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

Modeling Analysis Plan

October 13, 2017

Institute for Clinical and Economic Review

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1. Approach

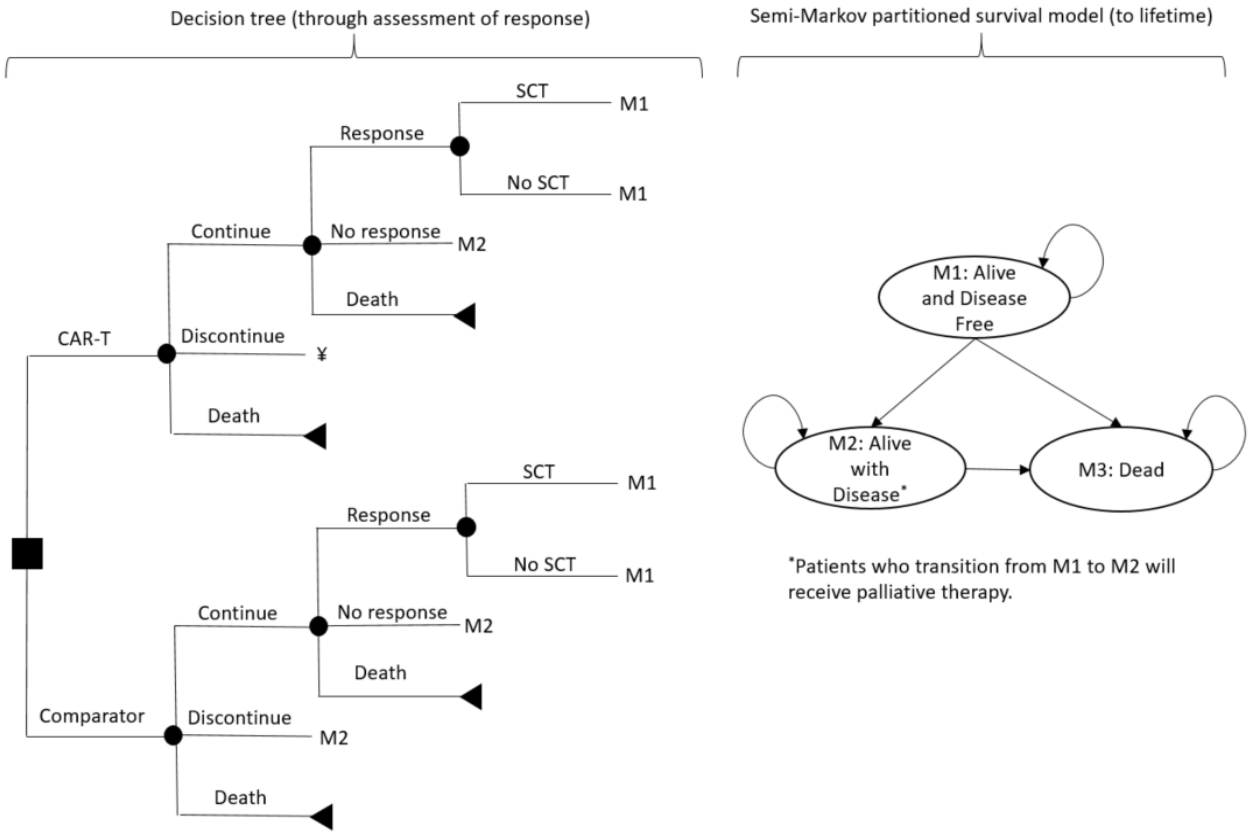
This report was drafted by University of Colorado Skaggs School of Pharmacy researchers in collaboration with the Institute for Clinical and Economic Review (ICER) staff and University of California San Francisco researchers. The primary aim of this analysis is to estimate the cost-effectiveness of chimeric 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, will compare CAR-T therapies to chemotherapy. Patient survival, quality-adjusted survival, and health care costs from the health-care system perspective will be estimated over a lifetime time horizon for each intervention and comparator. Costs and outcomes will be discounted at 3% per annum. Incremental costs and outcomes will be calculated comparing each intervention to its comparator. The base case analysis will take a health system perspective, but productivity losses and other potential costs to the patient and caregiver will be considered in a scenario analysis if data allow. The model will be developed in Microsoft Excel. The model framework and assumptions are described in detail below.

