Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value

Evidence Report

February 15, 2018

Prepared for

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/topic/car-t/.

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Table of Contents

List of Acronyms Used in this Report

AE	Adverse event
AIC	Akaike information criterion
AHRQ	Agency for Healthcare Research and Quality
B-ALL	B-cell Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplant
ASP	Average sales price
Auto-SCT	Autologous stem cell transplant
CAR-T	Chimeric antigen receptor T-cell
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery (leukemia)
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
DLCBL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group Performance Status
FDA	US Food and Drug Administration
F/U	Follow up
ICU	Intensive care unit
IAMC	University of Iowa/Mayo Clinic
LP	Lumbar puncture
MDACC	MD Anderson Cancer Center
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
OS	Overall survival
ORR	Objective remission rate (leukemia), objective response rate (lymphoma)
Ph+/-	Philadelphia chromosome positive/negative
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial remission (leukemia); partial response (lymphoma)
PFS	Progression-free survival
RFS	Relapse-free survival
SCT	Stem cell transplant
US	United States
TFL	Transformed follicular lymphoma
TKI	Tyrosine kinase inhibitor
Tx	Treatment or therapy
WAC	Wholesale acquisition cost

Executive Summary

Background

Lymphomas and leukemias are cancers of the white blood cells. While both cancers arise in the bone marrow, lymphomas tend to form solid masses in lymph nodes and other places in the body, while leukemias primarily circulate in the bloodstream. There are many different types of lymphomas and leukemias. Both can arise from a subset of white blood cells called lymphocytes. There are two primary kinds of lymphocytes: B-lymphocytes and T-lymphocytes. The B-cells primarily produce antibodies that help to fight off infections while the T-cells help to kill off abnormal cells, like cancer cells and those infected by viruses. Both types of lymphocytes are important for this review, which focuses on chimeric antigen receptor T-cell (CAR-T) therapy for B-cell malignancies.

Childhood B-Cell Acute Lymphoblastic Leukemia (B-ALL)

Pediatric acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. There are over 3,000 new cases of ALL diagnosed in children and adolescents (ages 0-19) each year in the United States (US).[1] Over the past few decades, treatment has improved dramatically and the five-year survival rate, which is generally considered clinically equivalent to a cure, is approximately 85%.[2-4] Among the 15% of patients who do not respond to initial treatment or relapse after initial treatment, the prognosis is poor. Current salvage regimens for pediatric ALL may include clofarabine (Clolar®, Sanofi-Genzyme) or blinatumomab (Blincyto®, Amgen). Allogenic stem cell transplant (allo-SCT) is used for appropriate patients who attain remission with salvage treatment. Better therapies are needed for those children with relapsed/refractory disease.

Aggressive B-Cell Non-Hodgkin's Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of adult non-Hodgkin's lymphoma (NHL), accounting for approximately 25% of newly diagnosed cases of NHL in the United States. DLBCL is an *aggressive* (i.e., fast-growing) lymphoma. Other aggressive B-cell lymphomas include transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL). The usual treatment for aggressive B-cell lymphoma involves systemic chemoimmunotherapy. Five-year survival is approximately 50-70%.[5,6] Current salvage regimens for DLBCL may include R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, and etoposide phosphate), and others. Patients who do not respond to second-line therapy or progress after transplant currently only have palliative options available.

Chimeric Antigen Receptor T-Cell Therapy as a New Treatment Option

CAR-T therapy is a novel cellular therapy that uses genetic engineering to alter a patient's own T-cells to produce transmembrane proteins on their cell surface with an extracellular antibody fragment domain that recognizes a specific protein. Both tisagenlecleucel (Kymriah™, Novartis) and axicabtagene ciloleucel (Yescarta™, Kite Pharma/Gilead) are second-generation CAR-T therapies that target the CD19 antigen, which is exclusively expressed on B cells, including the cancer cells in B-ALL and the aggressive B-cell NHLs described above.

Studies of tisagenlecleucel have primarily focused on patients with relapsed/refractory B-ALL up to the age of 25 years.[7-9] In addition, Novartis has applied to the FDA for an indication for tisagenlecleucel to treat relapsed/refractory DLBCL and has plans to file for other indications in 2018.[10] Studies of axicabtagene ciloleucel have to date focused on patients with relapsed/refractory aggressive NHL.[11-14]

Both therapies require leukapheresis, in which the patient's own peripheral blood mononuclear cells containing T-cells are removed from their body. The cells are then shipped to a central facility that engineers the CAR T-cells using retroviruses to insert the DNA for the chimeric protein into the DNA of the patient's T-cells. The newly engineered cells are then frozen and shipped back to the treating institution, where they are infused back into the patient's bloodstream to fight the cancer. Currently, this manufacturing process takes a minimum of about two to three weeks from leukapheresis to the time the engineered cells are ready to be infused back into the patient. During that time period, some of the patients will die and others will become too sick to tolerate treatment with the CAR-T cells. In addition, the manufacturing process occasionally fails to produce an adequate number of CAR-T cells for infusion.

During the manufacturing process, the majority of patients require some form of bridging chemotherapy to keep their cancer stable. Just prior to infusion of the T-cells, patients also undergo lymphodepleting chemotherapy (often fludarabine plus cyclophosphamide) in order to decrease the number of competing lymphocytes.

As the CAR T-cells proliferate in the patient and kill tumor cells, they release cytokines, which are chemical messengers used by cells to communicate with each other. A prominent side effect of CAR-T therapy is cytokine release syndrome (CRS), in which the release of many cytokines by the CAR T-cells causes high fevers, low blood pressure, and respiratory distress that may require care in an intensive care unit (ICU). This serious side effect has been observed in about one-third of patients treated with CAR-T therapy and may be related to the volume of cancer cells at the time of treatment, though it remains an area of active research.[15] Another common and feared side effect is neurotoxicity, which also affects more than a third of patients. The most common neurologic side effects include encephalopathy, headache, delirium, aphasia, anxiety, and tremors.

Costs for the approved therapies may range from approximately $350,000 to $500,000. This does not include potential hospital mark-up for the therapy, nor the additional costs of hospital care during the preparation and administration of the CAR-T therapy as well as management of side effects. Novartis has entered into an outcomes-based pricing arrangement with the Centers for Medicare and Medicaid Services (CMS) in which it appears that payment will be provided only for pediatric and young adult patients who respond to treatment with tisagenlecleucel at the end of the first month post-infusion.[10]

Insights Gained from Discussions with Patients and Patient Groups

Several themes emerged from our discussion with patients and patient groups. One was hope – CAR-T therapy represented hope for a cure in patients who had run out of treatment options. They were encouraged by the high initial response rates seen in the clinical trials. In addition, they hoped that CAR-T therapy would be less toxic than chemoradiation and SCT: no hair loss, mucositis, diarrhea, and nausea, and less time in the hospital.

A second related theme was fear of the unknown. Patients understood that very few other patients have been treated with CAR-T therapy and were worried about the side effects. Neurotoxicities were particularly terrifying. It is scary for patients to think that they will be mentally impaired, not in control of their thoughts, and unaware of what is going on. It is also frightening for loved ones who have to witness those symptoms. Patients felt that it was particularly important to educate both prospective patients and their families about what to expect in detail, not just in general terms. Patients and parents spoke of the comfort of talking to those who had already gone through treatment with CAR-T – that this was a way to alleviate some of the fear and anxiety.

They also spoke of the many other uncertainties. Would the early remission rates hold up over time? Were there long-term side effects that would only become evident five or 10 years from now? Would they need to undergo SCT following CAR-T therapy?

Some patients highlighted the non-medical costs associated with treatment. Most had to travel long distances to the centers that offered CAR-T therapy. The time off work for family members loomed large, as did the cost of travel, including living expenses during treatment periods and post-treatment surveillance for side effects, but they felt that they had no choice; parents, in particular, spoke of doing anything for their child with leukemia.

In addition to education about side effects, patients and parents spoke of the emotional toll of the cancer and cancer treatment. They pointed to post-traumatic stress that continues long after therapy is completed. They felt that it was important to include emotional/psychological counseling for both the patient and their loved ones.

Potential Cost-Saving Measures in ALL/Lymphoma

We sought to identify areas of waste and low-value care in the treatment of leukemias and lymphomas that could be reduced to increase the capacity of health care budgets to pay for new innovations. The American Society of Clinical Oncology (ASCO) has several Choosing Wisely recommendations that have the potential to be cost-saving in the treatment of leukemias and lymphomas:[16]

- Do not routinely use PET or PET-CT scans for follow-up visits to detect cancer recurrence in asymptomatic patients who have completed initial treatment, unless high-level evidence suggests that such imaging will change the outcome.
- Avoid the use of white cell stimulating factors for primary prevention of febrile neutropenia in patients whose risk for this complication is less than 20%.

Comparative Clinical Effectiveness

The comparative clinical effectiveness review of the CAR-T therapies with other salvage therapies for ALL or DLBCL was challenged because all of the clinical studies were small, single-arm designs with limited follow-up and incomplete reporting. Since no trials had control groups, it was not possible to estimate the comparative benefits or harms of these novel therapies in relation to prior therapies with FDA indications for the same patient populations using either direct or indirect comparisons. Thus, all comparisons of outcomes of CAR-T therapy to other therapies used for the same indication are naïve indirect comparisons that should be considered descriptive and potentially subject to significant selection bias and other confounding factors. Furthermore, the small sample sizes and short follow-up add to the uncertainty for estimates of clinical efficacy. Finally, some of the pivotal trials have yet to be published in peer-reviewed journals, so we are dependent on grey literature for our data including conference presentations, public FDA submission documents, data supplied by manufacturers, and the package inserts for the therapies.

Clinical Benefits

The results are organized by clinical indication. In the first section, we review CAR-T therapy for relapsed or refractory pediatric B-cell ALL. Our search identified three single-arm trials of tisagenlecleucel for this indication. Caution should be taken when interpreting any comparisons across trials due to the potential for significant selection bias.

In the second section, we review CAR-T therapy for relapsed or refractory aggressive B-cell lymphomas (primarily DLBCL). For both tisagenlecleucel and axicabtagene ciloleucel, our search identified one single-site, single-arm trial and one multi-center pivotal single-arm trial. We used the SCHOLAR-1 trial[17] as an example of outcomes of alternative therapies in a similar population.

Pediatric B-Cell ALL

There are three single-arm trials of tisagenlecleucel for pediatric ALL. The three trials and four additional studies of other FDA-approved therapies for similar patient populations are summarized in Table ES1 below.

Table ES1. Summary of Treatments for Relapsed/Refractory Pediatric B-ALL

Trial/Therapy	N Infused	Median Age (Years)	Median Number Prior Treatments	Prior SCT
B2101J;[18] tisagenlecleucel	55	11	4	72%
B2205J;[18] tisagenlecleucel	29	12	3	59%
B2202/ELIANA;[19] tisagenlecleucel	68	11	3	61%
Jeha 2006;[20] clofarabine	61	12	3	30%
Hijiya 2011;[21] clofarabine + etoposide, cyclophosphamide	25	14	2	16%
Von Stackelberg 2016 (MT103-205);[22] blinatumomab	70	8	2	57%
Locatelli 2017 (RIALTO);[23] blinatumomab	40	9	2	53%

B-ALL: B-cell Acute lymphoblastic leukemia, SCT: Stem cell transplant

Quality of Individual Studies

The three studies of tisagenlecleucel are considered to be of lower quality because they lack comparators. Furthermore, the studies are small and have short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for pediatric B-cell ALL.

Clinical Benefits

The key clinical outcome from the patient's perspective is curing the cancer. There is no accepted definition of a cure, as relapses can rarely occur more than 10 years after remission. A recent proposal is that children in remission four years after the completion of treatment could be considered cured (< 1% chance of relapse).[24,25] Thus, four-year event-free survival would be an ideal outcome. Thus far, none of the trials of CAR-T therapy have followed patients for that long.

The reported overall remission rates for tisagenlecleucel in the three trials (from 69% to 95%) represents an optimistic presentation of the results that violates the intention to treat principle because they exclude patients who did not receive the therapy because of manufacturing failures, death prior to infusion, or adverse events (AEs). Table ES2 estimates the overall remission rates in the trials based on the number of patients enrolled in each trial (i.e., on an intention to treat basis).

Table ES2. Overall Remission Rates in Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Overall Remission*
B2101J[18]	Tisagenlecleucel	52/71 = 73% (61% to 83%)
B2205J[18]	Tisagenlecleucel	20/35 = 57% (39% to 74%)
B2202 / ELIANA[19]	Tisagenlecleucel	61/92 = 66% (56% to 76%)
Jeha 2006[20]	Clofarabine	12/61 = 20% (11% to 32%)
Hijiya 2011[21]	Clofarabine/etoposide/ cyclophosphamide	11/25 = 44% (24% to 65%)
Von Stackelberg 2016[22]	Blinatumomab	27/70 = 39% (27% to 51%)
Locatelli 2017[23]	Blinatumomab	25/40=63% (46% to 77%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells

While this presentation suggests more modest benefits, the overall remission rates are higher with tisagenlecleucel than with the other therapies.

Table ES3 below estimates the overall event-free survival in the trials based on the number of patients enrolled.

Table ES3. Estimated Event-Free Survival at Six Months in Therapies for Relapsed or Refractory Childhood B-ALL

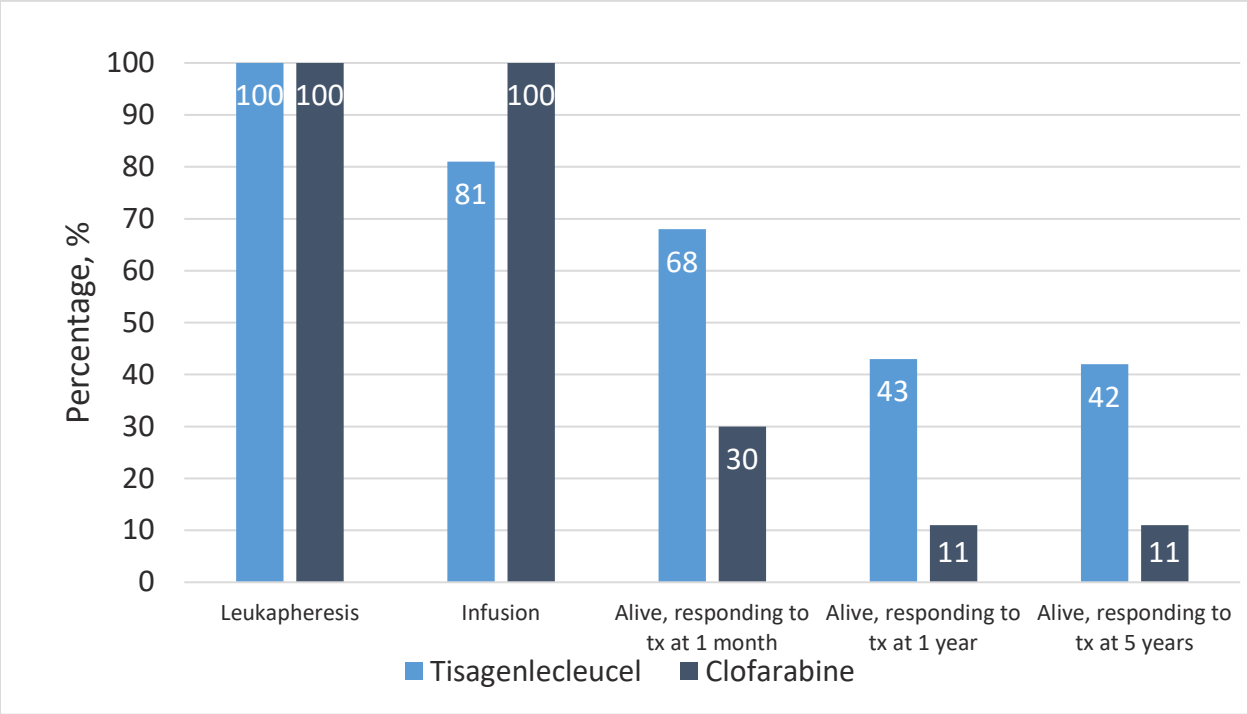
Trial	Therapy	Event-free Survival at 6 Months*	Overall Survival at 12 Months
B2101J[18]	Tisagenlecleucel	58%	81%
B2205J[18]	Tisagenlecleucel	46%	62%
B2202 / ELIANA[19]	Tisagenlecleucel	60%	62%
Jeha 2006[20]	Clofarabine	11%	20%
Hijiya 2011[21]	Clofarabine/etoposide/ cyclophosphamide	35%	35%
Von Stackelberg 2016[22]	Blinatumomab	16%	38%
Locatelli 2017[23]	Blinatumomab	NR	NR

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells or the number responding to treatment

Based on the reported event-free survival curves, we estimated the long-term survival of patients treated with tisagenlecleucel[26] or with clofarabine[20] using the parametric extrapolation used for the cost-effectiveness evaluation, as described in Section 4.2 of the full report. Data for tisagenlecleucel were pooled from all three available trials. We made the comparison at the time of leukapheresis for CAR-T therapy to account for the time required to manufacture the CAR-T cells, which is time that would otherwise be spent undergoing treatment. These estimates suffer from considerable uncertainty because the trials are small, have median follow-ups of less than two years, and had different inclusion and exclusion criteria. However, the comparisons are useful as a

guide to the potential magnitude of benefit for tisagenlecleucel compared to other recent therapies for children with relapsed or refractory ALL.

Figure ES1. Comparison of Estimated Outcomes for Tisagenlecleucel and Clofarabine*



*For clofarabine, the data for leukapheresis and infusion represent the same time point, since no leukapheresis is necessary
tx: treatment

Harms

The key AEs experienced by the first 68 patients who received an infusion of tisagenlecleucel in the ELIANA trial were reported in the package insert[27] and are summarized in Table ES4 below.

Table ES4. Key Adverse Events in the ELIANA trial (n=68)[27]

Adverse Reaction	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	79%	49%
Neurologic Toxicities	65%	18%
Fever	50%	15%
Encephalopathy	34%	10%
Headache	37%	3%
Acute Kidney Injury	22%	13%
Hypotension	31%	22%
Hypoxia	24%	18%
Infections – Pathogens Unknown	41%	16%
Viral Infections	26%	18%
Bacterial Infections	19%	13%
Fungal Infections	13%	7%

Additional important grade three or higher adverse events include disseminated intravascular coagulation (9%), histiolymphocytic hemophagocytosis (7%), heart failure (7%), cardiac arrest (4%), seizures (3%), and intracranial hemorrhage (1%). There were 11 deaths: 7 from disease progression, 3 from infections, and one from intracranial hemorrhage.

An additional important toxicity is hypogammaglobulinemia due to B-cell aplasia. B-cells are the target of tisagenlecleucel in order to keep the leukemia in remission. Patients without the immunoglobulins produced by B-cells are at risk for infections and are typically treated with monthly intravenous infusions of pooled immunoglobulins (IVIG). The Novartis briefing document for the FDA Advisory Committee states that "responding patients experienced continued B-cell aplasia indicating the long-term effect of tisagenlecleucel" and notes "B-cell aplasia ongoing for > 3 years."[18] For those who require IVIG, the typical duration of use is unknown.

Adult Aggressive B-Cell Lymphoma

There are two single-arm trials of axicabtagene ciloleucel for adult B-cell lymphoma and two single-arm trials of tisagenlecleucel for the same population. The four CAR-T trials and an additional study of other therapies in similarly heavily pre-treated patients with B-cell lymphomas (SCHOLAR-1) are summarized in Table ES5 below.

Table ES5. Summary of Treatments for Relapsed/Refractory Adult B-Cell Lymphoma

Trial	N Infused	Median Age (Years)	Median Number Prior Treatments	Prior SCT
Axicabtagene Ciloleucel				
NCT00924326[12]	22	58	4	23%
ZUMA-1[28]	101	58	3	21%
Tisagenlecleucel				
JULIET[29]	99	56	3	47%
NCT02030834[30]	28	57	4	35%
Mix of Salvage Chemoimmunotherapies				
SCHOLAR-1[17]	636	55	2	22%

SCT: stem cell transplant

Quality of Individual Studies

The ZUMA-1 and JULIET studies as well as the two single site studies were considered to be of lower quality because they lack comparators. Furthermore, the studies were small and of short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for adult aggressive B-cell lymphoma.

Clinical Benefits

As with ALL above, the clinical outcome that matters most to a patient with lymphoma is curing the cancer. There is no accepted definition of a cure in relapsed or refractory lymphoma. A 2014 publication proposed that event-free survival two years after the completion of treatment could be a reasonable surrogate outcome.[31] Both the ZUMA-1 and JULIET studies of CAR-T therapies for lymphoma followed patients for less than a median of two years, which limits conclusions about long term impact. Complete remission is a marker for long-term survival, but the majority of patients with B-cell lymphoma who have failed prior therapy usually relapse even after achieving subsequent remission.

Axicabtagene Ciloleucel

There are two trials of axicabtagene ciloleucel in patients with relapsed or refractory aggressive B-cell lymphoma: a single-site trial performed at the National Cancer Institute (NCI) and the pivotal multi-center ZUMA-1 trial (Table ES6 below). For context, we abstracted data from the SCHOLAR-1 trial, which used the same inclusion and exclusion criteria as ZUMA-1 trial to select a subset of patients with aggressive DLBCL.

Table ES6. Objective Response Rates Reported for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
ZUMA-1[28]	Axicabtagene ciloleucel	82%	54%
NCT00924326[12]	Axicabtagene ciloleucel	73%	55%
SCHOLAR-1[17]	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for axicabtagene ciloleucel in ZUMA-1 (54%) shown in Table ES6 represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR-T cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs. Table ES7 below estimates the complete remission rate based on the number of patients enrolled in the trial.

Table ES7. Estimated Complete Remission Rates for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1s

Trial	Therapy	Complete Remission Rate*
ZUMA-1[28]	Axicabtagene ciloleucel	52/111 = 47% (37% to 57%)
NCT00924326[12]	Axicabtagene ciloleucel	12/NR = NR
SCHOLAR-1[17]	Mix of salvage therapies	7% (3% to 15%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells
NR: Not reported

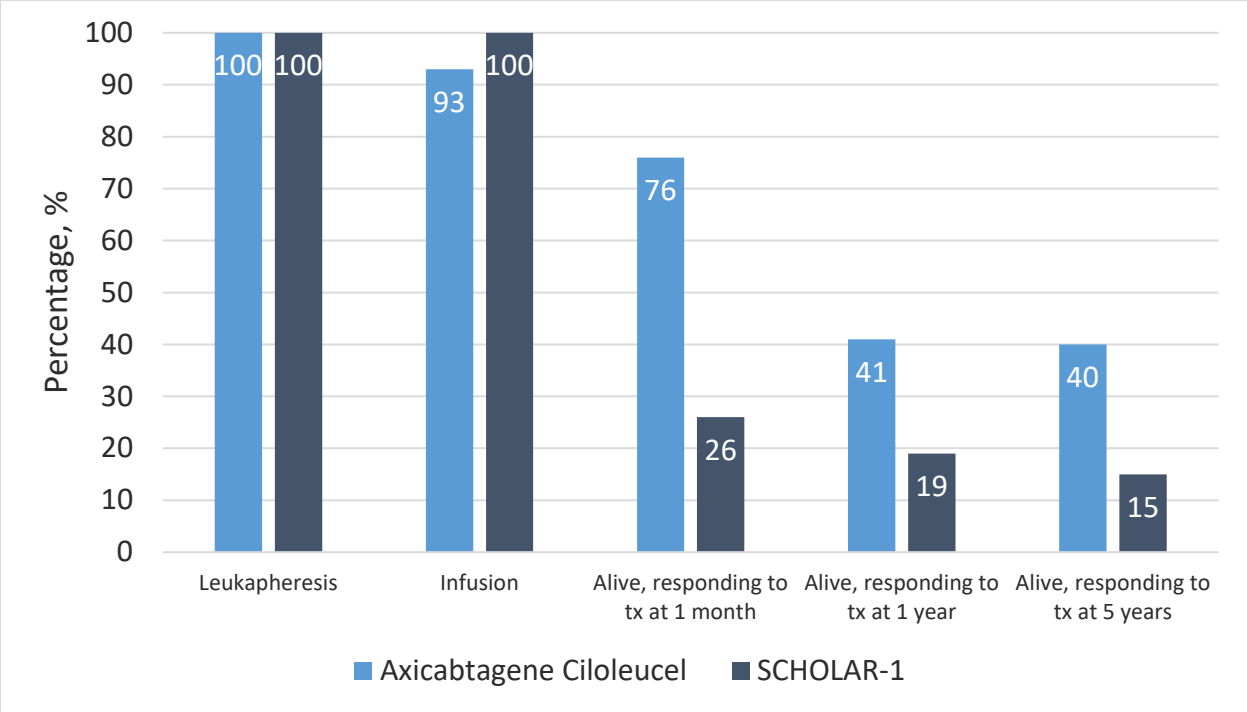
Even with this change, the complete remission rate is much higher with axicabtagene ciloleucel than with the other therapies. In SCHOLAR-1, the median overall survival was 6.3 months and the Kaplan-Meier estimates for one and two-year survival rates were 28% and 20% respectively. At six months, the Kaplan-Meier estimates for overall survival were 80% in ZUMA-1 and 55% in SCHOLAR-1.[32]

Neelapu and colleagues presented a propensity-score-matched analysis comparing the outcomes of ZUMA-1 to those of SCHOLAR-1 at ASH in December 2017.[33] They reported that after matching, the ORR was 83% in ZUMA-1 and 33% in SCHOLAR-1 (treatment difference 49%, 95% CI 33% to 63%). Similarly, the estimated CR was 57% in ZUMA-1 and 12% in SCHOLAR-1 (treatment difference 46%, 95% CI 26% to 59%). The estimated HR for overall survival was 0.28 (95% CI 0.15 to 0.40) with 18-month OS estimated to be 47% in ZUMA-1 and 23% in SCHOLAR-1.

Based on approximations of the event-free survival curves, we estimated the long-term survival of patients treated with axicabtagene ciloleucel and for patients in SCHOLAR-1 using the parametric extrapolation described in Section 4.2 of the full report. We made the comparison at the time of leukapheresis for CAR-T therapy to account for the time required to manufacture the CAR-T cells,

which is time that would otherwise be spent undergoing re-induction treatment. As noted above, these are estimates have considerable uncertainty because the trials are not directly comparable (concerns about selection bias) and because the ZUMA-1 trial is small with median follow-up of 15.4 months. However, the comparisons are useful as a guide to the potential magnitude of benefit for axicabtagene ciloleucel compared to other recent salvage therapies for adults with relapsed or refractory aggressive B-cell lymphoma.

Figure ES2. Comparison of Estimated Outcomes for Axicabtagene Ciloleucel and SCHOLAR-1*



*For the salvage regimens in SCHOLAR-1, the data for leukapheresis and infusion represent the same timepoint, since no leukapheresis is necessary
tx: treatment

Tisagenlecleucel

There are two trials of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphoma: a single site trial performed at the University of Pennsylvania and the pivotal multi-center JULIET trial. The primary reported outcomes are summarized in Table ES8 below.

Table ES8. Objective Response Rates Reported for Tisagenlecleucel for Relapsed or Refractory Adult B-Cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
JULIET[29]	Tisagenlecleucel	53%	40%
NCT00924326[30]	Tisagenlecleucel	64%	57%
SCHOLAR-1[17]	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for tisagenlecleucel in JULIET (40%) represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR-T cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs, nor does it include patients treated with tisagenlecleucel who had less than three months follow-up at the time of analysis. It was not possible to estimate a complete remission rate using an intent-to-treat analysis based on the data available from the public presentations. The reported CR and ORR in the JULIET trial (40% and 53% respectively) were slightly lower compared to the CR and ORR of the subset of patients with DLBCL in the ZUMA-1 trial (n=77) who were treated with axicabtagene ciloleucel (49% and 82%, respectively).[32] However, the confidence intervals overlap extensively, and selection bias may also explain part of the differences. For example, the JULIET trial recruited patients from 10 different countries on 4 continents, while 21/22 sites for the ZUMA-1 trial were in the US (one in Israel). The complete remission rate (43%) among patients who received tisagenlecleucel was markedly higher than that observed in the SCHOLAR-1 trial (7%), which predominantly included adults with DLBCL (87% DLBCL). Given the paucity of the currently reported results for the ongoing JULIET trial, we were unable to project long-term outcomes for comparison with axicabtagene ciloleucel or the salvage regimens included in the SCHOLAR-1 study.

Harms

The key AEs experienced by the 101 patients who received an infusion of axicabtagene ciloleucel in the ZUMA-1 trial are summarized in Table ES9 below.[34]

Table ES9. Key Adverse Events in the ZUMA-1 Trial (n=101)

Adverse Event	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	94%	13%
Neurologic Toxicities	87%	31%
Fever	86%	16%
Encephalopathy	57%	29%
Headache	45%	1%
Renal Insufficiency	12%	5%
Hypotension	57%	15%
Hypoxia	32%	11%
Infections – Pathogens Unknown	26%	16%
Viral Infections	16%	4%
Bacterial Infections	13%	9%
Fungal Infections	5%	NR

Additional important grade 3 or higher adverse events include histiolymphocytic hemophagocytosis (1%), heart failure (6%), cardiac arrest (4%), seizures (4%) and pulmonary edema (9%). There were 44 deaths: 37 from disease progression, two from CRS, one from a pulmonary embolus, and four in patients with disease progression who were on subsequent therapies.

The key AEs experienced by the 99 patients who received an infusion of tisagenlecleucel in the JULIET trial are summarized in Table ES10 below.[29]

Table ES10. Key Adverse Events in the JULIET Trial (n=99)

Adverse Event	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	58%	23%
Neurologic Toxicities	21%	12%
Infections	34%	20%
Cytopenias Not Resolved by Day 28	36%	27%
Febrile Neutropenia	13%	13%
Tumor Lysis Syndrome	1%	1%

There were no deaths or reported cases of cerebral edema.

Finally, there are theoretical concerns about mutagenesis from the insertion of the transgene into the patient's T-cells for both CAR-T therapies. The risk is likely to be quite low, but is an important long-term concern for further study.

Controversies and Uncertainties

First, as highlighted throughout the review, the studies of CAR-T therapies are all single-arm trials. Given the possibility of selection bias in these trials, it is impossible to compare outcomes from these trials to those of other trials without considerable uncertainty.

Second, the trials themselves are small and have short follow-up. The sample sizes with outcomes in the trials are less than 100 participants, and the median follow-up in the trials is less than two years. Thus, estimates of outcomes from the trials have wide confidence intervals; as such, both the benefits and duration of and long-term relapse-free survival is unknown at this point.

A related uncertainty is the long-term harms of therapy. In the intermediate term, there is insufficient data to estimate how many patients will continue to have clinically important hypogammaglobulinemia from B-cell aplasia. There are also theoretical concerns about complications from the viral vectors used in the manufacturing process and of secondary malignancies related to mutations in the T-cells due to the manufacturing process. Finally, there may be unanticipated harms that arise as larger numbers of patients are followed for several years.

All of the uncertainties highlighted above make our comparative efficacy analyses versus standard therapy controversial. Similar concerns apply when comparing tisagenlecleucel to axicabtagene ciloleucel, which are likely to share an indication for DLBCL in the near future.

Summary and Comment

Pediatric B- ALL

The ELIANA trial demonstrated CR rates for tisagenlecleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated pediatric patients with B-cell ALL. In addition, the disease-free survival and OS were also greater than those observed with other therapies, particularly in the earlier Phase I trials that have longer follow-up. There are important harms that occur commonly with tisagenlecleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (clofarabine, blinatumomab, etc.) is low because there are no comparative trials and the existing single-arm trials are small with relatively short follow-up (8.7 months median for the pivotal ELIANA trial). Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy, although the benefit may be substantial ("B+" rating).

Adult Aggressive B-Cell Lymphoma

The ZUMA-1 trial demonstrated CR rates for axicabtagene ciloleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated adults with B-cell lymphoma as reported in the SCHOLAR-1 study. In addition, the disease-free survival and OS appear to be greater than those observed with other therapies, but follow-up in the ZUMA-1 trial is short (median 15.4 months). There are important harms that occur commonly with axicabtagene ciloleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by

clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (R-DHAP, R-ICE, etc.) is low because there are no comparative trials, and the existing single-arm trial is small with short follow-up. Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy although the benefit may be substantial ("B+" rating).

The JULIET trial demonstrated CR rates for tisagenlecleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated adults with B-cell lymphoma as reported in the SCHOLAR-1 study. The follow-up in the JULIET trial is shorter than that for the ZUMA-1 trial, but the earlier single-site trial of tisagenlecleucel provides evidence that the results are likely to be robust with longer follow-up. There are important harms that occur commonly with tisagenlecleucel (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (R-DHAP, R-ICE, etc.) is low because there are no comparative trials and the existing single-arm trial is small with short follow-up and incomplete reporting. Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy, although the benefit may be substantial ("B+" rating).

There are no head to head trials of axicabtagene ciloleucel and tisagenlecleucel for patients with relapsed/refractory B-cell lymphomas. The ORR and CR with axicabtagene ciloleucel are somewhat higher than those for tisagenlecleucel, but could easily reflect differences in the patient populations or chance. Patients treated with axicabtagene ciloleucel appeared to have fewer grade 3/4 CRS events, but more grade 3/4 neurologic events. Again, this may represent real differences in the two CAR-T therapies because of differences in their co-stimulatory domains, selection bias, or chance. The lack of head-to-head randomized trials and the small number of patients studied render such judgements premature. Given the level of uncertainty, the evidence is insufficient to judge whether one of the CAR-T therapies is superior to the other ("I" rating).

Long-Term Cost Effectiveness

The primary aim of this analysis was to estimate the cost-effectiveness of chimeric antigen receptor T-cell (CAR-T) therapies for the treatment of B-cell malignancies. A two-part model, consisting of a short-term decision tree and long-term semi-Markov partitioned survival model, was constructed to compare CAR-T therapies to chemotherapy. Patient survival, quality-adjusted survival, and health care costs from the third-party payer perspective were estimated over a lifetime time horizon for each intervention and comparator. Patient survival was calculated from available Kaplan Meier survival curves which were digitized and extrapolated through five years after treatment initiation, at which point those alive and responding to treatment were considered effectively cured. After

five years, those that were effectively cured exhibited mortality consistent with that of the general population, with adjustments made for the excess mortality (using a standardized mortality ratio) observed among long-term survivors of each B-cell malignancy. Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated by comparing each intervention to its comparator within each B-cell malignancy. While the base-case analysis took a payer perspective, productivity losses to the patient and caregiver were considered in a scenario analysis.

Two separate cohorts were modeled for this review, 1) patients ages 0-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) and 2) adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for auto-SCT. Two CAR-T therapies, tisagenlecleucel and axicabtagene ciloleucel, were compared to chemotherapy. Tisagenlecleucel was modeled in pediatric B-ALL; axicabtagene ciloleucel was modeled in adult B-cell lymphoma. We note that while the available grey literature suggested an evidence rating of "B+" for tisagenlecleucel in B-cell lymphoma, the available data are insufficient to allow for full estimation in our model; therefore, tisagenlecleucel was not modeled in B-cell lymphoma. For tisagenlecleucel, the payment strategy used in the base-case analysis was payment *only* for responders at one month, consistent with public statements from the manufacturer.[10] For axicabtagene ciloleucel, the payment strategy used in the base-case analysis was payment at infusion, consistent with public statements from the manufacturer.[35] Model inputs were informed by existing CAR-T and comparator clinical evidence and any published economic evaluations. No controlled trials were available for inclusion in the model. Key model inputs included progression-free survival, overall survival, occurrence of adverse events, quality of life, and health care costs. Further detail on model inputs can be found in Section 4.2 of the full report.

