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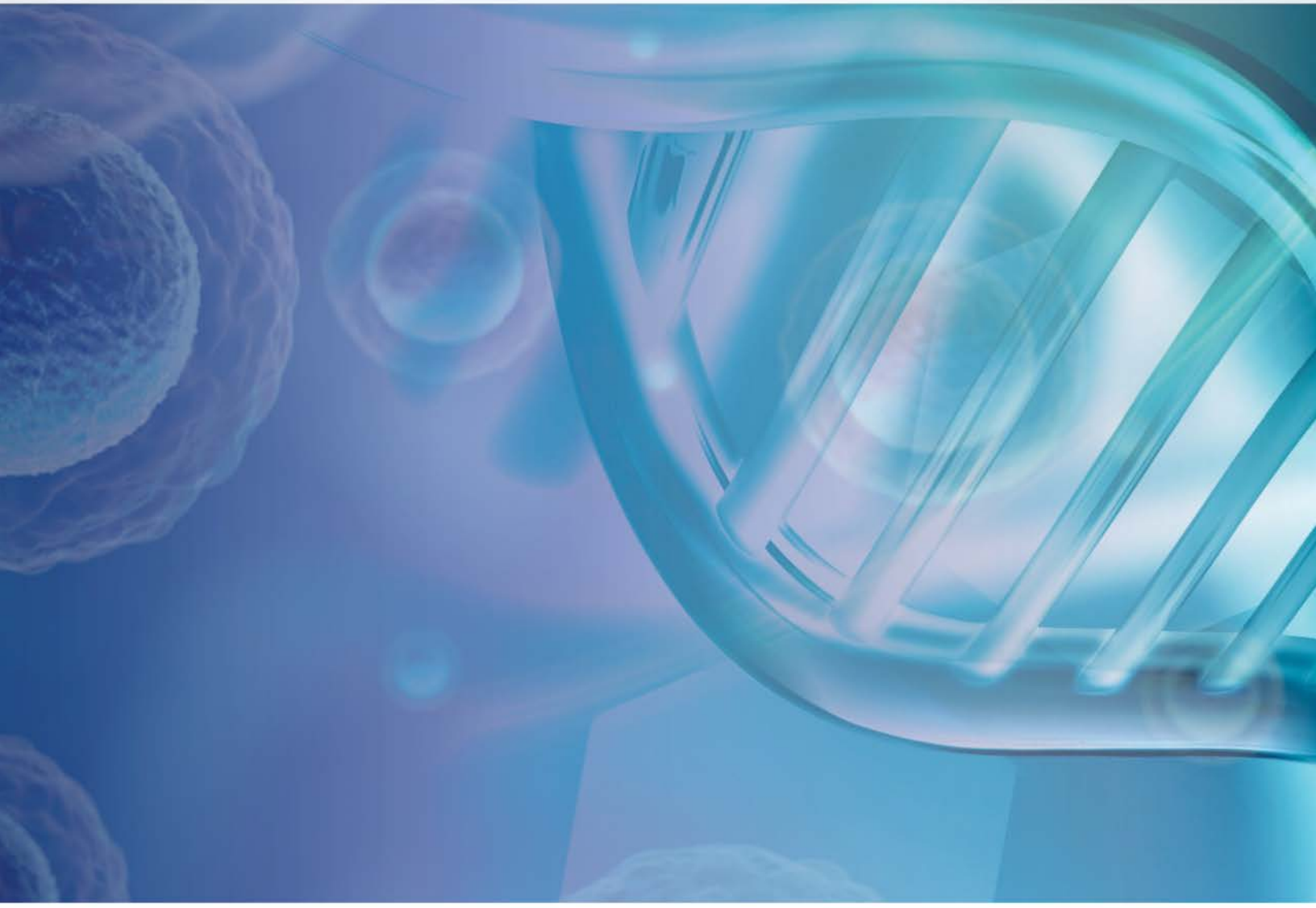

B-cell Lymphoma and Non-Hodgkin's Lymphoma Treatment:

How Do Participants of Chimeric Antigen Receptor T-cell (CAR-T) Therapy Research Studies Compare With Patients in the US Population?

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Conflicts of interest

The authors have no conflicts of interest to declare.

Abstract

Human gene therapy has evolved rapidly, and chimeric antigen receptor T-cell (CAR-T) therapy appears to be a promising treatment for B-cell lymphoma and non-Hodgkin's lymphoma. In 2017, the US Food and Drug Administration approved 2 CAR-T interventions, Kymriah (Tisagenlecleucel) and Yescarta (Axicabtagene ciloleucel), to treat adult relapsed or refractory B-cell lymphoma. Disease severity justified not performing controlled trials, and phase II trials provided the strongest evidence at the time for efficacy. A third CAR-T intervention, JCAR017 (Lisocabtagene maraleucel), is also under consideration for approval to treat adult non-Hodgkin's lymphoma and B-cell lymphoma. However, it is unclear whether treatment response to CAR-T therapy is the same outside of trial settings, as study participants may differ in important ways from the general population with the same diagnosis. We sought to address this concern by comparing CAR-T trial and participant characteristics with a population-based sample of adult non-Hodgkin's lymphoma and B-cell lymphoma patients.

We reviewed study populations in CAR-T studies for treatment of adult B-cell lymphoma and non-Hodgkin's lymphoma. Although we searched for both experimental and observational studies, all identified studies were trials, predominantly single-arm trials. To describe the general population with comparable diagnoses for CAR-T, we used the US Surveillance, Epidemiology, and End Results (SEER) 18 1975-2016 data for patients diagnosed with non-Hodgkin's lymphoma and B-cell lymphoma between 2000 and 2015. We compared participant eligibility criteria for the research studies and characteristics of study participants against those of the SEER non-Hodgkin's lymphoma and B-cell lymphoma population.

Available trial data made it impossible to definitively compare demographics, comorbidities, or disease severity between trial participants and the SEER population. However, trial participants appeared to be younger and include more males compared with the SEER population. Furthermore, comorbidity in trial participants may have been lower than that of the SEER population, as most trials restricted participation by patients with comorbidities that would interfere with treatment or assessment. Trials also often enrolled only patients with relapsed disease that was refractory to prior treatment. Finally, the length of follow-up in trials was shorter than the average survival time of patients documented in the SEER population.

Treatment effectiveness among the general patient population may be lower than in research studies because trials were designed to demonstrate efficacy in patients with severe disease. CAR-T may also be less effective for patients in the general population, who may have more comorbidities than did trial participants. However, treatment may be more successful in general practice with patients whose disease is not as advanced as that observed in study participants. Although we found no published observational studies, newly established CAR-T patient registries aim to follow patients for longer than their untreated life expectancy. In the future, these registries may provide information about how treatment effectiveness might vary between trial participants and the general population. In the meantime, understanding differences between the trial populations and the comparable SEER population provides some insight into how these therapies will function in general practice.

Report purpose

Genetic therapy is a rapidly evolving field in medicine. Given the increase in approved therapies, the Patient-Centered Outcomes Research Institute (PCORI) commissioned a landscape review and evidence map in 2019. In response, we published 2 reports that reviewed the published trial findings of therapies that met the FDA's definition of gene therapy.[1] The second of these reports reviewed chimeric antigen receptor (CAR)-T-cell therapies, which are of increasing interest in cancer treatment. In 2017, the FDA approved 2 CAR-T therapies, Yescarta (Axicabtagene ciloleucel) and Kymriah (Tisagenlecleucel), to treat adults with relapsed or refractory large B-cell lymphoma. In our review, we also identified JCAR017 (Lisocabtagene maraleucel), which is a CAR-T intervention in the research pipeline that may gain FDA approval to treat adults with non-Hodgkin's lymphoma and multiple types of B-cell lymphoma. Due to the severity of the disease these treatments target, the FDA did not require randomized control trials for Yescarta and Kymriah before approving the interventions, and the best evidence available at the time did not include untreated control groups. While such approval decisions may reflect how unmet medical need can outweigh risk, the lack of internal control groups in the studies limited investigators' ability to compare treatment outcomes. Given the lack of controlled comparison groups, as well as the limited duration of patient follow-up and small sample sizes characteristic of such studies, it is unclear whether treatment response among the general population with the same diagnosis would be as positive as it was for those enrolled in the trials.

The purpose of this report was to compare participants in the CAR-T research studies that support Yescarta and Kymriah approval against adults in the general population with adult non-Hodgkin's and B-cell lymphomas. We used the US Surveillance, Epidemiology, and End Results (SEER) database as the sample of those patients with these diagnoses in the general population, comparing their characteristics with those of trial participants to understand whether these 2 populations with the same lymphoma diagnoses differed. If the trial participants were not representative of the general population, then it is possible that treatment outcomes will differ in the general population. We describe research study eligibility criteria, characteristics of included participants, length of follow-up, and any relevant treatment success biomarkers in relation to the SEER population characteristics.

Methodology

The project builds on the 2 reports described above,[2,3] which described the results of a landscape review of multiple data sources on gene therapies. In this report, we updated the literature search (April 2020) and now focus on CAR-T interventions for the adult treatment of non-Hodgkin's or B-cell lymphoma.

Research studies

We searched multiple data sources to ensure we identified all current gene therapy interventions. To collect evidence about the CAR-T interventions in adult patients with non-Hodgkin's or B-cell lymphoma, we searched for empirical published literature in the research databases PubMed, EMBASE, and the Web of Science. Searches were executed by an Evidence-based Practice Center librarian experienced in transparent and comprehensive literature searches. The search strategy is shown in Appendix A.

Two independent reviewers screened search outputs. All citations deemed potentially relevant by at least one reviewer were obtained as full text. Full text publications were screened against the eligibility criteria. We documented the reasons for exclusion in a citation management database. One reviewer abstracted and appraised publications, and content and methodological experts checked summaries. We applied explicit inclusion and exclusion criteria designated a priori:

- Participants: Human adults (aged 18+ years)
- Interventions: Axicabtagene ciloleucel (Axi-cel, Yescarta); Tisagenlecleucel (Kymriah); Lisocabtagene maraleucel (JCAR017, Liso-cel); and unnamed CAR-T interventions
- Comparator: Any comparator or no comparator studies
- Outcomes: Disease-related effectiveness/benefit indicators such as complete response (eg, remission), partial response, disease recurrence, mortality, patient-centered outcomes including psychosocial outcomes such as anxiety and worry, and treatment-associated adverse events/harms (eg, cytokine release syndrome)
- Timing: Any treatment duration and follow-up of included studies
- Setting: Any geographic location and medical setting
- Study design: Primary research studies in English since 1989. Studies published only as a conference abstract without trial record or full text publication were excluded.

The literature flow diagram is shown in Appendix B.

We used a standardized form with explicit and pilot-tested categorization rules to extract data. All reports of the same participants were consolidated into one study entry. The results of the data abstraction are shown in Appendix C.

Patient population

We used the SEER 18 1975-2016 Research Data full data files (https://seer.cancer.gov/data/). We used incidence data from all regions in the data files containing leukemia and lymphoma cases, although we excluded Louisiana cases in 2005 because Hurricane Katrina disrupted reporting. We limited diagnosis dates to 2000-2015, since the values for the 2016 lymphoma subgroup variable were missing for the year 2016. Data were processed by a research programmer experienced in using SEER data.

