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

Research Protocol

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Institute for Clinical and Economic Review

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Background and Overview

Background

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.[1] The usual treatment for childhood ALL consists of induction, consolidation, and maintenance chemotherapy. Over the past few decades, treatment has improved dramatically and the five-year survival rate, which is considered 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 autologous stem cell transplant 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. Typical treatments for relapsed/refractory ALL include re-induction therapy with different chemotherapy drugs; clofarabine, which has been used as a bridge to stem cell transplant with some success; and allogeneic stem cell transplant for appropriate patients who attain remission with salvage treatment. Stem cell transplant has been associated with improved survival in some children, but has been associated with an increased mortality in infants.[5,6] 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) and accounts for about 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.[7]

DLBCL is an *aggressive* (i.e., fast-growing) lymphoma that can arise in lymph nodes or 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 includes radiation and systemic chemotherapy plus rituximab. Rituximab is a monoclonal antibody that targets the CD20 antigen, which is a protein expressed in high concentration on the surface of B cells and not on the surface of other cells in the body. The addition of rituximab has markedly improved survival in patients with DLBCL. Five-year survival with this regimen is approximately 95%. Options are fewer for those patients whose cancer is refractory to therapy or who relapse after initial therapy. If patients do not respond to second-line chemotherapy, then they are

considered for autologous stem cell transplant. However, even after stem cell transplant, five-year disease-free survival is only about 10-20%.[8-10] Thus, new treatment options are needed.

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

Chimeric antigen receptor T-cell (CAR-T) therapy is a novel cellular therapy that uses genetic engineering to alter a patient's own T-cells to produce unique receptors on their cell surface that recognize a specific protein. The CAR-T therapies of interest in this review target the CD19 antigen on B cells, which are the cancer cells in B-ALL and the aggressive B-cell NHLs described above.

There are two CAR-T therapies being evaluated in this review. The first, manufactured by Novartis, is tisagenlecleucel (Kymriah™ [CTL-019]), which was approved by the FDA on August 30, 2017.[11] The second, manufactured by Kite Pharma, is axicabtagene ciloleucel (axi-cel [KTE-C19]). Both therapies require leukapheresis, a process that allows T-cells to be removed from the patient's body. The cells are then shipped to a central facility that engineers the CAR T-cells, which are then infused back into the patient's bloodstream to fight the cancer.

As the CAR T-cells fight the cancer they release cytokines, which are chemical messengers used by cells to communicate with each other. A side effect of CAR-T therapy is cytokine release syndrome, in which the release of many cytokines by the CAR T-cells causes high fevers and low blood pressure requiring intensive care unit (ICU) care. This serious side effect has been observed in about one-third of patients treated with CAR-T therapy and appears to be related to the volume of cancer cells at the time of treatment.[12]

Studies of tisagenlecleucel have primarily focused on patients with relapsed/refractory B-ALL up to the age of 25 years.[13-15] In addition, Novartis has announced that it will be seeking an FDA indication for tisagenlecleucel to treat relapsed/refractory DLBCL later this year and has plans to file for other indications in 2018.[16] Studies of axicabtagene ciloleucel have focused on patients with relapsed/refractory aggressive NHL.[17-20]

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 cytokine release syndrome, and their costs relative to other therapeutic approaches. The clinical evidence to date is limited to single-arm trials with short median follow-up time, and as of yet there are no real-world data on clinical benefits and/or harms.

Overview

This project will evaluate the health and economic outcomes of CAR-T therapies for B-cell cancers. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically

captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[21]

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 paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *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: *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 or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS related elements: Patient, Interventions, Comparisons, Outcomes, Timing, and Setting.

Populations

The two separate populations of interest for the review are:

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 relapsed/refractory aggressive B-cell lymphoma (DLBCL, TFL, PMBCL)

Interventions

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

Comparators

In the leukemia population, we intend to compare CAR-T therapy to palliative therapy, clofarabine-based therapy, and to blinatumomab-based therapy.[22]

In the lymphoma population, we intend to compare CAR-T therapy to salvage chemotherapy regimens such as those used in the SCHOLAR-1 study.[23]

Because there are no randomized trials comparing CAR-T therapy to salvage chemotherapy, any comparisons will be at risk for selection bias. We will carefully describe the populations in each of the trials including the number of prior chemotherapy lines that failed, prior stem cell transplants, age, blast levels, and other important prognostic features. Similarly, we will describe 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.[24]

Outcomes

The primary goal of treatment is to cure the cancer. Overall survival is 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 stem cell transplant subsequently. We will describe any stem cell transplants that follow treatment with CAR-T therapy or the comparator therapies.