Key model assumptions are detailed in Table ES11.

Table ES11. Key Model Assumptions

Assumption	Rationale
Stem cell transplantation (SCT), if it occurred, occurred within two months of the model start and no further SCT events were modeled.	Based on mean time from CAR-T therapy to stem cell transplantation estimated by Lee et al.[7,36]
Patients received a single full course of CAR-T therapy.	CAR-T therapies are considered an end-of-line treatment with no clinical evidence on re-treatment.
After year five, survivors experienced a mortality risk profile consistent with that of a long-term survivor, after adjustments were made for excess mortality.	At year five, those who were alive were assumed to be effectively cured. For the pediatric B-ALL cohort, a standardized mortality ratio of 9.1 was applied to all-cause risk of death for long-term survivors.[37] Evidence did not suggest a standardized mortality ratio greater than 1 for the adult B-cell lymphoma cohort, although this input was varied in sensitivity analyses.
Any person alive but not responding to treatment transitioned to death by the end of year five.	Those alive at year five are considered long-term survivors.
All patients who transitioned to the alive and not responding to treatment health state received palliative chemotherapy.	The intervention and comparator therapies are considered an end-of-line treatment.
Patients who discontinued CAR-T due to an AE before receiving the infusion received no further antileukemic/antilymphomic therapy.	Those who experienced a severe AE would be unable to tolerate further active therapy.
Patients who did not receive CAR-T therapy due to a manufacturing failure received the active comparator.	Those who experienced a manufacturer failure would be able to tolerate further active therapy.
The model included costs and outcomes associated with grade 3/4 AEs.	Less severe adverse events are not expected to significantly impact patient health or costs.
The cost of a hospital admission for treatment administration included the per diem cost for hospital days and the costs of therapies administered during the hospitalization.	Future bundled payments were assumed to approximate the cost of the resources used under a fee-for-service framework.

The unit cost for each treatment is reported in Table ES12. The average sales price (ASP) for all treatments was used except for the two CAR-T therapies, where wholesale acquisition cost (WAC) was the only available estimate. A hospital mark-up was added for each hospital-administered treatment. Hospital mark-ups were capped at $100,000 per treatment (including for CAR-T therapy). Full details on hospital mark-up assumptions can be found in Section 4 of the main report.

Table ES12. Treatment Acquisition Costs

B-ALL	Unit	Price per Unit*	Price per Unit with Estimated Mark-Up
Tisagenlecleucel	0.2 to 5.0 × 10^6 CAR-T cells/kg	$475,000†	$575,000
Clofarabine	1mg/1ml	$150	$264
Methotrexate	1mg/1ml	$0.05	$0.09
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Cytarabine	1mg/1ml	$0.01	$0.02
Etoposide	1mg/1ml	$0.05	$0.09
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous Immunoglobulin	1mg/1ml	$0.08	$0.14
B-cell Lymphoma	**Unit**	**Price per Unit***	**Price per Unit with Estimated Mark-Up**
Axicabtagene Ciloleucel	2 x 10^6 CAR-T cells/kg	$373,000†	$473,000
Dexamethasone	1mg	$0.33	$0.49
Cytarabine	1mg/1ml	$0.01	$0.01
Cisplatin	1mg/1ml	$0.21	$0.31
Rituximab	1mg/1ml	$8.48	$12.55
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous Immunoglobulin	1mg/1ml	$0.08	$0.14

*Price as of October 8th, 2017; average sales price for all products except CAR-T
†Represents the total, not unit, wholesale acquisition costs of CAR-T therapy
B-ALL: B-cell acute lymphoblastic leukemia

Base-Case Results

The total discounted costs, life years (LYs), and quality-adjusted life years (QALYs) over the lifetime time horizon are detailed in Table ES13. In the B-ALL cohort, the tisagenlecleucel arm had a total discounted cost of approximately $667,000 with discounted LYs and QALYs gained of 10.34 and 9.28, respectively. The clofarabine comparator arm had a total discounted cost of approximately $337,000 with discounted life years and QALYs gained of 2.43 and 2.10, respectively.

In the B-cell lymphoma cohort, the axicabtagene ciloleucel arm had a total discounted cost of approximately $617,000 with discounted LYs and QALYs gained of 7.35 and 5.87, respectively. This contrasted with the chemotherapy comparator arm, which had a total discounted cost of approximately $155,000 with LYs and QALYs gained of 3.23 and 2.48, respectively.

Table ES13. Base-Case Discounted Lifetime Costs and Outcomes

	B-ALL		B-cell Lymphoma	
	Tisagenlecleucel	Clofarabine	Axicabtagene Ciloleucel	Chemotherapy
Total Cost	$666,754	$337,256	$616,927	$154,884
Life Years	10.34	2.43	7.35	3.23
QALYs	9.28	2.10	5.87	2.48

B-ALL: B-cell acute lymphoblastic leukemia, QALYs: quality-adjusted life year

Table ES14 presents the incremental results from the base-case analysis, which include LYs gained, QALYs gained, and incremental cost-effectiveness ratios for both incremental cost per LY gained and incremental cost per QALY gained.

In the B-ALL cohort, total costs for the tisagenlecleucel arm were nearly two times greater than total costs for clofarabine; gains in life years and QALYs were more than four times greater for tisagenlecleucel. This resulted in an incremental cost-effectiveness ratio of approximately $46,000 per QALY gained and approximately $42,000 per LY gained for tisagenlecleucel as compared to clofarabine.

In the B-cell lymphoma cohort, total costs for the axicabtagene ciloleucel arm were nearly four times greater than total costs for the chemotherapy arm; gains in life years and QALYs were more than twice that of those on chemotherapy. This resulted in an incremental cost-effectiveness ratio of approximately $136,000 per QALY gained and approximately $112,000 per LY gained for axicabtagene ciloleucel as compared to chemotherapy.

Table ES14. Base-Case Incremental Results

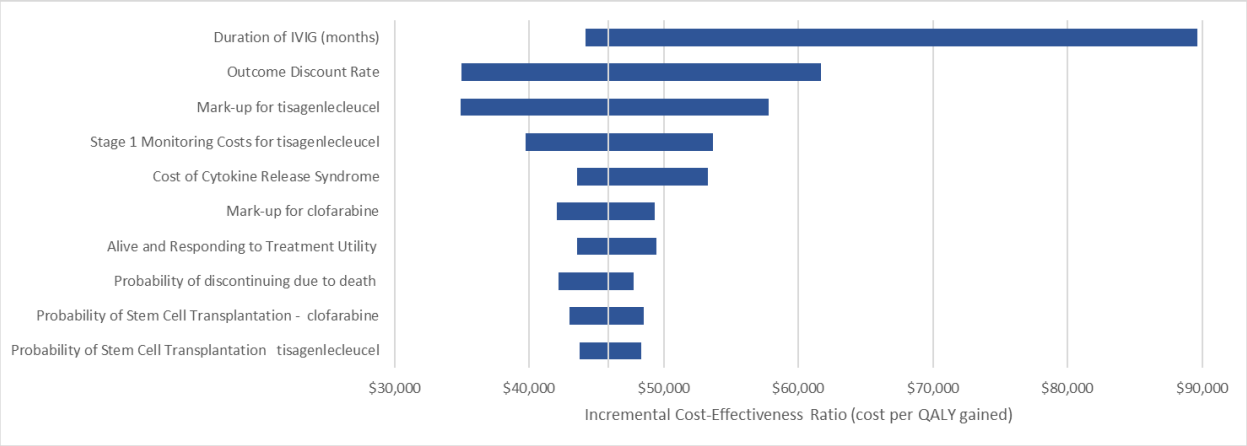
B-ALL	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Tisagenlecleucel vs. Clofarabine	$329,498	7.91	7.18	$41,642	$45,871
B-cell Lymphoma	**Incremental Costs**	**Incremental LYs**	**Incremental QALYs**	**Incremental CE Ratio per LY**	**Incremental CE Ratio per QALY**
Axicabtagene Ciloleucel vs. Chemotherapy	$462,043	4.12	3.40	$112,168	$136,078

Base-case payment for tisagenlecleucel assumes payment only for responders at one month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
B-ALL: B-cell acute lymphoblastic leukemia, CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors or plausible parameter ranges). Figure ES3 presents the tornado diagram resulting from the one-way sensitivity analysis for tisagenlecleucel versus clofarabine in B-ALL. Key drivers of the model included the duration of IVIG therapy for B-cell aplasia, "outcome discount rate" (i.e., the discount percentage applied to future clinical benefits), and hospital mark-up percentage for tisagenlecleucel. The incremental cost-effectiveness ratio assuming no hospital mark-up for tisagenlecleucel was approximately $35,000 per QALY gained. Across broad ranges in influential model inputs when varied one-by-one, the incremental cost-effectiveness ratio remained within acceptable cost-effectiveness thresholds.

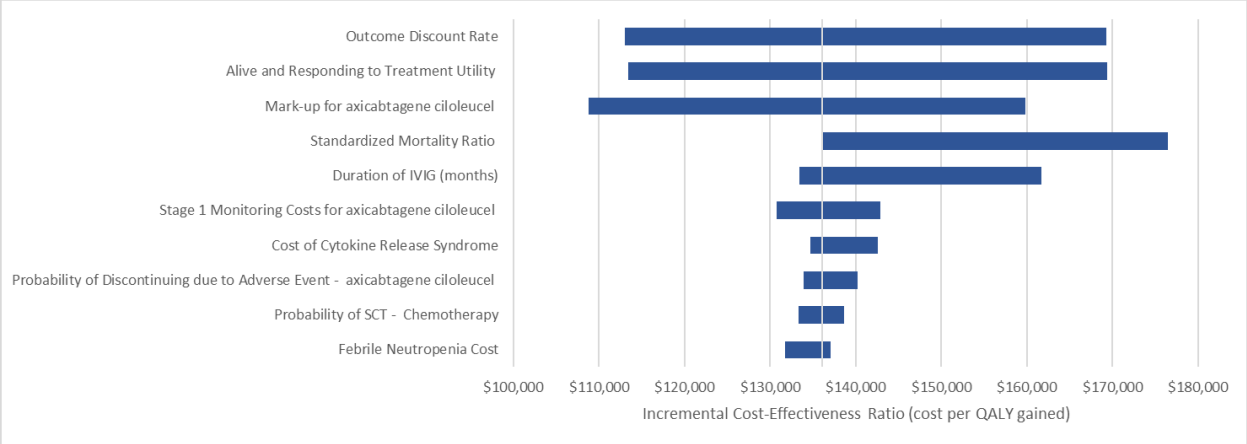
Figure ES3. Tornado Diagram for One-Way Sensitivity Analyses of Tisagenlecleucel versus Clofarabine



Base-case incremental cost-effectiveness ratio: $45,871 per QALY gained

Figure ES4 presents the tornado diagram resulting from the one-way sensitivity analysis for axicabtagene ciloleucel versus chemotherapy in B-cell lymphoma. Key drivers of the model included the outcome discount rate, utility for the "alive and responding to treatment" health state, mark-up percentage for axicabtagene ciloleucel, the standardized mortality ratio, and the duration of IVIG therapy. In this case, when model inputs were varied within plausible ranges one by one, cost-effectiveness estimates frequently did extend above commonly cited cost-effectiveness thresholds, highlighting the uncertainty in some of the parameter values. The incremental cost-effectiveness ratio assuming no hospital mark-up for axicabtagene ciloleucel was approximately $109,000.

Figure ES4. Tornado Diagram for One-Way Sensitivity Analyses of Axicabtagene Ciloleucel versus Chemotherapy



Base-case incremental cost-effectiveness ratio: $136,078 per QALY gained

With noted uncertainty outside of that modeled, a probabilistic sensitivity analysis was conducted to assess variation across all model inputs with quantified uncertainty simultaneously and to vary the results over 5,000 iterations. Table ES15 presents the probability of reaching certain willingness-to-pay thresholds. All of the iterations for tisagenlecleucel versus clofarabine were below a threshold of $150,000 per QALY gained. Seventy percent of the iterations for axicabtagene ciloleucel versus chemotherapy were beneath a threshold of $150,000 per QALY gained.

Table ES15. Probabilistic Sensitivity Analysis Results

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Tisagenlecleucel vs. Clofarabine	70.6%	100.0%	100.0%
Axicabtagene Ciloleucel vs. Chemotherapy	0.0%	3.0%	70.8%

Scenario Analyses

We conducted two scenario analyses to account for the uncertainty around survival beyond the trial follow-up, due to the inability to include variation around survival curve parameters in the sensitivity analyses. First, we conducted a scenario analysis of different model time horizons, from one year to a lifetime time horizon. This scenario analysis is intended to provide decisionmakers with the ability to make judgements around the duration and forecasting of the cure-related benefits observed in the single-arm trials. For example, assuming a 10-year time horizon would suggest that no cure-related benefits (or costs) are assigned beyond 10 years post therapy for a CAR-T or its comparator. For tisagenlecleucel versus clofarabine in B-ALL, the incremental cost-effectiveness ratio fell below $150,000 per QALY gained when the model time horizon was seven years or longer. For axicabtagene ciloleucel versus chemotherapy in B-cell lymphoma, the

incremental cost-effectiveness ratio fell below $150,000 per QALY gained when the model time horizon was 24 years or longer.

Secondly, in the base-case analysis, we introduced a knot in the survival curve fit once the curve flattened (i.e., the slope equaled zero). In a scenario analysis, we removed the knot to produce a lower bound for survival. Using this standard parametric modeling practice, tisagenlecleucel resulted in 5.15 life years (4.49 QALYs), clofarabine resulted in 0.66 life years (0.49 QALYs), axicabtagene ciloleucel resulted in 3.17 life years (2.19 QALYs), and its chemotherapy comparator resulted in 0.94 life years (0.55 QALYs) over a lifetime time horizon. The incremental cost-effectiveness ratios increased to $77,511 per QALY gained for tisagenlecleucel as compared to clofarabine in B-ALL and $259,378 per QALY gained for axicabtagene ciloleucel as compared to chemotherapy in B-cell lymphoma. These and other scenario analyses are discussed in further detail in the full report.

A threshold analysis was also conducted to determine the treatment acquisition cost needed to achieve thresholds of $50,000, $100,000, and $150,000 per QALY gained. Table ES16 presents the unit price needed for each therapy to reach these commonly cited cost-effectiveness thresholds. The price needed to achieve the thresholds presented in Table ES15 includes both the manufacturer price and associated mark-up.

Table ES16. Threshold Analysis Results

	Price	Net Price (with Mark-Up)	Price* to Achieve $50,000 per QALY	Price* to Achieve $100,000 per QALY	Price* to Achieve $150,000 per QALY
Tisagenlecleucel (B-ALL)	$475,000	$575,000	$636,894	$1,162,563	$1,688,232
Axicabtagene Ciloleucel (B-cell Lymphoma)	$373,000	$473,000	$157,578	$340,797	$524,015

Payment assumed for tisagenlecleucel was payment for responders at one month. Payment assumed for axicabtagene ciloleucel was payment at infusion.
*Price needed to achieve the thresholds includes both the acquisition cost and associated mark-up.
QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Summary and Comment

The base-case findings from our analysis suggest that the use of tisagenlecleucel in B-ALL provides clinical benefit in terms of gains in quality-adjusted and overall survival over clofarabine. This translated into cost-effectiveness estimates that met commonly-cited cost-effectiveness thresholds in the pediatric relapsed/refractory B-ALL cohort under the assumptions used in this analysis. The results were robust through one-way and probabilistic sensitivity analyses given the parameter uncertainty quantified. Although sensitive to the outcome discount rate, hospital mark-up for tisagenlecleucel, and survival assumptions, cost-effectiveness estimates remained less than

$150,000 per QALY gained. After a model time horizon of seven years, the incremental cost-effectiveness ratio for tisagenlecleucel versus clofarabine was less than $150,000 per QALY gained. Therefore, if one accepts that patients who are alive and responding to treatment at five years are effectively cured, and that the model's other assumptions hold for at least seven years after treatment with no differences in costs or outcomes beyond that duration, tisagenlecleucel would meet commonly cited cost-effectiveness thresholds.

Similarly, the base-case findings from our analysis suggest that the use of axicabtagene ciloleucel in B-cell lymphoma also provides clinical benefit in terms of gains in quality-adjusted and overall survival over chemotherapy. This translated into cost-effectiveness estimates that met commonly cited cost-effectiveness thresholds in the adult relapsed/refractory B-cell lymphoma cohort under current assumptions used in the base-case analysis. Given the parameter uncertainty quantified through one-way and probabilistic sensitivity analyses, some cost-effectiveness ratios exceeded $150,000 per QALY gained. Results were most sensitive to the outcome discount rate, utility for the alive and responding to treatment health state, hospital mark-up percentage for axicabtagene ciloleucel, the standardized mortality ratio, the duration of IVIG, and the survival assumptions. After a model time horizon of 24 years, the incremental cost-effectiveness ratio for axicabtagene versus chemotherapy was less than $150,000 per QALY gained. Therefore, if one accepts that patients who are alive and responding to treatment at five years are effectively cured, and that the model's other assumptions hold for at least 24 years after treatment with no differences in costs or outcomes beyond that duration, axicabtagene ciloleucel would meet commonly cited cost-effectiveness thresholds.

In conclusion, the findings of our analysis suggest that the CAR-T therapies of focus for this review provide gains in quality-adjusted and overall survival over alternative chemotherapies. With the evidence available at this time, these therapies seem to be priced in alignment with clinical benefits over a lifetime time horizon. Scenario analyses detailed in the main report showed, however, that the cost-effectiveness was sensitive to the time horizon and long-term benefit forecasting of the therapies.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Tables ES17-ES18 below.

Other Benefits

Table ES17. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	None
This intervention offers reduced complexity that will significantly improve patient outcomes.	None
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	None
This intervention will significantly reduce caregiver or broader family burden.	None
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	CAR-T therapy represents a novel mechanism of action: introducing a new gene into the patient's own T-cells that produces a chimeric protein with an extracellular antibody specific for CD-19, the target protein expressed by B-cells, and two other domains that activate the T-cell to kill of the bound cell and stimulates replication of the T-cell. This novel mechanism appears to offer significantly greater remission rates than other therapies for patients who have failed standard first and second-line therapy for these B-cell cancers.
This intervention will have a significant impact on improving return to work and/or overall productivity.	For the pediatric patients with ALL, CAR-T therapy may offer them the opportunity to live a nearly normal life and to contribute substantially to society. This applies less to the patients with B-cell lymphomas, because they are significantly older, but many will return to productive lives. In addition, despite early toxicity in the first month of therapy, the patient's subsequent care is less demanding than that required by salvage chemotherapy or SCT, thus allowing for an earlier return to productivity for patients and their families.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	None

Contextual Considerations

Table ES18. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	This is true for both patients with B-ALL and DLBCL who are refractory or relapsed following standard therapy as their life expectancy would otherwise be very limited.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	This is particularly true for childhood ALL.
This intervention is the first to offer any improvement for patients with this condition.	None
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	The limited clinical experience with CAR-T therapy and the short follow-up of the pivotal trials leads to uncertainty about the potential for unexpected long-term serious side effects due to the presence of cells that have been genetically manipulated and may persist for the remainder of the patient's life.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	Given the limited clinical experience with CAR-T therapy, there is considerable uncertainty about the long-term durability of the response to therapy. This is highlighted by the conflicting viewpoints among treating oncologists about the need to proceed to SCT following CAR-T therapy.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	None

Value-Based Benchmark Prices

Our annual value-based price benchmarks for tisagenlecleucel's use in patients ages 0-25 with relapsed or refractory B-cell ALL and axicabtagene ciloleucel's use in adult patients with relapsed or refractory aggressive NHL are presented in Table ES19. As noted in the ICER methods document (https://icer-review.org/material/final-vaf-2017-2019/), the value-based benchmark price for a therapy is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For tisagenlecleucel, price premiums could be applied to the WAC with mark-up to meet these threshold prices. For axicabtagene ciloleucel a price discount from the WAC with mark-up is required to reach the $100,000 per QALY threshold price while a price premium from the WAC with mark-up is required to reach the $150,000 per QALY threshold price.

Table ES19. Value-Based Price Benchmarks for Tisagenlecleucel and Axicabtagene Ciloleucel

	WAC	Net Price (with Mark-Up)	Price* to Achieve $100,000 per QALY	Price* to Achieve $150,000 per QALY	Discount from WAC with Mark-Up to Reach Threshold Prices
Tisagenlecleucel (B-ALL)	$475,000	$575,000	$1,162,563	$1,688,232	+102% to +194%
Axicabtagene Ciloleucel (B-cell Lymphoma)	$373,000	$473,000	$340,797	$524,015	28% to +11%

Payment assumed for tisagenlecleucel was payment for responders at one month. Payment assumed for axicabtagene ciloleucel was payment at infusion.
*Price needed to achieve the thresholds includes both the acquisition cost and associated mark-up.
B-ALL: B-Cell acute lymphoblastic leukemia, QALY: quality-adjusted life year
+Indicates premium

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. ICER's methods for estimating potential budget impact are described in detail in section 7.2 and have recently been updated; additional information can be found at https://icer-review.org/material/final-vaf-2017-2019/. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including therapy costs) minus any offsets in these costs from averted health care events.

For tisagenlecleucel, we determined the size of the eligible population using estimates based on SEER data and observational studies, resulting in an annual eligible cohort size of 400 patients. We used the total treatment cost including WAC and hospital mark-up at infusion, based on treatment response at different time points and at the three cost-effectiveness threshold prices, using the response to treatment at one month in our estimates of budget impact. For axicabtagene ciloleucel, we determined the size of the eligible cohort using observational study data, resulting in an annual eligible cohort size of 5,902 patients. We used the total treatment cost that included WAC and hospital mark-ups at infusion, and at the three cost-effectiveness threshold prices irrespective of treatment response in our estimates of budget impact. A detailed description of our methods in estimating budget impact including the determination of eligible population for each of the two CAR-T therapies is available in section 7.2 of the report.

Tisagenlecleucel

Table ES20 illustrates the per-patient potential budget impact calculations for tisagenlecleucel, based on payment at infusion, treatment response at one month and one year, and the prices to

reach $50,000, $100,000, and $150,000 per QALY using response to treatment at one month for tisagenlecleucel ($636,894, $1,162,563, and $1,688,232, respectively) compared to clofarabine.

Table ES20. Per-Patient Budget Impact Calculations for Tisagenlecleucel Over a Five-year Time Horizon, Assuming 400 Patients per Year Over Five Years

	Average Annual Per Patient Budget Impact					
	Payment at:			Threshold Prices:		
	Infusion	Response to Treatment at 1 Month	Response to Treatment at 1 Year	$50,000/QALY*	$100,000/QALY*	$150,000/QALY*
Tisagenlecleucel	$310,618	$277,457	$216,384	$296,769	$460,784	$624,799
Clofarabine	$149,799					
Difference	$160,818	$127,658	$66,585	$146,969	$310,984	$474,999

*Based on response to treatment at one month
QALY: quality-adjusted life year

The annual potential budgetary impact of treating the entire eligible population did not exceed the $915 million threshold at any of our modeled prices and are not presented in a figure (Table ES21). The potential budget impact ranged from 6% of the threshold when using the price based on treatment response at one year, to 46% of the threshold when using the price to reach the $150,000 per QALY threshold.

Table ES21. Estimated Annualized Total Potential Budget Impact (BI) of Tisagenlecleucel Using Different Prices Over a Five-year Time Horizon, Assuming 617 Eligible Patients per Year

	Total Annual Budget Impact	Percent of Threshold
Payment at Infusion	$141,020,175	15%
Payment Based on Treatment Response at One Month	$111,955,077	12%
Payment Based on Treatment Response at One Year	$58,424,621	6%
$150,000 per QALY Threshold Price*	$416,399,062	46%
$100,000 per QALY Threshold Price*	$272,640,318	30%
$50,000 per QALY Threshold Price*	$128,882,611	14%

*Based on response to treatment at one month
QALY: quality-adjusted life year

Axicabtagene Ciloleucel

Table ES22 illustrates the per-patient budget impact calculations for axicabtagene ciloleucel in more detail, based on payment at infusion and the prices to reach $50,000, $100,000, and $150,000 per QALY compared to salvage chemotherapy, irrespective of treatment response ($157,578, $340,797 and $524,015, respectively). Treatment costs in years two through five are substantially lower than

in year one in keeping with the curative assumption of CAR-T therapy employed in our cost-effectiveness model's base-case. When these costs are averaged over five years, the per-patient CAR-T therapy costs reported are lower than those used in the long-term cost-effectiveness model.

Table ES22. Per-Patient Budget Impact Calculations for Axicabtagene Ciloleucel Over a Five-Year Time Horizon, Assuming 5,902 Patients per Year Over Five Years

	Average Annual Per Patient Budget Impact			
	Payment at Infusion	$50,000/QALY*	$100,000/QALY*	$150,000/QALY*
Axicabtagene ciloleucel	$238,007	$104,536	$182,065	$259,594
Salvage Chemotherapy	$54,010			
Difference	$183,997	$50,527	$128,056	$205,585

QALY: quality-adjusted life year

*Based on payment at infusion, irrespective of treatment response

The average potential budgetary impact when using the treatment cost at infusion, irrespective of treatment response, was an additional per-patient cost of approximately $184,000. Average potential budget impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $51,000 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold ($157,578) to approximately $206,000 per patient using the annual price to achieve $150,000 per QALY cost-effectiveness threshold ($524,015).

As shown in Figure ES5, approximately 38% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC ($473,000). Approximately 34% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($524,015), while 55% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price ($340,797). At the $50,000 per QALY threshold price ($157,578), the entire eligible cohort could be treated without exceeding the $915 million threshold, reaching only 71% of the total.

Figure ES5. Potential Budgetary Impact of Axicabtagene Ciloleucel in Patients with Relapsed/Refractory DLBCL*

*Graph shows the relation between annual price and proportion of relapsed/refractory DLBCL patients eligible for treatment with axicabtagene ciloleucel who could be treated over five years without crossing $915-million budget impact threshold.
Note: All prices are based on payment at infusion, irrespective of response to treatment.

In summary, the annual budget impact over a five-year time-horizon for treating eligible patients with relapsed/refractory B-cell ALL with tisagenlecleucel rather than clofarabine was estimated to be approximately $128,000 per patient if payment was made only on response to therapy at one month. Using different payment mechanisms, such as payment at infusion and payment based on treatment response at one year, as well as using prices to achieve cost-effectiveness thresholds from $50,000 to $150,000 per QALY gained, did not result in the total annual potential budget impact exceeding ICER's annual $915 million budget impact threshold.

The annual budget impact of axicabtagene ciloleucel for treating eligible patients with relapsed/refractory DLBCL, PMBCL, TFL, and high-grade B-cell lymphoma with payment at infusion was estimated to be approximately $184,000 per patient. At all except the price to achieve a cost-effectiveness threshold of $50,000 per QALY, the total annual budget exceeded ICER's $915 million annual budget impact threshold.

1. Introduction

1.1 Background

Lymphomas and leukemias are cancers of the white blood cells. While both cancers arise in the bone marrow, lymphomas tend to form solid masses in lymph nodes and other places in the body, while leukemias primarily circulate in the bloodstream. There are many different types of lymphomas and leukemias. Both can arise from a subset of white blood cells called lymphocytes. There are two primary kinds of lymphocytes: B-lymphocytes and T-lymphocytes. The B-cells primarily produce antibodies that help to fight off infections while the T-cells help to kill off abnormal cells like cancer cells and those infected by viruses. Both types of lymphocytes are important for this review, which focuses on chimeric antigen receptor T-cell (CAR-T) therapy for B-cell malignancies.

Childhood B-Cell Acute Lymphoblastic Leukemia (B-ALL)

Pediatric acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. There are over 3,000 new cases of ALL diagnosed in children and adolescents (ages 0-19) each year in the United States (US).[1] The usual treatment for childhood ALL consists of induction, consolidation, delayed intensification, and maintenance chemotherapy with a variety of agents. Over the past few decades, treatment has improved dramatically and the five-year survival rate, which is considered clinically equivalent to a cure, is approximately 85%.[2-4]

Treatment options are fewer for those children with relapsed or refractory disease (i.e., patients who have relapsed within 12 months of an allogeneic stem cell transplant (allo-SCT) or whose disease did not respond to their last line of chemotherapy). Among the approximately 15% of patients who do not respond to initial treatment or relapse after initial treatment, the prognosis is very poor, even with stem cell transplant (SCT). Fewer than one in three of these patients survive five years.[38-40] Current salvage regimens for pediatric ALL may include clofarabine (Clolar®, Sanofi-Genzyme) or blinatumomab (Blincyto®, Amgen), if they have not previously been used.[41] Allo-SCT is used for appropriate patients who attain remission with salvage treatment. SCT has been associated with improved survival in some children, but has been associated with an increased mortality in infants.[42,43] Better therapies are needed for those children with relapsed/refractory disease.

Aggressive B-Cell Non-Hodgkin's Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of adult non-Hodgkin's lymphoma (NHL) accounting for approximately 25% of newly diagnosed cases of NHL in the United States.

Although DLBCL can occur in childhood, its incidence generally increases with age, and roughly half of patients are over the age of 60 at the time of diagnosis.[44]

DLBCL is an *aggressive* (i.e., fast-growing) lymphoma that can occur in lymph nodes, outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. Other aggressive B-cell lymphomas include transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL). The usual treatment for aggressive B-cell lymphoma involves systemic chemoimmunotherapy with rituximab (R-CHOP) sometimes combined with radiation. Five-year survival with this regimen is approximately 50-70%.[5,6] Options are fewer for those patients whose cancer is refractory to therapy or who relapse after initial therapy. If patients respond to second-line chemotherapy, then they are considered candidates for auto-SCT. Current salvage regimens for DLBCL may include R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, and etoposide phosphate), R-ESHAP (rituximab, etoposide, methylprednisone, cytarabine, and cisplatin), and others.[45] However, even after SCT, five-year disease-free survival is only about 10-20%.[46-48] Patients who do not respond to second line therapy or progress after transplant, currently only have palliative options available. Thus, new treatment options are needed.

Chimeric Antigen Receptor T-Cell Therapy as a New Treatment Option

CAR-T therapy is a novel cellular therapy that uses genetic engineering to alter a patient's own T-cells to produce transmembrane proteins on their cell surface with an extracellular antibody fragment domain that recognizes a specific protein. Both tisagenlecleucel and axicabtagene ciloleucel are second generation CAR-T therapies that include two intracellular domains as part of the chimeric protein. One of the domains activates the T-cell when it binds to the target protein (signaling domain) and the other stimulates cellular replication (costimulatory domain). This ensures a durable supply of chimeric T-cells with the ability to eliminate cells that express the target protein. The CAR-T therapies of interest in this review target the CD19 antigen, which is exclusively expressed on B cells, including the cancer cells in B-ALL and the aggressive B-cell NHLs described above.

There are two CAR-T therapies evaluated in this review. The first, manufactured by Novartis, is tisagenlecleucel (Kymriah™ [CTL-019]), which was approved by the FDA on August 30, 2017 for use in relapsed or refractory pediatric ALL.[49] The second, manufactured by Kite Pharma (now owned by Gilead Pharmaceuticals), is axicabtagene ciloleucel (Yescarta™ [KTE-C19]), which was approved by the FDA on October 18, 2017 for use in relapsed or refractory adult lymphoma.[50] Both therapies require leukapheresis, in which the patient's own peripheral blood mononuclear cells containing T-cells are removed from their body. The cells are then shipped to a central facility that engineers the CAR T-cells using retroviruses to insert the DNA for the chimeric protein into the DNA of the patient's T-cells. The newly engineered cells are then frozen and shipped back to the treating institution where they are infused back into the patient's bloodstream to fight the cancer.

Currently, this manufacturing process takes a minimum of about two to three weeks from leukapheresis to the time the engineered cells are ready to be infused back into the patient. During that time period, some of the patients will die and others will become too sick to tolerate treatment with the CAR-T cells. In addition, the manufacturing process occasionally fails to produce an adequate number of CAR-T cells for infusion. The primary reason for manufacturing failure appears to be the number and quality of the T-cells gathered during leukapheresis. To minimize this problem, some facilities require that the absolute lymphocyte count be at least 100 cells per microliter prior to leukapheresis.

During the manufacturing process, the majority of patients require some form of bridging chemotherapy to keep their cancer stable. Just prior to infusion of the T-cells, patients undergo lymphodepleting chemotherapy (often fludarabine plus cyclophosphamide) in order to decrease the number of competing lymphocytes and increase levels of cytokines such as interleukin 15, which stimulate T-cell proliferation and allow the infused CAR T-cells to establish themselves in the patient's body.

The primary difference in the structure of the chimeric proteins lies in the co-stimulatory domain. Tisagenlecleucel utilizes the 4-1BB domain, while axicabtagene ciloleucel uses the CD28 domain. Some data suggest that CD28-based CAR-T cells have a more rapid initial proliferative response, while the 4-1BB-based CAR-T cells may drive more progressive T cell accumulation, which serves as a counterbalance to their lower immediate potency.[51]

To be eligible for the CAR-T therapies evaluated in this review, patients were required to have:

- Tumors that expressed the CD19 antigen
- Adequate T-cell levels to allow for their collection during leukapheresis
- Normal or only mildly diminished performance status
- No active infections
- No significant cardiac, neurologic, or immune dysfunction

As the CAR T-cells proliferate in the patient and kill tumor cells, they release cytokines, which are chemical messengers used by cells to communicate with each other. A prominent side effect of CAR-T therapy is cytokine release syndrome (CRS), in which the release of many cytokines by the CAR T-cells causes high fevers, low blood pressure, and respiratory distress that may require care in an intensive care unit (ICU). This serious side effect has been observed in about one-third of patients treated with CAR-T therapy and may be related to the volume of cancer cells at the time of treatment, though it remains an area of active research.[15] Another common and feared side effect is neurotoxicity, which also affects more than a third of patients. The most common neurologic side effects include encephalopathy, headache, delirium, aphasia, anxiety, and tremors.