Frequencies for all patients with non-Hodgkin's lymphomas contain subtypes 7 to 45 and frequencies for patients with large B-cell lymphoma contain subtypes 8 to 26. After limiting to non-Hodgkin's lymphomas, we deduplicated records by patient. We kept the first diagnosis for each patient, unless a later diagnosis was for a higher-priority subtype because it was a more specific diagnosis. For example, if a patient had a diagnosis of primary mediastinal B-cell lymphoma after a diagnosis of a different type of diffuse large B-cell lymphoma, we kept the record with the primary mediastinal B-cell lymphoma diagnosis.

Lymphomas in the dataset were categorized into primary mediastinal B-cell, follicular, mantle-cell, diffuse large B-cell, large B-cell, or non-Hodgkin's, based on the lymphoma subtype. Since some of the cancer types of interest were subtypes of larger groups, we used a hierarchy to categorize patients according to cancer type by prioritizing the most specific level of cancer type for which they received a diagnosis, as shown in Table 1. In the cases in which a patient was diagnosed with multiple cancers we prioritized as level 2, we categorized them as the cancer type that was first diagnosed.

Table 1. Lymphoma Types and Priority Ranking to Categorize Patients' Cancer

Lymphoma Type	Priority
Primary mediastinal B-cell lymphoma	1
Follicular lymphoma	2
Mantle-cell lymphoma	2
Diffuse large B-cell lymphoma	2
Large B-cell lymphoma	3
Non-Hodgkin's lymphoma	4

Prior to deduplication of reports, we limited the sample to patients with a current age of 18 years or older. SEER provides survival months calculated as number of months from diagnosis to date of last contact or study cutoff date and vital status. Since only the birth year is recorded, current age is not exact and is calculated as of the end of the date of last contact or study cutoff. We calculated current age using birth year, date of diagnosis, and survival months.

We used the race and origin recode variables to create a race/ethnicity variable (Hispanic, white, black, American Indian/Alaskan Native, Asian or Pacific islander, or unknown).

To capture disease progression, we report the Ann Arbor stage, which is a classification system developed by the American Joint Committee on Cancer for describing the extent of disease progression in cancer patients.[4] Comorbidity data were not available.

Description of Yescarta, Kymriah, and JCAR017

CAR-T is a specific application of autologous cell therapy in which patients' T cells are removed, genetically modified to attack specific cancer cells, and then infused back into the patient.

- Yescarta (Axicabtagene ciloleucel) was approved in 2017 to treat relapsed or refractory large B-cell lymphoma after significant health benefits were reported in a phase II multicenter trial with 111 adult patients.[5] Despite adverse events, including death and neurologic events, the objective response rate (calculated as the combined rates of complete response and partial response) was 82%, and the complete response rate was 54% after a median of 7.9 months of follow-up, which attenuated to 40% after a median follow-up of 15 months.
- Kymriah (Tisagenlecleucel) gained approval in 2018 to treat adult patients with relapsed or refractory large B-cell lymphoma, after a phase II trial involving 28 adult patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma.[6] Complete remission occurred in 6 of 14 patients (43%) with diffuse large B-cell lymphoma at 6 months. At a median follow-up of 28 months, 86% of the diffuse large B-cell lymphoma patients and 89% of the lymphoma patients who responded to treatment maintained the response.
- JCAR017 (Lisocabtagene maraleucel) is a CAR-T therapy to treat non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, and primary mediastinal B-cell lymphoma. While the FDA has not yet approved

JCAR017, Celgene announced in its second quarter of 2019 that it would file for approval in the fourth quarter of 2020.

CAR-T therapies Kymriah and Yescarta are expected not to require repeated administrations, providing a unique advantage for patients. However, therapy expectations may rest on unproven assumptions since trials would need to follow participants past their life expectancy to provide evidence that CAR-T treatment can cure B-cell lymphoma and non-Hodgkin's lymphoma in the general population. Both Yescarta and Kymriah have been shown to have a durable response, as documented in the CAR-T evidence table in Appendix C.[5,7] However, short follow-up of treated patients and small study samples threaten the strength of the positive treatment findings.

Studies that support Yescarta, Kymriah, and JCAR017 FDA approval

We sought to extract information about trial participants that may suggest which patients might benefit more or less from treatment. In addition to demographic and clinical eligibility criteria, we also searched for reported disease stage, comorbidities, and biological markers, such as genetic polymorphisms. We did this with an eye toward examining whether differences between trial participants and the SEER population might suggest variation in treatment effectiveness.

In Appendix C, we describe the 15 studies that used a CAR-T intervention to treat adults with either diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, primary mediastinal B-cell lymphoma, or non-Hodgkin's lymphoma. We also searched for observational studies of CAR-T treatment in general practice, but all identified research studies were experimental studies, predominantly single-arm trials. All studies were based in the United States. Two studies treated patients with the named intervention Yescarta[5,8] and one study treated patients with Kymriah.[7] The remaining studies described the treatments mechanistically as either a CD19- or CD20-type CAR-T intervention.[6,9-19] These could, but not necessarily, have tested 1 of the 3 studied agents. The most common design in ongoing studies is a single-arm trial (80%)[5-9,11-14,16,17,19] followed by clinical trials with multiple study arms in which patients are treated with different doses of the same intervention (20%).[10,15,18]

Age was the only demographic eligibility criterion in most studies (80%).[5-9,11-13,15,16,19] All but one study[12] required patients to be older than the age of 18. The one study that included children (ages 6 and older) did so because the investigators also tested treatment for pediatric acute lymphoblastic leukemia. We did not include the pediatric sample in our analyses. We did not find any studies with explicit race/ethnicity or sex eligibility criteria. Clinical eligibility criteria were more extensive: We present common criteria in Table 2. The most common clinical eligibility criterion was the absence of any comorbidity that would interfere with treatment or assessment of treatment effectiveness (94%).[5,7-19] The next most common criterion was the requirement that patients had relapsed disease that had become unresponsive to prior treatments (87%).[5,7-15,18,19]

More than half of the studies required that female patients could not be pregnant, and all patients had to agree to use contraception (67%).[5,7,10-15,17,18] Similarly, more than half of studies required that patients had histologically confirmed CD19 or CD20 expression (60%)[6,9,12-18] or a given life expectancy (53%).[7,10,11,13-15,17,18] A third of the studies included clinical eligibility criteria that required patients to be able to understand what the treatment entailed.[11-15] Fewer

studies restricted study participation to patients who had never undergone prior CAR-T or gene therapy (27%)[5,7,8,19] or prior stem-cell transplant (27%).[7,8,13,15] We list detailed clinical eligibility criteria in the evidence table in Appendix C.

We define 5 categories of CAR-T effectiveness at reducing or eliminating symptoms of non-Hodgkin's or B-cell lymphoma: durable improvement (ie, reduction in symptoms for at least 1 year with a single course of treatment); sustained improvement (ie, reduction in symptoms for at least 1 year with multiple courses of treatment); improvement (ie, reduction in symptoms for less than 1 year); no improvement (ie, intervention does not improve symptoms compared with control); or deterioration (ie, intervention worsens symptoms compared with control, including treatment-related mortality). The category unclear was used when the reporting was insufficient to assess treatment success. More than half of the studies reported durable improvement.[5-8,11-13,15] For example, Locke et al reported that the proportion of 108 patients treated with Yescarta with progression-free survival at 24 months was 72%.[8] Sustained improvement was observed in 27% of the studies.[9,10,18,19] One study (7%) reported improvement,[14] and treatment effect was unclear in 2 studies (13%).[16,17]

No studies reported an assessment of biological markers (eg, genetic) that had been linked to treatment success. We were not able to identify any studies that reported a characteristic (eg, genetic) that could potentially predict whether CAR-T therapy would result in favorable outcomes.

Table 2. Eligibility Criteria in CAR-T Studies Treating Adults With Non-Hodgkin's Lymphoma or B-cell Lymphoma (N = 15)

Intervention	N (%)
Yescarta (Axicabtagene ciloleucel)	2 (13.3)
Kymriah (Tisagenlecleucel)	1 (6.7)
CD19- or CD20-type CAR-T cell intervention	12 (80.0)
Demographic eligibility criteria – N (%)	
Specified an age criteria	12 (80.0)
Clinical eligibility criteria – N (%)	
No comorbidity that would interfere with treatment/assessment	14 (93.3)
Refractory/prior treatment	13 (86.7)
Not pregnant/contraception use	10 (66.7)
CD19 or CD20 expression	9 (60.0
Given life expectancy	8 (53.3)
Adequate cognition/understanding of treatment	5 (33.3)
No prior CAR-T or gene therapy	4 (26.7)
No prior stem-cell transplant	4 (26.7)

Comparison of study participants and SEER population

In Table 3 we present the patient characteristics of those who participated in the CAR-T studies and those from the SEER populations with comparable indications. The CAR-T studies include a much smaller sample of potentially eligible participants (n = 522) than does the SEER population (n = 417 492).

The CAR-T studies included participants who may have been younger than those in the SEER population. Studies reported age in a variety of ways, including categorically as a series of age bands (eg, 21-30, 31-40) or as measures of central tendency, such as medians and means (along with range). We could not estimate age statistics across the participant samples that could be used to directly compare the ages of study participants versus patient ages in the SEER population. Therefore, we summarized age across studies as having an age range that was either less than 70 years of age or older than 70 years of age (see Appendix C). About half the studies included only patients younger than 70 years of age (47%).[8,9,12-16] In the SEER population, 42% were younger than the age of 70 at the time of their last contact in 2015.

All CAR-T studies reported gender. The CAR-T study participants were more likely than the SEER population to be male. The average of the reported proportions of female participants across studies was 32% while 44% of the SEER population was female.

Among the 15 CAR-T studies, 12 followed patients for a shorter time than the average survival time seen in the SEER population. Trial follow-up was on average 46 months, with a range of 12 to 180 months. The SEER database tracks survival time of patients to 57 months on average, with a range of 0 to 203 months.

It is difficult to compare CAR-T study participants' diagnoses with those in the SEER population since trials included groups of patients with multiple types of diagnoses. Most commonly, studies included patients with a mix of lymphoma diagnoses, including B-cell lymphoma (60%).[6,9,10,12-17] Only a few studies tested treatments on groups of patients with indications only for diffuse large B-cell lymphoma (7%), mantle-cell lymphoma (7%), primary mediastinal B-cell lymphoma (7%), or non-Hodgkin's lymphoma (7%).[5,7,8,11,18,19] In the SEER population, the most common indication was large B-cell lymphoma (52%), followed by diffuse large B-cell lymphoma (23%), follicular lymphoma (12%), non-Hodgkin's lymphoma (10%), mantle-cell lymphoma (3%), and primary mediastinal B-cell lymphoma (0.2%).

Only 5 studies reported patients' disease stage[5,7,8,18]: 24% to 43% of patients were categorized as either stage I or stage II. Patients with either stage III or stage IV disease appeared to be more common in these 5 CAR-T studies; the proportion ranged from 11% to 88%. In contrast, 24% of the SEER population were either stage I or II and almost 30% were categorized as stage III or IV.

Studies did not report race/ethnicity, but the SEER population with similar indications was mostly white (73%), followed by Hispanic (11%), black (10%), Asian or Pacific Islander (5%), unknown race/ethnicity (1%) and American Indian/Alaskan Native (0.4%).