Table 1. Key Outcomes and Harms

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

Timing

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

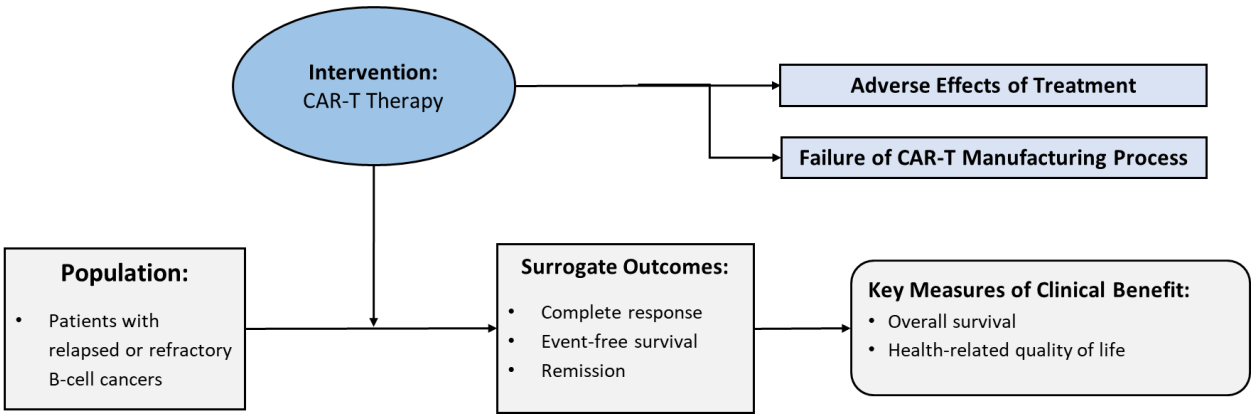
Settings

All relevant settings will be considered including inpatient, clinic, and outpatient settings.

Analytic Framework

The general analytic framework for assessment of therapies for B-cell cancers is depicted in Figure 1 below.

Figure 1. Analytic Framework: CAR-T Therapy for B-cell Cancers



Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on CAR-T therapies for B-cell cancers will follow established best methods.[25,26] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. The search will be limited to English-language studies of human subjects and will focus on trials of at least three months duration; articles indexed as guidelines, letters, editorials, narrative reviews, or news items will be excluded.

The search strategies include 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 Tables 1-6 on the following pages. In order to supplement the above searches and ensure optimal and complete literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

Table 1. Medline search for B-cell 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 2. 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 3. Cochrane Central Register of Controlled Trials search for B-cell 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 4. 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 5. Embase search for B-cell 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 6. 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

Selection of Eligible Studies

After the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. The titles and abstracts of all publications identified through electronic searches per the inclusion and exclusion criteria defined by the PICOTS elements. No study will be excluded at abstract-level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

- Two reviewers will extract information from the full articles.
- Extracted data will be reviewed for consistency.

Information from the accepted studies will be extracted into data extraction forms (see Appendix B), which will also be validated.

Publication Bias Assessment

We will scan the ClinicalTrials.gov site to identify studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies, in order to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. Evidence table shells are presented in Appendix B: Data Extraction Summary Table Shells.

We will not attempt to conduct network meta-analyses (NMA) or other quantitative syntheses of data, as the trials of CAR-T therapy are all single arm studies, so there is no method for estimating incremental benefit nor is there a common comparator to use to generate indirect comparisons.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[27] Additional explanation of each item can be found in Liberati et al. 2009.[28]

Section/Topic	#	Checklist Item	Reported on Page #
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 and (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., health care 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.	

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Appendix B. Data Extraction Summary Table Shell

Table B1. Summary of the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Study	Medication	N planned therapy	N received therapy	Median F/U, (months)	Age, years	Prior Lines Chemo	Prior SCT	Apheresis Turnaround Time

Table B2. Inclusion/Exclusion Criteria for the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Study	Inclusion	Exclusion	Co-intervention

Table B3. Baseline Characteristics of the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Medication	Median Age	Median Weight	%F	Primary diagnosis	ECOG PS	Disease Stage	Baseline Performance Status	Refractory Category	Other

Table B4. Quality Assessment of the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Comparable Groups	Maintain Comparability	Double blind	Measurements Equal and Valid	Clear Definition of Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality

Table B5. Key Outcomes of the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Group	OS	CR	PR	% Dead Before Response Assessment	% Achieving no Response	Duration Remission	Allo-SCT	Auto-SCT	Other

OS: Overall Survival, median in months

RFS: Relapse free survival, median in months

CR: Complete response, %

PR: Partial response, %

Table B6. Key Harms in the Clinical Trials of CAR-T Therapy for B-cell ALL

Reference	Group	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

AE: Adverse events

CRS: Cytokine release syndrome

Table B7. Summary of the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Study	Treatment	N planned therapy	N received therapy	Median F/U, (months)	Age, years	Prior Lines Chemo	Prior SCT	Apheresis Turnaround

Table B8. Inclusion/Exclusion Criteria for the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Study	Inclusion	Exclusion	Co-intervention

DLCBL: Diffuse Large B Cell Lymphoma
PMBCL: Primary Mediastinal B Cell Lymphoma
TFL: Transformed Follicular Lymphoma

Table B9. 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	IP Risk Classification	Refractory Category

Table B10. 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

Table B11. Key outcomes of the Clinical Trials of CAR-T Therapy for Aggressive B-cell Lymphoma

Reference	Study	Drug	OS	CR	PR	% dead Before Receiving Therapy	% achieving no response	Duration Remission	Allo-SCT	Auto-SCT	Other

OS: Overall Survival Median in Months

RFS: Relapse free survival, median in months

CR: Complete response, %

PR: Partial response, %

Table B12. 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

AE: Adverse events

CRS: Cytokine release syndrome

NP: Neutropenia

LP: Leukopenia