

Introduction

LEUKEMIA AND LYMPHOMA

This review focuses on two types of B-cell cancers: **childhood B-cell acute lymphoblastic leukemia (B-ALL)**, and **aggressive B-cell non-Hodgkin's lymphoma (NHL) in adults**. While chemotherapy treatments and stem cell transplants are effective options for many patients, there have been few options available for patients whose disease does not respond to initial treatment (i.e. “refractory” disease) or whose disease relapses following initial treatment.

CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY

CAR-T therapy is a new cellular therapy intended for patients for whom other treatment options have failed. ICER's report examined two CAR-T therapies approved by the FDA in 2017: **tisagenlecleucel (Kymriah™, Novartis)** and **axicabtagene ciloleucel (Yescarta™, Kite/Gilead)**.

Tisagenlecleucel is approved for patients under age 25 with B-ALL that has relapsed or is refractory to two lines of treatment. It is also under FDA review for use in relapsed or refractory NHL. Axicabtagene ciloleucel is approved for adult patients with certain subtypes of NHL, including

diffuse large B-cell lymphoma, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma, that are relapsed or refractory to two lines of treatment.

Both therapies involve drawing a patient's white blood cells (a process called “leukapheresis”), shipping the cells to a facility that genetically modifies them into CAR-T cells, and infusing them back into the bloodstream to fight the cancer. The manufacturing process typically takes two to three weeks, during which time some patients may die or become too sick to receive the treatment.

Summary

Key Report Findings

ICER's report found that both therapies provide a **net health benefit** compared to standard chemoimmunotherapy regimens and found both therapies to be **cost-effective in the long-term** for the specified indications. The report was the subject of a public meeting of the California Technology Assessment Forum (CTAF).

Affordability and Access Alert

ICER issued this alert for axicabtagene ciloleucel in adults with NHL to signal that the **added health care costs may be difficult for the system to absorb over the short term**. At current costs, only 38% of the eligible population of 5,900 could be treated before crossing the affordability threshold.

Key Policy Recommendations

- Manufacturers, public and private insurers, and providers should meet prior to FDA approval to address uncertainty regarding payment arrangements, a step that will reduce unnecessary delays in delivering care to patients and financial uncertainties for insurers and providers.
- Value-based pricing should be viewed in context with the affordability of a new treatment based on the size of the population eligible to receive the therapy.
- Manufacturers and insurers should ensure that outcomes-based pricing arrangements are linked to meaningful clinical outcomes assessed with sufficient follow up.

Clinical Analyses: ICER Evidence Rating

How strong is the evidence CAR-T therapies improve outcomes?

Pediatric Patients with B-ALL	Tisagenlecleucel	Evidence provides moderate certainty of a small or substantial net health benefit in comparison to standard chemotherapy, with high certainty of at least a small net health benefit.
Adults with NHL	Tisagenlecleucel	
	Axicabtagene ciloleucel	

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

ICER’s analyses reviewed outcomes for tisagenlecleucel in B-ALL and NHL and axicabtagene ciloleucel in NHL compared to outcomes in patients who received other therapies with similar FDA indications.

Evidence is insufficient to judge whether one CAR-T therapy is superior to the other for NHL.

	TISAGENLECLEUCEL FOR B-ALL	TISAGENLECLEUCEL FOR NHL	AXICABTAGENE CILOLEUCEL FOR NHL
Overall survival	 Greater	 Greater	 Greater
Complete Remission	 Greater	 Greater	 Greater
Disease-free survival	 Greater	Not reported in this population	 Greater

Clinical Analyses: ICER Evidence Rating (continued)

HARMS

The most significant known side effects of CAR-T therapy are:

- **Cytokine release syndrome (CRS)** occurs in about a third of patients and causes high fevers, low blood pressure, and respiratory distress that may require intensive care.
- **Neurological symptoms** also affect more than a third of patients, with the most common effects being encephalopathy, headache, delirium, aphasia, anxiety, and tremors.
- **B-cell aplasia**, or the absence of B-cells, can put patients at increased risk of infection.

While these harms can be severe, they are generally manageable and perceived by clinicians as no worse than the serious harms associated with traditional chemotherapy.

