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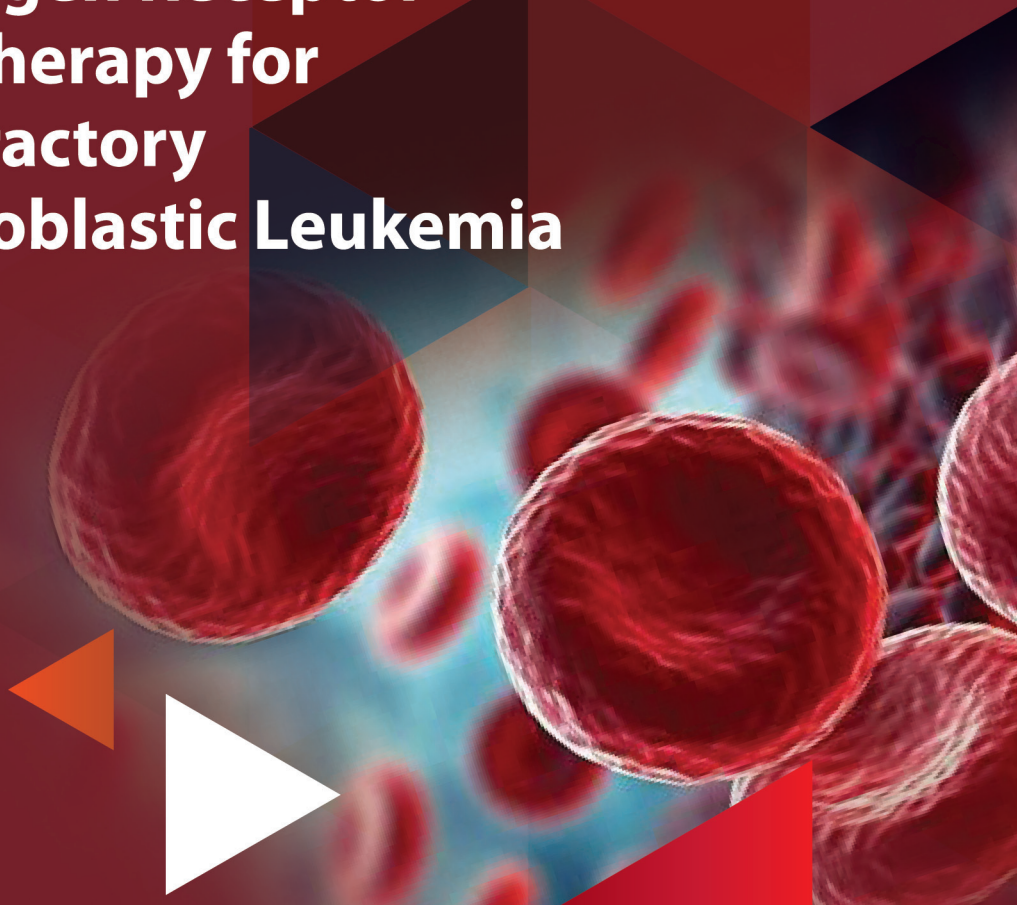
MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

Chimeric Antigen Receptor (CAR)-T Cell Therapy for Relapsed/refractory Acute Lymphoblastic Leukemia



MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
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DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations available at the time of development. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since completion of the review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

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EVIDENCE INFORMED DELIBERATIVE PROCESS

This Health Technology Assessment underwent an evidence informed deliberative process during the Health Technology Assessment (HTA) Technical Advisory Committee meeting, chaired by the Director, Medical Development Division, MOH. Then it was endorsed in the HTA-CPG Council meeting chaired by the Director General of Health.

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Complex E, Precinct 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 603 8883 1229
Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

ISBN: 978-629-7842-09-7

Cataloguing-in-Publication Data
Perpustakaan Negara Malaysia
A catalogue record for this book is available from the National Library of Malaysia

eISBN 978-629-7842-03-5

MOH/P/PAK/484.22(TR)-e

This HTA report has been endorsed in HTA & CPG Council Meeting 2/2024 (November 2024).

SUGGESTED CITATION: Roza S, Nurul Nashriq MH, Nurkhodrulnada ML, Khairil Idham I and Izzuna MMG. Chimeric Antigen Receptor (CAR) – T cell for relapse/refractory Acute Lymphoblastic Leukemia : Health Technology Assessment. Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2024. 61 p. Report No.: 04/2024. ISBN: 978-629-7842-09-7

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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ACKNOWLEDGEMENT

The authors of this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.
- Technical Advisory Committee for Health Technology Economic Evaluation.

Dato' Dr Saunthari Somasundaram, President & Medical Director, National Cancer Society Malaysia (NCSM); Dr. Kavinash Loganathan, Research Coordinator, Health Literacy, Education and Public Policy; and Dr. Jason Chin Yu Aun, Operations Lead, CARE Department, NCSM.

EXECUTIVE SUMMARY

Acute lymphoblastic leukemia (ALL) is a life threatening blood cancer, which rapidly progressing, defined by high percentage of blast in the blood, bone marrow and by the predominant lineage of malignant cells.It is the most common type of cancer in pediatric patients, accounting for 26% of childhood cancer; and the most common form of childhood leukemia representing 75% to 80% of acute leukemias, while ALL represents approximately 20% of all leukemias among adults. Its age-adjusted incidence rate in the United States is 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths (2021). The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and the second peak around the age of 50. In Malaysia, its incidence and mortality was 3.8% and 5.2% (2022). It is the sixth most common cancer with 4273 cases registered in Malaysia (2012 to 2016), and majority of them were from 0 to 14 years. ALL can be classified as B-cell precursor ALL (B-ALL), which occurs in 85% of diagnosed patients and T-cell ALL (T-ALL), accounting for 15% of cases, according to the 2017 revision to the WHO classification. B-cell ALL is primarily diagnosed in children, with three quarter of cases were diagnosed in children less than six years.

The progress of ALL treatment is reflected by the increase in the 5-year overall survival (OS) from 57% (1970s) to 96% recently; and the 5-year event free survival (EFS) reaches 92%. Nevertheless, the estimated 5-year survival rates in Asia range between 44.3% and 80%. Despite advances in treatment, the relapse rate remains high (20% of children). Patients with relapsed or refractory (r/r) B-ALL have a lower cure rate, with an estimated 20% overall 5-year survival. ALL is much less frequent in adults, representing 0.2% of all cancers. Prognosis is less encouraging, with an expected 5-year OS between 20% and 40%, despite complete remission (CR) rates of 85% to 90%. After relapse, the reported OS was only about 7%.

Complexity of ALL treatment regimens involve risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative ALL; and supportive care consideration. Standard treatment paradigms for acute leukemia have centered on high-intensity induction chemotherapy to achieve complete remission (CR) followed by allogeneic hematopoietic cell transplant (allo-HCT) in certain patients to eradicate residual disease.The treatment regimens are typically intense involving many chemotherapeutic agents that carry a multitude of toxicity risks. However, despite the highly toxic intensified therapies, durable remission is difficult to achieve.For patients with high-risk features in first complete remission (CR1), refractory or relapsed disease; treatment option remains allo-HCT. Most children, prior to allogenic HSCT, receive conditioning that include total body irradiation, which could impact their adult life. Hematopoietic Stem Cell Transplantation (HSCT) presents significant limitations and the outcome is patient dependent, therefore, using alternative method to address these challenges is crucial. For patients having relapsed or refractory B-cell ALL, there is no standard treatment approach and outcomes are poor. Treatment options are limited for these patients and include salvage chemotherapy, subsequent allogeneic stem cell transplant (SCT) if appropriate, enrolment in clinical trial and palliative care.

The introduction of safer therapies has become a priority in the management of hematological cancer patients. The advent of cancer immunotherapy offers additional options beyond standard regimen. Targeted immunotherapy utilizing antibodies, antibody–drug conjugates (ADCs), immunotoxins, bi-specific antibody T cell engagers (BiTEs), and chimeric antigen receptor (CAR)-T cells have changed the treatment landscape for relapsed and high-risk B-ALL. Advances in harnessing the immune system in cancer treatment have defined the past decade of progress in oncology.

CAR-T cell therapy is an individualized cell-based gene therapy that harness the natural function of body's T lymphocytes. T cells are genetically engineered to express a specific CAR, designed to recognize a specific tumor associated antigen, allowing the T-cells to actively target and selectively kill cells expressing that antigen (e.g.CD19). Various CAR designs are being studied, with CD19 being the most commonly targeted antigen, and CD28 and 4-1BB being the most widely used co-stimulatory domain. CAR-T cells are a cellular immunotherapy with remarkable efficacy in treating multiple hematologic malignancies, however they are associated with prices that are prohibitively expensive for many countries. In Malaysia, approximately 20 adult patients in Ampang Hospital were started on CAR-T cell therapy manufactured by China via compassionate use, and several patients from University Hospital received CAR-T which is locally manufactured. However as of now, there is no CAR-T cells being registered with the National Pharmaceutical Regulatory Agency (NPRA), and they are not available in the MOH formulary. Addressing the feasibility of CAR-T cell as therapy with better efficacy and lower toxicity to achieve durable remission is pivotal to meet the increasing needs of patients with r/r ALL in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CAR-T cells in the management of r/r ALL patients in Malaysia as requested by a pediatric Haemato-Oncologist from Hospital Tunku Azizah, Kuala Lumpur.

Technical features

CAR-T cell therapies use genetically modified, autologous T cells to target and destroy cancer cells. The therapy involves expressing engineered receptors (known as CARs) in a patient's immune cells (i.e. a T cell), to direct their action to specific cancer cells.

White blood cells are taken from a patient in a procedure called "apheresis" or leukapheresis and sent to a laboratory or manufacturing facility. The T cells are separated and then modified so that they express an artificial receptor on their surface, allowing the engineered T-cell to find and attack the cancer cell. These artificial receptors are called "chimeric antigen receptors" (CARs). The number of engineered CAR T cells is multiplied in the laboratory or manufacturing facility. When there are enough of these cells, they are frozen and sent to the patient's treatment center. There, the CAR T cells are thawed and given back to the patient via an intravenous infusion. The most frequently targeted antigen in CAR T-cell immunotherapy for leukemia and lymphoma is called "cluster of differentiation (CD) 19" (CD19).

The first step is leukapheresis, which involves harvesting the patient's T cells from peripheral blood. Protocol requirements can vary, but a circulating CD3 count of at least 150/mm^3 is needed. Commonly used apharesis platform is Spectra Optia system. Harvested T cells are sent to a specialist or certified laboratory to be genetically modified to express a CAR specific to CD19 B lymphocytes (i.e. cancerous cells). This is accomplished using either viral or non-viral methods. Transduction involves the use of viral vectors to deliver RNA into the patient's T cells. After selection of modified cells, the cells are cultured (grown in expanded numbers) until there are enough of them for clinical use. The CAR-T cells are generally returned to the hospital for infusion into the patient three to four weeks after leukapheresis.

In the meantime, patients may receive bridging chemotherapy to control their disease while the CAR-T cells are being manufactured. To promote persistence and expansion of the CAR-T after infusion, lymphodepleting chemotherapy is given the week before the CAR-T infusion. To decrease potential reactions to the CAR-T infusion, patients are pre-medicated with antihistamines prior to the infusion (30 to 60 minutes). Finally, patients receive the CAR-T cells as a one-off intravenous infusion, and are then monitored for adverse events in the in-patient setting. The dose of CAR-T cells administered to patients is dependent on the patients' diagnosis, body weight, and type of therapy (i.e. Axi-cel, Tisa-cel etc).

Table 1: List of FDA-approved CAR T-cell products

Generic name	Brand name	Approved indication	Approval date	Acronym for pivotal trial	List price (2023) (USD)
Tisagenlecleucel (Tisa-cel)	Kymriah (Novartis)	r/r pediatric & young adult (<25) B-ALL	30 Aug 2017	ELIANA	543,828
		r/r adult DLBCL, HGBL, transformed DLBCL	1 May 2018	JULIET	427,048
		r/r FL	27 May 2022	ELARA	427,048
Axicabtagene ciloleucel (Axi-cel)	Yescarta (Kite)	r/r DLBCL	18 Oct 2017	ZUMA-1	424,000
		r/r FL	2 Apr 2021	ZUMA-5	424,000
Lisocabtagene maraleucel (Liso-cel)	Breyanzi (Bristol Myers Squibb)	r/r DLBCL, HGBL, transformed DLBCL,PMBL	5 Feb 2021	TRANSCEND-NHL-001	447,227
Brexucabtagene autoleucel (Brexu-cel)	Tecartus (Kite)	r/r MCL, adult r/r B-ALL	24 Jul 2020	ZUMA-2, ZUMA-3	424,000
Idecabtagene vicleucel (Ide-cel)	Abecma (Bristol Myers Squibb)	r/r MM	1 Oct 2021	KarMMa	457,255
Ciltacabtagene autoleucel	Carvykti (Janssen Oncology & Legend Biotech)	r/r MM	28 Feb 2022	CARTITUDE-1	465,000

Policy question

Should CAR-T cell therapy be used as a standard treatment option for patients with relapse or refractory Acute Lymphoblastic Leukemia in Malaysia?

Objective

i. To assess the comparative effectiveness and safety of CAR-T cell therapy in the treatment of patients with relapsed or refractory Acute Lymphoblastic Leukemia.
ii. To evaluate the economic, organizational, social, ethical and legal implications of CAR-T cell therapy in the treatment of patients with relapsed or refractory Acute Lymphoblastic Leukemia.

Methods

Part A: Systematic Review of Effectiveness, Safety & Cost-Effectiveness

Systematic literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to September 2024, EBM Reviews - Health Technology Assessment (3rd Quarter 2024), EBM Reviews - Cochrane Database of Systematic Review (2005 to September 2024), EBM Reviews - Cochrane Central Register of Controlled Trials (September 2024), EBM Reviews - NHS Economic Evaluation Database (3rd Quarter 2024), and EMBASE. Parallel searches were run in PubMed, INAHTA database and regulatory agency websites such as US FDA. Search was limited to articles in English and in human. Detailed search strategy is as in Appendix 3. The last search was performed on 15 September 2024. Additional articles were identified from reviewing the references of retrieved articles.

Part B: Economic Evaluation

A cost-effectiveness analysis (CEA) was conducted from the perspective of Ministry of Health (MOH), Malaysia, in which a partitioned survival model with three-health states was constructed and analysed using R software and Microsoft Excel 2019. A lifetime horizon with four-week cycle was applied in the base case analysis. The objective of this CEA is to assess the incremental cost-effectiveness ratio (ICER) of chimeric antigen receptor T-cell (CAR-T) therapy when compared to blinatumomab, a bispecific T-cell engager (BiTE) and salvage chemotherapy regimen (SCR) in relapsed/ refractory B-ALL cases among patients age 25 and younger. The primary outcomes included total cost and quality-adjusted life years (QALYs) gained for each treatment strategy as well as incremental cost-effectiveness ratios (ICERs) of CAR-T against BiTE and SCR. An annual discount rate of three per cent was applied to both costs and outcomes estimated in the base case analysis.

Input on the treatment effects was drawn from the systematic review carried out in Section A of this report as well as external data from published literature, which included the landmark trials on CAR-T, BiTE and SCR. Meanwhile, costs for drug acquisition and disease management were based on the available local data. Health utility values for event-free and progressive disease states and other key parameters applied to the model were sourced from previously published studies. As there was no explicit national cost-effectiveness threshold (CET) available, one time of the gross domestic product (GDP) per capita of Malaysia in 2023 was used in this analysis (MYR 55,000/QALY).

Results & Conclusion

Part A: Systematic Review of Effectiveness, Safety, Cost-effectiveness

The 19 full text articles which were finally selected in this review comprised of 15 systematic review (SR), with or without meta-analysis, network meta-analysis, two non randomized trial, one RCT and one CUA.

All SR included were published in English language between 2019 and 2024 and primary studies included in the SR on effectiveness and cost-effectiveness were from multicountries; including the United States, Canada, UK, Germany, Italy, China, Spain, Netherland, Japan, Australia, Switzerland, as well as CUA conducted in Singapore, and primary studies from China. The SR included in this review comprised mainly of SR of clinical trial; and clinical trial with observational studies. A range of five to 38 primary studies were included in the SR in this review. Overall in total, this review enrolled 8,585 participants with r/r B-ALL (range of 120 to 2134 participants). Age of participants in the review ranged from 0 to 84 years old. Study population involved patients with hematological malignancy in some of the SR included.

The longest time of follow-up documented in the review was up to 77 months. Of the SR assessing effectiveness and safety, five evaluated CD19 CAR-T cell, while six evaluated CD19/CD22 or CD19 and CD22 CAR-T cell therapy in these population. One of the SR included involved patients with r/r CNS leukaemia. There is scarce information on prior treatment or intervention received by the study population, with one SR documented history of patients with prior one HSCT in their review.

There was variation in the dose of CAR-T cell received by the study population, ranging from 0.2 x 1^{05}/kg to 5 x 10^{8}/kg or 2.5 x 10^{5}/ m2 to 3.3 x 10^{9}/m2. The SR of CUA included were varied in perspective namely healthcare, provider, public healthcare, payer, and societal.

Effectiveness

Based on the above review, there was good level of evidences on CAR-T cells to be used in the management of patients with r/r B-ALL.

This review showed overall CAR-T cells appeared beneficial in achieving Complete Remission/ CRi and improving in OS, compared to Blinatumomab, Inotuzumab ozogamicin, and standard chemotherapy in patients with r/r B-ALL.CAR-T cells. CAR-T cells demonstrated ability to achieve MDR negative CR, best complete response with low incidence of relapse.

CD19 CAR T-cells was superior in achieving CR/CRi compared with: Blinatumomab (OR=8.32, 95% CI: 1.18 to 58.44) and Standard chemotherapy (OR=16.4, 95% CI: 2.76 to 97.45). Multiple treatment comparison showed CD19 CAR-T rank the highest with SUCRA of 88.2%, followed by dual CD19/CD22 CAR-T, sequential CD19-22 CAR-T, Inotuzumab Ozogamicin, Blinatumomab and standard chemotherapy. CR rate ranges from 81% to 93% at day 30.

The MRD negative Complete Remission achieved 81% (ranged from 64% to 87%), at 4 weeks post-infusion. The MRD negative CR rate was higher (70%) with anti CD19 or anti CD-22, compared to dual anti-CD19/22 (64%)

CD19 CAR T-cells and dual CD19/CD22 CAR T-cells significantly improved 1-year OS rate vs Blinatumomab, Inotuzumab ozogamicin, and standard chemotherapy. Network comparison showed Dual CD19/CD22 CAR-T rank the highest with SUCRA of 99.3%, followed by CD19 CAR T, Blinatumomab, Inotuzumab izogamicin and standard chemotherapy.

- The 1-year OS rates ranged from 58% to 84%; 2-year OS and 5-year OS were 56.5% and 44.1% respectively. The median OS was 36.2 months (95% CI 28.9, NR).
- The 1-year EFS rates following CAR-T cell therapy ranged from 46% to 76%, 2-year and 5-year were 42.1% and 35%. The Median EFS was 13.3 months (95% CI 12.2 to 17).
- Best Complete Response is higher following CD22, and CD19/CD22 CAR-T cells in patients with r/r ALL (75% and 90%) vs NHL (64% and 47%).
- Incidence of relapse is lowest following anti-CD22 (24%), and in terms of costimulatory domain, relapse is lowest with CD28ζ domain (16%).

Similarly, in patients with r/r ALL with CNSL, CAR-T cells demonstrated ability to achieve 87.5% CR/Cri and 72.9% MRD negative CR at day-30. The median OS was 16.0 months, with median EFS of 8.7 months. The 6-month OS rate was 72% (95%CI: 55.6 to 86.1) and EFS rate was 53.3% (95%CI: 36.5 to 68.1).

Safety

Tisagenlecleucel received regulatory approval from USFDA, EMA, Health Canada, Ministry of Health and Welfare, Japan. Tisagenlecleucel was designated an orphan medicinal product for the treatment of B lymphoblastic leukaemia/lymphoma (2014) (EU/3/14/1266).

Following CAR-T cell therapy, CRS was reported in 81 to 92% of patients, with higher grade CRS (>3) occurred in 6% to 27% of cases. Incidence of any grade CRS occurred in CD22 targeted and CD19/CD22 targeted was almost comparable. Any grade neurotoxicity occurred in 30 to 37% of cases, while severe ICANS were reported in 3% to 14% of patients whom underwent CAR-T cell therapy. Higher neurotoxicity was reported with anti-CD22 than anti-CD19/CD22 [0.83 (95% CI: 0.60 to 0.98)] and [0.77 (95% CI: 0.71 to 0.83)],respectively. Other reported AE includes infection: 12.2%, Graft vs Host Disease: 23.4%, and all cause 30-days mortality 1%.

