with [redacted]% lower hazard of death compared to blinatumomab ([redacted] [redacted]

(b) Patients aged 15 years old or above

The analysis included [redacted] tisagenlecleucel patients aged ≥15 from the three tisagenlecleucel trials, and a total of 70 patients of all ages from the Gore 2018 study. All the patients from the Gore 2018 study were included because only 8 patients were aged ≥15. The unadjusted HR of death between two treatments was [redacted](95% CI: [redacted]

In the adjusting for patient characteristics using a multivariable Cox regression model, tisagenlecleucel was associated with [redacted]% lower hazard of death compared to blinatumomab ([redacted] [redacted]]).

Limitation

- The current study adjusted patient characteristics that were consistently reported in the trials of both treatments. However, some factors were not able to be adjusted due to inconsistent definitions across trials (e.g., refractory to the last line of treatment). In addition, there may be unobserved or unmeasurable differences between the tisagenlecleucel trials and the Gore 2018 study that could confound the comparison results.
- The analyses using pooled data from three tisagenlecleucel trials (B2202, B2205J, and B2101J) ensured a sufficient sample size and statistical power to detect the difference between treatments. However, the potential heterogeneities across the three tisagenlecleucel trials (B2202, B2205J, and B2101J) were not adjusted for in the analyses.
- The Gore 2018 study included an extremely small number of patients aged ≥15. All patients in the Gore 2018 study were used in the comparisons of treatment effects on OS for patients aged ≥15. The comparison results rely on the assumption that blinatumomab patients had similar survival as the overall pediatric patient population.

- Since the primary goal of treatment is to cure the cancer, OS should be considered as one of the primary endpoints to evaluate the treatment efficacy. In addition, survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. The other outcomes were not compared due to data unavailability in Gore 2018 study (e.g., PFS) or inconsistent definition between the tisagenlecleucel trials and Gore 2018 study (e.g., complete remission and minimal residual disease).

3.7.2 B-ALL: Kymriah (tisagenlecleucel) vs. Inotuzumab

Data Sources

Patient-level data from three tisagenlecleucel trials (B2202, B2205J, and B2101J)

As same as ITC vs Blinatumoma, Patient-level data on patient characteristics and OS for patients treated with tisagenlecleucel from the B2202 (ELIANA; NCT02435849), B2205J (ENSIGN; NCT02228096), and B2101J (NCT01626495) trials were pooled and 15-25 age sub-group used in the analyses.[25]–[27]

Published aggregate data from a Inotuzumab trial (Bhojwani 2019)[16]

A retrospective cohort reported on the results for Intuzumab in a compassionate use program of heavily pretreated patients ≤21 years of age. The study population was comprised mainly of those refractory to prior treatment (80%) and 71% of patients had received 4 or more prior treatment regimens. In addition, 43% of patients had received prior treatment with blinatumomab, and 29% had been treated with CAR-T therapy. At 12 months, the OS and EFS rates were 36.3% and 23.4%, respectively. Median duration of survival was not reported.

Methods

We conducted an indirect comparison for the two datasets, using matching indirect comparisons (MAICs). MAICs adjust for the differences in selected baseline characteristics by assigning balancing weights to the tisagenlecleucel patients so that their re-weighted baseline matches the comparator patient baseline. In order to prioritize the characteristics to adjust, the available matching characteristics were assessed on their relative predictive value on outcomes in this heavily pre-treated r/r pALL population based on clinician input and the literature.

Although prior lines of therapy was ranked high as a matching characteristic, there was a large imbalance between the trials. Matching on previous relapses, disease status, prior lines of therapy, and prior HSCT did not converge. Therefore, we only matched on previous relapses, disease status, and prior HSCT in the main analyses.

Results

The analysis included [redacted] tisagenlecleucel patients aged ≥15 from the three tisagenlecleucel trials, and a total of 51 patients of all ages from the Bhojwani 2019 study. Before matching, tisagenlecleucel was associated with a [redacted]% lower hazard of death than inotuzumab (log-rank p-value<0.01; HR [95% CI] = [redacted] [redacted] After matching, the hazard of death remained significantly lower with tisagenlecleucel vs. salvage chemotherapies (weighted log-rank p-value<0.01; HR [95% CI] = [redacted] [redacted]

Limitation

- Accuracy in the relative efficacy estimates increases as the number of baseline characteristics that are adjusted for increases in the MAIC. That is, this adjustment for treatment population differences between CTL019 treatment population and the inotuzumab treatment populations aims to make treatment populations more similar and thus improving the accuracy in the relative efficacy estimates. However, this comes a cost of losing precision as we increase the number of baseline characteristics used in the adjustment. The decrease in precision stems from reducing the effective sample size which is dependent on the weights derived during the matching adjustment in the MAIC, giving more weights to the CTL019 patients that more closely resemble those patients from the comparator population, and less weight to those patients that were not. Furthermore, the highest level of precision possible occurs in the naïve comparison, which also has minimal accuracy since no adjustment for baseline characteristics was made. During the MAIC, we attempt to balance accuracy and precision by using the largest set of baseline characteristics to match on (increasing accuracy) without reducing the effective sample size (decreasing precision) below what is reasonable.
- Based on the available baseline characteristics in the Bhojwani 2019 publication, the number of patients ≥ 15 years old was not available (only given Age 10-17 years: N=31, %=61). The subgroup OS is not available either. There was no sub-setting of the INO (Bhojwani) study population as it's not possible to do this with summary level data. The assumption here is that the published INO outcomes from Bhojhwani (2019) had similar results for age ≥ 15 subgroup and all INO treatment patients (aged 2-21).
- The three CTL019 trial populations from B2202, B2205J, and B2101J were pooled and adjusted together in the attempt to match the study populations of each comparator treatment population included in the MAIC. However, the three CTL019 trial populations were not adjusted with each other as this is not necessary for the MAIC. The assumption is that all three CTL019 trials had similar study designs, inclusion/exclusion criteria, baseline characteristics and treatment regimen and can thus could be treated as a single study in the MAIC.

3.7.3 DLBCL: Kymriah(tisagenlecleucel) vs. Salvage Chemotherapy +/- HSCT

Data Sources

Patient-level data from C2201 (JULIET)

JULIET is an ongoing pivotal single-arm, open-label, multi-center, phase II study to determine the safety and efficacy of tisagenlecleucel in adults with r/r DLBCL.[29] Adults with relapsed or refractory disease after ≥2 lines of chemotherapy, including rituximab and anthracycline, and either having failed ASCT or were ineligible for or did not consent to ASCT, were enrolled. There are two cohorts of patients in JULIET:

Main Cohort: Patients treated with tisagenlecleucel (for mITT patients) or intended to receive tisagenlecleucel (for non-infused patients) from the United States manufacturing facility in [redacted]

Cohort A: Patients treated with tisagenlecleucel (for mITT patients) or intended to receive tisagenlecleucel (for non-infused patients) from the European Union manufacturing facility, [redacted] in [redacted]

As of [redacted] a total of [redacted] patients were enrolled (i.e., ITT population),

and [redacted] patients were infused with tisagenlecleucel (i.e., mITT population, [redacted] in the Main Cohort and [redacted] in Cohort A, which comprised the FAS). The EAS includes patients who received a tisagenlecleucel infusion[redacted]) prior to data cutoff. In the current data, all FAS patients are included in the EAS (N=[redacted]), which consisted of [redacted] patients from the Main Cohort and [redacted] patients from Cohort A. The following patient sets were used in the comparisons with historical controls: mITT patients in both cohorts (FAS) for OS analysis.

Published aggregate data from the CORAL extension studies

CORAL is a phase III, multi-center, randomized trial that compared the efficacy of three cycles of rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) as second-line therapy, followed by ASCT with or without rituximab maintenance, in patients with relapsed DLBCL.[11], [12]

Among the 477 patients randomized to R-ICE or R-DHAP, 255 patients who achieved CR, PR, or stable disease (SD) after the third cycle of salvage treatment with adequate stem cell collection received consolidation with BEAM (carmustine, etoposide, cytarabine, and melphalan), followed by ASCT; 75 patients relapsed thereafter and received mixed third-line salvage chemotherapies. The remaining 222 patients did not proceed to planned ASCT according to the protocol because of an event leading to withdrawal between cycle 1 of R-ICE or R-DHAP and scheduled ASCT. Among these 222 patients, 6 withdrew their consent, and 13 died before planned ASCT. All patients in the CORAL extension studies were under age 70. CORAL patients enrolled in the following two extension studies were included in the current analysis:

- CORAL extension study 1: 75 patients in the CORAL observational follow-up phase who relapsed after ASCT
- CORAL extension study 2: 203 patients in the CORAL observational follow-up phase who failed to proceed to ASCT

Methods

When comparing outcomes between JULIET and historical control groups deemed suitably similar, additional steps were undertaken to account for any differences in patient baseline characteristics via statistical adjustment when possible. These adjustments were accomplished using the MAIC approach, which is an extension of propensity score weighting to settings in which only aggregate data are available for external controls. In particular, each patient in the study with available IPD (patients from JULIET, in this case) is re-weighted based on a propensity score model such that after re-weighting, the average baseline characteristics among these patients match those reported for the external control group.

The following three sets of analyses were performed:

(a) Comparison of OS in overall population: JULIET mITT patients in both cohorts of the FAS vs. pooled CORAL patients

(b) Comparison of OS in age <70 group: JULIET mITT patients under the age of 70 in both cohorts of the FAS vs. pooled CORAL patients (all CORAL patients were with age < 70 years)

In each comparison, JULIET patients with missing values in the baseline characteristics to be matched were excluded from the analysis. Variables included in the matching adjustment were:

- Gender
- International Prognostic Index (IPI) risk classification (<3 vs. ≥3)
- ASCT as the most recent therapy and relapsed after ASCT (yes vs. no)
- Refractory to last line of treatment (yes vs. no)

Results

(a) Comparison of OS in overall population

The comparisons of baseline characteristics before and after matching between JULIET (FAS, both cohorts) and CORAL extension patients are shown in Table 10. Before matching, gender, the proportion with IPI risk classification <3, the proportion with ASCT as the most recent relapsed therapy and relapsed after ASCT, and the proportion who were refractory to last line of treatment were comparable between the two populations. After matching, all matched-on baseline characteristics were exactly balanced between the study populations. The effective sample size after matching was [redacted], indicating that there was no evidence of extreme weights.

Table 10. Matching Patient Characteristics between JULIET mITT (EAS, Main Cohort) and Pooled CORAL Extension Studies

	Before Matching			**After Matching**		
	JULIET mITT FAS Both Cohorts	**CORAL Extension Studies**	**P-value**	**JULIET mITT FAS Both Cohorts**	**CORAL Extension Studies**	**P-value**
	N[redacted]	**N=278**		**N=[redacted]**	**N=278**	
Male	[redacted]%	[redacted]%	[redacted]	[redacted]%	[redacted]%	1.00
Low IPI risk classification (< 3)	[redacted]%	[redacted]%	[redacted]	[redacted]%	[redacted]%	1.00
ASCT as the most recent therapy and relapsed after ASCT	[redacted]%	[redacted]%	[redacted]	[redacted]%	[redacted]%	1.00
Refractory to last line of treatment	[redacted]%	[redacted]%	[redacted]	[redacted]%	[redacted]%	1.00

For OS from most recent relapse, before matching, tisagenlecleucel was associated with a [redacted]% lower hazard of death than salvage chemotherapies (log-rank p-value<0.01; HR [95% CI] = [redacted] After matching, the hazard of death remained significantly lower with tisagenlecleucel vs. salvage chemotherapies (weighted log-rank p-value<0.01; HR [95% CI] = [redacted], [redacted]).

(b) Comparison of OS in age <70 group

The comparisons of baseline characteristics before and after matching between JULIET (FAS, both cohorts, under age 70) and CORAL extension patients are shown in Table 11. Before matching, gender, the proportion with IPI risk classification <3, the proportion with ASCT as the most recent relapsed therapy and relapsed after ASCT, and the proportion who were refractory to last line of treatment were comparable between the two populations. After matching, all matched-on baseline characteristics were balanced between the study populations. The effective sample size after matching was [redacted], indicating that there was no evidence of extreme weights.

Table 11. Matching Patient Characteristics between JULIET mITT (FAS, Both Cohorts, Age <70) and Pooled CORAL Extension Studies

	Before Matching			**After Matching**		
	JULIET mITT FAS Both Cohorts, Age < 70 Years	**CORAL Extension Studies**	**P-value**	**JULIET mITT Both Cohorts, Age < 70 Years**	**CORAL Extension Studies**	**P-value**
	N=[redacted]	**N=278**		**N=[redacted]**	**N=278**	
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.00
Low IPI risk classification (< 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.00
ASCT as the most recent therapy and relapsed after ASCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.00
Refractory to last line of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.00

For OS from most recent relapse, before matching, tisagenlecleucel was associated with a [redacted]% lower hazard of death than salvage chemotherapies (log-rank p-value<0.01; HR [95% CI] = [redacted] After matching, the hazard of death remained significantly lower with tisagenlecleucel vs. salvage chemotherapies (weighted log-rank p-value<0.01; HR [95% CI] = [redacted]).

Limitation

- Not all cross-study differences could be addressed by baseline population adjustment. For example, although the inclusion criteria required two or more prior lines of treatment in the JULIET study, [redacted]% of patients in the FAS received at least three lines of prior treatment, while the patients presented

in the CORAL extension study were required to be candidates for third-line chemotherapy by design. As patients who received more prior therapies are expected to have worse efficacy outcomes with chemotherapies compared to patients who received fewer prior therapies, this difference in populations would be expected to bias the comparison of outcomes against the JULIET population. Additionally, in the CORAL extension study where patients failed to proceed to ASCT, 26 (out of 203) patients achieved CR/CRu to second-line regimen, and 30 (out of 203) patients achieved PR to second-line regimen. Those patients who had responses to the second-line might be more likely to respond to the third-line regimen. However, given that more than half of the patients in the JULIET study had at least three lines of prior treatment, it is not feasible to adjust for such differences, which may bias the comparison results. JULIET patients had either failed ASCT or were ineligible for ASCT at enrollment, and the JULIET trial inclusion criteria required patients to have failed at least two prior lines of therapies with the majority ([redacted]%) failing three of more lines of treatment, while all patients in CORAL extensions received only two prior lines of therapy. In addition, approximately 30% of patients in CORAL extensions received SCT during the follow up. These factors could favor bias toward historical controls from CORAL extensions over JULIET, as SCT has been shown to extend survival. Lastly, IPI data were only available for 115 (out of 203) patients who failed to proceed to ASCT and 67 (out of 75) patients who relapsed after ASCT in the CORAL extension studies, which may result in residual confounding due to inadequate adjustment for baseline IPI. As with any comparison of non-randomized treatment groups, this comparison was subject to potential bias due to unobserved or unmeasurable confounding.

- The analysis of OS comparison among patients aged ≥70 years was not feasible between JULIET and CORAL patients, as no patients in the CORAL extension studies were aged ≥70 years, and only [redacted] ([redacted]%) JULIET patients were aged ≥70 years.

3.8 追加的有用性の有無に関する評価

【B-ALL】

対象集団	15 歳未満の B-ALL
介入	キムリア点滴静注
比較対照	ブリナツモマブ +/- 同種 HSCT
アウトカム	Overall Survival
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	□ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 ■ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	Pooled trial data(B2101J、ELIANA/B2202、ENSIGN/B2205)の 15 歳未満集団と Gore 2018 の 15 歳未満集団との間接比較（OS）において、conditional HR は [redacted](95% CI: [redacted])であった。

	このことから、本製品は比較対照技術に対して追加的有用性を有すると判断した。

対象集団	15 歳以上 25 歳未満の B-ALL
介入	キムリア点滴静注
比較対照	ブリナツモマブ +/- 同種 HSCT イノツズマブ +/- 同種 HSCT
アウトカム	Overall Survival
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	□ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 ■ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	ブリナツモマブを比較対照にした場合、Pooled trial data（B2101J、ELIANA/B2202、ENSIGN/B220）の 15 歳以上集団と Gore 2018 の全体集団との MAIC 分析（OS）において、conditional HR は [redacted]（95%CI: [redacted] であった。 イノツズマブを比較対照にした場合、Pooled trial data（B2101J、ELIANA/B2202、ENSIGN/B2205）の 15 歳以上集団と Bhojwani 2019 の全体集団との MAIC 分析（OS）において、conditional HR は [redacted]（95%CI: [redacted] であった。このことから、本製品は比較対照技術に対して追加的有用性を有すると判断した。

【DLBCL】

対象集団	70 歳未満の DLBCL
介入	キムリア点滴静注
比較対照	救援化学療法 +/- 同種 HSCT
アウトカム	Overall Survival
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	□ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 ■ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	JULIET 試験の 70 歳未満集団と CORAL extention studies（すべての患者が 70 歳以下）との MAIC 分析（OS）において、conditional HR は [redacted]（95% CI: [redacted] であった。このことから、本製品は比較対照技術に対して追加的有用性を有すると判断した。

対象集団	70 歳以上の DLBCL

介入	キムリア点滴静注
比較対照	救援化学療法
アウトカム	Overall Survival
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	□ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 ■ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	介入群（tisagenlecleucel）の有効性データについて、JULIET 試験において本製品が投与された患者のうち、本対象集団に該当する 70 歳以上の患者は[redacted] 症例に限られる。また、全生存期間や無増悪生存期間の解析上の情報量（生存時間解析手法におけるイベント数）は[redacted] 例である。 もともと JULIET 試験は年齢別の解析を想定せずにデザインされており、年齢で層別化した場合のサンプルサイズが極めて小さくなり、統計的検出力は低下する。それゆえ間接比較における比較可能性の検討や、統計的手法による調整も困難になる。以上より、JULIET 試験の 70 歳以上の症例のみを抽出した結果をもとに追加的有用性のみを判断することは極めて困難である。 2019 年[redacted] 月[redacted] 日に開催された第 3 回費用対効果評価専門組織において C2H より、元々想定されていないサブ集団を構築したことによって追加的有用性を示すことが困難になった場合には、切り分け前の全体集団、この場合であれば年齢の区切りのない全体集団の結果を参照することを容認する旨のコメントを得ている。 JULIET 試験の全体集団と CORAL extention studies（すべての患者が 70 歳以下）との MAIC 分析（OS）において、conditional HR は[redacted]（95% CI: [redacted]）であった。全体集団の間接比較で追加的有用性が確認されていることから、本患者集団についても本製品は比較対照技術に対して追加的有用性を有すると判断した。

4. 分析方法の詳細

4.1 分析方法

4.1.1 費用対効果の算出方法

4.1.1.1 B-ALL

・医療経済評価モデル（マルコフモデル）の概要

The cost-effectiveness model was developed in Microsoft Excel®. The analysis used a decision tree approach to determine the proportion of patients initially assigned to tisagenlecleucel who continued to infusion (Figure 9).

After the initial decision-tree partition, patients on tisagenlecleucel enter into the partitioned survival model. Patients on the comparators directly enter into the partitioned survival model. The model comprised of three mutually exclusive health states: (i) event-free survival (EFS), (ii) progressive disease (PD) and (iii) death (Figure 10). EFS was defined as the time from the date of treatment initiation to the earliest date of death, relapse, or treatment failure. All patients began in EFS at the model start. The proportion of patients in the EFS health state of the model was set to be equal to the EFS curve of each treatment. The PD state included alive patients who progressed or relapsed. The proportion of patients in the PD health state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of EFS patients. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. A monthly model cycle was used for estimating the proportion of patients in each heath state over time.

Figure 9. Tisagenlecleucel decision tree structure

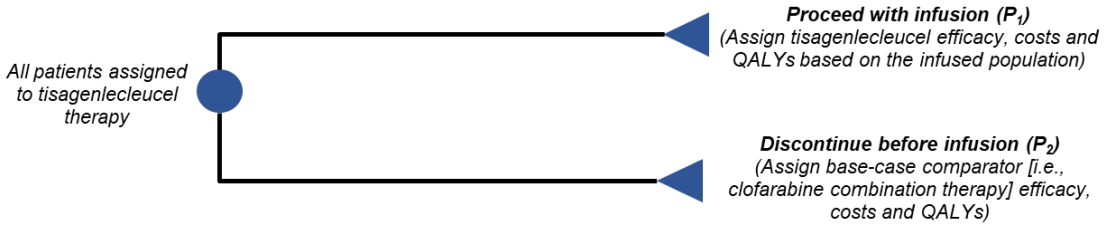
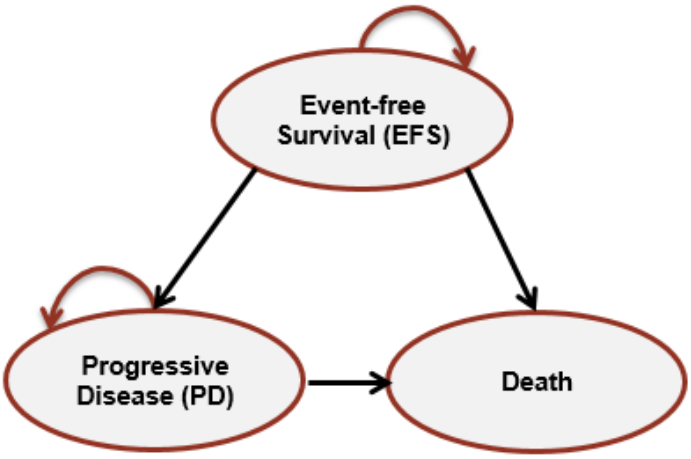


Figure 10. Partitioned survival model structure



Subsequent HSCT was considered in the model since subsequent HSCT is an important treatment option in the clinical pathway of r/r pALL patients. Subsequent HSCT was not modelled as a distinct health state, but the efficacy benefit of subsequent HSCT was captured in the OS and EFS estimates of each treatment arm, and the cost and disutility of subsequent HSCT was added separately for each treatment arm using age-group specific HSCT rate data if available.
Half-cycle correction was applied, in order to account for the real-world in which patients transition to the subsequent health state continuously throughout a given cycle. It did this by assuming that patients transition, on average, halfway through a cycle. This correction was applied to avoid an over- or under-estimation of the results that might occur without the correction (i.e., assuming patients only transition at the beginning or end of a cycle). Treatment costs before maintenance therapy initiation (if applicable) were applied as one-time costs in the model, which were not affected by the half-cycle correction.

4.1.1.2 DLBCL

・医療経済評価モデル（マルコフモデル）の概要

The cost-effectiveness model was developed in Microsoft Excel®. The analysis used a decision tree approach to determine the proportion of patients initially assigned to tisagenlecleucel who continued to infusion (Figure 11).
After the initial decision-tree partition, patients on tisagenlecleucel enter into the partitioned survival model. Patients on salvage chemotherapy directly enter into the partitioned survival model. The model comprised of three mutually exclusive health states: (i) PFS, (ii) PD/RL and (iii) death (Figure 12). PFS was defined as the time from the date of tisagenlecleucel infusion or treatment initiation to the date of first documented progression or death due to any cause. All patients began in PFS at the model start. The proportion of patients in the PFS health state of the model was set to be equal to the PFS curve of each treatment. The PD/RL state included alive patients who progressed or relapsed. The proportion of patients in the PD/RL health state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of PFS patients. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. A monthly model cycle was used for estimating the proportion of patients in each heath state over time.

Figure 11. Tisagenlecleucel decision tree structure

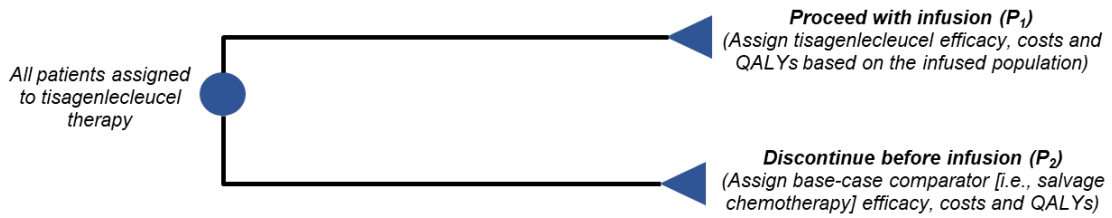
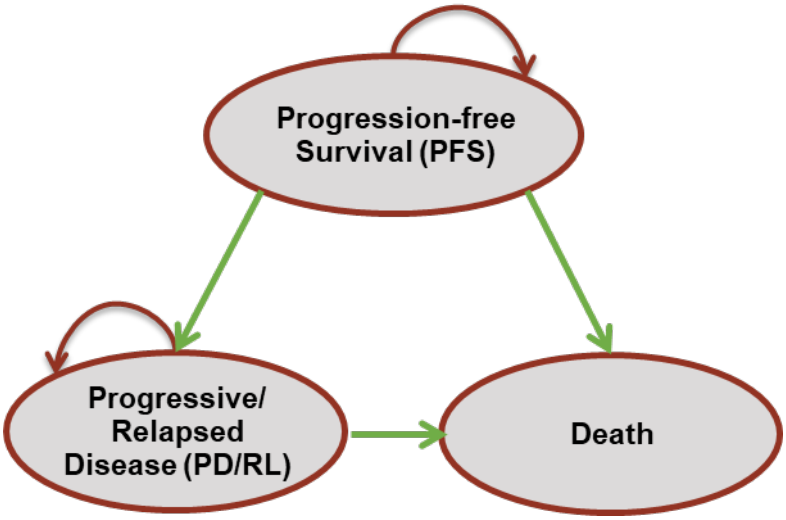


Figure 12. Partitioned survival model structure



Subsequent SCT, including both allo SCT and auto SCT, was considered only in the < 70 model. The efficacy benefit of subsequent SCT was captured in the OS and PFS estimates of each treatment arm. The cost and disutility of subsequent SCT were added separately for the proportion of patients who received the SCT treatment based on trial observation for tisagenlecleucel and literature for the comparator.

Half-cycle correction was applied, in order to account for the real-world in which patients transition to the subsequent health state continuously throughout a given cycle. It does this by assuming that patients transition, on average, halfway through a cycle. This correction was applied to avoid an over- or under-estimation of the results that may occur without the correction (i.e., assuming patients only transition at the beginning or end of a cycle). Treatment costs were applied as one-time costs in the model, which were not affected by the half-cycle correction.

4.1.2 モデルで使用した仮定

B-ALL

Parameter	Assumption
Health states and utilities by health states	• Utilities of health states were assumed to be dependent only on health states and independent on treatment arms • At the start of each model cycle, patients were redistributed among the 3 health states (EFS, PD and death), with death being the absorbing state
Disutility	• Treatment disutilities for comparators were considered for the duration of the treatment; Treatment disutilities for tisagenlecleucel were considered for the duration of hospitalization after the infusion • These treatment disutilities included disutilities of AEs during the treatment period, except for CRS (cytokine release syndrome). Disutilities of CRS were added separately

Parameter	Assumption
Subsequent HSCT	• Subsequent HSCTs after the initial treatment were considered in the model to reflect the natural treatment course patients experienced • Efficacy benefit of subsequent HSCT were captured in the EFS and OS estimations • Cost and disutility of subsequent HSCTs were considered for the proportion of patients who received subsequent HSCT
Efficacy	• In the base-case, the observed data was used during the trial period. Afterwards, parametric survival models were used to project OS and EFS for tisagenlecleucel and ITC analysis result was used to project OS and EFS for comparators using tisagenlecleucel as the reference arm up to year 5. After year 5, the model estimated the OS based on long-term ALL survivors and assumed there was no difference in mortality risk across treatment arms. • EFS data were not reported for blinatumomab arm in the publications; EFS for blinatumomab were estimated based on the OS data assuming a constant cumulative HR over time between EFS and OS. After year 5, the model assumed that was no additional events beyond death in the base-case
Medical costs and AE costs	• In addition to treatment and AE costs, the model considered additional medical costs including follow-up costs, post-progression costs and terminal care costs • AE costs are only considered for tisagenlecleucel and blinatumomab to be conservative, which composes of costs for treating CRS and B-cell aplasia. Costs of other AEs are reflected in the hospitalization costs. • All patients incur one-time terminal care costs before death
Discontinuation prior to tisagenlecleucel infusion	• A proportion of patients in the clinical trials of tisagenlecleucel did not go on to receive tisagenlecleucel due to manufacture failure or withdrawal due to adverse events or death in the period post-leukapheresis and pre-infusion • It was assumed that these patients would therefore instead receive the blinatumomab comparator, and have the same efficacy, cost, and disutility as the comparator treatment
Societal Costs	• Societal costs were not considered in the base-case model, but were considered in the DSA. Employment rates by age and the average wage were used to calculate the societal costs

DLBCL

Parameter	Assumption
Health states and utilities by health states	• Utilities of health states were assumed to depend only on health state and be independent on treatment arm • At the start of each cycle, patients were redistributed among the 3 health states, PFS, PD/RL, and death, with death being the absorbing state
Disutility	• Treatment disutilities for chemotherapies were considered for the duration of the treatment; Treatment disutilities for tisagenlecleucel were considered for the duration of hospitalization after the infusion • These treatment disutilities included disutilities of AEs during the treatment period, except for CRS. Disutilities of CRS were added separately
Subsequent SCT (for aged less than 70)	• Subsequent SCTs after the initial treatment were considered in the model to reflect the natural treatment course patients experienced. Both auto SCT and allo SCT could be feasible as subsequent SCT, and both were considered • Efficacy benefit of subsequent SCT were captured in the PFS and OS estimations • Cost and disutility of subsequent SCT were considered for the proportion of patients who received subsequent SCT
Efficacy	• In the base-case analysis, the observed OS data from tisagenlecleucel trial and CORAL extension studies were used directly until year 3. Afterwards, the model used literature for DLBCL long-term survivors to inform the mortality risk and assumed there was no difference in mortality risk across treatments. • Observed PFS data for tisagenlecleucel was used until year 3. PFS data are not reported for salvage chemotherapy in the literature and is estimated based on the OS data assuming a constant cumulative hazard ratio (HR) over time. After year 3, the model assumed no additional progression in the base-case
Medical costs and AE costs	• In addition to treatment and AE costs, the model considered additional medical costs including follow-up costs, post-progression costs and terminal care costs • AE costs were only considered for tisagenlecleucel to be conservative, which composes of costs for treating CRS and B-cell aplasia. Costs of other AEs are reflected in the hospitalization costs • All patients incur one-time terminal care costs before death

Parameter	Assumption
Discontinuation prior to tisagenlecleucel infusion	• A proportion of patients in the clinical trial of tisagenlecleucel did not receive tisagenlecleucel due to manufacture failure, or withdrawal due to AEs or death in the period post-leukapheresis and pre-infusion • It was assumed that these patients would therefore instead receive the comparator treatment (i.e., salvage chemotherapy), and have the same efficacy, cost, and disutility as patients with the comparator treatment
Societal Costs	• Societal costs were not considered in the base-case model, but were considered in the DSA. Employment rates by age and the average wage were used to calculate the societal costs