2. Methods

2.1 Overview and Model Structure

The decision analytic model structure will include a short-term decision tree and long-term semi-Markov partitioned-survival model (Figure 1). The two-part model will link the short-term measures reported in the evidence (e.g., objective response) to longer-term health outcomes (e.g., survival). The decision tree will calculate the costs and consequences from treatment initiation (considered to be leukapheresis for CAR-T therapies) to assessment of response, per trial protocol. Long-term survival and outcomes will be modeled using parametric survival modeling from the direct extrapolation of event-free survival and overall survival data for five-years after therapy completion. Mortality after five years will be based on the general population age- and sex-adjusted all-cause risks of mortality with adjustments made for excess morbidity and mortality for each population.[1] Five years was chosen because at that time, those who are alive are assumed to be long-term survivors and are considered to be effectively cured.[1] Patient survival, quality-adjusted survival, and health care costs from the health-care system perspective will be estimated over a lifetime time horizon for each intervention and comparator. Costs and outcomes will be discounted at 3% per annum. Incremental costs and outcomes will be calculated comparing each intervention to its comparator.

Figure 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 therapy and will enter the semi-Markov partitioned survival model at M2.
CAR-T: Chimeric antigen receptor T-cell therapies
SCT: Stem cell transplantation

The decision tree will calculate the costs and consequences for each intervention and comparator from treatment initiation (considered leukapheresis for CAR-T therapies) to assessment of best overall response, per trial protocol. The CAR-T arm will include patients who are eligible for CAR-T therapy and who have undergone leukapheresis. At the first event node, patients can continue with CAR-T after undergoing leukapheresis to receive the infusion; discontinue CAR-T therapy (before infusion but after leukapheresis) because of adverse events or manufacturing failures; or die before receiving the infusion. 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 therapy. Those who discontinued CAR-T due to manufacturing failures were assumed to receive the active comparator treatment average costs and outcomes. For those patients who receive the CAR-T infusion (second event node), their response will be assessed. They can either achieve remission and therefore respond to CAR-T therapy, not achieve remission and therefore not respond to CAR-T therapy, or die. The non-responders will go on to receive palliative therapy (low dose chemotherapy without curative intent). The model will be flexible enough to allow for the responders to either receive stem-cell transplantation or not (third event node) based on these outcomes as reported in available evidence. The comparator arm will follow a similar pathway. The

decision tree will track the patient from comparator treatment initiation through assessment of response and receipt of stem-cell transplantation.

From the decision tree, the cohort will be assigned to three mutually exclusive health states in a semi-Markov partitioned survival model that will model patients for the remainder of their lifetime. The semi-Markov partitioned-survival model will include three health states (with data dependent on intervention and population), including (1) alive and event free, (2) alive with relapsed disease, and (3) dead from cancer or other causes. Patients will transition between states during predetermined cycles (one month) over a lifetime time horizon. The health state of alive and disease-free will include all patients who have stable disease and have thus responded to therapy. The health state of alive with relapsed disease will include all patients who are living with the disease and did not respond to therapy or relapsed after previously responding to therapy. Patients in the alive with relapsed disease health state will remain there until they die from their cancer or other causes, and will receive palliative therapy. The dead state will include patients who have died from their cancer or some other cause. Health state occupancy will be derived using partitioned survival techniques that involve the direct extrapolation of event-free survival (EFS) and overall survival (OS) Kaplan-Meier curves:

alive and event free (t)=P(EFS, t)

alive with relapsed disease (t)=(P(OS, t)-P(EFS, t)

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

Similar to modeling done by Hettle and colleagues,[1] we will create a forecasting model that models treatment response and survival over the first five years following treatment completion by extrapolating data from published Kaplan-Meier curves. Responders at five years post treatment, assumed to be long-term survivors and considered effectively cured,[1] will be assumed to follow the long-run costs and outcomes consistent with the general population of the same age and gender, after adjustments are made for excess morbidity and mortality.[1]

For up to five years following treatment completion, parametric curve functions will be fit for the intervention and comparator in each population. Kaplan-Meier curves from the evidence will be digitized using the algorithm by Guyot and colleagues[2] to impute patient-level time-to-event data. We will extract data points from the digitized copies of published survival curves, then use the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data and extrapolate the values to up to five years following treatment completion. The model curves considered will include the distributional forms Weibull, exponential, log-normal, log-logistic, and Gompertz.