Studies of tisagenlecleucel have primarily focused on patients with relapsed/refractory B-ALL up to the age of 25 years.[7-9] In addition, Novartis has applied to the FDA for an indication for tisagenlecleucel to treat relapsed/refractory DLBCL and has plans to file for other indications in 2018.[10] Studies of axicabtagene ciloleucel have to date focused on patients with relapsed/refractory aggressive NHL.[11-14]

While use of CAR-T therapies in patient populations with limited options has generated much clinical excitement, questions remain regarding the durability of their effects, management of adverse effects such as CRS, the infrastructure and specialized training required to perform leukapheresis, perform the CAR-T infusion, and monitor for side effects, and the costs of CAR-T relative to other therapeutic approaches. Both Novartis and Kite/Gilead have limited the availability of their CAR-T therapies to certified treatment centers and expect the list of accredited centers to increase over time. As of February 15, 2018, tisagenlecleucel was available at 34 centers, while axicabtagene ciloleucel was available at 28 locations.[52,53]

Costs for the approved therapies may range from approximately $350,000 to $500,000. This does not include potential hospital mark-up for the therapy, nor the additional costs of hospital care during the preparation and administration of the CAR-T therapy as well as management of side effects. Novartis has entered into an outcomes-based pricing arrangement with the Centers for Medicare and Medicaid Services (CMS) in which it appears that payment will be provided only for pediatric and young adult patients who respond to treatment with tisagenlecleucel at the end of the first month post-therapy.[10] Public statements by the company indicate that Novartis may also pursue outcomes-based contracting for any additional indications granted to the treatment. Kite/Gilead have not, as of the publication of this report, publicly stated that they have entered a similar arrangement, but have indicated that they would be open to entering value- or outcomes-based payment contracts with payers on a case-by-case basis.[35]

1.2 Scope of the Assessment

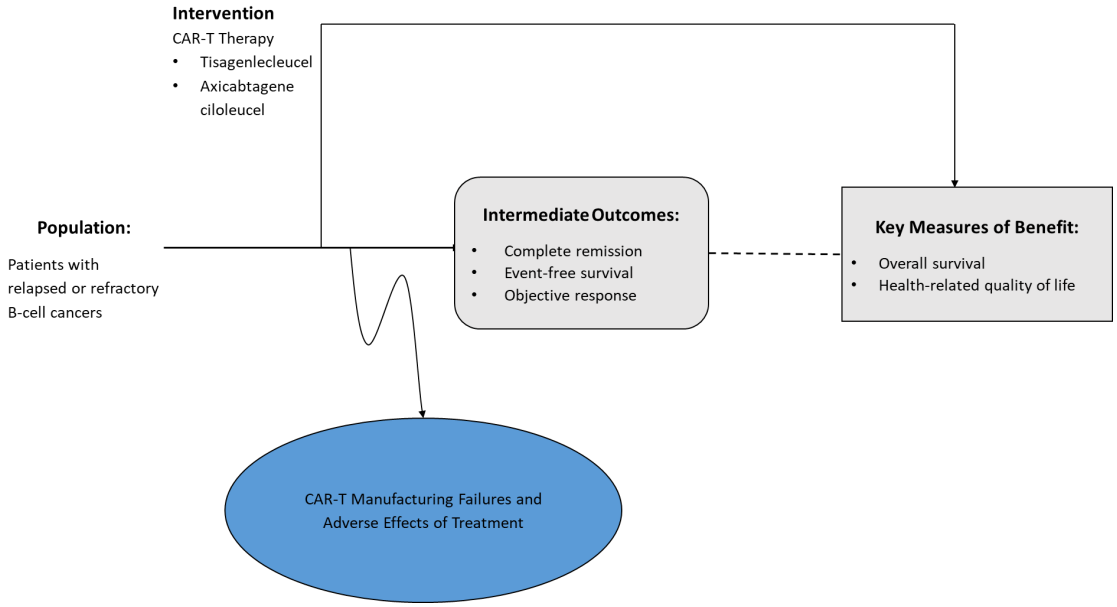
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials, high-quality comparative cohort studies, and case-series given the limited evidence base for these novel interventions. Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

We sought out head-to-head studies for these interventions, but none were identified. Recognizing the current state of the evidence base for CAR-T therapy, we included single-arm trials and compared outcomes with historical control data.

Analytic Framework

The general analytic framework for assessment of therapies for B-cell cancers is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: CAR-T Therapy for B-Cell Cancers



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., complete remission), and those within the squared-off boxes are key measures of clinical benefit (e.g., overall survival). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events (AEs) of an action (typically treatment), which are listed within the blue ellipsis.[54]

Populations

The two separate populations of interest for the review were developed in a fashion consistent with the entry criteria for major clinical trials, as described below:

1. Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse
2. Adults ages 18 years and older with aggressive B-cell lymphoma (DLBCL, TFL, PMBCL) that is refractory to two lines of therapy or in second or later relapse

Interventions

- CAR-T therapy
    - Tisagenlecleucel (Kymriah™ [CTL019], Novartis) for both B-ALL and aggressive B-cell lymphomas
    - Axicabtagene ciloleucel (Yescarta™ [KTE-C19], Kite Pharma/Gilead) for aggressive B-cell lymphomas

Comparators

In the leukemia population, we compared CAR-T therapy to clofarabine-based therapy and to blinatumomab-based therapy.[20-22,41]

In the lymphoma population, we compared CAR-T therapy to salvage chemotherapy regimens such as those used in the SCHOLAR-1 study.[17]

Because there are no randomized or observational trials directly comparing CAR-T therapy to salvage chemotherapy, any comparisons were at substantial risk for selection bias. To facilitate discussion about the potential direction in bias due to patient selection in the trials, we have carefully described the study sample characteristics for each of the trials including the number of prior chemotherapy lines that failed, prior SCTs, age, blast levels, as well as the inclusion and exclusion criteria (see Appendix Tables C1-3). Similarly, we described all patients enrolled in the CAR-T trials, including those who did not receive CAR-T therapy due to manufacturing failures or disease progression prior to infusion.[45]

Outcomes

The primary goal of treatment is to cure the cancer. As such, overall survival was the primary outcome of interest. Even though CAR-T therapy can be used with curative intent, some patients treated with CAR-T therapy go on to SCT. We described any SCTs that followed treatment with CAR-T therapy or the comparator therapies.

Where possible, we reported the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Table 1.1. Key Outcomes and Harms

Outcomes	Harms
Overall Survival	Cytokine release syndrome
Relapse-free survival	Neurotoxicity
Complete remission	Grade 3 or 4 AEs
Overall remission rate	Discontinuations due to AEs (for comparator treatments only)
Event-free survival	Treatment-related deaths
Duration of response	Infections
Quality of life	Secondary cancers
Receipt of SCT	Failed CAR-T therapy manufacturing process
	Disease progression that precludes CAR-T infusion

Timing

Evidence on intervention effectiveness and harms was derived from studies with a median duration of at least three months.

Settings

All relevant settings were considered including inpatient, clinic, and outpatient settings.

1.3 Definitions

B-cell aplasia: Normal lineage B cells are eliminated after CD19 CAR-T infusion. This can cause long lasting hypogammaglobulinemia, which requires monthly intravenous immunoglobulin replacement to prevent serious infections until the B-cell aplasia resolves.

Complete remission (CR; leukemia): All of the following criteria must be met:

- Bone marrow <5% blasts
- Peripheral blood
- Neutrophils > 1 x 10^9/L
- Platelets > 100 x 10^9/L
- Circulating blasts < 1%
- No clinical evidence of extramedullary disease (by physical examination and CNS symptom assessment)
- If additional assessments performed (e.g., cerebrospinal fluid [CSF] assessment by lumbar puncture [LP], central nervous system [CNS] imaging, biopsy, etc.) results must show remission
- Transfusion independence
    - No platelet and or neutrophil transfusions ≤ seven days before the date of the peripheral blood sample for disease assessment

Complete remission with incomplete hematologic recovery (CRi; leukemia): All criteria for CR are met, except that the following exist

- Neutrophils ≤ 1 x10^9/L, or
- Platelets ≤ 100 x 10^9/L, or
- Platelet and or neutrophil transfusions ≤ seven days before the date of the peripheral blood sample for disease assessment

Complete remission (CR; lymphoma): Complete absence of detectable clinical evidence of disease and disease-related symptoms that were present prior to beginning therapy.

Cytokine release syndrome (CRS): CRS is caused by a large rapid release of cytokines into the blood from immune cells affected by immunotherapy. CRS occurs as the adverse effects of some drugs and a form of systemic inflammatory response syndrome. Two different grading systems have been used in studies of CAR-T therapy:

1) The National Cancer Institute (NCI) Consensus criteria described by Lee et al.[55]
    - Grade 1: Not life-threatening, requires only symptomatic treatment such as antipyretics and anti-emetics
    - Grade 2: Requires and responds to moderate intervention such as supplemental oxygen, low dose vasopressors; accompanied by grade 2 organ toxicity
    - Grade 3: Requires and responds to aggressive intervention such as high oxygen supplementation, high dose, or multiple vasopressors; accompanied by grade 3 organ toxicity
    - Grade 4: Life-threatening consequences, ventilator support indicated; grade 4 organ toxicity
    - Grade 5: Death.[55]

2) The University of Pennsylvania / Children's Hospital of Philadelphia (UPENN/CHOP) scale[56] is an alternative for grading CRS:
    - Grade 1: A mild reaction treated with supportive care only
    - Grade 2: A moderate reaction requiring intravenous therapies or parenteral nutrition; mild signs of organ dysfunction or hospitalization of CRS or febrile neutropenia
    - Grade 3: A more severe reaction, requiring hospitalization, moderate signs of organ dysfunction related to CRS, hypotension treated with intravenous fluids or low-dose pressors; hypoxemia requiring oxygenation, bilevel positive airway pressure, or continuous positive airway pressure
    - Grade 4: Life threatening complications including hypotension requiring high dose vasoactive medications or hypoxemia requiring mechanical ventilation.

- Grade 5: Death

Given the differences in scales, a patient with CRS could receive a different grade depending on which scale is being used. A patient with hypotension receiving low dose vasopressors would receive a grade 2 on the NCI scale and a grade 3 on the UPENN/CHOP scale.

Eastern Cooperative Oncology Group (ECOG) Performance Status: ECOG score is a measure of the impact the cancer has on a patient's daily activities. It ranges from 0-5 with 0 denoting perfect health. One is defined as restricted in strenuous physical activities, but ambulatory and able to carry out light or sedentary work. Two is defined as ambulatory and capable of self-care, but unable to work. Three is defined as capable of limited self-care and confined to bed or chair more than 50% of waking hours. Four is defined as completely disabled and confined to bed or chair 100% of the time, and 5 is death.

Event-free survival: After starting primary cancer treatment, the duration of time that the patient remains free of complications or events that the treatment was intended to prevent or delay (e.g., relapse, bone pain from cancer that has spread to the bone, the onset of significant symptoms).

Hypogammaglobulinemia: A condition in which the level of immunoglobulins (antibodies) in the blood is low, and the risk of infection is high.

Karnofsky/Lansky Performance Status: A standard score that measures cancer patients' ability to perform ordinary tasks. The Karnofsky/Lansky scores range from 0-100, with a higher score indicating that the patient is better able to perform daily activities. Karnofsky/Lansky scores may be used to determine prognosis, to measure changes in function, or as inclusion criteria for a clinical trial. The Karnofsky scale is designed for recipients aged 16 years and over, and the Lansky scale is designed for recipients less than 16 years old.

Objective response rate (ORR; lymphoma): CR plus partial response.

Overall remission rate (ORR; leukemia): CR plus CRi.

Overall survival (OS): The time from clinical trial entry until death from any cause.

Partial remission (leukemia) / response (lymphoma): A decrease in the size of a tumor or in the extent of the cancer in response to treatment.

Progression-free survival (PFS): The time from clinical trial entry until lymphoma progression or death from any cause.

Relapsed disease (leukemia): Only in patients who achieved CR or CRi and who have:

- Reappearance of blasts in the blood (≥ 1%)

- Reappearance of blasts in the bone marrow (≥ 5%) or
- (Re)appearance of any extra-medullary disease after CR or CRi

Relapsed/refractory large B-cell lymphoma: Lymphoma that is relapsed or refractory after two or more lines of systemic therapy.

Salvage chemotherapy: Chemotherapy given to a patient after other treatment options have been exhausted.

1.4 Insights Gained from Discussions with Patients and Patient Groups

Several themes emerged from our discussion with patients and patient groups. One was hope – CAR-T therapy represented hope for a cure in patients who had run out of treatment options. They were encouraged by the high initial response rates seen in the clinical trials. In addition, they hoped that CAR-T therapy would be less toxic than chemoradiation and stem cell transplantation: no hair loss, mucositis, diarrhea, and nausea, and less time in the hospital.

A second related theme was fear of the unknown. Patients understood that very few other patients have been treated with CAR-T therapy and were worried about the side effects. Neurotoxicities were particularly terrifying. It is scary for patients to think that they will be mentally impaired, not in control of their thoughts, and unaware of what is going on. It is also frightening for loved ones who have to witness those symptoms. Patients felt that it was particularly important to educate both prospective patients and their families about what to expect in detail, not just in general terms. Patients and parents spoke of the comfort of talking to those who had already gone through treatment with CAR-T – that this was a way to alleviate some of the fear and anxiety.

They also spoke of the many other uncertainties. Would the early remission rates hold up over time? Were there long-term side effects that would only become evident five or 10 years from now? Would they need to undergo SCT following CAR-T therapy?

Patient advocacy organizations stressed the importance of understanding that when you meet one patient, you meet one patient. Every patient is unique in terms of their disease, their personality, and their preferences. They cautioned us against "lumping and generalizing."

Some patients highlighted the non-medical costs associated with treatment. Most had to travel long distances to the centers that offered CAR-T therapy. The time off work for family members loomed large, as did the cost of travel, including living expenses during treatment periods and post-treatment surveillance for side effects, but they felt that they had no choice; parents, in particular, spoke of doing anything for their child with leukemia.

In addition to education about side effects, patients and parents spoke of the emotional toll of the cancer and cancer treatment. They pointed to post-traumatic stress that continues long after

therapy is completed. The felt that it was important to include emotional/psychological counseling for both the patient and their loved ones.

1.5 Potential Cost-Saving Measures in ALL/Lymphoma

We sought to identify areas of waste and low-value care in the treatment of leukemias and lymphomas that could be reduced to increase the capacity for health care budgets to pay for new innovations. The American Society of Clinical Oncology (ASCO) has several Choosing Wisely recommendations that have the potential to be cost-saving:[16]

- Do not routinely use PET or PET-CT scans for follow-up visits to detect cancer recurrence in asymptomatic patients who have completed initial treatment, unless high-level evidence suggests that such imaging will change the outcome.
- Avoid the use of white cell stimulating factors for primary prevention of febrile neutropenia in patients whose risk for this complication is less than 20%.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for CAR-T therapies, we reviewed publicly-available coverage policies from CMS, California Department of Health Care Services (DHCS), and from regional and national commercial insurers (Aetna, Anthem, Blue Shield of California [BSCA], Cigna, Health Net, Humana, Kaiser Permanente, and United HealthCare [UHC]). As many insurers are still developing their coverage policies for CAR-T therapies, we have summarized their existing policies on stem cell transplantation as illustrative examples.

Childhood B-Cell Acute Lymphoblastic Leukemia

In this section, we have summarized only the portions of coverage policies that pertain to pediatric and young adult B-ALL, although all policies contained information about SCT in adults. We have not summarized CMS guidance related to SCT for ALL, as it is relevant only for adult patients.

Tisagenlecleucel

We were unable to locate any publicly-available coverage policies from California DHCS pertaining to tisagenlecleucel. Health Net, which is one of the managed care organizations that offers Medi-Cal policies, has issued a Medi-Cal coverage policy for tisagenlecleucel that is identical to its commercial policy (see below).[57]

We identified coverage policies for tisagenlecleucel from Anthem, Aetna, Cigna, Humana, UHC and Health Net.[58-63] Plans consider the treatment medically necessary for patients ages 25 years or younger with B-cell ALL that is refractory or in second or later relapse with CD19 tumor expression, which matches the FDA indication for the therapy. Aetna and Health Net further specify that for patients whose disease is Philadelphia chromosome positive (Ph+), there must be documented failure of two tyrosine kinase inhibitors (TKIs) at up to maximally indicated doses, unless contraindicated or in the case of clinically significant adverse effects. Anthem also specifies that the patient's Karnofsky/Lansky performance score must be at least 50%, or alternatively that the patient's ECOG performance score range from 0-3. Cigna and UHC did not list additional criteria beyond the FDA labeled indication. All policies except for Cigna and UHC's specified that repeat treatment is not covered in patients who have previously received any CAR-T treatment. Aetna, Humana, and UHC require prior authorization.

Stem Cell Transplant

We were unable to locate any publicly-available coverage policies from California DHCS pertaining to SCT.

We identified coverage policies for SCT for ALL from Aetna, Anthem, Cigna, UHC, and BSCA.[62,64-67] Humana's policy does not provide publicly available criteria for coverage, but instead provides a hotline for members to call for information. We were unable to locate a publicly-available policy from Kaiser Permanente.

With the exception of Aetna, all plans cover allo-SCT during the first remission for pediatric patients with high-risk factors for relapse, or during second or subsequent remission regardless of risk. Risk factors are largely similar across payers, and include Ph+ status, inadequate response to conditioning chemotherapy assessed at either four or six weeks depending on the payer, extramedullary disease, and hypodiploidy (45 or fewer chromosomes) among other criteria. Aetna considers allo-SCT medically necessary for patients with ALL meeting the transplanting institution's selection criteria. If the institution does not have such criteria, Aetna considers allo-SCT medically necessary for treatment of ALL including primary refractory ALL, but not for patients in refractory relapse (i.e., patients with relapsed disease that is unresponsive to three or more months of chemotherapy). Coverage of allo-SCT performed during relapse varies, with Aetna covering the therapy for patients except those in refractory relapse; Anthem covering allo-SCT during any relapse; and Cigna covering it for patients with late marrow relapses and high tumor load, or for patients with T-cell lineage ALL and marrow relapse. Policies from the other commercial payers did not include information on this circumstance. Anthem covers repeat allo-SCT in cases of primary graft failure or failure to engraft, Cigna when a relapse occurs more than six months after the initial allo-SCT, and UHC after primary or secondary graft failure and relapse. Policies from other payers did not specify how repeat transplants would be considered.

BSCA covers auto-SCT's use in children with ALL with high risk factors during first remission, for children at any risk level during the second or subsequent relapse, and to treat relapsed ALL after a prior auto-SCT. Among the other payers, coverage for auto-SCT is more limited. Aetna and Anthem consider auto-SCT to be investigational for patients with ALL. Cigna's policy did not contain criteria pertaining to auto-SCT.

Aggressive B-Cell Non-Hodgkin's Lymphoma

Axicabtagene Ciloleucel

We were unable to locate any CMS national or local coverage determinations (NCDs or LCDs, respectively) pertaining to axicabtagene ciloleucel or publicly-available policies from California DHCS.

We identified coverage policies for axicabtagene ciloleucel from Aetna, Anthem, Cigna, Humana, Health Net, and UHC,.[62,63,68-71] Cigna's policy states only that it will cover axicabtagene ciloleucel when medically necessary. All other insurers cover axicabtagene ciloleucel in individuals with large B-cell NHL who are at least 18 years of age and have disease that is refractory or has relapsed following two or more lines of systemic therapy, with or without auto-SCT. Anthem and Health Net specify that, at a minimum, patients must have tried an anthracycline-containing chemotherapy regimen and anti-CD20 monoclonal antibody (for patients with CD20+ disease); Anthem also requires patients with transformed follicular lymphoma to have attempted prior chemotherapy for follicular lymphoma with chemotherapy refractory disease after transformation to DLBCL. Patients must also have documentation of ECOG performance status of 0 or 1, absolute neutrophil count (ANC) ≥ 1000/uL, absolute lymphocyte count (ALC) > 100/uL, and platelet count ≥ 75,000/uL. Aetna, Humana, and UHC require patients to seek prior authorization for coverage.

Stem Cell Transplant

We were unable to locate any publicly-available coverage policies from California DHCS pertaining to SCT. CMS has issued a NCD pertaining to SCT and considers auto-SCT to be medically necessary for the treatment of resistant NHLs or those with poor prognosis following an initial response to treatment.[72] The NCD does not contain details about whether allo-SCT would be covered for NHL, indicating that Medicare Administrative Contractors may cover it at their discretion. For example, National Government Services, a Medicare Authorized Contractor (MAC) that operates in Illinois, Minnesota, New York, the six New England States, and Wisconsin, has issued a Local Coverage Article that provides coverage of allo-SCT for the treatment of primary refractory NHL.[73]

We identified coverage policies for SCT in NHL from Aetna, Anthem, Cigna, BSCA, Health Net, and UHC.[62,74-78] As in ALL, Humana's policy does not provide publicly available criteria for coverage but provides a hotline for members to call for more information. We were unable to locate a publicly-available coverage policy from Kaiser Permanente.

UHC covers allo- and auto-SCT for most subtypes of NHL, including DLBCL, PMBCL, and TFL provided that the patient achieves CR or PR following initial treatment. Both Anthem and BSCA cover allo-SCT and auto-SCT for patients who do not achieve CR following first-line chemotherapeutic treatment, or to achieve or consolidate CR for patients with chemosensitive tumors that are in first or subsequent relapse. Both Anthem and BSCA also consider allo- or auto-SCT to be medically necessary for patients who achieve CR following chemotherapy but have prognostic factors that indicate a high-intermediate to high risk of relapse.

Cigna covers auto-SCT for patients with stage II through IV NHL and allo-SCT for patients who are not candidates for auto-SCT if there is an appropriate human leukocyte antigen donor. Health Net covers auto-SCT (preferred) for NHL for patients under the age of 70 with stage III or IV A or B intermediate- to high-grade NHL in second or later remission; stage II or IIB relapsed disease; as

salvage therapy for relapsed, chemosensitive intermediate- to high-grade lymphoma; relapsed, low-grade, follicular NHL (transformed or untransformed); follicular NHL that has not responded to primary therapy; chemosensitive disease that is in partial remission; and for patients that are over the age of 60 with poor prognostic features during first remission, among several other indications. Health Net notes that allo-SCT with high-dose chemotherapy should be reserved for patients for whom other therapies have failed, and authorizes coverage for patients with stage III or IV A or B that is refractory to initial chemotherapy or in second or later PR/CR; relapsed low-grade follicular NHL; and stage IV A or B NHL with a lymphoma mass over 10 cm and more than one extranodal site in first remission, among other indications. Aetna covers auto- or allo-SCT for patients with relapsed or primary refractory NHL if the patient meets the transplanting institution's eligibility criteria. If the institution does not have such criteria, Aetna considers auto-SCT medically necessary for NHL for patients whose disease is responsive to chemotherapy and have evidence of serious organ dysfunction, and allo-SCT medically necessary when the patient has an appropriately matched donor and no evidence of organ dysfunction.

2.2 Clinical Guidelines

National Comprehensive Cancer Network (NCCN)

Acute Lymphoblastic Leukemia[41]

The NCCN guidelines list separate treatment pathways for adolescents and young adults ages 15 to 39 years with relapsed or refractory ALL, depending on whether the patient is Ph+ or Ph-. The NCCN recommends clinical trial participation for both groups of patients.

Patients who are Ph+ may be treated with a TKI that was not used in earlier induction therapy (e.g., imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), a TKI in combination with multi-agent chemotherapy, or a TKI in combination with corticosteroids. ABL1 kinase domain mutation testing is recommended to identify the most appropriate TKI among dasatinib, nilotinib, bosutinib, and ponatinib. Patients who are refractory to TKIs may receive treatments indicated for relapsed/refractory Ph- ALL (described below), blinatumomab, or inotuzumab ozogamicin. Each of the above options may be combined with allo-SCT. Tisagenlecleucel is recommended for patients under the age of 26 with refractory disease or for patients with two or more relapses who have experienced treatment failure with two TKIs.

Patients who are Ph- may be treated with single-agent chemotherapy, multi-agent chemotherapy, chemotherapy ± allo-SCT, blinatumomab, inotuzumab ozogamicin, or tisagenlecleucel if the patient is under the age of 26 with refractory disease or two or more relapses. Patients who relapse more than three years after their initial diagnosis may be retreated with the same induction chemotherapy regimen that was previously used.

In both Ph+ and Ph- patients, retreatment with allo-SCT ± donor lymphocyte infusion may be considered if a patient experiences a relapse after the allo-SCT treatment.

Diffuse Large B-Cell Lymphoma[45]

NCCN recommends that patients with relapsed or refractory DLBCL seek treatment in a clinical trial, especially for those with disease progression after three successive treatment attempts. In the absence of an appropriate trial, NCCN divides their recommendations into separate pathways for patients who are eligible or not eligible for high-dose therapy. For patients who can tolerate high-dose therapy, NCCN recommends the following chemotherapy regimens, with or without rituximab: DHAP (dexamethasone, cisplatin, cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin, or carboplatin), ICE (ifosfamide, carboplatin, etoposide), or MINE (mesna, ifosfamide, mitoxantrone, etoposide). Patients who experience CR or PR with high-dose therapy should be considered candidates for auto-SCT, with or without involved-site radiation therapy (ISRT). In the case of another relapse, or when there is no response to the previous second-line therapy, patients may be treated with palliative radiation therapy (RT) or supportive care. Patients who achieve CR may proceed to consolidation with high-dose therapy with auto-SCT with or without ISRT, or allo-SCT in certain cases such as mobilization failures or persistent bone marrow involvement. Patients who achieve PR may be considered candidates for axicabtagene ciloleucel or the same treatments listed for those who achieve CR. If the patient does not respond to second-line therapy or has progressive disease, clinicians may use axicabtagene ciloleucel if it has not already been used, an alternate second-line therapy, palliative radiation therapy, or best supportive care.

Patients who are ineligible for high-dose therapies may be treated with rituximab alone, or rituximab ± the following regimens: bendamustine, brentuximab vedotin (for CD30+ disease), CEPP (cyclophosphamide , etoposide, prednisone, procarbazine), CEOP (cyclophosphamide, etoposide, vincristine, prednisone), DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), GDP, GemOx (gemcitabine, carboplatin, etoposide), a combination of gemcitabine/vinorelbine, or lenalidomide (for non-germinal center B-cell DLBCL). Treatments for any additional relapse after second-line therapy include axicabtagene ciloleucel, palliative radiation therapy, and the provision of supportive care.

Transformed Follicular Lymphoma[45]

NCCN recommends that patients with TFL seek treatment as part of a clinical trial. If no suitable trials are open, patients who have previously been treated with multiple prior therapies should be treated with radioimmunotherapy, chemotherapy ± rituximab ± ISRT, ISRT, axicabtagene ciloleucel (for patients who have attempted two or more prior chemotherapy regimens and have not already been treated with axicabtagene ciloleucel), or best supportive care. Those who respond are considered candidates for observation, high-dose therapy with auto-SCT rescue, or allo-SCT, while

those who do not respond/have progressive disease proceed to supportive care if they are able to tolerate additional therapy. Patients who have had little to no prior chemotherapy may be treated with anthracycline- or anthracenedione-based chemotherapy + rituximab ± ISRT. Axicabtagene ciloleucel is recommended for patients with PR, no response, or progressive disease, provided the patient has attempted at least two prior lines of therapy. In addition, consolidation treatment with high-dose therapy with auto-SCT or, alternatively, allo-SCT is an option for all patients who respond to initial treatment. Patients who experience CR to initial therapy may be monitored, while those who experience PR may be treated with radioimmunotherapy. Patients who do not respond to treatment, or whose disease progresses, should be treated with radioimmunotherapy, palliative therapy, or best supportive care.

Primary Mediastinal Large B-Cell Lymphoma[45]

The NCCN guidelines recommend that patients with PMBCL be treated with one of the following regimens: DA-EPOCH plus rituximab with radiation therapy for individuals with persistent focal disease, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), , or R-CHOP followed by ICE ± radiation therapy. Patients with relapsed or refractory disease may be treated with the regimens recommended for patients with relapsed or refractory DLBCL (described above).

National Institute for Health and Care Excellence (NICE)

Diffuse Large B-Cell Lymphoma[79]

NICE recommends multi-agent chemotherapy, preferably with R-GDP as it is less toxic, for patients who have relapsed or refractory diffuse large B-cell lymphoma and can tolerate intensive therapy. Patients who respond to therapy may proceed to consolidation with auto-SCT or allo-ASCT, with the latter considered appropriate for patients who relapse after or are ineligible for auto-SCT.

Pixantrone monotherapy is also recommended by NICE for patients who have experienced multiple relapses or refractory disease who have previously been treated with rituximab and now receiving third- or fourth-line treatment.

Transformed Follicular Lymphoma[79]

NICE recommends that patients with TFL be treated auto-SCT consolidation therapy, if they are healthy enough for transplantation and their disease has responded to treatment. Patients who require more than one line of treatment may also be candidates for auto-SCT or allo-SCT. Patients who have a diagnosis of both DLBCL and TFL should not be offered high-dose therapy with allo- or auto-SCT.

3. Comparative Clinical Effectiveness

3.1 Overview

The comparative clinical effectiveness review of the CAR-T therapies with other salvage therapies for ALL or DLBCL was challenged because all of the clinical studies were small, single-arm designs with limited follow-up and incomplete reporting. Since no trials had control groups, it was not possible to estimate the comparative benefits or harms of these novel therapies in relation to prior therapies with FDA indications for the same patient populations using either direct or indirect comparisons. Thus, all comparisons of outcomes of CAR-T therapy to other therapies used for the same indication are naïve indirect comparisons that should be considered descriptive and potentially subject to significant selection bias and other confounding factors. Furthermore, the small sample sizes and short follow-up add to the uncertainty for estimates of clinical efficacy. Finally, some of the pivotal trials have yet to be published in peer reviewed journals, so we are dependent on grey literature for our data including conference presentations, public FDA submission documents, data supplied by manufacturers, and the package inserts for the therapies.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CAR-T therapies for pediatric ALL and adult B-cell lymphoma followed established best methods.[80,81] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[82] The PRISMA guidelines include a list of 27 checklist items, which are described in further detail in Appendix A1.

We searched MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant studies, performing separate searches for pediatric ALL and adult B-cell lymphoma. We limited the searches to English-language studies of human subjects and focused on trials of at least three months' duration. We excluded any articles indexed as guidelines, letters, editorials, narrative reviews, or news items.

The search strategies included a combination of indexing terms (MeSH terms in MEDLINE/PubMed and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2-A7. To supplement the above searches and optimize complete literature retrieval, we performed a manual check of the references of recent relevant peer-reviewed publications and public reports. As noted above, we were cognizant of the evolving evidence base since none of the pivotal trials have been published to date; therefore, we relied heavily on grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-

methods/icer-value-assessment-framework/grey-literature-policy/). We also contacted manufacturers, specialty societies, and patient advocacy organizations to ensure that we captured all the relevant literature.

Study Selection

We selected studies that evaluated the use of one of the two CAR-T therapies of interest (axicabtagene ciloleucel or tisagenlecleucel) in patients with either pediatric ALL or adult DLBCL and reported on clinically relevant outcomes such as overall survival, complete remission, or partial response. Reasons for exclusion included incorrect drug, incorrect patient population, shorter study duration, review article, commentary, lack of relevant outcomes, and duplication.

Data Extraction and Quality Assessment

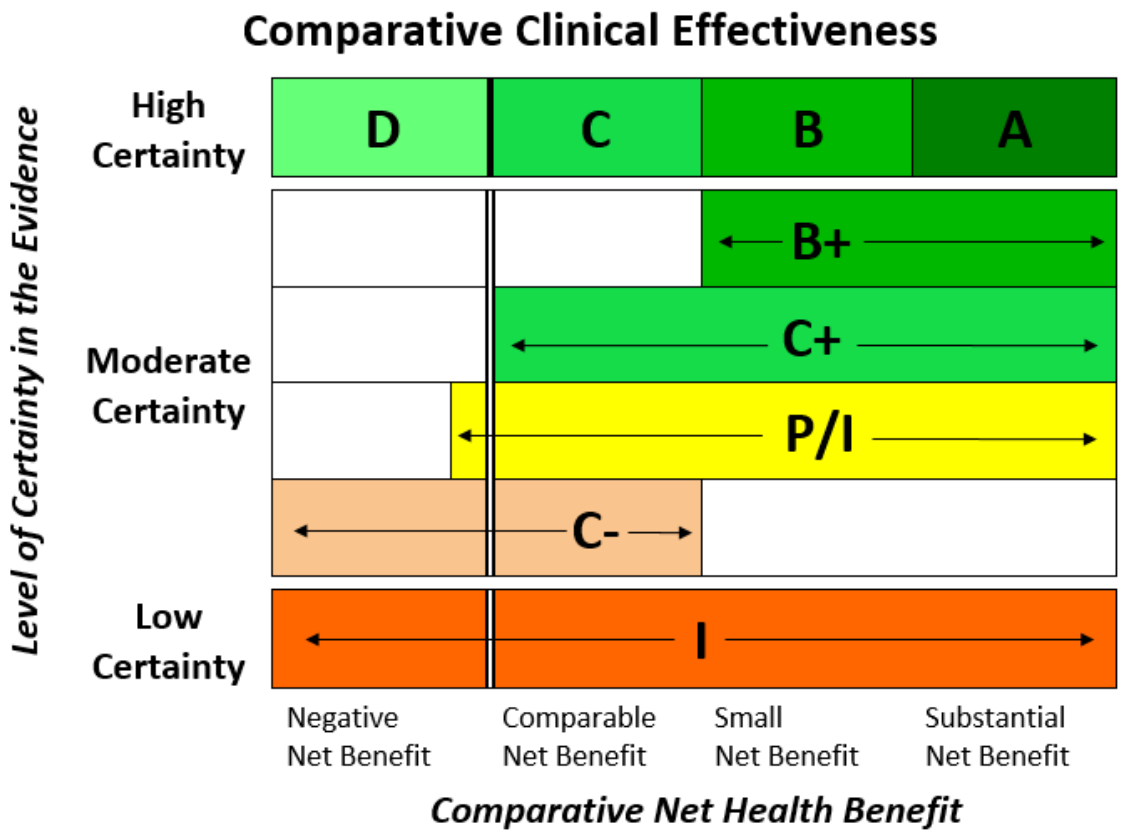
Data were extracted by a single reviewer and then verified by three reviewers. Quality assessment was performed using standard criteria, including presence of comparable groups, whether comparability was maintained, whether studies were double blind, whether measurements were equal and valid, whether there was a clear description of the intervention, whether key outcomes were assessed, and whether the analysis was appropriate.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[83]

Figure 3.1. ICER Evidence Rating Matrix



*A = **"Superior"** - High certainty of a substantial (moderate-large) net health benefit*
*B = **"Incremental"** - High certainty of a small net health benefit*
*C = **"Comparable"**- High certainty of a comparable net health benefit*
*D = **"Negative"**- High certainty of an inferior net health benefit*
*B+ = **"Incremental or Better"** - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
*C+ = **"Comparable or Better"** - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
*P/I = **"Promising but Inconclusive"** - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
*C- = **"Comparable or Inferior"** - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
*I = **"Insufficient"** - Any situation in which the level of certainty in the evidence is low*

Assessment of Bias

All of the studies were single-arm trials. Single-arm trials are at high risk for bias and are, therefore, generally considered to be of lower quality.

Data Synthesis and Statistical Analyses

Since none of the studies included comparator groups, we were unable to perform any statistical comparisons, including meta-analyses and network meta-analyses.

3.3 Results

The results are organized by clinical indication. In the first section, we review CAR-T therapy for relapsed or refractory pediatric B-cell ALL. Our search identified three single-arm trials of tisagenlecleucel for this indication. As noted above, no formal direct or indirect comparisons with other therapies for this indication could be made. However, we summarized several trials of drugs approved by the FDA for the same indication. Caution should be taken when interpreting any comparisons across trials, because they have a high degree of uncertainty due to the potential for significant selection bias.

In the second section, we review CAR-T therapy for relapsed or refractory aggressive B-cell lymphomas (primarily DLBCL). For both tisagenlecleucel and axicabtagene ciloleucel, our search identified one single-site, single-arm trial and one multi-center pivotal single-arm trial. Again, because there were only single-arm trials and we did not have access to patient level data, we could not directly or indirectly compare the results to any other therapy. We used the recently published SCHOLAR-1 trial[17] as an example of outcomes of alternative therapies in a similar population.

Pediatric B-Cell ALL

There are three single-arm trials of tisagenlecleucel for pediatric ALL. The first, B2101J, was a single site Phase I/IIa trial that used split dosing of CAR-T cells manufactured at the University of Pennsylvania. The subsequent multi-center trials used a single infusion of CAR-T cells at the current standard dose. For B2205J, the CAR-T cells were manufactured using the University of Pennsylvania process, while the pivotal study for FDA submission (B2202, ELIANA) used the Novartis manufacturing process at a facility in Morris Plains, NJ. The three trials and four additional studies of other FDA approved therapies for similar patient populations are summarized in Table 3.1 below. Additional details about the trials can be found in Appendix Tables C1-C6.