SOURCES OF UNCERTAINTY

- **The studies of CAR-T therapies are all single-arm trials.** Given the possibility of selection bias in trials, it is impossible to compare outcomes from these trials to those of other trials without considerable uncertainty.
- **Trials are small and have short follow-up.** The benefits and duration of long-term relapse-free survival is unknown, as are the long-term harms. Unanticipated harms may arise as larger numbers of patients are followed for several years.
- **Comparisons with historical controls.** Supportive care in cancer treatment improves over time, so outcomes reported in older studies may be unduly pessimistic.
- **Improvements in the CAR-T manufacturing process** with experience may lead to fewer manufacturing failures and shorter times from leukapheresis to infusion.

These uncertainties make the comparative efficacy analyses versus standard therapy controversial.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS AT LIST PRICE

Do CAR-T therapies meet established thresholds for long-term cost-effectiveness?

Tisagenlecleucel in pediatric B-ALL

WAC*: \$475,000

Long-term cost effectiveness vs. chemotherapy with clofarabine:

\$45,871
per QALY gained

Axicabtagene ciloleucel in adults with NHL

WAC*: \$373,000

Long-term cost effectiveness vs. salvage chemotherapy**

\$136,078
per QALY gained

*Wholesale Acquisition Cost

**Effectiveness assumptions for chemotherapy based on average of salvage chemotherapy regimens from SCHOLAR-1 trial; cost assumptions based on cost of R-DHAP chemotherapy regimen

The cost-effectiveness of each therapy for the population assessed fell below or within commonly cited thresholds of \$50,000 to \$150,000 per quality-adjusted life year (QALY) over a lifetime horizon.

Analyses used the wholesale acquisition cost (WAC) plus an assumed hospital mark-up and assumed that survival benefits seen in clinical trials would continue beyond the duration of the trial. For tisagenlecleucel, it was assumed that the drug manufacturer would receive payment only if patients had responded to treatment at one month, based on the company's announced outcomes-based pricing arrangement with treatment centers.

Further analyses suggested that cost-effectiveness findings would be less favorable if the possibility of late relapses (after available follow-up in the trials) was included.

ICER'S VALUE-BASED PRICE BENCHMARKS

What is a fair price for CAR-T therapies based on their value to patients and the health care system?

After accounting for price mark-ups typical of hospital-administered therapies, **tisagenlecleucel's** price would remain in alignment with value even if price premiums of 102%-194% were applied.

Axicabtagene ciloleucel's price could be increased by up to 11% and remain in alignment with the upper threshold (\$150,000 per QALY gained) but would need to be discounted by 28% to align with the lower boundary (\$100,000 per QALY gained).

Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients could be treated with CAR-T therapies before crossing a \$915 million budget impact threshold?

Tisagenlecleucel for B-ALL

Due to the small number of patients expected to receive treatment in any given year, tisagenlecleucel used for B-ALL was not projected to cross the budget impact threshold.

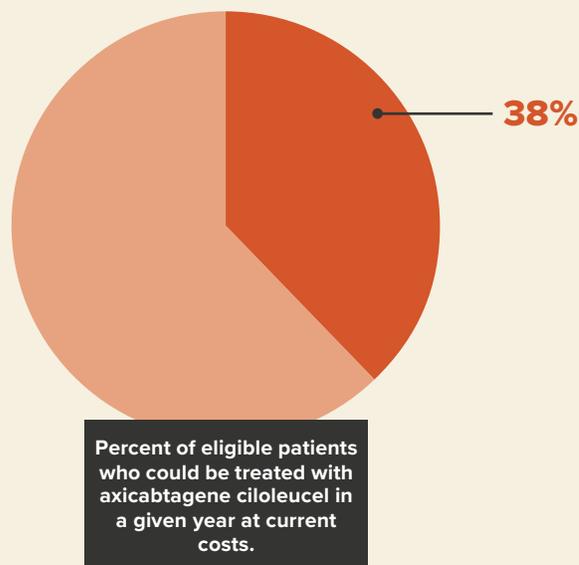
Axicabtagene Ciloleucel for Relapsed or Refractory NHL

While cost-effective in the long-term, potential budget impact analyses found that the short-term costs of axicabtagene ciloleucel for relapsed or refractory NHL could exceed ICER's \$915 million threshold for annual budget impact at its current price; only 38% of the estimated 5,900 eligible patients could be treated in a given year before crossing the threshold.