Because of the expected curative nature of CAR-T therapies, “flattening” of survival curves may occur. Therefore, we will explore the best time points to split survival curves into separate analyses. For example, a parametric curve function may be fit from 0 to 12 months, and then a separate parametric curve function may be fit from one to five years with a flatter slope than the first

function to account for the plateau expected at the end of these curves. The time point chosen to split the analyses will be empirically driven based on curve fit. The base-case parametric function will be selected based on best model fit using Akaike information criterion (AIC) values and visual comparison. Transition probabilities will be derived on a monthly basis using the survival function with the best model fit. These steps will allow us to extrapolate survival beyond the observed trial evidence to a time-period of approximately five years. In the absence of EFS curves, the EFS curve will be derived from available OS data, through assuming a proportional relationship between EFS and OS.[1]

Therefore, the two-part decision analytic model will include 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 (Markov model)
- Stage 3: intermediate-run costs and outcomes from approximately one year post-assessment of response through five years (Markov model)
- Stage 4: long-run costs and outcomes after five years post-assessment of response (Markov model)

Model inputs will be informed by existing CAR-T and selected comparator clinical evidence and any published economic evaluations. Key model inputs will include the probability of response, event-free survival, overall survival, occurrence of adverse events, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions within the same disease, but may allow for intervention-specific disutilities if evidence is available.

2.2 Target Populations

There are two separate populations of focus for this review, each of which will be modeled separately. They include:

- Population 1: patients ages 3-25 years old with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL)
- Population 2: patients ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma

Characteristics of each population are detailed in Table 1. The model is mostly agnostic to the population characteristics (except for the effects of age and gender on general mortality risk and weight on weight-based treatments), but they provide a context for describing the model inputs and assumptions.

Table 1. Base-Case Model Cohort Characteristics

POPULATION 1: B-cell acute lymphoblastic leukemia	Value	Primary Source
Median age	11.5 years	Study B2202[3]
Percent female	45%	Study B2202[3]
Median weight (kg)	43.0	Study B2202[3]
POPULATION 2: B-cell lymphoma	**Value**	**Primary Source**
Median age	58.0 years	Locke et al., 2017[4]
Percent female	32%	Locke et al., 2017[4]
Median weight	TBD	TBD

2.3 Treatments

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Population 1: Tisagenlecleucel-T (Kymriah™, Novartis)
- Population 2: Tisagenlecleucel-T (Kymriah™, Novartis) and Axicabtagene ciloleucel (KTE-C19, Kite Pharma)

Comparators

The list of comparators was also developed with input from stakeholders. The primary comparator for each population is detailed below. Because of the differences in population, interventions will not be compared across populations. Further, the two CAR-T lymphoma products will not be compared to each other due to the lack of head-to-head trials, no available indirect quantitative comparisons, and differences in the patient population in each pivotal trial.

- Population 1: Clofarabine 52mg/m^2 intravenously over 2 hours daily for 5 consecutive days, every 2 to 6 weeks
- Population 2: Chemotherapies (from SCHOLAR-1)[5] for the treatment of diffuse large B-cell lymphoma (DLBCL)

Pending available evidence, the interventions will also be compared to palliative therapy (i.e., low-dose chemotherapy without curative intent).

2.4 Key Model Choices and Assumptions

The base case analysis will take a health system perspective and thus focus on direct medical care costs only. However, a modified societal perspective that includes productivity losses and other potential costs to the patient and caregiver will be considered in a scenario analysis, if data allow. Outcomes will be 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 will be discounted at 3% per annum. Model assumptions are described in Table 2.