Table 3.1. Summary of Treatments for Relapsed/Refractory Pediatric B-ALL

Trial/Therapy	N Infused	Median Age (Years)	Median Number Prior Treatments	Prior SCT
B2101J[18], tisagenlecleucel	55	11	4	72%
B2205J[18], tisagenlecleucel	29	12	3	59%
B2202/ELIANA[19], tisagenlecleucel	68	11	3	61%
Jeha 2006[20]; clofarabine	61	12	3	30%
Hijiya 2011[21]; clofarabine + etoposide, cyclophosphamide	25	14	2	16%
Von Stackelberg 2016[22] (MT103-205); blinatumomab	70	8	2	57%
Locatelli 2017[23] (RIALTO), blinatumomab	40	9	2	53%

B-ALL: B-cell acute lymphoblastic leukemia, SCT: stem cell transplant

Quality of Individual Studies

As noted in Appendix Table C4, all three of the studies of tisagenlecleucel are considered to be of lower quality because they lack comparators. Furthermore, the studies are small and have short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for pediatric B-cell ALL.

Clinical Benefits

The key clinical outcome from the patient's perspective is curing the cancer. There is no accepted definition of a cure, as relapses can rarely occur more than 10 years after remission, though Pui et al suggest that 10 years of complete remission would be a reasonable standard.[84] A 2014 paper proposed that with contemporary treatment, children in remission four years after the completion of treatment could be considered cured (<1% chance of relapse).[24,25] Thus, four-year event-free survival would be an ideal outcome. Thus far, none of the trials of CAR-T therapy have followed patients for that long. Complete remission is a marker for long term survival, but the majority of patients with ALL who have failed prior therapy usually relapse even after achieving subsequent remission.

As noted above, there are three single-arm trials of tisagenlecleucel in patients with relapsed or refractory ALL. The patients in these trials had relapsed after a median of three lines of prior chemotherapy and more than half had relapsed following allo-SCT (Table 3.1 and Appendix Table C1). For context, in the same table, we abstracted the same data from four trials of two agents that also received FDA approval for relapsed or refractory ALL on the basis of single-arm trials (clofarabine, blinatumomab). It is worth noting that the patients in these trials, while also heavily pretreated, either had a lower median number of prior lines of therapy (2)[21-23] or had lower rates of prior allo-SCT.[20,21] Thus, patient selection suggests that the patients in the trials of tisagenlecleucel had undergone more prior therapies and, thus, had a worse prognosis at enrollment.

Table 3.2. Overall and Complete Remission Rates in Heavily Pre-treated Patients Who Received Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Overall Remission Rate	Complete Remission
B2101J[18]	Tisagenlecleucel	95%	69%
B2205J[18]	Tisagenlecleucel	69%	62%
B2202 / ELIANA[19]	Tisagenlecleucel	81%	60%
Jeha 2006[20]	Clofarabine	20%	11%
Hijiya 2011[21]	Clofarabine/etoposide/ cyclophosphamide	44%	28%
Von Stackelberg 2016[22]	Blinatumomab	39%	17%
Locatelli 2017[23]	Blinatumomab	NR	63%

B-ALL: B-cell Acute lymphoblastic leukemia, NR: not reported

The reported overall remission rates for tisagenlecleucel in the three trials (from 69% to 95%, Table 3.2) represents an optimistic presentation of the results that violates the intention to treat principle because they are based on patients who received successful infusion of CAR-T cells, thereby excluding patients who did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs. Table 3.3 estimates the overall remission rates in the trials based on the number of patients enrolled in each trial (i.e., on an intention to treat basis).

Table 3.3. Overall Remission Rates in Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Overall Remission*
B2101J[18]	Tisagenlecleucel	52/71 = 73% (61% to 83%)
B2205J[18]	Tisagenlecleucel	20/35 = 57% (39% to 74%)
B2202 / ELIANA[19]	Tisagenlecleucel	61/92 = 66% (56% to 76%)
Jeha 2006[20]	Clofarabine	12/61 = 20% (11% to 32%)
Hijiya 2011[21]	Clofarabine/etoposide/ cyclophosphamide	11/25 = 44% (24% to 65%)
Von Stackelberg 2016[22]	Blinatumomab	27/70 = 39% (27% to 51%)
Locatelli 2017[23]	Blinatumomab	25/40=63% (46% to 77%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells

B-ALL: B-cell Acute lymphoblastic leukemia

While this presentation suggests more modest benefits, the overall remission rates are higher with tisagenlecleucel than with the other therapies. These response rates for CAR-T therapy may improve if the number of manufacturing failures decreases with time and experience.

As noted above, event-free survival at four years would be the most robust estimate of cure, but follow-up was too short in the trials to attempt an estimation. All three trials of tisagenlecleucel estimated the event-free survival six months after infusion, which ranged from 55% to 75%. Again, this fails to account for patients who were enrolled, but could not receive CAR-T therapy. Table 3.4 below estimates the overall event-free survival in the trials based on the number of patients enrolled.

Table 3.4. Estimated Event-Free Survival at Six Months in Therapies for Relapsed or Refractory Childhood B-ALL

Trial	Therapy	Event-free Survival at 6 Months*	Overall Survival at 12 Months
B2101J[18]	Tisagenlecleucel	58%	81%
B2205J[18]	Tisagenlecleucel	46%	62%
B2202 / ELIANA[19]	Tisagenlecleucel	60%	62%
Jeha 2006[20]	Clofarabine	11%	20%
Hijiya 2011[21]	Clofarabine/etoposide/ cyclophosphamide	35%	35%
Von Stackelberg 2016[22]	Blinatumomab	16%	38%
Locatelli 2017[23]	Blinatumomab	NR	NR

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells or the number responding to treatment

B-ALL: B-cell Acute lymphoblastic leukemia

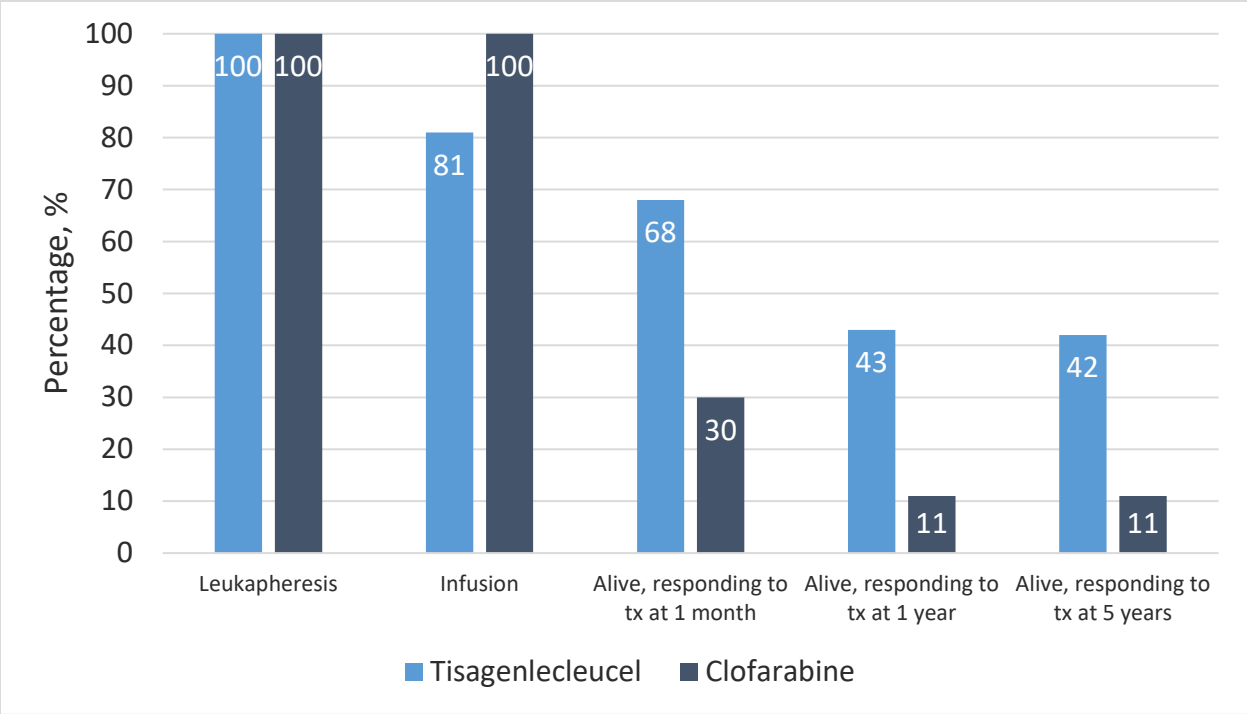
The ELIANA trial is the pivotal trial for tisagenlecleucel and was designed with input from the FDA. It is an ongoing, single-arm clinical trial that required participants to be between the ages of three and 21 years with relapsed or refractory B-cell ALL and a Karnofsky/Lansky performance status of at least 50%.[19] In addition, the study required ≥ 5% blasts in the bone marrow at screening and the expression of CD-19 on tumor cells in the blood or bone marrow. Among the 92 participants enrolled in the trial, 75 (82%) received the infusion with tisagenlecleucel. There were several reasons that the 20 participants did not receive the infusion, including failure to manufacture the CAR T-cells (n=7), death (n=7), and AEs (n=3). The median time from enrollment to infusion was 45 days (range 30 to 105). The median time from infusion to data cut off for the analyses was 13.1 months.

Among the 75 patients infused with tisagenlecleucel, the ORR (CR plus CRi) was 81% (95% confidence interval [CI] 71% to 89%). In an intention to treat analysis that included all of the enrolled patients (N=92), the overall remission rate was 66% (95% CI 56% to 76%). The event-free survival for the 75 patients infused with tisagenlecleucel was 73% (95% CI 60% to 82%) at 6 months and 50% at 12 months (95% CI 35% to 64%). The overall survival was 90% (95% CI 81% to 95%) at 6 months and 76% (95% CI 63% to 86%) at 12 months. Although tisagenlecleucel is intended to be curative therapy, 8 patients chose to have allo-SCT while in remission and an additional two patients received allo-SCT following relapse.[19]

Based on the reported event-free survival curves, we estimated the long-term survival of patients treated with tisagenlecleucel[26] or with clofarabine[20] using the parametric extrapolation used for the cost-effectiveness evaluation, as described below in Section 4.2. Data for tisagenlecleucel were pooled from all three available trials. We made the comparison at the time of leukapheresis for CAR-T therapy to account for the time required to manufacture the CAR-T cells, which is time that

would otherwise be spent undergoing re-induction treatment. As noted above, these are estimates with considerable uncertainty because the trials are not directly comparable, and because the trials were small with median follow-ups of less than two years. However, the comparisons are useful as a guide to the potential magnitude of benefit for tisagenlecleucel compared to other recent therapies for children with relapsed or refractory ALL.

Figure 3.2. Comparison of Estimated Outcomes for Tisagenlecleucel and Clofarabine*



*For clofarabine, the data for leukapheresis and infusion represent the same time point, since no leukapheresis is necessary
tx: treatment

Harms

The key AEs experienced by the first 68 patients who received an infusion of tisagenlecleucel in the ELIANA trial were reported in the package insert[27] and are summarized in Table 3.5 below.[27] Appendix Table C13 summarizes additional AE information for tisagenlecleucel as reported in the peer-reviewed publication of the ELIANA trial[19] and the briefing document submitted by Novartis to the FDA.[18] It is important to keep in mind that some of these AEs reflect the conditioning chemotherapy and/or progression of the leukemia, and are not a direct effect of tisagenlecleucel.

Table 3.5. Key Adverse Events in the ELIANA trial (n=68)[27]

Adverse Reaction	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	79%	49%
Neurologic Toxicities	65%	18%
Fever	50%	15%
Encephalopathy	34%	10%
Headache	37%	3%
Acute Kidney Injury	22%	13%
Hypotension	31%	22%
Hypoxia	24%	18%
Infections – Pathogens Unknown	41%	16%
Viral Infections	26%	18%
Bacterial Infections	19%	13%
Fungal Infections	13%	7%

Additional important grade three or higher adverse events include disseminated intravascular coagulation (9%), histiolymphocytic hemophagocytosis (7%), heart failure (7%), cardiac arrest (4%), seizures (3%), and intracranial hemorrhage (1%). There were 11 deaths: 7 from disease progression, 3 from infections, and one from intracranial hemorrhage.

The two most important harms caused by CAR-T therapy are CRS and neurotoxicity. CRS was common (79%) and often severe (49% with grade 3 or higher).[27] Patients with grade three CRS require close monitoring, usually in an ICU. In the ELIANA trial, the average ICU stay for patients with Grade 3 or 4 CRS was 8 days (n=33 patients).[26] CRS is associated with very high interleukin-6 (IL-6) levels and the anti-IL-6 antibody tocilizumab is often used to treat CRS. Tocilizumab was used to treat 27/68 patients. Seventeen patients received one dose, 7 received two doses, and 3 received 3 doses. No patients died due to CRS.

Neurologic toxicities (65%, 18% grade 3 or higher) included headaches, encephalopathy, delirium, anxiety, disorientation, aphasia, and seizures. Most occurred in the first eight weeks following infusion. Treatment for neurologic toxicities is usually supportive care.

An additional important toxicity is hypogammaglobulinemia due to B-cell aplasia. B-cells are the target of tisagenlecleucel in order to keep the leukemia in remission. Patients without the immunoglobulins produced by B-cells are at risk for infections and are typically treated with monthly intravenous infusions of pooled immunoglobulins (IVIG). The Novartis briefing document for the FDA Advisory Committee states that "responding patients experienced continued B-cell aplasia indicating the long-term effect of tisagenlecleucel" and notes "B-cell aplasia ongoing for > 3 years."[18] For those who require IVIG, the typical duration of use is unknown.

Finally, there are theoretical concerns about mutagenesis from the insertion of the chimeric gene into the patient's T-cells. The risk is likely to be quite low but is an important long-term concern.

Adult Aggressive B-Cell Lymphoma

There are two single-arm trials of axicabtagene ciloleucel for adult B-cell lymphoma and two single-arm trials of tisagenlecleucel for the same population. For axicabtagene ciloleucel, there is a single-site NCI study and the pivotal multi-center ZUMA-1 trial.[12,28] For tisagenlecleucel, there is a single-site University of Pennsylvania study and the pivotal multi-center JULIET trial.[29] The four CAR-T trials and an additional study in similarly heavily pre-treated patients with B-cell lymphomas (SCHOLAR-1) are summarized in Table 3.6 below. Additional details about the trials can be found in Appendix Tables C7-C12.

Table 3.6. Summary of Treatments for Relapsed/Refractory Adult B-Cell Lymphoma

Trial	N Infused	Median Age (Years)	Median Number Prior Treatments	Prior SCT
Axicabtagene Ciloleucel				
ZUMA-1[28]	101	58	3	21%
NCT00924326[12]	22	58	4	23%
Tisagenlecleucel				
JULIET[29]	99	56	3	47%
NCT02030834[29]	28	57	4	35%
Mix of Salvage Chemoimmunotherapies				
SCHOLAR-1[17]	636	55	2	22%

SCT: stem cell transplant

Quality of Individual Studies

As noted in Appendix Table C10, the ZUMA-1 and JULIET studies as well as the two single site studies were considered to be of lower quality because they lack comparators. Furthermore, the studies were small and of short median follow-up, which adds to the uncertainty about long term outcomes with CAR-T therapy for adult aggressive B-cell lymphoma.

Clinical Benefits

As with ALL above, the clinical outcome that matters most to a patient with lymphoma is curing the cancer. There is no accepted definition of a cure in relapsed or refractory lymphoma. A 2014 publication proposed that event-free survival two years after the completion of treatment could be a reasonable surrogate outcome.[31] However, a more recent publication demonstrated that more than 10% of treated DLBCL patients who survived two years after treatment died from their lymphoma over the next eight years and the survival curve had not yet flattened.[85] Both the ZUMA-1 and JULIET studies of CAR-T therapies for lymphoma followed patients for less than a median of two years, which limits conclusions about long term impact. Complete remission is a marker for long-term survival, but the majority of patients with B-cell lymphoma who have failed prior therapy usually relapse even after achieving subsequent remission.

Axicabtagene Ciloleucel

There are two trials of axicabtagene ciloleucel in patients with relapsed or refractory aggressive B-cell lymphoma: a single-site trial performed at the NCI and the pivotal multi-center ZUMA-1 trial.[28] For context, we abstracted data from the SCHOLAR-1 trial, which used the same inclusion and exclusion criteria as ZUMA-1 trial to select a subset of patients with aggressive DLBCL treated in two randomized trials and two academic databases. Even so, there are concerns about selection bias as noted in the commentary that accompanied the publication of the SCHOLAR-1 trial.[86]

Table 3.7. Objective Response Rates Reported for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
ZUMA-1[28]	Axicabtagene ciloleucel	82%	54%
NCT00924326[12]	Axicabtagene ciloleucel	73%	55%
SCHOLAR-1[17]	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for axicabtagene ciloleucel in ZUMA-1 (54%) represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR-T cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs. Table 3.8 below estimates the complete remission rate based on the number of patients enrolled in the trial.

Table 3.8. Estimated Complete Remission Rates for Axicabtagene Ciloleucel for Relapsed or Refractory Adult B-cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	Complete Remission Rate*
ZUMA-1[28]	Axicabtagene ciloleucel	52/111 = 47% (37% to 57%)
NCT00924326[12]	Axicabtagene ciloleucel	12/NR = NR
SCHOLAR-1[17]	Mix of salvage therapies	7% (3% to 15%)

*Based on the number enrolled, not the number receiving the infusion with CAR-T cells
NR: Not Reported

Even with this change, the complete remission rate is much higher with axicabtagene ciloleucel than with the other therapies.

As noted above, event-free survival would be the most robust estimate of cure, but it has not been reported for either ZUMA-1 or SCHOLAR-1. In SCHOLAR-1, the median overall survival was 6.3 months and the Kaplan-Meier estimates for one and two-year survival rates were 28% and 20% respectively. At six months, the Kaplan-Meier estimates for overall survival were 80% in ZUMA-1 and 55% in SCHOLAR-1.[32]

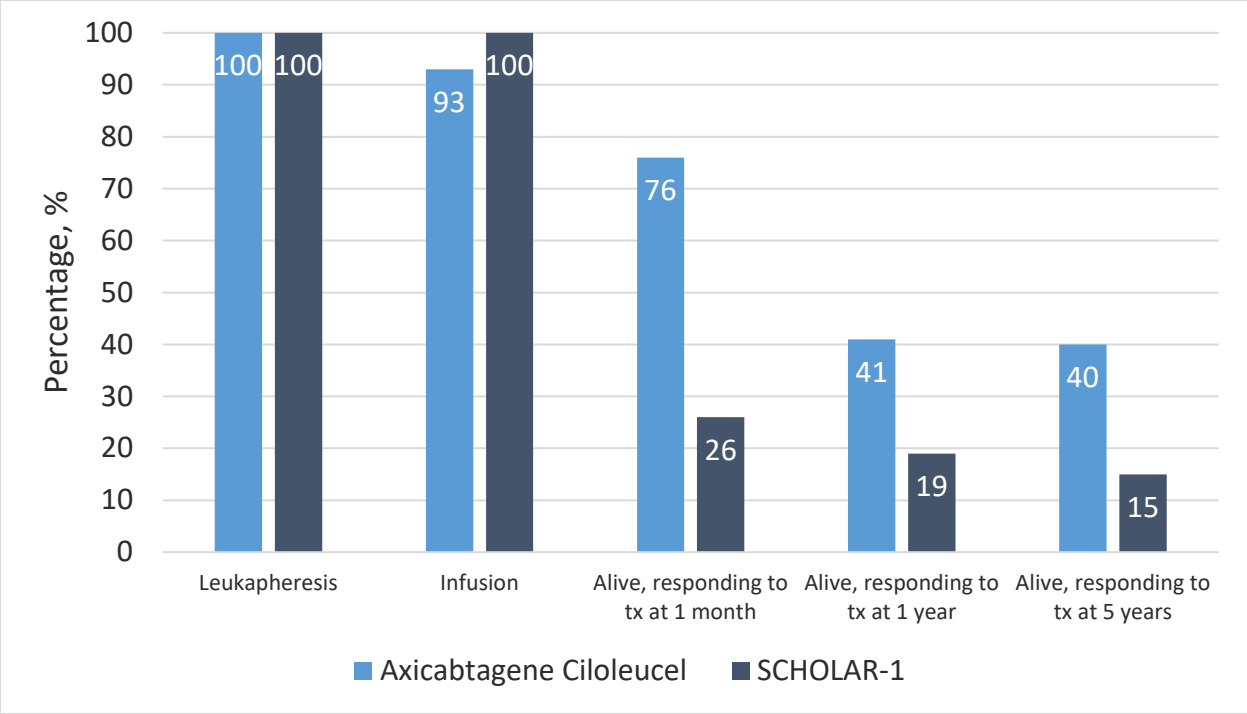
The ZUMA-1 trial was a single-arm clinical trial that required participants to be ages 18 years or older with histologically confirmed B-cell lymphoma (DLBCL, PMBCL, or TFL) that is refractory to chemotherapy with an ECOG performance status 0 or 1.[28] In addition, the study required that prior therapy include an anti-CD20 monoclonal antibody-containing regimen and an anthracycline-containing regimen. Among the 111 participants enrolled in the trial, 101 (91%) received the infusion with axicabtagene ciloleucel. There were a number of reasons that the 10 participants did not receive the infusion including failure to manufacture the CAR T-cells (n=1), and AEs or disease progression (n=9). The median time from enrollment to infusion was 24 days. An additional seven patients treated during the Phase I portion of ZUMA-1 were included in their updated analysis.

Among the 101 patients who received axicabtagene ciloleucel, the complete remission rate was 54% (52/101, 95% CI 41% to 62%) and the ORR (CR plus PR) was 72% (73/101, 95% CI 62% to 81%).[34] When the additional seven Phase I patients are added, the CR was 58%, and the ORR was 82%. When the enrolled patients who discontinued prior to axicabtagene ciloleucel infusion are included in the analysis, the CR rate was 46.8% (95% CI 37% to 57%), and the ORR was 65.8% (95% CI 56% to 75%). The median OS was not reached at 15.4 months follow-up; the Kaplan-Meier estimated OS based on 108 patients was 78% at six months, 59% at 12 months, and 52% at 18 months.[28] If the 10 patients who were unable to receive CAR-T therapy are assumed to have died, the OS estimates would be approximately 68%, 49% and 42% at six, 12, and 18 months respectively. The median PFS among the 108 patients was 5.8 months with Kaplan-Meier estimates for PFS at six, 12, and 18 months of 49%, 44%, and 41%.

Neelapu and colleagues presented a propensity-score-matched analysis comparing the outcomes of ZUMA-1 to those of SCHOLAR-1 at ASH in December 2017.[33] They reported that after matching, the ORR was 83% in ZUMA-1 and 33% in SCHOLAR-1 (treatment difference 49%, 95% CI 33% to 63%). Similarly, the estimated CR was 57% in ZUMA-1 and 12% in SCHOLAR-1 (treatment difference 46%, 95% CI 26% to 59%). The estimated HR for overall survival was 0.28 (95% CI 0.15 to 0.40) with 18-month OS estimated to be 47% in ZUMA-1 and 23% in SCHOLAR-1.

Based on approximations of the event-free survival curves, we estimated the long-term survival of patients treated with axicabtagene ciloleucel and for patients in SCHOLAR-1 using the parametric extrapolation described below in Section 4.2 of the report. We made the comparison at the time of leukapheresis for CAR-T therapy to account for the time required to manufacture the CAR-T cells, which is time that would otherwise be spent undergoing re-induction treatment. As noted above, these are estimates have considerable uncertainty because the trials are not directly comparable (concerns about selection bias) and because the ZUMA-1 trial is small with median follow-up of 15.4 months. However, the comparisons are useful as a guide to the potential magnitude of benefit for axicabtagene ciloleucel compared to other recent salvage therapies for adults with relapsed or refractory aggressive B-cell lymphoma.

Figure 3.3. Comparison of Estimated Outcomes for Axicabtagene Ciloleucel and SCHOLAR-1*



*For the salvage regimens in SCHOLAR-1, the data for leukapheresis and infusion represent the same timepoint, since no leukapheresis is necessary
tx: treatment

Tisagenlecleucel

There are two trials of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphoma: a single site trial performed at the University of Pennsylvania and the pivotal multi-center JULIET trial.[29,30]

In the JULIET trial, patients were recruited at 27 sites in 10 countries. JULIET is a single-arm, open-label, clinical trial that required participants to be ages 18 years or older with histologically confirmed DLBCL who had been treated with at least two prior chemotherapy regimens and had relapsed after or were ineligible for auto-SCT.[29] In addition, the study required that patients have an ECOG performance status 0 or 1 at screening and no prior anti-CD19 therapy. The study excluded patients with known CNS disease. Among the 147 participants enrolled in the trial, 99 (67%) received the infusion with tisagenlecleucel.[29] There were a number of reasons that the 48 participants did not receive the infusion including failure to manufacture the CAR T-cells (n=9), and AEs or disease progression (n=34 including 16 deaths). The remaining five patients were still awaiting infusion. Safety data are based on the 99 patients who received the infusion of CAR-T cells and clinical response data are based on the 81 patients with at least three months of follow-up (median time from infusion to analysis = 3.7 months).

Among the 81 patients who received tisagenlecleucel and provided at least three months follow-up, the complete remission rate was 40% (95% CI NR) and the best overall response rate was 53% (95% CI 42% to 64%).[29] The ORR was 38% (32% CR, 6% PR) at three months follow-up and 37% (30% CR, 7% PR) at six months. If the enrolled patients who discontinued prior to tisagenlecleucel infusion for patient reasons or manufacturing failure are included in the analysis (n=43), the ORR and CR at three months would be much lower. Among the 43 patients with a response, the estimated relapse-free survival was 74% at six months.

The primary reported outcomes are summarized in Table 3.9.

Table 3.9. Objective Response Rates Reported for Tisagenlecleucel for Relapsed or Refractory Adult B-Cell Lymphoma Compared with SCHOLAR-1

Trial	Therapy	ORR	CR
JULIET[29]	Tisagenlecleucel	53%	40%
NCT02030834[30]	Tisagenlecleucel	64%	57%
SCHOLAR-1[17]	Mix of salvage therapies	26%	7%

CR: complete remission, ORR: objective response rate

The complete remission rate for tisagenlecleucel in JULIET (40%) represents an optimistic presentation of the results that violates the intention to treat principle because it is based on patients who received the infusion of CAR-T cells and does not include the patients who enrolled in the trials but did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs, nor does it include patients treated with tisagenlecleucel who had less than three months follow-up at the time of analysis. It was not possible to estimate a complete remission rates based on the data available from the public presentations. The reported CR and ORR in the JULIET trial (40% and 53% respectively) were slightly lower compared to the CR and ORR of the subset of patients with DLBCL in the ZUMA-1 trial (n=77) who were treated with axicabtagene ciloleucel (49% and 82%, respectively).[32] However, the confidence intervals overlap extensively, and selection bias may also explain part of the differences. For example, the JULIET trial recruited patients from 10 different countries on 4 continents, while 21/22 sites for the ZUMA-1 trial were in the US (one in Israel). The complete remission rate (43%) among patients who received tisagenlecleucel was markedly higher than that observed in the SCHOLAR-1 trial (7%), which predominantly included adults with DLBCL (87% DLBCL). Given the paucity of the currently reported results for the ongoing JULIET trial, we were unable to project long-term outcomes for comparison with axicabtagene ciloleucel or the salvage regimens included in the SCHOLAR-1 study.

Harms

The key AEs experienced by the 101 patients who received an infusion of axicabtagene ciloleucel in the ZUMA-1 trial are summarized in Table 3.10 below.[34] It is important to keep in mind that some

of these AEs reflect the lymphodepleting chemotherapy and/or progression of the lymphoma and are likely not a direct effect of axicabtagene ciloleucel.

Table 3.10. Key Adverse Events in the ZUMA-1 Trial (n=101)

Adverse Events	All Grades	Grade 3 or Higher
Cytokine Release Syndrome	94%	13%
Neurologic Toxicities	87%	31%
Fever	86%	16%
Encephalopathy	57%	29%
Headache	45%	1%
Renal Insufficiency	12%	5%
Hypotension	57%	15%
Hypoxia	32%	11%
Infections – Pathogens Unknown	26%	16%
Viral Infections	16%	4%
Bacterial Infections	13%	9%
Fungal Infections	5%	NR

Additional important grade 3 or higher adverse events include histiolymphocytic hemophagocytosis (1%), heart failure (6%), cardiac arrest (4%), seizures (4%) and pulmonary edema (9%). There were 44 deaths: 37 from disease progression, two from CRS, one from a pulmonary embolus, and four in patients with disease progression who were on subsequent therapies.

The two most important harms are the cytokine release syndrome and neurotoxicity. Cytokine release syndrome was common (94%) and often severe (13% with grade 3 or higher using the NCI grading system). Patients with grade 3 CRS require close monitoring usually in an ICU. CRS is associated with very high interleukin-6 (IL-6) levels and the anti-IL-6 antibody tocilizumab is often used to treat CRS. The lower incidence of severe CRS in ZUMA-1 compared to that observed in the ELIANA trial is in part due to the different grading scales used for CRS in the two studies. In addition, severe CRS may be more common in the pediatric population.

Neurologic toxicities (87%, 31% grade 3 or higher) include headaches, encephalopathy, delirium, anxiety, tremor, aphasia, and seizures. Most occurred in the first eight weeks following infusion with a median onset of four days and a median duration of 17 days. There is one reported case of encephalopathy lasting 173 days. Fatal cases of cerebral edema occurred in patients treated with axicabtagene ciloleucel. Treatment for neurologic toxicities is usually supportive care, though corticosteroids are used in more severe cases.

The key AEs experienced by the 99 patients who received an infusion of tisagenlecleucel in the JULIET trial are summarized in Table 3.11 below.[29] It is important to keep in mind that some of these AEs reflect the lymphodepleting chemotherapy and/or progression of the lymphoma and are likely not a direct effect of tisagenlecleucel.

Table 3.11. Key Adverse Events in the JULIET Trial (n=99)

Adverse Events	All Grades	Grade 3 or higher
Cytokine Release Syndrome	58%	23%
Neurologic Toxicities	21%	12%
Infections	34%	20%
Cytopenias Not Resolved by Day 28	36%	27%
Febrile Neutropenia	13%	13%
Tumor Lysis Syndrome	1%	1%

There were no deaths or reported cases of cerebral edema.

The two most important harms are the CRS and neurotoxicity. Cytokine release syndrome was common (58%) and often severe (23% with grade 3 or higher using the University of Pennsylvania grading system). The higher percentage of grade 3/4 CRS for tisagenlecleucel compared with axicabtagene ciloleucel in the adult B-cell lymphoma population despite fewer patients experiencing CRS overall likely reflects the different grading systems used in the two studies (Penn Scale for tisagenlecleucel and the NCI scale for axicabtagene ciloleucel).

Neurologic toxicities (21%, 12% grade 3 or higher) include headaches, encephalopathy, delirium, anxiety, tremor, aphasia, and seizures. These were notably lower than those reported for axicabtagene ciloleucel in the ZUMA-1 trial, which may be a chance finding, but could also reflect the different kinetics of T-cell proliferation of the two drugs due to the differences in their co-stimulatory domains. The small sample sizes and the lack of head to head studies precludes any firm conclusions, but this warrants further study.

Finally, there are theoretical concerns about mutagenesis from the insertion of the transgene into the patient's T-cells for both CAR-T therapies. The risk is likely to be quite low, but is an important long-term concern for further study.

Controversies and Uncertainties

There are many controversies and uncertainties and they apply equally to the CAR-T therapies for both leukemia and lymphoma.

First, as highlighted throughout the review, the studies of CAR-T therapies are all single-arm trials. Given the possibility of selection bias in these trials, it is impossible to compare outcomes from these trials to those of other trials without considerable uncertainty. For example, clinicians may not have considered enrolling patients with very aggressive or rapidly-progressing disease in the trials because of the known three-week time lag between leukapheresis and CAR-T cell infusion.

Second, the trials themselves are small and have short follow-up. The sample sizes with outcomes in the trials are less than 100 participants, and the median follow-up in the trials is less than two

years. Thus, estimates of outcomes from the trials have wide confidence intervals; as such, both the benefits and duration of and long-term relapse-free survival is unknown at this point.

A related uncertainty due to short follow-up is the long-term harms of therapy. In the intermediate term, there is insufficient data to estimate how many patients will continue to have clinically important hypogammaglobulinemia from B-cell aplasia. There are also theoretical concerns about complications from the viral vectors used in the manufacturing process and of secondary malignancies related to mutations in the T-cells due to the manufacturing process. Finally, there may be unanticipated harms that arise as larger numbers of patients are followed for several years.

Improvements in the manufacturing process with experience may lead to fewer manufacturing failures and shorter times from leukapheresis to infusion. There are also likely to be improvements in the management of CRS and neurologic toxicities as centers gain more experience with these important toxicities.

All of the uncertainties highlighted above make our comparative efficacy analyses versus standard therapy controversial. Similar concerns apply when comparing tisagenlecleucel to axicabtagene ciloleucel, which are likely to share an indication for DLBCL in the near future.

3.4 Summary and Comment

Pediatric B-ALL

The ELIANA trial demonstrated CR rates for tisagenlecleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated pediatric patients with B-cell ALL. In addition, the disease-free survival and OS were also greater than those observed with other therapies, particularly in the earlier Phase I trials that have longer follow-up. There are important harms that occur commonly with tisagenlecleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (clofarabine, blinatumomab, etc.) is low because there are no comparative trials and the existing single-arm trials are small with relatively short follow-up (8.7 months median for the pivotal ELIANA trial). Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy although the benefit may be substantial ("B+" rating).

Adult Aggressive B-Cell Lymphoma

The ZUMA-1 trial demonstrated CR rates for axicabtagene ciloleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated adults with B-cell lymphoma as reported in the SCHOLAR-1 study. In addition, the disease-free survival and OS

appear to be greater than those observed with other therapies, but follow-up in the ZUMA-1 trial is short (median 15.4 months). There are important harms that occur commonly with axicabtagene ciloleucel therapy (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (R-DHAP, R-ICE, etc.) is low because there are no comparative trials, and the existing single-arm trial is small with short follow-up. Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy although the benefit may be substantial ("B+" rating).

The JULIET trial demonstrated CR rates for tisagenlecleucel that were substantially higher than those observed in recent trials of other drug therapies for heavily pre-treated adults with B-cell lymphoma as reported in the SCHOLAR-1 study. The follow-up in the JULIET trial is shorter than that for the ZUMA-1 trial, but the earlier single-site trial of tisagenlecleucel provides evidence that the results are likely to be robust with longer follow-up. There are important harms that occur commonly with tisagenlecleucel (CRS, neurotoxicity, B-cell aplasia), but they are manageable and perceived by clinicians as arguably no worse than the serious AEs associated with chemotherapy in this patient population. Thus, the estimated net health benefit is substantial. However, the level of certainty about the magnitude of the net health benefit compared to other therapies (R-DHAP, R-ICE, etc.) is low because there are no comparative trials and the existing single-arm trial is small with short follow-up and incomplete reporting. Given these uncertainties, there is at least a small net health benefit compared with current salvage chemotherapy, although the benefit may be substantial ("B+" rating).

There are no head to head trials of axicabtagene ciloleucel and tisagenlecleucel for patients with relapsed/refractory B-cell lymphomas. The ORR and CR with axicabtagene ciloleucel are somewhat higher than those for tisagenlecleucel, but could easily reflect differences in the patient populations or chance. Patients treated with axicabtagene ciloleucel appeared to have fewer grade 3/4 CRS events, but more grade 3/4 neurologic events. Again, this may represent real differences in the two CAR-T therapies because of differences in their co-stimulatory domains, selection bias, or chance. The lack of head-to-head randomized trials and the small number of patients studied render such judgements premature. Given the level of uncertainty, the evidence is insufficient to judge whether one of the CAR-T therapies is superior to the other ("I" rating).