Cost-effectiveness

Cost-utility analysis conducted in various countries from payer and provider perspective estimated the incremental cost-effectiveness ratio (ICER) for CAR-T therapies ranged from: USD$21,623 to USD$97,511 per QALY in adults; and USD$18,753 to USD$246,177 per QALY in paediatric patients. The evidence demonstrated that Tisagenlecleucel is expensive therapy than conventional alternatives, generated more QALYs than comparators, but their cost-effectiveness was uncertain. However, CAR-T was likely to be cost-effective compared to the other treatment strategies (studies such as in Switzerland, Japan, Singapore), with varied WTP thresholds. Median cost (USD 2019) for CAR-T cell therapy in the reported studies was USD$561,075, with the list drug price as the main cost driver.

Organizational

Patient eligibility should be assessed by a CAR-T center multidisciplinary team (MDT) including cellular therapy and haematology/oncology disease specialists. Patients should be evaluated for their general suitability to receive CAR T-cell therapy prior to leukapheresis; for factors such as age, Eastern Cooperative Oncology Group performance status (ECOG PS), history of prior malignancies, active infections and history of central nervous system disease.

Implementation of CAR-T cells require collaboration across the MDT and comprehensive training of personnel involved in CAR-T delivery including haematology, intensive care, neurology, pharmacy and laboratory. In addition to the training, high demands are placed on quality management by both the pharmaceutical industry and the government. The relevant standards in accreditation scheme in cellular therapy require that clinical, collection, and processing facility personnel participate in continuous education activities to ensure high quality patient care, medical and laboratory practice.

Post-marketing pharmacovigilance over a defined period post-infusion is mandated to ensure ongoing evaluation of the efficacy and safety of licensed CAR-T in the real-world setting via dedicated registry. Registries such as Centre for International Blood & Marrow Transplant Research (CIBMTR) or European Society for Blood and Marrow Transfusion (EBMT) may become essential tools for this endeavour, to capture infrequent and delayed events.

Given the complexity of ALL treatment regimens and the required supportive care measures, patients should be treated at a specialized cancer centre with expertise in managing ALL. CAR-T is best delivered from within an accredited haematopoietic cell transplantation (HCT) program. In Europe, to be a CAR-T delivery site, accreditation with Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE is recommended.

For safe delivery of CAR-T therapy, a robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain-of-custody and chain-of-identity of the cellular product, and facilitate communication to manage potentially severe toxicities. To fulfill these robust requirements for a safe delivery of CAR-T, only selected larger institutions are identified for performing CAR-T therapy, these are typically centers with allo-HCT experience. Centres should have regulatory approval for storage of genetically modified organisms (GMOs). Before infusion, patients are medically assessed to ensure they are fit to proceed; identity and consent is confirmed. ESMO guideline recommend that patients remain hospitalised for at least 14 days following infusion.

The European Society for Blood and Marrow Transplantation (EBMT) and American Society for Blood and Marrow Transplantation (ASBMT) suggested referring patients with induction failure, early relapse after achieving first complete remission, and adult patients with relapsed/refractory B-ALL to CAR-T cell therapy programs to allow discussion of the optimal timing of apheresis and potential of enrollment in CAR-T trials. Prompt referral to a CAR-T center should be made as soon as a patient meets referral criteria (e.g., at the time of relapse, before starting therapy if possible) especially as specified recovery periods from prior therapy are required before leukapheresis.

Chemotherapy after T-cell collection by leukapheresis is usually required to control disease until the manufacturing of CAR-T is complete. Bridging chemotherapy should focus on disease control rather than remission induction while minimizing organ toxicity or risk of infections.

The EBMT & ASBMT (2019) recommended that patients receive fludarabine/cyclophosphamide lymphodepleting (LD) chemotherapy to enhance CAR-T proliferation the week before CAR-T infusion with a minimum of 2 rest days. Where CAR-T infusion is delayed by >4 weeks, repeat LD is recommended.

The Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on immunotherapy for the treatment of acute leukaemia recommended;

– New, experimental drugs should be administered at centers that have proper support, infrastructure, and subspecialties.
– CAR-T cell therapy is strongly recommended for patients with relapsed ALL after second-line and/or third-line therapy.
– Patients treated with CAR-T cells or blinatumomab should be monitored vigilantly for signs of CRS and neurotoxicity including (but not limited to) fever, hypotension, and altered mental state. The management of CRS or neurotoxicity secondary to approved CAR-T cell therapy should follow established guidelines.

– Prior to being treated with immunotherapy, patients and caregivers should be educated about potential AEs and given clear instructions for call parameters for any toxicities.

The US Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T cells expressing at least one chimeric antigen receptor (CAR) when administered at health care facilities enrolled in the FDA risk evaluation and mitigation strategies and when used for FDA approved indication. Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL) when the identified criteria's are met.

The Malaysia National Guidelines for Haemopoietic Stem Cell Therapy Second Edition (2023) highlighted that CAR-T therapies shall be performed in recognised haemopoietic stem cell transplant centres with experience in handling leukapheresis, administration of conditioning regimen and infusion of cellular products. The centres shall have experienced physicians/ paediatricians who are trained in patient selection, planning of appropriate bridging and lymphodepletion conditioning regimen, product infusion and management of ensuing CAR-T-related complications. Mononuclear cell collection shall be performed at an accredited apheresis centre. Generation of CAR-T cells shall be performed in ISO5 clean room/Grade B cGMP. CAR-T centers are encouraged to participate in national/or international registries to ensure ongoing evaluation of safety, efficacy and long-term outcomes. This guideline also pointed that improving access to more affordable CART-cell therapies should be a priority.

In Malaysia, registration of cell and gene therapy should follow requirements as stipulated in the guidance document and guidelines for registration of cell and gene therapy products in Malaysia.

Social, Ethical

No evidence on social or ethical issues or implication on CAR-T therapy for patients with r/r B-ALL. The Malaysia National Cancer Society supported this assessment, which is timely to address the patients unmet need in the country. The society provide services and supporting facilities to patients with ALL; namely children's home of hope, dietitian support and play therapy. It was highlighted that together, these services will ensure for children with cancer, including those with relapsed/refractory ALL, receive not just medical care but holistic support addressing their physical, emotional, and nutritional needs during challenging time.

Legal

The EU pioneered the development of a specific regulatory framework by defining a specific classification for Advance Therapy Medicinal Product (ATMP) and establishing a centralised approval procedure for them. The cornerstone of this regulation is that marketing authorisation must be obtained prior to the marketing of ATMPs. The autogenous transplantation of cells has been defined as transplant products. For transplant products that are based on an individual patient's cells and can therefore not be standardised, marketing authorisation is granted for the manufacturing process.

Part B: Local Economic Evaluation

In the base case analysis, the ICERs estimated between CAR-T and BiTE to that of CAR-T and SCR were around MYR 181,400 per QALY gained and MYR 147,600 per QALY gained, respectively. The incremental gain in QALYs was notably larger for CAR-T compared to SCR, estimated at about eight years of quality-adjusted life. In contrast, the difference in QALYs gained between CAR-T and BiTE was approximately six years. The analysis has also shown that simulated patients receiving CAR-T therapy demonstrated longer event-free survival, estimated at approximately 10 years, compared to those treated with BiTE and SCR, with estimated durations of four years and one year, respectively.

Several scenario analyses were also performed, which included much lower CAR-T cost, different simulation durations, lower discount rate on the benefit gained and shorter duration for patients to be considered as long-term survivors were explored. Relative to the CET applied in this evaluation, the base case and all scenarios, with the exception of one, suggest that CAR-T therapy is not a cost-effective option, despite reductions in the estimated ICERs observed in several scenarios. From the deterministic sensitivity analysis, the cost of CAR-T has the largest impact on the estimated ICERs. Hence, reducing the cost of CAR-T to approximately one third of the base case cost would have led to significant reduction in ICER, making CAR-T a cost-effective treatment option when compared to the other treatment strategies. In addition, reduced discount rate of 1.5% on all the benefits accrued over the simulation time across all treatment strategies has led to considerable decrease in estimated ICERs and greater benefits gained, though still not cost-effective.

Other key-drivers identified to have great influence on the ICERs health utility value for health states associated with each treatment and proportion of eligible patients successfully infused with CAR-T. In the probabilistic sensitivity analysis, the graph suggests that while CAR-T therapy may offer more QALYs than BiTE and SCR, it often comes at a higher incremental cost, exceeding the base case CE threshold in most cases. A much higher threshold of approximately MYR 180,000 (3.3 times the base case threshold), and MYR 150,000 (2.7 times the base case threshold) is required for CAR-T to surpass BiTE and SCR, respectively, as a more cost-effective treatment strategy. Hence, it indicates that from a cost-effectiveness standpoint, CAR-T therapy may not be justifiable at the set threshold of MYR 55,000 per QALY gained. These findings suggest that, for CAR-T therapy to become a feasible option in Malaysia, significant reductions in price or adjustments in CETs would be necessary.

Conclusion

Part A: Systematic Review of Effectiveness, Safety, Cost-effectiveness

Based on the above review, there was moderate certainty evidences retrieved on CAR-T cells in its use in the management of patients with r/r B-ALL.

This review showed overall CAR-T cells appeared beneficial in achieving Complete Remission/ Complete Remission with incomplete hematologic recovery (Cri) and improving OS, compared to Blinatumomab, Inotuzumab ozogamicin, and standard chemotherapy in patients with r/r B-ALL.CAR-T cells. CAR-T cells demonstrated ability to achieve MDR negative CR, best complete response with low incidence of relapse.

Tisagenlecleucel received regulatory approval from USFDA, EMA, Health Canada, Ministry of Health and Welfare, Japan. Following CAR-T cell therapy, CRS (any grade) was commonly reported, followed by neurotoxicity (any grade). Other reported AE include infection, Graft vs Host disease and all-cause 30-days mortality.

Cost-utility analysis conducted in various countries from payer and provider perspective estimated the incremental cost-effectiveness ratio (ICER) for CAR-T therapies ranged from: $21,623 to $97,511 per QALY in adults; and $18,753 to $246,177 per QALY in paediatric patients. Though evidence demonstrated that Tisagenlecleucel is expensive than conventional alternatives, CAR-T was likely to be cost-effective compared to the other treatment strategies (in Switzerland, Japan, Singapore), with varied WTP thresholds.

Implementation of CAR-T cells require collaboration across the MDT and comprehensive training of personnel involved in CAR-T delivery including haematology, intensive care, neurology, pharmacy and laboratory. Post-marketing pharmacovigilance over a defined period post-infusion is mandated to ensure ongoing evaluation of the efficacy and safety of licensed CAR-T in the real-world setting via dedicated registry. Given the complexity of ALL treatment regimens and the required supportive care measures, patients should be treated at a specialized centre with expertise in managing ALL. CAR-T is best delivered from within an accredited haematopoietic cell transplantation (HCT) program.

Part B: Economic Evaluation

The findings from the CEA highlight both the clinical benefits and economic challenges of CAR-T cell therapy. While CAR-T cell therapy provides an estimated gain of six to eight additional QALYs for pediatric and young adult patients with r/r B-ALL, its high costs result in ICERs that exceed the acceptable threshold by 2.7 to 3.3 times. Consequently, CAR-T cell therapy is not a cost-effective alternative compared to current options like BiTE and SCR. Scenario analyses indicate that a significant reduction in CAR-T pricing could greatly enhance its cost-effectiveness. The adoption of this advanced therapy could be more feasible with substantial cost reductions and more flexible thresholds. In addition, innovative funding models and value-based payment structures could be explored to ensure continued assessments of its value as well as to mitigate CAR-T's financial burden and facilitate access without overextending MOH budgets. An investment in research to evaluate the real-world outcomes of CAR-T cell therapy in local settings could also yield data which would help validate model assumptions and refine ICER estimates, making the case for CAR-T cell therapy adoption in Malaysia more precise.

TABLE OF CONTENTS

ABBREVIATION

ADC	antibody–drug conjugates
AEs	Adverse events or adverse effects
Allo-HCT	allogeneic hematopoietic cell transplant
ALL	Acute lymphoblastic leukaemia
B-ALL	B cell Acute lymphoblastic leukaemia
BiTEs	bi-specific antibody T cell engagers
BSC	Best supportive care
CD19	Cluster of differentiation (CD) 19
CAR	Chimeric antigen receptor
CASP	Critical Appraisal Skills Programme
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CET	Cost-effectiveness threshold
CI	Confidence interval
CrI	Credible interval
CR	Complete Remission
CRS	Cytokine Release Syndrome
GvHD	Graft versus Host Disease
HTA	Health Technology Assessment
HSCT	Hematopoietic Stem Cell Transplantation
HR	Hazard ratio
HRQoL	Health Related Quality of Life
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
LY	Life year

MaHTAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
NCCN	National Cancer Care Network
NICE	National Institute for Health and Care Excellent
NMB	Net monetary benefit
ORR	Overall Response Rate
OS	Overall Survival
OSR	Overall Survival Rate
PFS	Progression Free Survival
PDSR	Progression Free Survival Rate
PSA	Probabilistic sensitivity analysis
PRISMA	Preferred Reporting Format for Systematic Review & Meta Analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
r/r	Relapsed / Refractory
ROB	Cochrane Risk of Bias Tool
ROBIS	National Collaborating Centre for Methods and Tools
SAE	Serious adverse event
SUCRA	Surface under the cumulative ranking
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WTP	Willingness to pay

CHAPTER 1.0

BACKGROUND

CHAPTER 1.0
BACKGROUND

Acute lymphoblastic leukemia (ALL) is rapidly progressing form of leukemia, defined by high percentage of blast in the blood, bone marrow and by the predominant lineage of malignant cells.[1] The disease is resulted from deregulation in various pathways in the cell cycle, characterized by uncontrolled proliferation of malignant cells and arrest in normal lymphoid progenitor cell development thereby inhibiting homeostatic hematogenous and immune functions.[2] It is the most common type of cancer in pediatric patients, accounting for 26% of childhood cancer; and the most common form of childhood leukemia representing 75% to 80% of acute leukemias, while ALL represents approximately 20% of all leukemias among adults.[3,4] Its age-adjusted incidence rate in the United States is 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths estimated in 2021. The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years.[5] The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and the second peak around the age of 50.[6] In Malaysia, the incidence and mortality of leukemia was 3.8% and 5.2% respectively (2022).[7] It is the sixth most common cancer in Malaysia with a total of 4273 cases registered (2012 to 2016) compared to 4573 cases (2007 to 2011). Majority of them were from 0 to 14 years. The lifetime risk was 1 in 307 (male) and 1 in 388 (female). [8]

ALL can be classified as B-cell precursor ALL (B-ALL), which occurs in 85% of diagnosed patients and T-cell ALL (T-ALL), accounting for the remaining 15% of cases, according to the 2017 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, based on the immunophenotype assessment. B-cell ALL is primarily diagnosed in children, with three quarter of cases were diagnosed in children less than six years.[9]

The progress of ALL treatment is reflected by the increase in the 5-year overall survival (OS) from 57% (1970s) to up to 96% in the most recent studies, depending on clinical and cytogenic features; and the 5-year event free survival (EFS) reaches 92%.[10,11] Nevertheless, the estimated 5-year survival rates in Asia range widely between 44.3% and 80%.[12] Despite significant advances in treatment, the relapse rate remains high (15 to 20% of children).[13] Patients with relapse or refractory (r/r) B-ALL have a much lower cure rate with an estimated 20% overall 5-year survival.13 In adults, ALL is much less frequent representing 0.2% of all cancers. Prognosis is less encouraging with ALL, with an expected 5-year OS between 20% and 40%, despite complete remission (CR) rates of 85% to 90%. [14] Adults with r/r ALL historically have a poor prognosis, with cure rate below 40%. After relapse, the reported overall survival was only about 7%.[15]

Complexity of ALL treatment regimens involve risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative ALL; and supportive care consideration.[16] Standard risk was assigned to patients age one to less than ten years and with WBC count less than 50x109 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk. Very high risk was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of BCR-ABL1 fusion protein; hypodiploidy; BCR-ABL1–like or Ph-like ALL; iAMP21; or failure to achieve remission with induction therapy.[17]

Standard treatment paradigms for acute leukemia have centered on high-intensity induction chemotherapy to achieve complete remission (CR) followed by allogeneic hematopoietic cell transplant (allo-HCT) in certain patients to eradicate residual disease.[1] The treatment regimens are typically intense involving many chemotherapeutic agents that carry a multitude of toxicity risks.[18] The first-line treatment of pediatric ALL is conducted in phases; induction, consolidation, intensification (reinduction, delayed intensification in some protocols), and remission maintenance therapy. Induction of remission is based on steroid therapy accompanied by cytostatic administration. Consolidation of remission and maintenance therapy in most protocols is based on systemic and intrathecal cytostatic administration. Commonly used cytostatic are methotrexate, daunorubicin, doxorubicin, vincristine, cytarabine, cyclophosphamide, thioguanine, and 6-mercaptopurine, and the entire therapy usually takes about two to three years. However, despite the highly toxic intensified therapies, durable remission is difficult to achieve.[9]

Radiation is used to treat ALL in selected groups of patients. Formerly, craniospinal irradiation was a crucial departure point in the treatment of leukemia. Currently, its eligibility depends on a specific central nervous system (CNS) status at diagnosis. CNS irradiation is used to control CNS recurrence, which commonly given in high-risk ALL patients with CNS status 3.[19] For patients with high-risk features in first complete remission (CR1), refractory or relapsed disease; treatment option remains allogenic hematopoietic stem cell transplantation (HSCT). Most children, prior to allogenic HSCT, receive conditioning that include total body irradiation, following which could impacting their adult life with condition such as hypothyroidism, delayed puberty and infertility.[9] Side effects such as Graft versus Host Disease (GvHD) in allogeneic HSCT are common. Hematopoietic Stem Cell Transplantation (HSCT) presents significant limitations and outcome of the consolidation treatment is patient dependent, therefore, using alternative method to address these challenges is crucial.[20]

The introduction of safer therapies has become a priority in the management of hematological pediatric patients. Genetic characterization of ALL has revolutionized treatment approaches with targeted therapies such as Tyrosine Kinase Inhibitors (imatinib, dasatinib, nilotinib) for ALL patients with Philadelphia chromosome, and Janus Kinase inhibitor (ruxolitinib) by targeting and blocking JAK proteins.[9] The advent of cancer immunotherapy offers additional options beyond standard regimen. Targeted immunotherapy utilizing antibodies, antibody–drug conjugates (ADCs), immunotoxins, bi-specific antibody T cell engagers (BiTEs), and chimeric antigen receptor (CAR)-T cells have changed the treatment landscape for relapsed and high-risk B-ALL. [1]

Advances in harnessing the immune system in cancer treatment have defined the past decade of progress in oncology. Development of CAR-T cell therapy represents a breakthrough in ALL therapeutics and transformed treatment paradigm for r/r B-ALL in children and young adults.[21] CAR-T cell therapy is an individualized cell-based gene therapy that harness the natural function of body's T lymphocytes. T cells are genetically engineered to express a specific CAR, designed to recognize a specific tumor associated antigen, allowing the T-cells to actively target and selectively kill cells expressing that antigen (e.g.CD19).[22]

Various CAR designs are being studied, with CD19 being the most commonly targeted antigen, and CD28 and 4-1BB being the most widely used co-stimulatory domain.[23] CD19 CAR-T cell has demonstrated complete remission rate as high as 90% in r/r B-ALL patients.24 The USFDA approved Tisagenlecleucel (Kymriah) for pediatric and young adults up to 25 years with r/r B-ALL in 2017 incorporates the 4-1BB co-stimulatory domain, while Brexucabtagene autoleucel (Tecartus) which incorporates the CD28 co-stimulatory domain, was approved for patients ≥18 years with r/r B-ALL (2021).[25]

CAR-T cells are a cellular immunotherapy with remarkable efficacy in treating multiple hematologic malignancies, however they are associated with high prices that are prohibitively expensive for many countries.[26] In Malaysia, approximately 20 adult patients in Ampang Hospital were started on CAR-T cell therapy manufactured by China via compassionate use, and several patients from University Hospital received CAR-T which is locally manufactured through AuxiTherapeutics and Plutonet. An open label phase II clinical trial is underway at Cell Therapy Centre, HCTM UKM involving patients with r/r B-ALL aged between 10 and 65 years. However as of now, there is no CAR-T cells being registered with the National Pharmaceutical Regulatory Agency (NPRA), and they are not available in the MOH formulary. Addressing the feasibility of CAR-T cell as therapy with better efficacy and lower toxicity to achieve durable remission is pivotal and timely to meet the increasing needs of patients with r/r ALL in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CAR-T cells in the management of r/r ALL patients in Malaysia as requested by a pediatric Haemato-Oncologist from Hospital Tunku Azizah, Kuala Lumpur.