Table 2. Key Model Assumptions

Assumption	Rationale
Stem cell transplantation, if it occurs, will occur within two months (stage 1 of model), and no further stem cell transplantation events will be modeled.	Based on mean time from CAR-T therapy to stem cell transplantation estimated by Lee et al.[1,6]
Patients will receive a single full course of therapy. Retreatment with CAR-T therapy or comparator therapy will not be permitted.	CAR-T therapies are considered an end-of-line treatment.
Parametric curve functions will be fit separately for each population/treatment and used to extrapolate the data up to five years post response assessment.	Between the populations modeled, there is not one baseline comparator across treatments/populations.
After year 5, survivors will experience a mortality risk profile consistent with that of a long-term survivor, after adjustments are made for excess morbidity and mortality.	At year 5, those who are alive are assumed to be long-term survivors and are considered to be effectively cured.[1]
All patients who relapse following CAR-T will be assumed to get palliative therapy.	CAR-T therapies are considered an end-of-line treatment.
Patients who discontinue CAR-T due to an adverse event before receiving the infusion will receive no further antileukemic therapy.	CAR-T therapies are considered an end-of-line treatment and those who experience a severe adverse event were assumed unable to tolerate further active therapy.
Patients who discontinue CAR-T due to a manufacturing failure before receiving the infusion will receive the active comparator.	Patients who experience a manufacturing failure will go on to receive the comparator active treatment.
The model will include only grade 3/4 adverse events. Costs and consequences will occur during the assessment of treatment response (stage 1), except for B-cell aplasia, which will have costs that extend beyond the assessment of treatment response.	Less severe events are not expected to significantly impact patient health or costs.

2.5 Input Parameters

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

Treatment Response

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 3.

Table 3. Treatment Response Rates

POPULATION 1: B-cell acute lymphoblastic leukemia	Tisagenlecleucel-T	Clofarabine
Percent achieving response	84.4%[7]	30.0%[8]
Percent dead before assessment of response	7.4%[7]	25.0%[8]
Percent achieving no response	8.2%[7]	45.0%[8]

POPULATION 2: B-cell lymphoma	Tisagenlecleucel-T	Axicabtagene ciloleucel	Chemotherapy
Percent achieving response	TBD	82.0%[4]	26%[5]
Percent dead before assessment of response	TBD	0.0%[4]	0%[5]
Percent achieving no response	TBD	18.0%[4]	74%[5]

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 population, the percents shall sum to 100 with response and death categories being mutually exclusive and exhaustive.

Survival

Base case survival will be derived from parametric fits to each intervention's available EFS and OS Kaplan-Meier curves, stratified by response and transplant status if available. We will then calculate individual transition probabilities as described in Section 2.1. Table 4 describes the evidence that will be used to calculate transition probabilities.

Table 4. Source of Kaplan-Meier Curves to Calculate Transition Probabilities

POPULATION 1: B-cell acute lymphoblastic leukemia	Tisagenlecleucel-T	Clofarabine
Event-Free Survival	Pooled event-free survival curve for Study B2202, B2205J, and B2101J[7]	No published event-free survival curve; therefore, the event-free survival curve will be derived from available overall survival data for clofarabine, through assuming a proportional relationship from a published event-free survival and overall survival curve in the same disease state.[1]
Overall Survival	Pooled overall survival curve for Study B2202, B2205J, and B2101J[7]	Figure 1, Overall Survival of Patients Receiving Clofarabine in Jeha et al., 2006[8]

POPULATION 2: B-cell lymphoma	Tisagenlecleucel-T	Axicabtagene ciloleucel	Chemotherapy
Event-Free Survival	TBD	Duration of response curve for ZUMA-1[4]	No published event-free survival curve; therefore, the event-free survival curve will be derived from available overall survival data for SCHOLAR-1 chemotherapies, through assuming a proportional relationship from a published event-free survival and overall survival curve for R-DHAP in the same disease state.[1]
Overall Survival	TBD	Overall survival curve for ZUMA-1[4]	Figure 3A in SCHOLAR-1[5]

Stem Cell Transplantation

A subset of the treatment responders may elect to receive stem cell transplantation, given the larger evidence base around the curative nature of stem cell transplantation. Table 5 provides inputs used in the model related to the proportion of the cohort that received stem cell transplantation.