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of chimeric antigen receptor T-cell (CAR-T) therapies for the treatment of B-cell malignancies. A two-part model, consisting of a short-term decision tree and long-term semi-Markov partitioned survival model, was constructed to compare CAR-T therapies to chemotherapy. Patient survival, quality-adjusted survival, and health care costs from the third-party payer perspective were estimated over a lifetime time horizon for each intervention and comparator. Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated by comparing each intervention to its comparator within each B-cell malignancy. While the base-case analysis took a payer perspective, productivity losses to the patient and caregiver were considered in a scenario analysis.

We modeled two separate cohorts for this review:

- B-cell acute lymphoblastic leukemia (B-ALL)
    - Patients ages 0-25 years with relapsed/refractory B-ALL
- B-cell lymphoma
    - Adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for auto-SCT

Two CAR-T therapies, tisagenlecleucel and axicabtagene ciloleucel, were compared to chemotherapy. Tisagenlecleucel was modeled in pediatric B-ALL; axicabtagene ciloleucel was modeled in adult B-cell lymphoma. We note that while the available grey literature suggested an evidence rating of "B+" for tisagenlecleucel in B-cell lymphoma, the available data were insufficient to allow for full estimation in our model; therefore, tisagenlecleucel was not modeled in B-cell lymphoma. Therapies were not compared across B-cell malignancies.

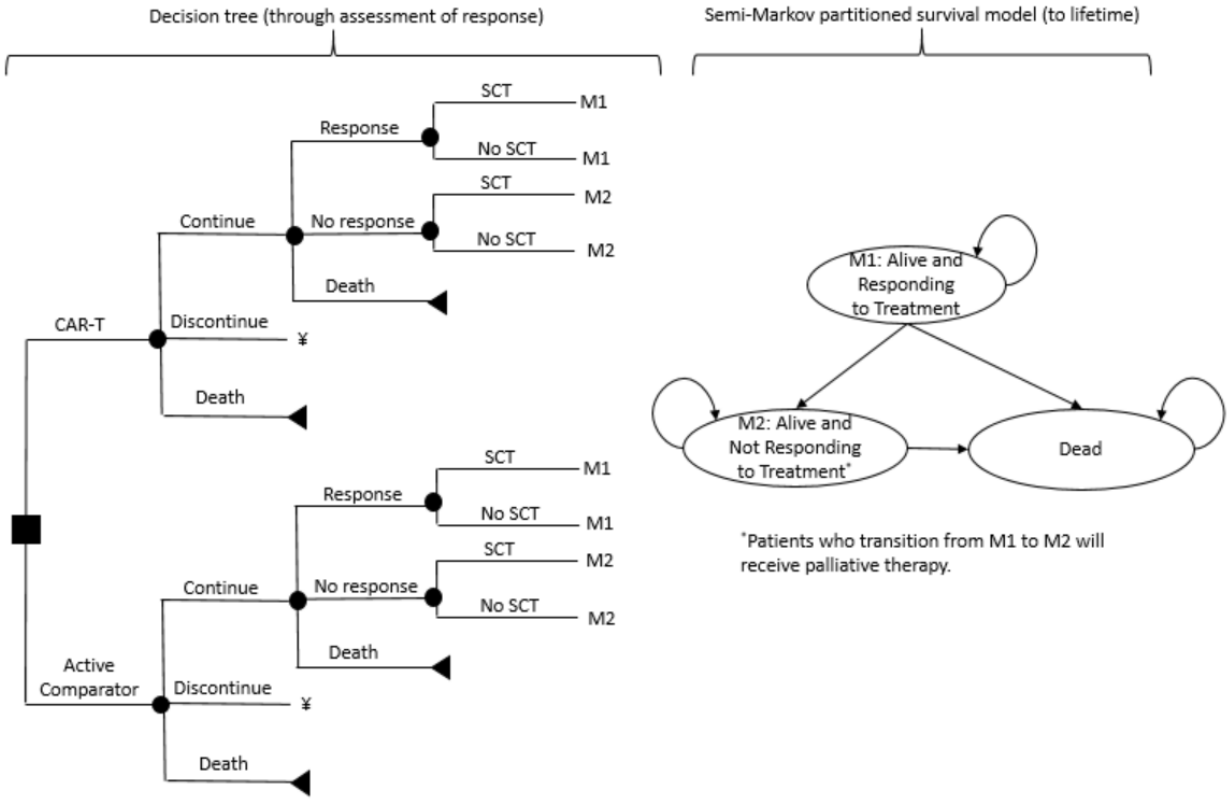
4.2 Methods

Model Structure

The decision analytic model included a short-term decision tree and a long-term semi-Markov partitioned-survival model (Figure 4.1). Long-term survival and outcomes derived from the long-term partitioned-survival model are dependent on the treatment received in the short-term decision tree model and are simulated using parametric survival modeling from the direct extrapolation of progression-free survival (PFS) and overall survival (OS) curves for five years after therapy completion. Mortality after five years was based on the general population age- and gender-adjusted all-cause risks of mortality with modifications for excess disease-related mortality experienced by long-term survivors of each B-cell malignancy.[36] Thus, we used a partitioned

survival model from assessment of response to five years after treatment completion, followed by a Markov model from five years until death; we have elected to refer to the complete model as a semi-Markov partitioned-survival model. Five years was chosen as a transition time between the partitioned survival model and the Markov model because those who were alive and responding to treatment at that time were assumed to be long-term survivors and considered to be effectively cured, though this assumption was also tested in a scenario analysis.[36] Accordingly, those that were alive and not responding to treatment died within five years of treatment completion. Patient survival, quality-adjusted survival, and health care costs from the third-party payer perspective were estimated over a lifetime time horizon for each intervention and comparator. An impact inventory detailing what cost components were included in the analysis is provided in Appendix Table D1. A detailed description of the model and survival curve extrapolation can be found in Appendix D. The model was developed in Microsoft Excel.

Figure 4.1. Model Framework



¥Patients who discontinue due to manufacturing failure will transition to the active comparator. Patients who discontinue due to adverse event will receive no further antileukemic/antilymphomic therapy and will enter the semi-Markov partitioned survival model at M2.
CAR-T: Chimeric antigen receptor T-cell therapies
SCT: Stem cell transplantation

Model inputs were informed by existing CAR-T and comparator clinical evidence and any published economic evaluations. Key model inputs included PFS, OS, occurrence of AEs, quality of life, and health care costs. Probabilities, costs, and other inputs differed between treatments to reflect varying effectiveness across interventions. However, health state utility values were consistent

across interventions within the same disease while allowing for evidence-based intervention-specific disutilities.

Model Parameters

The base-case analysis took a third-party payer perspective and focused on direct medical care costs only. A modified societal perspective including productivity losses to the patient and caregiver was evaluated in a scenario analysis. Outcomes were estimated over a lifetime time horizon using a monthly cycle to capture the potential lifetime impacts of short-term and ongoing morbidity and mortality. Costs and outcomes were discounted at 3% per year. For tisagenlecleucel, the payment strategy used in the base-case analysis was payment *only* for responders at one month, consistent with public statements the manufacturer has made.[10] For axicabtagene ciloleucel, the payment strategy used in the base-case analysis was payment at infusion, as the manufacturer has stated that pricing is not expected to vary by treatment outcome.[35]

Target Population

There were two independent cohorts for this review, each of which was modeled separately. The first cohort included patients 0-25 years old with B-ALL that is refractory or in second or later relapse. Cohort characteristics for the B-ALL cohort are described in Table 4.1. Age and gender affected mortality risk. Weight was used to calculate weight-based treatment regimens.

Table 4.1. B-ALL Cohort Characteristics

B-ALL	Value	Primary Source
Median Age	11.5 years	Study B2202[26]
Percent Female	45%	Study B2202[26]
Average Weight (Kg)	43.0	Study B2202[26]

B-ALL: B-Cell lymphoblastic leukemia

The second cohort included patients 18 years and older with relapsed or refractory DLBCL after two or more lines of systemic therapy. Cohort characteristics for the B-cell lymphoma cohort are described in Table 4.2. Age and gender affected mortality risk. Weight was used to calculate weight-based treatment regimens.

Table 4.2. B-cell Lymphoma Cohort Characteristics

B-cell Lymphoma	Value	Primary Source
Median Age	58.0 years	Locke et al., 2017[13]
Percent Female	32%	Locke et al., 2017[32]
Average Weight (Kg)	82.8	Data on file for ZUMA-1[34]

No sub-populations (e.g. responders only) were modeled because survival evidence was only available for the total cohort, not stratified by certain sub-populations.

Treatment Strategies

Interventions

- B-ALL
    - Tisagenlecleucel
- B-cell lymphoma
    - Axicabtagene ciloleucel

While tisagenlecleucel for B-cell lymphoma was included in our scope, we did not have enough data to include it in the model at this time.

Comparators

Comparator selection was informed by stakeholders and clinical experts and was based on the next best available therapy as well as the availability of evidence from patients with similar characteristics (e.g. demographics, disease severity, etc.) as the patients in each CAR-T trial. The comparators are detailed below.

- B-ALL
    - Two cycles of clofarabine 52 mg/m^2 intravenously for five consecutive days, every two to six weeks[20]
- B-cell lymphoma
    - Chemotherapies (from SCHOLAR-1)[17] for the treatment of DLBCL; the regimen used for cost was R-DHAP

Appendix Table D2 provides additional details on the regimens used for each treatment occurring in each modeled cohort.

Key Model Characteristics and Assumptions

Table 4.3. Key Model Assumptions

Assumption	Rationale
Stem cell transplantation (SCT), if it occurred, occurred within two months of the model start and no further SCT events were modeled.	Based on mean time from CAR-T therapy to stem cell transplantation estimated by Lee et al.[7,36]
Patients received a single full course of CAR-T therapy.	CAR-T therapies are considered an end-of-line treatment with no clinical evidence on re-treatment.
After year five, survivors experienced a mortality risk profile consistent with that of a long-term survivor, after adjustments were made for excess mortality.	At year five, those who were alive were assumed to be effectively cured. For the pediatric B-ALL cohort, a standardized mortality ratio of 9.1 was applied to all-cause risk of death for long-term survivors.[37] Evidence did not suggest a standardized mortality ratio greater than 1 for the adult B-cell lymphoma cohort, although this input was varied in sensitivity analyses.
Any person alive but not responding to treatment transitioned to death by the end of year five.	Those alive at year five are considered long-term survivors.
All patients who transitioned to the alive and not responding to treatment health state received palliative chemotherapy.	The intervention and comparator therapies are considered end-of-line treatments.
Patients who discontinued CAR-T due to an AE before receiving the infusion received no further antileukemic/antilymphomic therapy.	Those who experienced a severe AE would be unable to tolerate further active therapy.
Patients who did not receive CAR-T therapy due to a manufacturing failure received the active comparator.	Those who experienced a manufacturer failure would be able to tolerate further active therapy.
The model included costs and outcomes associated with grade 3/4 AEs.	Less severe adverse events are not expected to significantly impact patient health or costs.
The cost of a hospital admission for treatment administration included the per diem cost for hospital days and the costs of therapies administered during the hospitalization.	Future bundled payments were assumed to approximate the cost of the resources used under a fee-for-service framework.

Model Inputs

Model inputs were estimated from the clinical review as well as from published literature and information provided by stakeholders. The inputs that informed the model are described below.

Clinical Inputs

Response to Treatment

Treatment response rates were obtained from published literature and information provided from manufacturers. The initial response rates used in the short-term decision tree are provided in

Appendix Table D3. It is important to note that PFS and OS curves were not stratified by response status. Response status is only important in our model when assigning payment within the CAR-T outcomes-based pricing scenarios.

Transition Probabilities and Survival

Base-case survival was derived from parametric fits to each intervention's available PFS and OS Kaplan-Meier curves. Individual transition probabilities were calculated as described in the Appendix. Appendix Table D4 details the evidence used to calculate transition probabilities. Appendix Table D5 includes the survival curve fit, shape, and scale parameters for each curve used in the model and Appendix Table D6 includes the proportion of the cohort in each health state (alive and responding to treatment, alive and not responding to treatment, and dead) at one year, two years, and five years after assessment of treatment response.

Stem Cell Transplantation

A subset of treatment recipients elected to receive SCT. Table 4.4 provides the inputs used in the model for the proportion of treatment recipients that received SCT. In line with the reported evidence, separate proportions of responders and non-responders received SCT. Proportions in Table 4.4 are for the total cohort (including both responders and non-responders) that received SCT.

Table 4.4. Receipt of Stem Cell Transplantation

B-ALL	Tisagenlecleucel*	Clofarabine
Percent That Receive Transplantation	10.5%; (16/152)[26]	14.8%; (9/61)[20]
B-Cell Lymphoma	**Axicabtagene Ciloleucel***	**Chemotherapy**
Percent That Receive Transplantation	2.97%; (3/101)[34]	29.9%; (180/603)[17]

*Denominator is the number of patients that received a CAR-T infusion regardless of response status
B-ALL: B-Cell Acute lymphoblastic leukemia

Adverse Events

The model included any grade 3/4 AE that occurred in ≥ 5% of patients in any of the treatments and comparators, as listed in Appendix Table D7. Costs and disutilities associated with AEs are described below.

Utilities

To adjust for quality of life, utilities were applied for each model health state. Health state utilities were derived from publicly available literature and applied to the disease states. Utilities for the B-ALL cohort were derived from self-reported quality of life data in pediatric patients undergoing SCT (for the alive and not responding to treatment health state) and in pediatric patients that were

long-term survivors of relapsed pediatric ALL (for the alive and responding to treatment health state).[87] Patient data were collected and mapped to the EuroQol-5D (for the alive and not responding to treatment health state) and Health Utilities Index 2 (for the alive and responding to treatment health state). Utilities for the B-cell lymphoma cohort were derived from self-reported quality of life data on the EuroQol-5D in adult patients with non-Hodgkin's lymphoma.[88,89]

Utilities differed by cohort but remained consistent within a cohort across different treatments. The utilities for each model health state are presented in Appendix Table D8. The utility for a long-term survivor was assumed to equal the utility of the alive and responding to treatment health state.[36] It is worth noting, however, that the long-term survivor utility (equivalent to the alive and responding to treatment utility) is similar to the general population mean EQ-5D score for the age band corresponding to each population, which is 0.922 for ages 18-29 years and 0.823 for ages 60-69 years.[90]

Disutilities were applied for each treatment, including pre-treatment regimens for CAR-T, to account for the potential reduction in quality of life while receiving treatment. Appendix Table D9 details the disutilities and duration of reduction in quality of life applied for each treatment.

Further, disutilities for AEs were considered. All disutilities due to AEs associated with CAR-T, stem cell transplantation, and chemotherapy were assumed to be accounted for in the treatment disutility estimates provided in Appendix Table D9. Only occurrences of grade 3/4 CRS were expected to impact quality of life outside of what was included in the treatment disutilities. In alignment with a mock health technology appraisal conducted for regenerative medicines, a utility of 0 was applied for any grade 3 or higher case of CRS.[36] This disutility lasted for eight days, which equated to the median duration of ICU stay due to CRS.[36]

Economic Inputs

Treatment Acquisition Costs

The unit cost for each treatment is reported in Tables 4.5 and 4.6. The regimens used for each treatment can be found in Appendix Table D2. The average sales price (ASP) for all treatments was used, except for the two CAR-T therapies, where wholesale acquisition cost (WAC) was the only available estimate. Patients that discontinued the CAR-T pathway before receiving the CAR-T infusion were not charged the CAR-T acquisition costs; however, patients that discontinued in the axicabtagene ciloleucel pathway had costs associated with leukapheresis. The manufacturer of tisagenlecleucel covers the cost of leukapheresis.[26]

Table 4.5. Treatment Acquisition Costs for B-ALL Cohort

B-ALL	Unit	Price per Unit*	Price per Unit with Estimated Mark-Up
Tisagenlecleucel	0.2 to 5.0 × 10^6 CAR-T cells/kg	$475,000†	$575,000
Clofarabine	1mg/1ml	$150	$264
Methotrexate	1mg/1ml	$0.05	$0.09
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Cytarabine	1mg/1ml	$0.01	$0.02
Etoposide	1mg/1ml	$0.05	$0.09
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous Immunoglobulin	1mg/1ml	$0.08	$0.14

*Price as of October 8th, 2017; average sales price for all products except CAR-T
†Represents the total, not unit, wholesale acquisition costs of CAR-T therapy
B-ALL: B-cell acute lymphoblastic leukemia

Table 4.6. Treatment Acquisition Costs for B-Cell Lymphoma Cohort

B-cell Lymphoma	Unit	Price per Unit*	Price per Unit with Estimated Mark-Up
Axicabtagene Ciloleucel	2 x 10^6 CAR-T cells/kg	$373,000†	$473,000
Dexamethasone	1mg	$0.33	$0.49
Cytarabine	1mg/1ml	$0.01	$0.01
Cisplatin	1mg/1ml	$0.21	$0.31
Rituximab	1mg/1ml	$8.48	$12.55
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous immunoglobulin	1mg/1ml	$0.08	$0.14

*Price as of October 8th, 2017; average sales price for all products except CAR-T
†Represents the total, not unit, wholesale acquisition costs of CAR-T therapy

Hospital Mark-Up Costs

A hospital mark-up was added for hospital-administered treatments. Stakeholders and experts were engaged to inform the mark-up selection. A wide range of potential mark-ups was provided by stakeholders and experts, ranging from a 0% mark-up (no mark-up) to a mark-up similar to other oncology drugs (ASP+152%). Our approach for hospital mark-up that incorporated this feedback is provided below.

We assumed each cohort represented a 50:50 split of publicly and privately insured patients. For pediatric B-ALL, the hospital mark-up for treatments administered in the CAR-T and comparator arms was price+76%. The 76% was calculated by averaging the expected hospital mark-up for Medicaid (ASP+0%, no mark-up) and commercial insurance for academic/tertiary hospitals

(ASP+152%).[91] We assumed all pediatric ALL patients would be treated in academic/tertiary settings. Both tisagenlecleucel and clofarabine were assumed to be administered as inpatient treatments.

For adult B-cell lymphoma, the hospital mark-up for treatments administered in the CAR-T arm was price+76%. The 76% was calculated by averaging the inpatient hospital mark-up for Medicare (ASP+0%, no mark-up) and commercial insurance for academic/tertiary hospitals (ASP+152%).[91] All administrations were assumed to happen in the academic/tertiary hospital inpatient setting. For the adult B-cell lymphoma comparator chemotherapy arm, the hospital mark-up was price+48%. The 48% was calculated by averaging the outpatient mark-up for Medicare (ASP+6%) and mark-up for commercial insurers, assuming that half of commercial patients would receive chemotherapy in academic/tertiary settings and half would receive treatment in community settings (ASP+152% for hospital administration and ASP+28% for community administration).

Based on comments from stakeholders and CAR-T experts, mark-ups for CAR-T were capped at $100,000 to account for some facilities that may not negotiate a mark-up (i.e., they will manage CAR-T as a pass-through) while other facilities may charge a mark-up. Most stakeholders with hospital billing expertise agreed that CAR-T mark-ups will be varied and may not follow the relative multiplier norms for other hospital administered therapies.

Health Care Utilization-Related Costs

Costs associated with other healthcare utilization that resulted from administration and monitoring were included in the model. Appendix Table D10 details the healthcare utilization unit costs used in the model. Unit costs for healthcare utilization were the same across different treatments within a cohort. Appendix Table D11 includes the schedule of healthcare utilization modeled for a lifetime time horizon.

The cost of a hospital admission for treatment administration (CAR-T and clofarabine) was estimated using a fee-for-service approach, which included the per-diem cost for hospital days and added on costs of therapies administered during the hospitalization. Hospitalizations might in the future be paid through a bundled payment mechanism (e.g., for Medicare beneficiaries); however, the bundled payment for the CAR-T hospital admission is unknown at this time. Hospitalization costs associated with the administration of CAR-T were included regardless of treatment response status or outcomes-based payment strategy.

The cost of SCT was retrieved from the literature. A separate cost was identified for each cohort and SCT type modeled. The total cost for pediatric allo-SCT, inflated to present value dollars, was approximately $560,000.[92] The total cost for adult auto-SCT, inflated to present value dollars, was approximately $208,000.[93] The total cost for adult allo-SCT, inflated to present value dollars, was approximately $485,000.[94]

Based on recommended practices by the Second Panel of Cost-Effectiveness, future related and unrelated healthcare costs were included in the model for patients who were alive and responding to treatment after five years. The average monthly healthcare costs by age band were assigned to patients for the remainder of their lifetime if they were alive and responding to treatment after five years.

Adverse Event Costs

The model included any grade 3/4 AE that occurred in ≥ 5% of patients in any of the treatments and comparators, as listed above in Appendix Table D7. AE costs were derived from reasonable treatment assumptions used in previous analyses and from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUPnet).[95] For all AEs associated with inpatient administered treatments (CAR-T and clofarabine), the cost of the hospitalization for treatment administration was assumed to include the cost of AEs except for AEs that were expected to prolong the hospitalization (CRS) or extend beyond discharge (B cell aplasia). The unit cost for a grade 3/4 episode of CRS included the cost of tocilizumab (calculated by multiplying the unit cost from Tables 4.5 and 4.6 by the regimen in Appendix Table D2) and an ICU stay.[36] The duration of an ICU stay for a grade 3/4 episode of CRS was assumed to be eight days.[18] The unit cost of a day in the ICU was $5,296.[96] The unit cost for B-cell aplasia included the cost of IVIG treatment for 11.4 months following CAR-T and 4.5 months following R-DHAP (calculated by multiplying the unit cost from Tables 4.5 and 4.6 by the regimen in Appendix Table D2).[36] Only patients experiencing hypogammaglobulinemia received IVIG. AE unit costs for outpatient administered treatments can be found in Appendix Table D12. Costs of all AEs, except B-cell aplasia, were assumed to occur in the first stage of the model.

All model costs are in 2017 US dollars.

Sensitivity Analyses

One-way sensitivity analyses were conducted to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or plausible parameter ranges for inputs described above (including, but not limited to, SCT rate and manufacturing failure rate). Probabilistic sensitivity analyses were performed by jointly varying model parameters with uncertainty able to be quantified over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Sensitivity around survival curve parameters was not modeled; however, uncertainty around long-term survival was explored through variation in the discount rate used in the sensitivity analysis. Thus, the resulting one-way and probabilistic sensitivity analysis findings were not fully able to quantify the uncertainty within this appraisal. Scenario analyses described below further attempt to capture the uncertainty in long-term survival evidence.

Scenario Analyses

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions. First, the perspective was expanded to a restricted societal one that included the potential impact that the treatment Phase (stage 1) has on lost productivity and caregivers' time. Second, an approach of no antileukemic/antilymphomic therapy was modeled as a comparator instead of an active chemotherapy regimen. We acknowledge that this comparison may not be pragmatic, especially in the pediatric B-ALL cohort; however, it illustrates the incremental cost and effectiveness of CAR-T therapy in the absence of other active treatments. Third, due to the uncertainty surrounding CAR-T payment, we modeled an outcomes-based reimbursement strategy, with payment of CAR-T only for responders within different assessment time points, including one month and one year. We assumed the hospital mark-up was not included as part of the outcomes-based contract between the manufacturer and the payer, and thus that payment from the payer to the hospital for the mark-up occurred regardless of response status. We assumed payment for the mark-up occurred at infusion. Fourth, to account for uncertainties in the long-term effectiveness of CAR-T, we presented the incremental cost-effectiveness ratio for multiple model time horizons, from one year to lifetime. This scenario analysis provides decision makers with the ability to make judgements around the duration and forecasting of the cure-related benefits observed in the single-arm trials. For example, assuming a 10-year time horizon would suggest that no cure-related benefits (or costs) are assigned beyond 10 years post therapy for CAR-T or its comparator. Fifth, to account for uncertainty around the curative assumption itself (i.e., that those alive and responding to treatment after five-years following treatment completion will be long-term survivors), we modeled a different curative assumption using late-relapse rates in patients with refractory disease. In this scenario analyses, we assumed that 80% of those alive and responding to treatment at five years would be long-term survivors in B-ALL[97-99] and that 95% of those alive and responding to treatment at five years would be long-term survivors in B-cell lymphoma.[100-103] This fifth scenario may address stakeholder concerns raised around the likelihood of the recurrence of cancer being non-zero over-and-above that assumed within the standardized mortality ratio applied to the cohort after year five. Sixth, to account for uncertainty in survival following the trial time horizon, a scenario analysis was conducted under different parametric assumptions. In the base-case analysis, a knot was added when the slope of the Kaplan-Meier curve was zero (i.e. flat). In this scenario analysis, the knot was removed which made the parametric curve extend out through five years. Seventh, because the costs and outcomes in the base-case results are weighted and should be interpreted as the average costs and outcomes for a patient initiating treatment, we present different total cost estimates in this scenario analysis for the certain pathways a patient could follow (i.e. subsets of the cohort following certain treatment pathways). This should aid in the interpretation of the weighted estimates. Last, a threshold analysis was conducted to determine the price needed to achieve value-based price benchmarks of $50,000, $100,000, and $150,000 per QALY gained, using the

base-case deterministic inputs and assumptions. The price needed to reach these thresholds included both the manufacturer price of the product and the hospital mark-up.

4.3 Results

Base Case

The total discounted costs over the lifetime time horizon are detailed in Table 4.7. The total discounted life years (LYs) and quality-adjusted life years (QALYs) are detailed in Table 4.8.

In the B-ALL cohort, the tisagenlecleucel arm had a total discounted cost of approximately $667,000 with discounted LYs and QALYs gained of 10.34 and 9.28, respectively. The clofarabine comparator arm had a total discounted cost of approximately $337,000 with discounted life years and QALYs gained of 2.43 and 2.10, respectively.

In the B-cell lymphoma cohort, the axicabtagene ciloleucel arm had a total discounted cost of approximately $617,000 with discounted LYs and QALYs gained of 7.35 and 5.87, respectively. This contrasted with the chemotherapy comparator arm, which had a total discounted cost of approximately $155,000 with LYs and QALYs gained of 3.23 and 2.48, respectively.

Table 4.7. Base-Case Discounted Lifetime Costs from Model

	B-ALL		B-cell Lymphoma	
Cost Category	**Tisagenlecleucel**	**Clofarabine**	**Axicabtagene Ciloleucel**	**Chemotherapy**
CAR-T Treatment Costs	$405,490	$0	$438,284	$0
Chemotherapy Treatment Costs	$15,309	$163,686	$0	$40,142
Palliative Chemotherapy Treatment Costs	$2,648	$3,973	$3,748	$6,103
Pre-Treatment Costs	$2,979	$0	$4,585	$0
SCT Costs	$47,744	$64,648	$13,345	$62,094
Adverse Event Costs*	$33,534	$0	$16,029	$7,046
Administration/ Monitoring Costs	$111,548	$93,032	$44,165	$1,045
Future Healthcare Costs	$45,901	$9,069	$95,223	$36,286
End of Life Costs	$1,602	$2,848	$1,547	$2,169
TOTAL COSTS	**$666,754**	**$337,256**	**$616,927**	**$154,884**

Base-case payment for tisagenlecleucel assumes payment only for responders at 1 month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion

*For inpatient administered therapies, costs associated with adverse events only included costs associated with adverse events that were expected to increase the length of stay (cytokine release syndrome) or extend beyond discharge (B cell aplasia).

B-ALL: B-cell Acute lymphoblastic leukemia, SCT: stem cell transplant

Table 4.8. Base-Case Discounted Lifetime Outcomes from Model

	B-ALL		B-cell Lymphoma	
Outcome	**Tisagenlecleucel**	**Clofarabine**	**Axicabtagene Ciloleucel**	**Chemotherapy**
Life Years (responding to treatment)	9.84	2.09	6.92	2.91
Life Years (not responding to treatment)	0.51	0.34	0.43	0.32
TOTAL LIFE YEARS	**10.34**	**2.43**	**7.35**	**3.23**
QALYs (responding to treatment)	8.95	1.90	5.74	2.42
QALYs (not responding to treatment)	0.33	0.20	0.13	0.06
TOTAL QALYs	**9.28**	**2.10**	**5.87**	**2.48**

B-ALL: B-cell Acute lymphoblastic leukemia, QALY: quality-adjusted life year

Base-Case: Incremental Results

Table 4.9 presents the incremental results from the base-case analysis, which include LYs gained, QALYs gained, and incremental cost-effectiveness ratios for both incremental cost per LY gained and incremental cost per QALY gained.

In the B-ALL cohort, total costs for the tisagenlecleucel arm were nearly two times greater than total costs for clofarabine; gains in life years and QALYs were more than four times greater for tisagenlecleucel. This resulted in an incremental cost-effectiveness ratio of approximately $46,000 per QALY gained and approximately $42,000 per LY gained for tisagenlecleucel as compared to clofarabine.

In the B-cell lymphoma cohort, total costs for the axicabtagene ciloleucel arm were nearly four times greater than total costs for the chemotherapy arm; gains in life years and QALYs were more than twice that of those on chemotherapy. This resulted in an incremental cost-effectiveness ratio of approximately $136,000 per QALY gained and approximately $112,000 per LY gained for axicabtagene ciloleucel as compared to chemotherapy.

Table 4.9. Base-Case Incremental Results

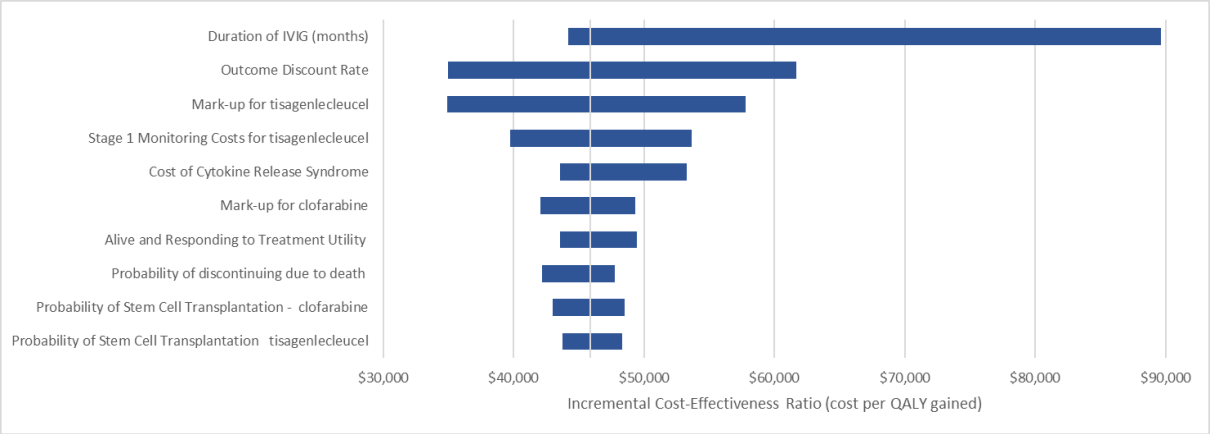
B-ALL	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Tisagenlecleucel vs. Clofarabine	$329,498	7.91	7.18	$41,642	$45,871
B-cell Lymphoma	**Incremental Costs**	**Incremental LYs**	**Incremental QALYs**	**Incremental CE Ratio per LY**	**Incremental CE Ratio per QALY**
Axicabtagene Ciloleucel vs. Chemotherapy	$462,043	4.12	3.40	$112,168	$136,078

Base-case payment for tisagenlecleucel assumes payment only for responders at one month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied model inputs with available measures of parameter uncertainty (i.e. standard errors or plausible parameter ranges). Figure 4.2 presents the tornado diagram resulting from the one-way sensitivity analysis for tisagenlecleucel versus clofarabine in B-ALL. Key drivers of the model included the duration of IVIG for B-cell aplasia, outcome discount rate (i.e., the discount percentage applied to future clinical benefits), and hospital mark-up percentage for tisagenlecleucel. Table 4.10 presents the lower and upper incremental cost-effectiveness ratios for the ten most influential inputs, as well as the ranges of each input used in the model. The incremental cost-effectiveness ratio assuming no hospital mark-up for tisagenlecleucel was approximately $35,000 per QALY gained. Across broad ranges in model inputs with quantifiable uncertainty, the incremental cost-effectiveness ratio remained within acceptable cost-effectiveness thresholds.

Figure 4.2. Tornado Diagram for One-Way Sensitivity Analyses of Tisagenlecleucel versus Clofarabine



Base-case incremental cost-effectiveness ratio: $45,871 per QALY gained

Table 4.10. Lower and Upper Inputs for Influential Inputs (Tisagenlecleucel vs. Clofarabine)

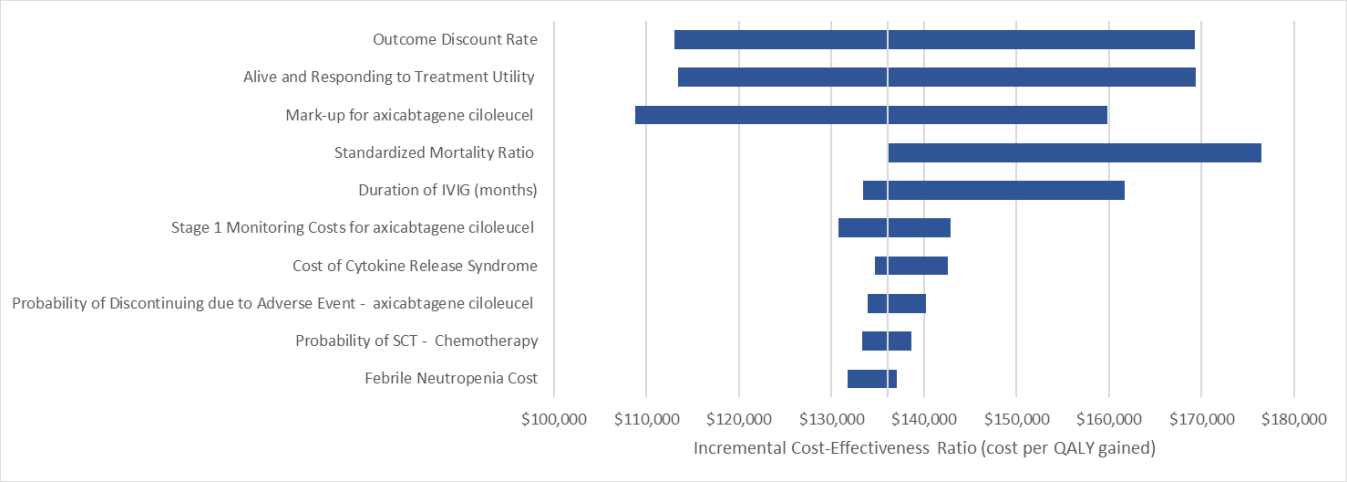
	Lower Input Value	Upper Input Value	Lower Input Incremental CE Ratio	Upper Input Incremental CE Ratio	Standard Error (Source) for Input Range
Duration of IVIG (months)	0	Lifetime	$44,212	$89,662	Ranged from 0 months to a lifetime
Outcome Discount Rate	1.5%	5.0%	$35,002	$61,689	0.009 (assumption to get to a range of 1.5% to 5%)
Mark-Up For Tisagenlecleucel	0%	43%	$34,945	$57,790	0.11 (10% of base-case)
Stage 1 Monitoring Costs For Tisagenlecleucel	$72,600	$196,399	$39,739	$53,690	$31,754 (25% of base-case)
Cost of Cytokine Release Syndrome	$10,657	$200,665	$43,574	$53,287	Range based on cost of tocilizumab and ICU stay
Mark-Up For Clofarabine	46%	108%	$49,354	$42,071	0.16 (10% of base-case)
Alive and Responding to Treatment Utility	0.84	0.96	$49,432	$43,540	0.03[87]
Probability of Discontinuing Due to Death - Tisagenlecleucel	1.9%	15.6%	$47,739	$42,169	0.04 (25% of base-case)
Probability of SCT - Clofarabine	24%	54%	$48,500	$43,035	0.015 (25% of base-case)
Probability of SCT - Tisagenlecleucel	7.0%	15.5%	$43,784	$48,349	0.03 (25% of base-case)

CE: cost-effectiveness, IVIG: intravenous immunoglobulin, SCT: stem cell transplant

Figure 4.3 presents the tornado diagram resulting from the one-way sensitivity analysis for axicabtagene ciloleucel versus chemotherapy in B-cell lymphoma. Key drivers of the model included the outcome discount rate, utility for the "alive and responding to treatment" health state, mark-up percentage for axicabtagene ciloleucel, the standardized mortality ratio, and the duration of IVIG for B-cell aplasia. In this case, when model inputs were varied within plausible ranges one by one, cost-effectiveness estimates frequently did extend above commonly cited cost-effectiveness thresholds, highlighting the uncertainty in some of the parameter values. The incremental cost-effectiveness ratio assuming no hospital mark-up for axicabtagene ciloleucel was approximately $109,000. Table 4.11 presents the lower and upper incremental cost-effectiveness ratios for the ten most influential inputs, as well as the ranges of each input used in the model. The

incremental cost-effectiveness ratio assuming no hospital mark-up for axicabtagene ciloleucel was approximately $109,000.