CHAPTER 2.0

TECHNICAL FEATURES

CHAPTER 2.0
TECHNICAL FEATURES

CAR-T cell therapies use genetically modified, autologous T cells to target and destroy cancer cells. The therapy involves expressing engineered receptors (known as CARs) in a patient's immune cells (i.e. a T cell), to direct their action to specific cancer cells. [27]

The concept of using CAR-T cell to target tumour surface antigen was described in the late 1980s. The first-generation CAR-T, which included only the receptor component CD3z as an intracellular domain showed limited efficacy. The subsequent second-generation CAR-T then have the addition of co-stimulatory domain derived from either CD28 or 4-1BB. A viral vector is used to deliver the genetic material; which include the targeting antibody-based variable region, a transmembrane domain, a co-stimulatory domain, and the CD3z signaling domain into the patients' T cell. The third generation CAR-T contain additional costimulatory domains, aiming to improve proliferation, cytokine secretion, and in-vivo persistence.[27] (**Figure 1**)

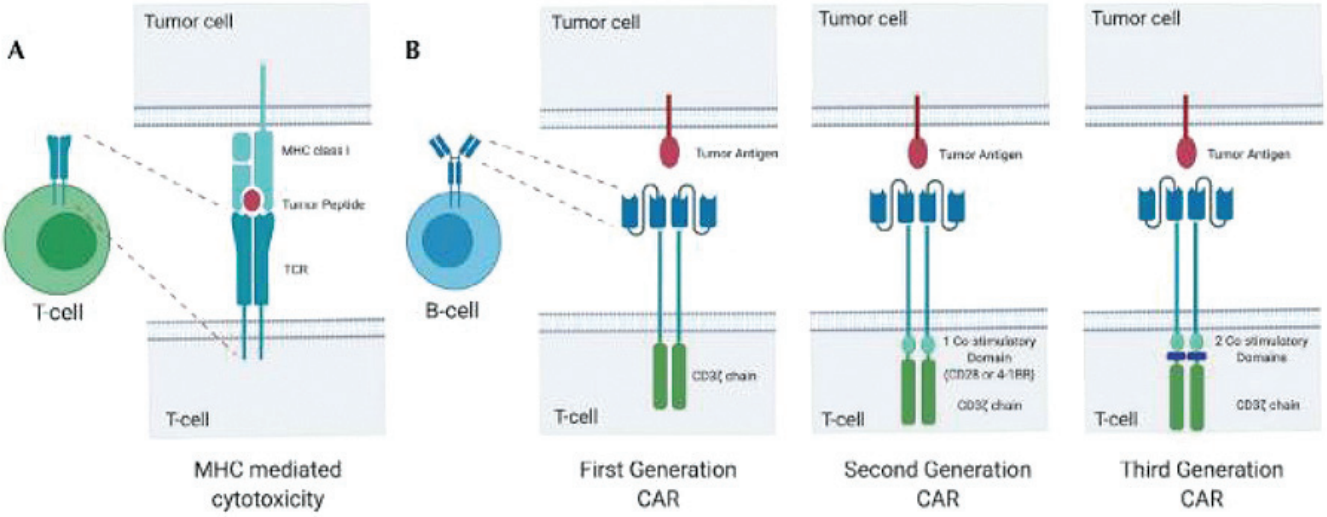


Figure 1: Mechanism of action for CAR-T cell therapy.

(A) Cytotoxicity mediated by T cell receptor of the major histocompatibility complex of a cell-surface antigen (B) Cytotoxicity through direct targeting of a cell-surface antigen by a CAR-T cell. (Source: Wall DA & Krueger J 2020)

The USFDA and Health Canada have approved two constructs for CAR-T production; Tisagenlecleucel, a-41BB based construct for R/R ALL in children and R/R B-cell lymphoma in adults; and Axicabtagene ciloleucel which uses the CD28 costimulatory construct for the treatment of R/R B-cell lymphoma in adults.Since the first CAR-T cell therapy was approved by the USFDA in 2017, (tisagenlecleucel (tisa-cel) for the treatment of B-ALL), there are now six CAR-T cell therapies approved in the United States for the treatment of hematologic malignancies (**Table 2**). [27]

Table 2: List of FDA-approved CAR T-cell products

Generic name	Brand name	Approved indication	Approval date	Acronym for pivotal trial	List price (2023) (USD)
Tisagenlecleucel (Tisa-cel)	Kymriah	r/r pediatric & young adult (<25) B-ALL	30 Aug 2017	ELIANA	543,828
		r/r adult DLBCL, HGBL, transformed DLBCL	1 May 2018	JULIET	427,048
		r/r FL	27 May 2022	ELARA	427,048
Axicabtagene ciloleucel (Axi-cel)	Yescarta	r/r DLBCL	18 Oct 2017	ZUMA-1	424,000
		r/r FL	2 Apr 2021	ZUMA-5	424,000
Lisocabtagene maraleucel (Liso-cel)	Breyanzi	r/r DLBCL, HGBL, transformed DLBCL,PMBL	5 Feb 2021	TRANSCEND-NHL-001	447,227
Brexucabtagene autoleucel (Brexu-cel)	Tecartus	r/r MCL, adult r/r B-ALL	24 Jul 2020	ZUMA-2, ZUMA-3	424,000
Idecabtagene vicleucel (Ide-cel)	Abecma	r/r MM	1 Oct 2021	KarMMa	457,255
Ciltacabtagene autoleucel	Carvykti	r/r MM	28 Feb 2022	CARTITUDE-1	465,000

HGBL : High grade B-cell lymphoma
PMBL : Primary mediastinal B-cell lymphoma
MCL : Mantle cell lymphoma
MM: Multiple myeloma
FL: Follicular lymphoma
DLBCL: Diffuse large B-cell lymphoma

According to EMA, Kymriah is classified as an advanced therapy medicinal product (ATMP), a medicine for human use that is based on genes, tissues or cells. It offers groundbreaking new opportunities for the treatment of disease and injury. This medicine was designated an orphan medicine, which means that it was developed for use against a rare, life-threatening or chronically debilitating condition or, for economic reasons, it would be unlikely to have been developed without incentives.

This medicine was granted entry to the EMA Priority Medicines (PRIME) scheme during its development. PRIME is a scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines reach patients earlier.[28]

Production and administration of CAR T cell therapies

CAR T-cell therapy is a type of immunotherapy that involves engineering patients' own T cells to recognize and attack cancer cells. White blood cells are taken from a patient in a procedure called "apheresis" and sent to a laboratory or manufacturing facility. The T cells are separated and then modified so that they express an artificial receptor on their surface, one that will allow the engineered T cell to find and attack the cancer cell. These artificial receptors are called "chimeric antigen receptors" (CARs). The number of engineered CAR T cells is multiplied in the laboratory or manufacturing facility. When there are enough of these cells, they are frozen and sent to the patient's treatment center. There, the CAR T cells are thawed and given back to the patient via an intravenous infusion.The most frequently targeted antigen in CAR T-cell immunotherapy for leukemia and lymphoma is called "cluster of differentiation (CD) 19" (CD19).

The process of producing CAR-T cell therapies is presented in Figure 2. The first step is **leukapheresis**, which involves harvesting the patient's T cells from peripheral blood. Protocol requirements can vary, but a circulating CD3 count of at least 150/mm^3 is needed to reliably collect a number of T-cells sufficient for manufacturing. Any apharesis platform can be used for cell collection, example of commonly used platform is Spectra Optia system.[29]

In the current CAR-T cell therapies, harvested T cells are sent to a specialist or certified laboratory to be genetically modified to express a CAR specific to CD19 B lymphocytes (i.e. cancerous cells). This is accomplished using either viral or non-viral methods. Transduction involves the use of viral vectors to deliver ribonucleic acid (RNA) into the patient's T cells. The RNA is subsequently reverse transcribed and integrated into the T cells' deoxyribonucleic acid (DNA), facilitating receptor expression; additional methods to insert RNA/DNA include chemical transfection, electroporation and the use of nanoparticles.[29]

After selection of modified cells, the cells are cultured (grown in expanded numbers) until there are enough of them for clinical use. The CAR-T cells are generally returned to the hospital for infusion into the patient three to four weeks after leukapheresis. [30]

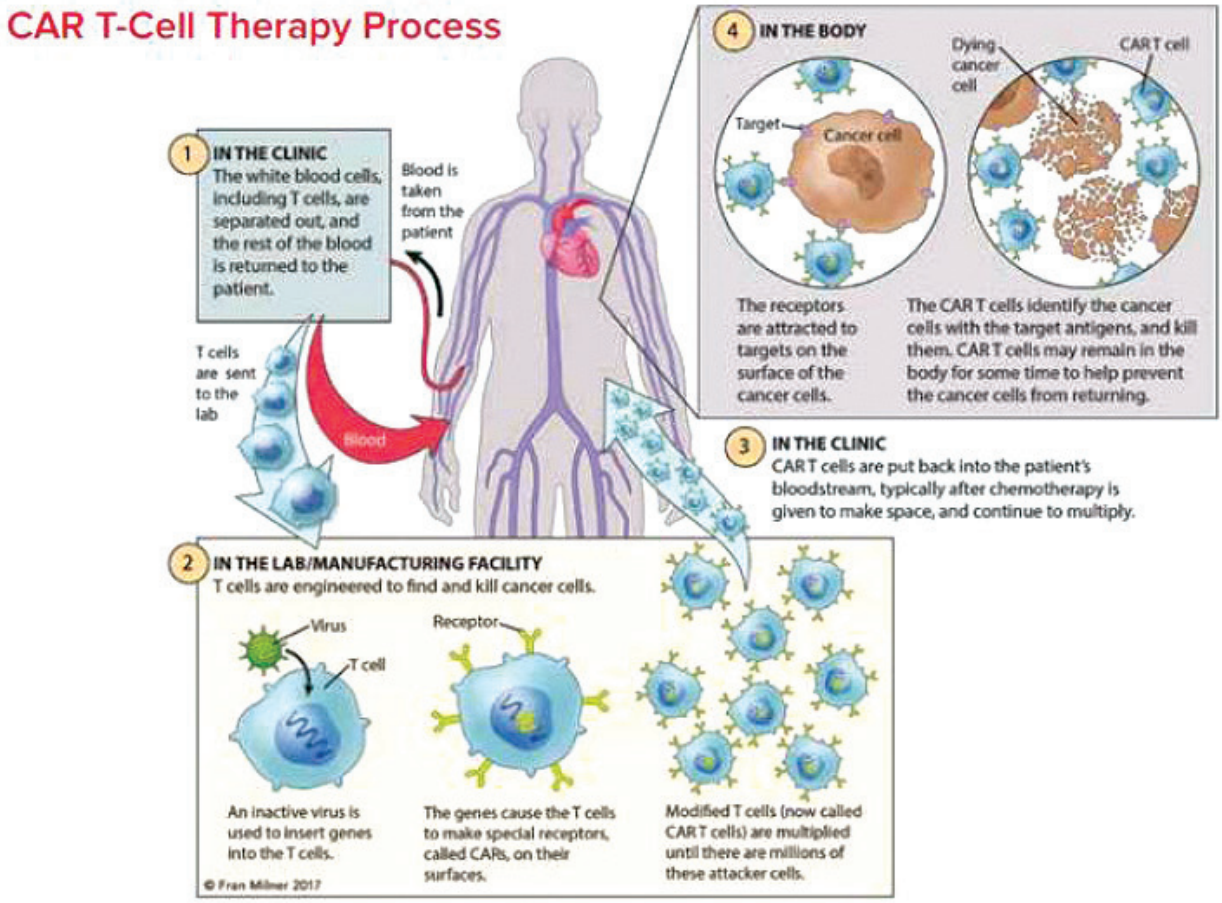
CAR-T cell manufacturing is conducted over approximately 8 to 12 days in an approved cGMP clean room facility in a closed or functionally closed system to reduce the risk of product contamination.Upon completion of manufacturing, CAR-T products must comply with quality control/end-product specifcations stipulated in the certifcate of analysis. Parameters may vary, but CAR-T products are usually characterized for release according to immunophenotypic, functional, and sterility assessments. An out-of specifcation (OOS) product cannot be released in the usual way, and its clinical use is at the discretion of the treating physician in concert with the regulatory authorities, informed through an OOS report.

In the meantime, patients may receive bridging chemotherapy to control their disease while the CAR-T cells are being manufactured. The optimal chemotherapy regimen for bridging depends on the patient's treatment history and prior toxicities. Drugs commonly used for bridging regimens include steroid, vincristine, mercaptopurine, methotrexate, low dose cytosine arabinoside, cyclophosphamide, etoposide and asparaginase. It is important that enough time be allowed between drug dosing and CAR-T infusion, the washout time, so as to not impair CAR-T function.[27]

To promote persistence and expansion of the CAR-T after infusion, lymphodepleting chemotherapy is given the week before the CAR-T infusion. Patients typically receive lymphodepleting chemotherapy with fludarabine, cytarabine, cyclophosphamide or bendamustine in different combinations depending on the indication. For patients with low cell or lymphocyte count, CAR-T could be infused without prior lymphodepleting chemotherapy. To decrease potential reactions to the CAR-T infusion, patients are pre-medicated with antihistamines prior to the infusion (30 to 60 minutes). Finally, patients receive the CAR-T cells as a one-off intravenous infusion, and are then monitored for adverse events in the in-patient setting. [31]

Therapy with CAR-T has unique toxicities that require coordinated management by multiple teams. Major acute toxicities include cytokine release syndrome (CRS), neurologic toxicity, tumour lysis syndrome and cytopenia. Four grades of CRS (depending of the presence of fever, degree of hypoxia and hypotension) standardize the reporting of CRS. The dose of CAR-T cells administered to patients is dependent on the patients' diagnosis, body weight, and type of therapy (i.e. Axi-cel, Tisa-cel).[31]

Contraindications to tisa-cel include known hypersensitivity to tisa-cel or any of the excipients (e.g. dimethyl sulfoxide, dextran 40, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium).[32] For safe delivery of CAR-T therapy, a robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain of custody and chain of identity of the cellular product, and facilitate communication to manage potentially severe toxicities.[33]



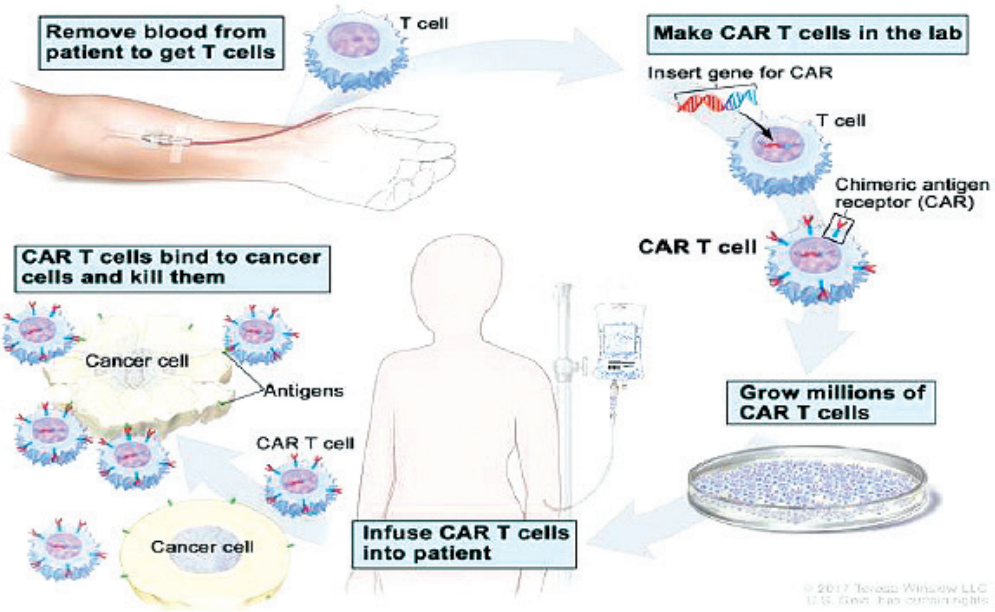


Figure 2: CAR-T process [Source; Leukemia and Lymphoma Society (above) National Cancer Institute (below)]

Dosage and method of administration

Each dose of CAR-T is customized treatment created using an individual patient's T-cells. For relapsed or refractory CD19-positive B-cell ALL, the usual dosage for patients aged ≤25 years (at the time of administration) is determined according to body weight and administered as a single intravenous dose.

– Body weight ≤50 kg: CAR-positive viable T cells at 0.2×10^6 to 5.0×10^6 /kg
– Body weight >50 kg: CAR-positive viable T cells at 0.1×10^8 to 2.5×10^8 (irrespective of body weight)

Kymriah should be used only in patients with relapsed or refractory CD19-positive B-cell ALL meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:[34]

- Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy
- Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy
- Patients who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation

Clinical Pharmacology

After the infusion of Kymriah into pediatric and young adult patients with r/r B-cell ALL and r/r DLBCL, Kymriah typically exhibited an initial rapid expansion followed by a slower biexponential decline. In patients with ALL, tisagenlecleucel was present in the blood and bone marrow beyond 2 years, whereas in patients with DLBCL with complete response, tisagenlecleucel was detected for up to 2 years in peripheral blood and up to month 9 in bone marrow. There was no apparent relationship between cellular kinetic and dose or body weight. In the pediatric group, a high tumor burden at baseline resulted in higher expansion of CAR T cells. Tocilizumab (used for treatment of cytokine release syndrome [CRS]) was not shown to have an impact on the cellular kinetics of tisagenlecleucel, as the transgene continued to expand and persist following tocilizumab administration. Treatmentinduced anti-murine CAR19 antibodies were shown in 34.6% of pediatric and young adult patients with ALL and in 5% of adult patients with DLBCL. However, preexisting and treatment-induced antibodies were not associated with an impact on clinical response, nor did they have an impact on the expansion and persistence of tisagenlecleucel. [28]

CHAPTER 3.0

POLICY QUESTION

CHAPTER 3.0
POLICY QUESTION

Should CAR-T cell therapy be used as a standard treatment option for patients with relapse or refractory B-cell Acute Lymphoblastic Leukemia in Malaysia?