Table 5. Receipt of Stem Cell Transplantation and Associated Response Rates

POPULATION 1: B-cell acute lymphoblastic leukemia	Tisagenlecleucel-T	Clofarabine
Percent that receive transplantation	10.5%[7]	14.8%[8]

POPULATION 2: B-cell lymphoma	Tisagenlecleucel-T	Axicabtagene ciloleucel	Chemotherapy
Percent that receive transplantation	TBD	TBD	28.3%[5]

Adverse Events

The model will include any grade 3/4 adverse event that occur in ≥20% of patients in any of the treatments and comparators, as listed in Table 6.

Table 6. Included Adverse Event Rates

Grade 3/4 Adverse Event	Tisagenlecleucel-T[9] (Leukemia)	Clofarabine[10]	Tisagenlecleucel-T[9] (Lymphoma)	Axicabtagene ciloleucel	Chemotherapy
Abdominal pain	3%	7%	TBD	TBD	TBD
Acute kidney injury	13%	N/R	TBD	TBD	TBD
Anxiety	3%	2%	TBD	TBD	TBD
B-Cell Aplasia	84.4%	N/R	TBD	TBD	TBD
Chills	0%	3%	TBD	TBD	TBD
Cytokine release syndrome	49%	0%	TBD	TBD	TBD
Decreased appetite	15%	12%	TBD	TBD	TBD
Delirium	4%	N/R	TBD	TBD	TBD
Diarrhea	1%	12%	TBD	TBD	TBD
Encephalopathy	10%	N/R	TBD	TBD	TBD
Epistaxis	N/R	13%	TBD	TBD	TBD
Fatigue	0%	5%	TBD	TBD	TBD
Febrile neutropenia	40%	54%	TBD	TBD	TBD
Flushing	N/R	0%	TBD	TBD	TBD
Headache	3%	5%	TBD	TBD	TBD
Hypogammaglobinemia	7%	N/R	TBD	TBD	TBD
Hypotension	22%	19%	TBD	TBD	TBD
Hypoxia	18%	N/R	TBD	TBD	TBD
Infections-pathogen unspecified	16%	N/R	TBD	TBD	TBD
Nausea	3%	15%	TBD	TBD	TBD
Pain in extremity	1%	5%	TBD	TBD	TBD
Petechiae	N/R	6%	TBD	TBD	TBD
Pruritus	N/R	1%	TBD	TBD	TBD
Pyrexia	15%	14%	TBD	TBD	TBD
Tachycardia	4%	5%	TBD	TBD	TBD
Viral infectious disorders	18%	N/R	TBD	TBD	TBD
Vomiting	1%	9%	TBD	TBD	TBD

N/R: Not reported

Utility Inputs

Model Health States

To adjust for quality of life, utilities will be applied for each model health state. Health state utilities will be derived from publicly available literature and applied to the disease states. Utilities may differ by population, but will remain consistent within a population across different treatments. The utilities for each model health state are presented in Table 7. Among long-term survivors (those alive after five years), the utility score for the remission health state will be assumed with an additional age-adjusted decrement. Scenario analyses will explore the impact of differences in utility across disease population.

Table 7. Model Health State Utilities

POPULATION 1: B-cell acute lymphoblastic leukemia	Utility	Notes	Source
Relapsed/recurrent disease (Alive with Disease)	0.75		Kelly et al., 2015[1,11]
Remission (Alive and Disease Free)	0.91		Kelly et al., 2015[1,11]
Long-term survivor (Alive and Disease Free)	0.91	An age-adjusted decrement (-0.0016 per year) was applied once the cohort was 40 years old.[1,12]	Kelly et al., 2015[1,11]
POPULATION 2: B-cell lymphoma	**Utility**	**Notes**	**Source**
Relapsed/recurrent disease (Alive with Disease)	0.68		Muszbek et al., 2016[13]
Remission (Alive and Disease Free)	0.76		Muszbek et al., 2016[13]
Long-term survivor (Alive and Disease Free)	0.76	An age-adjusted decrement (-0.0016 per year) was applied once the cohort was 40 years old.[1,12]	Muszbek et al., 2016[13]

Treatment Disutilities

Disutilities will also be applied for each treatment, including pre-treatment regimens for CAR-T, to account for the potential reduction in quality of life while receiving treatment. Table 8 details the disutilities and duration of reduction in quality of life applied for each treatment. All treatment-related disutilities will be included Stage 1 of the model.