4.2 分析で使用したパラメータ
B-ALL：15 歳未満

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Patient characteristics				
Starting age (years)	[redacted]	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
Percent female	[redacted]%	NA	NA	
BSA	[redacted]	NA	NA	
Mean weight (kg)	[redacted]	NA	NA	
Proportion receiving infusion (tisagenlecleucel arm only)	[redacted]%	NA	NA	
Efficacy & Safety (4.2.1)				
OS (tisagenlecleucel)	Observed data	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
EFS (tisagenlecleucel)	Observed data	NA	NA	
OS (blinatumomab)	Observed data followed by ITC adjusted OS	NA	NA	
EFS (blinatumomab)	EFS estimated based on OS	NA	NA	
Hazard ratio (HR) of OS: blinatumomab vs. tisagenlecleucel	[redacted]	([redacted])	NA	von Stackelberg et al., 2016[17]; Gore et al., 2018[28]; ELIANA, ENSIGN, B2101J[25]–[27]
Subsequent HSCT rate for tisagenlecleucel (infused patients)	[redacted]%	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
Subsequent HSCT rate for blinatumomab	30.65%	NA	NA	Gore et al., 2019[28]
Utility (4.2.2)				

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Utility for EFS	0.91	NA	NA	Kelly et al., 2015[30]
Utility for PD	0.75	NA	NA	
Disutility for tisagenlecleucel (infused patients)	-0.42	NA	NA	Sung et al., 2003[31]
Disutility for blinatumomab	-0.42	NA	NA	
HSCT disutility	-0.57	NA	NA	Sung et al., 2003[31]
Age-related utility (absolute value)	Age <25: 0.97 Age 25-34: 0.96 Age 35-44: 0.97 Age 45-54: 0.94 Age 55-64: 0.91	NA	NA	Janssen 2014[32]
Cost (4.2.3)				
Pre-treatment cost (tisagenlecleucel only)	Leukapheresis: ¥174,400 Bridging chemotherapy: ¥[redacted] Lymphodepleting regimen: ¥[redacted]	NA	NA	See Section 4.2.3
Tisagenlecleucel treatment (infused patients)	Tisagenlecleucel infusion: ¥34,113,655 Administration: ¥308,500 Hospitalization: [redacted] ICU: ¥[redacted]	NA	NA	
Blinatumomab	Drug: ¥11,478,876 Administration: ¥393,720 Hospitalization: ¥214,804	NA	NA	
HSCT cost	[redacted]	NA	NA	

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Medical costs per cycle in EFS for tisagenlecleucel (infused patients)	Year 1: [redacted] Year 2: Year 3-5: Year 5+:	NA	NA	
Medical costs per cycle in EFS for comparators	Year 1: Year 2: Year 3-5: ¥ Year 5+:	NA	NA	
Medical costs per cycle in PD	[redacted]	NA	NA	
One-time terminal care cost	¥747,787	NA	NA	
AE: Tisagenlecleucel (infused patients)	CRS: ¥[redacted] IVIG: ¥	NA	NA	
AE: Blinatumomab	¥101,010	NA	NA	

B-ALL: 15 歳以上 25 歳未満

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Patient characteristics				
Starting age (years)	[redacted]	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
Percent female	[redacted]%	NA	NA	
BSA	[redacted]	NA	NA	

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Mean weight (kg)	[redacted]	NA	NA	
Proportion receiving infusion (tisagenlecleucel arm only)	[redacted]%	NA	NA	
Efficacy & Safety (4.2.1)				
OS (tisagenlecleucel)	Observed followed by extrapolation using weighted AIC approach	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
EFS (tisagenlecleucel)	Observed followed by extrapolation using weighted AIC approach	NA	NA	
OS (comparator)	Observed followed by ITC-adjusted OS	NA	NA	
EFS (comparator)	Blinatumomab: EFS estimated based on OS Inotuzumab: observed followed by ITC-adjusted EFS	NA	NA	
Hazard ratio (HR) of OS: blinatumomab vs. tisagenlecleucel	[redacted]	([redacted])	NA	von Stackelberg et al., 2016[17]; Gore et al., 2018[28]; ELIANA, ENSIGN, B2101J[25]–[27]
Hazard ratio (HR) of OS: inotuzumab vs. tisagenlecleucel	[redacted]	([redacted])	NA	Bhojwani et al., 2019[16]; ELIANA, ENSIGN, B2101J[25]–[27]
Subsequent HSCT rate for tisagenlecleucel (infused patients)	[redacted]%	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Subsequent HSCT rate for blinatumomab	35.71%	NA	NA	Gore et al., 2019[28]
Subsequent HSCT rate for inotuzumab	41.18%	NA	NA	Bhojwani et al., 2019[16]
Utility (4.2.2)				
Utility for EFS	0.91	NA	NA	ELIANA, ENSIGN, B2101J[25]–[27]
Utility for PD	0.75	NA	NA	
Disutility for tisagenlecleucel (infused patients)	-0.42	NA	NA	Sung et al., 2003[31]
Disutility for comparator	-0.42	NA	NA	
HSCT disutility	-0.57	NA	NA	Sung et al., 2003[31]
Age-related utility (absolute value)	Age <25: 0.97 Age 25-34: 0.96 Age 35-44: 0.97 Age 45-54: 0.94 Age 55-64: 0.91	NA	NA	Janssen 2014[32]
Cost (4.2.3)				
Pre-treatment cost (tisagenlecleucel only)	Leukapheresis: ¥174,400 Bridging chemotherapy: ¥[redacted] Lymphodepleting regimen: ¥[redacted]	NA	NA	See Section 4.2.3
Tisagenlecleucel treatment (infused patients)	Tisagenlecleucel infusion: ¥34,113,655 Administration: ¥308,500 Hospitalization: ¥[redacted]	NA	NA	

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
	ICU: ¥[redacted]			
Blinatumomab	Drug: ¥11,478,876 Administration: ¥393,720 Hospitalization: ¥214,804	NA	NA	
Inotuzumab	Drug: ¥8,443,814 Administration: ¥46,519 Hospitalization: ¥393,331	NA	NA	
HSCT cost	¥[redacted]	NA	NA	
Medical costs per cycle in EFS for tisagenlecleucel (infused patients)	Year 1: [redacted] Year 2: [redacted] Year 3-5: ¥[redacted] Year 5+: [redacted]	NA	NA	
Medical costs per cycle in EFS for comparators	Year 1: ¥[redacted] Year 2: ¥[redacted] Year 3-5: [redacted] Year 5+: [redacted]	NA	NA	
Medical costs per cycle in PD	[redacted]	NA	NA	
One-time terminal care cost	¥747,787	NA	NA	
AE: Tisagenlecleucel (infused patients)	CRS: ¥[redacted] IVIG: ¥[redacted]	NA	NA	
AE: Blinatumomab	¥106,100	NA	NA	
AE: Inozutumab	¥0	NA	NA	

DLBCL: 70 歳未満

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Patient characteristics				
Starting age (years)	[redacted]	NA	NA	JULIET trial data among patients <70 years[29]
Percent female	[redacted]%	NA	NA	
BSA	[redacted]	NA	NA	
Mean weight (kg)	[redacted]	NA	NA	
Proportion receiving infusion (tisagenlecleucel arm only)	[redacted]%	NA	NA	
Efficacy & Safety (4.2.1)				
OS (tisagenlecleucel)	Observed followed by long-term survivor data	NA	NA	JULIET trial data among patients <70 years and CORAL extension studies[11], [12], [29]
EFS (tisagenlecleucel)	Observed followed by assumption	NA	NA	
OS (comparator)	Observed followed by long-term survivor data	NA	NA	
PFS (comparator)	PFS estimated based on OS	NA	NA	
Subsequent Allo SCT rate for tisagenlecleucel (infused patients)	[redacted]%	NA	NA	JULIET trial data among patients <70 years[29]
Subsequent Allo HSCT rate for comparator	7.55%	NA	NA	Van Den Neste et al. 2016 and Van Den Neste et al. 2017[11], [12]
Subsequent Auto SCT rate for tisagenlecleucel (infused patients)	[redacted]%	NA	NA	JULIET trial data among patients <70 years[29]
Subsequent Auto HSCT rate for comparator	21.22%	NA	NA	Van Den Neste et al. 2016 and Van Den Neste et al. 2017[11], [12]

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Utility (4.2.2)				
Utility for PFS	0.83	NA	NA	Chen et al. 2017[33]
Utility for PD	0.39	NA	NA	
Disutility for tisagenlecleucel (infused patients)	-0.15	NA	NA	Guadagnolo et al. 2006[34]
Disutility for comparator	-0.15	NA	NA	
HSCT disutility	-0.30	NA	NA	Guadagnolo et al. 2006[34]
Cost (4.2.3)				
Pre-treatment cost (tisagenlecleucel only)	Leukapheresis: ¥174,400 Bridging chemotherapy: ¥[redacted] Lymphodepleting regimen: ¥[redacted]	NA	NA	See Section 4.2.3
Tisagenlecleucel treatment (infused patients)	Tisagenlecleucel infusion: ¥34,113,655 Administration: [redacted] Hospitalization: [redacted] ICU: ¥[redacted]	NA	NA	
Salvage Chemotherapy	Drug: ¥1,301,260 Administration: ¥98,480 Hospitalization: ¥266,068	NA	NA	

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Allo SCT cost (one-time)	[redacted]	NA	NA	
Auto SCT cost (one-time)	[redacted]	NA	NA	
Medical costs per cycle in PFS for tisagenlecleucel (infused patients)	Year 1: [redacted] Year 2: [redacted] Year 3-5: ¥[redacted] Year 5+: [redacted]	NA	NA	
Medical costs per cycle in PFS for comparators	Year 1: [redacted] Year 2: [redacted] Year 3-5: [redacted] Year 5+: [redacted]	NA	NA	
Medical costs per cycle in PD	¥[redacted]	NA	NA	
One-time terminal care cost	¥741,143	NA	NA	
AE: Tisagenlecleucel (infused patients)	CRS: [redacted] IVIG: ¥[redacted]	NA	NA	
AE: Comparator	¥0	NA	NA	

DLBCL: 70 歳以上

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Patient characteristics				
Starting age (years)	[redacted]	NA	NA	JULIET trial data among patients >=70 years[29]
Percent male	[redacted]%	NA	NA	
BSA	[redacted]	NA	NA	

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Mean weight (kg)	[redacted]	NA	NA	
Proportion receiving infusion (tisagenlecleucel arm only)	[redacted]%	NA	NA	
Efficacy & Safety (4.2.1)				
OS (tisagenlecleucel)	Observed followed by long-term survivor data	NA	NA	JULIET trial data among patients >=70 years and CORAL extension studies w/o HSCT[11], [12], [29]
EFS (tisagenlecleucel)	Observed followed by assumption	NA	NA	
OS (comparator)	Observed followed by long-term survivor data	NA	NA	
PFS (comparator)	PFS estimated based on OS	NA	NA	
Utility (4.2.2)				
Utility for PFS	0.83	NA	NA	Chen et al. 2017[33]
Utility for PD	0.39	NA	NA	
Disutility for tisagenlecleucel (infused patients)	-0.15	NA	NA	Guadagnolo et al. 2006[34]
Disutility for comparator	-0.15	NA	NA	
Cost (4.2.3)				
Pre-treatment cost (tisagenlecleucel only)	Leukapheresis: ¥174,400 Bridging chemotherapy: [redacted] Lymphodepleting regimen: [redacted]	NA	NA	See Section 4.2.3

変数名	値	(該当する場合) 95% CI	分布[該当する場合]	設定根拠
Tisagenlecleucel treatment (infused patients)	Tisagenlecleucel infusion: ¥34,113,655 Administration: ¥308,500 Hospitalization: [redacted] ICU: [redacted]	NA	NA	
Comparator	Drug: ¥1,298,563 Administration: ¥98,480 Hospitalization: ¥266,068	NA	NA	
Medical costs per cycle in PFS for tisagenlecleucel (infused patients)	Year 1: [redacted] Year 2: [redacted] Year 3-5: ¥[redacted] Year 5+: ¥[redacted]	NA	NA	
Medical costs per cycle in PFS for comparators	Year 1: ¥[redacted] Year 2: [redacted] Year 3-5: ¥[redacted] Year 5+: ¥[redacted]	NA	NA	
Medical costs per cycle in PD	¥[redacted]	NA	NA	
One-time terminal care cost	¥747,787	NA	NA	
AE: Tisagenlecleucel (infused patients)	CRS: ¥[redacted] IVIG: [redacted]	NA	NA	
AE: Comparator	¥0	NA	NA	

4.2.1 有効性･安全性等のパラメータの詳細

4.2.1.1 B-ALL

生存曲線の推計（OS）

The OS associated with tisagenlecleucel infusion was based on the IPD pooled from 3 clinical trials of tisagenlecleucel using the most recent data cut: ELIANA (data cut-off: [redacted]), ENSIGN (data cut-off: [redacted]) and B2101J (data cut-off: [redacted]).[25]–[27] The OS was defined among infused population and was evaluated from the time of infusion. The OS for patients in the tisagenlecleucel arm but not infused was the same as that of the blinatumomab comparator. The OS associated with the comparator treatment arms were derived from the published Kaplan-Meier (K-M) curves or the IPD reported in the comparator trials. Age group-specific data were used whenever feasible to inform the OS among patients aged < 15 years and aged 15-25 years, respectively.

For tisagenlecleucel, the IPD of OS was directly used. For each comparator arm, IPD or pseudo IPD data were either directly obtained from the literature, or derived from the published K-M curves using algorithm outlined in Guyot et al. 2012.[35] The number at risk and number of event information were incorporated into the reconstruction of pseudo IPD where available. Parametric function was used to fit to the OS data and to project survival estimates in the CEA model. Specifically, the following survival distributions were considered: exponential, Weibull, log-logistic, log-normal, Gompertz and generalized Gamma. Because of the potential curative nature of tisagenlecleucel therapy, a series of flexible cubic spline models were also implemented in this analysis. The cubic spline model were developed based on the algorithm by Royston and Parmer 2002.[36] A series of one-, two-, three-, and four-knot spline models expressed on the proportional hazard scale were considered. The knot locations were chosen at quantiles of the log uncensored death times in the study, per the default settings for the FlexSurv package in R. The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were estimated for each parametric function.

A single survival distribution might not be able to adequately characterize the true efficacy of the treatment. To account for the uncertainty of choosing specific survival distribution, a model averaging approach was used in the base-case model using the methods described in Jackson et al., 2009.[37] This technique includes all plausible survival functions as part of a weighted distribution to estimate the joint distribution of uncertainty around the parameter estimates and the choice of survival function. The weights were calculated based on AIC score using the following equation: $Wgt = Ak/(\sum Ak)$, where $Ak = e^{-(0.5 \times AIC)}$. The weighted distribution was then applied in the base-case analysis. Parametric estimates and goodness-of-fit criteria were estimated for each survival distributions. The weighted distribution applied different weights to each distribution, with zero weight assigned to the poorly fitted curves. A visual comparison of the survival data based on the observed data, all considered distributions, and the weighted distribution are reported in Figure 13-14 for patient population with age < 15 years, and Figure 15-17 for age 15-25 years. The summary of AIC values and the weights considered for each survival distribution by age group are presented in Appendix C

Figure 13. Parametric functions for OS - tisagenlecleucel (age < 15 years)

Figure 14. Parametric functions for OS - blinatumomab (age < 15 years)

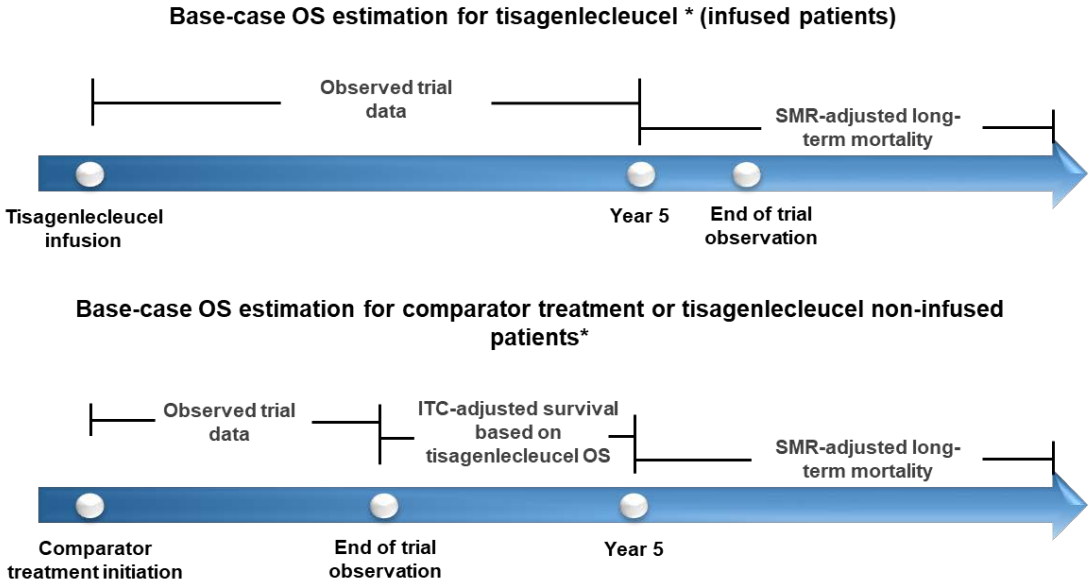
Figure 15. Parametric functions for OS - tisagenlecleucel (age 15-25 years)

Figure 16. Parametric functions for OS - blinatumomab (age 15-25 years)

Figure 17. Parametric functions for OS - inotuzumab (age 15 - 25 years)

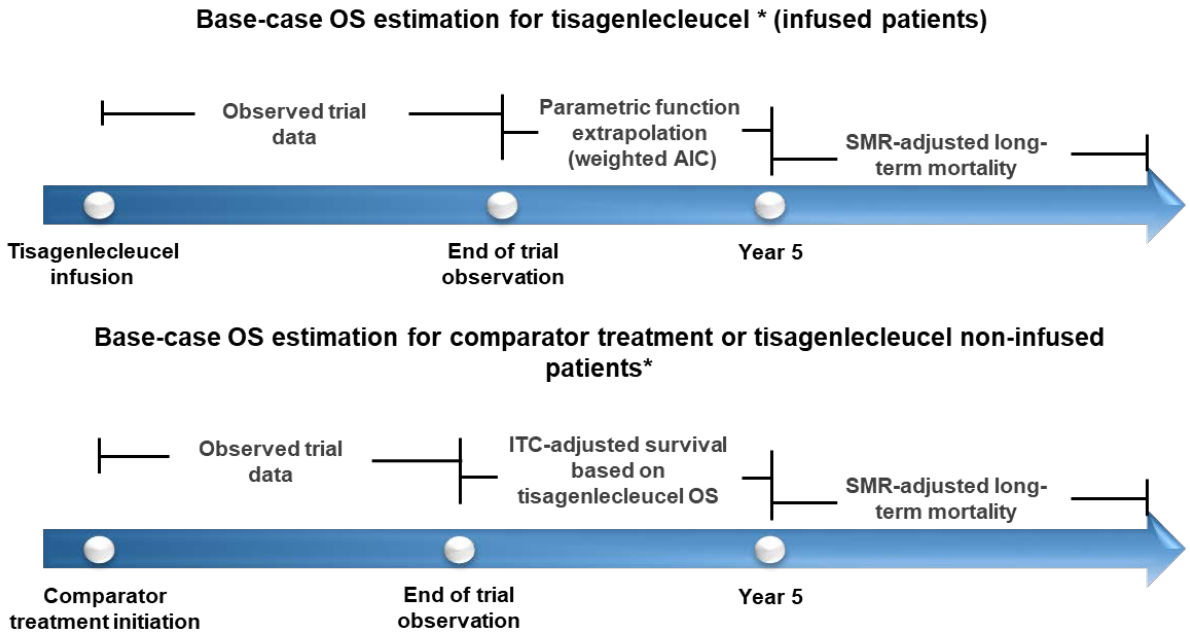
In the base-case CEA model for patient population aged < 15 years, the observed data was used to inform OS for tisagenlecleucel infused patients during the trial period until up to year 5. Given the observed trial period in this subpopulation went beyond year 5, no parametric extrapolation was applied. In the base-case for patient population aged 15-25 years, the observed data was used to inform OS for tisagenlecleucel infused patients during the trial period. Afterwards, parametric function was used to project OS estimates up to year 5 for tisagenlecleucel infused patients. To adjust for the potential differences in patient population between tisagenlecleucel and comparators, ITC analyses were conducted comparing the OS of tisagenlecleucel infusion with each of the comparators. The HRs from the ITC results were applied to the predicted OS curve of tisagenlecleucel infusion to estimate the OS for the comparators. For the blinatumomab comparator, IPD data is available. The HRs of blinatumomab vs. tisagenlecleucel were estimated via a multivariable Cox regression fitted with treatment and prognostic factors (age, prior HSCT and number of prior relapses) as covariates using IPD from both blinatumomab and tisagenlecleucel trials. For the inotuzumab comparator, no IPD data is available. The HRs of inotuzumab vs. tisagenlecleucel were estimated via a matching-adjusted indirect treatment comparison (MAIC) analysis, which adjusted for key baseline differences (previous relapses, disease status, and prior HSCT) by matching tisagenlecleucel population to the reported summary statistics of inotuzumab baseline characteristics. Tisagenlecleucel was selected as the reference arm because it has the longest follow-up time (maximum OS follow-up time = [redacted] months vs. 20.8-26.5 months from comparators) and therefore reduced the uncertainty associated with the extrapolation. This HR approach was applied after end of trial observation until year 5 to extrapolate the OS for comparators. Two demonstrative diagrams for the base-case OS scenarios are presented in Figure 18 and Figure 19.

Figure 18. Base-case OS estimation diagram for tisagenlecleucel and comparators (age < 15 years)



*Note: Efficacy for the overall tisagenlecleucel arm as estimated using a decision-tree structure, For patients who proceeded with infusion, the efficacy was based on the tisagenlecleucel infused population. For patients who discontinued or died prior to infusion, the efficacy was based on blinatumomab comparator.

Figure 19. Base-case OS estimation diagram for tisagenlecleucel and comparators (age 15-25 years)



*Note: Efficacy for the overall tisagenlecleucel arm as estimated using a decision-tree structure, For patients who proceeded with infusion, the efficacy was based on the tisagenlecleucel infused population. For patients who discontinued or died prior to infusion, the efficacy was based on blinatumomab comparator.

The HR inputs are described in Table 12 and the predicted OS curves for tisagenlecleucel and comparators from the base-case model are presented in Table 13-17. Because the model had a lifetime horizon and the follow-up times were limited for the observed data in the majority of the treatment arms, the model assumed the same mortality risk for all arms from year 5 onwards. Please refer to Table 13 for details related to long-term survival extrapolation.

Table 12. HR inputs for ITC-estimated OS curves

Comparator	HR (95% CI)	Source
Blinatumomab vs. tisagenlecleucel (age < 15 years)	[redacted]	von Stackelberg et al., 2016[17]; Gore et al., 2018[28]; ELIANA, ENSIGN, B2101J[25]–[27]
Blinatumomab vs. tisagenlecleucel (age 15-25 years)	[redacted]	von Stackelberg et al., 2016[17]; Gore et al., 2018[28]; ELIANA, ENSIGN, B2101J[25]–[27]
Inotuzumab vs. tisagenlecleucel (age 15-25 years)	[redacted]	Bhojwani et al., 2019[16]; ELIANA, ENSIGN, B2101J[25]–[27]
Abbreviations: CI, confidence interval; HR, hazard ratio		

Figure 20. Predicted OS curves for tisagenlecleucel and comparator in the base-case (age < 15 years)

Figure 21. Predicted OS curves for tisagenlecleucel and comparators in the base-case (age 15-25 years)

At year 5 of the model simulation, those who remained alive were subsequently assumed long-term survivors of ALL. The NICE committee believes that ALL patients with 3- or 5-year EFS should be long-term survivors. 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 target 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.[39]

Table 13. Long-term survival input sources

Publication	Population	Sample Size	SMR Measure
MacArthur et al., 2007	Individuals less than 20 years of age diagnosed with cancer	Overall sample size: 2,354; Sample size for	SMR for childhood cancer 5-year

	who survived 5 years or more after diagnosis	ALL patients: 429	survivors: 9.05
Abbreviations: ALL, acute lymphoblastic leukemia; SMR, standardized mortality ratio			

生存曲線の推計（PFS）

The EFS of tisagenlecleucel infused patients was based on the IPD pooled from 3 clinical trials of tisagenlecleucel: ELIANA (data cut-off: [redacted]), ENSIGN clinical trials (data cut-off: [redacted]) and B2101J (data cut-off: [redacted]) trials.[25]–[27] Similar to OS, the EFS was defined among infused population and was evaluated from the time of infusion. The EFS for patients in the tisagenlecleucel arm but not infused was the same as that of the blinatumomab comparator. No EFS data was available for the blinatumomab comparator, and was estimated based on OS assuming a constant cumulative HR. EFS data was also available for the inotuzumab comparator and was reported in Bhojwani et al 2019.[16] Age group-specific data were used whenever feasible to inform the EFS among patients aged < 15 years and aged 15-25 years, respectively.

Parametric function and ITC method was used to inform and project EFS estimates in the CEA model after the end of trial observation. Parameter estimates and goodness-of-fit criteria were estimated for EFS using the same approach as described above for OS, and each survival distribution was described. Due to the limited number of events over the long-term in subgroup analysis (tisagenlecleucel arm among patients aged 15-25 years), some spline models for the EFS parametric estimation could not converge. A weighted distribution based on various parametric survival curves was then derived and applied in the base-case analysis. A visual comparison of the survival data based on the observed data, all considered distributions, and the weighted distribution are reported in Figure 22-24, by age groups. The summary of AIC values and the weights considered for each survival distribution are presented in Appendix C.

Figure 22. Parametric functions for EFS - tisagenlecleucel (age < 15 years)

Figure 23. Parametric functions for EFS - tisagenlecleucel (age 15-25 years)

Figure 24. Parametric functions for EFS - inotuzumab (age 15-25 years)

In the base-case model, observed data was used during the trial period until up to year 5. If the observed data ends before year 5, parametric function was used to project EFS estimates after the end of trial observation until year 5 for tisagenlecleucel infused patients. To adjust for the potential difference in patient population between tisagenlecleucel and inotuzumab, MAIC analyses were conducted comparing the EFS of tisagenlecleucel infusion with inotuzumab. The HR from the MAIC analysis (HR = [redacted] 95% CI: [redacted]) was applied to the predicted EFS curve of tisagenlecleucel infusion to estimate the EFS for inotuzumab and was applied after the end of trial observation until year 5. EFS data was not available in the literature for blinatumomab comparator arm. 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] After year 5, the cumulative survival probabilities of EFS were assumed to flatten up until they reached OS. The 5-year period is consistently cited in existing ALL studies and represents a clinically important time point for patients to reach given the limited risk of relapses after year 5.[41] EFS was assumed to be less than or equal to OS at all time points. The predicted EFS curves for tisagenlecleucel and the comparators by age groups are reported in Figure 25 and Figure 26.

Figure 25. Predicted EFS curves for tisagenlecleucel and comparator (age < 15 years)

Figure 26. Predicted EFS curves for tisagenlecleucel and comparators (age 15-25 years)

4.2.1.2 DLBCL: 70 歳未満

生存曲線の推計(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 long-

term 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 target 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.

Figure 27. Predicted OS curves for tisagenlecleucel and salvage chemotherapy

生存曲線の推計（PFS）
The PFS of tisagenlecleucel infused patients was based on the data from the JULIET trial (data cut-[redacted]9) 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.

Figure 28. Predicted PFS curves for tisagenlecleucel and salvage chemotherapy

4.2.1.3 DLBCL: 70 歳以上

生存曲線の推計(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

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 long-term DLBCL survival was modelled using the 2018 Japan life table, with a mortality adjustment using the standardized mortality ratio (SMR) of DLBCL long-term 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 target 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.

Figure 29. Predicted OS curves for tisagenlecleucel and salvage chemotherapy

生存曲線の推計（PFS）

The PFS of tisagenlecleucel infused patients was based on the data from the JULIET trial (data cut-off: [redacted]) 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

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.

Figure 30. Predicted PFS curves for tisagenlecleucel and salvage chemotherapy

4.2.2 QOL 値の詳細

4.2.2.1 B-ALL

変数名	使用した尺度	測定者数	reference
Health states utility (base-case)			
EFS	Convertfrom SF36 to HUI2	457	Kelly et al. 2015[30]
PD	EQ-5D	588/20,400	
Treatment disutility			

Tisagenlecleucel(infused patients) Blinatumomab Inotuzumab	SG	NA	Sung et al., 2003[31]
Other utility/disutility			
ICU stay not due to CRS	NA	NA	Assumption: utility=0 during ICU admission
Grade3/4 CRS disutility	NA	NA	Assumption: utility=0 during ICU admission
HSCT disutility	SG	NA	Sung et al., 2003[31]
Age-related utility	EQ-5D	NA	Janssen 2014[32]

Health states utility

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.

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).

Additional treatment disutilities associated with CRS were considered for patients with grades 3 or 4 CRS. The CRS rate for tisagenlecleucel was derived from the ELIANA trial data and the rate for blinatumomab was derived from von Stackelberg et al., 2016.[17] No patients from the inotuzumab arm experienced grades 3 or 4 CRS. Patients were assumed to have a utility of 0 (a disutility of 0.91 based on EFS utility) for the duration of the CRS ICU based on the ELIANA trial. For the tisagenlecleucel arm, an additional treatment disutility was also considered for ICU stays not due to CRS by assuming that patients in the ICU would have a utility value of 0. The treatment and adverse events disutility considered in the model are summarized in Section 4.2.

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.

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 [redacted] and were applied to all alive patients over the modelled time horizon.

4.2.2.2 DLBCL

変数名	使用した尺度	測定者数	reference
Health states utility (base-case)			
PFS	EQ-5D	NA	Chen et al. 2017[a][33]
PD/RL	EQ-5D	NA	
Treatment disutility			
Tisagenlecleucel (infused patients), Salvage chemotherapy,	NA	NA	Guadagnolo et al. 2006[b][34]
Other utility/disutility			
HSCT disutility	NA	NA	Guadagnolo et al. 2006[b][34]
Grade3/4 CRS disutility	NA	NA	Assumption: utility=0 during ICU admission

a. Micro-simulation models were developed to study the cost-effectiveness of precision treatment strategies for DLBCL patients

b. A decision-analytical model to evaluate follow-up strategies for patients with Hodgkin's disease

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 target 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.

Treatment disutility
Inputs for treatment disutility were obtained from Guadagnolo et al. 2006.[34] Guadagnolo et al. 2006 developed a decision-analytical model to evaluate follow-up strategies for patients with Hodgkin's disease. Utility and disutility inputs for patients with Hodgkin's disease were consolidated from prior published studies and used in the analysis. A decrement of 0.15 for patients undergoing conventional dose salvage chemotherapy was reported and assumed to capture the utility decrements for all short-term AEs associated with the tisagenlecleucel or salvage chemotherapy, with the exception of the CRS.
For the tisagenlecleucel arm, additional treatment disutilities were considered for grade 3 or 4 CRS and intensive care unit (ICU) stays not due to CRS. For both events, the patients were assumed to have a utility of 0 (a disutility of -0.83 based on PFS utility).