Figure 4.3. Tornado Diagram for One-Way Sensitivity Analyses of Axicabtagene Ciloleucel versus Chemotherapy



Base-case incremental cost-effectiveness ratio: $136,078 per QALY gained

Table 4.11. Lower and Upper Inputs for Influential Inputs (Axicabtagene Ciloleucel vs. Chemotherapy)

	Lower Input Value	Upper Input Value	Lower Input Incremental CE Ratio	Upper Input Incremental CE Ratio	Standard Error (Source) for Input Range
Outcome Discount Rate	1.5%	5.0%	$113,033	$169,240	0.009 (assumption to get to a range of 1.5% to 5%)
Alive and Responding to Treatment Utility	0.66	1.00	$169,346	$113,430	0.03[88]
Mark-up for axicabtagene ciloleucel	0%	50%	$108,788	$159,820	0.11 (10% of base-case)
Standardized Mortality Ratio	1.00*	3.40	$136,078	$176,491	Ranged from 1 to 3.40
Duration of IVIG	0 months	Lifetime	$133,436	$161,672	Ranged from 0 months to a lifetime
Stage 1 Monitoring Costs for axicabtagene ciloleucel	$26,039	$70,440	$130,752	$142,869	$11,389 (25% of base-case)
Cost of Cytokine Release Syndrome	$12,935	$235,487	$134,702	$142,597	Range based on cost of tocilizumab and ICU stay
Probability of Discontinuing due to AE - axicabtagene ciloleucel	1.5%	12.0%	$133,956	$140,229	2.8% (50% of base-case)
Probability of SCT - Chemotherapy	24%	36%	$138,653	$133,355	2.9% (10% of base-case)
Febrile Neutropenia Cost	$0	$78,070	$137,024	$131,736	$22,204[95]

*The lower input value is also the base-case value

AE: adverse event, IVIG: intravenous immunoglobulin, CE: cost-effectiveness

With noted uncertainty outside of that modeled, a probabilistic sensitivity analysis was conducted to assess variation across all model inputs with quantified uncertainty simultaneously and to vary the results over 5,000 iterations. Table 4.12 presents the probability of reaching certain willingness-to-pay thresholds. All of the iterations for tisagenlecleucel versus clofarabine were below a threshold of $150,000 per QALY gained. Seventy percent of the iterations for axicabtagene ciloleucel versus chemotherapy were beneath a threshold of $150,000 per QALY gained. A scatterplot of the 5,000 iterations for each comparison can be found in Appendix Figures D1 and D2.

Table 4.12. Probabilistic Sensitivity Analysis Results

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Tisagenlecleucel vs. Clofarabine	70.6%	100.0%	100.0%
Axicabtagene Ciloleucel vs. Chemotherapy	0.0%	3.0%	70.8%

Scenario Analyses Results

Modified Societal Perspective

The base-case third party payer perspective was expanded to a modified restricted societal perspective to account for patient/caregiver-level costs during treatment administration. Long-term productivity benefits were not included. To account for lost productivity during inpatient administered treatments, we assumed the amount of time missed from work was equal to the total number of days in which care was provided.[104] For CAR-T, clofarabine, and SCT, the days missed from work equated to the time spent hospitalized. For chemotherapy in B-cell lymphoma, the days missed from work equated to the number of days an intravenous administration was received. A half day of work was missed for each IVIG administration. An average hourly wage of $27.19 was used as the unit cost for one hour of work missed.[105] For B-ALL, lost productivity was the result of the caregiver having to miss work to accompany the patient during treatment. For B-cell Lymphoma, lost productivity was the result of the patient having to miss work to receive the treatment. We assumed transportation costs of $1,600 (for CAR-T administration), and a nightly cost in a hotel (for the caregiver of a patient receiving CAR-T) of $150 (applied for the number of days inpatient care was provided). For clofarabine, because administration does not have to be at a specialized site, transportation costs were not included in this restricted societal perspective.

Discounted societal costs for the tisagenlecleucel arm were nearly $12,000, whereas discounted societal costs for clofarabine were less than $5,000. Discounted societal costs for the axicabtagene ciloleucel arm were approximately $7,500, whereas discounted societal costs for chemotherapy were less than $2,500. Table 4.13 reports the incremental results from a modified societal perspective.

Table 4.13. Incremental Results for Modified Societal Perspective

	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Tisagenlecleucel vs. Clofarabine	$336,709	7.91	7.18	$42,553	$46,875
Axicabtagene Ciloleucel vs. Chemotherapy	$467,609	4.12	3.40	$113,520	$137,717

Base-case payment for tisagenlecleucel assumes payment only for responders at one month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

No Active Treatment Comparator

A scenario analysis was conducted with no further antileukemic/antilymphomic therapy as the comparator, instead of an active comparator. We acknowledge that a no further treatment comparator may not be pragmatic, especially in the pediatric B-ALL cohort; however, this

comparison illustrates the incremental cost and effectiveness of CAR-T therapy in the absence of other active treatments. Table 4.14 presents the incremental results for this comparison. Incremental cost-effectiveness ratios were less than $150,000 per QALY gained for both comparisons.

Table 4.14. Incremental Results for No Active Treatment Comparator

	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Tisagenlecleucel vs. No Antileukemic Therapy	$664,163	10.22	9.19	$64,996	$72,292
Axicabtagene Ciloleucel vs. No Antilymphomic Therapy	$614,332	7.22	5.78	$85,034	$106,305

Base-case payment for tisagenlecleucel assumes payment only for responders at one month. Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Alternate Payment Strategies

Scenario analyses were conducted to examine the results based on different CAR-T payment strategies, including payment at infusion, payment for responders at one month, and payment for responders at one year. Health outcomes and non-treatment costs for CAR-T did not change based on payment strategy. Neither costs nor outcomes changed for the comparator based on payment strategy. Table 4.15 presents the incremental cost-effectiveness results for tisagenlecleucel versus clofarabine assuming the three different payment strategies. All payment strategies resulted in incremental cost-effectiveness ratios less than $100,000 per QALY gained when comparing tisagenlecleucel to clofarabine.

Table 4.15. Other Payment Strategies: Incremental Results for B-ALL

Tisagenlecleucel vs. Clofarabine	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY Gained
Payment at Infusion	$389,483	7.91	7.18	$49,222	$54,222
Payment for Responders at One Month*	$329,498	7.91	7.18	$41,642	$45,871
Payment for Responders at One Year	$212,785	7.91	7.18	$26,891	$29,623

*Base case
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Table 4.16 presents the incremental cost-effectiveness ratios for axicabtagene ciloleucel versus chemotherapy, assuming the three different payment strategies. All payment strategies resulted in

incremental cost-effectiveness ratios less than $150,000 per QALY gained when comparing axicabtagene ciloleucel to chemotherapy.

Table 4.16. Other Payment Strategies: Incremental Results for B-cell Lymphoma

Axicabtagene Ciloleucel vs. Chemotherapy	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY Gained
Payment at Infusion*	$462,043	4.12	3.40	$112,168	$136,078
Payment for Responders at One Month	$399,831	4.12	3.40	$97,065	$117,756
Payment for Responders at One Year	$322,112	4.12	3.40	$78,198	$94,866

*Base case

CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Cost-Effectiveness by Time Horizon

We conducted a scenario analysis of different model time horizons, from one year to a lifetime time horizon; incremental cost-effectiveness ratios for each comparison are provided in Table 4.17. When the model time horizon is seven years or longer, the incremental cost-effectiveness ratio is beneath $150,000 per QALY gained for tisagenlecleucel versus clofarabine in B-ALL. When the model time horizon is 24 years or longer, the incremental cost-effectiveness ratio is beneath $150,000 per QALY gained for axicabtagene ciloleucel versus chemotherapy in B-cell lymphoma. Note that a time horizon, such as 24 years, does not assume that everyone in the model lives for 24 years (in fact, at a median age of 58 for B-cell lymphoma, few patients will live this long), but for those within the treated cohort that do live this long, their costs and outcomes are tracked and contribute proportionally toward the average findings that are aggregated across time. Figures showing the cost-effectiveness over all time horizons (from one year to lifetime) are provided in Appendix Figures D3 through D6.

Table 4.17. Cost-Effectiveness by Time Horizon: Incremental Results

	Tisagenlecleucel vs. Clofarabine		Axicabtagene Ciloleucel vs. Chemotherapy	
Time Horizon	Incremental CE Ratio: $/QALY gained	Incremental CE Ratio: $/LY gained	Incremental CE Ratio: $/QALY gained	Incremental CE Ratio: $/LY gained
1 Year	$928,685	$851,384	$4,021,598	$3,259,368
5 Years	$170,358	$189,318	$466,024	$376,570
10 Years	$97,279	$107,571	$207,689	$253,803
Lifetime	$41,642	$45,871	$136,078	$112,168

CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

Alternate Curative Assumption

We also modeled a different curative assumption that assumed 80% of those alive and responding to treatment at five years would be long-term survivors for B-ALL and 95% of those alive and responding to treatment at five years would be long-term survivors for B-cell lymphoma. With this scenario, we conservatively assumed 20% of those alive and responding to treatment at five years for B-ALL and 5% of those alive and responding to treatment at five years for B-cell lymphoma died at five years.[97-103] The incremental cost-effectiveness ratio for tisagenlecleucel versus clofarabine in B-ALL increased to $53,195 per QALY gained. In B-cell lymphoma, the incremental cost-effectiveness ratio for axicabtagene ciloleucel versus chemotherapy increased to $140,443. We acknowledge that, in the real world, these late-relapse patients may relapse at time points after five years and that this scenario could underestimate life years gained by assuming all relapses and deaths occur at five years. It is also conceivable that rates of late relapse may increase over historical estimates given a potentially larger pool of patients responding to treatment of refractory disease.

Alternative Survival Assumption

In the base-case analysis, we introduced a knot in the survival curve fit once the curve flattened (slope equaled zero). In this scenario analysis, we removed the knot. This scenario should be interpreted as a lower bound for survival. Using this standard parametric modeling practice, tisagenlecleucel resulted in 5.15 life years (4.49 QALYs), clofarabine resulted in 0.66 life years (0.49 QALYs), axicabtagene ciloleucel resulted in 3.17 life years (2.19 QALYs), and chemotherapy resulted in 0.94 life years (0.55 QALYs). The incremental cost-effectiveness ratios increased to $77,511 per QALY gained for tisagenlecleucel as compared to clofarabine and $259,378 per QALY gained for axicabtagene ciloleucel as compared to chemotherapy.

CAR-T Pathway Costs for Subsets of Cohort

The base-case results show the weighted costs and outcomes for the average patient initiating treatment. For certain subsets of the cohort, total costs and outcomes may be lower and, for others, total costs and outcomes may be higher than the base-case results. Table D13 in the appendix details the total costs for certain subsets of the cohort. We were unable to present outcomes (e.g. life years and quality-adjusted life years gained) this way due to the lack of survival curves stratified by these cohort subsets.

Threshold Analyses

A threshold analysis was conducted to determine the treatment acquisition cost needed to achieve thresholds of $50,000, $100,000, and $150,000 per QALY gained. Table 4.18 presents the unit price needed for each therapy to reach these commonly cited cost-effectiveness thresholds. A hospital mark-up of $100,000 was assumed for the CAR-T therapies in the base-case results. The price

needed to achieve the thresholds presented in Table 4.18 includes both the manufacturer price and associated mark-up.

Table 4.18. Threshold Analysis Results

	Price	Net Price (with Mark-Up)	Price* to Achieve $50,000 per QALY	Price* to Achieve $100,000 per QALY	Price* to Achieve $150,000 per QALY
Tisagenlecleucel (B-ALL)	$475,000	$575,000	$636,894	$1,162,563	$1,688,232
Axicabtagene Ciloleucel (B-cell Lymphoma)	$373,000	$473,000	$157,578	$340,797	$524,015

Payment assumed for tisagenlecleucel was payment for responders at one month. Payment assumed for axicabtagene ciloleucel was payment at infusion.

*Price needed to achieve the thresholds includes both the acquisition cost and associated mark-up.

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Model Validation

We used several approaches to validate the model. First, we presented preliminary methods and results to manufacturers, patient groups, and clinical experts, and based on feedback from these groups, refined data inputs used in the model as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed verification of model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

Prior Published Evidence on Costs and Cost-Effectiveness

We found only one published study on the potential cost-effectiveness of CAR-T therapy for the treatment of B-ALL, and none for CAR-T treatment of B-cell lymphoma. A "mock technology appraisal" was conducted for the UK National Institute for Health and Care Excellence (NICE) by Hettle et al. which included as an example a case study of a hypothetical CD19 CAR-T therapy for the treatment of relapsed or refractory B-ALL in those under 30 years old.[36] Their analysis considered both "curative intent" and "bridging to SCT" scenarios, compared to best supportive care (clofarabine), using the data from Jeha et al.[20]). Their analysis explored different levels of assumed evidence availability (using imputed data sets), alternative evaluation frameworks (e.g., "end-of-life" criteria), and alternative pricing scenarios (e.g., pay for performance, leasing arrangements). The model used in the current ICER report was based on the "curative intent" model developed by Hettle and colleagues; therefore, the two models are similar and employ many of the same assumptions, such as those related to long-term survival. The model structure used in the current ICER report did allow for a proportion of individuals that received treatment to also receive SCT, as did the model by Hettle et al.

While Hettle et al. used a somewhat higher baseline age (mean of 14.0 vs. median of 11.5 years in the ICER model) and higher discount rate (3.5% vs. 3.0% in the ICER model), their model also estimated higher gains in life years (13.42 vs. 10.34) and QALYs (11.18 vs. 9.28) for CAR-T therapy. This may be driven by the fact that the survival probability at 12 months through 5 years in the Hettle model (leveling out around 70%) is higher than that in the ICER model, which levels out at around 50%. For clofarabine, life years from the Hettle et al. analysis (1.47) were lower than those estimated using the ICER model (2.43), as were QALYs (1.11 and 2.10, respectively). These differences in estimates between the two models are likely due to the use of two different approaches to curve extrapolation. The ICER model assumed a flattening of the curves at the plateaus provided in the evidence (for both CAR-T and clofarabine), whereas Hettle et al. used spline models which may dip below the observed Kaplan-Meier curves. Incremental QALY gains from CAR-T versus clofarabine were therefore higher in the Hettle model (10.07 in Hettle et al. vs. 7.18 in the ICER model).

Total costs in the Hettle et al. analysis were estimated at approximately £583,000 ($757,600) for CAR-T, and approximately £80,000 ($104,000) for clofarabine, for an incremental cost of £503,000 ($653,600). Total costs in the ICER model were somewhat lower for tisagenlecleucel, at approximately $667,000, but much higher for clofarabine, at approximately $337,000, leading to an incremental cost of $329,000. Combined with the QALY estimates above, this led to an estimated ICER of £49,994 per QALY ($65,000 per QALY) in the UK mock technology appraisal, and approximately $46,000 per QALY in the ICER model.

One key difference between the two analyses is that Hettle and colleagues were modeling prior to any CAR-T price being available, and therefore assumed that the CAR-T therapy would be priced such that its incremental cost-effectiveness ratio would approach the NICE cost-effectiveness threshold. In addition, other health care costs, such as those for clofarabine treatment, would be expected to differ between the two models due to the different settings considered (US and UK National Health Service [NHS]).

4.3 Summary and Comment

The base-case findings from our analysis suggest that the use of tisagenlecleucel in B-ALL provides clinical benefit in terms of gains in quality-adjusted and overall survival over clofarabine. This translated into cost-effectiveness estimates that met commonly-cited cost-effectiveness thresholds in the pediatric relapsed/refractory B-ALL cohort under the assumptions used in this analysis. The results were robust through one-way and probabilistic sensitivity analyses given the parameter uncertainty quantified. Although sensitive to the outcome discount rate and mark-up for tisagenlecleucel, cost-effectiveness estimates remained less than $150,000 per QALY gained. The payment strategy used in the base case for tisagenlecleucel assumed payment for responders at one month; however, even with different payment strategies, including payment at infusion, cost-effectiveness estimates for tisagenlecleucel remained below commonly cited cost-effectiveness

thresholds. The base-case findings used a lifetime time horizon, while cost-effectiveness estimates for tisagenlecleucel at other time horizons were presented in a scenario analysis. After a model time horizon of seven years, the incremental cost-effectiveness ratio for tisagenlecleucel versus clofarabine fell below $150,000 per QALY gained. Therefore, if one accepts that patients who are alive and responding to treatment at five years are effectively cured, and that the model's other assumptions hold for at least seven years after treatment with no differences in costs or outcomes beyond that duration, tisagenlecleucel would meet commonly cited cost-effectiveness thresholds.

Similarly, the base-case findings from our analysis suggest that the use of axicabtagene ciloleucel in B-cell lymphoma also provides clinical benefit in terms of gains in quality-adjusted and overall survival over chemotherapy. This translated into cost-effectiveness estimates that met commonly cited cost-effectiveness thresholds in the adult relapsed/refractory B-cell lymphoma cohort under current assumptions used in this analysis. When accounting for model input uncertainty through one-way and probabilistic sensitivity analyses, however, some cost-effectiveness ratios did exceed $150,000 per QALY gained. Results were most sensitive to the outcome discount rate, utility for the alive and responding to treatment health state, mark-up percentage for axicabtagene ciloleucel, the standardized mortality ratio, and the duration of IVIG. The payment strategy used in the base-case for axicabtagene ciloleucel assumed payment at infusion. When outcomes-based payment scenarios were evaluated (i.e., payment for responders only), the cost-effectiveness estimates were more favorable. The base-case findings took a lifetime time horizon, and cost-effectiveness estimates for axicabtagene ciloleucel at other time horizons were presented in a scenario analysis. After a model time horizon of 24 years, the incremental cost-effectiveness ratio for axicabtagene versus chemotherapy was less than $150,000 per QALY gained. Therefore, if one accepts that patients who are alive and responding to treatment at five years are effectively cured, and that the model's other assumptions hold for at least 24 years after treatment with no differences in costs or outcomes beyond that duration, axicabtagene ciloleucel would meet commonly cited cost-effectiveness thresholds.

Limitations

Our analysis had important limitations and assumptions. This analysis was limited primarily by the lack of comparative evidence available for these therapies. Evidence was abstracted from single-arm trials, which resulted in challenges in selecting the most appropriate comparator therapies. We believe we chose the most appropriate comparators based on cohort similarities between trials; however, a different comparator could produce different results. For comparator therapies, there was also limited comparative evidence on the relationship between PFS and OS; however, we assumed a proportionate relationship from published PFS and OS curves in the same cancer. Sensitivity analyses did not attempt to quantify the uncertainty associated with single-arm trials and possible differences across CAR-T and comparator populations. Thus, the uncertainty produced from this analysis likely underestimates the total uncertainty.

Further, long-term follow-up on PFS and OS is limited for CAR-T therapies. Because of this, evidence on long-term effectiveness is still unknown, which resulted in assumptions being made related to trial survival curve extrapolation and the time point at which long-term survivors would be considered effectively cured. Uncertainty in inputs and long-term survival were partially quantified in sensitivity and scenario analyses that evaluated different curative assumptions and model time horizons.

Also, mechanisms for payment of CAR-T therapies are still largely unknown (e.g., bundled payment vs. fee-for-service, amount of hospital mark-up, outcomes-based pricing, etc.), requiring several assumptions around costs and payment of these therapies. Also, one uniform source for cost was not available, which could lead to variation between sources in cost calculations. These uncertainties were partially addressed through adding wide variation around cost inputs in sensitivity analyses and through the presentation of cost-effectiveness estimates for three different payment strategies.

Survival curve fitting relies on assumptions that may differ substantially between different parametric models. We ensured our assumptions did not lead to invalid models and unrealistic PFS or survival rates, such as the tail of the extrapolated PFS curve crossing the tail of the OS curve. However, our model structure in combination with no comparative clinical evidence (i.e. no controlled trials) limited our ability to generate uncertainty estimates around transition probabilities.

Last, we acknowledge the importance of including a societal perspective, but we were only able to model a restricted societal perspective based on evidence available at this time. Our restricted societal perspective focused on productivity losses and patient-level costs (e.g. transportation, lodging, etc.) during treatment administration. Due to uncertainty in the evidence and the potential for it to already be included in the utility score, we did not include any long-term productivity gains that may be associated with treatment. The societal perspective results should thus be viewed as a limited societal perspective.

Conclusions

In conclusion, the findings of our analysis suggest that the CAR-T therapies of focus for this review provide gains in quality-adjusted and overall survival over alternative chemotherapies. With the evidence available at this time, these therapies seem to be priced in alignment with clinical benefits over a lifetime time horizon. However, the findings are sensitive to the time horizon and long-term benefit forecasting of the therapies.

5. Other Benefits and Contextual Considerations

5.1 Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and details about the considerations that are relevant for the comparison of tisagenlecleucel to clofarabine in patients with pediatric ALL and axicabtagene ciloleucel to SCHOLAR-1 chemotherapy regimens in patients with B-cell NHL are provided in the subsequent text.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

The primary potential other benefit that applies is that CAR-T therapy represents a novel mechanism of action: introducing a new gene into the patient's own T-cells that produces a chimeric protein with an extracellular antibody specific for CD-19, the target protein expressed by B-cells, and two other domains that activate the T-cell to kill of the bound cell and stimulates replication of the T-cell. This novel mechanism appears to offer significantly greater remission rates than other therapies for patients who have failed standard first and second-line therapy for these B-cell cancers.

For the pediatric patients with ALL, CAR-T therapy may offer them the opportunity to live a nearly normal life and to contribute substantially to society. This applies less to the patients with B-cell lymphomas, because they are significantly older, but many will return to productive lives. In addition, despite early toxicity in the first month of therapy, the patient's subsequent care is less demanding than that required by salvage chemotherapy or SCT, thus allowing for an earlier return to productivity for patients and their families.

The primary other contextual consideration has already been highlighted above in the section on Controversies and Uncertainties: given the limited clinical experience with CAR-T therapy, there is considerable uncertainty about the long-term durability of the response to therapy. This is highlighted by the conflicting viewpoints among treating oncologists about the need to proceed to SCT following CAR-T therapy. The same limitation in the data leads to uncertainty about the potential for unexpected long-term serious side effects due to the presence of cells that have been genetically manipulated and may persist for the remainder of the patient's life. It is also important to highlight that the conditions treated represent high severity with a high short-term mortality rate.

6. Value-Based Price Benchmarks

Our annual value-based price benchmarks for tisagenlecleucel's use in patients ages 0-25 with relapsed or refractory B-cell ALL and axicabtagene ciloleucel's use in adult patients with relapsed or refractory aggressive NHL are presented in Table 6.1. As noted in the ICER methods document (https://icer-review.org/material/final-vaf-2017-2019/), the value-based benchmark price for a therapy is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For tisagenlecleucel, price premiums could be applied to the WAC with mark-up to meet these threshold prices. For axicabtagene ciloleucel a price discount from the WAC with mark-up is required to reach the $100,000 per QALY threshold price while a price premium from the WAC with mark-up is required to reach the $150,000 per QALY threshold price.

Table 6.1. Value-Based Bench Mark Prices for Tisagenlecleucel and Axicabtagene Ciloleucel

	WAC	Net Price (with Mark-Up)	Price* to Achieve $100,000 per QALY	Price* to Achieve $150,000 per QALY	Discount from WAC with Mark-Up to Reach Threshold Prices
Tisagenlecleucel (B-ALL)	$475,000	$575,000	$1,162,563	$1,688,232	+102% to +194%
Axicabtagene Ciloleucel (B-cell Lymphoma)	$373,000	$473,000	$340,797	$524,015	28% to +11%

Payment assumed for tisagenlecleucel was payment for responders at one month. Payment assumed for axicabtagene ciloleucel was payment at infusion.

*Price needed to achieve the thresholds includes both the acquisition cost and associated mark-up.

+Indicates premium

QALY: quality-adjusted life year

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the total potential budgetary impact of tisagenlecleucel for patients 0-25 years of age with B-cell ALL that is refractory or in second or later relapse. We also used the model results to estimate the total potential budgetary impact of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high grade B-cell lymphoma, and DLBCL arising from transformed follicular lymphoma. For tisagenlecleucel, we used the total treatment cost including WAC and hospital mark-up at infusion, based on treatment response at different time points and at the three cost-effectiveness threshold prices, using the response to treatment at one month in our estimates of budget impact. For axicabtagene ciloleucel, we used the total treatment cost that included WAC and hospital mark-ups at infusion, and at the three cost-effectiveness threshold prices irrespective of treatment response in our estimates of budget impact.

7.2 Methods

Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. Cost estimates used in the budget impact model were derived from the cost-effectiveness analysis described earlier. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for each treatment. To estimate the size of the potential candidate population for tisagenlecleucel, we first identified the estimated 2017 incidence of ALL in the US (5,970 patients), based on Surveillance, Epidemiology, and End Results (SEER) data.[106] We then estimated the incidence in the population under 25 years of age using incidence from two cohorts: those under 20 years of age and an assumed 50% of those between 20 and 34 years of age. Of the 3,651 remaining ALL patients, we estimated that 82.5% would have B-cell ALL (3,012 patients).[107] We estimated that 3% of patients are refractory to initial therapy, while 20% of patients will experience relapse with initial therapy. Based on a retrospective cohort study, we estimated that approximately 15% of patients who relapsed first line therapy were refractory to second line therapy and 36.5% of patients who relapsed first-line also relapsed on second line therapy. Applying this estimate results in an annual eligible population for treatment with tisagenlecleucel of 400 patients.

To estimate the size of the potential candidate population for axicabtagene ciloleucel, we first identified the incidence of DLBCL (27,650 patients in 2016) as reported in a 2016 observational study by Teras et al.[108] We assumed that 35% of all DLBCL patients relapsed or were refractory to chemotherapy, based on data analyses by Shipp and Sehn et al.[109,110] Based on a review by Freidberg, 50% of the 9,678 relapsed/refractory DLBCL patients were transplant ineligible, of which 49% (2,371 patients) did not respond to salvage chemotherapy and were eligible for treatment with axicabtagene ciloleucel. Among those who were eligible for a transplant (4,839 patients), we estimated those eligible for treatment with axicabtagene ciloleucel comprised 2,371 (49%) patients who did not respond to salvage chemotherapy, as well as 47% of patients who responded to salvage chemotherapy and received an auto-SCT but were not cured by it (1,160 patients).[100,111] In total, the annual eligible population for axicabtagene ciloleucel was estimated to be 5,902 patients. It is important to note that we have not taken into consideration the current annual axicabtagene ciloleucel manufacturing capacity of 4,000 to 5,000 treatments per year.[112]

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail here and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new therapy that would take market share from one or more therapies, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that tisagenlecleucel would replace clofarabine, and axicabtagene ciloleucel would replace the salvage chemotherapies included in SCHOLAR-1.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015 and 2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.2 Results

Tisagenlecleucel

Table 7.2 illustrates the per-patient potential budget impact calculations for tisagenlecleucel, based on payment at infusion, treatment response at one month and one year, and the prices to reach $50,000, $100,000, and $150,000 per QALY using response to treatment at one month for tisagenlecleucel ($636,894, $1,162,563, and $1,688,232, respectively) compared to clofarabine.

Table 7.2. Per-Patient Budget Impact Calculations for Tisagenlecleucel Over a Five-year Time Horizon, Assuming 400 Patients per Year Over Five Years

	Average Annual Per Patient Budget Impact					
	Payment at:			Threshold Prices:		
	Infusion	Response to Treatment at 1 Month	Response to Treatment at 1 Year	$50,000/QALY*	$100,000/QALY*	$150,000/QALY*
Tisagenlecleucel	$310,618	$277,457	$216,384	$296,769	$460,784	$624,799
Clofarabine	$149,799					
Difference	$160,818	$127,658	$66,585	$146,969	$310,984	$474,999

*Based on response to treatment at one month

QALY: quality-adjusted life year

The average potential budgetary impact when using the treatment cost at infusion, irrespective of treatment response, was an additional per-patient cost of approximately $161,000, which decreased to approximately $128,000 and $67,000 using the treatment costs based on response to treatment at one month and one year, respectively. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $147,000 using the annual price ($636,894) to achieve a $50,000 per QALY cost-effectiveness threshold to approximately $475,000 per patient using the annual price ($1,688,232) to achieve $150,000 per QALY cost-effectiveness threshold. Treatment costs in years two through five are substantially lower than in year one in keeping with one-time nature of most of the fees associated with CAR-T. When these costs are averaged over five years, the per-patient CAR-T therapy costs reported are lower than those used in the long-term cost-effectiveness model.

The annual potential budgetary impact of treating the entire eligible population did not exceed the $915 million threshold at any of our modeled prices and are not presented in a figure (Table 7.3). The potential budget impact ranged from 6% of the threshold when using the price based on treatment response at one year, to 46% of the threshold when using the price to reach the $150,000 per QALY threshold.

Table 7.3. Estimated Annualized Total Potential Budget Impact (BI) of Relapsed/Refractory B-ALL Treatment Using Different Prices Over a Five-year Time Horizon, Assuming 617 Eligible Patients per Year

	Total Annual Budget Impact	Percent of Threshold
Payment at Infusion	$141,020,175	15%
Payment Based on Treatment Response at One Month	$111,955,077	12%
Payment Based on Treatment Response at One Year	$58,424,621	6%
$150,000 per QALY Threshold Price*	$416,399,062	46%
$100,000 per QALY Threshold Price*	$272,640,318	30%
$50,000 per QALY Threshold Price*	$128,882,611	14%

*Based on response to treatment at one month
QALY: quality-adjusted life year

Axicabtagene Ciloleucel

Table 7.4 illustrates the per-patient budget impact calculations for axicabtagene ciloleucel in more detail, based on payment at infusion and the prices to reach $50,000, $100,000, and $150,000 per QALY compared to salvage chemotherapy, irrespective of treatment response ($157,578, $340,797 and $524,015, respectively) Treatment costs in years two through five are substantially lower than in year one in keeping with the curative assumption of CAR-T therapy employed in our cost-effectiveness model's base-case. When these costs are averaged over five years, the per-patient CAR-T therapy costs reported are lower than those used in the long-term cost-effectiveness model.

Table 7.4. Per-Patient Budget Impact Calculations for Axicabtagene Ciloleucel Over a Five-Year Time Horizon, Assuming 5,902 Patients per Year Over Five Years

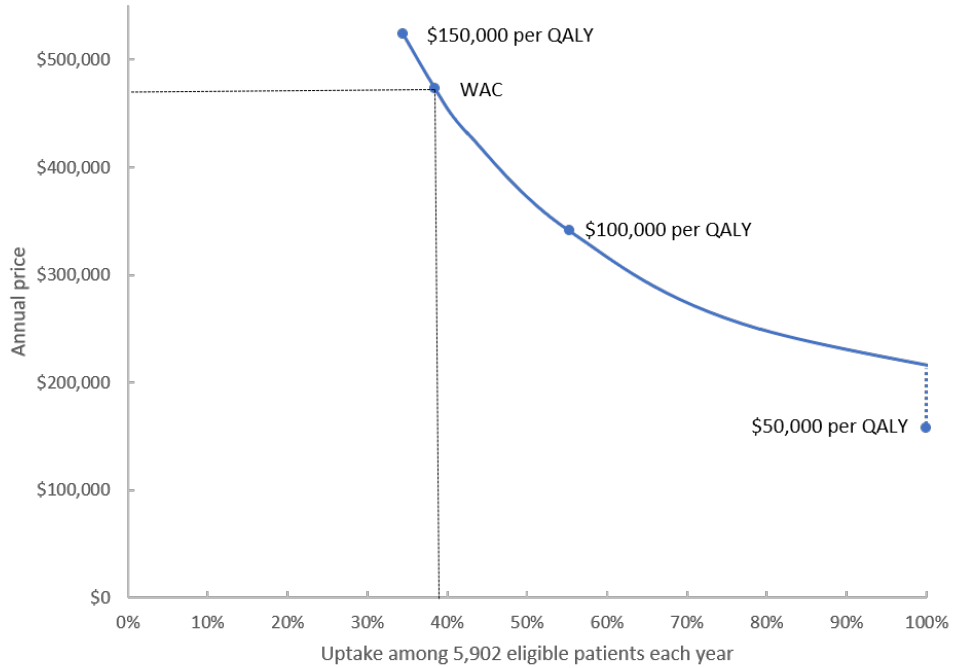
	Average Annual Per Patient Budget Impact			
	Payment at Infusion	$50,000/QALY*	$100,000/QALY*	$150,000/QALY*
Axicabtagene ciloleucel	$238,007	$104,536	$182,065	$259,594
Salvage Chemotherapy	$54,010			
Difference	$183,997	$50,527	$128,056	$205,585

*Based on payment at infusion, irrespective of treatment response
QALY: quality-adjusted life year

The average potential budgetary impact when using the treatment cost at infusion, irrespective of treatment response, was an additional per-patient cost of approximately $184,000. Average potential budget impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $51,000 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold ($157,578) to approximately $206,000 per patient using the annual price to achieve $150,000 per QALY cost-effectiveness threshold ($524,015).

As shown in Figure 7.1, approximately 38% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC ($473,000). Approximately 34% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($524,015), while 55% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price ($340,797). At the $50,000 per QALY threshold price ($157,578), the entire eligible cohort could be treated without exceeding the $915 million threshold, reaching only 71% of the total. As can be seen from the figure, treating a 100% of the eligible cohort without crossing the threshold can be achieved if the price were approximately $220,000 per patient.

Figure 7.1. Potential Budget Impact Scenarios at Different Prices for Axicabtagene Ciloleucel in Patients with Relapsed/Refractory DLBCL*



*Graph shows the relation between annual price and proportion of relapsed/refractory DLBCL patients eligible for treatment with axicabtagene ciloleucel who could be treated over five years without crossing $915-million budget impact threshold.
Note: All prices are based on payment at infusion, irrespective of response to treatment.