Table 8. 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.[1,14]
Stem cell transplantation	-0.57	Applied for duration of Stage 1 and includes all decrements due to adverse events.	Sung et al.[1,14]

Adverse Event Disutilities

All adverse events associated with stem cell transplantation and chemotherapy were assumed to be accounted for in the treatment disutility estimates. The only additional adverse events to model include those associated with CAR-T therapy. Only cytokine release syndrome and B-cell aplasia were expected to impact quality of life outside of what was included in the therapy 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 cytokine release syndrome.[1] This disutility lasted for eight days, which equated to the median duration of ICU stay due to CRS.[1] For B-cell aplasia, evidence did not suggest an impact on quality of life.[1] Therefore, no disutility was assigned for cases of B-cell aplasia.[1]

Therapy Utilization

The treatment regimen for each intervention and comparator is detailed in Table 9, including the dose, cycle schedule, and number of cycles.

Table 9. Treatment Regimens

POPULATION 1: B-cell acute lymphoblastic leukemia	Regimen	Notes	Source
Tisagenlecleucel-T	≤ 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[3]
Clofarabine	52mg/m^2 intravenously over 2 hours daily for 5 days, every 2 to 6 weeks		Jeha et al., 2006[8]
Bridging chemotherapy	TBD	CAR-T treatments only; 85.3% received bridging chemotherapy; duration assumed for one month	Study B2202[3]
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[3]
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	Kymriah package insert[9]
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 responders[15]	Maude et al., 2017[15]
POPULATION 2: B-cell lymphoma	**Regimen**	**Notes**	
Tisagenlecleucel-T	TBD		TBD
Axicabtagene ciloleucel	2 x 10^6 CAR-T cells/kg		Locke et al., 2017[4]
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 + rituximab 375 mg/m^2 weekly for 4 weeks starting on day 1 of first cycle		Hernandez-Ilizaliturri et al., 2016[16]
Bridging chemotherapy	No bridging chemotherapy used with Axicabtagene ciloleucel	No bridging chemotherapy used with Axicabtagene ciloleucel	Locke et al., 2017[4]
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[4]
Tocilizumab	TBD	For the management of cytokine release syndrome	TBD
Intravenous immunoglobulin	0.5 g/kg every 4 weeks[1] for 11.4 months[15]	For the management of B-cell aplasia	Maude et al., 2017[15]

Healthcare Utilization Inputs

Additional healthcare utilization could occur with treatment administration, treatment monitoring, and post-treatment. Table 10 details the healthcare utilization rates used in the two-part model for the first three stages. For stage 4 of the model, healthcare utilization for long-term survivors will be based on the average healthcare utilization costs by age.

Table 10. Mean Rate of Healthcare Utilization per Patient Receiving Treatment

POPULATION 1: B-cell acute lymphoblastic leukemia	Tisagenlecleucel-T	Clofarabine
Stage 1: From Administration through Assessment of Response		
Hospitalizations, not including ICU	29.8 days[17]	TBD
ICU Stays	1.2 days (not including cytokine-release syndrome days)[17]	TBD
Outpatient Visits	0	TBD
Laboratory Tests	0	TBD
Stage 2: For One Year After Assessment of Response		
Hospitalizations, not including ICU	0	TBD
ICU Stays	0	TBD
Outpatient Visits	12[18]	TBD
Laboratory Tests	12 hematology panels, 6 liver function tests[18]	TBD
Stage 3: From One Year After Assessment of Response through Five Years After Assessment of Response		
Hospitalizations, not including ICU	0	TBD
ICU Stays	0	TBD
Outpatient Visits	6[18]	TBD
Laboratory Tests	0	TBD