HSCT disutility
The model assumed patients could receive subsequent auto SCT or allo SCT after initial treatment. The efficacy of subsequent SCT was captured in the PFS and OS estimations. Patients receiving either subsequent auto SCT or allo SCT were assumed to have additional SCT disutility, derived from Guadagnolo et al. 2006.[34]

4.2.3 費用のパラメータの詳細
本品の対象疾患となる B-ALL および DLBCL は、いずれも患者数が少ないことから、レセプトデータを用いた費用の分析は不確実性が大きくなると判断し、標準治療モデルをベースにした推計を実施した。
B-ALL と DLBCL の両疾患について、原則として 2019 年 10 月時点の診療報酬点数表、薬価基準に基づき、積み上げ方式により分析対象技術及び比較対照技術にかかる費用を推計した。
資源消費量の推計に関しては、本品は臨床試験で使用されたレジメンの実績を、比較対照技術は診療ガイドラインで規定された標準的な用法を用いた。有害事象の治療費は、臨床試験の発症率に、予め設定した個別の有害事象治療フローのコストを乗じて、期待費用を計算した。なお、本邦では、DLBCL 患者の増悪後の統一された治療方針やコストに関するデータが存在しない。そのため、DLBCL の増悪後のコストは、海外データを日本円に換算して使用している。海外データの外挿は大きな不確実性を伴うため、感度分析での考慮を行った。以下に費用の各構成要素における詳細について記載する。

4.2.3.1 B-ALL
Tisagenlecleucel cost
For tisagenlecleucel arm, the model used a decision-tree approach to partition patients based on the infusion status to assign different effectiveness, cost and disutility inputs. For patients who proceeded with infusion, they were assumed to incur the cost related to tisagenlecleucel treatment. For patients who discontinued before infusion, they were assumed to incur the costs related to the blinatumomab comparator. The model considered [redacted] % and [redacted] % proceeded with infused for patients aged < 15 years and patients aged 15-25 years respectively, based on the observed infusion rate from the pooled trial data of ELIANA, ENSIGN, and B2101J.[25]–[27] Regardless of infusion, patients on tisagenlecleucel arm will incur pre-treatment leukapheresis cost. Table 14 summarizes how different cost components were attributed to patients in the tisagenlecleucel arm based on their infusion status.

Table 14. Attribution of cost for tisagenlecleucel arm based on patients' infusion status

Cost component	Infused patients	Non-infused patients
Pre-treatment: leukapheresis	Same leukapheresis cost for all patients regardless of infusion status	
Pre-treatment: bridging chemotherapy	Only considered for infused patients	NA
Pre-treatment: lymphodepleting regimen	Only considered for infused patients	NA
Treatment cost: tisagenlecleucel or comparator treatment	Drug, administration, and hospitalization cost associated with tisagenlecleucel infusion	Drug, administration, and hospitalization cost associated with blinatumomab
Adverse event	Adverse event associated with tisagenlecleucel	Adverse event associated with blinatumomab
Subsequent HSCT	Subsequent HSCT rate based on tisagenlecleucel trials	Subsequent HSCT rate based on blinatumomab
Follow-up	Tisagenlecleucel-specific follow-up cost by health states	Blinatumomab-specific follow-up cost by health states

Pre-treatment cost

Prior to tisagenlecleucel infusion, patients have to undergo three pre-treatment phases: leukapheresis, bridging chemotherapy, and lymphodepleting chemotherapy. The costs associated with each of these pre-treatment phases were applied in the first cycle of the model. The proportion of patients attributed the costs of each of three pre-treatment phases were specified in Table 15.

•Leukapheresis: collection of T-cells from the patients and consisted of leukapheresis and cryopreservation procedures.The cost of leukapheresis and cryopreservation was estimated to be ¥174,400 based on official gazette released by Ministry of Health, Labour and Welfare, and assumed to be the same across both age groups.[45] All patients in the tisagenlecleucel arm were assumed to incur the cost of leukapheresis and cryopreservation procedures, regardless of whether they received tisagenlecleucel infusion or not.

•Bridging chemotherapy: chemotherapy administered to stabilize disease whilst waiting for tisagenlecleucel manufacturing and infusion.Within the tisagenlecleucel clinical trials, the provision of bridging chemotherapy was left to investigator discretion and therefore a wide range of bridging chemotherapy regimens were received by patients in all three trials. As such, the costs of bridging chemotherapy (i.e., drug acquisition costs and administration costs) were assumed to be the average costs of the salvage chemotherapy regimens following the Children's Oncology Group AALL01P2 protocol.[46] Specifically, a total of ¥[redacted] was estimated for patients aged <15 years and ¥[redacted] was estimated for patients aged 15-25 years as the average BSA and weight profile differs between age groups. For patients who received tisagenlecleucel infusion, the model assumed [redacted]% of patients would receive bridging chemotherapy, based on pooled data from ELIANA, ENSIGN and B2101J, which was assumed to

be the same across age groups.[25]–[27] For patients who discontinued prior to tisagenlecleucel infusion, they were assumed to be managed by blinatumomab comparator, and would not need any bridging chemotherapy treatment.

•Lymphodepleting regimen: treatment administered to facilitate the engraftment and homeostatic expansion of tisagenlecleucel cells

In tisagenlecleucel trials, lymphodepleting regimen was administered to patients [redacted] days prior to the infusion. It was assumed that the cost of this regimen was only applied to the proportion of patients who received tisagenlecleucel infusion ([redacted] % for patients aged <15 years and [redacted] % for patients aged 15-25 years). The lymphodepleting regimens and resource use as observed in the ELIANA trial was used to model the cost associated with lymphodepleting. Drug costs for lymphodepleting regimens were calculated as a function of unit drug costs, dosing, and proportion of patients receiving each regimen. The unit costs of the treatment agent and the administration costs were based on the official gazette released by Ministry of Health, Labour and Welfare.[47] Two lymphodepleting regimens were available. The dosing and proportion of patients receiving each lymphodepleting regimen were based on ELIANA trial data.[26] Vial sharing was not considered when estimating the drug cost in the base-case. The hospitalization cost for lymphodepleting period was calculated separately based on ELIANA trial data.[26] An estimated [redacted] % of patients were hospitalized during lymphodepleting chemotherapy, with an average duration of [redacted] days. The total hospitalization cost during the pre-treatment period of tisagenlecleucel was estimated to be [redacted], using daily costs reported by the points of Notification Related to Reimbursement released by Ministry of Health, Labour and Welfare.[47]

Table 15. Dosing schedule, drug acquisition cost, and administration cost for lymphodepleting regimen

Treatment	Cost per package, package size	Dosing schedule	Daily administration cost	Total treatment cost[a]	Distribution of patients per regimen (%)	Source
Regimen 1				[redacted]	[redacted]%	ELIANA (dosing and patient distribution)[26]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Fludarabine	¥33,203, 50 mg	30 mg/m^2 intravenous (IV) daily for 4 doses	¥8,520			
Cyclophosphamide	¥1,254, 500 mg	500 mg/m^2 IV daily for 2 doses				
Regimen 2				Age < 15: [redacted] Age 15-25: [redacted]	[redacted]%	
Cytarabine	¥5,156, 1,000 mg	500 mg/m^2 IV daily for 2 days	¥8,520			
Etoposide	¥4,172, 100 mg	150 mg/m^2 IV daily for 3 days				

Abbreviations: IV, intravenous; mg, milligrams
[a] The treatment costs for regimen 2 differ as the BSA is different across age groups

Table 16. Hospitalization cost for lymphodepleting regimen

% patients require hospitalization before infusion	Daily hospitalization / administration cost	Number of days	Total cost	Source
[redacted] %	The first 14 days: ¥23,240; After 14 days: ¥20,660	[redacted]	[redacted]	ELIANA (resource use)[26]; The official gazette released by Ministry of Health, Labour and Welfare (hospitalization cost)[47]

Treatment cost

After the lymphodepleting chemotherapy, a one-time acquisition cost of ¥34,113,655 was considered for patients who received tisagenlecleucel infusion.[45] The administration cost of tisagenlecleucel was ¥308,500, which was obtained from the points of Notification Related to Reimbursement released by Ministry of Health, Labour and Welfare.[47] Hospitalization and ICU stay associated with tisagenlecleucel treatment were estimated based on ELIANA trial data.[26] In the ELIANA trial, all hospitalization and ICU stays initiated within [redacted] days after tisagenlecleucel infusion were assessed. Based on ELIANA trial data, an estimated [redacted]% of patients were ever hospitalized post tisagenlecleucel infusion for an average duration of [redacted] days. The calculated total hospitalization cost was ¥[redacted], based on daily costs of ¥23,240 and ¥20,660 for the first 14 days of hospitalization and for the hospitalization after 14 days, respectively, obtained from the official gazette released by Ministry of Health, Labour and Welfare.[47] On average, tisagenlecleucel patients had [redacted] days of ICU stay due to reasons other than CRS. The total ICU cost was estimated to be ¥[redacted], based on a daily ICU cost of ¥[redacted] specific to pediatric patients from the official gazette released by Ministry of Health, Labour and Welfare.[47] The cost of ICU stays due to CRS was calculated separately as part of the AE costs later/

For patients who discontinued prior to tisagenlecleucel infusion, the same drug, administration, and hospitalization cost as the blinatumomab comparator treatment was considered. The detailed cost inputs are described in the next section.

Comparator cost

Blinatumomab (for age < 15 years and age 15-25 years)

Drug acquisition costs were calculated as a function of unit drug costs, dosing, and treatment duration. The dosing schedule and the number of treatment cycles of blinatumomab were obtained from von Stackelberg et al., 2016, the same trial used for the efficacy input of blinatumomab in the model, and were considered the same for both age groups.[17] The model assumed 9 days of hospitalization in cycle 1 and 2 days in cycle 2 in accordance with the hospitalization recommendation in blinatumomab NICE submission ID804.[48] Accounting for the proportion of patients on each cycle shown in Table 17, the average LOS(length of stay) was estimated as [redacted] days. Thus, the total hospitalization cost was estimated to be [redacted], based on a daily cost of ¥23,240 for the first 14 days of hospitalization, obtained from the official gazette released by Ministry of Health, Labour and Welfare.[47] Detailed inputs for the cost of blinatumomab are presented in Table 17.

Inotuzumab (for age 15-25 years)

Drug acquisition costs were calculated as a function of unit drug costs, dosing, and treatment duration. The dosing schedule and the number of treatment cycles of blinatumomab was obtained from Bhojwani 2019, the same publication used for the efficacy input of inotuzumab in the model.[16] The model assumed 9.5 days of hospitalization per cycle in accordance with the hospitalization recommendation in inotuzumab adult ALL NICE submission TA541.[49] Accounting for the proportion of patients on each cycle shown in Table 18, the average LOS was estimated as [redacted] days. Thus, the total hospitalization cost was estimated to be [redacted], based on a daily cost of ¥23,240 for the first 14 days

of hospitalization and ¥20,660 after 14 days of hospitalization, obtained from the official gazette released by Ministry of Health, Labour and Welfare.[47] Detailed inputs for the cost of inotuzumab are presented in Table 18.

Table 17. Dosing schedule, drug acquisition cost, and administration cost for blinatumomab

Treatment	Cost per package or vial, package size	Dosing schedule	Daily administration cost	Distribution of patients per cycle or number of cycles	Total treatment cost	Source
Blinatumomab					¥ [redacted]	von Stackelberger al., 2016 (dosing schedule)[17]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Blinatumomab cycle 1	¥281,345, 35 mcg	5 mcg/m^2/day Day 1-7; 15 mcg/m^2/day Day 8-28	¥9,650	[redacted]%		
Blinatumomab cycle 2	¥281,345, 35 mcg	15 mcg/m^2/day Day 1-28	¥9,650	[redacted]		
Blinatumomab cycle 3	¥281,345, 35 mcg	15 mcg/m^2/day Day 1-28	¥9,650	[redacted]		
Blinatumomab cycle 4 and 5	¥281,345, 35 mcg	15 mcg/m^2/day Day 1-28	¥9,650	[redacted]%		
Abbreviations: mcg, micrograms						

Table 18. Dosing schedule, drug acquisition cost, and administration cost for inotuzumab

Treatment	Cost per package or vial, package size	Dosing schedule	Daily administration cost	Distribution of patients per cycle or number of cycles	Total treatment cost	Source
Inotuzumab					[redacted]	Bhojwani, et al 2019 (dosing schedule)[16]; The official
Inotuzumab cycle 1	¥1,307,092, 1 mg	0.8 mg/m^2 Week 1; 0.5 mg/m^2 Week 2 and 3	¥8,520	[redacted]%		

Inotuzumab cycle 2	¥1,307,092, 1 mg	0.5 mg/m^2 Day 1, 8, 15	¥8,520	[redacted]%		gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Inotuzumab cycle 3-5	¥1,307,092, 1 mg	0.5 mg/m^2 Day 1, 8, 15	¥8,520	[redacted]%		
Abbreviations: mg, milligrams						

Subsequent HSCT costs

The model assumed patients could receive subsequent HSCT after initial treatment. The cost and disutility of subsequent HSCT were added separately for the proportion of patients who received subsequent HSCT for each arm. The rates of subsequent HSCT were obtained from the same clinical trial study used for the efficacy estimation and are described in Section 4.2.

HSCT costs were considered in two parts: HSCT procedure cost, HSCT follow-up cost up to 24 months (Table 19). In the base-case, the HSCT procedure and follow-up costs were derived from an observational study using claims data in Japan, and considered, inpatient, outpatient, prescribed drug, and test costs. The costs specific to pediatric patients with a diagnosis of ALL were considered to be aligned with the target population. Based on the study, the HSCT procedure cost was estimated to be ¥[redacted], and the total follow-up cost up to 24 months after HSCT procedure was estimated to be ¥[redacted].

Table 19. HSCT costs

Component	Cost	Source
Total cost	¥[redacted]	
HSCT procedure + harvesting cost	¥[redacted]	pALL-specific HSCT cost based on JMDC claim data (relavant study: Wakase et al., 2018[50])
HSCT follow-up cost (up to 24 months)	[redacted]	
Abbreviations: HSCT, hematopoietic stem cell transplantation		

Follow-up costs

Follow-up costs consisted of the costs of the outpatient visits and laboratory tests and procedures (e.g., full blood count, electrocardiogram, and bone marrow biopsy). The costs were assumed to vary by treatment, health state, and the time horizon. The follow-up schedules and unit costs are summarized in Table 20 and Table 21. Table 22 summarizes the follow-up costs for each arm by health states and follow-up year.

For patients receiving blinatumomab and inotuzumab who remained in the EFS state, the frequency of follow-up was obtained from the National Comprehensive Cancer Network (NCCN) guideline.[9] For patients receiving tisagenlecleucel infusion who remain in the EFS state, the frequency of follow-up was derived from the ELIANA trial protocol.[26] The frequency of follow-up was assumed to be the same for PD state across all comparator arms, and was assumed to be the same as the EFS state of comparators during year 1, except that frequency of follow-up for cerebrospinal fluid and bone marrow aspirate was based on assumptions. Unit costs per provider visit and per test/procedure were collected from the official gazette released by Ministry of Health, Labour and Welfare.[47]

Table 20. Follow-up schedule and unit cost inputs for EFS patients

Parameter	Unit cost	Yearly frequency (Year 1)[a]	Yearly frequency (Year 2)[a]	Yearly frequency (Years 3-5)[a]	Yearly frequency (Years 5+)[a]	Code for unit cost
Source	Unit cost: the official gazette released by Ministry of Health, Labour and Welfare[47]; Frequencies: ELIANA (tisagenlecleucel)[26]; NCCN guideline (comparators)[9]					
Tisagenlecleucel (infused patients)						
Consultant visit	¥720	[redacted]	[redacted]	[redacted]	[redacted]	A002
Hematology panel	¥210	[redacted]	[redacted]	[redacted]	[redacted]	D005-5(R,W,Hb,Ht,PI)
Coagulation panel	¥180	[redacted]	[redacted]	[redacted]	[redacted]	D006-2
Chemistry panel (including liver function test)	¥170	[redacted]	[redacted]	[redacted]	[redacted]	D007-3(AST,ALT etc)
Cerebrospinal fluid (CSF)	¥5,000	[redacted]	[redacted]	[redacted]	[redacted]	D401
Serum test	¥3,900	[redacted]	[redacted]	[redacted]	[redacted]	D011-10
B cell and T cell test	¥2,040	[redacted]	[redacted]	[redacted]	[redacted]	D016-4
Electrocardiogram (ECG)	¥1,300	[redacted]	[redacted]	[redacted]	[redacted]	D208
Bone marrow aspirate	¥2,600	[redacted]	[redacted]	[redacted]	[redacted]	D404
Bone marrow biopsy	¥7,300	[redacted]	[redacted]	[redacted]	[redacted]	D404-2
Echocardiogram	¥5,300	[redacted]	[redacted]	[redacted]	[redacted]	D215
Liver function test	¥110	[redacted]	[redacted]	[redacted]	[redacted]	D007
Comparator regimens						
Consultant visit	¥720	[redacted]	[redacted]	[redacted]	[redacted]	A002
Hematology panel	¥210	[redacted]	[redacted]	[redacted]	[redacted]	D005-5(R,W,Hb,Ht,PI)

Parameter	Unit cost	Yearly frequency (Year 1)[a]	Yearly frequency (Year 2)[a]	Yearly frequency (Years 3-5)[a]	Yearly frequency (Years 5+)[a]	Code for unit cost
Coagulation panel	¥180	[redacted]	[redacted]	[redacted]	[redacted]	D006-2
Chemistry panel (including liver function test)	¥170	[redacted]	[redacted]	[redacted]	[redacted]	D007-3(AST,ALT etc)
Cerebrospinal fluid (CSF)	¥5,000	[redacted]	[redacted]	[redacted]	[redacted]	D401
Serum test	¥3,900	[redacted]	[redacted]	[redacted]	[redacted]	D011-10
B cell and T cell test	¥2,040	[redacted]	[redacted]	[redacted]	[redacted]	D016-4
Electrocardiogram (ECG)	¥1,300	[redacted]	[redacted]	[redacted]	[redacted]	D208
Bone marrow aspirate	¥2,600	[redacted]	[redacted]	[redacted]	[redacted]	D404
Bone marrow biopsy	¥7,300	[redacted]	[redacted]	[redacted]	[redacted]	D404-2
Echocardiogram	¥5,300	[redacted]	[redacted]	[redacted]	[redacted]	D215
Liver function test	¥110	[redacted]	[redacted]	[redacted]	[redacted]	D007
Abbreviations: CSF, cerebrospinal fluid; ECG, electrocardiogram a. Follow up frequencies for tisagenlecleucel were derived from ELIANA. Follow up frequencies for chemotherapy regimens were based on NCCN guideline.						

Table 21. Follow-up schedule and unit cost inputs for PD patients

Parameter	Unit cost	Yearly frequency[a]	Code for unit cost
Source	Unit cost: the official gazette released by Ministry of Health, Labour and Welfare[47]; Frequencies: assumed to be the same as the EFS state of comparators during year 1, except that cerebrospinal fluid, bone marrow aspirate and echocardiogram were based on assumptions		
Consultant visit	¥720	[redacted]	A002
Hematology panel	¥210	[redacted]	D005-5(R,W,Hb,Ht,PI)

Parameter	Unit cost	Yearly frequency[a]	Code for unit cost
Coagulation panel	¥180	[redacted]	D006-2
Chemistry panel (including liver function test)	¥170	[redacted]	D007-3(AST,ALT etc)
Cerebrospinal fluid (CSF)	¥5,000	[redacted]	D401
Serum test	¥3,900	[redacted]	D011-10
B cell and T cell test	¥2,040	[redacted]	D016-4
Electrocardiogram (ECG)	¥1,300	[redacted]	D208
Bone marrow aspirate	¥2,600	[redacted]	D404
Bone marrow biopsy	¥7,300	[redacted]	D404-2
Echocardiogram	¥5,300	[redacted]	D215
Liver function test	¥110	[redacted]	D007
Abbreviations: CSF, cerebrospinal fluid; ECG, electrocardiogram a. Follow up frequencies were assumed to be the same as the EFS state of chemotherapies during year 1, except that cerebrospinal fluid, bone marrow aspirate and echocardiogram were based on assumptions			

Table 22. Follow-up cost inputs summary (monthly cost by treatment)

	Tisagenlecleucel (infused patients)	Blinatumomab	Inotuzumab (for age 15-25)
EFS (year 1)	[redacted]	[redacted]	[redacted]
EFS (year 2)	[redacted]	[redacted]	[redacted]
EFS (year 3-5)	[redacted]	[redacted]	[redacted]
EFS (post 5 years)	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Abbreviations: EFS, event-free survival; PD, progressive disease			

Adverse event costs

AE costs were only considered for grade 3/4 CRS and B-cell aplasia. Hospitalization costs in the current model would comprise AE costs. To be conservative, AEs that are important for tisagenlecleucel including grade 3/4 CRS and B-cell aplasia were further added. Grade 3/4 CRS is also an AE incurred by blinatumomab. The AE rates for grade 3/4 CRS and B-cell aplasia were obtained from the ELIANA trial data for tisagenlecleucel, and von Stackelberg et al., 2016 for blinatumomab.[17], [26]

CRS is an AE that is specific to treatment with tisagenlecleucel and blinatumomab, and could be associated with substantial resource use. CRS event costs were calculated as the sum of the ICU admission cost and tocilizumab drug and administration costs. LOS for ICU and the dosing of tocilizumab related to CRS were obtained from ELIANA trial data.[26] The average daily cost per ICU stay and unit cost for tocilizumab treatment and administration were derived from the official gazette released by Ministry of Health, Labour and Welfare.[47] The detailed resource use inputs considered in the CRS AE cost estimation are listed in Table 23. The proportions of patients with CRS were estimated to be [redacted]% and 5.7% among patients treated with tisagenlecleucel and blinatumomab, respectively. For tisagenlecleucel, the total CRS costs were calculated to be [redacted] for patients aged <15 years and [redacted] for patients aged 15-25 years, as the average weight profile differs between the age groups. Similarly for blinatumomab, the total CRS costs were calculated to be ¥101,010 for patients aged <15 years and ¥106,100 for patients aged 15-25 years.

In addition to CRS, the model also considered one additional AE specific to the tisagenlecleucel arm: B-cell aplasia. B-cell aplasia is a common condition for patients managed by tisagenlecleucel and intravenous immunoglobulin (IVIG) is typically prescribed for patients for symptom management. The model considered [redacted]% patients with tisagenlecleucel infusion would receive IVIG with an average [redacted] dosage based on the ELIANA trial data.[26] Total monthly drug cost was calculated based on a dosing schedule obtained from Information Center for Specific Pediatric Chronic Diseases in Japan (dosing schedule) and respective unit costs and monthly administration costs obtained from the official gazette released by Ministry of Health, Labour and Welfare.[51] The total IVIG cost was calculated to be ¥[redacted] for patients aged <15 years and [redacted] for patients aged 15-25 years based on proportion of patients receiving IVIG and the average dosage, and was applied as a one-time cost in the model. Table 24 presents the detailed dosing and unit costs for B-cell aplasia.

Table 23. Costs of CRS

Parameter	Daily ICU cost / unit cost per infusion	Duration (days)/# of doses	Total cost per CRS event	Source
CRS cost per event			Age <15: ¥[redacted] Age 15-25: [redacted]	ELIANA (resource use), the official gazette released by Ministry of Health, Labour
Pediatric ICU admission	<8 days: ¥157,520 ≥8 days:	[redacted] days		

	¥137,200			and Welfare (ICU cost, drug cost, administration cost)[26], [47]
Tocilizumab treatment	Age<15: ¥74,368 Age 15-25: ¥146,387	[redacted]		
Tocilizumab administration	¥8,520	[redacted]		
Abbreviations: ICU, intensive care unit; CRS, cytokine release syndrome				

Table 24. Costs of B-cell aplasia

Parameter	Cost per package or vial, package size	Dosing schedule	Total drug cost per month	Total administration cost per month[a]	Source
IVIG drug cost	¥77,245, 10,000 mg	400 mg/kg every month	Age <15: [redacted] Age 15-25: [redacted]	¥8,520	Information Center for Specific Pediatric Chronic Diseases in Japan (dosing schedule), the official gazette released by Ministry of Health, Labour and Welfare (drug cost, administration cost)[47], [51]
Abbreviations: IVIG, intravenous immunoglobulin; mg, milligrams; kg, kilograms a. The model considered 1 infusion per cycle in the calculation of total administration cost per cycle.					

Terminal care costs

All patients who transition to death were assumed to incur one-time terminal care costs. The terminal care cost input was estimated to be ¥747,787 inflated to 2018 cost and based on Nichiisouken Working Paper No.144 for cancer patients.[52]

Productivity Losses

When the societal perspective was selected, the model considered additional

societal benefit associated with productivity gain for both tisagenlecleucel and comparators. Patients in the PFS state were assumed to incur work productivity benefit one year after treatment initiation based on the monthly wage and age-specific employment rate in Japan. The specific inputs used for the productivity gain estimation are presented in Table 25. The total societal benefit associated with productivity gain was calculated for each treatment over the modelled time horizon, and was subtracted from the total direct medical cost to estimate the total societal costs.

Table 25. Inputs for productivity losses

Parameter	Input value	Source/notes
Monthly Wage	¥427,877.33	Wage level data in Japan[53]
Age-specific employment rate		
15-24	43.50%	2018 Mar, Historical data 1 b-6 Employment rate [by age group] - Whole Japan, Monthly Data[54]
25-54	84.90%	
55-59	74.90%	
60-64	74.90%	
65 +	24.10%	

4.2.3.2 DLBCL

Tisagenlecleucel cost

For tisagenlecleucel arm, the model used a decision-tree approach to partition patients based on the infusion status to assign different effectiveness, cost and disutility inputs. For patients who proceeded with infusion, they were assumed to incur the cost related to tisagenlecleucel treatment. For patients who discontinued before infusion, they were assumed to incur the costs related to the comparator treatment (i.e., salvage chemotherapy). For the population less than 70 years, the model considered [redacted]% of patients proceeded with infused based on the observed infusion rate from the JULIET trial data among patients aged < 70 years. For the population aged 70 years or older, the model considered [redacted]% of patients proceeded with infused based on the observed infusion rate from the JULIET trial data among patients aged ≥70 years. Regardless of infusion, patients on tisagenlecleucel arm will incur pre-treatment leukapheresis cost. Table 26 summarized how different cost components were attributed to patients in the tisagenlecleucel arm based on their infusion status.

Table 26. Attribution of cost for tisagenlecleucel arm based on patients' infusion status

Cost component	Infused patients	Non-infused patients
Pre-treatment: leukapheresis	Same leukapheresis cost for all patients regardless of infusion status	
Pre-treatment: bridging chemotherapy	Only considered for infused patients	NA
Pre-treatment:	Only considered for infused	NA

lymphodepleting regimen	patients	
Tisagenlecleucel or comparator treatment	Drug, administration, and hospitalization cost associated with tisagenlecleucel infusion	Drug, administration, and hospitalization cost associated with salvage chemotherapy
AE	AE associated with tisagenlecleucel	AE associated with salvage chemotherapy
Subsequent SCT (only for <70 years)	Subsequent SCT rates based on tisagenlecleucel trials	Subsequent SCT rates based on salvage chemotherapy trials
Follow-up	Tisagenlecleucel-specific follow-up cost by health states	Salvage chemotherapy-specific follow-up cost by health states

Pre-treatment cost

Prior to tisagenlecleucel infusion, patients have to undergo three pre-treatment phases: leukapheresis, bridging chemotherapy, and lymphodepleting chemotherapy. The costs associated with each of these pre-treatment phases were applied in the first cycle of the model. The subgroups of patients based on infusion status attributed the costs of each of three pre-treatment phases were specified in Table 26.

- Leukapheresis: collection of T-cells from the patients and consisted of leukapheresis and cryopreservation procedures

The cost of leukapheresis and cryopreservation were estimated to be ¥174,400 based on the points of Notification Related to Reimbursement released by MHLW. All patients in the tisagenlecleucel arm were assumed to incur the cost of leukapheresis and cryopreservation procedures, regardless of whether they received tisagenlecleucel infusion or not.

- Bridging chemotherapy: chemotherapy administered to stabilize disease whilst waiting for tisagenlecleucel manufacturing and infusion

In the tisagenlecleucel clinical trial, the provision of bridging chemotherapy was left to investigator discretion and therefore a wide range of bridging chemotherapy regimens were received by patients in JULIET trial. As such, the costs of bridging chemotherapy were assumed to be equal to one cycle of drug and administration costs of salvage chemotherapy for DLBCL. For patients aged less than 70 years, the one cycle of drug acquisition and administration costs of salvage chemotherapy were calculated as the weighted average of different chemotherapy regimens, which were [redacted] and [redacted], respectively. For patients aged 70 years and above, the one cycle of drug acquisition and administration costs of salvage chemotherapy were calculated as the weighted average of different chemotherapy regimens, which were [redacted] and [redacted], respectively. For patients who received tisagenlecleucel infusion, the model assumed [redacted]% of patients would receive bridging chemotherapy, based on JULIET data. For patients who discontinued prior to tisagenlecleucel infusion, they were assumed to be managed by the comparator treatment (i.e., salvage chemotherapy), and would not need any bridging chemotherapy treatment.

- Lymphodepleting regimen: treatment administered to facilitate the engraftment and homeostatic expansion of tisagenlecleucel cells

In tisagenlecleucel trial, lymphodepleting regimen was administered to patients

2-14 days prior to the infusion. It was assumed that the cost of this regimen was only applied to the proportion of patients who received tisagenlecleucel infusion [redacted]% for <70 years, [redacted]% for ≥70 years). The lymphodepleting regimens and resource use as observed in the JULIET trial were used to model the costs associated with lymphodepleting. Drug costs for lymphodepleting chemotherapy were included in the model and were calculated as a function of unit drug costs, dosing, administration costs, and proportion of patients receiving each regimen (Table 27). The unit costs and administration costs of the treatment agent were based on official gazette released by MHLW. Two lymphodepleting regimens were available. The dosing and proportion of patients receiving each lymphodepleting regimen were based on the JULIET trial data. Vial sharing was not considered when estimating the drug cost in the base-case.