In summary, the annual budget impact over a five-year time-horizon for treating eligible patients with relapsed/refractory B-cell ALL with tisagenlecleucel rather than clofarabine was estimated to be approximately $128,000 per patient if payment was made only on response to therapy at one month. Using different payment mechanisms, such as payment at infusion and payment based on treatment response at one year, as well as using prices to achieve cost-effectiveness thresholds from $50,000 to $150,000 per QALY gained, did not result in the total annual potential budget impact exceeding ICER's annual $915 million budget impact threshold.

The annual budget impact of axicabtagene ciloleucel for treating eligible patients with relapsed/refractory DLBCL, PMBCL, TFL, and high-grade B-cell lymphoma with payment at infusion was estimated to be approximately $184,000 per patient. At all except the price to achieve a cost-effectiveness threshold of $50,000 per QALY, the total annual budget exceeded ICER's $915 million annual budget impact threshold.

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This is the first CTAF review of CAR-T therapies for B-cell cancers.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
Title		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
Abstract		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
Methods		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
Discussion		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items For Systematic Reviews And Meta-Analyses: The PRISMA Statement. Plos Med 6(6): E1000097. Doi:10.1371/Journal.Pmed1000097

Table A2. Search Strategies of Medline for B-ALL, September 25, 2017

1	"chimeric antigen receptor" AND (T-cell OR "T")
2	"CAR" AND T
3	"CAR-T" OR "CART-19"
4	tisagenlecleucel
5	axicabtagene ciloleucel OR Axi-Cel
6	Zuma-1
7	Kymriah OR CTL019 OR CTL-019
8	KTEC19 OR KTE-C19
9	"CAR" AND (T-cell OR "T")
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	(leukemia[mh] OR leukemia OR leukaemia)
12	10 AND 11

Table A3. Search Strategy of Medline search for Aggressive B-cell NHL, September 25, 2017

1	"chimeric antigen receptor" AND (T-cell OR "T")
2	"CAR" AND T
3	"CAR-T" OR "CART-19"
4	tisagenlecleucel
5	axicabtagene ciloleucel OR Axi-Cel
6	Zuma-1
7	Kymriah OR CTL019 OR CTL-019
8	KTEC19 OR KTE-C19
9	"CAR" AND (T-cell OR "T")
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	lymphoma[mh] OR lymphoma
12	10 AND 11

Table A4. Search Strategy of Cochrane Central Register of Controlled Trials search for B-ALL, September 27, 2017 (via Ovid)

1	"chimeric antigen receptor" AND (T-cell OR "T")
2	("CAR" AND T) OR "CAR-T" OR "CART-19"
3	tisagenlecleucel
4	axicabtagene ciloleucel OR Axi-Cel
5	Zuma-1
6	Kymriah OR CTL019 OR CTL-019
7	KTEC19 OR KTE-C19
8	"CAR" AND (T-cell OR "T")
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10	leukemia OR leukaemia
11	9 AND 10

Table A5. Search Strategy of Cochrane Central Register of Controlled Trials search for Aggressive B-cell NHL, September 27, 2017 (via Ovid)

1	"chimeric antigen receptor" AND (T-cell OR "T")
2	("CAR" AND T) OR "CAR-T" OR "CART-19"
3	tisagenlecleucel
4	axicabtagene ciloleucel OR Axi-Cel
5	Zuma-1
6	Kymriah OR CTL019 OR CTL-019
7	KTEC19 OR KTE-C19
8	"CAR" AND (T-cell OR "T")
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10	lymphoma
11	9 AND 10

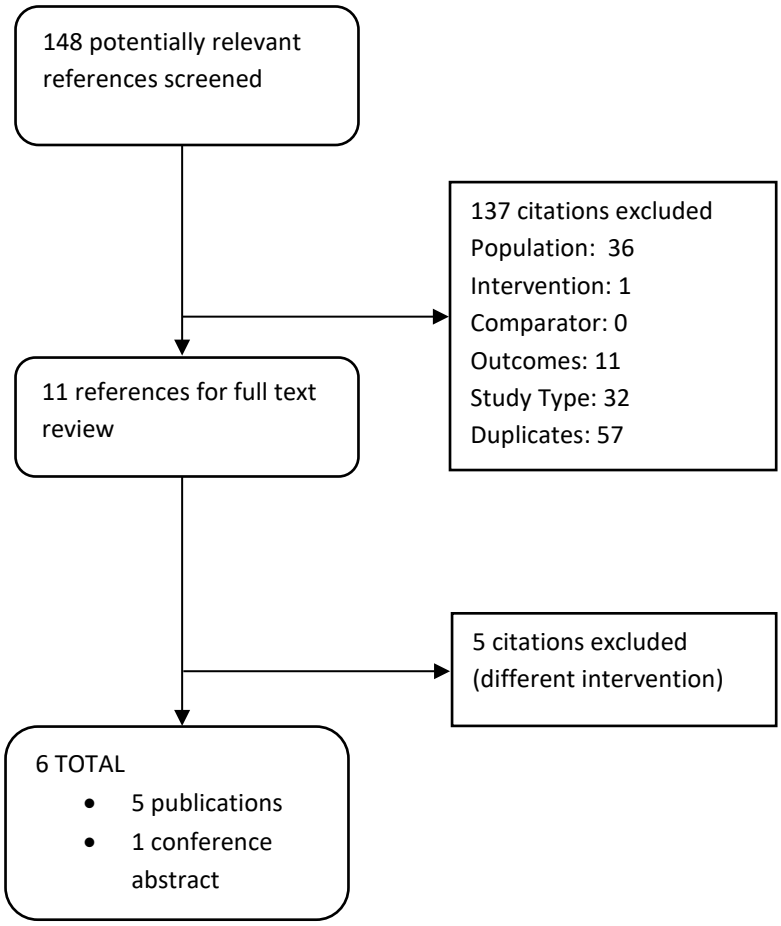
Table A6. Search of Embase search for B-ALL, September 25, 2017

#1	'tisagenlecleucel'/exp OR tisagenlecleucel
#2	(axicabtagene AND ciloleucel) OR 'axi cel'
#3	'zuma 1'
#4	Kymriah
#5	'ctl019'/exp OR ctl019 OR 'ctl 019'/exp OR 'ctl019'
#6	'ktec19'/exp OR ktec19 OR 'kte c19'/exp OR 'kte c19'
#7	('car'/exp OR 'car') AND ('t cell'/exp OR 't cell' OR t)
#8	('chimeric antigen receptor'/exp OR 'chimeric antigen receptor') AND ('t cell'/exp OR 't cell' OR t)
#9	('car'/exp OR 'car') AND t
#10	'car-t' OR 'cart-19'/exp OR 'cart-19'
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'leukemia'/exp OR 'leukemia'
#13	#11 AND #12
#14	AND ([adolescent]/lim OR [child]/lim OR [infant]/lim)
#15	#13 AND #15

Table A7. Search of Embase search for Aggressive B-cell NHL, September 25, 2017

#1	'tisagenlecleucel'/exp OR tisagenlecleucel
#2	axicabtagene AND ciloleucel OR 'axi cel'
#3	'zuma 1'
#4	Kymriah
#5	'ctl019'/exp OR ctl019 OR 'ctl 019'/exp OR 'ctl 019'
#6	'ktec19'/exp OR ktec19 OR 'kte c19'/exp OR 'kte c19'
#7	('car'/exp OR 'car') AND ('t cell'/exp OR 't cell' OR t)
#8	('chimeric antigen receptor'/exp OR 'chimeric antigen receptor') AND ('t cell'/exp OR 't cell' OR t)
#9	('car'/exp OR 'car') AND t
#10	'car-t' OR 'cart-19'/exp OR 'cart-19'
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'lymphoma'/exp OR 'lymphoma'
#13	#11 AND #12

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for B-ALL and B-cell Non-Hodgkin's Lymphoma for CAR-T Therapies.



Appendix B. Ongoing Studies

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Tisagenlecleucel					
Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET) Novartis Pharmaceuticals NCT02445248	Phase II Single Arm Multicenter Trial Estimated Enrollment: 130	1. Experimental: CTL019	Inclusion Criteria Life expectancy ≥12 weeks ECOG performance status that is either 0 or 1 at screening Adequate organ function Must have an apheresis product of non-mobilized cells accepted for manufacturing Adequate bone marrow reserve without transfusions Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air Exclusion Criteria Treatment with any prior gene therapy product Active Central Nervous System (CNS) involvement by malignancy Prior allogeneic HSCT Eligible for and consenting to ASCT Chemotherapy other than lymphodepleting chemotherapy within 2 weeks of infusion HIV positive patients Uncontrolled acute life threatening bacterial, viral, or fungal infection Patients with active neurological auto immune or inflammatory disorders Patients on oral anticoagulation therapy	Primary Outcome Measures Overall Response Rate (ORR) [Time Frame: 5 years] Secondary Outcome Measures Incidence and severity of AEs Time to response (TTR) Duration of overall response (DOR) Progression free survival (PFS) Event free survival (EFS) Overall survival (OS) Incidence of immunogenicity to CTL019 Prevalence of immunogenicity to CTL019 In vivo cellular Pharmacokinetic (PK) profile of CTL019 transduced cells into target tissues Number of Participants with presence of exposure to replication-competent lentivirus (RCL) as Assessed by quantitative polymerase chain reaction (qPCR)	January 1, 2024

Study of Efficacy and Safety of CTL019 in Pediatric ALL Patients Novartis Pharmaceuticals NCT02228096	Phase II Single Arm Multicenter Trial Estimated Enrollment: 67	1. Experimental: CTL019 (Pediatric patients with relapsed or refractory B-ALL)	Inclusion Criteria Relapsed or refractory pediatric B-ALL Adequate organ function Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening Life expectancy > 12 weeks Age 3 at the time of initial diagnosis to age 21 at the time of initial diagnosis Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening Once all other eligibility criteria are confirmed, must have an apheresis product of non-mobilized cells received and accepted by the manufacturing site Exclusion Criteria Isolated extra-medullary disease relapse Prior treatment with gene therapy product Prior malignancy, except carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) Active or latent hepatitis B or active hepatitis C or any uncontrolled infection at screening HIV positive test within 8 weeks of screening	Primary Outcome Measures Overall Remission Rate (ORR) [Time Frame: within 6 months after CTL019 administration] Safety [Time Frame: 12 months] Secondary Outcome Measures N/R	October 17, 2024

Axicabtagene Ciloleucel					
A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-4) Kite Pharma, Inc. NCT02625480	Phase I/II Single arm Open-label Multi-center Estimated Enrollment: 75	1. Experimental: KTE-C19 - A conditioning chemotherapy regimen of fludarabine and cyclophosphamide will be administered followed by a single infusion of CAR-T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg	Inclusion Criteria Relapsed or refractory B-precursor ALL Morphological disease in the bone marrow (≥ 5% blasts) Ages 2 to 21 at the time of Assent or Consent per IRB guidelines Lansky or Karnofsky performance status ≥ 80 at screening Adequate renal, hepatic, pulmonary and cardiac function Subjects with Ph+ disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs Exclusion Criteria Diagnosis of Burkitt's leukemia/lymphoma according to WHO classification or chronic myelogenous leukemia lymphoid blast crisis Presence of CNS-3 disease and CNS-2 disease with neurological changes History of concomitant genetic syndrome or any other known bone marrow failure syndrome History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment Primary immunodeficiency Known infection with HIV, hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive)	Primary Outcome Measures Phase 1: Safety (Incidence of adverse events defined as dose-limiting toxicities (DLT) [Time Frame: 30 Days] Phase 2: Overall complete remission rate [Time Frame: 8 weeks] Secondary Outcome Measures Duration of Remission [Time Frame: 12 Months] Minimum Residual Disease Negative Remission Rate [Time Frame: 8 Weeks] Allogeneic Stem Cell Transplant Rate [Time Frame: 12 Months] Overall Survival [Time Frame: 12 Months]	June 2019

A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5) Kite Pharma, Inc. NCT03105336	Phase II Open-label Multicenter Estimated Enrollment: 50	1. Biological: KTE-C19 A conditioning chemotherapy regimen of fludarabine and cyclophosphamide will be administered followed by a single infusion of CAR-T cells administered intravenously.	Inclusion Criteria • Subject has [follicular lymphoma that has progressed within 24 months of first diagnosis and treatment with combination chemoimmunotherapy] OR Progression of iNHL within 6 months of completion of second or later line therapy containing both an anti-CD20 antibody and alkylating agent OR Progression of iNHL at any point following autologous transplantation. • Subject has [measurable disease]. • Subject has no known presence or history of CNS involvement by lymphoma. • Subject has ECOG performance status of 0-1 and adequate renal, hepatic, pulmonary, and cardiac function Exclusion Criteria • Transformed FL • Small lymphocytic lymphoma • Histological Grade 3b FL • Subject will have undergone autologous transplant within 6 weeks of planned leukapheresis or has undergone allogeneic transplant. • Subject has evidence of involvement of the heart by lymphoma or requirement for urgent therapy due to ongoing or impending oncologic emergency	Primary Outcome Measures • Objective response rate [Time Frame: 6 months] Secondary Outcome Measures • Progression Free Survival [Time Frame: 12 months] • Overall Survival [Time Frame: 12 months] • Incidences of AEs [Time Frame: 12 months] • Clinical significant changes in lab values. [Time Frame: 12 months]	December 2018

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix C. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to tisagenlecleucel and axicabtagene ciloleucel. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[113] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patient

Table C1. Summary of the Clinical Trials of CAR-T Therapy for Pediatric B-ALL

Reference	Study	Medication	N Planned Therapy	N Received Therapy	Median F/U, (Months)	Age, Years	Prior Lines Chemo	Prior SCT	Apheresis Turnaround Time
CTTL019 B2202 (B2202)[19] Pivotal registration trial international multi- center phase II trial Buechner 2017	B2202 ELIANA Study 1 in Prescribing Information	Tisagenlecleucel (Kymriah)	92	75	13.1	11	3	61%	45 days
B2205J[18] Single arm open label US multi-center phase II efficacy and safety	B2205J	Tisagenlecleucel (Kymriah)	35	29	8.8	12	3	59%	
B2101J[18] Phase I/IIA trial Safety tolerability and engraftment NCT101626495	B2101J ENSIGN	Tisagenlecleucel (Kymriah)	71	55	18.6	11	4	64%	
Other FDA Approved Therapies for This Indication									
Jeha 2006[20]		Clofarabine	62	61	NR	12	3	30%	NA
Hijiya 2011[21]		Clofarabine + etoposide cyclophosphamide	25	25	NR	14	2	16%	NA
Von Stackelberg 2016[22]		Blinatumomab	70	70	23.8 months	8	2	57%	NA
Locatelli 2017[23]	RIALTO	Blinatumomab	Ongoing	40	NR	9	2	53%	NA

*5 received product from Germany and not included in efficacy analysis

Table C2. Inclusion/Exclusion Criteria for the Clinical Trials of CAR-T Therapy for B-ALL

Reference	Study	Inclusion	Exclusion	Co-intervention
B2202 **ELIANA**[19]	B2202 ELIANA Study 1 in Prescribing Information	Relapsed or refractory pediatric (3-21 years at screening) B-ALL. Presence of > 5% blasts at screening Second or subsequent bone marrow (BM) relapse, or Any BM relapse after allogeneic SCT and must be ≥ 6 months from SCT at the time of tisagenlecleucel infusion o Refractory is defined by not achieving an initial CR after 2 cycles of a standard chemotherapy regimen (primary refractory). Subjects who were refractory to subsequent chemotherapy regimens after an initial remission were considered chemorefractory. Ph + ALL eligible if failed two tyrosine kinase inhibitor therapies Karnofsky/Lansky Score >50 CD 19 tumor expression in blood or bone marrow	Burkitt's lymphoma/leukemia Genetic syndrome except Downs Prior gene therapy treatment	85% got Bridging chemo lymphodepletion: Fludarabine for 4 days before and cyclophosphamide for 2 days before in 94% and cytarabine and etoposide in 1.5%
B2205J[18] **NCT02228096**				
B2101J[18] **NCT01626495 and NCT01029366**	ENSIGN	Relapsed and Refractory CD 19+ cancers B-ALL in 1st to 4th relapse 3 refractory primary B-ALL		Lymphodepletion chemotherapy. Details in supplementary appendix
Other FDA Approved Therapies for This Indication				
Jeha 2006[20]	Clofarabine	ALL Age < 21 years at diagnosis Refractory or in second or subsequent relapse ≥ 25% blasts in bone marrow Performance status ≥50%	Systemic infection Symptomatic CNS disease Active graft versus host disease SCT in past 3 months	None
Hijiya 2011[21]	Clofarabine + etoposide cyclophosphamide	ALL Ages 1-21 years Refractory or in second or subsequent relapse ≥ 25% blasts in bone marrow	Systemic infection Symptomatic CNS disease	None

		Performance status ≥50%	> 3 prior induction regimens Prior clofarabine treatment	
Von Stackelberg 2016[22]	Blinatumomab	CD19 positive B-ALL Age < 18 years Refractory or in first or subsequent relapse ≥ 25% blasts in bone marrow Performance status ≥50%	Symptomatic CNS disease Active graft versus host disease	None
Locatelli 2017[23]	Blinatumomab	CD19 positive B-ALL Age>28 days and <18 years Refractory or in second or subsequent relapse ≥ 5% blasts in bone marrow	NR	None

Table C3. Baseline Characteristics of the Clinical Trials of CAR-T Therapy for B-ALL

Reference	Medication	Median Age	Median Weight	%F	Primary Diagnosis	Baseline Performance Status	Refractory Category	Other
B2202 ELIANA[19]	Tisagenlecleucel (N=75 infused)	11	43 kg[26]	43%	B-ALL	NR	Primary Refractory 8% Chemorefractory or Relapsed Disease 92%	96% received lymphodepleting chemotherapy
B2205J[18]	Tisagenlecleucel	12.0	NR	62%	B-ALL	All Karnofsky/Lansky performance status ≥ 50%	Primary Refractory 7% Chemorefractory 7% Relapsed 86%	
B2101J[18]	Tisagenlecleucel	11.0	NR	45%	B-ALL		Primary Refractory 6% Relapsed 94%	64% had prior SCT
Other FDA Approved Therapies for This Indication								
Jeha 2006[20]	Clofarabine	12	NR	39%	B-ALL (5% T-cell)	≥50%	57% refractory to last chemo	
Hijiya 2011[21]	Clofarabine + etoposide cyclophosphamide	14	NR	36%	B-ALL (4% T-cell)	Median 90%	60%	
Von Stackelberg 2016[22]	Blinatumomab	8	NR	33%	B-ALL	NR	56%	
Locatelli 2017[23]	Blinatumomab	9	NR	52%	B-ALL	NR	13% primary refractory	

Table C4. Quality Assessment of the Clinical Trials of CAR-T Therapy for B-ALL

Reference	Comparable Groups	Maintain Comparability	Double Blind	Measurements Equal and Valid	Clear Definition of Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality
B2202 ELIANA[19]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
B2205J[18]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
B2101J[18]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
Other FDA Approved Therapies for This Indication								
Jeha 2006[20]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
Hijiya 2011[21]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
Von Stackelberg 2016[22]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor
Locatelli 2017[23]	N/A	N/A	N/A	N/A	Yes	No	Yes	Poor

Table C5. Key Outcomes of the Clinical Trials of CAR-T Therapy for B-ALL

Reference	Group	Median OS	CR	PR	% Dead Before Response Assessment	% Achieving No Response	Median Duration Remission	Allo-SCT	Auto-SCT	Other
B2202 ELIANA[19]	Tisagenlecleucel (N=75 infused)	19.1 months	60%	NR	11%	8%	Not reached	10.7%		ORR 81% (60% CR + 21% CRi)
B2205J[18]	Tisagenlecleucel	Not reached	62%			24%	Not reached			ORR 69%
B2101J[18]	Tisagenlecleucel (n=55)	32.7 months	69%		0	5.5%	Not reached			ORR 95%. Event free survival at 6 months 74.6%. 6 months overall survival 85.1%.
Other FDA Approved Therapies for This Indication										
Jeha 2006[20]	Clofarabine	3 months	20%	10%	NR	70%	2.2 months	15%		
Hijiya 2011[21]	Clofarabine + etoposide cyclophosphamide	2.5 months	44%*	12%	NR	44%	15.5 months	40%		
Von Stackelberg 2016[22]	Blinatumomab	7.5 months	39%	6%	NR	30%	4.4 months	34%		
Locatelli 2017[23]	Blinatumomab	8.3 months	63%	NR	NR	NR	NR	32%		

CR: complete response, %; CRi: complete response with incomplete hematologic recovery; OS: overall survival, median in months - includes patients with a complete response without platelet recovery; PR: Partial response, %; RFS: Relapse free survival, median in months

Table C6. Key Harms in the Clinical Trials of CAR-T Therapy for B-ALL

Reference	Group	Grade 3/4 AEs	CRS	Grade 3/4 CRS	Neuro-Toxicity	Grade 3/4 Neuro-Toxicity	Grade 3/4 Infections	Treatment-Related Death	Prolonged B-Cell Aplasia
B2202 ELIANA[19]	Tisagenlecleucel N=75 infused	88%	77%	46%	40%	13%	24%	25% total death; 2.7% within 30 days of infusion	83% at 6 months; median time to B-cell recovery not reached. "Most patients" received immunoglobulin replacement
B2205J[18]	Tisagenlecleucel								
B2101J Maude, 2014[8]	Tisagenlecleucel		89%	47.3%	43%				90%
B2202 and B2205J COMBINED[18]	Tisagenlecleucel N=97 infused	82%	81%	44%	40%	11%	22%	4% in 1st 30 days; 2 due to disease progression	NR
Other FDA Approved Therapies for This Indication									
Jeha 2009[114]	Clofarabine	>69%	NR	NR	NR	NR		25%	NR
Hijiya 2011[21]	Clofarabine + etoposide cyclophosphamide	100%	NR	NR	NR	NR		28%	NR
Von Stackelberg 2016[22]	Blinatumomab	87%	NR	6%	24%	4%		8.6%	NR
Locatelli 2017[23]	Blinatumomab	73%	23%	NR	NR	NR	NR	5%	NR

AE: adverse events, CRS: cytokine release syndrome

Table C7. Summary of the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma in Adults

Reference	Study	Treatment	N Planned Therapy	N Received Therapy	Median F/U, (Months)	Age, Years	Prior Lines Chemo	Prior SCT	Apheresis Turnaround
Neelapu 2017[28]	ZUMA-1	Axicabtagene ciloleucel	111	101	15.4 months	58	69% 3 or more	21%	17 days
Kochenderfer, 2017[12]	NCT00924326	Axicabtagene ciloleucel	NR	22	NR	58	Median 4	23%	NR
Schuster, 2017[29]	JULIET NCT02445248	Tisagenlecleucel	147	99; 81 evaluated for response	NR	56	Median 3; 50% 3 or more	47%	22 days
Schuster, 2017[30]	NCT02030834	Tisagenlecleucel	38	28	28.6 months	57	Median 4	35%	NR
Other FDA Approved Therapies for This Indication									
Crump, 2017[17] (SCHOLAR 1)	SCHOLAR 1	Multi-agent chemoimmunotherapy	636	523 evaluated for response	NR, but > 24 months	55	Median 2	22%	NA

MDACC: MD Anderson Cancer Center

Table C8. Inclusion/Exclusion Criteria for the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Study	Inclusion	Exclusion	Co-intervention
Neelapu 2017[28]	ZUMA-1	≥18 years old with DLCBL, PMBCL, TFL ECOG performance status 0-1 Refractory disease (progressive or stable as best response to last therapy or relapsed ≤12 months of autologous stem cell transplant		Conditioning chemotherapy with cyclophosphamide (500 mg/m2) and fludarabine (30 mg/m2) for 3 days
Kochenderfer, 2017[12]	NCT00924326	Relapsed refractory DLBCL, follicular lymphoma, mantle cell lymphoma		Conditioning chemotherapy with Fludarabine and cyclophosphamide Once daily for 3 days
Schuster, 2017[29]	JULIET	r/r DLBCL		Bridging chemotherapy if needed Conditioning chemotherapy tailored to prior therapy
Schuster 2017[29]	NCT02030834	≥ 18 years old Refractory CD19+ DLBCL or follicular lymphoma including TFL Measurable disease ECOG performance status 0-1		Bridging chemotherapy if needed Conditioning chemotherapy tailored to prior therapy
Other FDA Approved Therapies for This Indication				
Crump, 2017[17]	SCHOLAR 1 (4 cohorts)	All who met refractory criteria and went on to subsequent treatment	Primary CNS lymphoma	
Crump, 2017[17]	MDACC	DLBCL and TFL relapsed/refractory to rituximab containing chemo, had failed salve platinum containing chemo and received second salvage therapy at MDACC	Primary CNS lymphoma	n/a
Crump, 2017[17]	IAMC	Relapsed refractory among newly diagnosed patients with lymphoma	Primary CNS lymphoma	n/a

Reference	Study	Inclusion	Exclusion	Co-intervention
Crump, 2017[17]	CCTG Ly.12	Relapse after anthracycline therapy and assigned to one of two salvage regimens with goal consolidative ASCT	Primary CNS lymphoma	n/a
Crump 2017[17]	CORAL	DLCBL with in first relapse or lymphoma refractory to first line Randomized to 1 of two salvage regimens before consolidative ASCT	Primary CNS lymphoma	n/a

DLCBL: Diffuse large B Cell lymphoma, PMBCL: Primary Mediastinal B Cell lymphoma, TFL: transformed follicular lymphoma

Table C9. Baseline Characteristics of the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Drug	Comparator	Age	Median Weight	%F	Primary Diagnosis	ECOG PS	Disease Stage	IPI Score	Refractory Category
Neelapu 2017[28] ZUMA 1	Axicabtagene ciloleucel	None	58	NR	33%	DLBCL, TFL or PMBCL	58% 1	85% stage 3/4	48% Score 3-4	26% primary refractory 54% refractory to ≥2 therapies
Kochenderfer, 2017[12]	Axicabtagene ciloleucel	None	26-67	NR	NR	DLBCL	NR	NR	50% Score 3-4	50% refractory
Schuster, 2017 JULIET[29]	Tisagenlecleucel	None	56	NR	NR	DLBCL	45% 1	NR	NR	52% refractory
Schuster NEJM 2017[30]	Tisagenlecleucel	None	57	NR	39%	DLBCL or FL	Median 1	79% stage 3/4	NR	79% refractory
Other FDA Approved Therapies for This Indication										
Crump, 2017[17] SCHOLAR 1	Multi-drug chemoimmunotherapy	NR	55	NR	36%	DLCBL	73% 0-1	72% stage ¾	33% IPI 3-4	28% primary refractory 50% refractory to ≥ 2 therapies

Table C10. Quality Assessment of the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Comparable Groups	Maintain Comparability	Double Blind	Measurements Equal And Valid	Clear Definition Of Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality
Neelapu 2017[28] ZUMA 1	no	n/a	n/a	no	yes	no	yes	Poor
Kochenderfer, 2017[12]	no	n/a	n/a	no	yes	no	yes	Poor
JULIET[29]	no	n/a	n/a	no	yes	no	yes	Poor
Schuster 2017[30]	no	n/a	n/a	no	yes	no	yes	Poor
Other FDA Approved Therapies for This Indication								
SCHOLAR 1[17]	no	n/a	n/a	no	yes	no	yes	Poor

Table C11. Key Outcomes of the Clinical Trials of CAR-T Therapy for Aggressive B-Cell Lymphoma

Reference	Study	Drug	Median OS	CR	PR	ORR	Median Duration of Remission	Allo-SCT	Auto-SCT	Other
Neelapu 2017[28]	ZUMA-1	Axicabtagene ciloleucel	Not reached	54%	28%	82%	8.1 months	2%		OS 78% at 6 months; 59% at 12 months; and 52% at 18 months Median PFS 5.8 months PFS 49% at 6 months; 44% at 12 months; and 41% at 18 months
Kochenderfer, 2017[12]	NCT00924326	Axicabtagene ciloleucel	Approximately 24 months estimated from K/M curve in supplement	55%	18%	73%	7-24 months median 12.5 months	5%		12-month PFS 63.3%
Schuster, 2017[29]	JULIET	Tisagenlecleucel	Not reached	40%	14%	53%	Not reached			
Schuster 2017[30] **Schuster NEJM 2017** [30]	NCT02030834	Tisagenlecleucel	Not reached overall. 22.2 months for DLBCL, not reached FL: 93% alive at 28.6 months FU.	57%	7%	64%	Not reached			57% of patients responding were progression free at 28.6 months follow-up.
Other FDA Approved Therapies for This Indication										
Crump 2017[17]	SCHOLAR 1	n/a	6.3 months	7%	19%	26%	NR		30%	

CR: complete response, %, OS: overall survival, median in months, PR: partial response, %, PFS: progression-free survival, median in months

Table C12. Key Harms in the Clinical Trials of CAR-T Therapy for Aggressive B-Cell Lymphoma

Reference	Medication	Grade 3/4 AEs	Discontinuation Due To AE	CRS	Grade 3/4 CRS	Neuro-Toxicity	Grade 3/4 Neuro-Toxicity	Treatment-Related Death	Prolonged B-Cell Aplasia
Neelapu 2017[28] ZUMA 1	Axicabtagene ciloleucel	66% NP 44% LP 43% anemia 31% febrile NP 95%	NR	93%	13%	64%	28%	2%	NR
Kochenderfer, 2017[12]	Axicabtagene ciloleucel	100%	NR	NR	NR	NR	55%	0%	NR
Schuster 2017 JULIET[29]	Tisagenlecleucel	NR	NR	58%	23%	21%	12%	0%	NR
Schuster 2017[30]	Tisagenlecleucel		NR	57%	18%	39%	11%	4%	NR
Other FDA Approved Therapies for This Indication									
SCHOLAR-1[17]	Chemoimmunotherapy	NR	NR	NR	NR	NR	NR	NR	NR

AE: adverse events, CRS: cytokine release syndrome, LP: leukopenia, NP: neutropenia

Table C13. Grade 3 or Higher Adverse Events Experienced by Patients in the First Eight Weeks Following Tisagenlecleucel Infusion

Adverse Reaction	B2101J[18] (N=55)	B2202 (ELIANA)[19] (n=75)	Combined B2202 and B2205J[18] (n=97)
Any Grade 3 or 4 Adverse Event	NR	69%	72%
Cytokine Release Syndrome	NR	46%	44%
Neurologic Toxicities	NR	13%	11%
Fever	NR	10%	11%
Encephalopathy	NR	5%	13%
Acute Kidney Injury	NR	8%	9%
Hypotension	NR	17%	24%
Hypoxia	NR	11%	16%
Infections	NR	24%	22%
Decreased Appetite	NR	14%	21%
Pulmonary edema	NR	6%	10%
AST Increased	NR	10%	18%
Febrile Neutropenia	NR	35%	36%
Low white blood cell count	NR	9%	23%
Tumor Lysis Syndrome	NR	4%	3%

Appendix D. Comparative Value Supplemental Information

Table D1. Impact Inventory

Sector	Type of Impact	Included in This Analysis from… Perspective?		Notes on Sources
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity Effects	✓	✓	
	Health-Related Quality of Life Effects	✓	✓	
	Adverse Events	✓	✓	
Medical Costs	Paid by Third-Party Payers	✓	✓	
	Paid by Patients Out-Of-Pocket	✓	✓	
	Future Related Medical Costs	✓	✓	
	Future Unrelated Medical Costs	✓	✓	
Informal Health Care Sector				
Health-Related Costs	Patient Time Costs	☐	✓	
	Unpaid Caregiver-Time Costs	☐	✓	
	Transportation Costs	☐	✓	
Non-Health Care Sectors				
Productivity	Labor Market Earnings Lost	☐	✓	
	Cost of Unpaid Lost Productivity Due to Illness	☐	☐	
	Cost of Uncompensated Household Production	☐	☐	
Consumption	Future Consumption Unrelated to Health	☐	☐	
Social services	Cost of Social Services as Part of Intervention	☐	☐	
Legal/Criminal Justice	Number of Crimes Related to Intervention	☐	☐	
	Cost of Crimes Related to Intervention	☐	☐	
Education	Impact of Intervention on Educational Achievement of Population	☐	☐	
Housing	Cost of Home Improvements, Remediation	☐	☐	
Environment	Production of Toxic Waste Pollution by Intervention	☐	☐	
Other	Other Impacts (If Relevant)	☐	☐	

Detailed Description of Model Structure

The decision analytic model structure included a short-term decision tree and a long-term semi-Markov partitioned-survival model. The decision tree calculated the costs and consequences from treatment initiation to assessment of response, per trial protocols, which was approximately one month.[26,32] From the decision tree, patients moved to the semi-Markov partitioned-survival model where they were then tracked for a lifetime time horizon. The purpose of the decision tree was to stratify the cohort by which treatment they ended up receiving, because the model starts at treatment initiation (considered leukapheresis for CAR-T therapies). Further, the decision tree allowed for allocation of upfront costs by treatment and the stratification of the cohort by response status, which becomes important when considering outcomes-based pricing.

For the decision tree, the CAR-T arm included patients who were eligible for CAR-T therapy and underwent leukapheresis. At the first decision tree event node of the CAR-T arm, patients had three possibilities: 1) continue with CAR-T after undergoing leukapheresis to receive the infusion; 2) discontinue CAR-T therapy (before infusion but after leukapheresis) because of adverse events or manufacturing failures; or 3) die before receiving the infusion. Patients with infusion pending were excluded from our analysis because outcomes data were not available for them. Those who discontinued CAR-T due to adverse events were assumed to not be able to tolerate other active therapies and therefore transitioned to receive no further antileukemic/antilymphomic therapy (i.e., palliative care only). Those who discontinued CAR-T due to manufacturing failures were assumed to receive the active comparator treatment's average costs and outcomes. Responses were assessed for patients who received the CAR-T infusion (second event node of decision tree), which could be: alive and responding to treatment; alive and not responding to treatment; or dead before assessment of response. The model was flexible enough to allow for patients to receive or not receive SCT (third event node of decision tree) based on percentages reported in available evidence. The decision tree's comparator arm followed a similar pathway to the CAR-T arm, tracking the patient from comparator treatment initiation through assessment of response and receipt of stem cell transplantation.

From the decision tree, the cohort was assigned to three mutually exclusive health states in a semi-Markov partitioned survival model that followed patients for the remainder of their lifetime using survival curve evidence. The three health states included: 1) alive and responding to treatment, 2) alive and not responding to treatment, and 3) death from modeled B-cell malignancy or other causes. Patients transitioned between states during predetermined cycles (one month) over a lifetime time horizon. The "alive and responding to treatment" health state included all patients who were alive and responding to treatment (complete or partial responders). The "alive and not responding to treatment" health state included all patients who were alive that did not respond to treatment or relapsed after previously responding to treatment. Patients in the "alive and not responding to treatment" health state remained in this health state until they died from their modeled B-cell malignancy or other causes. Patients not responding to treatment received

palliative chemotherapy. End-of-life hospice care costs were assigned to each death event. Health state occupancy was derived using partitioned survival techniques involving the direct extrapolation of PFS and OS Kaplan-Meier curves:

alive and responding to treatment (t)=P(PFS, t)

alive and not responding to treatment (t)=(P(OS, t)-P(PFS, t)

death (t) = 1-P(OS, t)

Although the decision tree separated the cohort based on response status, survival curves were not available stratified by response status for all treatments. Further, definitions of response may vary between treatments; thus, survival curves were based on aggregated cohort data and not stratified by response status. Thus, in our model, there is no structural link between response status and survival. Response status, from the decision tree, is only important when assigning payment within the CAR-T outcomes based-pricing scenarios.

Similar to modeling done by Hettle and colleagues,[36] we assessed treatment response and survival over the first five years following treatment completion by extrapolating data from published Kaplan-Meier curves. After year five, survivors experienced a mortality risk profile consistent with that of a long-term survivor, after adjustments were made for excess mortality.