Table 3. Participants in CAR-T Studies With Non-Hodgkin's Lymphoma or B-cell Lymphoma and SEER Adult Population

Descriptors	CAR-T Studies[a] (N = 15 Studies)	SEER Population (N = 417 492)
Proportion age of population[b]		
Aged < 70 years	46.7	42.2
Aged 70+ years	46.7	57.1
Not reported	6.7	NA
Proportion female participants[c]	32 (11-53)	44.3
Proportion male participants[c]	68 (47-89)	55.7
Proportion non-Hodgkin's indication[d]		
Diffuse large B-cell lymphoma	6.7	23.0
Large B-cell lymphoma	13.3	52.5
Mantle-cell lymphoma	6.7	2.5
Non-Hodgkin's lymphoma	6.7	10.3
Primary mediastinal B-cell lymphoma	6.7	0.2
At least 2 of the above	60.0	
Months of follow-up – mean (SD; min-max)	45.6 (55.1) [12-180]	NA
Months of survival – mean (SD; min-max)[e]	NA	57.1 (52.8) [0-203]
Proportion stage[f]		
Stage I or II	24-43	23.7
Stage III or IV	11-88	28.4
Proportion treatment effect		
Durable improvement	53.3	NA
Sustained improvement	26.7	NA
Improvement	6.7	NA
Unclear	13.3	NA

Abbreviations: CAR-T, chimeric antigen receptor T cells; NA, not applicable; SEER, US Surveillance, Epidemiology, and End Results.

[a] Treating non-Hodgkin's/B-cell lymphoma in 522 participants.
[b] CAR-T studies: Using range reported; SEER: using age at last contact by end of 2015.
[c] CAR-T studies: average percentage (min-max); SEER: percentage.
[d] CAR-T studies: using number of studies patient population diagnoses; SEER: percentage.
[e] Individuals in SEER N = 41 4181.
[f] CAR-T studies: percentage range reported in 5 studies; SEER: Ann Arbor stage, 43.7% NA, 4.3% unknown.

Implications of differences between study participants and the SEER population

We compared participants enrolled in the CAR-T studies against the SEER population with the same diagnosis and found several differences. We could not test for statistical significance because the unit of analysis in the CAR-T sample is study and the unit of analysis in the SEER sample is individual. Study participants seemed to be younger than the SEER population, were more likely to be male (and, by extension, less likely to be female), and were more likely to have refractory disease than the SEER population.

Over three-quarters of studies reported reduced symptoms for more than a year among patients treated with CAR-T.[5-13,15,18,19] Such positive findings support the FDA's approval of Kymriah (Tisagenlecleucel) and Yescarta (Axicabtagene ciloleucel) and potentially of JCAR017 (Lisocabtagene maraleucel) to treat adult non-Hodgkin's and B-cell lymphomas. However, participants were not followed in these studies for as long as the population's average expected survival duration, as reported in the SEER database. The length of study follow-up was 46 months on average, compared with the average survival of 57 months in the SEER population. Study follow-up duration may have been sufficient to demonstrate safety and efficacy, but to establish evidence that the treatment cured the disease would require following patients longer than their expected lifetime. However, 8 studies included Kaplan-Meier survival curves.[5-7,9,12,16,19]

On the one hand, we found reasons to believe that non-Hodgkin's lymphoma and B-cell lymphoma patients in the general population may fare better with CAR-T treatment than trial participants. Most identified research studies required that participants have relapsed disease refractory to prior treatment.[5,7-15,18,19] This suggests that study participants may have had more severe disease than adults in the general population with the same diagnosis. Treatment may be more successful in general practice with patients whose disease is not as advanced as that observed in study participants. On the other hand, we also found evidence that suggests treatment in CAR-T trials had an advantage. Trials that limited enrollment to only those patients with the most advanced disease could have improved investigators' ability to observe treatment efficacy. Treatment effectiveness can usually be assumed to be lower than initial efficacy estimates from trials. In addition, study participants did not have any comorbidities that could interfere with treatment, so in this respect they may have been healthier than their counterparts in the general population; SEER does not report on comorbidities. Given these competing factors and uncertainty, it is not clear how treatment effectiveness or durability would differ in real-world settings outside of research trials.

Reporting differences between the trials and the SEER database limit comparisons across populations. Trial reports aggregated participant characteristics in a variety of ways, whereas SEER reported individual patient-level data. As a result, we could not compare characteristics across populations at the true individual level. Comparisons should thus be interpreted with caution. Race/ethnicity was not reported in any of the studies; thus, it is not possible to assess how genetic ancestry in the study participant samples compares with the general population. Relatedly, studies did not report predictors of treatment response, such as biomarkers, and it was not possible to review the evidence base for predictors of treatment response.

Compared with the sample size of 522 participants in the CAR-T studies, SEER provides a large database of cancer patients in the United States, of which 417 492 patients had the same

diagnosis as the study participants. Study participants are likely included in the SEER population. If there is overlap in our samples, then any similarities we observe in our comparisons may be inflated.

While SEER reports detailed disease diagnosis data, we were not able to characterize comorbidities or clinical characteristics. This limits our ability to compare the disease burden between the SEER population and study participants. In addition, since investigators described trial participants as groups that included patients with multiple types of lymphoma, it is unclear how differences in actual diagnosis might impact treatment effectiveness outside of study trials. Based on the available information and differences we found between study participants and the SEER population, we cannot predict the direction of any differences in outcomes between trials and practice.

Assessing the potential success of CAR-T treatment for adults with non-Hodgkin's and B-cell lymphomas in general practice will require long-term observational studies and registries. Several registries have now been established. The Center for International Blood & Marrow Transplant Research recently announced collaborations between Kite Pharma and Novartis to track long-term outcomes of patients treated with Yescarta (Axicabtagene ciloleucel) and Kymriah (Tisagenlecleucel), respectively.[20,21,22,23] Although we searched for published findings of registry data, we did not find any. However, we expect that registry data will eventually be reported. Findings from registries have the potential to demonstrate how treatment effectiveness may vary between trial participants and the general population and will advance our knowledge substantially.

In summary, our findings suggest that study participants had more severe disease than did adults in the general population with the same diagnosis. Treatment effectiveness may be lower than initial efficacy estimates from trials, and treatment may be less effective for patients in the general population, who are likely to have more comorbidities than trial participants, since a lack of comorbidity was often a criterion for study eligibility. However, it is not clear how treatment effectiveness or durability would differ in the general population. We found no published observational studies, but newly established CAR-T patient registries aim to follow patients for longer than their untreated life expectancy. These registries may provide information about how treatment effectiveness varies between trial participants and the general population in the future. In the meantime, understanding differences between the trial populations and the comparable SEER population may provide some insight into how these therapies will function in general practice.

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Please note that, where possible, we have included the links that will take you directly to the full text articles or have included the PubMed ID (PMID) for further information. The PMID is the record number in the free search engine PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) that contains more information on the publication.

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Appendix

Appendix A: Search strategy

PubMed
Run April 17, 2020
Publication date from November 1, 2018, Humans, English
kymriah[tiab] OR tisagenlecleucel[tiab] OR yescarta[tiab] OR "axicabtagene ciloleucel" OR jcar017 OR liso-cel AND (observational study[pt] or cohort stud*[tiab] or case control stud*[tiab] OR observational stud*[tiab])
Results: 0
Run December 13, 2019
Filters activated: Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial, Randomized Controlled Trial, Publication date from November 1, 2018, Humans, English
kymriah[tiab] OR tisagenlecleucel[tiab] OR yescarta[tiab] OR "axicabtagene ciloleucel" OR jcar017 OR liso-cel
Results: 1
No restrictions
Search run: March 19, 2020
(kymriah OR tisagenlecleucel OR yescarta OR "axicabtagene ciloleucel")
AND
"Rare Disease Research Network"
Results: 0
(kymriah OR tisagenlecleucel OR yescarta OR "axicabtagene ciloleucel")
AND
PCORnet OR "national patient centered clinical research network"
Results: 0

Ovid Medline
No restrictions
Search run: March 19, 2020
(kymriah OR tisagenlecleucel OR yescarta OR "axicabtagene ciloleucel")
AND
"Rare Disease Research Network"
Results: 0

Embase
Limits: ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [english]/lim AND [humans]/lim AND [embase]/lim AND [2018-2020]/py
Exclude: conference abstract
Kymriah:ti,ab OR tisagenlecleucel:ti,ab OR yescarta:ti,ab OR "axicabtagene ciloleucel" OR jcar017 OR liso-cel
Results: 11 – duplicates = 10

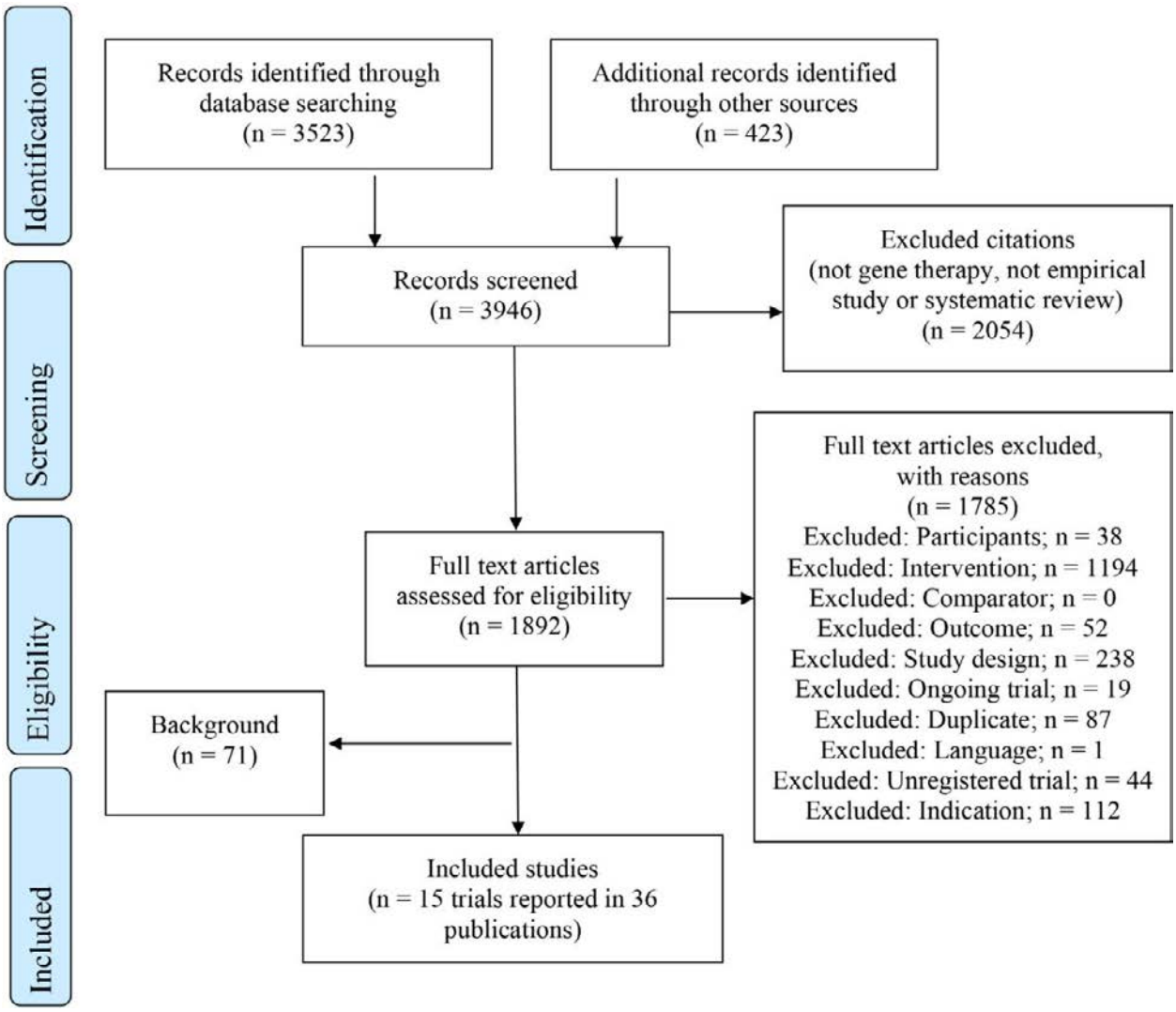
Web of Science
English: Article; Exclude: Proceedings papers
Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2018-2019
TS=(Kymriah OR tisagenlecleucel OR yescarta OR "axicabtagene ciloleucel" OR jcar017 OR liso-cel)
AND
TS=("randomized controlled trial") OR TS=(RCT) OR TS=("controlled clinical trial") OR TS=("clinical trial")
NOT
TS=(rat OR rats OR monkey OR monkeys OR primates OR primate OR macaque* OR mouse OR mice OR dog OR canine OR canines OR rabbit OR rabbits)
NOT
TI=("trial protocol") OR TI=("study protocol")
Results: 5 – duplicates = 5