Table 27. Dosing schedule, drug acquisition cost, and administration cost for lymphodepleting regimen

Treatment	Cost per package, package size	Dosing schedule	Total drug cost per regimen	Daily administration cost	Distribution of patients in each regimen (%)	Source
Regimen 1			[redacted]		[redacted]%	JULIET (dosing and patient distribution)[29]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Fludarabine	¥33,203, 50 mg	25 mg/m^2 daily for 3 doses		¥6,200		
Cyclophosphamide	¥1,254, 500 mg	250 mg/m^2 daily for 3 doses				
Regimen 2			[redacted]		[redacted]%	
Bendamustine	¥94,891, 100 mg	90 mg/m^2 daily for 2 days		¥6,200		
Abbreviations: mg, milligrams						

Treatment cost

After the lymphodepleting chemotherapy, one-time acquisition cost of ¥34,113,655 was considered for patients who received tisagenlecleucel infusion.[45] The administration cost of tisagenlecleucel was ¥308,500, which was obtained from the official gazette released by MHLW.[47] Hospitalization and ICU inputs were estimated based on the JULIET trial data. In the JULIET trial, all hospitalization and ICU stays were tracked starting from lymphodepleting unit 60 days after tisagenlecleucel infusion. Based on JULIET trial data, an estimated [redacted]% of patients were ever hospitalized starting from lymphodepleting for an average duration of [redacted] days. The calculated total hospitalization cost was ¥[redacted] based on daily costs of ¥20,410 and ¥17,830 for the first 14 days of hospitalization and for the hospitalization after 14 days, respectively, obtained from the official gazette released by MHLW. ICU cost was also estimated and added separately for tisagenlecleucel based on the JULIET trial data. On average, tisagenlecleucel patients had [redacted] days of ICU stay due to reasons other than CRS. Considering an average daily ICU cost of [redacted], obtained from the official gazette released by MHLW, the total non-CRS related ICU cost was estimated to be [redacted]. The cost of ICU stays due to CRS was calculated separately as part of the AE costs.

For patients who discontinued prior to tisagenlecleucel infusion, the same drug, administration, and hospitalization costs as the salvage chemotherapy treatment were considered.

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 base-case, 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]

The number of inpatient admission and total length of stay (LOS) per hospitalization for patients on salvage chemotherapy were obtained from Huntington 2016 and Healthcare Cost and Utilization Project (HCUP) 2014.[60], [61] The cost per inpatient day was obtained from the official gazette released by MHLW. Detailed inputs for the cost of salvage chemotherapy are presented in Table 28.

Table 28. Dosing schedule, drug acquisition cost, and administration cost for salvage chemotherapy

Treatment	Cost per package or vial, package size	Dosing schedule	Number of cycles	Total drug cost per cycle	Daily administration cost	Total treatment cost	Source
(R)-ICE			[redacted]	<70: [redacted] >=70: [redacted]	¥6,350	<70: [redacted] >=70: [redacted]	Kewalramani 2004 (dosing schedule, cycles) [55]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Etoposide	¥4,172, 100 mg	100 mg/m² on days 3-5					
Ifosfamide	¥2,997, 1000 mg	5000 mg/m² on day 4					
Carboplatin	¥24,464, 450 mg	800 mg on day 4					
Rituximab	¥157,855, 500 mg	375 mg/m² on day 1					
(R)-GDP			[redacted]	¥[redacted]	¥6,200	[redacted]	Crump

						[redacted]	2004 (dosing schedule, cycles) [56]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Gemcitabine	¥8,495, 1000 mg	1000 mg/m² on days 1 and 8					
Dexamethasone	¥314, 6.6 mg	40 mg (oral) daily on days 1-4					
Cisplatin	¥7,099, 50 mg	75 mg/m² on day 1					
Rituximab	¥157,855, 500 mg	375 mg/m² on day 1					
(R)-ESHAP			[redacted]	[redacted]	¥6,680	[redacted]	Martin 2008, National Guideline Alliance 2016 (dosing
Etoposide	¥4,172, 100 mg	40 mg/m² on days 1-4					
Methylprednisolone acetate	¥1,769, 1000 mg	500 mg on days 1-5					
Cytarabine	¥5,156, 1000 mg	2000 mg/m² on day 5					
Cisplatin	¥7,099,	25 mg/m² on					

	50 mg	days 1-4					schedule, cycles) [57], [62]; The official gazette released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
Rituximab	¥157,855, 500 mg	375 mg/m² on day 1					
(R)-DHAP			[redacted]	[redacted]	[redacted]	[redacted]	Oki 2008 (dosing schedule, cycles) [58]; The official gazette
Dexamethasone	¥314, 6.6 mg	40 mg daily on days 3-5					
Cytarabine	¥5,156, 1000 mg	2000 mg/m² on days 4 and 5					
Cyclophosphamide	¥1,254, 500 mg	1200 mg/m² on day 3					
Etoposide	¥4,172, 100 mg	100 mg/m² on days 3-5					

Rituximab	¥157,855, 500 mg	375 mg/m² on day 1					released by Ministry of Health, Labour and Welfare (unit drug cost; administration cost)[47]
(R)-EPOCH			[redacted]	[redacted]	¥6,560	[redacted]	Jerman n 2004 (dosing schedule, cycles) [59]; The official gazette released by Ministry of Health, Labour and Welfare
Doxorubixin	¥4,351, 50 mg	15 mg/m² on days 2-4					
Vincristine	¥2,638, 1 mg	0.5 mg on days 2-4					
Etoposide	¥4,172, 100 mg	65 mg/m² on days 2-4					
Cyclophosphamide	¥1,254, 500 mg	750 mg/m² on day 5					
Prednisone	¥167, 20 mg	60 mg/m² (oral) on days 1-14					
Rituximab	¥157,855, 500 mg	375 mg/m² on day 1					

							(unit drug cost; administration cost)[47]
Abbreviations: mg, milligrams							

Subsequent SCT costs (for age less than 70 years)
The model assumed patients could receive subsequent SCT, including both allo SCT and auto SCT, after initial treatment. The cost and disutility were added separately for the proportion of patients who received subsequent SCT for the tisagenlecleucel and salvage chemotherapy arms. The rates of subsequent SCT were obtained from the same clinical trial study used for the efficacy estimation and were described in the subsequent SCT disutility section of Table 29.
Allo and auto SCT costs were considered in two parts: SCT procedure cost (including harvesting cost) and SCT follow-up cost up to 24 months (Table 29). In the base-case, both allo and auto SCT procedure and follow-up costs were derived from an observational study using claims data in Japan, and considered, inpatient, outpatient, prescribed drug, and test costs. The costs specific to adult patients with a diagnosis of DLBCL were considered to be aligned with the target population. Based on Wakase et al. 2018, the allo and auto SCT procedure costs were estimated to be [redacted] and [redacted], respectively.[50] The total follow-up costs up to 24 months after the procedure were estimated to be ¥[redacted] and ¥[redacted] for DLBCL patients with allo SCT and auto SCT, respectively.

Table 29. Subsequent SCT costs

SCT	Cost	Source
Allogeneic SCT	[redacted]	Allo SCT costs for adult DLBCL patients based on JMDC claim data (relavant study: Wakase et al. 2018[50])
Procedure + harvesting cost	¥[redacted]	
Follow-up cost (up to 24 months)	¥[redacted]	
Autologous SCT	[redacted]	Auto SCT costs for adult DLBCL patients based on JMDC claim data (relavant study: Wakase et al. 2018[50])
Procedure + harvesting cost	[redacted]	
Follow-up cost (up to 24 months)	[redacted]	
Abbreviations: SCT, stem cell transplantation		

Other medical costs
Other medical costs included monthly follow-up costs before disease progression and post-progression costs. The pre-progression follow-up costs consisted of physical check-ups and routine monitoring labs/procedures and were assumed to be different by treatment and time horizon. The follow-up schedules and unit costs are summarized in Table 30. For patients receiving salvage chemotherapy who remained in the PFS state, the frequency of follow-up was obtained from the National Comprehensive Cancer Network (NCCN) guideline and Van Den Neste et al. (2013).[14], [63] For patients receiving tisagenlecleucel who remained in the PFS state, the frequency of follow-up was derived from JULIET trial protocol. The unit costs were obtained from the official gazette released by MHLW. The follow-up schedules and unit costs are summarized in Table 30.
A monthly post-progression cost of ¥525,220 was applied following disease progression until death, with the exception of the last month before death. In the base-case, the monthly post-progression cost was derived from Muszbek 2016 and converted to Japanese Yen in 2018, which included professional and social services cost, health care professional costs and treatment follow-up costs for r/r

DLBCL patients in progressive/relapsed disease state.[64] The costs were assumed to be the same for tisagenlecleucel and salvage chemotherapy.
Table 31 summarizes the monthly pre-progression and post-progression costs by treatment, health states, and follow-up year.

Table 30. Follow-up schedule and unit cost inputs for PFS patients

Parameter	Unit cost	Yearly frequency (Year 1)[a]	Yearly frequency (Year 2)[a]	Yearly frequency (Years 3-5)[a]	Yearly frequency (Years 5+)[a]	Code for unit cost
Source	Unit cost: the official gazette released by Ministry of Health, Labour and Welfare[47]; Frequencies: JULIET (tisagenlecleucel)[29]; National Comprehensive Cancer Network (NCCN) guideline and Van Den Neste 2013 (chemotherapy regimens)[14], [63]					
Tisagenlecleucel						
Consultant visit	¥720	[redacted]	[redacted]	[redacted]	[redacted]	A002
Hematology panel	¥210					D005-5(R,W,Hb,Ht,PI)
Coagulation panel	¥180					D006-2
Chemistry panel (including liver function test)	¥110					D007-1(cr, ALP, CK etc)
Serum test	¥3,900					D011-10
Bone marrow biopsy and/or aspirate	¥7,300					D404-2
Comprehensive metabolic panel	¥110					D007
positron emission tomography (PET)/ computerised tomography (CT) scan	¥10,200					E200
Chemotherapy regimens						
Consultant visit	¥720					A002
Hematology panel	¥210					D005-5(R,W,Hb,Ht,PI)
Coagulation panel	¥180					D006-2
Chemistry panel (including liver	¥110					D007-1(cr, ALP, CK

Parameter	Unit cost	Yearly frequency (Year 1)[a]	Yearly frequency (Year 2)[a]	Yearly frequency (Years 3-5)[a]	Yearly frequency (Years 5+)[a]	Code for unit cost
function test)						etc)
Serum test	¥3,900	[redacted]	[redacted]	[redacted]	[redacted]	D011-10
Bone marrow biopsy and/or aspirate	¥7,300	[redacted]	[redacted]	[redacted]	[redacted]	D404-2
Comprehensive metabolic panel	¥110	[redacted]	[redacted]	[redacted]	[redacted]	D007
PET/CT scan	¥10,200	[redacted]	[redacted]	[redacted]	[redacted]	E200
Abbreviations: PET: positron emission tomography; CT, computerised tomography a. Follow up frequencies for tisagenlecleucel were derived from JULIET.[2] Follow up frequencies for chemotherapy regimens were based on NCCN guideline[29] and Van Den Neste 2013[30]						

Table 31. Follow-up cost inputs summary (monthly cost by treatment)

Monthly costs by health state	Tisagenlecleucel	Salvage Chemotherapy
PFS (year 1)	[redacted]	[redacted]
PFS (year 2)	[redacted]	[redacted]
PFS (year 3-5)	[redacted]	[redacted]
PFS (year 5+)	[redacted]	[redacted]
PD/RL	¥[redacted]	[redacted]
Abbreviations: PFS, progression-free survival; PD, progressed disease		

Adverse event costs

AE costs were only considered for tisagenlecleucel to be conservative, which comprised of costs for treating grade 3/4 CRS and B-cell aplasia. Hospitalization costs in the current model would comprise AE costs. To be conservative, AEs that are important for tisagenlecleucel including grade 3/4 CRS and B-cell aplasia were further added. The AE rates for grade 3/4 CRS and B-cell aplasia were obtained from the JULIET trial data for tisagenlecleucel.

CRS is an AE that is specific to treatment with tisagenlecleucel, and could be associated with substantial resource use. CRS event costs were calculated as the sum of the ICU admission cost and tocilizumab drug and administration costs. The utilization data (i.e., days of ICU stay, doses of tocilizumab treatment) were obtained from the JULIET trial. The average daily cost per ICU stay was obtained from the official gazette released by MHLW. The detailed resource use inputs considered in the CRS AE cost estimation were listed in Table 32. The proportion of patients with CRS was estimated to be [redacted]% among patients treated with tisagenlecleucel. The total CRS cost was calculated to be [redacted] for tisagenlecleucel.

In addition to CRS, the model also considered one additional AE specific to the tisagenlecleucel arm: B-cell aplasia. B-cell aplasia is a common condition for patients managed by tisagenlecleucel and IVIG is typically prescribed for patients for symptom management. The model considered [redacted]% patients with tisagenlecleucel infusion would receive IVIG with an average [redacted] dosage based on the JULIET trial. The total IVIG cost was calculated to be ¥[redacted] for <70 years and ¥[redacted] for ≥70 years, based on the proportion of patients receiving IVIG and the average dosage, and was applied as a one-time cost in the model. Table 33 presents the detailed dosing and unit costs for B-cell aplasia.

Table 32. Cost of CRS

Parameter	Daily cost/unit cost per infusion	Duration (days)/# of doses	Total cost per CRS event
ICU admission (if LOS < 8 days)	¥136,500	[redacted] days	¥[redacted]
ICU admission (if LOS ≥ 8 days)	¥121,260		
Tocilizumab treatment	¥146,387	[redacted] doses	¥[redacted]
Tocilizumab administration	¥6,200	[redacted] doses	[redacted]
Total CRS cost per event	[redacted]		
Abbreviations: CRS, cytokine release syndrome; ICU, intensive care unit; LOS, length of stay			

Table 33. Costs of B-cell aplasia

Parameter	Cost per package or vial, package size	Dosing schedule	Total drug cost per month	Total administration cost per month[a]	Source
IVIG package 1	¥77,245, 10,000 mg	400mg/kg every 4 weeks	<70 age: [redacted] =70 age: [redacted]	¥6,200	Compagno et al. 2014 and medical input (dosing schedule), the official gazette released by Ministry of Health, Labour and Welfare (drug cost, administration cost)[47], [65]
IVIG package 2	¥4,687, 500 mg				
Abbreviations: IVIG, intravenous immunoglobulin; mg, milligrams; kg, kilograms a. The model considered 1 infusion per cycle in the calculation of total administration cost per cycle.					

Terminal care costs

All patients who transitioned to death were assumed to incur one-time terminal care costs. The terminal care costs were estimated to be ¥747,787 inflated to 2018 cost and based on Nichiisouken Working Paper No.144 for cancer patients.[52]

Productivity Losses

See Section *4.2.3.1 B-ALL*.

5. 分析結果

5.1 基本分析(費用対効果評価専門組織で決定された分析枠組みによる分析)の結果

2019 年 ■ 月 ▌ 日開催の費用対効果評価専門組織で決定された分析枠組み 4 つすべてに対して、増分費用効果比を算出する費用効果分析を実施した。

【B-ALL：15 歳未満】
・ 実施した分析

■ 費用効果分析（増分費用効果比を算出する）
□ 費用最小化分析（効果は同等として費用を比較する）

【B-ALL：15～25 歳】
・ 実施した分析

■ 費用効果分析（増分費用効果比を算出する）
□ 費用最小化分析（効果は同等として費用を比較する）

【DLBCL：70 歳未満】
・ 実施した分析

■ 費用効果分析（増分費用効果比を算出する）
□ 費用最小化分析（効果は同等として費用を比較する）

【DLBCL：70 歳以上】
・ 実施した分析

■ 費用効果分析（増分費用効果比を算出する）
□ 費用最小化分析（効果は同等として費用を比較する）

5.1.1 基本分析の増分費用、増分効果、増分費用効果比

2019 年 ■ 月 ▌ 日開催の費用対効果評価専門組織で決定された分析枠組み 4 つの基本分析は下記のとおりである。

B-ALL：15 歳未満
・ 分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
評価対象技術	11.11	9.05	¥40,448,386	¥18,882,649	¥2,087,581
比較対照技術	2.07		¥21,565,737		

	効果 (LY)	増分効果 (LY)	費用 (円)	増分費用 (円)	ICER (円/LY)
評価対象技術	12,69	9.95	¥40,448,386	¥18,882,649	¥1,898,514
比較対照技術	2.74		¥21,565,737		

・費用の内訳の詳細

B-ALL：15～25 歳

・分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用（円)	増分費用（円)	ICER (円/QALY)
評価対象技術	11.58		¥40,245,192		
比較対照技術 Blinatumomab	3.01	8.56	¥22,988,924	¥17,256,268	¥2,015,349
比較対照技術 Inotuzumab	2.03	9.55	¥21,196,012	¥19,049,180	¥1,994,592

	効果 (LY)	増分効果 (LY)	費用（円)	増分費用（円)	ICER (円/LY)
評価対象技術	13.62		¥40,245,192		
比較対照技術 Blinatumomab	3.88	9.74	¥22,988,924	¥17,256,268	¥1,772,153
比較対照技術 Inotuzumab	2.63	10.99	¥21,196,012	¥19,049,180	¥1,733,333

[redacted]

DLBCL：70 歳未満

・分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
評価対象技術	5.70	3.23	¥37,362,788	¥17,649,143	¥5,459,234
比較対照技術	2.46		¥19,713,646		

	効果 (LY)	増分効果 (LY)	費用 (円)	増分費用 (円)	ICER (円/LY)
評価対象技術	7.65	3.42	¥37,362,788	¥17,649,143	¥5,167,633
比較対照技術	4.23		¥19,713,646		

・費用の内訳の詳細

[redacted]

DLBCL：70 歳以上

・分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
評価対象技術	3.64	2.47	¥21,450,349	¥12,934,205	¥5,231,584
比較対照技術	1.16		¥8,516,144		

	効果 (LY)	増分効果 (LY)	費用 (円)	増分費用 (円)	ICER (円/LY)
評価対象技術	4.59	2.65	¥21,450,349	¥12,934,205	¥4,887,933
比較対照技術	1.95		¥8,516,144		

・ 費用の内訳の詳細

[redacted]

5.1.2 感度分析

5.1.2.1 DSA: B-ALL

B-ALL の基本分析の limitation は下記のとおりである。

The model presented in this document, while comprehensive, had some limitations. First, because the efficacy and safety data were sourced from single-arm trials of study treatments, there were inherent differences in patient populations across trials. Second, most of the studies used for the efficacy estimation had limited follow-up times. Thirdly, there is no reported efficacy of blinatumomab and inotuzumab in 15-25 years age group. The efficacy of these treatments from a broader age group (age<18 years for blinatumomab and 2-21 years for inotuzumab) were used as proxy for the efficacy in the 15-25 years age group. Finally, detailed hospitalization data was observed for tisagenlecleucel from the ELIANA trial but such information was not available for comparators. Therefore, it is likely the hospitalization duration for the comparator treatments (i.e., blinatumomab and inotuzumab) might not reflect the exact hospitalization duration incurred by patients and underestimate the resource use for the comparators.

B-ALL: age < 15 years

Table 34. DSA inputs – model parameters (age < 15 years)

Parameter	Base-case Input	DSA Input
Efficacy inputs		
HR for comparator vs. tisagenlecleucel	Blinatumomab: [redacted]	95% CI: [redacted]
SMR of long-term ALL survivor	9.05	95% CI: 7.69-10.42
EFS/OS cumulative HR for comparators without EFS input	[redacted]	±10% of base-case
Subsequent SCT		
Subsequent HSCT rate	Tisagenlecleucel (infused	95% CI: [redacted] %-

Parameter	Base-case Input	DSA Input
	patients): [redacted]% Blinatumomab: 30.65%	[redacted]% 95% CI: 19.17%-42.12%
Utility and disutility (upper utility limit capped at 1)		
Utility for PD	0.75	95% CI: 0.44-0.91
Utility for EFS	0.91	95% CI: 0.87-1.00
Treatment disutility	Tisagenlecleucel (infused patients): -0.04 Blinatumomab: -0.02	±10% of base-case
Subsequent HSCT disutility	-0.57	±10% of base-case
Cost		
Pre-treatment cost	Tisagenlecleucel (infused patients): ¥733,204	±25% of base-case
Hospitalization and administration cost for tisagenlecleucel	Tisagenlecleucel (infused patients): [redacted]	±25% of base-case
Treatment cost for comparators	Blinatumomab: ¥12,087,400	±25% of base-case
Follow-up cost	Multiple variables varied	±25% of base-case
Subsequent HSCT cost	[redacted]	±25% of base-case
CRS cost	[redacted]	±25% of base-case
Terminal care cost	¥747,787	±25% of base-case
IVIG dose	[redacted]	95% CI: [redacted]
Patient characteristics		
BSA	[redacted]	95% CI: [redacted]
Discount rate		
Cost and effectiveness	2.0%	0.0% and 4.0%
Abbreviations: AE, adverse events; BSA, body surface area; OS, overall survival; EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; CRS, cytokine release syndrome; PD, progressive disease; CI, confidence interval; ITT, intent-to-treat		

Table 35. DSA inputs – modelling scenarios (age < 15 years)

Parameter	Base-case Input	DSA Input
Utility		
Health state utilities	Based on Kelly et al. 2015[30]	Based on EQ-5D utility from ELIANA[26]
Alternative cost scenarios		
HSCT cost	Consider HSCT procedure cost and follow-up up to 24 months	Consider HSCT procedure cost and follow-up up to 12 months
Maintenance therapy	Do not consider maintenance therapy for comparators	Consider maintenance therapy for comparators
Alternative time horizon scenarios		

Parameter	Base-case Input	DSA Input
Time horizon	[redacted] (lifetime)	[redacted]
Different modelling scenarios		
Efficacy estimation for comparators before year 5	Observed within trial period and ITC-adjusted curves based on tisagenlecleucel after trial period	Observed within trial period and weighted average of parametric estimates based on AIC afterwards; Use ITC-adjusted curves from the beginning
ITC approach to estimate HR between blinatumomab vs. tisagenlecleucel	Use multivariable Cox regression to estimate HR (HR = [redacted])	Use stabilized inverse probability of treatment weighting approach to estimate HR (HR [redacted])
Long-term survival	Use SMR-adjusted survival to estimate OS after year 5	Use SMR-adjusted survival to estimate OS after year 3
Proportion of patients assigned to tisagenlecleucel to receive infusion	[redacted]% based on trial observation	Assume 100% patients assigned to tisagenlecleucel receive infusion
Alternative efficacy input source for tisagenlecleucel (infused patients)	Estimate OS and EFS using pooled trial data[25]–[27]	Estimate OS and EFS using ELIANA trial alone[26]
Vial sharing	Do not consider vial sharing	Consider vial sharing
Productivity gain	Do not consider productivity gain	Consider productivity gain
Abbreviations: OS, overall survival; EFS, event-free survival; ALL, acute lymphoblastic leukemia; SMR, standardized mortality ratio; AIC, Akaike information criterion; HSCT, hematopoietic stem cell transplantation; EQ-5D, EuroQol-5D		

DSA 結果については、下記のとおり、トルネードダイアグラムを示す。

Figure 31. Top 20 DSA ranked by impact on ICER values (age < 15 years)

B-ALL: age 15-25 years

Table 36. DSA inputs – model parameters (age 15-25 years)

Parameter	Base-case Input	DSA Input
Efficacy inputs		
HR for comparator vs. tisagenlecleucel	HR for Blinatumomab OS: [redacted] HR for Inotuzumab OS: [redacted] HR for Inotuzumab EFS: [redacted]	95% CI: [redacted] 95% CI: [redacted] 95% CI: [redacted]
SMR of long-term ALL survivor	9.05	95% CI: 7.69-10.42
EFS/OS cumulative HR for comparators without EFS input	Blinatumomab: [redacted]	±10% of base-case
Subsequent SCT		
Subsequent HSCT rate	Tisagenlecleucel (infused patients): [redacted]% Blinatumomab: 35.7% Inotuzumab: 41.2%	95% CI: [redacted] 95% CI: 24.5%-46.9% 95% CI: 27.7%-54.7%
Utility and disutility (upper utility limit capped at 1)		
Utility for PD	0.75	95% CI: 0.44-0.91
Utility for EFS	0.91	95% CI: 0.87-1.00
Treatment disutility	Tisagenlecleucel (infused patients): -0.04 Blinatumomab: -0.02	±10% of base-case

Parameter	Base-case Input	DSA Input
	Inotuzumab: -0.03	
Subsequent HSCT disutility	-0.57	±10% of base-case
Cost		
Pre-treatment cost	Tisagenlecleucel (infused patients): ¥[redacted]	±25% of base-case
Hospitalization and administration cost for tisagenlecleucel	Tisagenlecleucel (infused patients): [redacted]	±25% of base-case
Treatment cost for comparators	Blinatumomab: ¥12,087,400 Inotuzumab: ¥8,883,665	±25% of base-case
Follow-up cost	Multiple variables varied	±25% of base-case
Subsequent HSCT cost	¥[redacted]	±25% of base-case
CRS cost	[redacted]	±25% of base-case
Terminal care cost	¥747,787	±25% of base-case
IVIG dose	[redacted]	95% CI: [redacted]
Patient characteristics		
BSA	[redacted]	95% CI: [redacted]
Discount rate		
Cost and effectiveness	2.0%	0.0% and 4.0%
Abbreviations: AE, adverse events; BSA, body surface area; OS, overall survival; EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; CRS, cytokine release syndrome; PD, progressive disease; CI, confidence interval; ITT, intent-to-treat		

Table 37. DSA inputs – model scenarios (age 15-25 years)

Parameter	Base-case Input	DSA Input
Utility		
Health state utilities	Based on Kelly et al. 2015[30]	Based on EQ-5D utility from ELIANA[26]
Alternative cost scenarios		
HSCT cost	Consider HSCT procedure cost and follow-up up to 24 months	Consider HSCT procedure cost and follow-up up to 12 months
Maintenance therapy	Do not consider maintenance therapy	Consider maintenance therapy for comparators
Alternative time horizon scenarios		
Time horizon	[redacted] (lifetime)	[redacted]
Different modelling scenarios		
OS and EFS estimation for tisagenlecleucel after observed and before year 5	Weighted using AIC	Best fitting parametric function

Parameter	Base-case Input	DSA Input
Efficacy estimation for comparators before year 5	Observed within trial period and ITC-adjusted curves based on tisagenlecleucel after trial period	Observed within trial period and weighted average of parametric estimates based on AIC afterwards; Use ITC-adjusted curves from the beginning
ITC approach to estimate HR between blinatumomab vs. tisagenlecleucel	Use multivariable Cox regression to estimate HR (HR = [redacted])	Use stabilized inverse probability of treatment weighting approach to estimate HR (HR = [redacted])
Long-term survival	Use SMR-adjusted survival to estimate OS after year 5	Use SMR-adjusted survival to estimate OS after year 3
Proportion of patients assigned to tisagenlecleucel to receive infusion	[redacted]% based on trial observation	Assume 100% patients assigned to tisagenlecleucel receive infusion
Alternative efficacy input source for tisagenlecleucel (infused patients)	Estimate OS and EFS using pooled trial data[25]–[27]	Estimate OS and EFS using ELIANA trial alone[26]
Vial sharing	Do not consider vial sharing	Consider vial sharing
Productivity gain	Do not consider productivity gain	Consider productivity gain
Abbreviations: OS, overall survival; EFS, event-free survival; ALL, acute lymphoblastic leukemia; SMR, standardized mortality ratio; AIC, Akaike information criterion; HSCT, hematopoietic stem cell transplantation; EQ-5D, EuroQol-5D		

DSA 結果については、下記のとおり、トルネードダイアグラムを示す。

Figure 32. Top 20 DSA results ranked by impact on ICER values (tisagenlecleucel vs. blinatumomab, age 15-25 years)

Figure 33. Top 20 DSA results ranked by impact on ICER values (tisagenlecleucel vs. inotuzumab, age 15-25 years)

以上より、仮定に基づき設定したパラメータに関しては DSA を実施した場合に ICER が閾値で設定されている 750 万を超えることはなかった。

5.1.2.2 DSA: DLBCL

DLBCL の基本分析の limitation は下記のとおりである。

This CEA was subject to a few limitations, some of which are characteristic of economic modelling studies. First, because the efficacy and safety data were sourced from single-arm trials of study treatments, there were inherent differences in patient populations across trials. To the extent feasible, clinical trial publications with similar inclusion or exclusion criteria as the JULIET tisagenlecleucel trial were chosen to inform the efficacy of salvage chemotherapy. However, differences still exist. For example, for salvage chemotherapy, inputs were based on DLBCL patients that either failed an auto SCT or failed 2 prior regimens. The JULIET trial enrolled r/r DLBCL patients who failed or were not eligible for auto SCT and failed an average of 3 regimens.

Second, the clinical trial data used for the efficacy estimation for tisagenlecleucel had limited follow-up. To mitigate the longer-term uncertainties from the extrapolation of data, the model assumed that all patients who remained alive from year 3 onward would experience a mortality risk profile similar to that of a long-term survivor of DLBCL. The long-term survival was estimated using an SMR approach. Due to limited data, the identified SMR study reported the SMR of patients who are progression free at 24 months following initial diagnosis.Patients evaluated in this publication had newly diagnosed DLBCL and the impact of management after relapse were not assessed, therefore they may have been healthier than 3-year survivors considered in the model. To address this uncertainty, extensive sensitivity analyses were performed to vary the time point to introduce the long-term DLBCL survivor mortalities. The model results were not sensitive to these inputs.

Third, the OS definition was different in JULIET vs. CORAL extension studies. JULIET trial evaluated OS from time of infusions, whereas CORAL extension studies evaluated OS survival from time of last relapse and before the initiation of 3rd-line treatment. This might create a bias against tisagenlecleucel given there might be a gap between relapse from 2nd-line treatment to the initiation of 3rd-line therapy and the CORAL extension studies might overestimate the survival of salvage chemotherapy in target population.

Lastly, despite the best efforts to select the most accurate model inputs based on the existing literature, different data sources were used to describe resource utilization for each treatment arm. Detailed hospitalization data were observed for tisagenlecleucel from the JULIET trial, where such information was not available for salvage chemotherapy. Therefore, it is likely that the hospitalization duration for the salvage chemotherapy might not reflect the exact hospitalization duration incurred by patients treated with salvage chemotherapy. However, these inputs represented the best available sources, and the impact of these inputs on the model's results were extensively tested in the DSA and PSA. The results from the DSA and PSA generally supported the robustness of the model's results.

DLBCL: age < 70 years
Table 38. DSA inputs – model parameters (age <70 years)

Parameter	Base-case Input	DSA Input
Efficacy inputs		
PFS/OS cumulative HR for salvage chemotherapy	[redacted]	±10% of base-case
SMR of long term survivors	1.09	95% CI: 0.69-1.74
Subsequent SCT		
Subsequent SCT rate for tisagenlecleucel (infused patients)	Allo SCT rate: [redacted]% Auto SCT rate: [redacted]%	Allo SCT rate 95% CI: [redacted]% Auto SCT rate 95% CI: [redacted]%
Subsequent SCT rate for salvage chemotherapy	Allo SCT rate: 7.55% Auto SCT rate: 21.22%	±25% of base-case
Cost		
Pre-treatment cost	Tisagenlecleucel (infused patients): [redacted]	±25% of base-case
Hospitalization and administration cost for tisagenlecleucel	Tisagenlecleucel (infused patients): ¥[redacted]	±25% of base-case
Treatment cost for comparators	Salvage chemotherapy: ¥1,665,809	±25% of base-case
CRS cost for tisagenlecleucel (infused patients)	[redacted]	±25% of base-case
IVIG dose for tisagenlecleucel (infused patients)	[redacted]	95% CI: [redacted]
Pre-progression cost	Tisagenlecleucel (infused patients): [redacted] Salvage chemotherapy: [redacted]	±25% of base-case
Post-progression cost	[redacted]	±25% of base-case
Terminal care cost	¥747,787	±25% of base-case
Subsequent allo SCT cost	[redacted]	±25% of base-case
Subsequent auto SCT cost	[redacted]	±25% of base-case
Utility and disutility (upper utility limit capped at 1)		
Utility for PFS	0.83	±10% of base-case
Utility for PD	0.39	±10% of base-case

Treatment disutility	Tisagenlecleucel (infused patients): -0.02 Salvage chemotherapy: -0.01	±10% of base-case
Subsequent SCT disutility	-0.30	±10% of base-case
Patient characteristics		
BSA	[redacted]	95% CI: [redacted]
Discount rate		
Cost and effectiveness	2.0%	0% and 4.0%
Abbreviations: AE, adverse events; BSA, body surface area; DSA, deterministic sensitivity analysis; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; allo SCT, allogeneic stem cell transplantation; auto SCT, autologous stem cell transplantation; CRS, cytokine release syndrome; PD, progressive disease; HR, hazard ratio; CI, confidence interval.		