POPULATION 2: B-cell lymphoma	Tisagenlecleucel-T	Axicabtagene ciloleucel	Chemotherapy
Stage 1: From Administration through Assessment of Response			
Hospitalizations, not including ICU	TBD	TBD	TBD
ICU Stays	TBD	TBD	TBD
Outpatient Visits	TBD	TBD	TBD
Laboratory Tests	TBD	TBD	TBD
Stage 2: For One Year After Assessment of Response			
Hospitalizations, not including ICU	TBD	TBD	TBD
ICU Stays	TBD	TBD	TBD
Outpatient Visits	TBD	TBD	TBD
Laboratory Tests	TBD	TBD	TBD
Stage 3: From One Year After Assessment of Response through Five Years After Assessment of Response			
Hospitalizations, not including ICU	TBD	TBD	TBD
ICU Stays	TBD	TBD	TBD
Outpatient Visits	TBD	TBD	TBD
Laboratory Tests	TBD	TBD	TBD

Cost Inputs

Drug Acquisition Costs

The unit cost for each treatment is reported in Table 11. We will use net prices to include discounts and rebates from the wholesale acquisition cost as derived from the SSR health database for each drug, if available and estimates thereof if not. Discounts and rebates will not be assumed for generic drugs; however, a mark-up for hospital-administered drugs may be considered. For interventions without a list price, we will assume the price provided by the manufacturer. If neither a manufacturer-provided nor list price is available, threshold prices will be calculated at the three cost-effectiveness thresholds ($50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained).

Table 11. Drug Cost Inputs

POPULATION 1: B-cell acute lymphoblastic leukemia	Unit	WAC per Unit*	Net price per unit+
Tisagenlecleucel-T	≤ 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	$475,000	$475,000
Clofarabine	1mg/1ml	$146	$146
Bridging Chemotherapy	TBD	TBD	TBD
Fludarabine	1mg/1ml	$3.61	$3.61
Cyclophosphamide	1mg/1ml	$0.62	$0.62
Cytarabine	1mg/1ml	$0.03	$0.03
Etoposide	1mg/1ml	$0.10	$0.10
Tocilizumab (IV)	1mg/1ml	$4.97	$4.58
Intravenous immunoglobulin	1mg/1ml	$0.13	$0.13

Table continues on the next page.

*WAC as of October 8th, 2017

+Net price does not include any mark-up for hospital-administered drugs

Table 11 (continued). Drug Cost Inputs

POPULATION 2: B-cell lymphoma	Unit	WAC per Unit*	Net price per unit+
Tisagenlecleucel-T	TBD	TBD	TBD
Axicabtagene ciloleucel	2 x 10^6 CAR-T cells/kg	TBD	TBD
Dexamethasone	1mg	$0.03	$0.03
Cytarabine	1mg/1ml	$0.03	$0.03
Cisplatin	1mg/ml	$0.36	$0.36
Rituximab	1mg/1ml	$8.68	$7.46
Fludarabine	1mg/1ml	$3.61	$3.61
Cyclophosphamide	1mg/1ml	$0.62	$0.62
Tocilizumab (IV)	1mg/1ml	$4.97	$4.58
Intravenous immunoglobulin	1mg/1ml	$0.13	$0.13

*WAC as of October 8th, 2017

+Net price does not include any mark-up for hospital-administered drugs

Health Care Utilization Costs

Costs associated with healthcare utilization that result from administration and monitoring will be included in the model. Table 12 details the healthcare utilization unit costs used in the model. Unit costs for healthcare utilization were the same across different treatments and populations.

Table 12. Unit Costs for Healthcare Utilization

	Value	Source
Cost per hospital day*	$2,357	Kaiser State Health Facts, 2016[19]
Cost per day in ICU*	$3,305	Dasta et al., 2005[20]
Office Visit	$74	Physicians' Fee and Coding Guide[12] (HCPCS code 99213)
Intravenous treatment administration (first hour)	$140	Physicians' Fee and Coding Guide[12] (HCPCS code 96413)
Intravenous treatment administration (each additional hour)	$29	Physicians' Fee and Coding Guide[12] (HCPCS code 96415)
Intravenous treatment administration (each additional sequence)	$66	Physicians' Fee and Coding Guide[12] (HCPCS code 96417)
Hematology Panel	$11	Physicians' Fee and Coding Guide[12] (HCPCS code 82025)
Liver Function Test	$8	Physicians' Fee and Coding Guide[12] (HCPCS code 80076)

*Inflated to 2016 US dollars. They will be inflated to 2017 US dollars when an inflation index is available for 2017. All other costs reflect 2017 US dollars.