ClinicalTrials.gov
Searching the "other" field – limiting to: Active, Not Recruiting, Completed, Suspended, Terminated, Withdrawn Studies
Study Start; Primary Completion; First Posted; Last Update Posted: November 1, 2018
Kymriah OR tisagenlecleucel OR yescarta OR "axicabtagene ciloleucel" OR jcar017 OR liso-cel
Results: 25
TOTAL: 41 (*note this number includes results pre-November 2018)

PCORnet
https://pcornet.org/
Run: March 19, 2020
Terms searched: CAR-T OR kymriah OR yescarta
Results: 1

Rare Disease Research Network
https://www.rarediseasesnetwork.org/
Run: March 19, 2020
Terms searched: CAR-T OR kymriah OR yescarta
Reference lists also scanned for these terms.
Results: 0

Appendix B: Literature flow diagram



Appendix C: Evidence tables of published trials

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
Baylor College of Medicine et al, 2014[17]; Xu et al, 2014[24] NCT00586391 Single-arm trial N: 14	Eligibility criteria (demographics): None Eligibility criteria (clinical criteria): Inclusion criteria: Recurrent B-cell lymphoma or leukemia (ALL or CLL), or newly diagnosed patients unable to receive or complete standard therapy, or diagnosis of intermediate B-cell lymphoma with a treatment plan that will include high-dose therapy and autologous stem-cell transplantation If a patient is < 18 years of age, the lymphoma/leukemia is highly aggressive (ie, lymphoblastic, Burkitt, ALL). Life expectancy of at least 12 weeks Recovered from the toxic effects of all prior chemotherapy before entering this study ANC Age range of population 500, HgB > 8.0 Bilirubin < 3 times the upper limit of normal AST < 5 times the upper limit of normal Serum creatinine < 3 times the upper limit of normal Pulse oximetry of > 90% on room air Karnofsky/Lansky score of > 60% Available autologous transduced peripheral blood T cells with ≥ 15% expression of CD19CAR determined by flow cytometry Patients or legal guardians must sign an informed consent indicating that they are aware this is a research study and have been told of its possible benefits and toxic side effects. Patients or their guardians will be given a copy of the consent form. Sexually active patients must be willing to utilize one of the more effective birth control methods during the study and for 3 months after the study is concluded. The male partner should use a condom.	Age group: Children and adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Mixed (with included lymphoma): B-cell lymphoma, chronic lymphocytic leukemia, and acute lymphocytic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: NR Average year of diagnosis: NR	Other: CD19CAR-28-zeta T cells Follow-up: 180	Adverse event data per patient, survival and function of CD19CAR-T cells, number of patients with tumor response, correlation of additional doses and cumulative rise in the percentage of circulating gene-modified cells Effect: Unclear: No in vivo human clinical data Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Exclusion criteria: History of hypersensitivity reactions to murine protein-containing products Pregnant or lactating Tumor in a location where enlargement could cause airway obstruction Currently receiving any investigational agents or have not received any tumor vaccines within the previous 6 weeks			
Brudno et al, 2016[16] Single-arm trial N: 20	Eligibility criteria (demographics): Inclusion criteria: Adults Eligibility criteria (clinical criteria): Inclusion criteria: Measurable CD19+ B-cell malignancies Previously undergone HLA-matched sibling or unrelated donor (URD) alloHSCT URD cells were acquired through the National Marrow Donor Program. Uniform CD19 expression on malignant cells by immunohistochemistry or flow cytometry was required. Except for patients with ALL or DLBCL, at least one prior DLI was required for enrollment. An Eastern Cooperative Oncology Group performance status of 2 or less and essentially normal major organ function were required. Exclusion criteria: Immunosuppressive drugs, which included systemic corticosteroids above physiologic dosing, were not allowed within 4 weeks before CAR19 T-cell infusion. Chemotherapy and antibody therapies were	Age group: Adults Proportion of female participants: 45% Race/ethnicity: Other (specify): NR Large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, mixed (with included lymphoma): diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, acute lymphoblastic leukemia, and chronic lymphocytic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 20-68 Average year of diagnosis: NR	Other: CD19 CAR-T cells Follow-up: 30	Stable disease, progressive disease, partial response, complete remission, minimal residual disease Effect: Unclear: Eight of 20 treated patients obtained remission, which included 6 complete remissions (CRs) and 2 partial remissions. The response rate was highest for acute lymphoblastic leukemia, with 4 of 5 patients obtaining minimal residual disease negative CR. Responses also occurred in chronic lymphocytic leukemia and lymphoma. The longest ongoing CR was more than 30 months in a patient with chronic lymphocytic leukemia. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	required to be stopped by 2 weeks before CAR19 T-cell infusion, and staging was always performed more than 2 weeks after the last therapy before CAR-T cell infusions. Patients with evidence of a GVHD of greater than grade I26 and patients with evidence of chronic GVHD >a mild global score were excluded.			
Kebriaei et al, 2016[9] NCT01492036[25] (patients from NCT00968760[26] and NCT01497184[27]) Single-arm trial N: 26	Eligibility criteria (demographics): Inclusion criteria: Autologous trial: Between 18 and 75 years of age Allogenic trial: Between 1 and 65 years of age Eligibility criteria (clinical criteria): Inclusion criteria: Autologous trial: Advanced CD19+ lymphoid malignancies, including NHL, small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and mantle-cell lymphoma beyond first relapse or primarily refractory to conventional treatment Allogenic trial: Patients have advanced CD19+ lymphoid malignancies, including NHL, SLL, CLL, follicular lymphoma, mantle-cell lymphoma, and ALL. Both trials: Available HLA-identical donor, HLA 8/8–matched unrelated adult donor, or haploidentical family donor Adequate organ function, a Zubrod performance status of 0 to 1 or Lansky ≥ 60%; no evidence of uncontrolled infection; and negative serology for hepatitis B, hepatitis C, and human immunodeficiency virus	Age group: Children and adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Non-Hodgkin's lymphoma, mixed (with included lymphoma): non-Hodgkin's lymphoma and acute lymphoblastic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 21-61 Average year of diagnosis: NR	Other: CD19-specific CAR-T cells Follow-up: 32	Complete remission Effect: Sustained improvement: Some patients received multiple administrations. Following autologous hematopoietic stem cell transplantation (HSCT), 83% were progression-free and 100% had survived at 30 months. After allogeneic HSCT, the respective 12-month rates were 53% and 63%, respectively. Predictor of effectiveness: Allogenic/autologous cells