Table 39. DSA inputs – model scenarios (age <70 years)

Parameter	Base-case Input	DSA Input
Utility		
Health state utilities	Based on Chen et al. 2017[33]	Based on EQ-5D from JULIET trial data[29]
Alternative cost scenarios		
Salvage chemotherapy cost	Consider the weighted average cost of five common regimens: (R)-ICE, (R)-GDP, (R)-ESHAP, (R)-DHAP, and (R)-EPOCH	Consider the cost based on (R)-GDP (cheapest)
Salvage chemotherapy cost	Consider the weighted average cost of five common regimens: (R)-ICE, (R)-GDP, (R)-ESHAP, (R)-DHAP, and (R)-EPOCH	Consider the cost based on (R)-DHAP (most expensive)
Salvage chemotherapy costs	Do not consider radiotherapy cost	Consider radiotherapy cost
Alternative time horizon scenarios		
Time horizon	[redacted]	[redacted]
Different modelling scenarios		
Model starting age	[redacted] based on JULIET trial data	[redacted]
Proportion of patients assigned to tisagenlecleucel	[redacted] % based on trial observation	Assume 100% patients assigned to tisagenlecleucel receive infusion

Parameter	Base-case Input	DSA Input
receive infusion		
Long-term survival and model extrapolation	Use SMR-adjusted survival to estimate OS after year 3	Use SMR-adjusted survival to estimate OS after year 5 and parametric function approach for OS extrapolation after trial period and before year 5; Use SMR-adjusted survival to estimate OS after year 5 and MAIC approach for OS extrapolation after trial period and before year 5;
		Use SMR-adjusted survival to estimate OS after year 4 and MAIC approach for OS extrapolation after trial period and before year 4; Use SMR-adjusted survival to estimate OS after year 4 and parametric function approach for OS extrapolation after trial period and before year 4;
Efficacy estimation for tisagenlecleucel (infused patients) before year 3	Estimate OS using observed JULIET trial data before year 3[29]	Use MAIC-adjusted curve from the beginning to estimate tisagenlecleucel efficacy using salvage chemotherapy as the reference arm. The MAIC was conducted to compare tisagenlecleucel with salvage chemotherapy, adjusting for differences in baseline characteristics between studies
Alternative OS input source for salvage chemotherapy	CORAL extension studies[11], [12]	Overall patient population from SCHOLAR-1 study[5] The subgroup of SCHOLAR-1 patient population excluding patients who are primary refractory and with ECOG performance status>1, which was deemed to be more similar to the JULIET populations
Subsequent SCT rate for salvage chemotherapy	Subsequent allo SCT: [redacted] Subsequent auto SCT: [redacted]	Consider 20% subsequent SCT rate for salvage chemotherapy and re-estimate the efficacy using

Parameter	Base-case Input	DSA Input
		survival curves stratified by SCT status and specified SCT rate. Cost and disutility is re-estimated based on the specified SCT rate
Vial sharing	Do not consider vial sharing	Consider vial sharing
Productivity gain	Do not consider productivity gain	Consider productivity gain
Abbreviations: AE, adverse events; allo SCT, allogeneic stem cell transplantation; auto SCT, autologous stem cell transplantation; DSA, deterministic sensitivity analysis; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio; SCT, stem cell transplantation; CRS, cytokine release syndrome; PD/RL, progressive/relapsed disease; AIC, Akaike information criterion; MAIC, matching adjusted indirect comparison.		

DSA 結果については、下記のとおり、トルネードダイアグラムを示す。

Figure 34. Top 20 DSA results ranked by impact on ICER values (age <70 years)

DLBCL: age >= 70 years
Table 40. DSA inputs – model parameters (age >=70 years)

Parameter	Base-case Input	DSA Input
Efficacy inputs		
PFS/OS cumulative HR for salvage chemotherapy	[redacted]	±10% of base-case
SMR of long term survivors	1.09	95% CI: 0.69-1.74
Cost		
Pre-treatment cost	Tisagenlecleucel (infused patients): ¥[redacted]	±25% of base-case
Hospitalization and administration cost for tisagenlecleucel	Tisagenlecleucel (infused patients): [redacted]	±25% of base-case
Treatment cost for comparators	Salvage chemotherapy: ¥1,663,111	±25% of base-case
CRS cost for tisagenlecleucel (infused patients)	[redacted]	±25% of base-case
IVIG dose for tisagenlecleucel (infused patients)	[redacted]	95% CI: [redacted]
Pre-progression cost	Tisagenlecleucel (infused patients): ¥[redacted] Salvage chemotherapy: ¥5,496	±25% of base-case
Post-progression cost	¥525,220	±25% of base-case
Terminal care cost	¥747,787	±25% of base-case
Utility and disutility (upper utility limit capped at 1)		
Utility for PFS	0.83	±10% of base-case
Utility for PD	0.39	±10% of base-case
Treatment disutility	Tisagenlecleucel (infused patients): -0.02 Salvage chemotherapy: -0.01	±10% of base-case
Patient characteristics		
BSA	[redacted]	95% CI: [redacted]
Discount rate		
Cost and effectiveness	2.0%	0% and 4.0%
Abbreviations: AE, adverse events; BSA, body surface area; DSA, deterministic sensitivity analysis; OS, overall survival; PFS, progression-free survival; CRS, cytokine release syndrome; PD, progressive disease; HR,		

hazard ratio; CI, confidence interval.

Table 41. DSA inputs – model scenarios (age >=70 years)

Parameter	Base-case Input	DSA Input
Utility		
Health state utilities	Based on Chen et al. 2017[33]	Based on EQ-5D from JULIET trial data[29]
Alternative cost scenarios		
Salvage chemotherapy cost	Consider the weighted average cost of five common regimens: (R)-ICE, (R)-GDP, (R)-ESHAP, (R)-DHAP, and (R)-EPOCH	Consider the cost based on (R)-GDP (cheapest)
Salvage chemotherapy cost	Consider the weighted average cost of five common regimens: (R)-ICE, (R)-GDP, (R)-ESHAP, (R)-DHAP, and (R)-EPOCH	Consider the cost based on (R)-DHAP (most expensive)
Salvage chemotherapy costs	Do not consider radiotherapy cost	Consider radiotherapy cost
Alternative time horizon scenarios		
Time horizon	[redacted]	[redacted]
Different modelling scenarios		
Model starting age	[redacted] based on JULIET trial data	70 based on suggestion from C2H at a meeitng on [redacted]
Proportion of patients assigned to tisagenlecleucel receive infusion	[redacted] % based on trial observation	Assume 100% patients assigned to tisagenlecleucel receive infusion
Long-term survival and model extrapolation	Use SMR-adjusted survival to estimate OS after year 3	Use SMR-adjusted survival to estimate OS after year 5 and parametric function approach for OS extrapolation after trial period and before year 5; Use SMR-adjusted survival to estimate OS after year 4 and parametric function approach for OS extrapolation after trial period and before year 4;
Alternative OS input	CORAL extension	Overall patient population

Parameter	Base-case Input	DSA Input
source for salvage chemotherapy	studies[11], [12]	from SCHOLAR-1 study[13] The subgroup of SCHOLAR-1 patient population excluding patients who are primary refractory and with ECOG performance status>1, which was deemed to be more similar to the JULIET populations
Vial sharing	Do not consider vial sharing	Consider vial sharing
Abbreviations: AE, adverse events; DSA, deterministic sensitivity analysis; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio; CRS, cytokine release syndrome; PD/RL, progressive/relapsed disease; AIC, Akaike information criterion.		

DSA 結果については、下記のとおり、トルネードダイアグラムを示す。

Figure 35. Top 20 DSA results ranked by impact on ICER values (age >=70 years)

以上より、仮定に基づき設定したパラメータに関しては DSA を実施した場合に、多くの場合で ICER は閾値で設定されている 750 万以下であった。。

5.1.2.3 PSA: B-ALL

B-ALL: 15 歳未満

Probabilistic sensitivity analysis (PSA) was conducted to estimate the probability for tisagenlecleucel to be cost-effective compared to blinatumomab, based on different thresholds. A Monte-Carlo simulation with 5,000 iterations was

conducted. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarized in Table 42. The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original IPD or proxy IPD data used for OS and EFS estimation in the base-case. For each PSA iteration, all 10 parametric functions and their associated AIC values for each arm were estimated based on one bootstrapped sample, and were weighted using AIC to form the weighted average.
Whenever available, the standard error (SE) of the model input was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the SE for each cost parameter was assumed to be equal to the mean value divided by ten for efficacy and utility parameters and mean value divided by four for cost parameters.
In the PSA, the threshold of ¥7,500,000 per QALY gained was used as it is a commonly referenced the threshold for CEE evaluation in Japan.[66] Compared with blinatumomab, the probability of tisagenlecleucel being cost-effective at the specified threshold of ¥7,500,000 per QALY gained was 100%. The average probabilistic ICER for this comparison was ¥2,125,514 per QALY gained.

Table 42. PSA inputs

Parameter	Description
Parametric survival functions	The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original patient-level data or proxy patient-level data used for OS and EFS estimation in the base-case. For each PSA iteration, all ten parametric functions and their associated AIC values for each treatment arm were estimated based on one bootstrapped sample and are weighted using AIC to form the weighted average to be used in the model.
OS for tisagenlecleucel	
EFS for tisagenlecleucel	
Hazard ratios for tisagenlecleucel vs. comparator	Hazard ratio is modelled using lognormal distribution with the mean value as specified in the base-case model. Standard error (SE) was obtained from ITC analyses.
Utility for health states	Utilities were modelled using beta distributions with the mean values as specified in the base-case model and SEs based on the same source for the base-case input. It was assumed that the utility of PD health state should not exceed the utility of the EFS health state and vice versa.
EFS	
PD	
Treatment disutility	Treatment disutilities for each comparator were modelled using beta distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/10 of mean.
Treatment disutility for each treatment	
Additional AE disutility for tisagenlecleucel and blinatumomab	
Subsequent HSCT	Subsequent HSCT rates and disutility were modelled using beta distributions with the mean values as specified in the base-case model. SEs
Subsequent HSCT rate of each treatment	

Parameter	Description
Subsequent HSCT cost	of subsequent SCT rates were based on the same source for the base-case input. SE of subsequent SCT disutility was assumed to be 1/10 of mean. Subsequent HSCT costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Subsequent HSCT disutility	
Pre-treatment costs	Pre-treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug and administration and hospitalization costs for lymphodepleting, leukapheresis, and bridging chemotherapy	
Treatment costs	Treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug cost for all comparators	
Hospitalization and outpatient administration cost for all treatments	
Follow-up and other medical costs	Follow-up costs associated with each health state and terminal care costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
EFS follow-up cost	
PD follow-up cost	
Terminal care cost	
AE cost	AE costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Patient characteristics	Age, weight and BSA were modelled using normal distributions with the mean values as specified in the base-case model. SEs were obtained from the pooled data from three trials (ELIANA, ENSIGN, and B2101J). Gender was modelled using a beta distribution with the mean value as specified in the base-case model and SE based on the same source for the base-case input.
Age	
Weight	
BSA	
Gender	
Tisagenlecleucel infusion rate	Tisagenlecleucel infusion rate was modelled using beta distributions with the mean values as specified in the base-case model. SE was obtained from the pooled data from three trials (ELIANA, ENSIGN, and B2101J).
SMR for long-term ALL survivors	SMR was modelled using lognormal distribution with the mean value as specified in the base-case model. SEs were obtained from the same literature used for the base-case input.
Abbreviations: AE, adverse event; HSCT, hematopoietic stem cell transplantation; BSA, body surface area; PD, progressive disease; SMR, standardized mortality ratio; ALL, acute lymphoblastic leukemia; SE, standard	

Parameter	Description
error; OS, overall survival; EFS, event-free survival; PSA, probabilistic sensitivity analysis	

Table 43. PSA results for tisagenlecleucel vs. blinatumomab (age < 15 years)

	Average	Median
Incremental cost	¥18,930,135	¥19,078,680
Incremental QALY	8.91	9.01
Probabilistic ICER	¥2,125,514	
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio		

Figure 36. Cost-effectiveness acceptability curve: tisagenlecleucel vs. blinatumomab (age < 15 years)

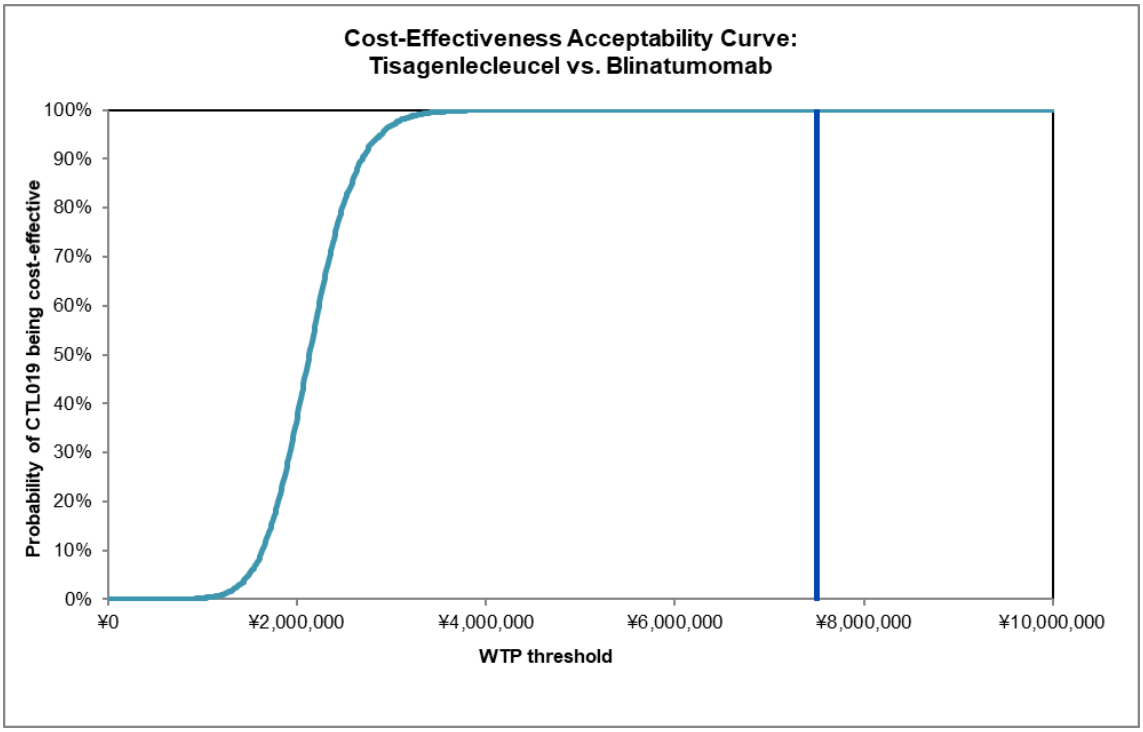
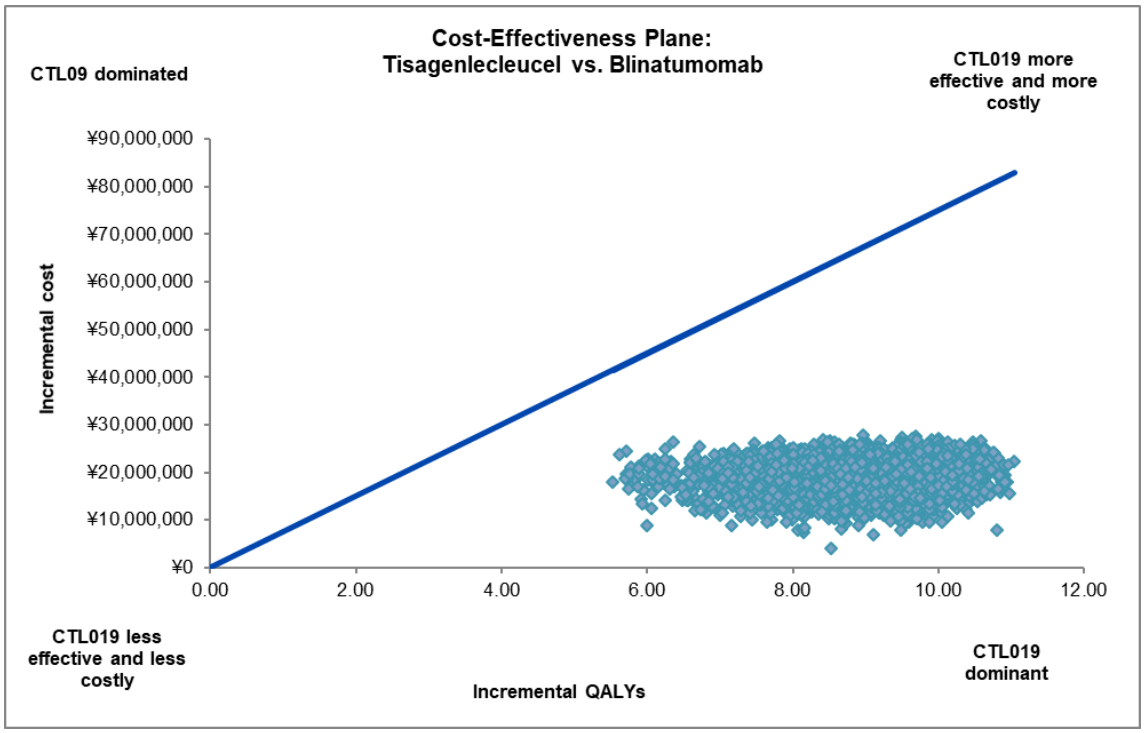


Figure 37. Cost-effectiveness plane: tisagenlecleucel vs. blinatumomab (age < 15 years)



B-ALL：15～25 歳

Probabilistic sensitivity analysis (PSA) was conducted to estimate the probability for tisagenlecleucel to be cost-effective compared to comparator treatments, based on different thresholds. A Monte-Carlo simulation with 5,000 iterations was conducted. Detailed information regarding PSA inputs are described in Table 42. The PSA results are presented in Table 44, Figure 38, Figure 39, Figure 40, and Figure 41. Compared with blinatumomab, the probability of tisagenlecleucel being cost-effective at the specified threshold of ¥7,500,000 per QALY gained was 100.0%. The average probabilistic ICER for this comparison was ¥2,122,818 per QALY gained. Compared with inotuzumab, the probability of tisagenlecleucel being cost-effective at the specified threshold of ¥7,500,000 per QALY gained was 100.0%, and the average probabilistic ICER for this comparison was ¥2,084,237 per QALY gained.

Table 44. PSA results for tisagenlecleucel vs. comparator treatments (age 15-25 years)

	Average	Median
Tisagenlecleucel vs. blinatumomab		
Incremental cost	¥17,334,847	¥17,447,077
Incremental QALY	8.17	8.18
Probabilistic ICER	¥2,122,818	
Tisagenlecleucel vs. inotuzumab		
Incremental cost	¥19,038,834	¥19,278,346
Incremental QALY	9.13	9.21

Probabilistic ICER	¥2,084,237	
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio		

Figure 38. Cost-effectiveness acceptability curve: tisagenlecleucel vs. blinatumomab (age 15-25 years)

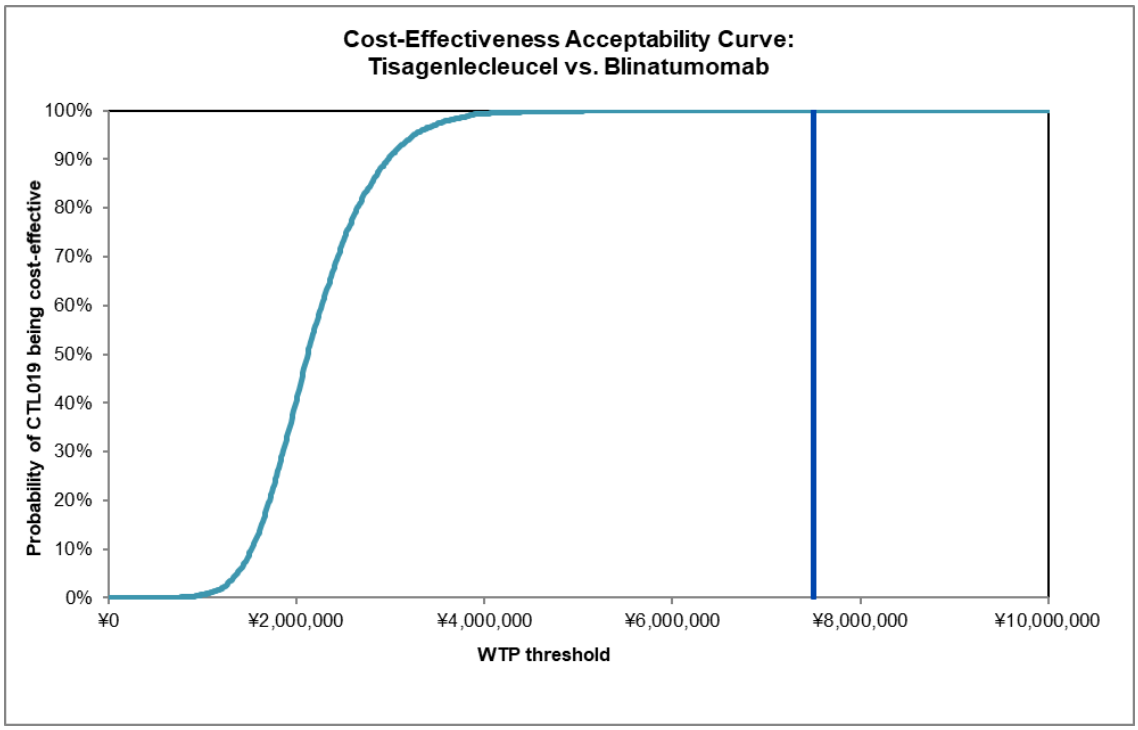


Figure 39. Cost-effectiveness plane: tisagenlecleucel vs. blinatumomab (age 15-25 years)

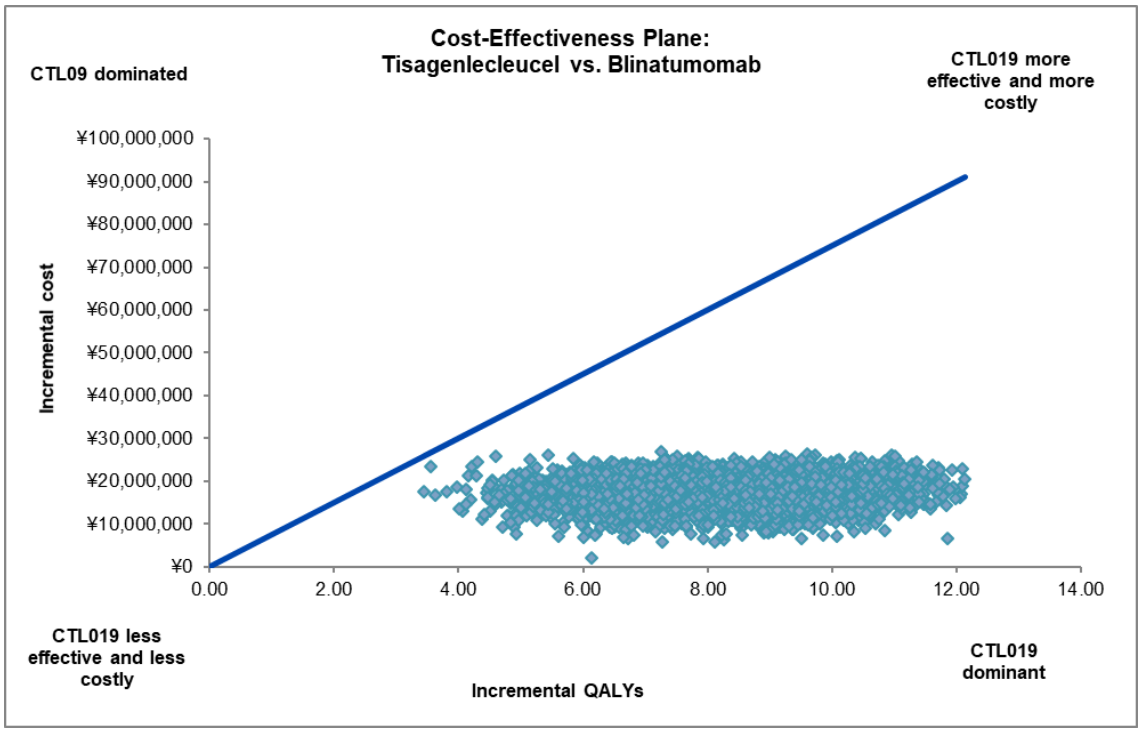


Figure 40. Cost-effectiveness acceptability curve: tisagenlecleucel vs. inotuzumab (age 15-25 years)

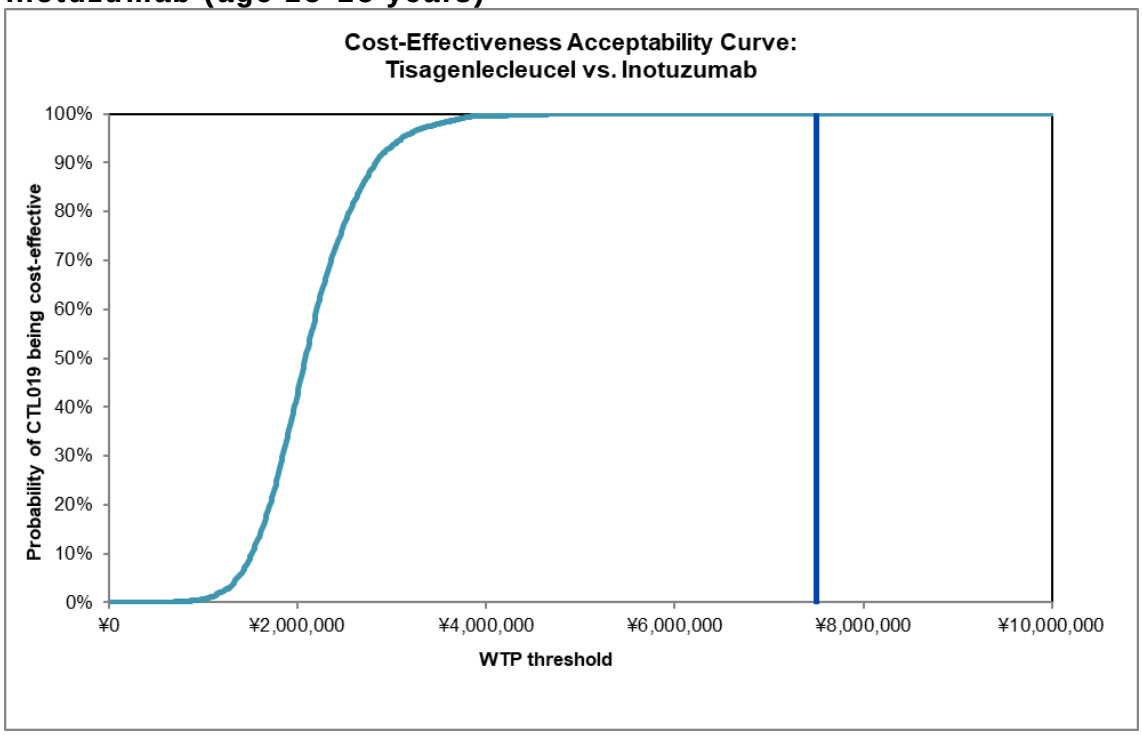
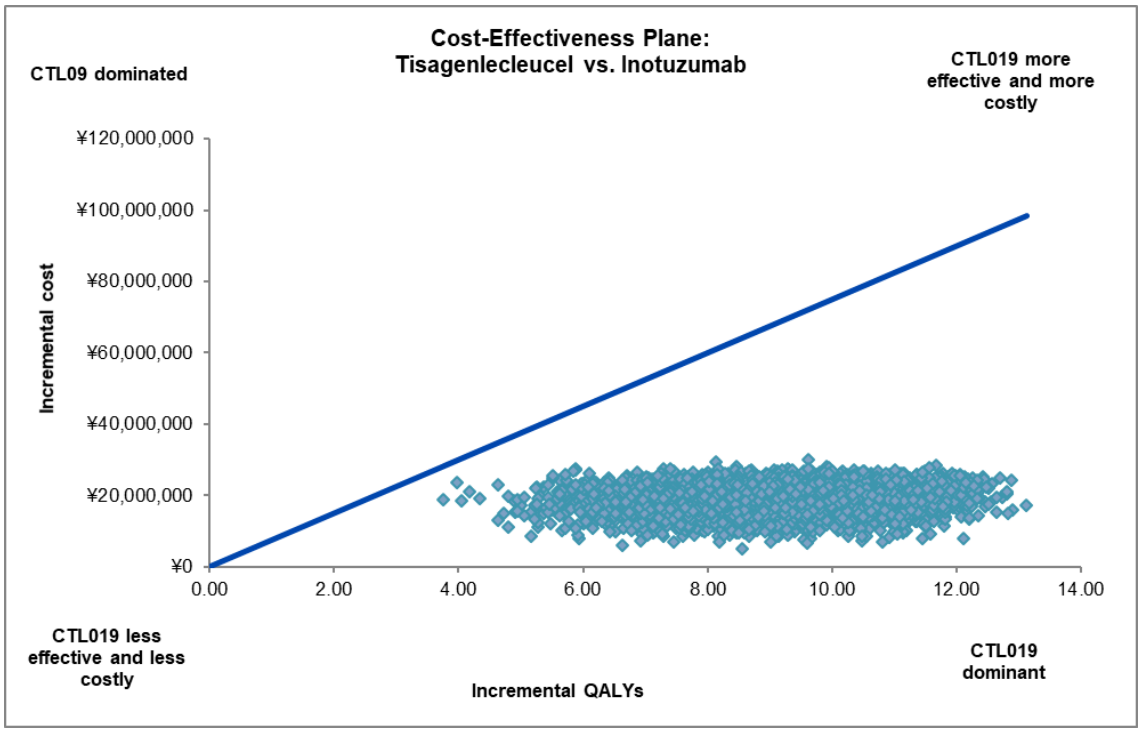


Figure 41. Cost-effectiveness plane: tisagenlecleucel vs. inotuzumab (age 15-25 years)



5.1.2.4 PSA: DLBCL

DLBCL：70 歲未滿

PSA was conducted to estimate the probability for tisagenlecleucel to be cost-effective compared to comparator treatments, based on different thresholds. A Monte-Carlo simulation with 5,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarized in Table 44. The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original IPD or proxy IPD data used for OS and PFS estimation in PSA. For each PSA iteration, all 10 parametric functions and their associated Akaike information criterion (AIC) values for each arm were estimated based on one bootstrapped sample, and were weighted using AIC to form the weighted average.