In summary, the two-part decision analytic model included four stages:

- Stage 1: Costs and outcomes from treatment initiation through assessment of response (decision tree)
- Stage 2: Short-run costs and outcomes from assessment of response through approximately one year (partitioned survival model)
- Stage 3: Intermediate-run costs and outcomes from approximately one year post-assessment of response through five years (partitioned survival model)
- Stage 4: Long-run costs and outcomes after five years post-assessment of response (Markov model)

Collectively, we describe Stages 2-4 as a semi-Markov partitioned survival model that models the cohort from assessment of response until death.

Detailed Description of Curve Digitization

Kaplan-Meier curves from the evidence were digitized using the algorithm by Guyot and colleagues[115] to impute patient-level time-to-event data. We extracted data points from the digitized copies of published survival curves,[116] then used the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data. Values were extrapolated for five years following treatment completion. The model curves considered included the distributional forms Weibull, exponential,

log-normal, log-logistic, and Gompertz. The base-case distributional form was selected separately for each curve based on best model fit using Akaike information criterion (AIC) values and visual comparison. A series of flexible cubic spline models were also considered, but they were not good fits for the Kaplan-Meier curves used in the model, based on AIC and visual comparison. Monthly transition probabilities were derived using the survival function with the best model fit. These steps allowed for the extrapolation of survival beyond the observed trial evidence to a time-period of approximately five years while also keeping as close as possible to the observed trial survival signals. In the absence of PFS curves, the PFS curve was derived from available OS data by assuming a proportional relationship between PFS and OS using a published relationship within the same B-cell malignancy.[36] Table D5 lists the shape and scale parameters, as well as the distributional form chosen for each curve.

Due to the potentially curative nature of CAR-T therapies, flattening of survival curves were observed. To account for the flattening, we explored the best time points to split survival curves into separate analyses. For example, a parametric curve function could be fit from 0 to 12 months, and then a separate parametric curve function could be fit from one to five years with a flatter slope than the first function to account for the plateau expected toward the end of the curves. The time point chosen to split the analyses was empirically driven based on curve fit and was selected once the fitted curve intersected the flattening (slope of 0) observed in the Kaplan Meier curve.

Treatment Regimens

Table D2 denotes the regimen used for noted treatments in B-ALL and B-cell Lymphoma, including the intervention and comparator therapies (tisagenlecleucel, clofarabine, axicabtagene ciloleucel, and chemotherapy) and the pre-treatment regimens and treatments for adverse events.

Table D2. Treatment Regimens

B-ALL	Regimen	Notes	Source
Tisagenlecleucel	≤ 50 kg: 0.2 to 5.0×106 transduced viable T cells/kg >50 kg: 0.1 to 2.5×108 transduced viable T cells		Study B2202[26]
Clofarabine	52mg/m^2 intravenously over 2 hours daily for 5 days, every 2 to 6 weeks		Jeha et al., 2006[20]
Bridging Chemotherapy	cytarabine 500mg/m2 IV for 2 days a week, 2 weeks total and methotrexate 1g/m2 IV for 1 day a week, 2 weeks total	CAR-T treatments only; 85.3% received bridging chemotherapy; duration assumed for one month	Study B2202[26]
Lymphocyte Depleting Chemotherapy	Fludarabine (30 mg/m^2 IV daily for 4 days) and cyclophosphamide (500 mg/m^2 IV daily for 2 days starting with the first dose of fludarabine) OR Cytarabine (500 mg/m^2 IV daily for 2 days) and etoposide (150 mg/m^2 IV daily for 3 days starting with the first dose of cytarabine)	CAR-T treatments only; 94.1% of patients received the first option and 1.5% received the second option	Study B2202[26]
Tocilizumab	< 30 kg: 12 mg/kg intravenously over 1 hour ≥ 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)	For the management of cytokine release syndrome	Tisagenlecleucel package insert[27]
Intravenous Immunoglobulin	0.5 g/kg every 4 weeks for 11.4 months	For the management of B-cell aplasia which occurred in all CAR-T patients experiencing hypogammaglobulinemia	Maude et al., 2017[117]
B-cell Lymphoma	**Regimen**	**Notes**	**Source**
Axicabtagene Ciloleucel	2 x 10^6 CAR-T cells/kg		Locke et al., 2017[32]
Chemotherapy (R-DHAP)	Dexamethasone 40 mg on days 1-4 + cytarabine 2 g/m^2 every 12h for 2 doses on day 2 + cisplatin 100 mg/m^2 on day 3; every 21 days for three cycles, rituximab 375 mg/m^2 on day 1 of each cycle; an additional rituximab (375 mg/m^2) was given on day -1 of the first cycle		Gisselbrecht et al., 2010[118]
Bridging Chemotherapy	No bridging chemotherapy used with axicabtagene ciloleucel		Locke et al., 2017[32]
Lymphocyte Depleting Chemotherapy	Fludarabine (30 mg/m^2 IV daily for 3 days) and cyclophosphamide (500 mg/m^2 IV daily for 3 days)	CAR-T treatments only	Locke et al., 2017[32]
Tocilizumab	8 mg/kg intravenously over 1 hour (maximum dose 800 mg)	For the management of cytokine release syndrome	Kymriah/Yescarta Package Insert[27,119]
Intravenous Immunoglobulin	0.5 g/kg every 4 weeks[36] for 11.4 months[117]	For the management of B-cell aplasia; costs only assigned to those who are alive and responding to treatment	Maude et al., 2017[117]

Model Parameters

Response to Treatment

Treatment response rates were obtained from published literature and information provided from manufacturers. The initial response rates used in the short-term decision tree are provided in Table D3.

Table D3. Response to Treatment

B-ALL	Tisagenlecleucel	Clofarabine
Percent Achieving Response (Complete or Partial)	84.4%[26]	30.0%[20]
Percent Dead Before Assessment of Response	7.4%[26]	25.0%[20]
Percent Achieving No Response	8.2%[26]	45.0%[20]
B-cell Lymphoma	Axicabtagene Ciloleucel	Chemotherapy
Percent Achieving Response (Complete or Partial)	82.0%[32]	26.0%[17]
Percent Dead Before Assessment of Response	0.0%[32]	0.0%[17]
Percent Achieving No Response	18.0%[32]	74.0%[17]

Note: The denominator is the number of people who received a CAR-T infusion for CAR-T therapies and the number of people who initiated the chemotherapy regimen for comparator therapies. Within treatment and B-cell malignancy, the percents sum to 100 with response and death categories being mutually exclusive and exhaustive.

Survival

Individual transition probabilities were calculated as described in the Model Structure section. Table D4 details the evidence used to calculate transition probabilities.

Table D4. Source of Kaplan-Meier Curves to Calculate Transition Probabilities

B-ALL	Tisagenlecleucel	Clofarabine
Event-Free Survival	Pooled event-free survival curve for Study B2202, B2205J, and B2101J	No published event-free survival curve; therefore, the event-free survival curve was derived from available overall survival data for clofarabine, by assuming the same proportional relationship seen in the tisagenlecleucel curve.
Overall Survival	Pooled overall survival curve for Study B2202, B2205J, and B2101J	Figure 1 (Overall Survival of Patients Receiving Clofarabine) in Jeha et al., 2006[20]
B-cell Lymphoma	**Axicabtagene Ciloleucel**	**Chemotherapy**
Progression-Free Survival	Progression-free survival curve (Figure 2B) for ZUMA-1[28]	No published progression-free survival curve; therefore, the progression-free survival curve was derived from available overall survival data for SCHOLAR-1 chemotherapies, by assuming the proportional relationship from a published progression-free survival and overall survival curve for R-DHAP in the same disease state.[120]
Overall Survival	Overall survival curve (Figure 2C) for ZUMA-1[28]	Figure 3A in SCHOLAR-1[17]

Table D5 presents the final distributions chosen for the model based on the lowest Akaike information criterion (AIC). The shape and scale parameters were used to generate time-dependent transition probabilities for each curve over a 5-year time horizon. This table also describes the survival curve knot location for piece-wise distributions.

Table D5. Survival Curve Fit, Shape, and Scale Parameters for Final Model

B-ALL						
	Outcome (Distribution Chosen)	**AIC**	**Shape**	**Scale**	**Source**	**Notes**
Tisagenlecleucel	Overall Survival (Log-Normal)	308.4	3.579	1.579	Pooled data from Study B2202, B2205J, and B2101J	Knot at 30 months, then death only due to all-cause mortality
	Event-Free Survival (Log-Normal)	419.6	2.627	1.605	Pooled data from Study B2202, B2205J, and B2101J	Knot at 13 months, then proportion remains constant
Clofarabine	Overall Survival (Log-Normal)	200.9	1.561	0.995	Jeha et al., 2006	Knot at 14 months, then death only due to all-cause mortality
	Event-Free Survival (Log-Normal)	N/A	1.146	1.011	Derived through assuming a proportional relationship between OS and PFS from the tisagenlecleucel curve	Knot at 13 months, then proportion remains constant
No Anti-Leukemic Therapy	Overall Survival (Gompertz)	16.5	2.402	0.273	Von Stackelberg et al., 2011	Knot at 3 months
B-cell lymphoma						
	Outcome (Distribution Chosen)	**AIC**	**Shape**	**Scale**	**Source**	**Notes**
Axicabtagene Ciloleucel	Overall Survival (Log-Normal)	381.3	2.986	1.390	ZUMA-1	Knot at 24 months, then death only due to all-cause mortality
	Progression-Free Survival (Log-Normal)	375	2.188	1.458	ZUMA-1	Knot at 11 months, then proportion remains constant
Chemotherapy	Overall Survival (Log-Logistic)	1613	2.180	6.705	SCHOLAR-1	Knot at 14 months, then death only due to all-cause mortality
	Progression-Free Survival (Log-Normal)	N/A	1.751	0.728	Derived through assuming a proportional relationship between OS and PFS for R-DHAP	Knot at 13 months, then proportion remains constant
No Antilymphomic Therapy	Overall Survival (Gompertz)	16.5	2.402	0.273	Von Stackelberg et al., 2011	Knot at 3 months

Table D6 includes the proportion of the cohort that is in each health state at one year, two years, and five years after treatment completion, stratified by treatment and cancer. The proportions presented in Table D6 are based on those that receive the CAR-T therapy infusion or initiate the chemotherapy regimens. Patients in the cohort may discontinue before receiving the infusion/initiating the chemotherapy regimen due to manufacturing failure, adverse events, or death; These patients who discontinue are not included in Table D6.

Table D6. Proportion of the Cohort in Each Health State

	B-ALL		B-cell Lymphoma	
	Tisagenlecleucel	Clofarabine	Axicabtagene Ciloleucel	Chemotherapy
Alive and Responding to Treatment				
1 Year	0.557	0.108	0.438	0.185
2 Years	0.515	0.108	0.433	0.153
5 Years	0.515	0.108	0.420	0.148
Alive and Not Responding to Treatment				
1 Year	0.216	0.092	0.221	0.070
2 Years	0.095	0.031	0.016	0.014
5 Years	0.000	0.000	0.000	0.000
Dead				
1 Year	0.227	0.800	0.341	0.744
2 Years	0.390	0.861	0.551	0.833
5 Years	0.485	0.892	0.580	0.852

Adverse Events

The model included any grade 3/4 adverse event that occurred in ≥ 5% of patients in any of the treatments and comparators, as listed in Table D7. Any grade of hypogammaglobulinemia was modeled based on clinical expert guidance that treatment with IVIG might still be necessary for grades 1 and 2. Costs and disutilities associated with adverse events are described later.

Table D7. Included Adverse Event Rates

Grade 3/4 Adverse Event	Tisagenlecleucel (Leukemia)[117]	Clofarabine[118]	Axicabtagene Ciloleucel[119]	Chemotherapy[17]
Abdominal Pain	3%	7%	1%	N/R
Acute Kidney Injury	13%	N/R	N/R	N/R
B-Cell Aplasia/ Hypogammaglobulinemia*	43%	N/R	15%	6.6%[121]
Cytokine Release Syndrome	49%	N/R	13%	N/R
Decreased Appetite	15%	12%	2%	N/R
Delirium	4%	N/R	6%	N/R
Diarrhea	1%	12%	4%	N/R
Encephalopathy	10%	N/R	29%	N/R
Epistaxis	N/R	13%	N/R	N/R
Fatigue	0%	5%	3%	9%
Febrile Neutropenia	37%	54%	36%	23%
Headache	3%	5%	1%	N/R
Hypotension	22%	19%	15%	N/R
Hypoxia	18%	N/R	11%	N/R
Infections	35%	77%	23%	9%
Nausea	3%	15%	0%	8%
Pain in Extremity	1%	5%	2%	N/R
Petechiae	N/R	6%	N/R	N/R
Pyrexia	15%	14%	N/R	N/R
Tachycardia	4%	5%	2%	N/R
Vomiting	1%	9%	1%	7%

N/R: Not reported
*Any grade, not just grades 3 or 4

Utilities

The utilities for each model health state are presented in Table D8.

Table D8. Model Health State Utilities

B-ALL	Utility	Source
Alive and Not Responding to Treatment	0.75	Kelly et al., 2015[36,87]
Alive and Responding to Treatment (i.e. progression-free or event-free survival)	0.91	Kelly et al., 2015[36,87]
Long-Term Survivor-Alive, Responding to Treatment after 5 Years (i.e. progression-free or event-free survival)	0.91	Kelly et al., 2015[36,87]
B-cell Lymphoma	Utility	Source
Alive and Not Responding to Treatment	0.39	Chen et al., 2017[88]
Alive and Responding to Treatment (i.e. progression-free or event-free survival)	0.83	Chen et al., 2017[88]
Long-Term Survivor-Alive, Responding to Treatment after 5 Years (i.e. progression-free or event-free survival)	0.83	Chen et al., 2017[88]

Disutilities were applied for each treatment, including pre-treatment regimens for CAR-T therapies, to account for the potential reduction in quality of life while receiving treatment. Table D9 details the disutilities and duration of reduction in quality of life applied for each treatment. All treatment-related disutilities were included in Stage 1 of the model.

Table D9. Treatment-Related Disutilities

Health State	Disutility	Notes	Source
Chemotherapy	-0.42	Applied for duration of treatment. Applies to pre-CAR-T treatment chemotherapies as well.	Sung et al.[36,122]
Stem cell transplantation	-0.57	Applied for duration of Stage 1 and includes all decrements due to adverse events.	Sung et al.[36,122]

Health Care Utilization Costs

Table D10 details the healthcare utilization unit costs used in the model.

Table D10. Unit Costs for Health Care Utilization

Cost Parameter	Value	Source
Cost per Hospital day (pediatric)	$4,049	HCUP Statistical Brief #132[123]
Cost per Hospital day (adult)	$3,037	HCUP Statistical Brief #125[124]
Cost per day in ICU	$5,296	Dasta et al., 2005[96]
Office Visit	$74	Physicians' Fee and Coding Guide[125] (HCPCS code 99213)
Leukapheresis (axicabtagene ciloleucel only)	$1,093	Physicians' Fee and Coding Guide[125] (HCPCS code 36511)
Intravenous Treatment Administration (first hour)	$140	Physicians' Fee and Coding Guide[125] (HCPCS code 96413)
Intravenous Treatment Administration (each additional hour)	$29	Physicians' Fee and Coding Guide[125] (HCPCS code 96415)
Intravenous Treatment Administration (each additional sequence/drug)	$66	Physicians' Fee and Coding Guide[125] (HCPCS code 96417)
Hematology Panel	$11	Physicians' Fee and Coding Guide[125] (HCPCS code 82025)
Liver Function Test	$8	Physicians' Fee and Coding Guide[125] (HCPCS code 80076)

Resource use for tisagenlecleucel, clofarabine, axicabtagene ciloleucel, and chemotherapy associated with administration and monitoring are shown in Table D11 for Stages 1-4. These costs relate to inpatient hospital days, outpatient visits, liver function test, complete blood counts, IV administration, and average healthcare utilization.

Table D11. Administration and Monitoring

Administration and Monitoring for Different Therapies				
Model Stage	**Tisagenlecleucel**	**Clofarabine**	**Axicabtagene Ciloleucel**	**Chemotherapy**
Stage 1	31 inpatient hospital days (1.2 of which are in intensive care unit)[26]	2 hours of IV administration per clofarabine administration, 22.5 days inpatient hospital days	Leukapheresis and 15 inpatient hospital days[34]	1 hour of IV administration per cytarabine, cisplatin, and rituximab administration
Stage 2	12 outpatient visits, 12 complete blood counts, and 6 liver function tests	12 outpatient visits, 12 complete blood counts, and 6 liver function tests	12 outpatient visits, 12 complete blood counts, and 6 liver function tests	12 outpatient visits, 12 complete blood counts, and 6 liver function tests
Stage 3	10 outpatient visits, 10 complete blood counts	10 outpatient visits, 10 complete blood counts	10 outpatient visits, 10 complete blood counts	10 outpatient visits, 10 complete blood counts
Stage 4	Average healthcare utilization for age group	Average healthcare utilization for age group	Average healthcare utilization for age group	Average healthcare utilization for age group

Adverse Event Costs

Table D12 includes the unit costs for adverse event. For all CAR-T and clofarabine associated adverse events, except for B-cell aplasia and CRS, the cost of the hospitalization associated with treatment administration was assumed to include the cost of the adverse events. Costs for B-cell aplasia and CRS were added in addition to the hospitalization because they were expected to either prolong the hospitalization or extend beyond discharge.

Table D12. Adverse Event Unit Costs

Adverse Event (ICD-9-CM)	Mean ($)	Standard Error ($)
Abdominal pain (789.0)	$6,766	$7,148
Acute kidney injury (584)	$17,357	$20,817
Decreased appetite (783.0)	$9,918	$14,317
Delirium (780.09)	$8,284	$11,440
Diarrhea (787.91)	$7,880	$10,698
Encephalopathy (348.30)	$11,222	$12,165
Epistaxis (784.7)	$9,054	$18,629
Fatigue (780.71)	$7,486	$11,105
Febrile neutropenia (288.00)	$13,975	$22,204
Headache (784.0)	$7,130	$7,810
Hypotension (458.9)	$8,362	$10,336
Hypoxia (799.02)	$8,472	$12,697
Infections (686.9)	$7,680	$10,857
Nausea (787.02)	$6,229	$7,314
Pain in extremity (729.5)	$6,863	$10,172
Petechiae (782.7)	$8,303	$12,486
Pyrexia (780.60)	$7,401	$9,826
Tachycardia (785.0)	$6,885	$9,431
Vomiting (787.03)	$5,731	$7,482

Other Results

Figure D1. Cost-Effectiveness Cloud for Tisagenlecleucel Versus Clofarabine

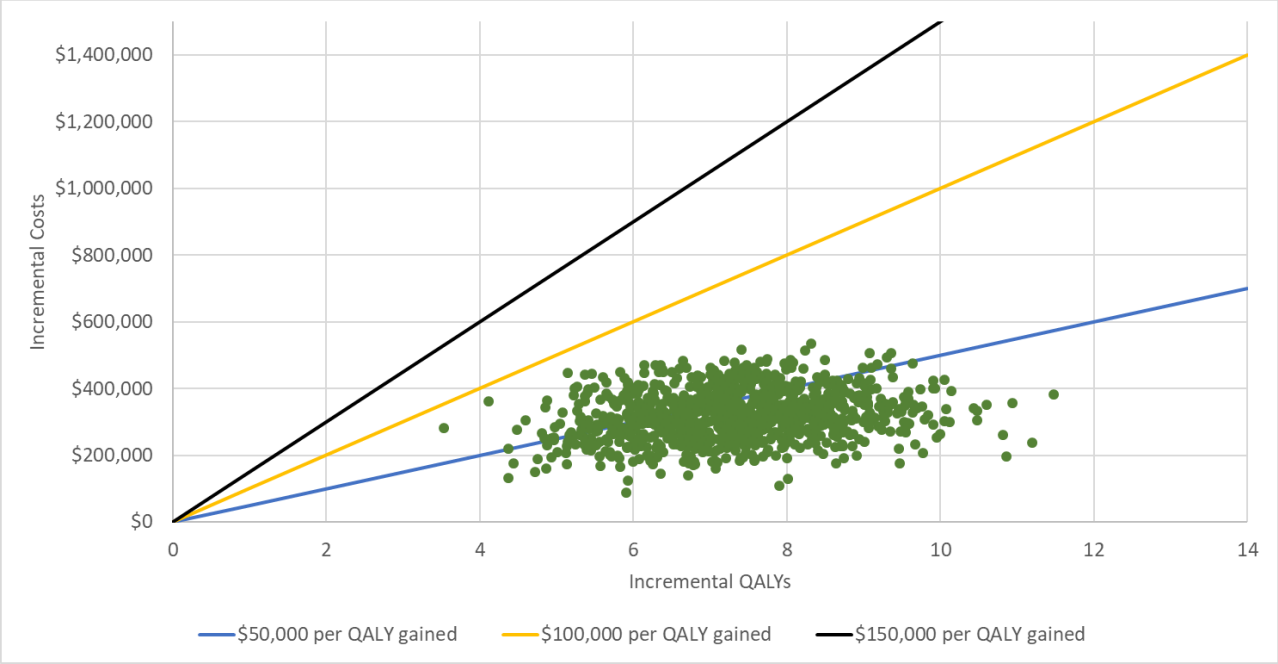


Figure D2. Cost-Effectiveness Cloud for Axicabtagene Ciloleucel Versus Chemotherapy

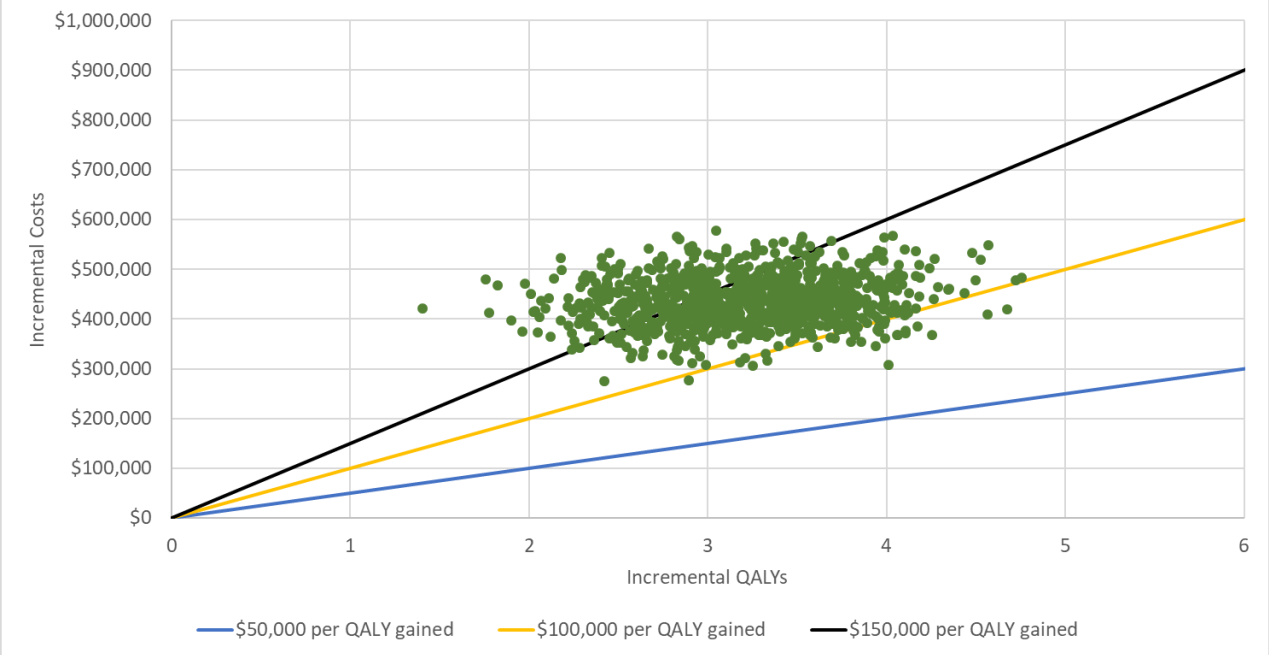


Figure D3. Cost-Effectiveness by Time Horizon: Tisagenlecleucel Versus Clofarabine

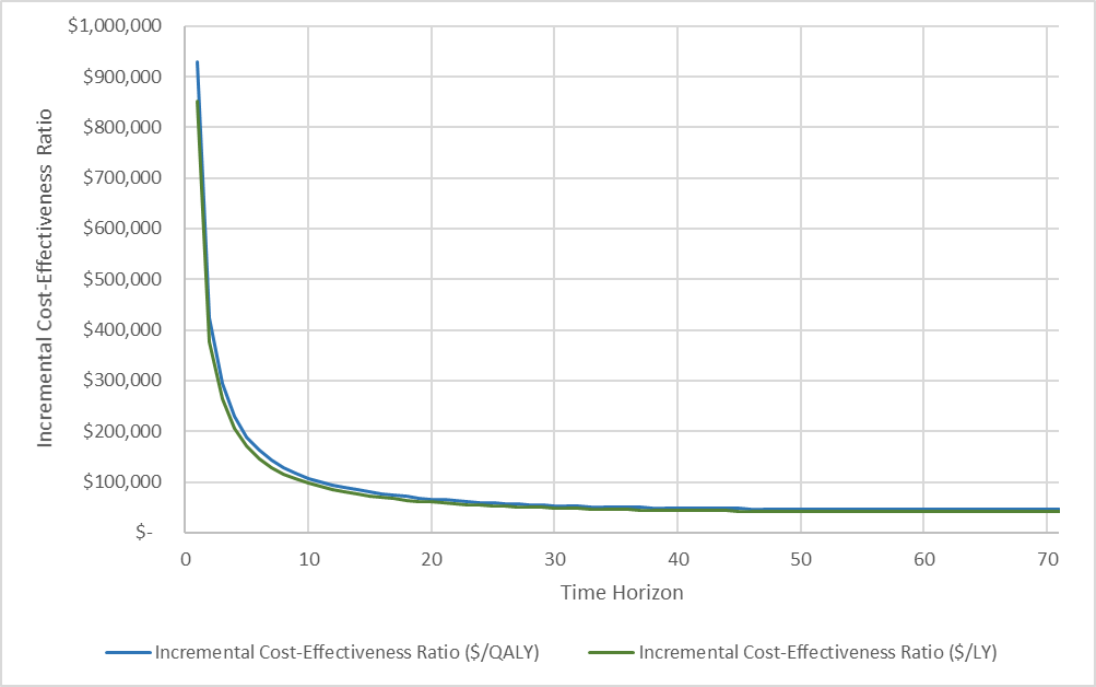


Figure D4. Cost-Effectiveness by Time Horizon: Tisagenlecleucel Versus Clofarabine (Zoomed in to 5 Years to Lifetime)

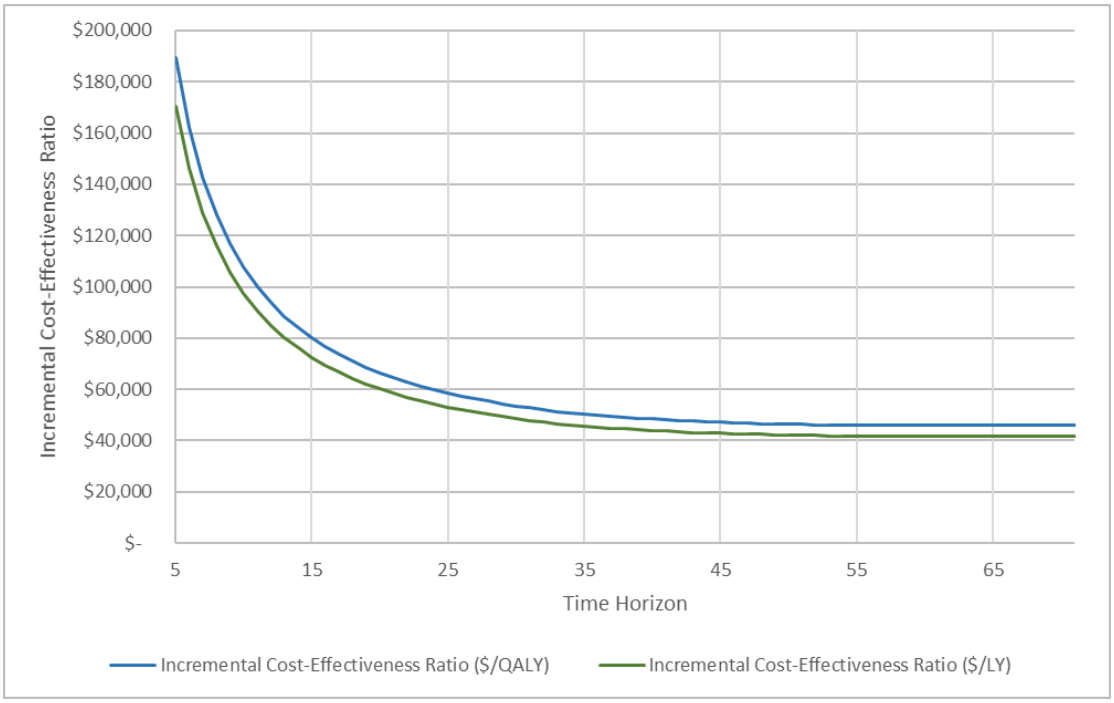


Figure D5. Cost-Effectiveness by Time Horizon: Axicabtagene Ciloleucel Versus Chemotherapy

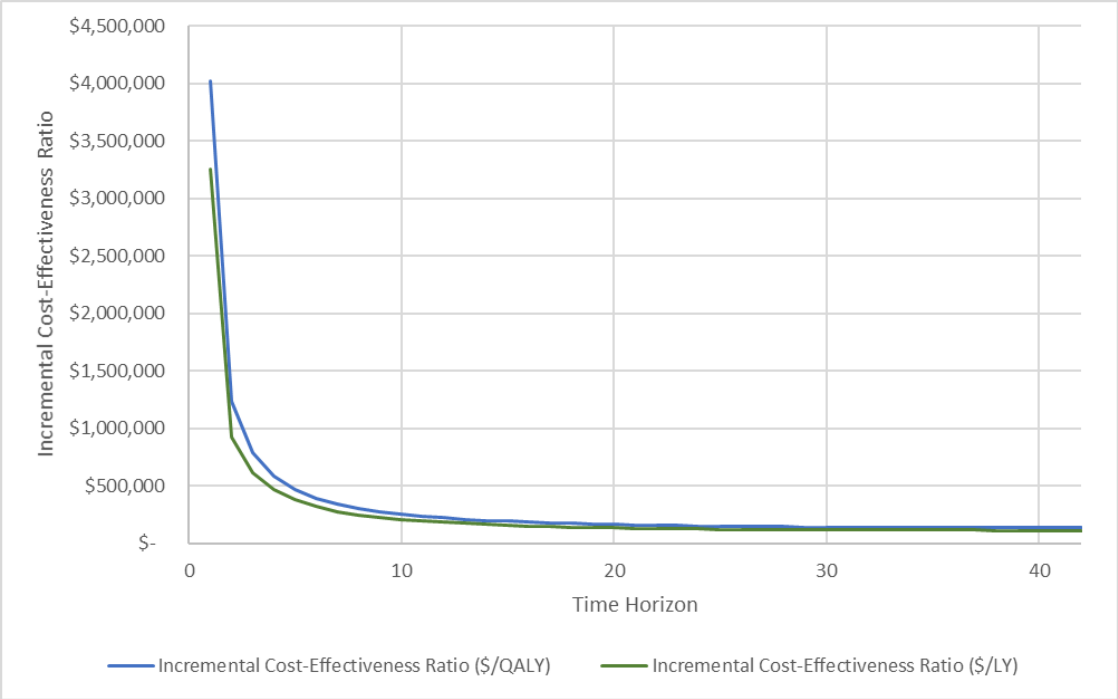


Figure D6. Cost-Effectiveness by Time Horizon: Axicabtagene Ciloleucel Versus Chemotherapy (Zoomed in to 5 Years to Lifetime)

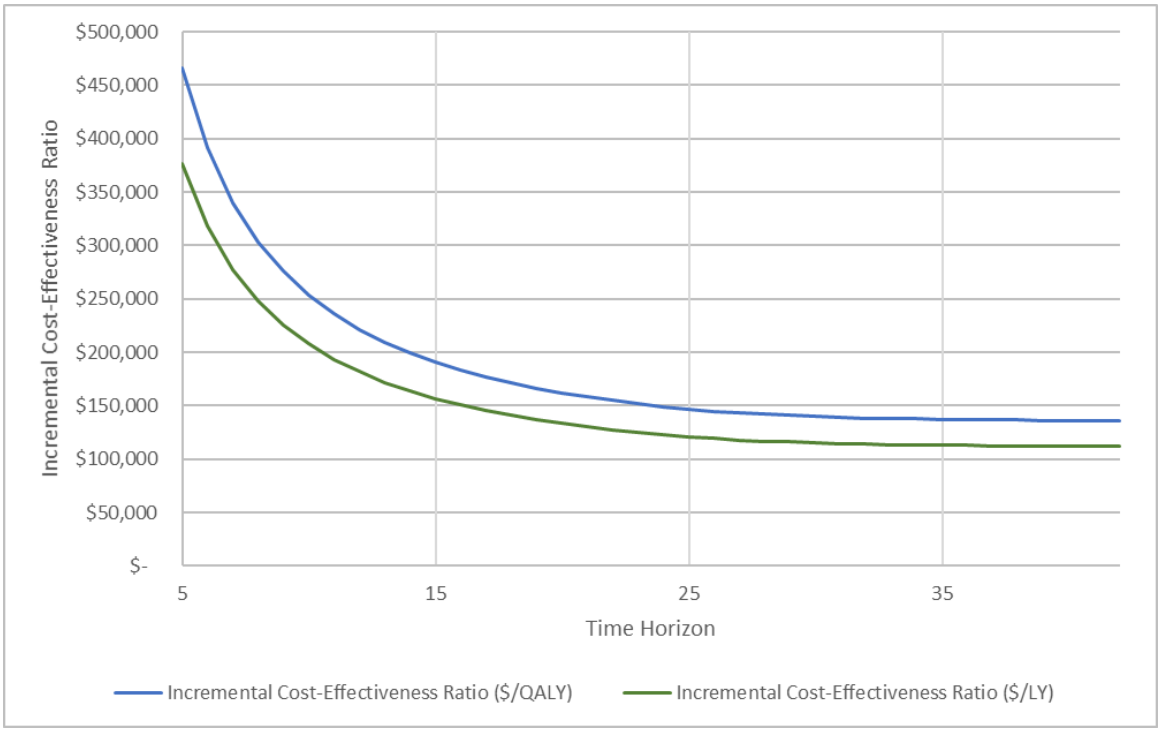


Table D13. Total CAR-T Pathway Costs for Subsets of Cohort

B-ALL	All Costs	CAR-T Treatment Costs	Other Costs
Tisagenlecleucel + no CRS or B-cell aplasia	$765,846	$575,000	$190,846
Tisagenlecleucel + CRS and B-cell aplasia	$854,966	$575,000	$279,966
Tisagenlecleucel + CRS and B-cell aplasia + SCT	$1,373,791	$575,000	$798,791
B-cell lymphoma	**All Costs**	**CAR-T Treatment Costs**	**Other Costs**
Axicabtagene ciloleucel + no CRS or B-cell aplasia	$633,523	$473,000	$160,523
Axicabtagene ciloleucel + CRS and B-cell aplasia	$755,740	$473,000	$282,740
Axicabtagene ciloleucel + CRS and B-cell aplasia + SCT	$1,240,626	$473,000	$767,626

Payment assumed is payment at infusion for both cohorts.