CHAPTER 4.0

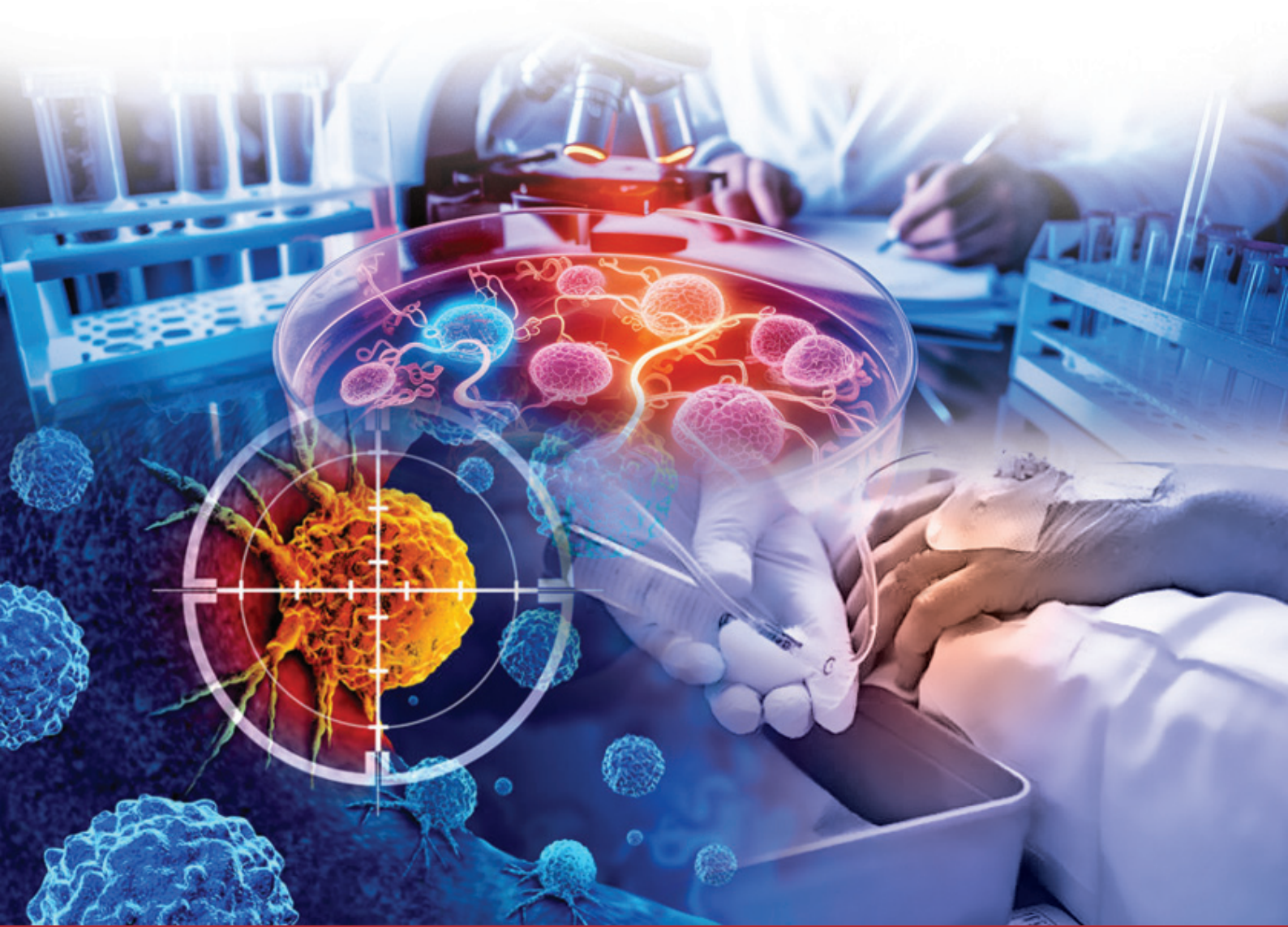
OBJECTIVE

CHAPTER 4.0
OBJECTIVE

The following are the objectives of this review:

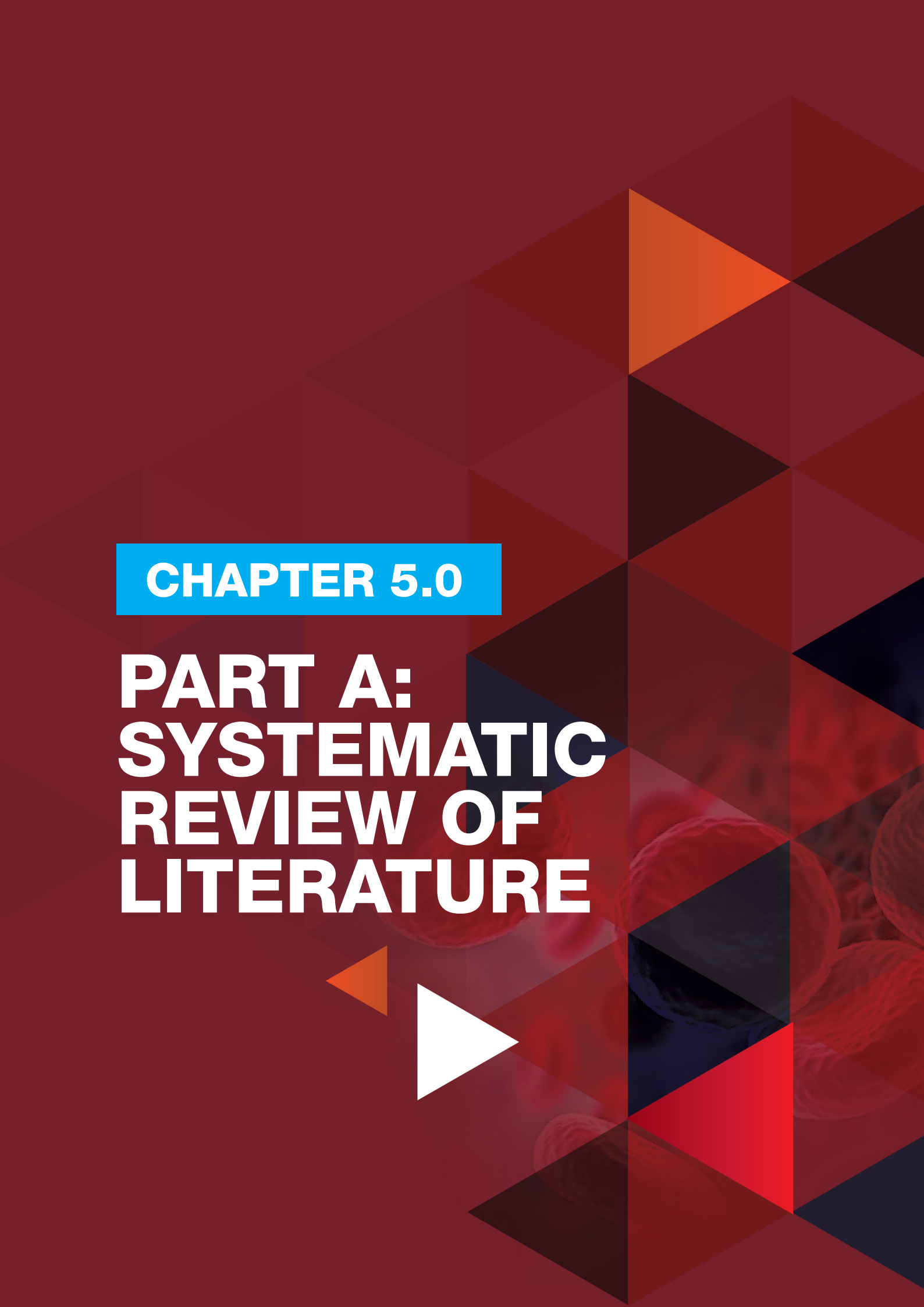
- To assess the comparative effectiveness and safety of CAR-T cell therapy in the treatment of patients with relapse or refractory B-Cell Acute Lymphoblastic Leukemia.

- To evaluate the economic, organizational, social, ethical and legal implications of CAR-T cell therapy in the treatment of patients with relapse or refractory B-Cell Acute Lymphoblastic Leukemia.



CHAPTER 5.0

PART A: SYSTEMATIC REVIEW OF LITERATURE



CHAPTER 5.0

PART A: SYSTEMATIC REVIEW OF LITERATURE

5.1 METHODS

5.1.1 Literature search strategy

Systematic literature search was developed by the main author and Information Specialist who searched for published articles pertaining to CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to September 2024, EBM Reviews - Health Technology Assessment (3rd Quarter 2024), EBM Reviews - Cochrane Database of Systematic Review (2005 to September 2024), EBM Reviews - Cochrane Central Register of Controlled Trials (September 2024), EBM Reviews - NHS Economic Evaluation Database (3rd Quarter 2024), and EMBASE. Parallel searches were run in PubMed, INAHTA database and regulatory agency websites such as US FDA. Search was limited to articles in English and in human. Detailed search strategy is as in **Appendix 3**. The last search was performed on 15 September 2024. Additional articles were identified from reviewing the references of retrieved articles.

5.1.2 Study selection

Two dedicated reviewers (RS and NNMH) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection. Disagreement was resolved by discussion.

Inclusion criteria:

a.	**Population**	Patients with relapse or refractory B-cell Acute Lymphoblastic Leukemia (ALL)
b.	**Intervention**	CAR-T cell therapy [(including Tisagenlecleucel (tisa-cel) and Brexucabtagene autoleucel (brexu-cel)]
c.	**Comparator**	• Standard care • Chemotherapy • Other or no comparator

d.	**Outcomes**	i. Effectiveness Overall survival (OS) Progression free survival (PFS) Overall response rate (ORR) Health-related quality of life (HRQoL) Complete response rate (CRR) Quality of life (QoL) Treatment free interval ii. Safety Adverse events, Complications, Treatment discontinuation iii. Economic impact Cost-effectiveness Cost-utility analysis Cost-benefit analysis Cost analysis, budget impact Any other measure of economic outcome iv. Organizational, social, ethical and legal implications
e.	**Study design**	HTA reports, systematic review with or without meta-analysis, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Animal study, laboratory study, case report, case series, narrative review
b.	Non-English full text articles	

5.1.3 Critical appraisal of literature/ assessment of risk of bias

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) for Systematic Review and Meta-analysis, ROBINS-I for non-randomized trial and Critical Appraisal Skill Programme (CASP) for economic studies. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (**Appendix 1**).

5.1.4 Analysis and synthesis of evidence

Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence* Table as shown in **Appendix 4**) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was also presented and discussed with the *Expert Committee*. The data extracted was as follows:

i. Details of method and study population characteristics
ii. Detail of intervention and comparators
iii. Details of individual outcomes specified

Methods of data synthesis

Data on the accuracy, effectiveness, safety and cost-effectiveness associated with CAR-T cell for patients with refractory/relapse ALL were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

5.2 RESULTS

5.2.1 Selection of included articles

An overview of the systematic search and selection of the studies are illustrated in **Figure 2**. A total of **455** records were identified through the Ovid interface and PubMed while 8 were identified from other sources (references of retrieved articles). Following the removal of **two** duplicates, **60** titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, **40** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **31** full text articles, 19 full text articles were included. **Twelve** articles were excluded following irrelevant study design (n=8), irrelevant population (3), irrelevant intervention (n=0) and irrelevant outcome (0). The excluded articles were listed as in **Appendix 5**.

The **19** full text articles which were finally selected in this review comprised of 15 systematic review (with or without meta-analysis, network meta-analysis) of clinical effectiveness, 2 non-randomised trials, one RCT and one CUA.

All SR included in this review were published in English language between 2019 and 2024, and primary studies included in the SR on effectiveness and cost-effectiveness were from multicountries; including the United States, Canada, UK, Germany, Italy, China, Spain, Netherland, Japan, Australia, Switzerland, as well as CUA conducted in Singapore, and primary studies from China. The SR included in this review comprised mainly of SR of clinical trial; and clinical trial with observational studies. A range of five to 38 primary studies were included in the SR in this review.

Overall in total, this review enrolled 8,585 participants with r/r B-ALL (range of 120 to 2134 participants). Age of participants in the review ranged from 0 to 84 years old. Study population involved patients with hematological malignancy in some of the SR included.

The longest time of follow-up documented in the review was up to 77 months. Of the SR assessing effectiveness and safety, five evaluated CD19 CAR-T cell, while six evaluated CD19/CD22 or CD19 and CD22 CAR-T cell therapy in these population. One of the SR included involved patients with r/r CNS leukaemia. There is scarce information on prior treatment or intervention received by the study population, with one SR documented history of patients with prior one HSCT in their review.

There was variation in the dose of CAR-T cell received by the study population, ranging from 0.2 x 10^5/kg to 5 x 10^8/kg or 2.5 x 10^5/ m^2 to 3.3 x 10^9/m^2. The SR of CUA included were varied in perspective namely healthcare, provider, public healthcare, payer, and societal.

The SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guideline.

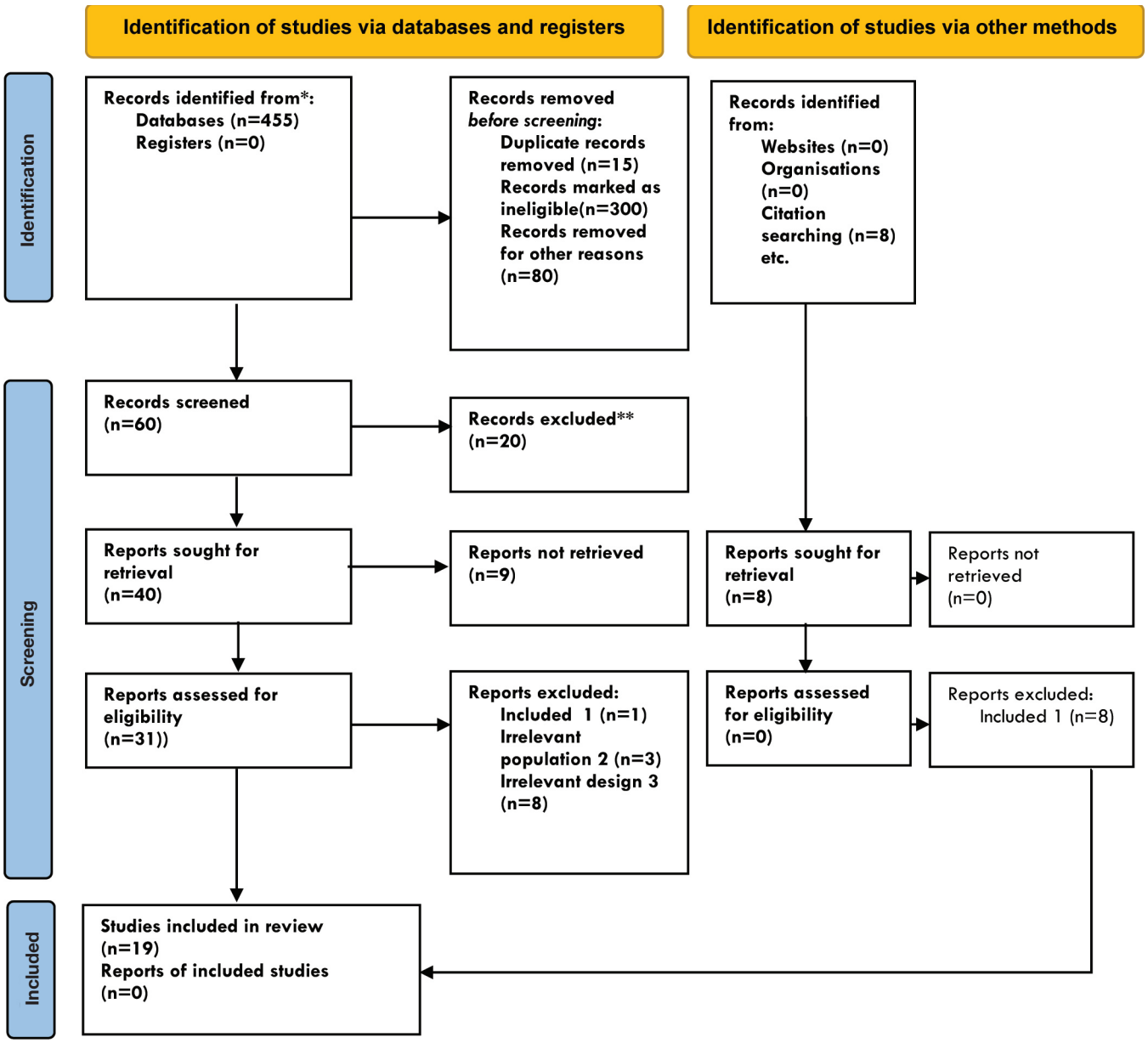


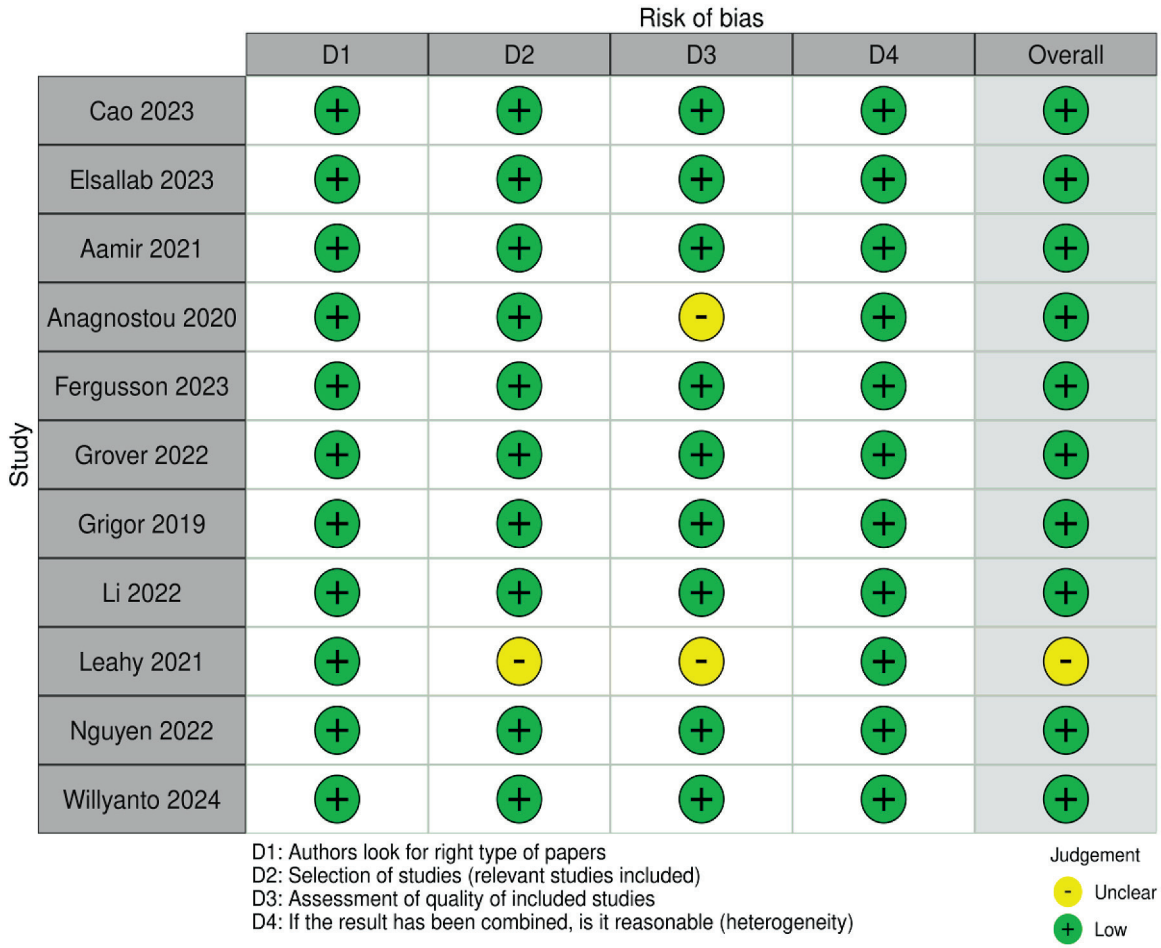
Figure 3: Flow chart of article retrieval and study selection

5.2.2 Quality assessment/ risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review and meta-analysis, ROBINS-I for non-randomised trial and Critical Appraisal Skill Programme (CASP) checklist for economic studies. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias. The risk of bias of the included studies was assessed independently by two reviewers. Any disagreements were resolved through discussion until consensus was reached.

Risk of bias assessment for included systematic review and meta-analysis

11 SR were included in this assessment. Using ROBIS, the risk of bias of each of the included study is displayed as in Figure 4 below. One SR included in the review was unclear as two of the domains judged as unclear. Otherwise, the rest of the SR were judged as having low risk of bias.



Figrue 4a: Risk of Bias assessment using ROBIS

Risk of bias assessment for included economic evaluation

Three systematic review of cost-effectiveness analyses were included in this assessment and risk of bias of individual CEA were summarised in Figure 5. Overall, the included studies were good, with low risk of bias. Two reviews were found with unclear criteria on of the domain evaluated. Overall, there was low risk of bias judged for the rest of the criteria's/domain in all the included studies.

Criteria assessed

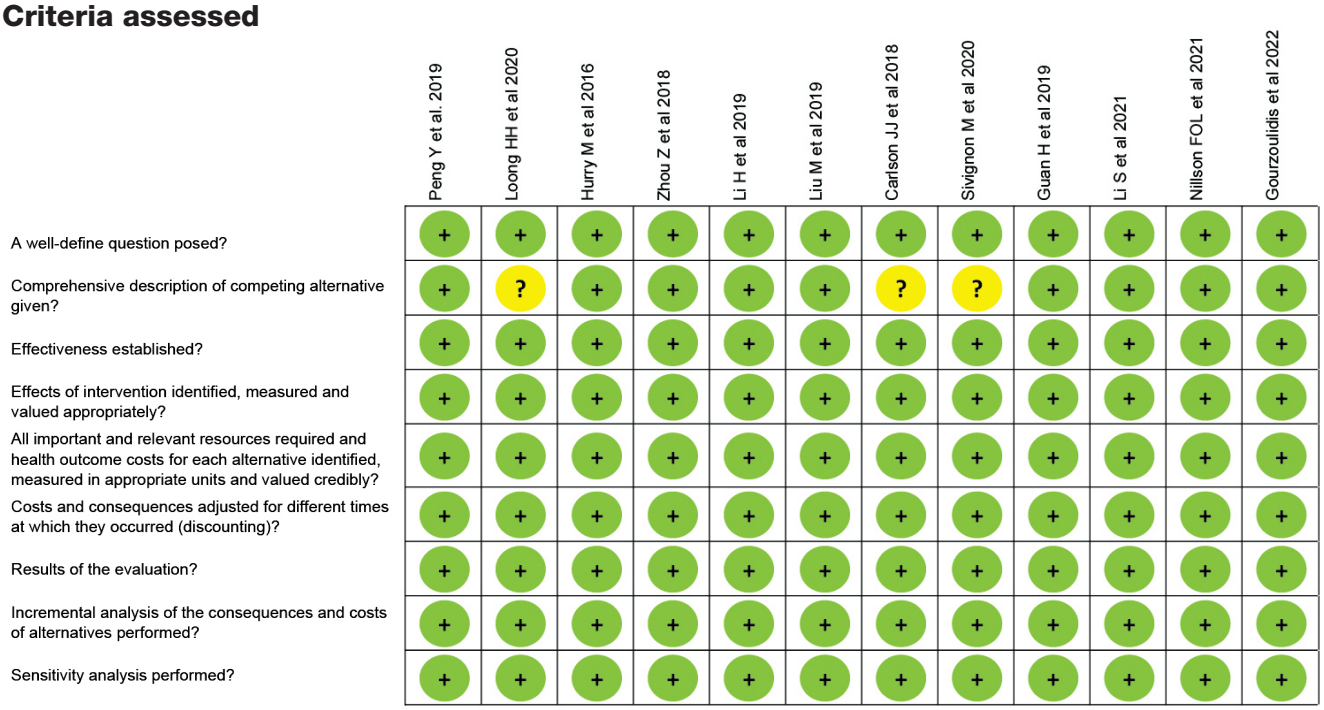


Figure 4b: Summary of risk of bias assessment for economic evaluation using CASP checklist

5.2.3 Effectiveness

There were 11 SR, two non-randomized trial and one RCT retrieved on the effectiveness of CAR-T cell in the treatment of patients with relapsed or refractory Acute Lymphoblastic Leukemia. The study characteristics were summarized as in the table below.