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Exclusion criteria: Both trials: Known allergy to bovine or murine products Receipt of systemic corticosteroids within 3 days before, or experiencing any new clinically significant toxicity within 24 hours before, a T-cell infusion			
Kochenderfer et al, 2013[14] NCT01087294[28] Single-arm trial N: 10	Eligibility criteria (demographics): Inclusion criteria: Recipient: Patients must be 18-75 years of age Eligibility criteria (clinical criteria): Inclusion criteria: Recipient: Recipients (patients with B-cell malignancy) must have received an HLA-identical or 9/10-matched sibling allogeneic hematopoietic stem-cell transplant, a 1-antigen mismatched related transplant, or a ≥ 9/10-matched unrelated donor (URD) alloHSCT for any CD19+ B-cell malignancy. Patients with any CD19+ B-cell malignancy that is persistent or relapsed after all of the following interventions are eligible: Donor T-cell engraftment after alloHSCT (>50% donor chimerism of the T-cell compartment and a peripheral blood T-cell number from the NIH, CC clinical laboratory of at least 50 CD3+ cells/uL) A trial of withdrawal of immunosuppressive therapy Exception: Prior (DCI) DLI is not an eligibility requirement for patients with ALL, Burkitt lyphoma, ALL-like high-grade lymphomas, or diffuse large B-cell lymphoma.	Age group: Adults Proportion of female participants: 20% Race/ethnicity: Other (specify): NR Large B-cell lymphoma, mixed (with included lymphoma): diffuse large B-cell lymphoma, mantle-cell lymphoma, and chronic lymphocytic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 44-66 Average year of diagnosis: NR	Other: Allogenic anti-CD19-CAR-T cells Follow-up: 18	Complete response, partial response, stable disease, progressive disease Effect: Improvement: Three patients had regressions of their malignancies. One patient with chronic lymphocytic leukemia (CLL) obtained an ongoing complete remission after treatment with allogeneic anti-CD19-CAR-T cells, another CLL patient had tumor lysis syndrome as his leukemia dramatically regressed, and a patient with mantle-cell lymphoma obtained an ongoing partial remission. None of the 10 patients developed graft-versus-host disease (GVHD); Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	At least 28 days must have elapsed since the latest trial of withdraw of immunosuppression or DLI until the patient can be deemed to have persistent disease. CD19 expression must be detected on most of the malignant cells by immunohistochemistry or by flow cytometry. Definition of which cells are malignant must be determined for each patient using techniques to demonstrate monoclonality, such as kappa/lambda restriction (other techniques can be used to determine monoclonality at the discretion of the Laboratory of Pathology). The choice of whether to use flow cytometry or immuohistochemistry will be determined by the most easily available tissue sample in each patient. Immunohistochemistry will be used for lymph node biopsies and bone marrow biopsies. Flow cytometry will be used for peripheral blood, fine needle aspirate, and bone marrow aspirate samples. Performance status: ECOG ≤ 2 Either no evidence of GVHD or minimal clinical evidence of acute GVHD and chronic GVHD while off of systemic immunosuppressive therapy for at least 28 days. Minimal clinical evidence of acute GVHD is defined as grade 0 to I acute GVHD. Minimal evidence of chronic GVHD is defined as mild global score chronic GVHD (as defined by the 2005 NIH consensus project) or no chronic GVHD. Subjects with disease that is controlled to stage I acute GVHD or to mild global score chronic GVHD with local therapy only (eg, topical cutaneous steroids or oral budesonide) will be eligible for enrollment. Ability to give informed consent Prior therapy: Therapy with monoclonal antibodies and/or chemotherapy must be stopped at least 7 days prior to anti-CD19 CAR-transduced T-cell infusion, and recovery of treatment-associated toxicity to ≤ grade 2 is required prior to infusion of cells. For patients who have received prior DLI, the last dose must be at least 28 days prior to anti-CD19			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	CAR-transduced T-cell administration. Note that patients can be enrolled on this study at any time after or during therapy, but at least 14 days must elapse from the time of prior monoclonal antibody administration or chemotherapy until anti-CD19 CAR-transduced T cells are infused, and at least 28 days must elapse from the end of immunosuppression, or DLI, or other immunomodulatory therapies such as lenalidomide until anti-CD19 CAR-transduced T cells are infused. Systemic immunosuppression must be stopped at least 28 days prior to protocol entry. There is no time restriction regarding prior intrathecal chemotherapy provided there is complete recovery from any acute toxic effects of such therapy. Recipients of unrelated donor transplants from a National Marrow Donor Program (NMDP) Center must sign a release of information form to authorize NMDP transfer of information to the NIH. Previous allogeneic donor must be willing and available to donate again. Patients of childbearing or child-fathering potential must be willing use an effective method of contraception while being treated on this study and for 4 months after the last cell infusion. Normal left ventricular function as evaluated by echocardiograph within 4 weeks of anti-CD19-CAR-transduced T-cell infusion Inclusion criteria: Donor Donors aged 18 years or older must be the same individual whose cells were used as the source for the patient's original stem-cell transplant. Adequate venous access for peripheral leukapheresis, or consent to use a temporary central venous catheter for leukapheresis			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Donors must be HIV negative, hepatitis B surface antigen negative, and hepatitis C antibody negative. Ability to give informed consent Donor selection will be in accordance with NIH/CC Department of Transfusion Medicine (DTM) criteria and, in the case of an unrelated donor from a Transplant Center, the National Marrow Donor Program (NMDP) standards. When a potentially eligible recipient of an unrelated donor product from an NMDP Center is identified, the recipient will complete an NMDP search transfer request to allow NIH NMDP staff to contact the NMDP Coordinating Center, which will, in turn, contact the donor's prior Donor Center. The NMDP Policy for Subsequent Donation Requests will be followed and the appropriate forms (Subsequent Donation Request form) and Therapeutic T Cell Collection Prescription will be submitted as required. Exclusion criteria: Recipients: Active infection that is not responding to antimicrobial therapy Evidence of infection with HIV, hepatitis B, or hepatitis C Patients must be HIV negative, hepatitis B surface antigen negative, and Hepatitis C antibody negative. The high degree of immune suppression that may be used in this study could lead to the activation or progression of these viral illnesses. Active psychiatric disorder that may compromise compliance with the treatment protocol, or that does not allow for appropriate informed consent (as determined by principal investigator and/or his or her designee) Pregnant or lactating. The effects of the immunosuppressive medications that could be required to treat GHVD are likely to be harmful to a fetus. The effects on breast milk are also unknown and may be harmful to an infant.			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Serum total bilirubin > 2.5 mg/dl, serum ALT and AST values ≥ 2.5 times the upper limit of normal based on age-specific normal values. If the abnormal liver function is attributable to liver involvement by malignancy, patients may be eligible with serum total bilirubin up to 5.0 mg/dl, and serum ALT and AST values up to 5.0 times the upper limit of normal, provided the patient has no evidence of impending hepatic failure (encephalopathy or prothrombin time > 2 times the upper limit of normal). Serum creatinine > 1.6 mg/dL Absolute neutrophil count of < 1000 cells/microL unless low neutrophil count is thought to be due to malignancy in the bone marrow and malignancy is documented in the bone marrow Active cerebrospinal fluid involvement with malignancy or brain metastasis Platelet count < 30 000/microL unless low platelet count is thought to be due to malignancy in the bone marrow and malignancy is documented in the bone marrow Hemoglobin < 8.0 g/dL Receiving corticosteroids above physiological dosing (> 5 mg per day of prednisone) within 28 days prior to anti-CD19-CAR-transduced T-cell administration Exclusion criteria: Donor: History of psychiatric disorder that may compromise compliance with this protocol or that does not allow for appropriate informed consent History of hypertension that is not controlled by medication, stroke, or severe heart disease (donors with symptomatic angina will be excluded). Donors with a history of coronary artery bypass grafting or angioplasty who are symptom-free will receive a cardiology evaluation and be considered on a case-by-case basis. Donors must not be pregnant.			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Anemia (Hb < 11 gm/dl) or thrombocytopenia (platelets < 100 000 per microL). However, potential donors with Hb levels <11 gm/dl that is due to iron deficiency will be eligible as long as the donor is initiated on iron replacement therapy. The NIH Clinical Center, Department of Transfusion Medicine/NMDP physicians will determine the appropriateness of individuals as donors.			
Kochenderfer et al, 2015[13]; Kochenderfer et al, 2012[29]; National Cancer Institute, National Institutes of Health Clinical Center, 2015[30]; Kochenderfer et al, 2010[31]; Morgan et al, 2006[32]; Rossi et al, 2018[33] NCT00924326 Single-arm trial N: 15	Eligibility criteria (demographics): Inclusion criteria: ≥ 18 years of age and ≤ 70 years of age Eligibility criteria (clinical criteria): Inclusion criteria: Patient must have a cluster of differentiation 19 (CD19)–expressing B-cell lymphoma. Patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and diffuse large B-cell lymphoma transformed from follicular lymphoma must have measurable disease after at least 2 prior chemotherapy regimens, one of which must have contained doxorubicin and rituximab. Confirmation of diagnosis of B-cell malignancy and positivity for CD19 confirmed by the Laboratory of Pathology of the National Cancer Institute (NCI). The choice of whether to use flow cytometry or immunohistochemistry will be determined by the most easily available tissue sample in each patient. Patients must have indications for treatment for their B-cell malignancy at the time of enrollment on this trial. Willing to sign a durable power of attorney Able to understand and sign the Informed Consent Document Clinical performance status of Eastern Cooperative Oncology Group (ECOG) 0 or 1 Life expectancy of > 3 months	Age group: Adults Proportion of female participants: 47% Race/ethnicity: Other (specify): NR Large B-cell lymphoma, mixed (with included lymphoma): large B-cell lymphoma, indolent lymphoma, and chronic lymphocytic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 30-68 Average year of diagnosis: NR	Other: Anti-CD19 CAR-T cells Follow-up: 23	Clinical response (complete response, partial response, stable disease, not evaluable), time to relapse, overall survival, progression-free survival Effect: Durable improvement: Of 15 patients, 8 achieved complete remissions (CRs), 4 achieved partial remissions, one had stable lymphoma, and 2 were not evaluable for response. CRs were obtained by 4 of 7 evaluable patients with chemotherapy-refractory diffuse large B cell lymphoma (DLBCL); 3 of these 4 CRs are ongoing, with durations ranging from 9 to 22 months. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Patients of both genders must be willing to practice birth control from the time of enrollment on this study and for 4 months after treatment. Women of childbearing potential must have a negative pregnancy test because of the potentially dangerous effects of the treatment on the fetus. Seronegative for human immunodeficiency virus (HIV) antibody. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune competence and thus be less responsive to the experimental treatment and more susceptible to its toxicities. Seronegative for hepatitis B antigen and hepatitis C antibody unless antigen negative. If the hepatitis C antibody test is positive, the patient must be tested for the presence of antigen by reverse transcription-polymerase chain reaction (RT-PCR) and be hepatitis C virus ribonucleic acid (HCV RNA) negative. Absolute neutrophil count ≥ 1000/mm^3 without the support of filgrastim Platelet count ≥ 50 000/mm^3 Hemoglobin > 8.0 g/dl Lymphocyte count ≤ 4000/ mm^3 Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5 times the upper limit of normal Serum creatinine ≤ 1.6 mg/dl Total bilirubin ≤ 1.5 mg/dl, except in patients with Gilbert's syndrome, who must have a total bilirubin of < 3.0 mg/dl More than 3 weeks must have elapsed since any prior systemic therapy at the time the patient receives the preparative regimen, and patient toxicities must have recovered to a grade 1 or less (except for toxicities such as alopecia or vitiligo).			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Normal cardiac ejection fraction and no evidence of pericardial effusion as determined by an echocardiogram. Exclusion criteria: Patients who require urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression Patients who have active hemolytic anemia Patients with active brain metastases, or with a history of any central nervous system (CNS) metastases or cerebrospinal fluid malignant cells Note: Patients who are asymptomatic but are found to have malignant cells in the cerebrospinal fluid (CSF) on lumbar puncture prior to treatment will be considered eligible. Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the treatment on the fetus or infant Active systemic infections, coagulation disorders, or other major medical illnesses of the cardiovascular, respiratory, or immune system; myocardial infarction; cardiac arrhythmias; or obstructive or restrictive pulmonary disease Any form of primary immunodeficiency (eg, severe combined immunodeficiency disease) Concurrent opportunistic infections. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who have decreased immune competence may be less responsive to the experimental treatment and more susceptible to its toxicities. Concurrent systemic steroid therapy History of severe immediate hypersensitivity reaction to any of the agents used in this study History of allogeneic stem-cell transplantation Patients with cardiac atrial or cardiac ventricular lymphoma involvement			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
Kochenderfer et al, 2017[15] ID NR, protocol approved by NIH Trial (multiple groups) N: 22	Eligibility criteria (demographics): Inclusion criteria: ≥ 18 years of age and ≤ 70 years of age Eligibility criteria (clinical criteria): Inclusion criteria: Patient must have a cluster of differentiation 19 (CD19)–expressing B-cell lymphoma. Patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or diffuse large B-cell lymphoma transformed from follicular lymphoma must have measurable disease after at least 2 prior chemotherapy regimens, one of which must have contained doxorubicin and rituximab. Confirmation of diagnosis of B-cell malignancy and positivity for CD19 confirmed by the Laboratory of Pathology of the National Cancer Institute (NCI). The choice of whether to use flow cytometry or immunohistochemistry will be determined by the most easily available tissue sample in each patient. Immunohistochemistry will be used for lymph node biopsies; flow cytometry will be used for peripheral blood, fine needle aspirates, and bone marrow samples. Patients must have indications for treatment for their B-cell malignancy at the time of enrollment on this trial. Willing to sign a durable power of attorney Able to understand and sign the Informed Consent Document Clinical performance status of Eastern Cooperative Oncology Group (ECOG) 0 or 1 Life expectancy of> 3 months Patients of both genders must be willing to practice birth control from the time of enrollment on this study and for 4 months after treatment.	Age group: Adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, mixed (with included lymphoma) Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 29-67 Average year of diagnosis: NR	Other: Anti-CD19 CAR-T cells Follow-up: 24	Remissions of lymphoma, toxicities Effect: Durable improvement: The 12-month progression-free survival of all patients was 63.6%. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Women of childbearing potential must have a negative pregnancy test because of the potentially dangerous effects of the treatment on the fetus. Seronegative for human immunodeficiency virus (HIV) antibody. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune competence and thus be less responsive to the experimental treatment and more susceptible to its toxicities. Seronegative for hepatitis B antigen and hepatitis C antibody unless antigen negative. If the hepatitis C antibody test is positive, the patient must be tested for the presence of antigen by reverse transcription-polymerase chain reaction (RT-PCR) and be hepatitis C virus ribonucleic acid (HCV RNA) negative. Absolute neutrophil count ≥ 1000/mm^3 without the support of filgrastim Platelet count ≥ 50 000/mm^3 Hemoglobin > 8.0 g/dl Lymphocyte count ≤ 4000/ mm^3 Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 5 times the upper limit of normal Serum creatinine ≤ 1.6 mg/dl Total bilirubin ≤ 1.5 mg/dl, except in patients with Gilbert's syndrome, who must have a total bilirubin of < 3.0 mg/dl More than 3 weeks must have elapsed since any prior systemic therapy at the time the patient receives the preparative regimen, and patient toxicities must have recovered to a grade 1 or less (except for toxicities such as alopecia or vitiligo). Normal cardiac ejection fraction and no evidence of pericardial effusion as determined by an echocardiogram Exclusion criteria:			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Patients who require urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression Patients who have active hemolytic anemia Patients with active brain metastases, or with a history of any central nervous system (CNS) metastases or cerebrospinal fluid malignant cells Note: Patients who are asymptomatic but are found to have malignant cells in the cerebrospinal fluid (CSF) on lumbar puncture prior to treatment will be considered eligible. Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the treatment on the fetus or infant Active systemic infections, coagulation disorders, or other major medical illnesses of the cardiovascular, respiratory, or immune system; myocardial infarction; cardiac arrhythmias; or obstructive or restrictive pulmonary disease Any form of primary immunodeficiency (eg, severe combined immunodeficiency disease) Concurrent opportunistic infections. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who have decreased immune competence may be less responsive to the experimental treatment and more susceptible to its toxicities. Concurrent systemic steroid therapy History of severe immediate hypersensitivity reaction to any of the agents used in this study History of allogeneic stem-cell transplantation Patients with cardiac atrial or cardiac ventricular lymphoma involvement			
Lee et al, 2015[12];	Eligibility criteria (demographics): Inclusion criteria: Aged 1-30 years	Age group: Children and adults	Other: CD19-CAR-T cells	Overall survival