AFFORDABILITY AND ACCESS ALERT: AXICABTAGENE CILOLEUCEL

ICER is issuing an Affordability and Access Alert for axicabtagene ciloleucel used in adults with NHL. This alert is intended to signal when the added health care costs associated with a new treatment may be difficult for the system to absorb over the short term without displacing other needed services or contributing to unsustainable growth in health care insurance costs.

During the public meeting clinical experts and patient advocates agreed that all eligible patients should have access to this treatment, and that insurance coverage should align with this goal. ICER encourages all stakeholders to consider whether action should be taken to achieve additional price discounts, prioritize treatment access, find ways to reduce waste, or take other policy steps to manage budget implications.



Voting Results

CTAF deliberated on key questions raised by ICER's report at a public meeting on March 2, 2018. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

CLINICAL EVIDENCE

The Panel found evidence sufficient to show a net health benefit of tisagenlecleucel versus chemoimmunotherapy in B-ALL* and NHL, and a net health benefit of axicabtagene ciloleucel versus chemoimmunotherapy** in NHL.

Evidence was voted insufficient to distinguish between tisagenlecleucel and axicabtagene ciloleucel in NHL.

**In B-ALL tisagenlecleucel was compared to clofarabine or comparable immunotherapy or chemotherapy regimens.*

***Regimens used in SCHOLAR-1 trial*

LONG-TERM VALUE FOR MONEY

A majority of the Panel voted that tisagenlecleucel represents an intermediate long-term value for money, nothing that despite the cost-effectiveness of the therapy falling within commonly-accepted thresholds, the level of uncertainty in the data precluded a high value vote. Votes on the value of axicabtagene ciloleucel were split between intermediate and low, with Panel members citing similar concerns around uncertainty.

Key Policy Implications

The CTAF Panel participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the [full report](#).

EARLY COMMUNICATION

For treatments with the potential to have a major impact on patterns of care and costs, manufacturers, insurers, and providers should meet prior to FDA approval to discuss the drug's potential role in therapy, key patient subpopulations, pricing parameters, and payment arrangements, a step that will reduce unnecessary delays in delivering care to patients by addressing financial uncertainties for insurers and providers.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Before voting on value, Panel members weighed other benefits and contextual considerations of the therapies. Many highlighted the effects on caregiver burden and the novel mechanism of action as key other benefits, while some discussed the potential negative effects on the potential effect on health disparities. Many felt that the high severity of the disease states and the uncertainty regarding both long-term risks and the magnitude and durability of long-term benefit were significant contextual considerations.

SETTINGS OF CARE

CAR-T should initially be delivered in manufacturer-accredited centers to ensure the quality and appropriateness of care. Once providers gain sufficient expertise to address the serious side effects that can accompany CAR-T therapy, it would be preferable to limit therapy to centers of excellence accredited by specialty societies.

Key Policy Implications (continued)

INNOVATIVE PAYMENT MODELS

- Value-based pricing should be viewed in context with the affordability of a new treatment based on the size of the population eligible to receive the therapy.
- Manufacturers and insurers should ensure that outcomes-based pricing arrangements are linked to meaningful clinical outcomes assessed with sufficient follow up.
- For novel therapies approved with limited evidence, manufacturers and payers should consider a lower launch price with potential for increase if clinical benefits are confirmed, or a higher initial price tied to requirement for refunds or rebates if real-world evidence fails to confirm high expectations.
- Manufacturers should acknowledge public contributions to the costs and the risk involved in the development of emerging therapies.
- Manufacturers, insurers, and governments should work to remove barriers to indication specific pricing.
- Hospital mark-up should reflect the expected additional cost for care delivered in the hospital, rather than a percentage of the drug cost.

GENERATING ADDITIONAL EVIDENCE

- All patients treated with CAR-T therapy should enter into a registry with planned long-term follow-up.
- Researchers, manufacturers, and specialty societies should standardize definitions of benefits and harms early in the development process so that outcomes can be credibly compared across therapies.
- Studies are needed to determine the optimal positioning of CAR-T therapy in the sequencing of treatments for both B-ALL and B-cell lymphomas.

PATIENT EDUCATION

Centers of excellence should ensure that patients receive education on what to expect while undergoing CAR-T therapy and the long-term consequences of these treatments.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: CTAF, the Midwest CEPAC, and the New England CEPAC. These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information, visit <http://icer-review.org>.