Table 3: Summary description of included studies

Study author, design	Population	Intervention vs comparator	Outcome
Cao H 2023 NMA	9 studies (N=1867) r/r ALL refractory to chemotherapy or relapsed after 1/ more prior induction regimen aged 7 to 84 years	Immunotheraphy and gene-modified cell theraphy vs salvage agents: 'standard chemotherapy', 'inotuzumab ozogamicin', 'blinatumomab', 'tisagenlecleucel' and 'CD19/CD22 CAR T'	– Complete Remission (CR) – Complete Remission with incomplete haematologic recovery (CRi) – Overall Survival (1-year)
Elsalab 2023 SR	38 studies (N=2134) Paediatric and adult	autologous anti-CD19 CAR T cell therapy	– Overall survival (12-month, 24-month, 5-year) – Event Free Survival – Response Rate – Proportion having HSCT – AE
Anagnostou 2020 SR	35 studies (N=953 patients) Aged 1 to 60 years old patients with r/r ALL	CD-19 CAR-T cell therapy	– Complete Remission – Overall Survival – Progression Free Survival -1 year – MRD negative
Aamir S 2020 SR	15 studies (448 patients) Aged 0 to 30 years with r/r ALL	CD-19 CAR-T cell therapy	– Complete Remission – Relapse – Overall Survival (12 month) – Event Free Survival (12 month) – CAR-T cell persistence
Fergusson 2023 SR	30 studies (N=637 patients) with ALL or NHL	CD-19 or CD-22 CAR-T cell therapy	– Best Complete Response – AE (Cytotoxic Release Syndrome, Neurotoxicity, All cause 30-d mortality)
Grover P 2022	16 studies (N=489 patients) Median age: 18 to 44 years old	CD-19 or CD-22 CAR-T cell therapy	– Complete Remission – Overall Survival (1-year) – Progression Free Survival (1-year) – Relapse, Target Ag at Relapse – AE (CRS, Neurotoxicity)

Study author, design	Population	Intervention vs comparator	Outcome
Li 2020 SR	10 studies (N=194 patients with hematologic malignancy) Paediatric and adult aged 8 to 49 years	CD-19 / CD-22 CAR-T cell therapy	– Complete Response – Minimal Residual Disease negative – Overall Response rate – Overall Survival (12-month, 18-month) – Event Free Survival (12-month, 18-month) – AE
Nguyen 2023 SR	14 studies (N=405 patients)	CD-19 / CD-22 CAR-T cell therapy (dual alone or combined with other treatment)	– Overall Response – Complete Remission – Partial Remission rate – Overall Survival (6-month, 1-year) – Progression Free Survival (6-month, 1-year) – Mode of administration
Grigor M 2019 SR	42 trials (N=913 patients with hematology malignancy)	CD-19/non-CD-19 Dose range: $2x10^5$ – 1x 10^{10} cell/kg $2.5x10^5$ – 3.3 x $10^9/m^2$	– Complete Response – Relapse – Overall Survival – AE
Wilyanto 2023 SR	29 studies(1367 patients) aged between 0 to 30.4 years, median:14.2 years	CD-19/CD-22 CD-19 and CD-22 combination	– Minimal Residual Disease Negative Complete Remission – Relapse Rate
Leahy 2021 SR	5 studies (n=195 patients) aged 1 to 29 years, with r/r B-ALL or lymphoma	CD-19	– Complete Response – CNS Relapse – Overall Survival (2-years) – AE
Zhang X 2020 (NRT)	N=115 patients with CD19 B-ALL Median age:12 (2-61) years	anti-CD19 CAR T cells	– Remission & MRD negative – OS & Leukemia Free Survival – Subgroup: Bridging into allo-HSCT, Previous transplantation – AE
Qi Y 2022 (RCT)	48 patients with R/R B-ALL diagnosed with CNSL median age was 31 years (range, 6-68)	CD19 CAR-T, and combined CD19 and CD22 CAR T-cell therapy	– Response Rate – Remission – OS and EFS – AE
Annesley 2019 (NRT)	18 patients with R/R infant ALL PLAT-02 (n=14) or PLAT-05 (n=4), median age of 22.5 months at enrollment (range: 14.5 - 40.1 months)	CD19-specific and CD19xCD22 dual specific CAR T cells	– MRD-Complete Remission – OS, LFS – AE

Table 4: Summary of study outcomes & effect measure

Outcome	Study (design)	Effect estimate
Complete Remission/ Complete Remission without hematologic recovery	Cao H 2023	*SUCRA rank* - CD19 CAR-T (SUCRA=88.2%), - Dual CD19/CD22 CAR-T (SUCRA=68.7%), - Sequential CD19-22 CAR T (SUCRA= 61.8%), - Inotuzumab Ozogamicin (SUCRA=48.7%), - Blinatumomab (SUCRA =26.6%) - Standard chemotherapy (SUCRA = 6%). CD19 CAR T-cells was superior in CR/CRi compared with: Blinatumomab (OR=8.32, 95% CI: 1.18 to 58.44) and Standard chemotherapy (OR=16.4, 95% CI: 2.76 to 97.45)
	Zhang X 2020 Non-randomized trial	CR-day 30 (93%) - morphologic complete remission Negative for MRD (87%) CR higher in patients without CNS leukaemia vs with CNS leukaemia (95.7% vs 76.5%, p=0.021).
	Grover 2022	Mean complete remission (CR) rate: 81%. Measurable residual disease (MRD)–negative remission rate : 81% (at four weeks post CAR-T infusion).
Overall Survival (1-year) (network comparison)	Cao H 2023	SUCRA rank - Dual CD19/CD22 CAR-T (SUCRA=99.3%) - CD19 CAR T (SUCRA=75.7%), - Blinatumomab (SUCRA=42.3%), - Inotuzumab izogamicin (SUCRA=18.5%) - Standard chemotherapy (SUCRA=14.2%). CD19 CAR T-cells significantly improved 1-year OS rate vs: - Blinatumomab (OR=8.24, 95% CI: 2.42 to 28.01), - Inotuzumab ozogamicin (OR=11.11, 95% CI: 2.90 to 42.51) - Standard chemotherapy (OR=12.17, 95% CI: 3.83 to 38.68). Dual CD19/CD22 CAR T-cells significantly improved the 1-year OS rate vs: - Blinatumomab (OR=31.11, 95% CI: 4.74 to 204.12), - Inotuzumab ozogamicin (OR=41.96, 95% CI: 5.91 to 297.86) - Standard chemotherapy (OR=45.99, 95% CI: 7.32 to 288.86).
Overall Survival	Zhang X 2020 (non-randomized trial)	1-year OS : 64%, in infused patients 1-year OS : 67.3%, in patients who achieved CR
	Anagnostou 2020 (SR)	1-year OS : 58% (95%CI 50.4 to 65.6%)
	Aamir 2020 (SR)	1-year OS: 63% to 84%
	Grover 2022 (SR)	Cumulative 1-year OS: 57% (95%CI 49 to 65)
	Elsalab 2023 (SR)	1-year OS : 70% (95% CI 67.7 to 72.8)
	Elsalab 2023 (SR)	2-year OS : 56.5% (95% CI 53.2 to 60
	Elsalab 2023 (SR)	5-year OS: 44.1% (95% CI 36.3 to 53.5)

Outcome	Study (design)	Effect estimate
Median OS	Elsalab 2023 (SR)	36.2 month (95%CI 2.9 to NR)
	Li 2020 (SR)	13.4 month (CD22)
Event Free Survival	Elsalab 2023 (SR)	1-year EFS : 53.2% (95% CI 50. to 56.2) 2-year EFS : 42.1% (95% CI 38.7 to 45.8). 5-year EFS : 35% (95% CI 28.8 to 42.5)
	Aamir 2020 (SR)	1-year EFS: 46% to 76%.
	Zhang X 2020 (non-randomized trial)	1-year LFS/EFS (58%) in infused patients 1-year LFS/EFS (63.2%) in patients achieved CR
Median EFS	Elsalab 2023	13.3 month (95%CI 12.2 to 17)
Progression Free Survival	Anagnostou 2020 (SR)	PFS-1 year : 37% (95%CI: 28.1 to 47.0)
	Grover 2022 (SR)	Cumulative 1-year of PFS: 37% (95%CI 26 to 48)
MRD negative	Anagnostou 2020 (SR)	72% (95%CI 65.3 to 78.5%)
	Li 2020 (SR)	0.54 (CD22) 0.91 (CD22/19)
	Wilyanto 2023 (SR)	***MRD negative Complete Remission*** ***Based on antigen target*** ER =0.70; 95%CI 0.61 to 0.80; 19 studies (Anti CD19) ER =0.70; 95%CI 0.41 to 0.99; 2 studies (Anti CD22) ER=0.64; 95%CI 0.16 to 1.12;2 studies (combination of anti-CD19/22) ***MRD-CR of the costimulatory domain*** The highest event rate of MRD-CR was from ER =0.89; 95%CI 0.76 to 1.02 (4-1BB & CD3ζ) ER =0.74; 95%CI 0.62 to 0.85); Fourth generation ER = 0.66; 95% CI = 0.47 to 0.86 (CD28ζ)
	Grover 2022 (SR)	Measurable residual disease (MRD)–negative remission rate : 81% (at four weeks post CAR-T infusion).
	Zhang X 2020 (NRT)	Negative for MRD (87%)

Outcome	Study (design)	Effect estimate
Complete Response	Fergusson 2023	Best Complete Response 90% (CD19/CD22 CAR T-cells) 68% (CD22 CAR-T cells) in patients with ALL Following CD22 68% (95% CI, 53 to 81%) in ALL, 64% (95% CI: 46 to 81%) in NHL Following CD19/CD22 CAR T-cells 90% (95% CI, 84 to 95%) in ALL 47% (95% CI, 34 to 61%) in NHL
	Nguyen 2023	Overall response (97%)
	Li 2020	Complete Response 0.75 (CD-22) 0.87 (CD22/19)
	Gregor 2019	Complete Response overall (ALL, CLL, NHL) 54.4% (CD-19) 24.4% (non CD-19) Following CD19 - 77.1% (95%CI 62.8% to 87.1%)-ALL - 25.5% (95%CI 13.9% to 42.1%)-CLL - 44.4% (95%CI 34.1% to 55.2%)-NHL
Relapse	Aamir 2020	Cumulative incidence of relapse after CD19-specific CAR-T therapy: 36% (95%CI 29% to 43%)
	Grover 2022	Target antigen status at the time of relapse; - antigen loss occurred in 26.7%, - target antigen retained in 73.2% of relapses
	Grigor 2019	37.0% (95% CI 29.4% to 45.4%) CD19 75.6% (95% CI, 56.4% to 88.2%) non-CD19
	Wilyanto 2023	***Relapse rate (RR) based on antigen target*** The anti-CD22 (2/17 studies) showed the lowest RR ER = 0.24 (95%CI: 0.09 to 0.40) (anti-CD22) ER = 0.29 (95%CI: 0.24 to 0.34 (anti-CD19 ER = 0.58 (95%CI: 0.44 to 0.72) (combination anti-CD19/CD22) ***RR of the co-stimulatory domain*** The CD28ζ CAR T-cell therapy showed the lowest RR, ER=0.16;95%CI 0.04 to 0.27 (CD28ζ) ER=0.28;95%CI 0.20 to 0.36 (4-1BB & CD3ζ) ER=0.33;95%CI 0.15 to 0.51 (CD3ζ & CD28ζ) ER=0.35; 95%CI 0.27 to 0.44 (4-1BB) ER=0.90;95%CI 0.57 to 1.23 (4th generation CAR T-cell)
CART persistence	Aamir 2020	Duration of CD19 CAR-T persistence ranged from 0 to 728 days

Cao H et al. (2023) conducted a SR with NMA of RCT, observational study to compare the efficacy and safety of immunotherapy and gene-modified cell therapy in R/R B-ALL patients. Databases including PubMed, Embase, Web of Science and Cochrane were searched for relevant studies from inception to January 31, 2022. Inclusion criteria were studies that involved patients who had a definitive diagnosis of R/R ALL who were initially refractory to chemotherapy or relapsed after one or more prior induction regimens. Studies were eligible if they were compared with the following salvage agents: 'standard chemotherapy', 'inotuzumab ozogamicin', 'blinatumomab', 'tisagenlecleucel' and 'CD19/CD22 CAR T'. Outcomes of interest were: Complete Remission/ CR with incomplete hematologic recovery (CR/CRi) rates and 1-year overall survival rates. Odds ratio (OR) were generated for binary outcomes, and mean difference (MD) was generated for consecutive outcomes by network meta-analysis using STATA. Complete Remission (CR) was defined as ≤5% bone marrow blasts, with a platelet count >100,000/μL, an absolute neutrophil count >1000/μL and no evidence of extramedullary disease. Complete remission with incomplete haematologic recovery (CRi) was defined as complete remission but with an absolute neutrophil count of <1000 μL, a platelet count of <100,000 μL or both. For continuous and dichotomous variable, SMD and OR with 95%CI were generated by network meta-analysis via Stata 16.0MP. Each outcome was ranked by the surface under the cumulative ranking curve (SUCRA). A higher SUCRA indicated a possibility of better efficacy. The review included a total of nine studies (from China, US, Germany, Italy) comprised of RCT (2), cohort and case-control (7), with total enrolled participants of 1867 patients whose age ranged from seven to 84 years old.[35 level I]

Complete Remission/CR with incomplete hematologic recovery (CR/Cri) (direct comparison)

CD19 CAR T-cells demonstrated a significantly better effect in improving the CR/CRi rate than blinatumomab (OR=8.32, 95%CI: 1.18 to 58.44) and chemotherapy (OR=16.4, 95% CI: 2.76 to 97.45). There was no significant difference between CD19 CAR T-cells and dual CD19/CD22 CAR T-cells in CR/CRi rates (OR=0.53, 95%CI 0.07 to 4.23). Inotuzumab ozogamicin significantly increased CR/CRi (OR=3.49, 95%CI: 1.58 to 7.72) versus standard chemotherapy. Blinatumomab had a superior CR/CRi rate versus standard chemotherapy (OR=2.15, 95% CI: 1.43 to 3.22). Blinatumomab showed no significant difference versus inotuzumab ozogamicin (OR=0.52, 95%CI: 0.12 to 2.24). [35 level I]

Overall Survival (direct comparison)

CD19 CAR T-cells and dual CD19/CD22 CAR T-cells both had a higher 1-year OS rate than blinatumomab, inotuzumab ozogamicin and chemotherapy. There was no significant difference between CD19 CAR T-cells and dual CD19/CD22 CAR T-cells in 1-year OS. Blinatumomab showed no significant difference versus standard chemotherapy on 1-year OS (OR=1.36, 95%CI 0.91 to 2.04). Blinatumomab showed no significant difference versus inotuzumab ozogamicin (OR = 0.74, 95%CI: 0.43 to 1.29) [35 level I]

Complete Remission rate (network comparison)

CD19 CAR T had the highest ranking (SUCRA =88.2%), followed by;

- Dual CD19/CD22 CAR-T (SUCRA = 68.7%),
- Sequential CD19-22 CAR T (SUCRA = 61.8%),
- Inotuzumab Ozogamicin (SUCRA = 48.7%),
- Blinatumomab (SUCRA = 26.6%)
- Standard chemotherapy ranked the last (SUCRA = 6%).

Out of six interventions, **only CD19 CAR T-cells** showed significant efficacy compared with: Blinatumomab (OR=8.32, 95% CI: 1.18 to 58.44) and standard chemotherapy (OR=16.4, 95% CI: 2.76 to 97.45) [35 level I]

Overall Survival (1-year) (network comparison)

Dual CD19/CD22 CAR-T had the highest ranking (SUCRA=99.3%), followed by
- CD19 CAR T (SUCRA=75.7%),
- Blinatumomab (SUCRA=42.3%),
- Inotuzumab izogamicin (SUCRA=18.5%)
- Standard chemotherapy ranked the last (SUCRA=14.2%).

The NMA reported that CD19 CAR T-cells significantly improved the 1-year OS rate compared with:
- blinatumomab (OR=8.24, 95% CI: 2.42 to 28.01),
- inotuzumab ozogamicin (OR=11.11, 95% CI: 2.90 to 42.51)
- standard chemotherapy (OR=12.17, 95% CI: 3.83 to 38.68).

Dual CD19/CD22 CAR T-cells also significantly improved the 1-year OS rate compared with:
- blinatumomab (OR=31.11, 95% CI: 4.74 to 204.12),
- inotuzumab ozogamicin (OR=41.96, 95% CI: 5.91 to 297.86)
- standard chemotherapy (OR=45.99, 95% CI: 7.32 to 288.86).

They highlighted that collectively, CAR-T therapy might be recommended for treating r/r B-ALL, especially under the condition that several salvage regimens containing immunotherapy are ineffective. Although the dual CD19/CD22 CAR-T cells and sequential CD19-22 CAR-T cells have a lower serious CRS rate, their safety profiles need more investigation.[35 level I]

Elsallab M et al (2023) in another SR investigated the use of autologous anti-CD19 CAR T cell therapy in both paediatric and adult patients with R/R B-ALL. Literature search was done using several databases including MEDLINE, Cochrane Central, ScienceDirect, Web of Science, Journals@Ovid, Embase, and clinicaltrial.gov until January 7th, 2022. Time-to-event endpoints, overall survival and event-free survival were estimated using reconstructed patient survival data from published Kaplan-Meyer curves. Meta-analysis of the response rates and adverse events associated with the treatment. Key modulators of response explored, including costimulatory domains, disease status, age, and lymphodepletion. Overall survival was defined as the time from the infusion of CAR T cells to death from any cause, and event-free survival was defined as the duration from the time of infusion to relapse or death from any cause. Overall response rate was defined as the proportion of patients who had a Complete Response (CR) or CR with incomplete hematologic recovery at the first disease evaluation after anti-CD19 CAR T cell infusion. CR was defined as less than 5% blast cells in the bone marrow with the restoration of normal haematopoiesis. Minimal residual disease negativity was defined as less than 0.01% blast cells in the bone marrow by either molecular methods or flow cytometry. This review included a total of 38 studies (phase I/II, retrospective, real world studies) which enrolled 2134 patients.

They found the median Overall Survival (OS), and Event Free Survival (EFS) were 36.2 months (95% CI 28.9, NR) and 13.3 months (95% CI 12.2 to 17), respectively.

OS (12-month, 24-month, 5-year)
The 12-month and 24- month OS rates were 70% (95% CI 67.7 to 72.8) and 56.5% (95% CI 53.2 to 60). At 5 years, the overall survival was 44.1% (95% CI 36.3 to 53.5)

EFS (12-month, 24-month, 5-year)
The 12-month and 24-month EFS rates were 53.2% (95% CI 50. to 56.2) and 42.1% (95% CI 38.7 to 45.8). At 5 years, the EFS was 35% (95% CI 28.8 to 42.5)

Response Rate
Overall response rate was 76% (95% CI 71 to 81). Of the responding patients, 98% (95% CI 94 to 99) achieved MRD-negative remission.

Proportion having HSCT
26% (95% CI 20 to 34) of the infused patients went on to have a HSCT.

They highlighted that these findings suggested that CAR T cell therapy may offer long-term benefits to patients with R/R B-ALL. However, further research is needed to optimize patient selection and better understand the impact of various factors on the outcome of CAR T cell therapy. [36 level I]

Anagnostou T et al. (2020) in another SR systematically analyse the outcomes of patients with acute lymphocytic leukaemia treated with anti-CD19 CAR T cells and identify factors associated with differences in outcomes. Systematic review and meta-analysis of published and unpublished clinical trials (both single-centre and multi-institutional trials) that reported data on the outcomes of adult or paediatric patients that were treated with anti-CD19 CAR T cells for relapsed or refractory B-cell acute lymphocytic leukaemia, reported between Jan 1, 2012, and April 14, 2020 were conducted. Studies with two patients or fewer were excluded and summary data were extracted from the reports. The primary outcome was complete remission (CR) at any time after anti-CD19 CAR T-cell infusion, defined as the number of patients that achieved complete remission relative to the number of patients infused. The secondary outcome was Progression-Free Survival at 1 year of follow-up, defined as the number of patients with no evidence of disease, relative to the number of patients infused, measured 1 year after the infusion of anti-CD19 CAR-T cells. Safety endpoints included cytokine release syndrome and neurotoxicity of any grade at any time after anti-CD19 CAR T-cell infusion, as reported by the individual trials. Other outcomes included the proportion of patients who achieved minimal residual disease (MRD) negativity (diagnosed by either PCR or flow cytometry) and overall survival at 1 year after anti-CD19 CAR T-cell infusion. Prespecified subgroup analyses were done for age group (paediatric [<18 years of age] vs adult [>18 years]), anti-CD19 CAR-T cell construct type (4-1BB co-stimulated vs CD28 co-stimulated vs third and fourth generation), CD19 single-chain variable fragment clone (FMC63 vs other), T-cell origin (autologous vs allogeneic). A tool designed specifically to evaluate the methodological quality of non-comparative studies was used. They finally included 35 studies in the final analysis (n=953 patients who received anti-CD-19 CAR T-cell therapy for relapsed or refractory B-ALL), median age ranged was between 1 year to 60 years.