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
Stroncek et al, 2016[34] NCT01593696[35] Single-arm trial N: 21	Eligibility criteria (clinical criteria): Inclusion criteria: Patient must have a CD19-expressing B-cell ALL or lymphoma and must have relapsed or refractory disease after at least one standard chemotherapy and one salvage regimen. In view of the PI and the primary oncologist, no alternative curative therapies must be available and subjects must either be ineligible for allogeneic stem-cell transplant (SCT), have refused SCT, or have disease activity that prohibits SCT. CD19 expression must be detected on > 15% of the malignant cells by immunohistochemistry or > 30% by flow cytometry in a CLIA-approved test . The choice of whether to use flow cytometry or immunohistochemistry will be determined by the most easily available tissue sample in each patient. In general, immunohistochemistry will be used for lymph node biopsies, and flow cytometry will be used for peripheral blood and bone marrow samples. Patients must have measurable or evaluable disease at the time of enrollment, which may include any evidence of disease, including minimal residual disease detected by flow cytometry, cytogenetics, or polymerase chain reaction (PCR) analysis. ≥ 1 year of age (and patient weight at least 15 kg) and ≤ 30 years of age Adequate absolute CD3 count estimated to be required to obtain target cell dose. Subjects with the following CNS statuses are eligible only in the absence of neurologic symptoms suggestive of CNS leukemia, such as cranial nerve palsy: CNS 1, defined as absence of blasts in cerebral spinal fluid (CSF) on cytospin preparation, regardless of the number of WBCs	Proportion of female participants: 33% Race/ethnicity: Other (specify): NR Non-Hodgkin's lymphoma, mixed (with included lymphoma): non-Hodgkin's lymphoma and acute lymphoblastic leukemia Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 6-27 Average year of diagnosis: NR	Follow-up: 42	Effect: Durable improvement: Intention-to-treat analysis shows a 66.7% (14/21) complete response rate (95% CI, 43.0-85.4). Of 20 patients with B-cell acute lymphoblastic leukemia (B-ALL), the complete response rate was 70% (95% CI, 45.7-88.1), with 12 of 20 patients with B-ALL achieving minimal residual disease (MRD) negative complete response (60%; 95% CI, 36.1-80.9) Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	CNS 2, defined as presence of <5/uL WBCs in CSF and cytospin positive for blasts, or >5/uL WBCs but negative by Steinherz/Bleyer algorithm CNS3 with marrow disease and has failed salvage systemic and intensive IT chemotherapy (and therefore not eligible for radiation) Patients with isolated CNS relapse will be eligible if they have previously been treated with cranial radiation (at least 1800 cGy). Ability to give informed consent. For subjects <18 years old, their legal guardian must give informed consent. Pediatric subjects will be included in age-appropriate discussion and verbal assent will be obtained for those aged 12 and older, when appropriate. Clinical performance status: Patients >10 years of age: Karnofsky ≥ 50%; patients aged 10 or younger: Lansky scale ≥ 50% Subjects who are unable to walk because of paralysis but who are upright in a wheelchair will be considered ambulatory for the purpose of calculating the performance score. Patients of childbearing or child-fathering potential must be willing to practice birth control from the time of enrollment on this study and for 4 months after receiving the preparative regimen. Women of childbearing potential must have a negative pregnancy test because of the potentially dangerous effects on the fetus. Cardiac function: Left ventricular ejection fraction ≥ 40% by MUGA or cardiac MRI, or fractional shortening ≥ 28% by ECHO or left ventricular ejection fraction ≥ 50% by ECHO Patients with a history of allogeneic stem-cell transplantation are eligible if they are at least 100 days post-transplant, if there is no evidence of active GVHD and they have not been			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	taking immunosuppressive agents for at least 30 days prior to enrollment. Exclusions criteria: Recurrent or refractory ALL limited to isolated testicular disease Hepatic function: Inadequate liver function defined as total bilirubin >2 times upper limit of normal (ULN), except for subjects with Gilbert's disease >3 times ULN or transaminase (ALT and AST) >20 times Renal function: > age-adjusted normal serum creatinine (see below) and a creatinine clearance < 60 mL/min/1.73 m^2 Age: ≤ 5 years (maximum serum creatinine = 0.8 mg/dL) 5 < age ≤10 years (maximum serum creatinine = 1.0 mg/dL) >10 years (maximum serum creatinine = 1.2 mg/dL) Hematologic function: Absolute neutrophil count (ANC) < 750/microliter, or platelet count < 50 000/microliter, if these cytopenias are not judged by the investigator to be due to underlying disease (ie, potentially reversible with anti-neoplastic therapy). A subject will not be excluded because of pancytopenia ≥ grade 3 if it is due to disease, based on the results of bone marrow studies. Hyperleukocytosis (≥ 50 000 blasts/microliter) or rapidly progressive disease that in the estimation of the investigator and sponsor would compromise ability to complete study therapy Pregnant or breastfeeding women Recent prior therapy: Systemic chemotherapy ≤ 2 weeks (6 weeks for nitrosoureas) or radiation therapy ≤ 3 weeks prior to apheresis Exceptions:			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	There is no time restriction regarding prior intrathecal chemotherapy provided there is complete recovery from any acute toxic effects of such therapy. Subjects receiving hydroxyurea may be enrolled provided there has been no increase in dose for at least 2 weeks prior to starting apheresis. Patients who relapse while receiving standard ALL maintenance chemotherapy will not be required to have a waiting period before entry onto this study provided they meet all other eligibility criteria. Subjects receiving steroid therapy at physiologic replacement doses only are allowed provided there has been no increase in dose for at least 2 weeks prior to starting apheresis. For radiation therapy: Radiation therapy must have been completed at least 3 weeks prior to enrollment, with the exception that there is no time restriction if the volume of bone marrow treated is < 10% and the subject has measurable/evaluable disease outside the radiation port. Other anti-neoplastic investigational agents currently or within 30 days prior to apheresis (ie, start of protocol therapy) Subjects must have recovered from the acute side effects of their prior therapy, such that eligibility criteria are met. Cytopenias deemed to be disease related and not therapy related are exempt from this exclusion. HIV/HBV/HCV infection: Seropositive for HIV antibody. Patients with HIV are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy in the future should study results indicate effectiveness. Seropositive for hepatitis C or positive for hepatitis B surface antigen (HbsAG)			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Monoclonal antibody therapy administered within 30 days of the agent prior to apheresis Uncontrolled, symptomatic, intercurrent illness including, but not limited to, infection, congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness, or social situations that would limit compliance with study requirements or in the opinion of the PI would pose an unacceptable risk to the subject Second malignancy other than in situ carcinoma of the cervix, unless the tumor was treated with curative intent at least 2 years previously and the subject is in remission History of severe, immediate hypersensitivity reaction attributed to compounds of similar chemical or biologic composition to any agents used in the study or in the manufacturing of the cells (ie, gentamicin)			
Locke et al, 2019[8] Single-arm trial N: 108	Eligibility criteria (demographics): Inclusion criteria: 18 years or older Eligibility criteria (clinical criteria): Inclusion criteria: Refractory large B-cell lymphoma, including diffuse large B-cell lymphoma Primary mediastinal B-cell lymphoma Transformed follicular lymphoma Lymphoid tissue classified according to 2008 WHO Classification of Tumours of Haematopoietic and histologically confirmed retrospectively by independent pathology review Eastern Cooperative Oncology Group performance status of 0 or 1 Absolute neutrophil count of at least 1000 per µL Platelet count of at least 75 000 per µL	Age group: Adults Proportion of female participants: Phase 1 29%; phase 2 33% Race/ethnicity: Other (specify): NR Large B-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma Genetic marker information: NR Disease stage: 43% of patients in phase 1 and 15% of patients in phase 2 were stage I or II, 57% of patients in phase 1 and 85% of patients in phase 2 were stage III or IV. Comorbidities: NR Age range of population: 34-69 (phase 1); 51-64 (phase 2)	Axicabtagene ciloleucel; Axi-cel; Yescarta: Axicabtagene ciloleucel Follow-up: 27	Objective response, duration of response, progression-free survival, overall response Effect: Durable improvement: In post hoc analyses, the estimated proportion of patients with progression-free survival at 24 months was 72.0%. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Adequate organ function Refractory disease was defined as progressive or stable disease as best response to the most recent chemotherapy regimen, or disease progression or relapse within 12 months of autologous stem-cell transplantation Previously received a regimen containing an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen Patients with transformed diffuse large B-cell lymphoma must have received previous chemotherapy for follicular lymphoma and developed chemorefractory disease after transformation Exclusion criteria: Autologous stem-cell transplantation within 6 weeks of informed consent for ZUMA-1 Had previously undergone allogeneic haemopoietic stem-cell transplantation Received previous CD19-targeted therapy or CAR-T cell therapy	Average year of diagnosis: NR		
Neelapu et al, 2017[5]; Locke et al, 2017[36]; Kite[37] NCT02348216 Single-arm trial N: 111	Eligibility criteria (demographics): Inclusion criteria: Aged 18 or older Eligibility criteria (clinical criteria): Inclusion criteria: Histologically confirmed aggressive B-cell NHL, including the following types defined by WHO 2008: DLBCL not otherwise specified; T-cell/histiocyte-rich large B-cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary cutaneous DLBCL, leg type; or primary mediastinal (thymic) large B-cell lymphoma. Transformation of follicular lymphoma to DLBCL will also be included.	Age group: Adults Proportion of female participants: DLBCL 35%; PMBCL or TFL 25% Race/ethnicity: Other (specify): NR Large B-cell lymphoma: Refractory Genetic marker information: NR Disease stage: Stage III or IV 85% Comorbidities: NR Age range of population: 23-76 Average year of diagnosis: NR	Axicabtagene ciloleucel, Axi-cel, Yescarta Follow-up: 15	Objective response rate (complete response, partial response, stable disease, not evaluated), time to response, duration of response, disease progression, best response, progression-free survival, overall survival Effect: Durable improvement Predictor of effectiveness: Refractory subgroup, age, disease stage, International Prognostic Index (IPI) risk score, extranodal disease, bulky disease, treatment history, CD19 status, CD19