Adverse Event Costs

Adverse event costs will be derived from reasonable treatment assumptions used in previous analyses and the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUPnet).[21] Unit costs for each adverse event, except for cytokine release syndrome and B-cell aplasia, are stated in Table 13. The unit cost for a grade 3/4 episode of cytokine release syndrome will include the cost of tocilizumab and an ICU hospitalization.[1] The unit cost for B-cell aplasia will include the cost of intravenous immunoglobulin treatment for twelve months.[1] Costs of all adverse events are assumed to occur in the first model stage, except for B-cell aplasia.

Table 13. Adverse Event Unit Costs

Adverse Event (ICD-9-CM)	Mean ($)	Standard Error ($)
Abdominal pain (789.0)	$6,601	$7,148
Acute kidney injury (584)	$16,934	$20,817
Anxiety (300.02)	$5,209	$5,684
Chills (780.64)	$6,601	$7,148
Decreased appetite (783.0)	$9,676	$14,317
Delirium (780.09)	$8,082	$11,440
Diarrhea (787.91)	$7,688	$10,698
Encephalopathy (348.30)	$10,948	$12,165
Epistaxis (784.7)	$8,833	$18,629
Fatigue (780.71)	$7,303	$11,105
Febrile neutropenia (288.00)	$13,634	$22,204
Flushing (782.62)	$3,974	$4,548
Headache (784.0)	$6,956	$7,810
Hypogammaglobinemia (279.00)	$13,589	$15,145
Hypotension (458.9)	$8,158	$10,336
Hypoxia (799.02)	$8,265	$12,697
Infections-pathogen unspecified (686.9)	$7,493	$10,857
Nausea (787.02)	$6,077	$7,314
Pain in extremity (729.5)	$6,696	$10,172
Petechiae (782.7)	$8,100	$12,486
Pruritus (698)	$6,491	$7,608
Pyrexia (780.60)	$7,220	$9,826
Tachycardia (785.0)	$6,717	$9,431
Viral infectious disorders (079.99)	$6,148	$6,955
Vomiting (787.03)	$5,591	$7,482

All costs inflated to 2016 US dollars. They will be inflated to 2017 US dollars when an inflation index is available for 2017.

2.6 Model Outcomes

The model will estimate the length of time, on average, patients spend alive and disease free and alive with relapsed disease as well as the total health care costs to treat a patient. Unadjusted and utility-adjusted time spent in each health state will be summed across model cycles to provide estimates of life expectancy and quality-adjusted life expectancy.

Model outcomes of interest will include:

- By intervention:
    - Life years (undiscounted and discounted)
    - Quality adjusted life years (undiscounted and discounted)
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios (per life year gained and per quality-adjusted life year gained) for each intervention versus the comparator

2.7 Analysis

Each model cycle will last one month. Patient survival, quality-adjusted survival, and health care costs will be estimated for each model cycle and then summarized over a lifetime time horizon for each treatment option. Differences in survival, quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analysis

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above (including, but not limited to, stem-cell transplantation rate, manufacturing failure rate, and discount rate) as certain model parameters such as the discount rate. Probabilistic sensitivity analyses will also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we will perform a threshold analysis by systematically altering the price of the acquisition cost for each treatment option to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

Multiple scenario analyses will be conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions. First, given available evidence on patient health-state level costs and lost productivity to the patient and caregiver, the perspective will be expanded to a modified societal one. Second, palliative therapy will be modeled as a comparator instead of an active chemotherapy regimen to assess the absolute incremental cost and effectiveness of CAR-T therapies. Third, an outcomes-based reimbursement strategy (payment of CAR-T only for responders within different assessment time points such as one month and one year) will be modeled.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

2.8 Acknowledgements

This report was drafted by University of Colorado Skaggs School of Pharmacy researchers (Melanie D. Whittington, PhD; Jonathan D. Campbell, PhD; and R. Brett McQueen, PhD) in collaboration with the Institute for Clinical and Economic Review (ICER) staff and University of California San Francisco researchers.

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