Complete Remission (CR)

The pooled complete remission was 80% (95% CI 75.5 to 84.8, I^2=56.96%).

In the prespecified subgroup analyses:

- *Adult vs children*
  195 (75% [95%CI 66.9 to 82.9, I^2=35.22%]) of 263 patients in adult studies achieved CR, and 242 (81% [95%CI 72.9 to 87.2, I^2=54.45%]) of 346 patients in children studies achieved CR.

- *Autologous vs allogenic*
  The pooled CR was higher with autologous T-cell origin [83%, 78.5 to 86.5, I^2=44.34%] (727 of 901 patients), compared with allogeneic T-cell origin [55%, 30.6 to 79.0, I^2=62.64%] (29 of 52 patients).

- *Construct type*
  The pooled CR did not significantly differ with anti-CD19 CAR T-cell construct type or single-chain variable fragment clone.

Overall Survival

361 (58% [95% CI 50.4 to 65.6%, I^2=66.39%]) of 613 patients with available data were alive at 1 year after anti-CD19 CAR T-cell infusion. The 1-year overall survival was not significantly different between adults and children, between 4-1BB and CD28 co-stimulated constructs, or for different single-chain variable fragment clones or T-cell origin.

PFS at 1-year

The pooled PFS at 1-year was 37% [95%CI: 28.1 to 47.0, I^2=82.30%] (278 of 696 patients) with reported data after anti-CD19 CAR T-cell infusion. The pooled 1-year PFS did not differ between adults and children, between 4-1BB and CD28 co-stimulated constructs, or for different single chain variable fragment clones or T-cell origin.

Minimal Residual Disease (MRD) negative

586 (72% [95%CI 65.3 to 78.5%, I^2=71.61%]) of 821 patients with available data achieved MRD negativity.

In the subgroup analysis;

- *CAR-T cell construct*
  MRD negativity was significantly associated with the type of anti-CD19 CAR T-cell construct used; 4-1BB co stimulated (76.8%, 95%CI 69.3 to 83.6) vs CD28 co stimulated (60.8%, 95%CI 52.5 to 68.8) (p=0.0094).

- *Adult and children, single-chain variable fragment clone, T-cell origin*
  No significant difference in the proportion of patients who achieved MRD negativity between adults and children or for different single-chain variable fragment clones or T-cell origin.

They highlighted the high response rates after anti-CD19 CAR T-cell therapy can be used to guide the use of therapy in patients with r/r acute lymphocytic leukaemia. Comparison studies are required to further determine differences in efficacy between different anti-CD19 CAR T-cell constructs in the setting of r/r acute lymphocytic leukaemia.[37 level I]

Aamir S et al. (2020) in a SR evaluated the efficacy and safety of CD19-specific CAR-T therapy in R/R B-cell ALL in the paediatric and young adult population. They searched the PubMed, EMBASE, Web of Science, Cochrane Library, and clinical trials databases. The efficacy data were extracted for CR, minimal residual disease (MRD)-negative CR, relapse rate, overall survival (OS), and event-free survival. The toxicity data were analysed for the following main categories: grade 3/4 CRS, and hematologic and nonhematologic toxicity. The duration of CAR-T persistence and B-cell aplasia (BCA) was also noted. The meta-analysis was conducted in R using the "meta" packages. The review included 15 studies (trials and observational studies) involving a total of 448 patients received a CD19-specific CAR-T product (446 patients had evaluable data). The age range was 0 to 30 years. Cyclophosphamide and fludarabine were used as lymphodepleting therapy followed by a single infusion of CAR-T at a dose ranging from $0.2x10^6$ to $5x10^6$ cells/kg. Second-generation CAR-T therapy with a 4-1BB signalling domain was used in 66.7% of studies (n=11/15).

Complete Remission

Incidence rate of complete remission was 82% (95% CI 76% to 87%) with CD19-specific CAR-T therapy for R/R B-ALL. Cumulative incidence of MRD-negative CR was 0.78 (95% CI, 0.72 to 0.84).

Overall Survival & Event Free Survival

The median OS at 12 months ranged from 63% to 84%., while the median event-free survival ranged from 46% to 76%.

Relapse

The cumulative incidence of relapse after CD19-specific CAR-T therapy is 36% (95%CI 29% to 43%)

CAR-T persistence

The duration of CD19 CAR-T persistence ranged from 0 to 728 days. The duration of B Cell Aplasia was 22.5% to 93% at 3 months.

They highlighted that CD19 CAR-T therapy can result in CR in RR B-ALL, and the remission is sustained until the patient receives a transplant. CD19 CAR-T therapy alone is not sufficient to maintain remission; it has to be bridged to either chemotherapy or SCT. Relapse is still possible after this treatment. The pathogenesis of relapse and its rates when CD20/CD22 CAR-T therapies are applied need to be explored.[38 level I]

Fergusson et al (2023) in another SR evaluated the efficacy and safety of CD22-targeting CAR T-cell therapies. They searched MEDLINE, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials from inception to March 3rd 2022 for full articles of clinical trials employing CD22-targeting CAR T-cells in acute lymphocytic leukaemia (ALL) and non-Hodgkin's lymphoma (NHL).Interventional studies, with or without a comparator, on CD22 CAR T-cell therapy in patients with B-cell malignancies were eligible for inclusion. The primary outcome was best CR rate (bCR), defined as the proportion of patients reported to have achieved CR at any point during follow-up. Secondary outcomes included overall response, relapse rate, and time-to-event data (overall survival and progression-free survival). Safety outcomes included reported incidence of adverse events (CRS, ICANS, graft-versus-host disease, infection, and other reported adverse events) and 30-day mortality rate. Study quality was assessed using a modified Institute of Health Economics (IHE) risk of bias tool. Meta-analyses were conducted using R statistical software (v.4.2.2). A DerSimonian and Laird random-effects model with arcsine transformation was used to pool outcome proportions. The review included 30 early phase studies included (637 patients), investigating CD22 or CD19/CD22 CAR T-cells. All studies were early-phase single-arm clinical trials. Majority of studies examined R/R B-ALL patients as the population of interest. Studies were conducted in US, China, UK, Canada.

Best Complete Response (bCR)

CD19/CD22 CAR T-cells had higher best complete response than CD22 CAR-T cells in patients with ALL, 90% vs 68% respectively.

CD22 CAR T-cells had a bCR of 68% [95% CI, 53 to 81%] in ALL (n= 116), and 64% [95% CI, 46 to 81%] in NHL (n= 28) with 74% and 96% of patients having received anti-CD19 CAR T-cells previously in ALL and NHL studies respectively. Meanwhile CD19/CD22 CAR T-cells had a bCR rate of 90% [95% CI, 84 to 95%] in ALL (n= 297) and 47% [95% CI, 34 to 61%] in NHL (n= 137).

They highlighted the early phase trials of CD22 and CD19/CD22 CAR T-cells show high remission rates in ALL and NHL. Severe CRS or ICANS were rare and dual-targeting did not increase toxicity. CD22 appears to be a viable antigen target and may be an option for those who relapse after CD19 CAR T-cell therapy. Variability in CAR construct, dose, and patient factors amongst studies limits comparisons, with long-term outcomes yet to be reported. Future trials are needed to determine the comparative efficacy of these therapies and identify strategies to improve the durability of response.[39 level I]

Grover P et al. (2022) in another SR investigated the efficacy and toxicity of CAR-T therapy in adults with r/r B-ALL. These databases were searched MEDLINE, Embase, and the Cochrane Library; for prospective interventional studies. The inclusion criteria were: (1) studies enrolling adults only (>18 years) or both paediatric and adult patients if the median age of the study population was ≥18 years and (2) studies enrolling ≥5 patients. All search strategies were completed and run on 16 November 2020.The efficacy outcomes were rate of complete remission (CR), measurable residual disease (MRD)–negative remission, progression free survival (PFS), and overall survival (OS). The toxicity outcomes were cytokine release syndrome (CRS) and neurotoxicity at any time after CAR-T therapy. Risk of bias was assessed with a modified Institute of Health Economics tool. For time-to-event end points (OS/PFS), they performed parametric meta-analyses. For binary end points (CR, MRD, CRS, and neurotoxicity), we fit the b-binomial random effects. They included 16 studies involving 489 patients in the final analysis, (sample size ranged from six to 58; range of median age were 18 to 44 years; median prior lines of therapy ranged from two to four across studies. Most of the patients were in morphological relapse or had a >5% blasts in the bone marrow before CAR-T (70.5%). Extramedullary disease was reported in 13.5% of patients, and 13 patients (8.6%) have CNS disease. Majority of the studies included both paediatric and adult patients (n=283), but five of the studies enrolled only adult patients (n=206).

Complete Remission

They found the mean complete remission (CR) rate was 81%. Measurable residual disease (MRD)–negative remission rate was 81% (at four weeks after CAR-T infusion).

Overall Survival and Progression Free Survival

The cumulative 12-month probabilities of PFS and OS were 37% (95%CI 26 to 48) and 57% (95%CI 49 to 65) respectively, with median follow-up across studies of 24 months.

Relapse

Relapse occurred in 40.3% of cases. Target antigen status at the time of relapse were; antigen loss occurred in 26.7%, whereas target antigen was retained in 73.2% of relapses, (reported in 131 patients across 11 studies).

They highlighted CAR-T therapy achieves high early remission rates in adults with r/r B-ALL and represents a significant improvement over traditional salvage chemotherapy. Relapses are common and durable response remains a challenge. Strategies aimed at improving durability and long-term outcomes through improved CAR T-cell persistence, multiantigen targeting, and optimization of patient selection will propel the next phase of CAR-T trials for adults with B-ALL. [40 level I]

Li L et al (2020) in **another review** assessed the efficacy and safety of CD22 and CD19/CD22 targeted CAR-T cell therapy by summarizing the existing evidence. Electronic databases including PubMed, Embase, and Scopus were comprehensively searched from inception up to November 30, 2022. Pooled response rates and minimal residual disease (MRD) negative response rates, cytokine release syndrome (CRS) rates and neurotoxicity rates were calculated. Subgroup analysis was performed based on the type of immunotherapy. Inclusion criteria were 1) Clinical studies investigating the efficacy and/or safety of anti-CD22 or anti-CD19/CD22 CAR-T cell therapy in the treatment of haematological malignancies. 2) Outcomes included complete response rate, partial response rate, overall response rate, minimal residual disease (MRD) negative response rate, progression-free survival, overall survival, cytokine release syndrome (CRS) rate and neurotoxicity rate. The Newcastle-Ottawa scale (NOS) was used to assess the quality of the included studies. Statistical analyses were performed utilizing R. This review included 10 clinical studies including 194 patients with hematologic malignancies, with age range between 8 and 49 years. Five included studies were trials investigating anti-CD22 CAR-T cell therapy for r/r B-ALL, and another five studies assessed the efficacy and safety of CD19/CD22 bispecific CAR-T cell therapy for r/r B-ALL; studies were mostly from China, US, UK, and the longest follow-up reported was 18 months.

Complete Response (CR)

The pooled CR rates of CD22 and CD19/CD22 CAR-T cell therapy for r/r B-cell lymphoblastic leukaemia (B-ALL) were: 0.75 (95% CI: 0.60 to 0.88) and 0.87 (95% CI: 0.76 to 0.96), respectively. (9 studies)

Minimal Residual Disease (MRD) negative

The overall MRD negative response rates of CD22 and CD19/CD22 CAR-T for r/r B-ALL were 0.54 (95% CI: 0.42 to 0.66) and 0.91 (95% CI: 0.47 to 0.88), respectively. (6 studies)

Overall Response rate

The ORR ranged from 87.5% to 100% in the study population.(two studies)

Overall Survival (OS)

Median OS of 13.4 months (95% CI: 7.7 to 20.3 months) for anti-CD22 CAR T cell therapy was reported from one study. The OS and event-free survival rates were 88.5% and 67.5%, respectively at both 12 months and 18 months. (one study)

They highlighted that both CD22 and CD19/CD22 bispecific CAR-T immunotherapy demonstrated favourable efficacy and manageable safety profiles in patients with relapsed/refractory B-ALL. Well-designed and large sample-sized clinical trials are warranted for further evaluation of the CAR-T cell efficacy and safety. [41 level I]

Nguyen TT et al (2023) in another review evaluated CD22/CD19 dual-targeting CAR-T-cell therapy efficacy and safety in relapsed/refractory B-cell malignancies. The Web of Science, PubMed, Cochrane, and Embase databases were searched until July 2022. Patients confirmed with any relapsed/refractory B-cell haematological malignancies were included regardless of age, gender, or ethnicity, receiving CD22 and CD19-dual-targeting CAR-T-cell therapy. The studies conducted on patients with coexisting other cancer were excluded. The primary outcomes were overall response (OR) and complete remission (CR). Secondary outcomes were partial response (PR). OR is defined as the sum of CR and PR. A minimal residual disease (MRD)-negative response was defined as a bone marrow blast proportion <10 -4 by multiparameter flow cytometry or real-time quantitative PCR. Overall survival is defined as the day from the start of therapy to the day of death of any reason, progression free survival is defined as the day from start of therapy today of disease progression. The toxicity results were classified into three main categories, cytokine release syndrome (CRS), severe CRS (sCRS), and neurotoxicity. sCRS was considered if it was Grade 3 or worse. Neurotoxicity, which was termed

"immune effector cell associated neurotoxicity syndrome" (ICANS), and other AEs followed "the US National Cancer Institute Common Terminology Criteria for Adverse Events" (CTCAE v4.03 or v5.0) Statistical analyses were performed using R software. They used random effect models to explore the outcome, and heterogeneity was investigated by subgroup analysis. The review included 14 studies; prospective (all phases, controlled/ uncontrolled) and retrospective clinical trials (a total of 405 patients; 120 patients with ALL and 285 were with NHL). Studies were published from 2019 to 2022, conducted in the USA, UK, and China. About 47.5% study participants in the review had one prior hematopoietic stem cell transplantation (HSCT). The intervention was CD22/CD19 dual-targeting CAR-T-cell therapy alone or combined with other treatments; most T-cell origin were autologous, most second-generation CD19/CD22-CARs were constructed, Fludarabine and cyclophosphamide were the most commonly used lymphodepleting conditioning therapies). The median follow-up time was 12.8 months (range 4.3 to 19.7).

Overall Response & Complete Remission

Following dual CAR-T-cell therapy in patients with ALL, the pooled overall response (OR) and complete remission (CR) were 97% (95% CI: 91% to 99%, I^2=0), and 93% (95%CI: 87% to 97%, I^2=0%) respectively. The Partial Remission rate was 2% (95% CI: 0% to 13%, I^2=0%), (seven studies).

While MRD-negative CR was 93% (95% CI: 87% to 97%, I^2=0%), obtained in 109 out of 117 patients.

While in patients with NHL, the pooled OR rates were 85% (95%CI 77% to 90%, ^{I2}=45%). The CR and PR were 57% (95%CI: 44% to 69%, I^2=70%), and 26% (95%CI: 19% to 34%, I^2=37%), respectively (8 studies).

Overall Survival (OS) & Progression Free Survival (PFS)

The pooled 6-month OS and 6-month PFS for this cohort were 83% (95% CI: 70% to 91%, I^2=0%) and 50% (95% CI: 36% to 64%, I^2=0%), respectively (five studies).

The pooled 1-year OS and PFS were; 70% (95% CI: 56% to 80%, I^2=25%) and 49% (95% CI: 36% to 62%, I^2=48%), respectively (five studies).

Meanwhile, in patients with NHL, the 12-month OS and 12-month PFS were 77% (95% CI: 65% to 85%, I^2=50%) and 56% (95% CI: 36% to 75%, I^2=80%), respectively.

Subgroup analysis:

- **Mode of administration**

  Patients who underwent infused coadministration of CD19 and CD22-CAR-Tcell or third-generation CAR-T cells had a significantly higher CR rate (68%, 95% CI: 59% to 75%), compared to patients who used tandem CAR or second-generation CAR-T cells (39%, 95% CI: 28% to 52%).

- **Type of treatment combination**

  Trials that combined HSCT treatment with dual-targeting CAR-T-cell infusion achieved a higher CR rate (81%, 95% CI: 73 to 87) than those using dual-targeting CAR-T or Fludarabine & Cyclophosphamide for lymphodepletion (46%, 95% CI: 39 to 54).

They highlighted that the CD22/CD19 dual targeting CAR-T-cell strategy has high efficiency with tolerable adverse effects in B-cell malignancies. The results suggest that dual-targeted CAR-T therapy should be considered for these patients and clinicians could further advance improvement in cancer care with this intervention.[42 level I]

Gregor EJM et al (2019) evaluated the efficacy and safety of CAR-T cell therapy in patients with relapsed or refractory hematologic or solid malignancies. Search was conducted from the MEDLINE, Embase, and the Cochrane Register of Controlled Trials (from inception to November 21, 2017). Interventional studies investigating CAR-T cell therapy in patients with malignancies were included. Two independent reviewers extracted relevant data, assessed risk of bias, and graded the quality of evidence using established methods. Full text eligibility criteria were reviewed independently using Distiller Systematic Review Software. Disagreement was settled through discussion with a third reviewer. Efficacy outcomes of interest were complete response (primary outcome), overall or objective response, relapse, and overall survival. Complete response was defined as the absence of detectable cancer following treatment with CAR-T cell therapy. Overall response was defined as the total sum of complete and partial responses. The review included 42 haematological malignancy trials and 18 solid tumour trials (913 participants). 19 (32%) studies were ALL, 18 (30.0%) solid malignancies (such as liver metastases, glioblastoma), 11 (18%) NHL, two (3%) AML, one (2%) CLL, one (2%) Hodgkin's lymphoma and eight (13%) included patients with more than one type of hematologic cancer. The included studies were published between 2008 and 2017, with sample sizes ranging from one to 133 participants. Intervention of interest in the review was CAR T cell (CD19, non CD19), with T cell origin was mostly autologous (31), compared to allogenic (7), and the dose range: ($2x10^5$ to $1x10^{10}$ cells/kg), and ($2.5x10^5$ to $3.3x10^9/m^2$). Follow-up of the studies ranged from 20 days to 77 months.

Complete response

The pooled CR was 54.4% [95% CI: 42.5% to 65.9%] in 27 CD19 CAR-T cell therapy studies (486 evaluable hematologic patients). The pooled CR were lower, 24.4% (95%CI: 9.4% to 50.3%) in seven **non-CD19 CAR-T cell** therapy studies (65 evaluable hematologic patients).

Table 5: Summary outcome in patients receiving CD19 compared to non-CD19 CAR-T

Outcome	CD19 CAR-T	Non-CD19 CAR-T
Complete response	54.4% (95% CI: 42.5% to 65.9%) 77.1%	24.4% (95%CI: 9.4% to 50.3%)
	(95%CI 62.8% to 87.1%)-ALL 25.5%	-
	(95%CI 13.9% to 42.1%)-CLL	-
	44.4% (95%CI 34.1% to 55.2%)-NHL	-
Relapse	37.0% (95% CI 29.4% to 45.4%)	75.6% (95% CI, 56.4% to 88.2%)
OS	5% to 95%	74% to 97%

Subgroup analysis of the CD19+ hematologic cancer types found:-

Patients with ALL had the highest complete response compared to CLL and lymphoma. Among the ALL patients, there was a complete response rate of 77.1% (95%CI 62.8% to 87.1%; I^2 58.5%) compared to the rates of CLL: 25.5% (95%CI 13.9% to 42.1%; I^2 0%) and NHL: 44.4% (95%CI 34.1% to 55.2%; I^2 35.3%) respectively.

However, there was no differences in CR among the CD19+ hematologic cancer studies, in subgroup analyses of T-cell origin categorized by autologous and allogeneic CAR-T cell therapies; and by age subgrouped by pediatric versus adult.