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Chemotherapy-refractory disease, defined as one or more of the following: stable disease (duration of stable disease must be ≤12 months) or progressive disease as best response to most recent chemotherapy-containing regimen; disease progression or recurrence ≤12 months of prior autologous SCT Subjects must have received adequate prior therapy including at a minimum anti-CD20 monoclonal antibody unless the investigator determines that the tumor is CD20 negative and an anthracycline-containing chemotherapy regime. Subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL. At least one measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy. MRI of the brain showing no evidence of CNS lymphoma ≥ 2 weeks must have elapsed since any prior radiation therapy or systemic therapy at the time the subject is planned for leukapheresis Toxicities due to prior therapy must be stable or recovered to ≤grade 1 (except for clinically nonsignificant toxicities such as alopecia). Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ANC ≥ 1000/uL Platelet count ≥ 50 000/uL Adequate renal, hepatic, and cardiac function defined as the following: Serum creatinine ≤ 1.5 mg/dL Serum ALT/AST ≤ 2.5 ULN			histologic score, cell of origin, CD4:CD8 ratio, tocilizumab use, glucocorticoid use

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an ECHO Women of childbearing potential must have a negative serum or urine pregnancy test. Exclusion criteria: History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) or follicular lymphoma unless disease-free for at least 3 years History of Richter's transformation of CLL Autologous stem-cell transplant within 6 weeks of informed consent History of allogeneic stem-cell transplantation Prior CD19-targeted therapy with the exception of subjects who received KTE-C19 in this study and are eligible for retreatment Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy Clinically significant active infection (eg, simple UTI, bacterial pharyngitis allowed) or currently receiving IV antibiotics or have received IV antibiotics within 7 days prior to enrollment Prophylaxis antibiotics, antivirals, and antifungals are permitted. Known history of infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti- HCV positive) Subjects with detectable cerebrospinal fluid malignant cells, brain metastases, or a history of cerebrospinal fluid malignant cells or brain metastases			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	History of a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement Subjects with cardiac atrial or cardiac ventricular lymphoma involvement Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression Primary immunodeficiency Any medical condition likely to interfere with assessment of safety or efficacy of study treatment Current or expected need for systemic corticosteroid therapy. Note: Topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency are allowed. Doses of corticosteroids of ≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids are not allowed. History of severe immediate hypersensitivity reaction to any of the agents used in this study Live vaccine ≤ 6 weeks prior to start of conditioning regimen Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant Women who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-C19 In the investigators' judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
Ramos et al, 2016[10] NCT00881920[38] Trial (multiple groups) N: 16	Eligibility criteria (demographics): Inclusion criteria: Aged 18 years or older Eligibility criteria (clinical criteria): Inclusion criteria: Blood procurement: B-CLL or recurrent or refractory B-cell lymphoma (or other B-cell neoplasm) and multiple myeloma (MM) or multiple myeloma monoclonal for Kappa-light chain Life expectancy of at least 12 weeks or greater No history of other cancer (except nonmelanoma skin cancer or in situ breast cancer or cervix cancer) unless the tumor was successfully treated with curative intent at least 2 years before trial entry Pheresis requires Cre and AST < 1.5 upper limit of normal Pheresis requires PT and PTTK < 1.5 upper limit normal T-cell treatment: Diagnosis of B-CLL monoclonal for Kappa-light chain with one of the following criteria: Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of < 6 months Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:	Age group: Adults Proportion of female participants: 22% Race/ethnicity: Other (specify): NR Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 53-72 Average year of diagnosis: NR	Other: Kappa CAR-T cells Follow-up: 24	Toxicity, complete/partial response, stable disease Effect: Sustained improvement: Of 9 patients with relapsed non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL), 2 entered complete remission after 2 and 3 infusions of κ.CARTs, and 1 had a partial response. Of 7 patients with MM, 4 had stable disease lasting 2 to 17 months. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Unintentional weight loss of 10% or more within the previous 6 months Significant fatigue (ie, ECOG PS 2 or worse, or inability to work or perform usual activities) Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection Night sweats for more than 1 month without evidence of infection Patients who have resistant disease after primary treatment Patients who have a short time to progression after the first treatment (< 2 years) Diagnosis of indolent or aggressive B-cell lymphoma (or other B-cell neoplasm) monoclonal for Kappa-light chain with measurable disease after receiving at least one chemotherapy regimen that includes rituximab or an equivalent monoclonal antibody Diagnosis of multiple myeloma monoclonal for Kappa-light chain with measurable disease after receiving at least one chemotherapy regimen Life expectancy of at least 12 weeks or greater Recovered from the toxic effects of all prior chemotherapy before entering this study. PD1/PDL1 inhibitors will be allowed if medically indicated. ANC > 500, Hgb ≥ 7.0 Bilirubin < 3 times the upper limit of normal AST < 5 times the upper limit of normal Estimated GFR > 50 mL/min Pulse oximetry > 90% on room air Karnofsky score > 60% Negative serology for HIV Available autologous transduced peripheral blood T cells with 15% or more expression of CAR-Kappa determined by flow cytometry			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Patients must sign an informed consent indicating that they are aware this is a research study and have been told of its possible benefits and toxic side effects. Patients will be given a copy of the consent form. Sexually active patients must be willing to utilize one of the more effective birth control methods during the study and for 3 months after the study is concluded. The male partner should use a condom. If patient has CLL, must have negative Coombs test Exclusion criteria: Blood procurement: Active infection requiring antibiotics Active autoimmune disease T-cell treatment: Symptomatic cardiac disease History of hypersensitivity reactions to murine protein-containing products Currently receiving any investigational agents within the previous 6 weeks or received any tumor vaccines within the previous 6 weeks Tumor in a location where enlargement could cause airway obstruction Pregnant or lactating			
Sauter et al, 2019[19]; Memorial Sloan Kettering Cancer Center, 2019[39] NCT01840566[39] Single-arm trial N: 15	Eligibility criteria (demographics): Inclusion criteria: 18 years of age or older Eligibility criteria (clinical criteria): Inclusion criteria: Aggressive B-cell non-Hodgkin's lymphoma subtypes including relapsed or refractory diffused large B-cell lymphoma (DLBCL) and transformed follicular lymphoma meeting at least one of the following criteria:	Age group: Adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Non-Hodgkin's lymphoma, follicular lymphoma, diffuse large B-cell lymphoma Genetic marker information: NR Disease stage: NR	Other: 19-28z CAR-T cells Follow-up: 37	Progression-free survival, progression of disease Effect: Sustained improvement: Progression-free survival (PFS) 30% at 2 years Predictor of effectiveness: Persistence in days or peak concentration of CAR-T not related to death or progression

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	(1) Bone marrow involvement at the time of relapse or refractory disease and not appropriate for allogeneic transplantation (2) PET-positive disease outside of one radiation port unless single-port disease treated with prior radiotherapy within the port, following ≥ 2 cycles of salvage chemotherapy. Creatinine ≤ 1.5 mg/100 ml (or measured 24-hour creatinine clearance of ≥50 cc/min) Bilirubin < 2.0 mg/100 ml, AST and ALT < 3 times the upper limit of normal, PT and PTT < 2 times normal outside the setting of stable chronic anticoagulation therapy, and adequate cardiac function (LVEF > 40%) as assessed by ECHO or MUGA scan performed within 1 month of treatment Adequate pulmonary function as assessed by DLCO of ≥ 45% adjusted for hemoglobin Life expectancy of >3 months Exclusion criteria: Karnofsky performance status ≤ 70 Patients with other aggressive B-cell malignancies including, but not limited to, Burkitt lymphoma or transformed CLL/SLL and transformed marginal zone lymphoma. Patients previously treated with autologous or allogeneic bone marrow or stem-cell transplantation are ineligible. Other past or current malignancy unless in the opinion of the investigator it does not contraindicate participation in the study Uncontrolled bacterial, viral, or fungal infection Patients with HIV, active hepatitis B, or hepatitis C infection	Comorbidities: NR Age range of population: 34-75 Average year of diagnosis: NR		
Schuster et al, 2017[6]; 	Eligibility criteria (demographics): Inclusion criteria: Adults Eligibility criteria (clinical criteria):	Age group: Adults	Other: CTL019 cells	Overall response rate at 3 months (including complete response), progression-free survival, duration