Whenever available, the stand error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost and efficacy parameter was assumed to be equal to the mean value divided by four and ten, respectively.

Thethreshold was specified at ¥7,500,000 per QALY because, in addition to the disease rarity of r/r DLBCL, tisagenlecleucel is an innovative therapy that brings significant survival and quality of life benefit for terminally ill patients without good alternative options.

The PSA results are presented in Table 45, Figure 42 and Figure 43. Compared with salvage chemotherapy, the probability of tisagenlecleucel being cost-effective for patients aged < 70 years at the specified threshold of ¥7,500,000 per QALY gained was 97.6%. The average probabilistic ICER for this comparison was ¥5,478,296 per QALY gained.

Table 45. PSA inputs

Parameter	Description
Parametric survival functions	The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original patient-level data used for OS and PFS estimation if parametric estimations are selected in the base-case. For each PSA iteration, all ten parametric functions and their associated AIC values for each treatment arm were estimated based on one bootstrapped sample and are weighted using AIC to form the weighted average to be used in the model.
OS for all treatments	
PFS for all treatments	
Pre-treatment costs	Pre-treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug and administration costs for lymphodepleting, leukapheresis, and bridging chemotherapy	
Treatment costs	Treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug cost for all comparators	
Hospitalization and outpatient administration cost for all treatments	
Utility for health states	Utilities were modelled using beta distributions with the mean values as specified in the base-case model and SEs were assumed to be 1/10 of mean. It is assumed that the utility of progressive disease health state should not exceed the utility of the progression-free survival health state.
PFS	
PD	
Treatment disutility	Treatment disutilities for each comparator were modelled using beta distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/10 of mean.
Treatment disutility for each comparator	
Additional AE disutility for tisagenlecleucel	
Follow-up and other medical costs	Follow-up costs associated with each health states and other medical costs are modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Follow-up cost during PFS	
Post-progression follow-up cost	
Terminal care cost	
Patient characteristics	Age, weight and BSA were modelled using normal distributions with the mean values as specified in the base-case model. SEs were obtained from the JULIET trial.[2] Gender was modelled using a beta distribution with the mean value as specified in the base-case model and SE based on the same source for the base-case input.
Age	
Weight	
BSA	
Gender	
Subsequent SCT	Subsequent SCT rates and disutility were modelled

Parameter	Description
Subsequent SCT rate of each comparator	using beta distributions with the mean values as specified in the base-case model; SEs were based on the same source for base-case input where available, and assumed to be 1/4 of mean where not available. Subsequent SCT costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Subsequent SCT cost	
Subsequent SCT disutility	
AE cost	AE costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Tisagenlecleucel infusion rate	Tisagenlecleucel infusion rate was modelled using beta distributions with the mean values as specified in the base-case model. SE was obtained from the JULIET trial.
SMR for long-term DLBCL survivors	SMR was modelled using a lognormal distribution with the mean value as specified in the base-case model. SEs were assumed to be 1/10 of mean.
Abbreviations: AE, adverse event; SCT, stem cell transplantation; auto SCT, autologous stem cell transplantation; BSA, body surface area; DLBCL, diffuse large B-cell lymphoma; PD/RL, progressive/relapsed disease; SE, standard error; AIC, Akaike information criterion; OS, overall survival; PFS, progression-free survival; PD, progressed disease; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PSA, probabilistic sensitivity analysis; SMR, standardized mortality ratio	

Table 46. PSA results for tisagenlecleucel vs. salvage chemotherapy

	Average	Median
Incremental cost	¥17,673,612	¥17,687,621
Incremental QALY	3.23	3.25
Probabilistic ICER	¥5,478,296	
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis		

Figure 42. Cost-effectiveness acceptability curve: tisagenlecleucel vs. salvage chemotherapy

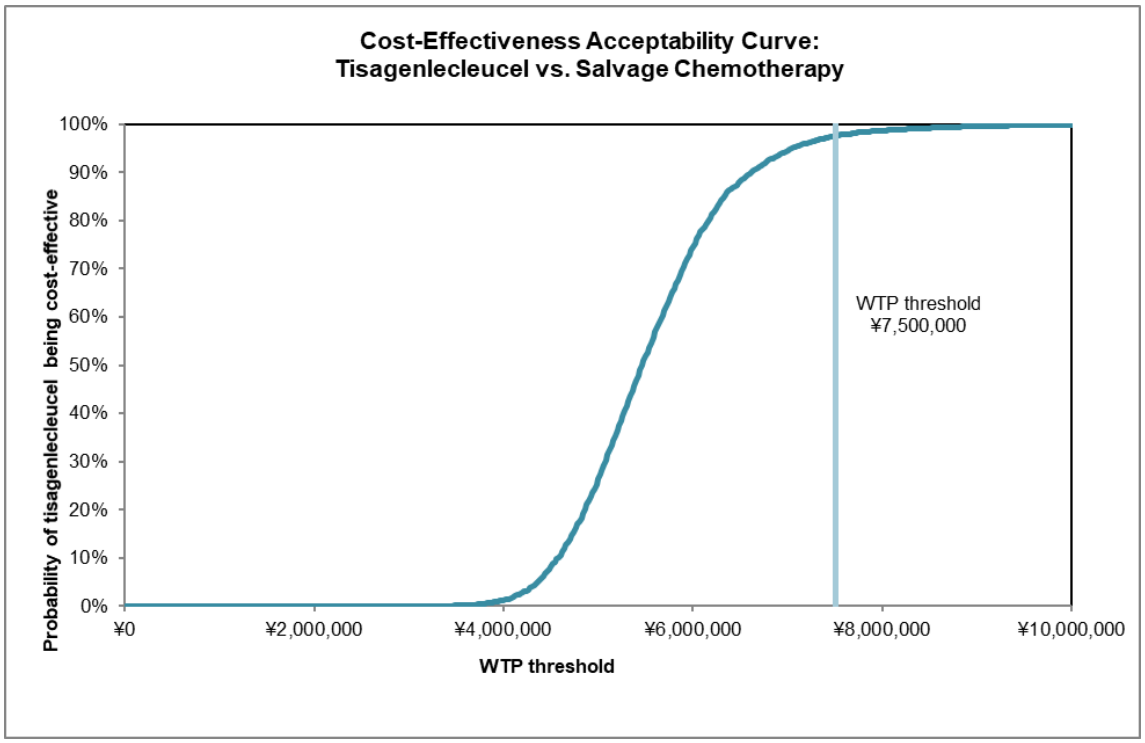
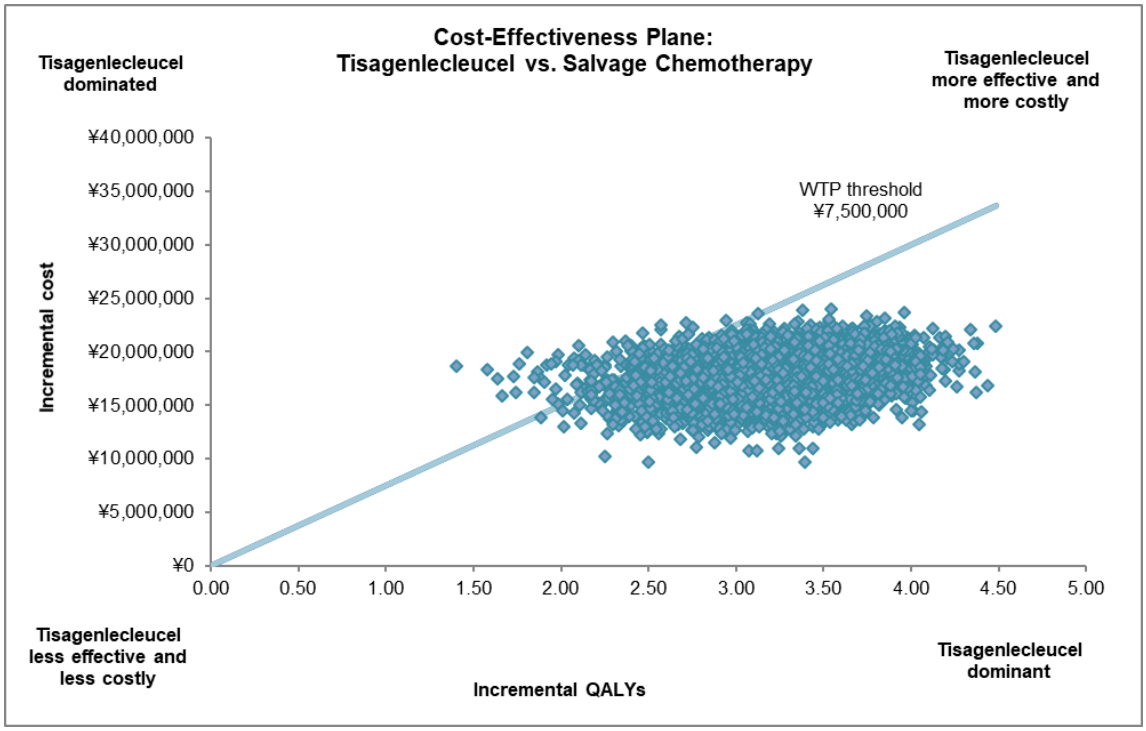


Figure 43. Cost-effectiveness plane: tisagenlecleucel vs. salvage chemotherapy



DLBCL：70 歲以上

PSA was conducted to estimate the probability for tisagenlecleucel to be cost-effective compared to comparator treatments, based on different thresholds. A Monte-Carlo simulation with 5,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarized in Table 47. The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original IPD or proxy IPD data used for OS and PFS estimation in PSA. For each PSA iteration, all 10 parametric functions and their associated Akaike information criterion (AIC) values for each arm were estimated based on one bootstrapped sample, and were weighted using AIC to form the weighted average.

Whenever available, the stand error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost and efficacy parameter was assumed to be equal to the mean value divided by four and ten, respectively.

The threshold was specified at ¥7,500,000 per QALY because, in addition to the disease rarity of r/r DLBCL, tisagenlecleucel is an innovative therapy that brings significant survival and quality of life benefit for terminally ill patients without good alternative options.

The PSA results are presented in Table 48, Figure 44 and Figure 45. Compared with salvage chemotherapy, the probabilities of tisagenlecleucel being cost-effective for patients aged ≥70 years at the specified threshold of ¥7,500,000 per QALY gained was 98.0%. The average probabilistic ICER for this comparison was ¥5,300,340 per QALY gained.

Table 47. PSA inputs

Parameter	Description
Parametric survival functions	The efficacy inputs were modelled using parametric estimates of bootstrapped samples of the original patient-level data used for OS and PFS estimation if parametric estimations are selected in the base-case. For each PSA iteration, all ten parametric functions and their associated AIC values for each treatment arm were estimated based on one bootstrapped sample and are weighted using AIC to form the weighted average to be used in the model.
OS for all treatments	
PFS for all treatments	
Pre-treatment costs	Pre-treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug and administration costs for lymphodepleting, leukapheresis, and bridging chemotherapy	
Treatment costs	Treatment costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Drug cost for all comparators	
Hospitalization and outpatient administration cost for all treatments	

Parameter	Description
Utility for health states	Utilities were modelled using beta distributions with the mean values as specified in the base-case model and SEs were assumed to be 1/10 of mean. It is assumed that the utility of progressive disease health state should not exceed the utility of the progression-free survival health state.
PFS	
PD	
Treatment disutility	Treatment disutilities for each comparator were modelled using beta distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/10 of mean.
Treatment disutility for each comparator	
Additional AE disutility for tisagenlecleucel	
Follow-up and other medical costs	Follow-up costs associated with each health states and other medical costs are modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Follow-up cost during PFS	
Post-progression follow-up cost	
Terminal care cost	
Patient characteristics	Age, weight and BSA were modelled using normal distributions with the mean values as specified in the base-case model. SEs were obtained from the JULIET trial.[2] Gender was modelled using a beta distribution with the mean value as specified in the base-case model and SE based on the same source for the base-case input.
Age	
Weight	
BSA	
Gender	
AE cost	AE costs were modelled using gamma distributions with the mean values as specified in the base-case model. SEs were assumed to be 1/4 of mean.
Tisagenlecleucel infusion rate	Tisagenlecleucel infusion rate was modelled using beta distributions with the mean values as specified in the base-case model. SE was obtained from the JULIET trial.
SMR for long-term DLBCL survivors	SMR was modelled using a lognormal distribution with the mean value as specified in the base-case model. SEs were assumed to be 1/10 of mean.
Abbreviations: AE, adverse event; BSA, body surface area; DLBCL, diffuse large B-cell lymphoma; PD/RL, progressive/relapsed disease; SE, standard error; AIC, Akaike information criterion; OS, overall survival; PFS, progression-free survival; PD, progressed disease; HR, hazard ratio; PSA, probabilistic sensitivity analysis; SMR, standardized mortality ratio	

Table 48. PSA results for tisagenlecleucel vs. salvage chemotherapy

	Average	Median
Incremental cost	¥13,059,645	¥13,017,239
Incremental QALY	2.46	2.47
Probabilistic ICER	¥5,300,340	
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis		

Figure 44. Cost-effectiveness acceptability curve: tisagenlecleucel vs. salvage chemotherapy

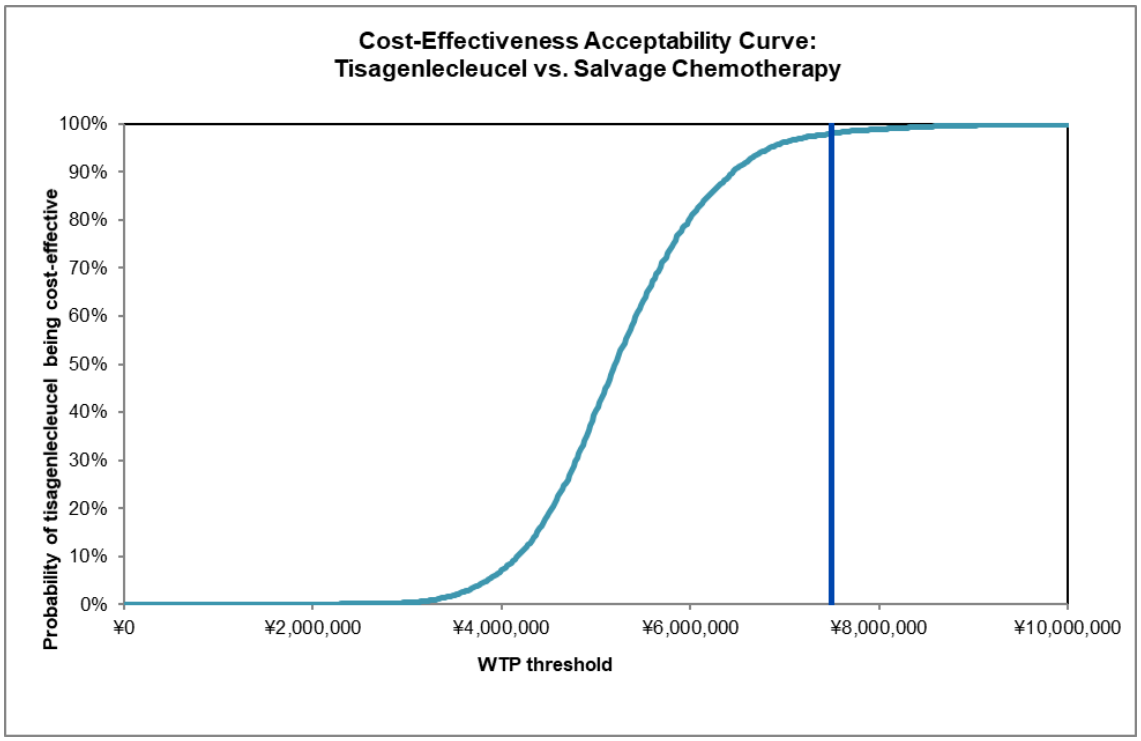
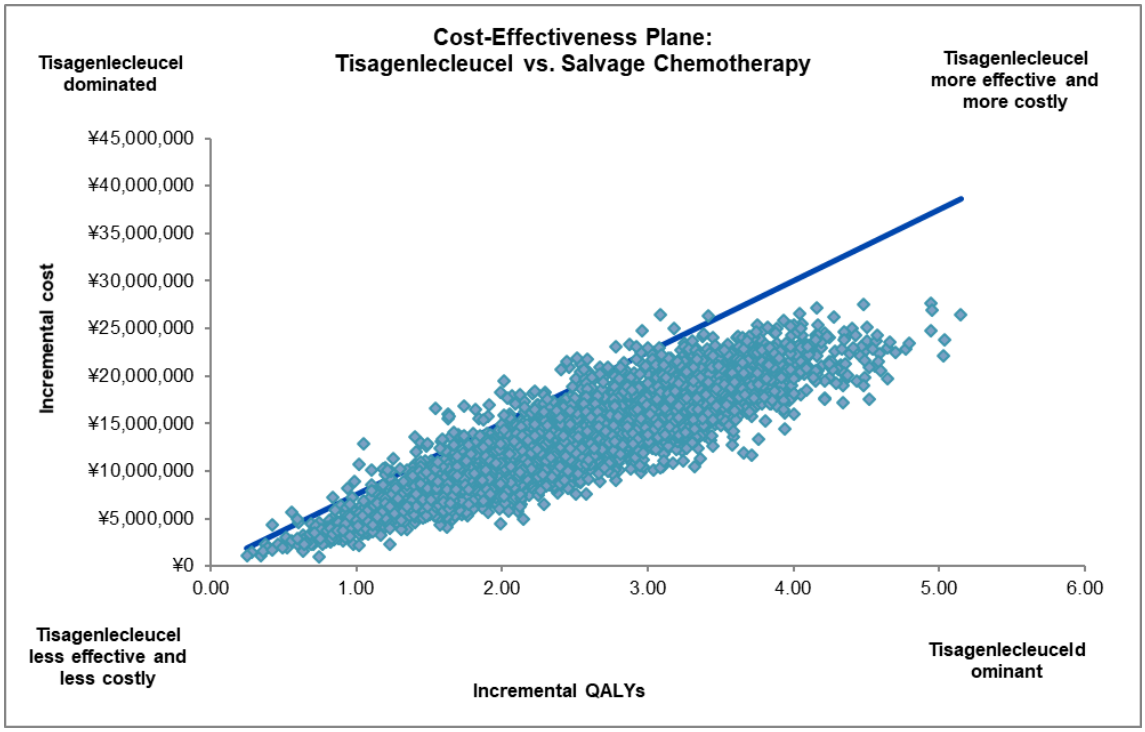


Figure 45. Cost-effectiveness plane: tisagenlecleucel vs. salvage chemotherapy



5.1.3 分析の妥当性の検討

5.1.3.1 B-ALL

The CAR-T therapy tisagenlecleucel is a highly effective treatment for pediatric and young adult r/r ALL, and its introduction has altered the treatment landscape of this disease by extending life as well as improving quality of life. The current model assessed cost-effectiveness of tisagenlecleucel in terms of LYs and QALYs in comparison with blinatumomab among patients age < 15 years and blinatumomab and inotuzumab among patients age between 15 to 25 years. The comparators were selected to reflect existing standard of care for r/r ALL patients in Japan clinical practice, which were validated by clinical input and were consistent with the model outline determined by C2H and MHLW. These treatment options have moderate clinical benefit, with median OS ranging between 6 months to 7.5 months.[16], [17], [28] Compared to existing treatments, tisagenlecleucel showed promising efficacy results (median OS of [redacted] months for <15 years age group, and [redacted] for 15-25 years age group). For patients with age < 15 years, the current model predicted an incremental LY of [redacted] years, an incremental QALY of [redacted] years, over the lifetime horizon when compared with blinatumomab. For patients with age 15-25 years, the current model predicted incremental LYs ranging from [redacted] years (vs. blinatumomab) to [redacted] years (vs. inotuzumab), and incremental QALYs ranging from [redacted] years (vs. blinatumomab) to [redacted] years (vs. inotuzumab) over the lifetime horizon. As a patient-specific, single infusion therapy, tisagenlecleucel is the first in this class of CAR-T therapy for the treatment of r/r B-cell ALL and represents a paradigm-shift in the treatment approach for this aggressive disease in children and young adults in Japan.

The current model used clinical trials data of tisagenlecleucel and comparators to simulate the disease course of r/r B-cell pALL over a lifetime horizon, stratified by two age groups (age < 15 years and 15-25 years) and used age group-specific data to the extent possible. The clinical trials explored in this model are the key clinical trials for each treatment. The populations evaluated in the clinical trials are representative of the target population of tisagenlecleucel in Japan. Because the clinical trials have limited follow-up (maximum follow-up ranged between [redacted] and [redacted] months), while the impact of the treatments on the disease is lifetime, it necessitates the use of modelling approach to evaluate the long-term value of the treatments.

Survival extrapolation was essential to quantify the survival benefit beyond the trial period and a robust and comprehensive approach was followed during the survival extrapolation to ensure the methods were statistically sound, but also clinically plausible. During model development, seven expert clinicians were consulted to evaluate efficacy inputs and long-term extrapolation from a clinical perspective. Based on feedback from these model validation meetings, the long-term extrapolation assumption considered in the CEA model were largely valid and consistent with expert expectations. The predicted survival rate from the model in the base-case at year 2, 3, 4, and 5 for age groups <15 and 15-25 were all within the range of expert estimation of the most likely values of OS for patients treated with tisagenlecleucel. Experts have estimated that the most likely values of OS for patients treated with tisagenlecleucel at 2, 3, 4, and 5 years were estimated to be approximately [redacted] % (95% credible interval: [redacted] For age group < 15 years, the base-case model prediction OS at 2, 3, 4, and 5 years were [redacted] For age group 15-25

years, the base-case model prediction OS at 2, 3, 4, and 5 years were [redacted]. In addition, the extrapolation assumption that patients were considered cured after year 5 to follow the mortality risk of long-term ALL survivors were also validated by the experts. This assumption conservatively assumes that there is no additional clinical benefit for tisagenlecleucel compared to existing treatments after year 5, which will make the ICER estimate from the current model being conservative against tisagenlecleucel. Given the uncertainty surrounding long-term OS extrapolation, scenario analyses were conducted varying the SMR input by 95% CI and varying the time point to introduce the long-term ALL survivor mortalities. The model was not sensitive to these parameters. The model also explored costs and utilities. The literature and data sources used for these inputs were valid and relevant to the population of interest.

5.1.3.2 DLBCL

Patients aged <70 years

The CAR-T therapy tisagenlecleucel is a highly effective treatment for adult patients with r/r DLBCL, and its introduction has altered the treatment landscape of this disease by extending life as well as improving quality of life. The current model assessed cost-effectiveness of tisagenlecleucel in terms of LYs and QALYs in comparison with salvage chemotherapy among patients aged < 70 years. The comparator was selected to reflect existing standard of care for r/r DLBCL patients aged <70 years in Japanese clinical practice, which were validated by clinical input. R/R DLBCL patients after two round of treatments or after auto SCT have very few treatment options and a poor prognosis. If left untreated, the estimated life expectancy for a patient with r/r DLBCL after at least two treatments is only three to four months.[67] Compared to salvage chemotherapy, tisagenlecleucel showed promising efficacy results. The current model predicted incremental LYs of 3.42 years and incremental QALYs of 3.23 years (vs. salvage chemotherapy) over the lifetime horizon for patients < 70 years. As a patient-specific, single infusion therapy, tisagenlecleucel is the first in this class of CAR-T therapy for the treatment of r/r DLBCL and represents a paradigm-shift in the treatment approach for this aggressive disease in adults in Japan.

The current model used clinical trial data of tisagenlecleucel and salvage chemotherapy to simulate the disease course of r/r DLBCL over a lifetime horizon for patients < 70 years. The clinical trials explored in this model were the key clinical trials for each treatment. The population evaluated in the JULIET clinical trial is representative of the target population of tisagenlecleucel in Japan. To the extent feasible, age-group specific inputs were derived to be consistent with the modeled population. In the model, the predicted median OS of patients in the tisagenlecleucel and salvage chemotherapy arms were [redacted] and 5.8 months, respectively. They are the same as that those observed among patients aged <70 in JULIET and extended CORAL studies. Additionally, the median OS of patients with salvage chemotherapy in the model was close to the median OS observed in SCHOLAR-1 (6.3 months). The clinical trial has limited follow-up (maximum follow-up of [redacted] months), while the impact of the treatments on the disease is lifetime. Therefore, the use of modelling approach to evaluate the long-term value of the treatments is necessary. Survival extrapolation is essential to quantify the survival benefit beyond the trial period. In the current model, followed by the observed trial data, patients who were alive at the end of three years were assumed to be long-term survivors and follow the mortality risk of

long-term DLBCL survivors as reported in the literature. A similar modelling approach was used in the NICE submissions of tisagenlecleucel. The NICE committee believed a cure point between 2 and 5 years was the most clinically plausible scenario with the former to be optimistic while the latter to be pessimistic. Therefore, 3-year cure point was considered in the base-case model as the midpoint between year 2 and year 5. This assumption conservatively assumed that there was no additional clinical benefit for tisagenlecleucel compared to salvage treatment after year 3, which will make the ICER estimate from the current model being conservative against tisagenlecleucel. Given the uncertainty surrounding long-term OS extrapolation, scenario analyses were conducted varying the time point to introduce the long-term DLBCL survivor mortality. The model was not sensitive to this parameter. The model also explored costs and utilities. The literature and data sources used for these inputs were valid and relevant to the population of interest.

Patients aged ≥ 70 years

The CAR-T therapy tisagenlecleucel is a highly effective treatment for adult patients with r/r DLBCL, and its introduction has altered the treatment landscape of this disease by extending life as well as improving quality of life. The current model assessed cost-effectiveness of tisagenlecleucel in terms of LYs and QALYs in comparison with salvage chemotherapy among patients aged ≥ 70 years. The comparator was selected to reflect existing standard of care for r/r DLBCL patients aged ≥70 years in Japanese clinical practice based on inputs from C2H and MHLW. R/R DLBCL patients after two round of treatments or after auto SCT have very few treatment options and a poor prognosis. If left untreated, the estimated life expectancy for a patient with r/r DLBCL after at least two treatments is only three to four months.[67] The prognosis is even worse among elderly patients ≥ 70 years because this patient population is generally not considered to suit for SCT, the only conventional treatment option with curative potential. Compared to salvage chemotherapy, tisagenlecleucel showed promising efficacy results. Elderly patients treated by tisagenlecleucel had the potential to achieve deep and durable remission without the need for subsequent SCT. The current model predicted incremental LYs of 2.65 years and incremental QALYs of 2.47 years (vs. salvage chemotherapy) over the lifetime horizon for patients ≥70 years. As a patient-specific, single infusion therapy, tisagenlecleucel is the first in this class of CAR-T therapy for the treatment of r/r DLBCL and represents a paradigm-shift in the treatment approach for this aggressive disease in adults in Japan.

The current model used clinical trial data of tisagenlecleucel and salvage chemotherapy to simulate the disease course of r/r DLBCL over a lifetime horizon for patients ≥ 70 years. The clinical trials explored in this model were the key clinical trials for each treatment. The population evaluated in the JULIET clinical trial is representative of the target population of tisagenlecleucel in Japan. To the extent feasible, age-group specific inputs were derived to be consistent with the modeled population. In the model, the predicted median OS of patients in the tisagenlecleucel arm was [redacted] months - the same as that the observed median OS from JULIET study. The predicted median OS of patients in the salvage chemotherapy arm was 4.5 months - reflecting the limited efficacy of conventional treatment on the target population. The clinical trial has limited follow-up (maximum follow-up of [redacted] months), while the impact of the treatments on the disease is lifetime. Therefore, the use of modelling approach

to evaluate the long-term value of the treatments is necessary. Survival extrapolation is essential to quantify the survival benefit beyond the trial period. In the current model, followed by the observed trial data, patients who were alive at the end of three years were assumed to be long-term survivors and follow the mortality risk of long-term DLBCL survivors as reported in the literature. The NICE committee believed a cure point between 2 and 5 years was the most clinically plausible scenario with the former to be optimistic while the latter to be pessimistic. Therefore, 3-year cure point was considered in the base-case model as the midpoint between year 2 and year 5. This assumption conservatively assumed that there was no additional clinical benefit for tisagenlecleucel compared to salvage treatment after year 3, which will make the ICER estimate from the current model being conservative against tisagenlecleucel. Given the uncertainty surrounding long-term OS extrapolation, scenario analyses were conducted varying the time point to introduce the long-term DLBCL survivor mortality. The model was not sensitive to this parameter. The model also explored costs and utilities. The literature and data sources used for these inputs were valid and relevant to the population of interest.