Relapse

A pooled prevalence of 37.0% (95% CI 29.4% to 45.4%; I^2 23.7%) was demonstrated among patients treated with CD19 targeted CAR-T cell therapy. While higher pooled prevalence was demonstrated among patients treated with non-CD19 CAR-T cell therapy, 75.6% (95% CI, 56.4% to 88.2%; I^2 0%).

Overall Survival

OS ranged from 5% to 95% (in CD-19 CAR-T cell studies), and 74% to 97% (in non-CD-19 hematologic studies). OS was reported in 24 CD19 CAR-T cell therapy hematologic cancer studies (460 evaluable patients) and six non-CD19 CART cell therapy studies (48 evaluable patients).

They highlighted there was a strong signal for efficacy of CAR-T cell therapy in patients with CD19+ hematologic malignancies and no overall signal in solid tumour trials published to date. These results will help inform patients, physicians, and other stakeholders of the benefits and risks associated with CAR-T cell therapy.[43 level I]

In another review, Wilyanto SE et al. (2023) assessed the efficacy and safety of CAR T-cell therapy for r/r B-ALL. The literature search was performed on four databases. Inclusion criteria set were (1) peer-reviewed clinical studies (2) published up to March 2023, (3) available or accessible in English (4) Involving children and/or adolescents (0 to 18years old) with refractory B-ALL and (5) employing CAR T-cell therapy as the intervention of interest. Efficacy parameters measured included minimal residual disease negative complete remission (MRD-CR) and relapse rate (RR). The MRD-CR is characterized by absence of leukaemia cells in the bone marrow by microscopic or sensitive tests, such as flow cytometry or PCR. Whereas RR is described as the rate of recurrence of the disease at any site after a period of complete remission, either while still on, or after completion of front-line therapy. Safety parameters constituted cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Cytokine release syndrome (CRS) was described as fatal adverse events appearing 14 days after CAR T-cell infusion due to systemic inflammatory response caused by rapidly activated CAR T-cells; and CRS was classified into four grades, of which the third and fourth grades were considered as life-threatening adverse events. ICANS is a severe form of neurotoxicity syndrome often starting at four to five days following CAR T-cell infusion; and ICANS is further classified into four grades based on the immune effector cell-associated encephalopathy (ICE) score. Risk of bias assessment was carried out using the Newcastle-Ottawa Scale (NOS) for non-randomized clinical trial. Meta-analysis was conducted using comprehensive meta-analysis (CMA) V3 and Review Manager 5.4. The review included 29 studies in the qualitative synthesis, while 28 of them were eligible for quantitative analysis (21 trials, 7 cohort). The 29 studies enrolled a total of 1367 participants, with a median of 37 (range 4 to 255) participants. The median age at enrolment was 14.2 (0 to 30.4) years. Median duration of study was 23.5 months (ranging from 1 to 60).

Minimal residual disease negative complete remission (MRD-CR)

Anti-CD22 showed superior efficacy with the highest MRD-CR event rate and lowest RR, compared to anti-CD19.

- MRD-CR based on antigen target
  Anti-CD19 and anti-CD22 groups displayed an equivalent event rate of MRD-CR
  ER =0.70; 95% CI 0.61 to 0.80; I^2 89.84% (19 studies) and ER =0.70;95% CI 0.41 to 0.99; I^2 53.72% (2 studies) followed by combination of anti-CD19/22, ER=0.64; 95% CI 0.16 to 1.12; I^2 82.56% (2 studies).

- MRD-CR based on the costimulatory domain
  The highest event rate (ER) of MRD-CR was from 4-1BB & CD3ζ (ER =0.89; 95%CI 0.76 to 1.02), fourth generation CAR-T cell (ER =0.74; 95%CI 0.62 to 0.85);CD28ζ (ER = 0.66; 95%CI 0.47 to 0.86)

Relapse Rate

- Relapse rate (RR) based on antigen target
  The anti-CD22 (2/17 studies) showed the lowest RR (ER = 0.24; 95% CI = 0.09 to 0.40; I^2 =53.72%); while anti-CD19 (12/17 studies) and combination anti-CD19/CD22 (3/17 studies) showed RR of 0.29 (95%CI = 0.24, 0.34; I^2 = 51.22%) and 0.58 (95% CI = 0.44, 0.72; I^2= 77.06%) respectively.

- RR based on the co-stimulatory domain
  The CD28ζ CAR T-cell therapy showed the lowest RR (ER=0.16; 95%CI 0.04 to 0.27; I^2= 53.21%); than 4-1BB & CD3ζ (ER=0.28;95%CI 0.20 to 0.36), CD3ζ and CD28ζ (ER=0.33; 95%CI 0.15 to 0.51), 4-1BB (ER=0.35; 95%CI 0.27 to 0.44) and fourth generation CAR T-cell (ER=0.90; 95%CI 0.57 to 1.23) respectively.

They highlighted that choosing a more efficacious and safer CAR T-cell treatment is crucial for improving overall survival in acute leukaemia. Beyond the promising anti-CD22 CAR T-cell, exploring costimulatory domains and new CD targets could enhance treatment effectiveness for r/r B-ALL. [44 level I]

Leahy et al. (2021) in another review assessed the safety and activity of CAR T-cell therapy in patients with a history of CNS relapsed or refractory B-cell acute lymphocytic leukaemia. Data of relapsed or refractory CD19-positive acute lymphocytic leukaemia or lymphocytic lymphoma from five clinical trials (Pedi CART19, 13BT022, ENSIGN, ELIANA, and 16CT022) done at the Children's Hospital of Philadelphia (Philadelphia, PA, USA), in which participants received CD19-directed CAR T-cell therapy between April 17, 2012, and April 16, 2019. The trials required control of CNS disease at enrolment and infusion and excluded treatment in the setting of acute neurological toxic effects (>grade 1 in severity) or parenchymal lesions deemed to increase the risk of neurotoxicity. 154 patients from Pedi CART19, ELIANA, ENSIGN, and 16CT022 received tisagenlecleucel and 41 patients from the 13BT022 trial received the humanised CD19-directed CAR, huCART19. They categorised patients into two strata on the basis of CNS status at relapse or within the 12 months preceding CAR T-cell infusion, either CNS-positive or CNS-negative disease. Patients with CNS-positive disease were further divided on the basis of morphological bone marrow involvement, either combined bone marrow and CNS involvement, or isolated CNS involvement. Endpoints were the proportion of patients with complete response at 28 days after infusion, Kaplan-Meier analysis of relapse-free survival and overall survival, and the incidence of cytokine release syndrome and neurotoxicity. The review included 195 patients (aged 1 to 29 years; 110 [56%] male and 85 [44%] female) with relapsed or refractory CD19-positive acute lymphocytic leukaemia or lymphocytic lymphoma. The median length of follow-up was 39 months (IQR 25 to 49) in the CNS positive stratum and 36 months (18 to 49) in the CNS-negative stratum. They found of all the 195 patients, 66 (34%) were categorised as having CNS-positive disease and 129 (66%) as having CNS-negative disease, and 43 (22%) as having isolated CNS involvement.

Complete response (CR)

The proportion of patients in the CNS-positive stratum with a CR at 28 days after infusion was similar to that in the CNS-negative stratum ([97%] 64 of 66 vs [94%]121 of 129; p=0 .74),

CNS relapse

Proportion of patients who had CNS relapse after CAR T-cell infusion = 4% (7of 169 patients). There was no difference in the proportion of patients who relapsed after CAR T-cell infusion in:- the CNS-positive stratum [42%] 27 of 66, vs the CNS-negative stratum [37%] 45 of 129; p=0·51, although patients in the CNS-positive stratum were significantly more likely to have CNS3 disease at relapse (p=0.0066).

Overall Survival (OS)

There was no significant difference at two years between the two groups, in:
- Relapse-free survival (60% [95% CI 49 to 74] vs 60% [51 to71]; p=0.50)
- Overall survival (83% [75 to 93] vs 71% [64 to 79]; p=0.39)

Overall survival at two years was significantly higher in patients with isolated CNS involvement compared with those with bone marrow involvement (91% [82 to 100] vs 71% [64 to 78]; p=0.046). They highlighted that CD19-targeted chimeric antigen receptor T-cell therapy is active at clearing CNS disease and maintaining durable remissions in children and young adults with CNS relapsed or refractory B-cell ALL or lymphocytic lymphoma, without increasing the risk of severe neurotoxicity; although care should be taken in the timing of therapy and disease control to mitigate this risk. These preliminary findings support the use of these CAR T-cell therapies for patients with CNS relapsed or refractory B-cell acute lymphocytic leukaemia. [45 level I]

Zhang X et al. (2020) in a non-randomized trial assessed the efficacy and safety of anti-CD19 CAR T cells in patients with R/R B-ALL. Patients with CD191 R/R B-ALL between ages two and 75 years with an Eastern Cooperative Oncology Group score between 0 and 3 were eligible. Patients with EMD or previous allo-HSCT without active graft-versus-host disease (GVHD) were also eligible. Complete Remission (CR), CR with incomplete count recovery (CRi), and minimal residual disease (MRD) were defined in accordance with the 2018 National Comprehensive Cancer Network guidelines. All 115 patients received fludarabine (30 mg/m2 per day) and cyclophosphamide (250 mg/m2 per day) lymphodepleting chemotherapy for three consecutive days before CAR T-cell infusion. The median time from leukapheresis to CAR T-cell infusion was 14 days (range, 9 to 35 days). A total of 85 of 115 patients received systemic bridging chemotherapy between leukapheresis and fludarabine cyclophosphamide lymphodepletion to control rapid disease progression. CAR T cells were produced using the Good Manufacturing Practice facilities at Beijing Immunochina Pharmaceuticals Co. Once patients had achieved CR, they were given options to proceed or not to consolidative allo-HSCT. Primary end points were CR, and MRD-negative CR on day 30, cytokine release syndrome (CRS) and neurotoxicity in patients with R/R B-ALL. The CRS and neurotoxicity were graded according to American Society for Transplantation and Cellular Therapy consensus guidelines. The secondary end points were overall survival (OS) and leukemia-free survival (LFS) after CAR T-cell therapy. OS was calculated from the date of CAR Tcell infusion to the date of last follow-up or death. LFS was calculated from the date of CR to the date of relapse, death, or the last follow-up.

The study involved 115 patients with CD19 B-ALL, with median age 12 years (range 2 to 61 years). Intervention was anti-CD19 CAR T cells with targeted infusion dose of 1 x 10^5 to 10 x 10^5 CAR T cells per kg. The median dose of infused cells was 3x 10^5 (range, 0.2-10 x 10^5) CAR T cells per kg. The cells were manufactured and infused in a single dose (110/115 patients). The median follow-up time was 233.5 days (range, 27- 478 days).

Remission & MRD negative

93% of patients achieved a morphologic complete remission at 30 days after anti-CD19 infusion and 87% became negative for minimal residual disease. The CR rate in patients without CNS leukaemia was higher vs patients with CNS leukaemia (95.7% vs 76.5%, p=0.021).There was no statistically significant difference in CR following CAR-T cell in group with/without EMD; patients who had previous allo-HSCT vs those without.

In terms of survival, 1-year overall survival (OS) was 64% and 1-year leukaemia free survival (LFS) was 58%, for the 110 infused patients. 1-year OS was 67.3% and 1-year LFS was 63.2%, for the 102 patients who achieved CR.

Subgroup

Mode of administration

Patients with a history of previous transplantation had a lower 1-year OS and LFS than those without previous transplantation (OS 30.5% vs 79.2%; 95%CI, 1.51 to 18.48; and LFS, 25.4% vs 69.4%; 95%CI, 0.07 to 0.71).

Bridging into allo-HSCT

Seventy-five non-randomly selected patients (73.5%) subsequently received an allogeneic hematopoietic stem cell transplant (allo-HSCT)

The LFS and OS were significantly better among patients who subsequently received allo-HSCT compared with those receiving CAR T-cell therapy alone; (76.9% vs 11.6%; p<0.0001; 95%CI: 11.6 to 108.4) and (79.1% vs 32.0%; p<0.0001; 95%CI: 0.02 to 0.22), respectively.

The data indicated that anti-CD19 CAR T-cell therapy is safe and effective in all B-ALL subgroups that have high-risk features. A high CR rate can be achieved for patients with R/R B-ALL who are treated with anti-CD19 CAR T-cell therapy, including patients with high-risk features such as EMD, BCR ABL1, CNS leukemia, TP53 mutation, and relapse after allo-HSCT. [46 level II-2]

Qi Y et al (2022) in RCT assessed the efficacy and safety of CD19-specific CAR T-cell therapy. B-ALL patients were diagnosed based on World Health Organization classification and R/R is based on National Comprehensive Cancer Network Guidelines. CNS-1 (no detectable blasts on cytology in a sample of CSF), CNS-2 (white blood cells [WBCs] ,5/mL; cytology positive for blasts), or CNS-3 (WBCs ≥5/mL; cytology positive for blasts or solid mass). 48 patients received CAR T-cell infusion and included in the analysis. After leukapheresis, 27 patients received CNS-directed bridging treatment. Patients

were categorised as CNS-1, CNS-2 or CNS-3 before CAR T-cell infusion. CNS-directed bridging therapy administered to patients with high burden at screening WBCs >20L in CSF. All patients were administered with fludarabine (30mg/m2 per day on days -5 to -3) and cyclophosphamide (750mg/m2 on day -5) for lymphodepletion chemotherapy. CNS remission refers to achievement of CNS-1 status in a patient with CNS-2/3 status, and CNS relapse requires new development of CNS-3 status or clinical signs of CNSL, brain/eye involvement, or hypothalamic syndrome. Cytokine release syndrome (CRS) was graded according to the ASTCT CRS Consensus Grading. Neurotoxic events (NEs) and other AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v.4.03.

The study involved 48 patients with R/R B-ALL diagnosed with CNSL, median age was 31 years (range, 6 to 68). All patients had received prior intensive cytotoxic chemotherapy, with a median of 4 lines of therapy. The 3 patients were identified with CNS-1 (6.3%), 15 with CNS-2 (31.2%), and 30 with CNS-3 status (62.5%). Extramedullary diseases other than CNS observed in 9 patients (18.8%), including kidney, pleura, or skeleton involvement or testicular leukemia. A total of N=37 patients (77.1%) were administered isolated anti-CD19 CAR T cells, and 11 patients (22.9%) received combined antiCD19 and anti-CD22 CAR T cells. Median follow up duration was 11.5 months.

Response Rates (CR/Cri and MRD negative CR)

At the day-30 assessment, 42 (87.5%) of 48 patients (95%CI: 75.3 to 94.1) had achieved CR/CR with incomplete blood count recovery for BM disease, and MRD–negative CR was observed in 35 patients (72.9%; 95% CI, 66.1 to 90)

Remission

Forty-one patients (85.4%; 95% CI, 72.8 to 92.8) achieved remission in CNSL. The remission rate from CNSL in patients receiving CNS-directed bridging treatment was higher than those who did not receive bridging treatment (96.3% vs. 71.4%, p=0.034).

OS and EFS

6-month OS rate was 72% (95% CI, 55.6 to 86.1) and EFS rate was 53.3% (95% CI, 36.5 to 68.1). The median EFS was 8.7 months (95% CI, 3.7 to 18.8), and the median OS was 16.0 months (95% CI, 13.5 to 20.1).

They highlighted that CD19-specific CAR T cell–based therapy can induce similar high response rates in both BM and CNS diseases. The duration of remission in CNSL was longer than that in BM disease. CD19 CAR T-cell therapy may provide a potential treatment option for previously excluded patients with CNSL, with manageable neurotoxicity.[47 level II-2]

Annesley C et al (2019) in another non-randomized trial reported their experience using CAR T cell immunotherapy for patients with R/R infant ALL. The LAT-02 is a phase 1/2 trial of CD19-specific CAR T cells, and PLAT-05 is a phase 1 trial of CD19xCD22 dual specific CAR T cells. Eligible subjects on both studies have R/R B-ALL, an absolute lymphocyte count ≥100 cells/μL, and were at least 1 year of age. In addition, subjects on PLAT-02 were ≥ 10kg, and ≥ 8kg on PLAT-05. Infant ALL subjects received a range of $5x10^5$ to $10x10^6$ CAR-T cells/kg following lymphodepleting chemotherapy. Disease response assessments were required at Day 21 and Day 63 following CAR T cell infusion. Adverse events were graded according to CTCAEv4, except CRS which was graded according to 2014 Lee criteria. The study involved 18 subjects with R/R infant ALL PLAT-02 (n=14) or PLAT-05 (n=4), median age of 22.5 months at enrolment (range: 14.5 - 40.1 months). The intervention was CD19-specific and CD19xCD22 dual specific CAR T cells, with median follow up of 26.9 months.

MRD-CR

14/15 (93.3%) achieved an MRD negative complete remission (MRD-CR) by Day 21. Of the 14 subjects with an MRD-CR, six went on to HCT with one subsequent CD19 negative relapse.

Lineage switch
Incidence of lineage switch among the infant ALL group was 1/15 (6.7%).

OS and LFS

The 1-year OS was 71.4% and 1-year LFS was 66.7%.

They highlighted that this is the largest reported cohort to date of R/R infant B-ALL subjects treated with CAR T cell therapy. Toxicity and MRD-CR rates are comparable to that of non-infant ALL subjects. Numbers in this report were too small to make definitive conclusions about the value of consolidative HCT. Future work is focused on overcoming feasibility issues to enable a larger number of these cases to access CAR T cell therapy. [48 level II-2]

5.2.4 Safety

CAR T cells are cell-based gene therapy (GT) products that are regulated under FDA's existing framework for biological products. Tisagenlecleucel (Kymriah®) is a CD19-directed genetically modified autologous T-cell immunotherapy approved in the United States indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.[49]

On October 1, 2021, the FDA granted approval to add a new indication for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) for Brexucabtagene autoleucel (Tecartus®).[50]

On June 28, 2018, the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Kymriah, (chimeric antigen receptor (CAR)–engineered T-cell therapy) for pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse after transplant, or in second or later relapse. Kymriah also received an orphan designation on April 29, 2014, following a positive recommendation by the Committee for Orphan Medicinal Products (COMP). Maintenance of the orphan designation was recommended at the time of marketing authorization as the COMP considered the product was of significant benefit for patients with both conditions. As per standard requirements, the CAT and CHMP conditions for approval included obligations for submission of periodic safety update reports via the European Medicines Agency web-portal. The marketing authorization holder shall submit the first periodic safety update report within 6 months following authorization. [51]

Health Canada approved Tisagenlecleucel for the treatment of patients aged 3 to 25 with r/r B-cell ALL (2018).[52] The Japan Ministry of Health, Labor and Welfare approved Tisagenlecleucel for the treatment of r/r pediatric and young adult (up to 25 years of age) acute lymphoblastic leukemia (ALL), and r/r adult diffuse large B-cell lymphoma (DLBCL)[1] in Japan (2019).[53] Tisagenlecleucel was designated an orphan medicinal product for the treatment of B lymphoblastic leukaemia/lymphoma on 29 April 2014 (EU/3/14/1266). It also meets SMC ultra-orphan and end of life criteria for this indication.[54]

A total of six SR was retrieved addressing adverse event of CAR-T cell therapy in the patients with relapsed/refractory ALL.