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
University of Pennsylvania, 2018[40] NCT02030834 Single-arm trial N: 28	Inclusion criteria: CD19+ diffuse large B-cell lymphoma or follicular lymphoma with no curative treatment options, a limited prognosis (<2 years of anticipated survival), and a partial response to or stable disease after the most recent therapy Patients with diffuse large B-cell lymphoma were eligible if they had measurable disease after primary and salvage therapies, had relapsed or residual disease after autologous stem-cell transplantation, or were not eligible for autologous or allogeneic stem-cell transplantation. Patients with follicular lymphoma were eligible if they had measurable progression of disease < 2 years after the second line of immunochemotherapy (excluding single-agent monoclonal antibody therapy).	Proportion of female participants: Follicular lymphoma 53%; DLBCL 30% Race/ethnicity: Other (specify): NR Large B-cell lymphoma: Relapsed/refractory, follicular lymphoma: relapsed/refractory, mixed (with included lymphoma) Genetic marker information: NR Disease stage: 87% of follicular lymphoma patients and 74% of diffuse large B-cell lymphoma were stage I or IV. Comorbidities: NR Age range of population: 25-77 Average year of diagnosis: NR	Follow-up: 180	of response, overall survival, probability of survival Effect: Durable improvement: A total of 28 adult patients with lymphoma received CTL019 cells, and 18 of 28 had a response (64%; 95% CI, 44-81). Complete remission occurred in 6 of 14 patients with diffuse large B-cell lymphoma (43%; 95% CI, 18-71) and 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42-92). Predictor of effectiveness: Tumor size, immunohistochemistry, T-cell phenotypes, disease type
Schuster et al, 2019[7]; Bishop et al, 2019[41]; Novartis Pharmaceuticals, 2023[42] NCT02445248[42] Single-arm trial N: 93	Eligibility criteria (demographics): Inclusion criteria: 18 years of age or older Eligibility criteria (clinical criteria): Inclusion criteria: Written informed consent must be obtained prior to any screening procedures. Histologically confirmed DLBCL at last relapse (by central pathology review before enrolment) Relapsed or refractory disease after ≥2 lines of chemotherapy including rituximab and anthracycline and either failed autologous hematopoietic stem-cell transplantation (ASCT), or were ineligible did not consent to ASCT. Measurable disease at time of enrollment Life expectancy ≥ 12 weeks	Age group: Adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Large B-cell lymphoma Genetic marker information: NR Disease stage: I (7%), II (17%), III (20%), IV (62%) Comorbidities: NR Age range of population: 22-76 Average year of diagnosis: NR	Kymriah, Tisagenlecleucel Follow-up: 26	Overall response, response duration Effect: Durable improvement: The best overall response rate was 52% (95% CI, 41-62); 40% of the patients had complete responses and 12% had partial responses. Response rates were consistent across prognostic subgroups. At 12 months after the initial response, the rate of relapse-free survival was estimated to be 65% (79% among patients with a complete response). Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Eastern Cooperative Oncology Group (ECOG) performance status that is either 0 or 1 at screening Adequate organ function: Renal function defined as the following: Serum creatinine of ≤1.5 x upper limit of normal (ULN) or Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m_2 Liver function defined as the following: Alanine aminotransferase (ALT) ≤ 5 times the ULN for age Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert-Meulengracht syndrome; patients with Gilbert-Meulengracht syndrome may be included if their total bilirubin is ≤3.0 times upper limit of normal (ULN) and direct bilirubin ≤ 1.5 times ULN. Must have a minimum level of pulmonary reserve defined as ≤grade 1 dyspnea and pulse oxygenation >91% on room air Hemodynamically stable and left ventricle ejection fraction (LVEF) ≥ 45% confirmed by echocardiogram or multigated radionuclide angiography (MUGA) Adequate bone marrow reserve without transfusions defined as the following: Absolute neutrophil count (ANC) > 1.000/mm3 Absolute lymphocyte count (ALC) ≥ 300/mm3 Platelets ≥ 50.000//mm3 Hemoglobin > 8.0 g/dl Must have an apheresis product of nonmobilized cells accepted for manufacturing Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants must agree to use highly effective methods of contraception for at least 12 months following CTL019 infusion and until CAR-T cells are no longer present by PCR on 2 consecutive tests.			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Exclusion criteria: Prior treatment with any prior anti-CD19/anti-CD3 therapy or any other anti-CD19 therapy 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 Investigational medicinal product within the past 30 days prior to screening The following medications are excluded: Steroids: Therapeutic doses of steroids must be stopped >72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: <6 to 12 mg/m2/day hydrocortisone or equivalent Immunosuppression: Any immunosuppressive medication must be stopped ≥4 weeks prior to enrollment. Antiproliferative therapies other than lymphodepleting chemotherapy within 2 weeks of infusion Antibody use including anti-CD20 therapy within 4 weeks prior to infusion or 5 half-lives of the respected antibody, whichever is longer CNS disease prophylaxis must be stopped >1 week prior to CTL019 infusion (eg, intrathecal methotrexate) Prior radiation therapy within 2 weeks of infusion Active replication of or prior infection with hepatitis B or active hepatitis C (HCV RNA positive) HIV positive patients			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Uncontrolled acute life-threatening bacterial, viral, or fungal infection (eg, blood culture positive ≤72 hours prior to infusion) Unstable angina and/or myocardial infarction within 6 months prior to screening Previous or concurrent malignancy with the following exceptions: Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry) In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to the study A primary malignancy that has been completely resected and in complete remission for ≥5 years Investigational medicinal product within the past 30 days prior to screening Pregnant or nursing (ie, lactating) women Intolerance to the excipients of the CTL019 cell product Cardiac arrhythmia not controlled with medical management Patients on oral anticoagulation therapy Prior treatment with any adoptive T-cell therapy Patients with active neurological autoimmune or inflammatory disorders (eg, Guillain-Barre syndrome, amyptrophic lateral sclerosis)			
Till et al, 2008[18] NCT00012207[43] Trial (multiple groups) N: 7	Eligibility criteria (demographics): Inclusion criteria: Any age Eligibility criteria (clinical criteria): Inclusion criteria: Disease characteristics:	Age group: Adults Proportion of female participants: 11% Race/ethnicity: Other (specify): NR Follicular lymphoma, mantle-cell lymphoma Genetic marker information: NR	Other: Autologous CD20-specific T cells Follow-up: 12	Clinical responses by International Working Group criteria, humoral immune response Effect: Sustained improvement: Two of the 7 patients achieved a complete response to cytoreductive chemotherapy administered before the T-cell infusions and remained

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Immunohistopathologically documented relapsed or refractory CD20+ indolent lymphomas or mantle-cell lymphoma Indolent B-cell lymphomas including any of the following subtypes: Follicular lymphoma (grade I, II, or III) Small lymphocytic lymphoma or chronic lymphocytic leukemia Marginal zone lymphoma (splenic, nodal, and extra-nodal) Lymphoplasmacytoid lymphoma Ineligible for or unwilling to participate in other FHCRC/UWMC protocols Serological evidence of prior exposure to Epstein-Barr virus Must agree to undergo peripheral blood drawing, bone marrow biopsy, lymph node biopsy, and nuclear medicine imaging Must agree to cytoreductive chemotherapy if necessary to reduce lymph nodes to <5 cm in diameter or circulating B lymphocyte counts to <5000/mm^3 Patient characteristics: Performance status: Not specified Life expectancy: At least 90 days No HIV positivity Not pregnant or nursing Fertile patients must use effective contraception. No history of hypersensitivity reactions to murine proteins Prior concurrent therapy: Biologic therapy: At least 4 months since prior rituximab, tositumomab, or ibritumomab Chemotherapy: At least 2 years since prior fludarabine or cladribine At least 4 weeks since prior chemotherapy and recovered	Disease stage: Stage II (11%), III (11%), IV (88%) Comorbidities: NR Age range of population: 43-77 Average year of diagnosis: NR		disease-free 3 months and 13 months after T-cell infusions. Another patient attained an objective partial response lasting 3 months after treatment with T-cell infusions plus IL-2. Four patients exhibited stable disease for 3, 5, 6, and 12 months. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Radiotherapy: Not specified Surgery: Not specified Other: At least 4 weeks since prior immunosuppressive therapy. Exclusion criteria: Disease characteristics: No pulmonary involvement No CNS involvement Patient characteristics: Hepatic: No active hepatitis B infection Prior concurrent therapy: Biologic therapy: No prior allogeneic stem-cell transplantation No other concurrent immunotherapy (eg, interferons, vaccines, or other cellular products) Endocrine therapy: No concurrent systemic corticosteroids except to treat toxicity from chemotherapy or cellular immunotherapy No concurrent pentoxifylline No other concurrent investigational agents			
Wang et al, 2016[11] NCT01318317[44] Single-arm trial N: 16	Eligibility criteria (demographics): Inclusion criteria: Aged 18 years or older Eligibility criteria (clinical criteria): NHL 1 trial: Inclusion criteria: City of Hope (COH) pathology review confirms that the research participant's diagnostic material is consistent with history of intermediate-grade B-cell NHL (eg, diffuse B-cell lymphoma, mantle-cell lymphoma, transformed follicular lymphoma)	Age group: Adults Proportion of female participants: NR Race/ethnicity: Other (specify): NR Non-Hodgkin's lymphoma Genetic marker information: NR Disease stage: NR Comorbidities: NR Age range of population: 50-75 Average year of diagnosis: NR	Other: TCM-derived CD19 CAR-T cells Follow-up: 14	Days post T-cell infusion, CAR area under the curve, peak expansion, and maximum persistence Effect: Durable improvement: Four of 8 patients (50%; 95% CI, 16%-84%) were progression-free at both 1 and 2 years. Predictor of effectiveness: NR

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	History of relapse after achieving first remission with primary therapy, or failure to achieve remission with primary therapy Life expectancy >16 weeks Karnofsky performance scale (KPS) ≥ 70% Negative serum pregnancy test for women of childbearing potential The research participant has an indication to be considered for autologous stem-cell transplantation. Exclusion criteria: Fails to understand the basic elements of the protocol and/or the risks and benefits of participating in this phase I/II study. Evidence of understanding includes passing the Protocol Comprehensive Screening given by the Research Subject Advocate (RSA). A legal guardian may substitute for the research participant. Any standard contraindications to myeloablative HSCT per standard of care practices at COH Dependence on corticosteroids Currently enrolled in another investigational therapy protocol Human immunodeficiency virus (HIV) seropositive based on testing performed within 4 weeks of enrollment History of allogeneic HSCT or prior autologous HSCT Active autoimmune disease requiring systemic immunosuppressive therapy Research participants who are to receive radioimmunotherapy Research participants with known active hepatitis B or C infection NHL 2 trial: Inclusion criteria: Enrolled research participants are patients with an indication to be considered for HSCT, who are diagnosed with			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	intermediate-grade B-cell NHL (eg, DLBCL, MCL, transformed NHL), and who have either recurrence/progression following prior therapy or verification of high-risk disease in first remission Karnofsky performance status of ≥ 70% and a life expectancy ≥ 16 weeks at time of enrollment Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for 6 months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately. City of Hope (COH) pathology review confirms that the research participant's diagnostic material is consistent with the history of intermediate-grade B-cell NHL (eg, DLBCL, MCL, transformed NHL) Negative serum pregnancy test for women of childbearing potential The research participant has an indication to be considered for autologous stem-cell transplantation. All patients must have the ability to understand and the willingness to sign a written informed consent Eligibility to undergo autologous myeloablative transplantation with hematopoetic progenitor cell (HPCA) rescue: The research participant meets all standard clinical parameters for candidates of autologous transplant at COH. The research participant is scheduled to receive a standard chemotherapy-based conditioning regimen, such as cyclophosphamide, carmustine, etoposide (CBV) or carmustine, etoposide, cytarabine, or melphalan (BEAM). The research participant has a cryopreserved unselected HPCA product of at least 3 x 10^6/kg CD34+ cells.			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	The research participant does not have evidence of disease progression after salvage therapy. Eligibility criteria at time of infusion of genetically modified autologous T cells: The research participant has a released cryopreserved T-cell product. The research participant has undergone an autologous HPCA procedure. Participants must not require supplemental oxygen or mechanical ventilation, oxygen saturation of 90% or higher on room air Participants must not pressor support, not having symptomatic cardiac arrhythmias Lack of acute renal failure/requirement for dialysis, as evidenced by creatinine <1.6 - Total bilirubin ≤ 5.0 Research participant without clinically significant encephalopathy/new focal deficits No clinical evidence of uncontrolled active infection Exclusion criteria: Research participants with any uncontrolled illness, including ongoing or active infection; research participants with known active hepatitis B or C infection; research participants who are human immunodeficiency virus (HIV) seropositive based on testing performed within 4 weeks of enrollment; and research participants with any signs of symptoms of active infection, positive blood cultures, or radiological evidence of infections Research participants receiving any other investigational agents or concurrent biological, chemotherapy, or radiation therapy History of allergic reactions attributed to compounds of similar chemical or biologic composition to cetuximab			

Citations Design N	Eligibility	Participant Information	Intervention Months of Follow-up	Health Outcomes Measured Effectiveness Predictors of Effects
	Research participants with known brain metastases (central nervous system [CNS] involvement or parenchymal or leptomeningeal involvement) Research participants with presence of other malignancy or history of prior malignancy within 5 years of study entry. Although patients treated with curative intent within 5 years are eligible, this exclusion rule does not apply to nonmelanoma skin tumors and in situ cervical cancer. Failure of research participant to understand the basic elements of the protocol and/or the risks and benefits of participating in this phase I/II study. A legal guardian may substitute for the research participant. History of allogeneic HSCT or prior autologous HSCT Any standard contrndications to myeloablative HSCT per standard of care practices at COH Dependence on corticosteroids Active autoimmune disease requiring systemic immunosuppressive therapy Research participants will be excluded who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.			

CI=confidence interval; NR=not reported