5.1.4 分析結果の解釈

5.1.1 から 5.1.3 に記載した内容について、下記のとおりまとめる。
また本品は、下記 3 つの条件すべてを満たすことから、価格調整における配慮を行うべき製品であり、ICER の閾値は 750 万円となる。

> ア 適用症の一部に治療方法が十分に存在しない疾病が含まれるものであって、当該疾病を分析対象集団として分析を行ったもの
> イ 小児に係る用法・用量等が承認された医薬品等又は医療機器等（小児のみに用いるものを除く。）であって、その小児に係る適用症を分析対象集団として分析を行ったもの
> ウ 承認された効能又は効果において悪性腫瘍が対象となっており、当該悪性腫瘍を分析対象集団として分析を行ったもの
> （通知より抜粋）

対象集団	15 歳未満の B-ALL
比較対照	ブリナツモマブ +/- 同種移植
ICER の基準値	□ 通常の品目 ■ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等（あるいは劣り）、かつ費用が高い
そのように判断した理由	本対象集団における ICER は¥2,087,581 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。

	また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 100％であった。以上より、「750 万円以下」が ICER の所属する区間として妥当と判断する。

対象集団	15 歳以上 25 歳未満の B-ALL
比較対照	ブリナツモマブ +/- 同種移植 イノツズマブ +/- 同種移植
ICER の基準値	□ 通常の品目 ■ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等（あるいは劣り）、かつ費用が高い
そのように判断した理由	【比較対照】ブリナツモマブ 本対象集団における ICER は¥2,015,349 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 100％であった。 【比較対照】イノツズマブ 本対象集団における ICER は¥1,994,592 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても基本分析と大きく結果が異なることはなかった。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 100％であった。 以上より、両比較対照群の分析結果を考慮すると、「750 万円以下」が ICER の所属する区間として妥当と判断する。

対象集団	70 歳未満の r/r DLBCL
比較対照	Salvage Chemotherapy +/- HSCT
ICER の基準値	□ 通常の品目 ■ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等（あるいは劣り）、かつ費用が高い
そのように判断した理由	本対象集団における ICER は¥5,459,234 であり、これは価格調整の閾値である 750 万円を下回り、DSA においても、ほぼ全ての場合において ICER が 750 万円を下回っており、750 万円を超えるのは割引率を 4％

	に変更した場合、及び分析期間を[redacted]年にした場合に限られる。その場合の ICER はそれぞれ¥[redacted]と[redacted]であった。分析期間については、『2.5 分析期間』で述べられている通り、「十分に長い分析期間」とされていることから生涯とすることが妥当と考える。他の DSA の結果を考慮しても ICER の所属する区間は 750 万円以下が妥当であると考える。 また、確率論的感度分析（PSA）においては、ICER が 750 万円以下となる確率は 97.6%であることから、「750 万円以下」が ICER の所属する区間として妥当と判断する。

対象集団	70 歳以上の r/r DLBCL
比較対照	Salvage Chemotherapy
ICER の基準値	□ 通常の品目 ■ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	■ 本対象集団の分析結果を価格調整に用いるべきでない □ 費用削減あるいはドミナント □ 500 万円以下 （750 万円以下） □ 500 万円超 （750 万円超)かつ 750 万円以下 （1125 万円以下） □ 750 万円超 （1125 万円超)かつ 1000 万円以下 （1500 万円以下） □ 1000 万円超 （1500 万円超） □ 効果が同等（あるいは劣り）、かつ費用が高い
そのように判断した理由	本報告においては、参考までに 70 歳以上の集団においても検証を行い、その結果は 5.1.2.2 に記載したとおりであり、基本分析における ICER は 5,231,584 円であった。 「3.8 追加的有用性の有無に関する評価」に記載する通り、本分析対象集団においては、介入群（tisagenlecleucel）と比較対照群ともに有効性データのリミテーションが大きく、これらのデータに基づく分析結果の解釈には、十分に留意する必要がある。現行のルールでは、いわゆる海外で言われるような総合的なアプレイザルは行われず、ICER の値をそのまま使用して意思決定がなされる。 臨床試験のデザインの段階で想定していなかったサブグループ解析を行うことによって検出力が著しく低下し、一部のサブグループで追加的有用性が示せなくなるような状況下では、通常のプロセス通りの意思決定（ICER の値に基づく価格調整）は行うべきでないと判断したものである。諸外国の HTA においても、サブグループの設定は"Clinically Distinct(臨床的に明確に区別可能)"な集団に対して行うことが前提となっており、設定時の結果の解釈にも十分に留意すべきとされる。あわせて、過度なサブグループ設定にともなう検出力低下などの危険性は一般的にも指摘されている。[68] 以上より、本集団の分析結果を価格調整には用いるべきでないと判断する。

なお、DLBCL の結果については、2019 年[redacted] 月[redacted] 日開催の費用対効果専門組織で決定された「がん登録データあるいは…疫学データなど臨床実態に合わせた年齢構成について、検討すること」との指示内容に基づき、下記のとおり検討を行った。

開始年齢の変更（DLBCL のみ）
基本分析の分析開始年齢は、70 歳未満の分析対象集団で[redacted] 歳、70 歳以上の分析対象集団で[redacted] 歳と設定した(Section 5.2)。これらは分析対象集団ごとの tisagenlecleucel の有効性データに含まれる患者の平均年齢である。一般に費用対効果分析において、有効性データに含まれる患者を代表する年齢が分析開始年齢として用いられる。また 70 歳以上の分析対象集団については、2019 年[redacted] 月[redacted] 日開催の C2H との協議の中で、C2H より分析開始年齢は 70 歳であるとのコメントを得ており[redacted] 歳はより保守的な設定であるといえる。
また、弊社で実施した臨床医に対する[redacted]調査（詳細については 5.1.5 を参照）によると、tisagenlecleucel を含む CAR-T 療法の処方意向は年齢階層によって大きく異なるため、がん登録データや疫学データなどの年齢構成をそのまま分析開始年齢として用いることは適切でない考えられる。なおシナリオ分析として、分析開始年齢を変更した場合の ICER を分析した（Section 5.1.2）。
シナリオ分析で考慮した年齢は[redacted]タより、70 歳未満の DLBCL 患者の平均年齢を算出した。開始年齢を[redacted] 歳とした場合にも base-case との結果に大きな違いがなかった。なお、70 歳以上においては、処方意向が著しく限定されるため、シナリオ分析は特に設定しておらず、C2H からコメントがあった 70 歳と比しても基本分析が保守的な分析であったことから開始年齢に関するシナリオ分析は実施していない。

5.1.5 価格調整率の重み [該当する場合のみ]

1. ALL と DLBCL の患者割合
2019 年 5 月収載時の本品のピーク時（2026 年）における予測本品投与患者数は、216 名であり、その内訳は、B-ALL で[redacted] 例（[redacted]%）、DLBCL で[redacted] 例（[redacted]）である。本市場規模予測は、[redacted]）から、適格患者数および本品投与対象患者数を推計したものである。本品は現時点で上市（2019 年 5 月）から 1 年未満であり、また施設要件などの手順により投与開始まで時間を要することから、既に実際に投与された患者数は限定的である。そのため、患者数分布のデータソースとして臨床実績ではなく、前述のピーク時患者割合を使用することとした。

2-1. B-ALL における患者数割合
ELIANA 及び B2101J、ENSIGN において本品が投与された患者[redacted] 人のうち、15 歳未満の患者は[redacted] 人[redacted]%）、15 歳以上 25 歳未満の患者は[redacted] 人（[redacted]%）である。

2-2. DLBCL における患者数割合
[redacted]より、全ラインの DLBCL 治療患者数割合は下記のとおりである。DLBCL に対する本製品を含む CAR-T 療法の標準的な対象年齢を明らかにするため、臨床医に対して処方意向に関する[redacted]実施した。[redacted]調査の概要を Table 50 に示す。CAR-T 治療の有効性や安全性、治療プロセス（実施施設の制約、転院の必要性、治療までの所要時間など）、およびコストを総合的に考慮した上で、3rd ライン以降の再発難治 DLBCL 患者に対して CAR-T 治療が実施可能だと思われる割合を年齢別に尋ねたところ、Table 49 の結果を得た。年齢別の CAR-T 療法実施可能割合をもとに、同インターネット調査から得た 3rd ライン以降の再発難治 DLBCL の持ち患者分布に重みづけしたところ、想定される患者数割合は 70 歳未満集団で[redacted]%、70 以上集団で[redacted]%となった（Figure 46）。

Table 49. 年齢別 CAR-T 療法実施可能割合

年齢階層	CAR-T 療法実施可能割合 （投与を検討する割合）
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
計	NA

[redacted]

Figure 46.年齢集団別の患者処方割合

[redacted]

Table 50 CAR-T 処方意向調査概要

調査目的	r/r DLBCL に対する CAR-T 療法（本製品を含む）の標準的な対象年齢を明らかにする
調査方法	[redacted]調査
調査実施機関	[redacted]
調査地域	全国
[redacted]	[redacted]
[redacted]	[redacted]
抽出方法	有意抽出
抽出条件	[redacted]

サンプルサイズ	[redacted]
実査期間	[redacted]

3. 価格調整率の重み

1 及び 2 より対象集団別の価格調整率の重みは以下の通りである。「5.1.4 分析結果の解釈」に記載の通り、70 歳以上集団の分析結果については価格調整に用いるべきでないと考える。なお 2 で算出した年齢集団別の患者処方割合を用いた場合、対象集団全体に占める DLBCL の 70 歳未満患者の割合は [redacted] % (= [redacted] %)、70 歳以上患者の割合は [redacted] % ([redacted] %) となる。

対象集団		患者割合	計算式
B-ALL	15 歳未満	[redacted]	[redacted]
	15 歳～25 歳		
DLBCL	70 歳未満	[redacted]	NA
	70 歳以上	NA	NA
	合計	100%	

5.1.6 価格の引き上げ [該当する場合のみ]

該当せず

5.2 公的介護費用や生産性損失を含めた分析 [該当する場合のみ]

既存の治療方法とは異なり、本製品の投与により持続的な有効性が期待できる。本製品の投与による患者の生産性への影響は大きいため、生産性損失を考慮した分析を実施する。分析における主要なインプットを Table 51 に示す。

Table 51. Inputs for productivity gain

Parameter		Input Value	Source / Notes
Monthly Wage		¥427,877.33	Wage level data in Japan[53]
Age-specific employment rate	15-24	43.50%	2018 Mar, Historical data 1 b-6 Employment rate [by age group] - Whole Japan, Monthly Data[54]
	25-54	84.90%	
	55-59	74.90%	
	60-64	74.90%	
	65 +	24.10%	

【B-ALL:15 歳未満】

生産性損失を含めた分析において、介入群の費用が比較対照群の費用を下回るため、ICER はドミナントとなる。

比較対照技術:Blinatumomab

	増分効果 (QALY)	増分費用 (円)	ICER(円 /QALY)
生産性損失を含めた分析	9.05	-¥9,897,380	Dominant
基本分析	9.05	¥18,882,649	¥2,087,581

【B-ALL:15 歳以上 25 歳未満】

生産性損失を含めた分析において、Blinatumomab と Inotuzumab の両比較対照技術につ

いて介入群の費用が比較対照群の費用を下回るため、ICER はドミナントとなる。

比較対照技術：Blinatumomab

	増分効果（QALY）	増分費用（円）	ICER(円/QALY)
生産性損失を含めた分析	8.56	-¥13,874,764	Dominant
基本分析	8.56	¥17,256,268	¥2,015,349

比較対照技術：Inotuzumab

	増分効果（QALY）	増分費用（円）	ICER(円/QALY)
生産性損失を含めた分析	9.55	-¥13,874,764	Dominant
基本分析	9.55	¥19,049,180	¥1,994,592

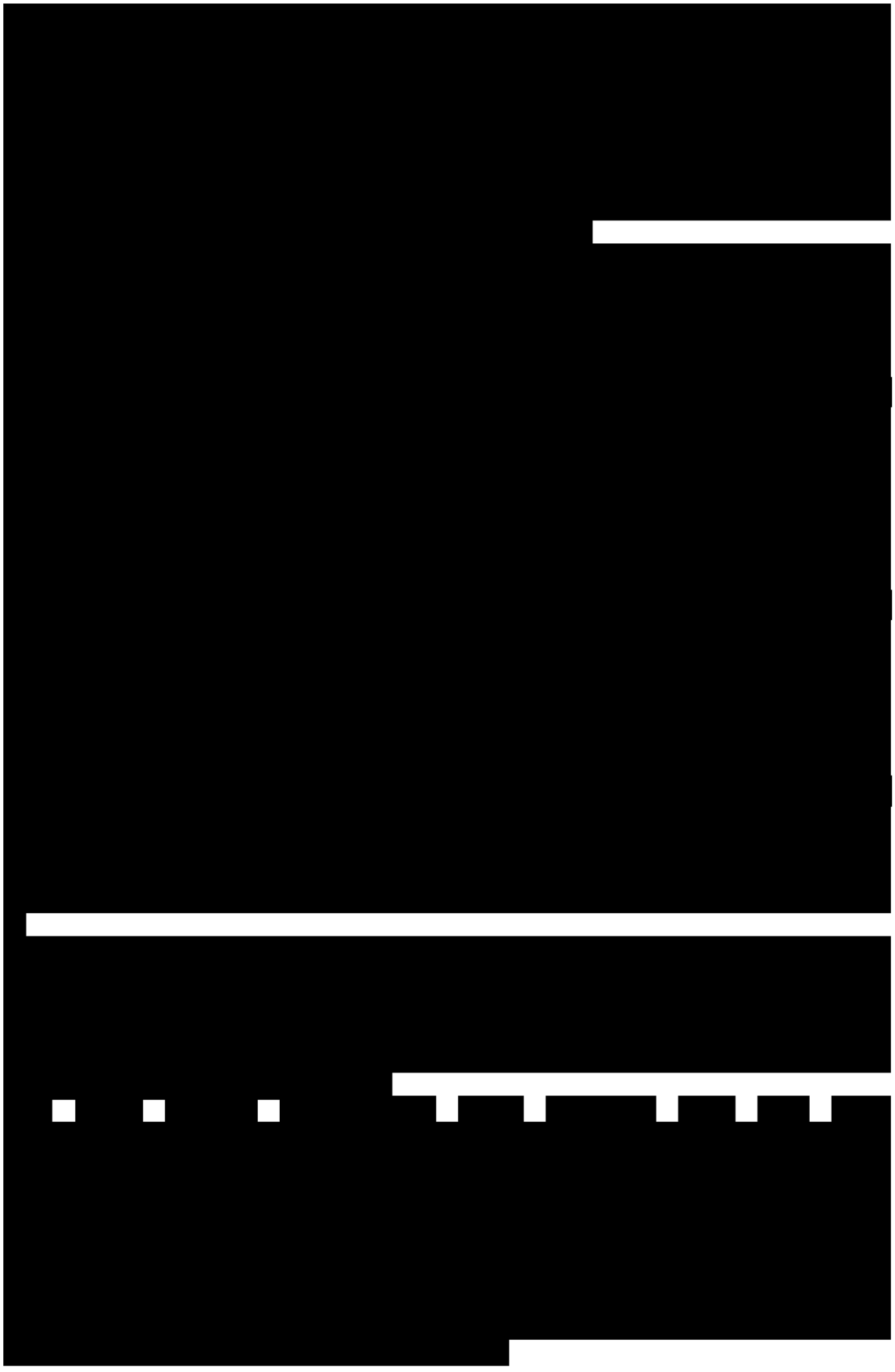
【DLBCL：70 歳未満】
生産性損失を含めた分析において、ICER は¥2,903,719 となる。
比較対照技術：salvagechemotherapy +/-同種 HSCT

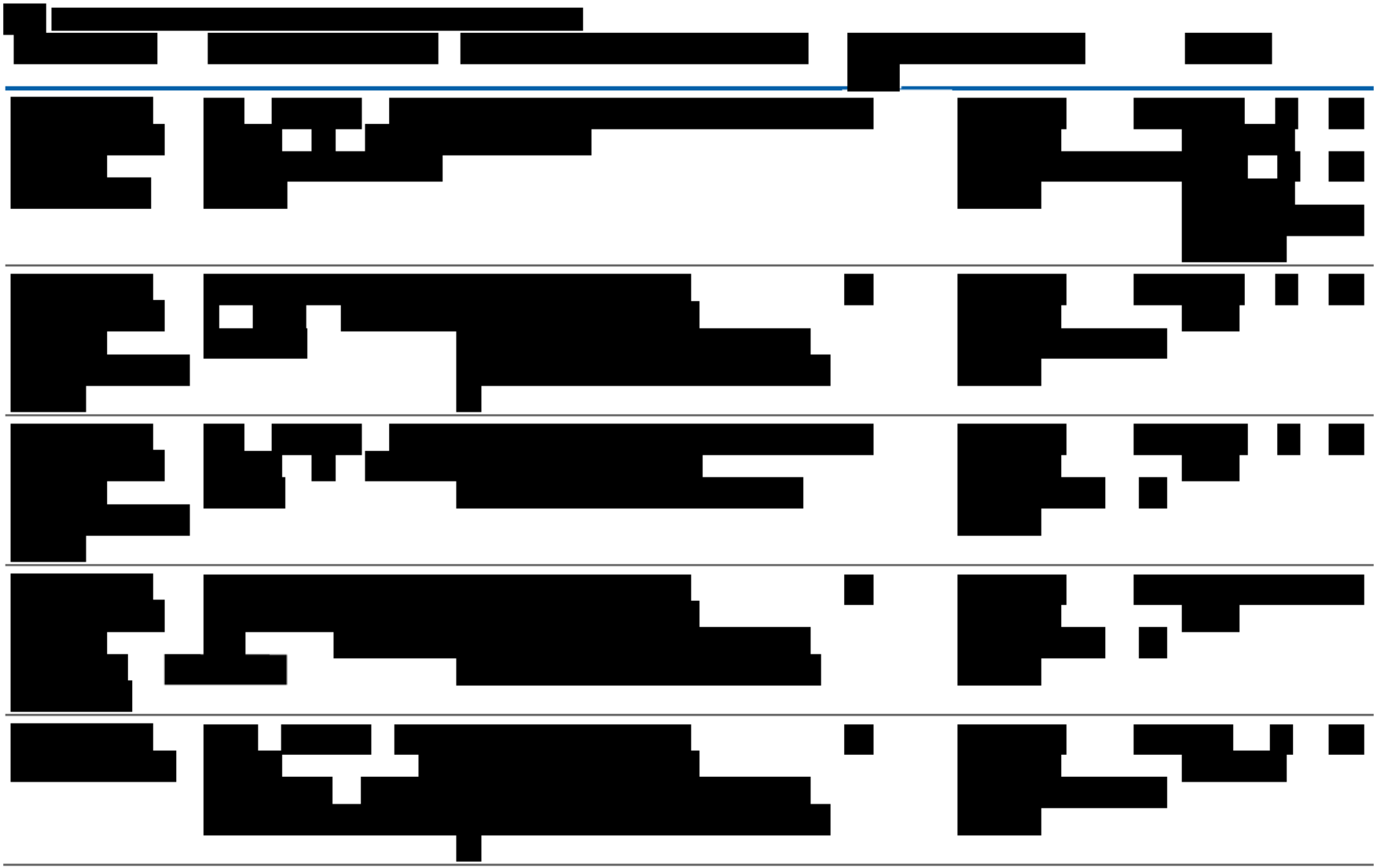
	増分効果（QALY）	増分費用（円）	ICER(円/QALY)
生産性損失を含めた分析	3.23	¥9,603,354	¥2,970,510
基本分析	3.23	¥17,649,143	¥5,459,234

【DLBCL：70 歳以上】
70 歳以上の集団において就労している人の割合は比較的少ないため、生産性損失を含めた分析を実施しない。

5.3 その他の分析［該当する場合のみ］
（参考情報）
参考情報として、弊社が第 1 回分析前協議で提示した全体集団を用いた分析につて、今回提出した資料の有効性のカットオフ時点の違いがあるものの結果を記載する。
全体集団を用いた場合にも、今回費用対効果評価専門組織で決定されたサブグループの結果と同様に、両疾患において、ICER は 750 万以下であった。[redacted]

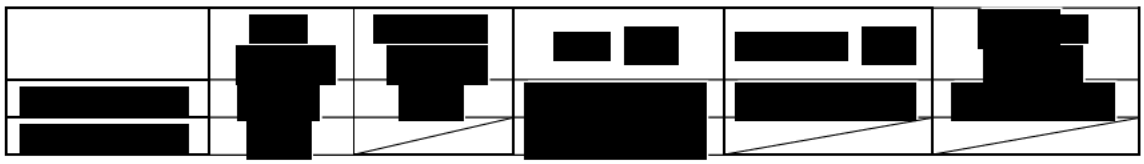
[redacted]

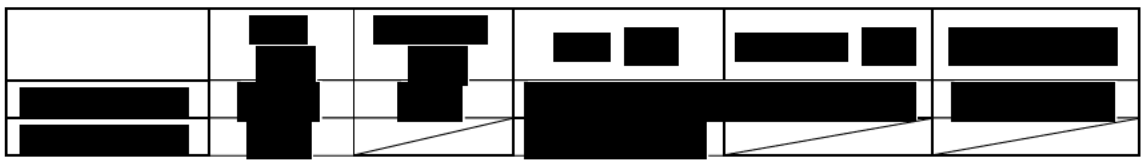




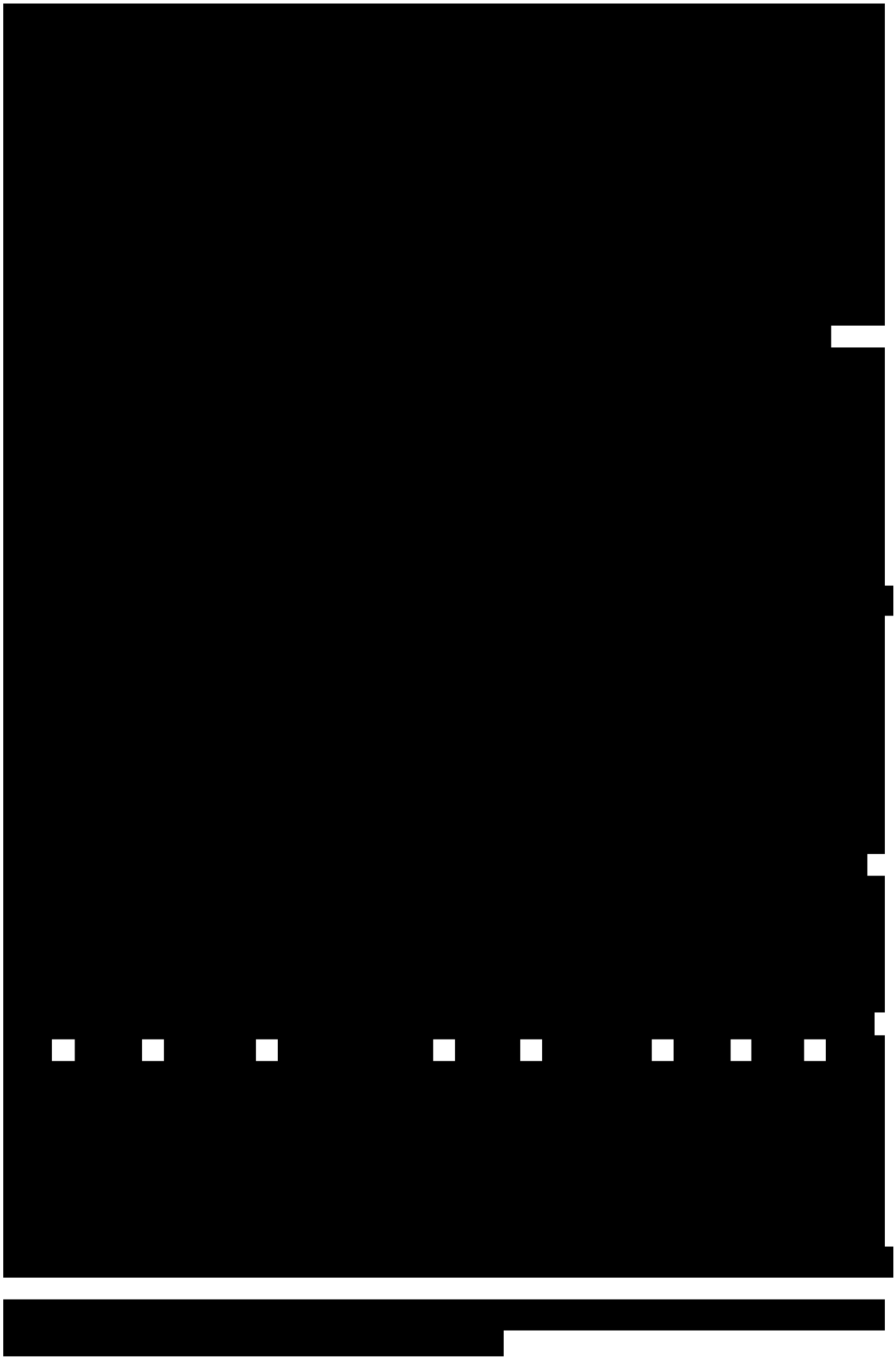
[redacted]

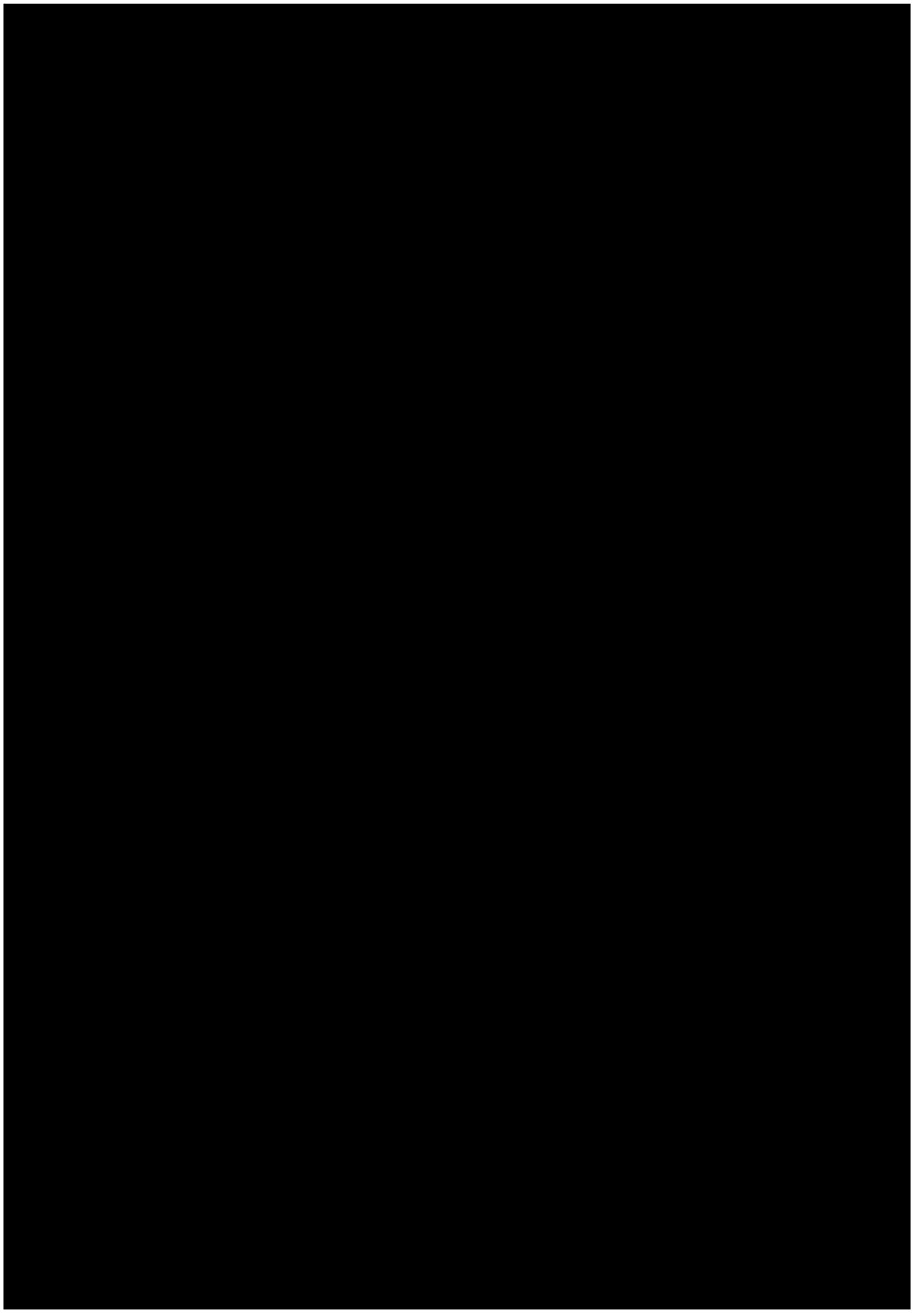
[redacted]





[redacted]





[redacted]

[redacted]

6. 再分析用のデータ

使用したソフトウェア	バージョン	ファイル名	提出メディア
Microsoft Excel®	2016	[redacted]	CD-R

7．実施体制

【社内メンバー】

氏名	所属
[redacted]	[redacted]
[redacted]	[redacted]

【社外専門家】

氏名	所属	役割
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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Appendix A. Detailed tables of clinical studies included in SLRs

A-1. B-ALL

	Bhojwani, 2019	MT103-205	RIALTO	Hijiya, 2011	Miano, 2012
Location where the test was performed	North America, Europe, and Australia	26 European and US centers	19 European and US centers	US	Italy
Participant recruitment period	January 2013 to December 2016	January 30, 2012 to June 3, 2014	NR	NR	August 2008 to February 2010
Population	Pediatric patients (≤21 years) with relapsed/ refractory B-ALL who received InO in the compassionate use program	Patients <18 years of age with B-Cell relapsed/ refractory B-ALL with >25% bone marrow blasts	Patients <18 years of age with CD19-positive B-precursor relapsed/ refractory B-ALL with ≥5% bone marrow blasts	Patients 0–20 years of age with relapse/refractory ALL with ≥25% bone marrow blasts	Patients 0–20 years of age with ALL or AML after 2nd or further relapse/refractory with >25% bone marrow blasts
Major exclusion criteria	NR	Patients with active acute or extensive chronic GVHD after HSCT, or active CNS or testicular involvement	Patients with clinically relevant CNS pathology, having received chemotherapy within 2 weeks, RT within 4 weeks, or IO therapy within 6 weeks, or with ≥grade 2 GVHD	Patients with prior HSCT, viral hepatitis, hepatitis C/B, cirrhosis, or elevated conjugated bilirubin levels at study entry, prior clofarabine treatment, uncontrolled systemic infections, the presence of severe concurrent disease	Isolated extramedullary relapse and active infections
Details of interventions	One cycle of inotuzumab	Blinatumomab administered as a	Blinatumomab administered as a 4-	Clofarabine (40 mg/m^2 /day) IV	Clofarabine (40 mg/m^2 /day) IV

	Bhojwani, 2019	MT103-205	RIALTO	Hijiya, 2011	Miano, 2012
	ozogamicin consisted of three doses: 0.8 mg/m2 on week 1, followed by 0.5 mg/m2 on weeks 2 to 3	4-week continuous IV infusion as 5 mg/m2/d for the first 7 days, followed by 15 mg/m2/d thereafter, followed by a 2-week treatment-free interval	week continuous IV infusion as 5 mg/m2/d for the first 7 days, followed by 15 mg/m2/d thereafter, followed by a 2-week treatment-free interval, for up to 5 cycles	over 2 hours, etoposide (100 mg/m^2 /day) IV over 2 hours, cyclophosphamide (440 mg/m^2 /day) over 30-60 minutes, all given daily for 5 consecutive days in induction and 4 consecutive days in consolidation	over 2 hours, etoposide (100 mg/m^2 /day) IV over 2 hours, cyclophosphamide (440 mg/m^2 /day) over 1 hour, administered all given daily for 5 consecutive days in induction (1-2 cycles) and 4 consecutive days in consolidation
Details of the comparison	None	None	None	None	None
Study Design	Retrospective cohort	Phase I/Phase II Trial	Open-label, expanded access study	Phase II Trial	Prospective cohort
Blinding method	None	None	None	None	None
Primary endpoint	CR rate	CR rate	Treatment-emergent adverse events and treatment-related treatment emergent adverse events	Overall response rate (CR + CRp)	CR or CRp rate
Key secondary endpoints	OS, EFS	AE incidence, proportion of patients undergoing allo-HSCT after	CR within the first two cycles MRD remission within the first two cycles	Safety, tolerability, rate of partial remission, duration of response, EFS, and OS	OS Toxicity

	Bhojwani, 2019	MT103-205	RIALTO	Hijiya, 2011	Miano, 2012
		blinatumomab treatment, RFS, and OS	RFS and OS Rate of allo-SCT after CR		
Statistical methods	Univariable and multivariable Cox regression analysis was used to assess the associations between EFS/OS and patient/ disease characteristics. Estimates of EFS or OS probability were based on the product limit estimator with Greenwood standard errors. Reported p-values are all two-sided.	The proportion of responders with exact 95% CIs was calculated. RFS and OS (time from enrollment to first relapse or death, respectively) were estimated using the Kaplan-Meier method.	NR	Descriptive statistics were used to describe response rates. Time-to-event outcomes, such as DOR and OS, were described using Kaplan-Meier estimates. DOR was calculated censoring patients known to be in remission at last follow-up, and separately with censoring at the time of alternative therapy or HSCT.	The probability of OS was estimated using the Kaplan–Meier method. The log-rank test was used to compare survival curves. A p-value less than 0.05 was considered statistically significant.
Sample size	51	70	98	25	24
Follow-up period	Median follow-up was 112.5 days in the 20 patients without an event, and 137 days in the 27 patients who were alive at	Median: 23.8 months	NR	NR	NR

	Bhojwani, 2019	MT103-205	RIALTO	Hijiya, 2011	Miano, 2012
	last contact				
Major background factors of subjects	Median age: 11.5 years 59% Males	Median age: 8 years 67% Males	Median age: 7.8 years 71% Males	Median age: 14 years 64% Males	Median age: 8.5 years 58% Males
Results of the primary endpoint	CR: 67% (28/42)	CR: 39% (27/70)	Treatment-emergent AE: 99% (97/98) Treatment-related AE: 77% (75/98)	ORR (CR + CRp): 44% (11/25)	CR: 38% (9/24) CRp: 8% (2/24)
Results of major secondary endpoints	PR: 7% (3/42) 12 Month EFS: 23.4% 12 month OS: 36.3%	PR: 6% (4/70) Median OS: 7.5 months (95% CI, 4.0–11.8) Median RFS: 4.4 months (95% CI, 2.3–7.6)	CR during the first 2 cycles: 60% (59/98) MRD response during the first 2 cycles: 80% (47/98) Rate of allo-HSCT: 46% (27/69) Median OS: 13.0 months (95% CI, 9.3–NE) Median RFS (N=59): 8.5 months (95% CI, 2.9–NE)	Median OS: 10.7 months (95% CI, 1.0–113.1) 4 month EFS: 44% Median DOR: 67.3 weeks All patients reported at least one ≥3 grade AE; 17 patients (68%) had at least one grade 4 AE, and 20 patients (80%) reported at least 1 related serious AE (88%)	OS at a median of 24 months after treatment: 25% (6/25) Toxicity data was not reported separately for patients with ALL
Limitation of the study	Reporting bias, retrospective design	NR	NR	Small sample size	Small sample size

Abbreviations: AE = adverse event; CI = confidence interval; CR = complete response/remission; CRp = complete response without platelet recovery; DOR = duration of response; EFS = event-free survival; GVHD = graft-versus-host disease; MRD

= minimum residual disease; N = number of patients; NE = not evaluable; NR = not reported; ORR = overall response rate; OS = overall survival; RFS = relapse-free survival

B-ALL (continued)

[Study 1]	Locatelli, 2009	Jeha, 2006	Von Stackelberg, 2011	Kuhlen, 2018
Location where the test was performed	Italy	United States	Germany, Austria, Switzerland, The Netherlands, Denmark and Russia	Austria
Participant recruitment period	October 2006 to August 2008	June 13, 200 to September 30, 2004	March 13, 1990 to June 30, 1999	NR to June 2016
Population	Patients aged ≤15 years at time of diagnosis and ≤21 years at the time of treatment with multiple relapsed or refractory ALL	Patients younger than 21 years of age at the time of original diagnosis with second or subsequent relapse and/or refractory ALL	Patients ≤18 years with ALL received ALL-REZ BFM regimen after their first relapse. Among non-responders to ALL-REZ BFM regimen, patients then received either supportive therapy, palliative care, or salvage chemotherapy with curative intent.	Patients ≤19 years with B- or T-cell recurrent ALL after relapse from their first SCT.
Major exclusion criteria	NR	The study was amended to also exclude patients with transplantation within the previous 3 months and active GVHD.	Patients with insufficient documentation	NR
Details of interventions	Clofarabine (40 mg/m^2 /day) IV over 2 hours, etoposide (100 mg/m^2 /day) IV over 2 hours,	Clofarabine was administered intravenously at 52 mg/m2 over 2 hours	The salvage chemotherapy regimens were heterogenous and only descriptively	Salvage chemotherapy without second SCT (46.3%), salvage chemotherapy with

[Study 1]	Locatelli, 2009	Jeha, 2006	Von Stackelberg, 2011	Kuhlen, 2018
	cyclophosphamide (400 mg/m^2 /day) over 1 hour, administered all given daily for 5 consecutive days	daily for 5 consecutive days every 2 to 6 weeks for up to 12 cycles	summarized in the publication	second SCT (25.2%). Chemotherapy was neurotoxic (Ara-G) alone (N=25) or in combination with cyclophosphamide and etoposide (n=27)
Details of the comparison	None	None	Palliative care or Supportive care (no antileukemic therapy)	Palliative therapy (24.4%), unknown (4.1%)
Study Design	Phase II Trial	Phase II Trial	Retrospective cohort	Retrospective cohort
Blinding method	None	None	None	None
Primary endpoint	Overall response (CR + CRp)	Overall response (CR + CRp)	CR	EFS and OS
Key secondary endpoints	OS and safety	DOR, PR, OS, and safety	OS, safety, quality of life	NR
Statistical methods	The probability of OS was estimated by the Kaplan–Meier method, and expressed as 18-month probability, with the corresponding 95% CI. P-values < 0.05 were considered significant	Kaplan-Meier methods were used to summarize duration of remission and overall survival	Differences in the distribution of variables among subgroups were assessed by the Mann–Whitney U- or Kruskal–Wallistest for continuous variables. Exact Fischer-test was used to analyze the independency of two, Pearson-test of more than two qualitative variables. Kaplan–Meier life-table-analysis was used for survival data of the total	

[Study 1]	Locatelli, 2009	Jeha, 2006	Von Stackelberg, 2011	Kuhlen, 2018
			cohort and subgroups only considering disease- or treatment-related deaths as subsequent events. Subgroups were compared by the two-sided log-rank-test. In all tests, two-sided p≥0.05 or higher was regarded as not significant. Multivariate Cox stepwise-forward-conditional–regression-analysis was done to determine statistically significant independent indicators of outcome	
Sample size	25	61	93 overall, 51 receiving salvage chemotherapy	242 overall, 61 salvage therapy with SCT, 112 salvage therapy alone
Follow-up period	NR	NR	NR	Median: 3.4 years
Major background factors of subjects	Median age: 12.5 years; 72% males	Median age: 12 years; 61% males	Median age: 8 years; 71% males	Median age: 11.3 years; 65% males
Results of the primary endpoint	ORR: 56% (14/25)	ORR: 20% (12/61)	CR: 31% (16/51)	EFS not reported by treatment 3-year OS in salvage + SCT: 41% (25/61) 3-year OS in salvage alone: 19.6% (22/112)

[Study 1]	Locatelli, 2009	Jeha, 2006	Von Stackelberg, 2011	Kuhlen, 2018
Results of major secondary endpoints	18-month OS: 20% PR: 8% (2/25) Median DOR: 6 months (range 3–8.5)	Median OS: 13 weeks (1-89) PR: 10% Median DOR: 29 weeks (range 1–49)	Median OS: 3.97 months (95% CI, 1.08–61.01) 12-month OS: 12% PR: 10% (5/51)	NR
Limitation of the study	Small sample size	NR	Retrospective design, no details on specific chemotherapy used.	Retrospective design, no details on specific chemotherapy used, selection bias.

Abbreviations: ALL = acute lymphoblastic leukemia; CI = confidence interval; CR = complete response/remission; CRp = complete response without platelet recovery; DOR = duration of response; EFS = event-free survival; GVHD = graft-versus-host disease; N = number of patients; NR = not reported; ORR = overall response rate; OS = overall survival; PR = partial response; RFS = relapse-free survival

A-2. DLBCL

CORAL extension study 1

Location where the test was performed	Multiple countries (e.g., US, UK, Germany, Australia, etc.)
Participant recruitment period	July 2003-June 2008
Population	• Patients included in the CORAL trial who relapsed after ASCT either before or after randomization to rituximab or observation were included in the extension study 1 *Patients enrolled in the CORAL trial*[14] – Were with age 18 to 65 years – Were with aggressive CD20+ B-cell NHL, including DLBCL. Before enrolment, CD20+ aggressive B-cell lymphoma was histologically confirmed in all patients – Had experienced relapse or did not achieve CR with a standard anthracycline-based regimen composed of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)

	– Had ECOG performance status of 0 or 1
Major exclusion criteria	*Exclusion criteria for the CORAL trial*[14]: • CNS or meningeal involvement by lymphoma • Burkitt, mantle cell, T-cell lymphoma • History of HIV infection • Prior transplantation at CORAL enrolment
Details of interventions	• Chemotherapy (e.g., +/- rituximab and ICE, DHAP, CHOP-like, etc.) • ASCT or Allo-SCT
Details of the comparison	N/A
Study Design	• Extension study of CORAL, a randomized, multi-center, multi-country, phase III trial
Blinding method	None (open label)
Primary endpoint	• ORR • CR/CRu • PR • OS
Key secondary endpoints	N/A
Statistical methods	• Kaplan–Meier method was used to estimate OS • Wilcoxon's signed rank test was used to compare patient characteristics • Cox regression analysis was used to calculate the hazard ratio (HR) between different patient categories
Sample size	• Full analysis set (baseline characteristics reported): N = 75 • Patients evaluated for response: N = 75 • Patients evaluated for survival: N = 73
Follow-up period	Median 32.8 months (range: 24.3-45.8 months)
Major background factors of subjects	• Age: median 56 years • Sex: 68% male • Predominant histology: 100% DLBCL • IPI risk classification: 72% 0-2, 28% >2

Results of the primary endpoint	• ORR: 44% • CR/CRu: 32% • PR: 12% • Median OS: 10.0 (95% CI: [6.6, 12.6]) months
Results of major secondary endpoints	N/A
Limitation of the study	Not reported

Abbreviations: allo-SCT: allogenic stem cell transplant; ASCT: autologous stem cell transplant; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CI: confidence interval; CNS: central nervous system; CR/CRu: complete response/complete response unconfirmed; DHAP: dexamethasone, cytarabine, cisplatinum; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HIV: human immunodeficiency virus; HR: hazard ratio; ICE: ifosfamide, carboplatinum, etoposide; IPI: International Prognosis Index; N/A: not applicable; NHL: non-Hodgkin lymphoma; ORR: overall response rate; OS: overall; PR: partial response

CORAL extension study 2

Location where the test was performed	Multiple countries (e.g., US, UK, Germany, Australia, etc.)
Participant recruitment period	July 2003-June 2008
Population	• Patients included in the CORAL trial who did not proceed to per-protocol ASCT because of an event leading to withdrawal between cycle 1 and scheduled ASCT and who were candidates for third-line regimen were included in the extension study 2 *Patients enrolled in the CORAL trial*[14] – Were with age 18 to 65 years – Were with aggressive CD20+ B-cell NHL, including DLBCL. Before enrolment, CD20+ aggressive B-cell lymphoma was histologically confirmed in all patients – Had experienced relapse or did not achieve CR with a standard anthracycline-based regimen composed of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) – Had ECOG performance status of 0 or 1
Major exclusion	*Exclusion criteria for the CORAL trial*[14]:

criteria	• CNS or meningeal involvement by lymphoma • Burkitt, mantle cell, T-cell lymphoma • History of HIV infection • Prior transplantation at CORAL enrolment
Details of interventions	• Chemotherapy (+/- rituximab and ICE-type, DHAP-type, gemcitabine-containing, CHOP-like, etc.) • ASCT or allo-SCT
Details of the comparison	N/A
Study Design	• Extension study of CORAL, a randomized, multi-center, multi-country, phase III trial
Blinding method	None (open label)
Primary endpoint	• ORR • CR/CRu • PR • OS
Key secondary endpoints	N/A
Statistical methods	• Kaplan–Meier method was used to estimate OS • Wilcoxon's signed rank test was used to compare patient characteristics • Cox regression analysis was used to calculate the hazard ratio (HR) between different patient categories
Sample size	• Full analysis set (baseline characteristics reported): N = 203 • Patients evaluated for response: N = 203 • Patients evaluated for survival: N = 193
Follow-up period	Median 30.1 months
Major background factors of subjects	• Age: median 55 years • Sex: 61% male • Predominant histology: 100% DLBCL • IPI risk classification: 30% 0-1, 52% 2-3, 17% 4-5
Results of the primary endpoint	• ORR: 39% • CR/CRu: 27%

	• PR: 12% • Median OS: 4.4 months (95% CI: not reported)
Results of major secondary endpoints	N/A
Limitation of the study	Even with the limitation of missing data, this cohort is the largest ever described in that situation and provides interesting parameters, which can be validated in future studies to better describe who could be eligible for experimental third-line salvage regimens.

Abbreviations: allo-SCT: allogenic stem cell transplant; ASCT: autologous stem cell transplant; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CI: confidence interval; CNS: central nervous system; CR/CRu: complete response/complete response unconfirmed; DHAP: dexamethasone, cytarabine, cisplatinum; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HIV: human immunodeficiency virus; N/A: not applicable; ICE: ifosfamide, carboplatinum, etoposide; IPI: International Prognosis Index; NHL: non-Hodgkin lymphoma; NR: not reported; ORR: overall response rate; OS: overall; PR: partial response

SCHOLAR-1

Location where the test was performed	Multiple countries (e.g., US, Canada, UK, etc.)
Participant recruitment period	2001-2014
Population	• All patients from each data source who met criteria for refractory DLBCL, including tFL and primary mediastinal B-cell lymphoma (PMBCL), who went on to receive subsequent therapy were considered for analysis; tFL and PMBCL were included because they are histologically similar and clinically treated as large cell lymphoma • Refractory DLBCL, defined as progressive disease or stable disease as best response to chemotherapy (received ≥4 cycles of first-line therapy or 2 cycles of later-line therapy, respectively) or relapse ≤12 months (365 days) post-ASCT • Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as one of their prior regimens
Major exclusion criteria	• Patients with primary central nervous system lymphoma were excluded
Details of interventions	Chemotherapies (e.g., +/- rituximab and GDP, DHAP, ICE, etc.)

Details of the comparison	N/A
Study Design	Retrospective meta-analysis of four studies (multi-country): • 2 phase III randomized controlled trials - Lymphoma Academic Research Organization-CORAL - Canadian Cancer Trials Group study LY.12 • 2 observational cohorts - MDACC - IA/MC
Blinding method	None (open label)
Primary endpoint	• ORR • CR • PR • OS
Key secondary endpoints	N/A
Statistical methods	• Higgin's Q statistic was used to assess the heterogeneity of response rate between the source databases • Response rates were estimated from the pooled data with a random effects model • Covariates for response were evaluated with a Cochran-Mantel-Haenszel test stratified by institution • Survival was estimated, and covariates were assessed by a Cox proportional hazards model stratified by data source
Sample size	• Primary abstraction: N=861 • Analysis set (baseline characteristics reported): N=636 - MDACC: N=165 (out of 191) - IA/MC: N=82 (out of 107) - LY.12: N=219 (out of 353) - CORAL: N=170 (out of 210) • Patients evaluated for response: N=523 • Patients evaluated for survival: N=603
Follow-up period	Range: 1-14 years
Major background factors of subjects	• Age: median 55 years • Sex: 64% male

	• Predominant histology: 87% DLBCL, 4% tFL, 2% PMBCL, 7% missing • ECOG performance status: 73% 0-1, 14% 2-4, 13% missing • Disease stage: 27% I-II, 72% III-IV, <1% missing • Number of lines of prior chemotherapy and ASCT: 28% 1, 49% 2-3, <1% ≥4 • IPI risk classification: 25% low risk, 57% intermediate-high risk , 18% missing or incompletely assessed
Results of the primary endpoint	• ORR: 26% • CR: 7% • PR: 18% • Median OS: 6.3 (95% CI: [5.9, 7.0]) months
Results of major secondary endpoints	N/A
Limitation of the study	As a retrospective study, limitations of the direct applicability of the results to future studies may exist.

Abbreviations: ASCT: autologous stem cell transplant; CI: confidence interval; CR: complete response; DHAP: dexamethasone, cytarabine, cisplatinum; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; GDP: Gemcitabine, Cisplatin, and Dexamethasone; IA/MC: Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence; ICE: ifosfamide, carboplatinum, etoposide; IPI: International Prognosis Index; MDACC: MD Anderson Cancer Center; N/A: not applicable; PMBCL: primary mediastinal B-cell lymphoma; tFL: transformed follicular lymphoma; ORR: overall response rate; OS: overall; PR: partial response

Appendix B. Search Terms for SLRs
B-1. B-ALL (Global)

Database	Medline und Medline In-Process
Interface/URL	PubMed
Date run	[redacted]
Search Period	

#	Search terms	Results
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])	50,600
2	relapsed OR relapses OR relapsing OR refractory OR chemorefractory OR drug-resistant OR "drug resistant" OR failed OR failure OR "transplant ineligible" OR "stem cell transplant ineligible" OR "SCT ineligible"	2,168,848
3	#1 AND #2	12,148
4	"Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [ptyp] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [ptyp] OR "Cross-Over Studies"[Mesh] OR "Prospective Studies"[Mesh] OR random* OR "random allocation" OR randomized OR randomised OR "double-blind" OR "single-blind" 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"[ptyp] OR "Clinical Trial, Phase I"[ptyp] OR "Clinical Trial, Phase II"[ptyp] OR "Clinical Trial, Phase III"[ptyp] OR "Clinical Trial, Phase IV" [ptyp] OR "Controlled Clinical Trial"[ptyp] OR "Multicenter Study"[ptyp] OR placebo* OR "prospective study" OR single-arm 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	1,718,977
5	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 non-randomized OR nonrandomized	9,570,347
6	#4 OR #5	10,009,891
7	#3 And #6	6,520
8	#7 limited to articles published in English or German language	5,992

Database EMBASE Addressembase.com Date Searched [redacted] Search Period [redacted]		
#	Search terms	Results
1	('acute lymphocytic leukemia'/exp OR 'acute lymphocytic leukaemia' OR 'acute lymphoblastic leukemia'/exp OR 'acute lymphoblastic leukaemia') OR ((lymphocyt* OR lymphoblast* OR lymphat* OR lymphoid*) NEAR/1 (leukemi* OR leukaemi*)):ab,ti AND (acute NEAR/3 (lymphocyt* OR lymphoblast* OR lymphat* OR lymphoid*)):ab,ti	71,154
2	relapsed OR relapses OR relapsing OR refractory OR chemorefractory OR failed OR failure OR 'transplant ineligible' OR 'stem cell transplant ineligible' OR 'SCT ineligible'	1,972,579
3	#1 AND #2	13,534
4	'crossover procedure' OR random* OR 'random allocation' OR randomized OR randomised OR 'double-blind' OR 'single-blind' OR 'single blind' OR 'double blind' OR 'clinical trial' OR 'phase 1' OR 'phase 2' OR 'phase 1/2' OR 'phase 1/phase 2' OR 'phase 3' OR 'phase 4' OR placebo* OR 'prospective study' OR 'single arm' 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 'clinical trial'/it OR 'clinical trial (topic)'/it OR 'controlled clinical trial'/it OR 'controlled study'/it OR 'major clinical study'/it OR 'multicenter study'/it OR 'phase 1 clinical trial'/it OR 'phase 2 clinical trial'/it OR 'phase 2 clinical trial (topic)'/it OR 'prospective study'/it OR 'randomized controlled trial'/it	3,331,653
5	'controlled study' OR 'treatment outcome' OR 'major clinical study' OR change OR changes OR evaluate OR evaluated OR evaluating OR reviewed OR prospective OR prospectively OR retrospective OR prospectively OR baseline OR cohort OR consecutive OR consecutively OR compare OR compares OR compared OR comparison OR comparisons OR 'case series' OR 'comparative studies' OR 'follow-up studies' OR registry OR observational OR non-randomized OR nonrandomized	16,263,005
6	#4 OR #5	16,885,992
7	#3 And #6	10,137
8	#7 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	6,466
9	#8 limited to articles published in English or German language	6,048

Database	COCHRANE Central Register of Controlled Trials	
Interface/URL	Cochrane Library	
Date Run	[redacted]	
Search Period	[redacted]	
#	Search terms	Results
1	MeSH descriptor: [Precursor Cell Lymphoblastic Leukemia-Lymphoma] explode all trees	1,030
2	"acute lymphocytic leukemia" OR "acute lymphoblastic leukemia" OR "acute lymphocytic leukaemia" OR "acute lymphoblastic leuakemia" OR ((lymphocyt* OR lymphoblast* OR lymphat* OR lymphoid*) NEAR/1 (leukemi* OR leukaemi*)):ab,ti AND (acute NEAR/3 (lymphocyt* OR lymphoblast* OR lymphat* OR lymphoid*)):ab,ti	3,128
3	relapsed OR relapses OR relapsing OR refractory OR failed OR failure OR "transplant ineligible" OR "stem cell transplant ineligible" OR "SCT ineligible"	139,258
4	(#1 OR #2) AND #3	913

Trial Register	clinicaltrials.gov
Internet address	www.clinicaltrials.gov
Date Searched	[redacted]
Search Terms	Search Terms = (Acute Lymphocytic Leukemia OR Acute Lymphoblastic Leukemia OR Acute Lymphocytic Leukaemia OR Acute Lymphoblastic Leukaemia) AND (relapsed OR refractory)
Results	**907**

Trial Register	ICTRP
Internet address	http://apps.who.int/trialsearch/Default.aspx
Date Searched	[redacted]
Search Terms	Advanced Search: in the Title: Acute lymphocytic leukemia OR acute Lymphoblastic leukemia OR Acute lymphocytic leukaemia OR acute Lymphoblastic leukaemia in the Condition: refractory OR relapsed Recruitment Status: ALL
Results	**89**

Trial Register	EU-CTR
Internet address	www.clinicaltrialsregister.eu/ctr-search/search
Date Searched	[redacted]
Search Terms	Search Terms= ((acute lymphocytic leukemia OR acute lymphoblastic leukemia) AND (relapsed OR refractory)) OR

	((acute lymphocytic leukaemia OR acute lymphoblastic leukaemia) AND (relapsed OR refractory))
Results	**62**

B-2. B-ALL (Japanese)
Pubmed

項目	通番	検索式	結果数
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])	51,670
	#2	relapsed OR relapses OR relapsing OR refractory OR chemorefractory OR drug-resistant OR "drug resistant" OR failed OR failure OR "transplant ineligible" OR "stem cell transplant ineligible" OR "SCT ineligible"	2,223,236
	#3	#1 AND #2	12,485
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 "single-blind" 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 single-arm 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	10,287,833

		"comparative studies" OR "follow-up studies" OR registry OR observational OR non-randomized OR nonrandomized	
Combined terms and limits	#5	#3 AND #4	6,709
	#6	#5 AND [redacted][DP]	4,121
Japanese population	#7	#6 AND (Japan*[all fields] or Asia*[all fields])	273

医中誌

項目	通番	検索式	結果数*
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))	18,293
	#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))	386,962
	#3	#1 AND #2	2,796
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	36,277

Combined terms and limits	#5	#3 AND #4	22
	#6	#5 AND (DT=[redacted])	21

B-3. DLBCL (Global)
Search terms for studies through Ovid

#	Search Term
1	exp Lymphoma, Large B-Cell, Diffuse/ or exp Lymphoma, Large-Cell, Anaplastic/ or exp Lymphoma, Primary Cutaneous Anaplastic Large Cell/ or ('Lymphoma$, Large B-Cell, Diffuse' OR 'diffuse large B-cell lymphoma$' OR 'diffuse large B cell lymphoma$' OR 'DLBCL' OR 'Lymphoma$, Large-Cell, Anaplastic' OR 'Lymphoma$, Primary Cutaneous Anaplastic Large Cell' OR 'Aggressive non Hodgkin$ lymphoma$' OR 'Aggressive NHL' OR 'large B cell lymphoma$' OR 'diffuse lymphoma$' OR 'diffuse non Hodgkin$ lymphoma$' OR 'large B cell non-Hodgkin$ lymphoma$' OR 'Large Cell Lymphoma$').ab,ti
2	(Recurrence or recurrent or recurring or refractory or relaps$ or "R/R" or fail$).tw.
3	***1 AND 2***
4	exp animal/
5	nonhuman/
6	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.
7	OR/4-6
8	exp Human/ or "Human Experiment"/
9	7 NOT (7 AND 8)
10	***3 NOT 9***
11	remove duplicates from 10
12	limit 11 to English
13	***limit 12 to yr=*** [redacted]

Search terms for clinical trials in clinical trial registries (clinicaltrials.gov)

#	Search Term
1	Diffuse Large B Cell Lymphoma Refractory
2	Diffuse Large B Cell Lymphoma Recurrent
3	1 OR 2

Search terms for clinical trials in clinical trial registries (EU-CTR)

#	Search Term
1	DLBCL
2	"diffuse large B cell lymphoma"
3	("Refractory" OR "Relapsed")

4	1 OR 2
5	3 AND 4

Search terms for clinical trials in clinical trial registries (ICTR)

#	Search Term
1	DLBCL
2	diffuse large b cell lymphoma
3	diffuse large b-cell lymphoma
4	refractory OR relapsed
5	1 OR 2 OR 3
6	4 AND 5

B-4. DLBCL (Japanese)
PubMed

項目	通番	検索式	結果数
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]))	90,288
	#2	Recurrence[TIAB] OR recurrent[TIAB] OR recurring[TIAB] OR refractory[TIAB] OR relaps*[TIAB] OR "R/R"[TIAB] OR fail*[TIAB]	1,739,474
	#3	#1 AND #2	16,187
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 "single-blind" 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 single-arm OR "single arm" OR open-label OR "open label" OR trial OR "nonblinded" OR non-blinded	10,287,833

		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 non-randomized OR nonrandomized	
Combined terms and limits	#5	#3 AND #4	8,955
	#6	#5 AND [redacted][DP]	6,801
Japanese population	#7	#6 AND (Japan*[all fields] or Asia*[all fields])	634

医中誌

項目	通番	検索式	結果数
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))	71,195
	#2	(再発/TH or 再発/AL or relapse/AL) or (難治性/AL or refractory/AL) or 失敗/AL	295,196
	#3	#1 AND #2	7,365
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	36,277

		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	
Combined terms and limits	#5	#3 AND #4	81
	#6	#5 AND (DT=[redacted]	80

Appendix C. Summary of goodness of fit statistics and weights for survival distributions

C-1. B-ALL: OS

Summary of goodness of fit statistics and weights for OS survival distributions (age < 15 years)

Distribution	AIC[b]	AIC based weight[c]
Tisagenlecleucel		
Exponential	[redacted]	[redacted]
Weibull		
Gompertz		
Log-Normal		
Log-Logistic		
Gamma		
Spline with single knot[a]		
Spline with two knots[a]		
Spline with three knots		
Spline with four knots[a]		
Blinatumomab		
Exponential	309.73	2.0%
Weibull	310.23	1.6%
Gompertz	305.97	13.1%
Log-Normal	304.33	29.9%
Log-Logistic	305.07	20.6%
Gamma	306.02	12.8%
Spline with single knot[a]	306.03	12.8%
Spline with two knots[a]	308.09	4.6%
Spline with three knots[a]	309.77	2.0%
Spline with four knots[a]	311.90	0.7%

Abbreviation: AIC, Akaike information criterion

a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.

b. A smaller AIC value represents a better goodness of fit.

c. The weights were calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

Summary of goodness of fit statistics and weights for OS survival distributions (age 15-25 years)

Distribution	AIC[b]	AIC based weight[c]
Tisagenlecleucel		
Exponential	[redacted]	[redacted]
Weibull		
Gompertz		
Log-Normal		
Log-Logistic		
Gamma		
Spline with single knot[a]		

Distribution	AIC[b]	AIC based weight[c]
Spline with two knots[a]	[redacted]	[redacted]
Spline with three knots[a]		
Spline with four knots[a]		%
Blinatumomab		
Exponential	349.27	0.7%
Weibull	348.91	0.9%
Gompertz	343.23	14.7%
Log-Normal	341.89	28.6%
Log-Logistic	343.08	15.8%
Gamma	343.15	15.3%
Spline with single knot[a]	343.11	15.6%
Spline with two knots[a]	345.20	5.5%
Spline with three knots[a]	346.95	2.3%
Spline with four knots[a]	349.12	0.8%
Inotuzumab		
Exponential	280.94	0.5%
Weibull	281.58	0.4%
Gompertz	274.47	13.4%
Log-Normal	274.06	16.5%
Log-Logistic	274.17	15.6%
Gamma	274.91	10.7%
Spline with single knot[a]	274.30	14.6%
Spline with two knots[a]	273.78	18.9%
Spline with three knots[a]	276.23	5.6%
Spline with four knots[a]	276.98	3.8%

Abbreviation: AIC, Akaike information criterion
a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.
b. A smaller AIC value represents a better goodness of fit.
c. The weights were calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and are used in the calculation for the weighted distribution.

C-2. B-ALL: EFS

Summary of goodness of fit statistics and weights for tisagenlecleucel EFS survival distributions (age < 15 years)

Distribution	AIC[b]	AIC based weight[c]
Tisagenlecleucel		
Exponential	[redacted]	[redacted]
Weibull		
Gompertz		
Log-Normal		
Log-Logistic		
Gamma		
Spline with single knot		
Spline with two knots[a]		

Distribution	AIC[b]	AIC based weight[c]
Spline with three knots[a]	[redacted]	[redacted]
Spline with four knots[a]		

Abbreviation: AIC, Akaike information criterion

a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.

b. A smaller AIC value represents a better goodness of fit.

c. The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and were used in the calculation for the weighted distribution.

Summary of goodness of fit statistics and weights for tisagenlecleucel EFS survival distributions (age 15-25 years)

Distribution	AIC[b]	AIC based weight[c]
Tisagenlecleucel		
Exponential	[redacted]	[redacted]
Weibull		
Gompertz		
Log-Normal		
Log-Logistic		
Gamma		
Spline with single knot[a,d]		
Spline with two knots[a,d]		
Inotuzumab		
Exponential		
Weibull		
Gompertz		
Log-Normal		
Log-Logistic		
Gamma		
Spline with single knot[a,d]		
Spline with four knots[a,d]		

Abbreviation: AIC, Akaike [redacted] n criterion

a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.

b. A smaller AIC value represents a better goodness of fit.

c. The weights are calculated based on AIC scores using the method outlined in Jackson 2009. The weights represent the adequacy of each distribution in predicting the efficacy and were used in the calculation for the weighted distribution.

d. Cubic spline models with three and four knots could not converge using observed EFS data based on the pooled trial data. Cubic spline model with two and three knots could not converge using observed EFS data of inotuzumab. No parametric functions were estimated for tisagenlecleucel or inotuzumab using these models. The AIC weight calculation was based on the remaining functions.