Table 6: Summary of safety outcomes from included studies

Study	AE	Effect measure
Elsalab 2023 (SR)	CRS Neurotoxicity treatment-related deaths	83% (95%CI: 76 to 89) (CRS any grade) 21% (95%CI: 16 to 26) (grade 3 or higher) 30% (95%CI: 24 to 38) (any grade) 4% (95%CI: 3 to 6)
Fergusson 2023 (SR)	CRS	87% (95%CI: 80 to 92%) (total) 6% (95%CI: 3 to 9%) (Severe (grade >3)
	Neurotoxicity Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Severe ICANS	16% (95%CI: 9 to 25%) 3% (95%CI: 1 to 5%)
	All-cause 30-days mortality	1% (95%CI: 0 to 3%)
Grover 2022 (SR)	CRS	82% (95%CI: 61 to 95) (any grade) 27% (95%CI: 18 to 36) (grade 3 or higher)
	Neurotoxicity	34% (95%CI 24 to 47). 14% (95%CI 1 to 25) (grade 3 or higher)
Leahy 2020 (SR)	CRS	CNS negative vs CNS negative - any grade, 110 (85%) vs 53 (80%); - grade 3, 18 (14%) vs 7 (11%) - grade 4, 19 (15%) vs 6 (9%);
	Neurotoxicity	-any grade; 53 (41%) vs 38 (58%); -grade 3, 12 (9%) vs 6 (9%), -grade 4, 3 (2%) vs 2 (3%);
Li 2022 (SR)	CRS (pooled)	CD22 targeted and CD19/CD22 targeted 0.92 (95%CI: 0.82 to 0.98) and 0.94 (95%CI: 0.82 to 1.00) Grade 1&2 CRS for CD22 targeted and CD19/CD22 targeted 0.83 (95% CI: 0.60 to 0.98) and 0.77 (95% CI: 0.61 to 0.90),
	Neurotoxicity (pooled)	The pooled neurotoxicity rates for anti-CD22 and anti-CD19/CD22 0.83 (95% CI: 0.60 to 0.98) and 0.77 (95% CI: 0.71 to 0.83).
Gregor 2022 (SR)	CRS Neurotoxicity Infection (pooled) Graft vs host disease (pooled)	55.3% (95%CI: 40.3% to 69.4%) and 37.2% (95%CI: 28.6% to 46.8%) 12.2% (95%CI: 8.1% to 18.0%; I2 9.9%) 23.4% (95%CI: 8.6% to 49.8%; I2 49.7%)

Study	AE	Effect measure
Zhang X 2020 (NRT)	CRS	92% (102/110) overall; 76% (84/110) grade 1 to 2 CRS 16% (18/110) grade 3 to 4 CRS 3.6% (4/110) grade 4 CRS
	Neurotoxicity	21% (23/110) had neurotoxicity 7% (8/110) had grade 1 neurotoxicity 14% (15/110) had grade 2 to 3 neurotoxicity
Qi Y 2022 (RCT)	CRS	89.5% (43/48 patients) 18.7% (9/48) Grade 3 to 5
	Neurotoxic	37.5% (18/48 patients) 22.9% (11/48 patients)(severe NE). Common NE were encephalopathy, depressed level of consciousness, delirium, headache and seizure.
	Death	4.1% (2/48) Two deaths were reported within the first 30 days after CAR-T cell infusion as a result of grade 5 CRS and refractory E.coli sepsis

CRS is characterised by fever >380C, haemodynamic instability and hypoxemia. Severity is graded according to the American Society for Transplantation and Cellular Therapy consensus criteria. The CRS management combines symptomatic measures (antipyretics, fluids) with tocilizumab (IL-6 receptor antagonist) ± corticosteroids.[55]

Elsalab (2023) in the SR conducted evaluated AE related to CAR-T cell therapy in patients with r/r ALL. Cytokine release syndrome (CRS) of any degree was reported in 83% (95% CI 76 to 89) of the infused patients, while 21% (95% CI 16 to 26) developed grade 3 or higher CRS. Neurotoxicity of any grade was reported in 30% (95% CI 24 to 38) of the infused patients. Of the infused patients 4% (95% CI 3 to 6) suffered from treatment-related deaths.[36]

Fergusson et al (2023) in another SR evaluated AE as well as other outcomes in addressing effectiveness and safety of CAR-T cell in patients with r/r ALL. These are the results: [39]

CRS
Incidence of total and severe (grade ≥3) CRS were 87% [95% CI: 80 to 92%] and 6% [95%CI: 3 to 9%] respectively. Meta-regression revealed no significant difference in the incidence of AE (total or severe) between those treated with CD22 versus CD19/CD22 CAR T-cells.

Neurotoxicity
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and severe ICANS had an estimated incidence of 16% [95%CI: 9 to 25%] and 3% [95%CI: 1 to 5%] respectively.

All-cause 30-day mortality
Estimated incidence of all cause 30-day mortality from these studies was 1% [95% CI: 0 to 3%] (18 studies (n=457)).

Similarly, Grover et al (2022) in another SR evaluating AE of CAR-T cell therapy in patients with r/r ALL and found that: [40]

Cytokine release syndrome (CRS)
Any grade of cytokine release syndrome (CRS) occurred in 82% of patients (95% CI 61 to 95). Grade 3 or higher CRS in 27% (95% CI 18 to 36)

Neurotoxicity
Neurotoxicity of any grade occurred in 34% of patients (95% CI 24 to 47). Grade 3 or higher neurotoxicity in 14% (95% CI 1 to 25).

Leahy et al (2020) in another SR found that the incidence and severity did not differ between the CNS-negative and the CNS-positive disease on;[45]

Cytokine release syndrome
- (any grade, 110 [85%] vs 53 [80%];
- grade 1, 12 [9%] vs 2 [3%];
- grade 2, 61 [47%] vs 38 [58%];
- grade 3, 18 [14%] vs 7 [11%] and
- grade 4, 19 [15%] vs 6 [9%]; p=0.26)

Neurotoxicity
- (any grade) 53 [41%] vs 38 [58%];
- grade 1, 24 [19%] vs 20 [30%];
- grade 2, 14 [11%] vs 10 [15%];
- grade 3, 12 [9%] vs 6 [9%], and
- grade 4, 3 [2%] vs 2 [3%]; p=0.20)

Li et al (2022) in another SR assessed AE together with other outcomes following CAR-T cell (CD22 targeted and CD19/CD22 targeted) in patients with r/r ALL. The pooled Cytokine Release Syndrome (CRS) rates of CD22 targeted and CD19/CD22 targeted immunotherapy were 0.92 (95% CI: 0.82 to 0.98) and 0.94 (95% CI: 0.82 to 1.00), respectively. Overall rates of Grade 1 and 2 CRS for CD22 targeted and CD19/CD22 targeted therapies; 0.83 (95% CI: 0.60 to 0.98) and 0.77 (95% CI: 0.61 to 0.90), respectively. The pooled rates for neurotoxicity following anti-CD22 and anti-CD19/CD22 therapies were 0.83 (95% CI: 0.60 to 0.98) and 0.77 (95% CI: 0.71 to 0.83).[41]

Grigor et al (2022) in another SR evaluated CAR-T cell therapy in patients with r/r ALL. They found that: Cytokine release syndrome was experienced by 55.3% (95%CI: 40.3% to 69.4%) of patients and neurotoxicity 37.2% (95%CI: 28.6% to 46.8%) of patients with hematologic malignancies. A pooled prevalence of infection was 12.2% (95%CI, 8.1% to 18.0%; I^2 9.9%) demonstrated among patients treated with CAR-T cell therapy. A pooled prevalence of Graft versus host disease (GVHD) was 23.4% [95% CI, 8.6% to 49.8%; I^2 49.7%] was demonstrated among patients treated with CAR-T cell therapy. B-cell aplasia was reported in seven of the CD19 CAR-T cell therapy hematologic cancer studies and one non-CD19 CAR-T cell therapy hematologic cancer study reviewed.[43]

Zhang X et al (2020) in a non-randomized trial assessed AE together with efficacy outcomes following CAR-T cells therapy in patients with r/r B-ALL. They found that for AE, most patients had mild cytokine release syndrome and neurotoxicity. The main adverse effect was fever.[46]

Qi Y et al (2022) in the RCT conducted found CRS occurred in 43 out of 48 patients. Nine of them were having CRS Grade 3 to 5. Meanwhile, neurotoxic events were observed in 18 patients (37.5%), with severe NE observed in eleven patients. Common NE were encephalopathy, depressed level of consciousness, delirium, headache and seizure. Two deaths were reported within the first 30 days after CAR-T cell infusion as a result of grade 5 CRS (patient 37) and refractory E.Coli sepsis (patient 42).[47]

Annesley et al. (2019) in the non-randomized trial found in the infant patients studied, the maximum grade of CRS was 3, occurring in 2/15 evaluable subjects (13%), while neurotoxicity was limited to a maximum grade of 2 in these patients following CAR-T therapy. [48]

5.2.5 Cost-effectiveness / Economic implication

There were four systematic review of cost-utility analysis (CUA) studies and one CEA retrieved and included in this review. These SR were published recently, between 2022 and 2024. The SR included six, 12, 14 and 47 CEA/CUA; from US, Netherland, Spain, Japan, Europe including Netherland, Switzerland, Asia, Canada, Australia; CEA from Singapore; from health system, payer/private health payer, and societal perspective. Main findings from the included SR was as summarized in the table below.

Table 7: Summary of findings from SR of CEA included in the review

Study	Perspective	Comparison	ICER (Base case analysis)	Treatment setting/ population
Andrade 2023 (SR of 6 CEA)	NA	Tisagenlecleucel compared with conventional salvage therapies	ICER per QALY gained for tisagenlecleucel compared with Clo-C and Blina averages was $38,837 and $25,569 Tisagenlecleucel is expensive therapy than conventional alternatives. However, tisagenlecleucel performed well on the ICER, not exceeding $100 000/QALY	Patients aged 0-25 years wwith r/r B-ALL
Thavorn 2024 (SR of 44 CEA)	Mostly public or private health payer perspective, 19 used a health system perspective, four societal perspective	Tisa-cel, Breu-cel compared to Blinatumomab, Inotuzumab, salvage chemotheraphy	$21 623, $80 282, and $97 511 per QALY (Brexu-cel compared with blinatumomab, inotuzumab, and salvage chemotherapy) Ranged between $20,784 and $246,177 per QALY (tisagenlecleucel) CAR-T therapies were more expensive, generated more QALYs than comparators, but their cost-effectiveness was uncertain	r/r B ALL in adults r/r B-ALL in paediatric

Study	Perspective	Comparison	ICER (Base case analysis)	Treatment setting/ population
Soliman 2023 (SR of 12 studies, CEA and cost analysis)	Health system/payer	Tisa-cel compared to any of the other comparators: Blinatumomab (Blina); Clofarabine therapy [Clofarabine monotherapy (Clo–M)] or Clofarabine combination therapy (Clo–C; Clofarabine/ cyclophosphamide/ etoposide); FLA-IDA salvage chemotherapy (Fludarabine/ cytarabine/ idarubicin)	CAR-T cell therapy relative to other comparators) ranged from **$18,753 to $157,026/QALY gained** CAR-T more cost-effective compared to the other treatment strategies (9 studies), including Japan, Switzerland. WTP thresholds varied among studies Median cost (USD 2019) for CAR-T cell therapy in the reported studies was **$561,075** (IQR: $464,335–$612,779). *The estimated costs of CAR-T cell therapy included all cost components of treatment calculated over a life-time horizon, not just the listing price of tisagenlecleucel,* Main cost driver - drug list price, other top cost drivers - AE management (51.6%), inpatient and ICU admissions not attributed to AE (42.1%), laboratory tests and procedures (3.8%).	relapsed/ refractory (r/r) acute leukemia in children and young adults
Gye 2022 (SR)	Health system perspective	Tisa-cel, Axi-cel compared to Blinatumomab, Clofarabine, Clofarabine & Etoposide / Cyclophosphamide	ICERs ranged from **$39 146** (NICE) to **$98 450**	Paediatric ALL
Wang 2022 (CEA with BIA)	Health system perspective	Tisagenlecleucel compared to salvage chemotherapy regimen (SCR) or blinatumomab (BLN)	Tisagenlecleucel demonstrated cost-effectiveness with an ICER of S$45,840 (US$34,762) per QALY (vs SCR) and S$51,978 (US$39,315) per QALY (vs BLN). Estimated budget ranges from S$477,857 (US$361,438) to S$1.4 million (US$1.05 million) annually for the initial 5 years. Tisagenlecleucel is likely to be a cost-effective treatment option with limited budget implications while treating r/r ALL patients who have failed at least 2 lines of prior therapies	Pediatric and young adult patients with relapsed/refractory B-cell ALL

Current list pricing ranges between $373,000 and $475,000 per one-time infusion for the fve CAR-T-cell therapies currently approved by the FDA (tisagenlecleucel, Kymriah®; axicabtagene ciloleucel, Yescarta®; brexucabtagene autoleucel, Tecartus®; lisocabtagene maraleucel, Breyanzi®; idecabtagene vicleucel, Abecma®). In addition to the cost of the CAR-T-cell product, patient preparation (leukapheresis and/or lymphodepletion), product infusion, pre- and post-infusion patient management, and monitoring for side effects significantly add to the final price tag.[55]

Andrade et al. (2023) evaluated the cost-effectiveness of tisagenlecleucel compared with conventional salvage therapies in paediatric and young adult patients with R/R B-ALL. This systematic review followed the Preferred Reporting Items for Systematic Reviews and MetaAnalyses parameters as registered in International Prospective Register of Systematic Reviews (CRD42021266998). Literature was searched using the MEDLINE databases via PubMed, EMBASE, Lilacs, the Cochrane Central Register of Controlled Trials and Web of Science in January 2022. Inclusion criteria was phase 1, 2 and 3 randomized controlled clinical trials and prospective/retrospective cohort studies that compared the cost-effectiveness between tisagenlecleucel therapy and conventional therapies in people aged 0 to 25 years with R/R B-ALL. The Rayyan QCRI platform was used for the selection of articles. itles were screened independently by two reviewers. Life years (LYs) and quality adjusted life years (QALYs) gained were considered to indicate treatment efficacy outcomes. For treatment safety assessment, the occurrence and costs of treating adverse events resulting from the use of tisagenlecleucel were considered. For cost-effectiveness, total costs, administration costs, drug costs and incremental cost-effectiveness ratio (ICER) with a discount for QALY gained were considered. Cost data were presented in 2018 US dollars. Quality of reporting and the risk of bias of the selected studies were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The GRADEpro online software was used to appraise the quality of evidence. In this review, six eligible studies were included involving 1580 (ranged 100 to 380 patients per study) paediatric and young adults patients up to 25 years old. Most studies were conducted in the US (3), Netherland (1), Spain (1), Japan (1). Study times ranged from 3 months to 5 year. Most frequently applied economic models were decision tree and Markov model. Eighty three percent of the studies used the time horizon until the end of the individuals' lives.

They found the values of LY gained for patients treated with tisagenlecleucel were significantly superior compared with conventional treatments by approximately two times compared with Blina, four times compared with

Clo-M, 3.7 times compared with Clo-C and 12 times compared to the FLU-IDA. In terms of QALYs gained, tisagenlecleucel were superior to conventional treatments by 4.4 times compared with Blina, five times compared with Clo-M, three times compared to Clo-C and 20 times for QALY gained compared to FLU-IDA. The mean costs associated with AE (safety) were CRS ($24794.38), febrile neutropenia ($6098.40), acute kidney failure ($8508.53), encephalopathy ($5424.06), thrombocytopenia ($5048.17), anaemia ($4605.65).

The ICER per quality-adjusted life year (QALY) gained for tisagenlecleucel compared with Clo-C and Blina averages was $38,837 and $25,569, respectively.The average cost of tisagenlecleucel was approximately 4.3 times, 10.8 times or 4.7 times greater than the Clo-M, Clo-C and Blina, respectively. This systematic review highlighted that tisagenlecleucel is a much more expensive therapy than conventional alternatives. However, tisagenlecleucel performed well on the ICER, not exceeding $100 000/QALY. It was also found that the advanced therapy product was more effective than the conventional small molecule and biological drugs, in terms of life years and QALY gained.[56]

Thavorn et al (2024) in another SR of CEA aimed to systematically review evidence on the cost-effectiveness of chimeric antigen receptor T-cell (CAR-T) therapies for patients with cancer. Electronic databases were searched in October 2022 and updated in September 2023. Databases searched included Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid. MEDLINE, Embase Classic 1 Embase, and The Cochrane Library (HTA database, NHSEED, DSR, DARE, and CENTRAL). Systematic reviews, health technology assessments, and economic evaluations that compared costs and effects of CAR-T therapy in patients with cancer were included. Two reviewers independently screened studies, extracted data, synthesized results, and critically appraised studies using the Philips checklist. The checklist consists of 62 questions across 3 dimensions (model structure, data, and assessment of uncertainty and consistency) used to critically appraise economic models. Cost data were presented in 2022 US dollars. Comparators of interest included standard of care available for each type of cancer, for example, a combination of chemotherapies, bone marrow transplant, palliative care, and other immunotherapies. Outcomes of interest were cost-effectiveness measures, such as ICER or incremental cost-utility ratio or incremental net benefit. 47 studies were included.

The review included 44 studies which were cost-utility analyses, two (cost-effectiveness analyses using an efficiency frontier) and one (cost-minimization analysis). Most studies took on a public or private health payer perspective, 19 used a health system perspective, and four considered the societal perspective.Twenty studies were conducted in the United States, 11 (Europe), nine (Asia), four (Canada) and one (Australia). Most studies were published between 2018 and 2023. Ten studies focused on pediatric and young adult patients (25 years and younger; age range 10 to 12) who had r/r BALL; the rest conducted in adults (40 to 65) with r/r large B-cell lymphoma.

The intervention assessed in this review was tisagenlecleucel, axicabtagene ciloleucel, idecabtagene vicleucel, ciltacabtagene autoleucel, lisocabtagene maraleucel, brexucabtagene autoleucel, and relmacabtagene autoleucel. Among these, two most prevalent treatments were axicabtagene, which was used for adults with r/r LBCL, and tisagenlecleucel, which was used for both the pediatric population with r/r B-ALL and adults diagnosed of r/r LBCL.

The incremental cost-effectiveness ratio (ICER) for CAR-T therapies ranged from: $9,424 to $4,124,105 per QALY in adults; $20,784 to $243,177 per QALY in paediatric patients.

ICER of CAR-T in rr B ALL (adults)

Cost-effectiveness of brexucabtagene was $21 623, $80 282, and $97 511 per QALY compared with blinatumomab, inotuzumab, and salvage chemotherapy, respectively. (One study evaluated use of brexucabtagene in the adult B-ALL setting). Results were most sensitive to changes in time horizon (10 and 20 years vs lifetime) and when the excess mortality among long-term remission patients was high, particularly when comparing axicabtagene with inotuzumab and salvage chemotherapy.

ICER of CAR-T in rr B ALL (paediatric)

Cost-effectiveness results for tisagenlecleucel among paediatric patients with r/r B-ALL ranged between $20,784 and $246,177 per QALY over a lifetime horizon. Results were largely affected by variations in assumptions regarding long-term survival and remission.

They highlighted CAR-T therapies were more expensive and generated more QALYs than comparators, but their cost-effectiveness was uncertain and dependent on patient population, cancer type, and model assumptions. This underscores the need for more nuanced economic evaluations and continued research to better understand the value of CAR-T therapies in diverse patient populations.[57]

Soliman et al (2022) in another SR aimed to establish the health-economic evidence base for costs and cost-effectiveness of treatment for relapsed/refractory (r/r) acute leukemia in children and young adults from the health system/payer perspective. Systematic search of Medline, Embase, and Cochrane databases until August 13th, 2021.Inclusion criteria were: (1) relapsed acute leukemia in children and young adults (up to 25 years old) (2) analysis of the cost, cost-effectiveness analysis (CEA), cost-utility (CUA), or cost-benefit of any interventions to treat relapsed/refractory (r/r) acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML); (3) measurement of economic costs, cost per life year gained (LYG) or quality-adjusted life year (QALY) gained, cost per life saved, cost per Disability-Adjusted Life Year (DALY) averted, incremental cost-effectiveness ratio (ICER), or any other measures of economic evaluations without restrictions. Quality assessment was conducted using Consolidated Health Economics Evaluation (CHEERS) Checklist.

Table 8: Summary outcomes of few studies included in the review

Author (Year)	Country, Currency (Ref. Year)	Discount rate	Time horizon	Costs of alternative treatment strategies	Clinical effects/outcomes	Cost-effectiveness (ICER/ICUR) *	WTP threshold	Conclusion/ comments
Furzer *et al* (2020)[30]	Canada, CaD (2018)	1.5% (costs, effects).	Lifetime horizon	• Tisa-cel: 584,000 CaD • Chemo/HSCT: 114,000 CaD.	• Tisa-cel: 5-year overall survival (OS): 0.22; 9.72 LYG and 6.79 QALYs gained. • Chemo/HSCT: 5-year OS: 0.16; LYG: 5.05; 3.46 QALYs gained.	Incremental cost per QALY gain ranging from CaD $71,000 at 40% cure rate, to CaD $281,000 at 10% cure rate.	$150,000 per QALY gained	At a WTP $150,000/QALY, Tisa-cel had a 32% likelihood of being cost-effective. Cost-effectiveness would fall below $50,000/QALY with a long-term cure rate of >40% or a price discount of 49%.
Yang *et al* (2020)[31]	USA, USD (2019)	Not reported.	Costs were estimated from time of leukapheresis to 2 months post-infusion.	• Tisa-cel: $612,779	N/A	N/A	N/A	In addition to the Tisa-cel price, costs of adverse event management, and inpatient and ICU admissions were main cost drivers.
Schultheiss *et al* (2021)[32]	USA (USD, 2019)	3% (costs, effects).	3 years of outcomes	• CAR-T cell therapy: $590,112 • HCT: $303,065	• CAR-T cell therapy: 3-year RFS 46% (95% CI: 08–79%) • HCT: 3-year RFS 68% (95% CI: 46–83%)	N/A	N/A	Lower RFS probability with CAR-T compared to HCT is due to CAR-T cohort had a far higher level of disease burden.
Wakase *et al* (2021)[33]	Japan (JPY, 2018)	2% (costs, effects).	Lifetime horizon	• Tisa-cel: JPY 40,276,340 • Blinatumomab: JPY 22,976,259 • Clo-C: JPY 14,986,473	• Tisa-cel: 13.3 LYG; 11.6 QALYs gained • Blinatumomab: 4.0 LYG; 3.1 QALYs gained. • Clo-C: 2.7 LYG; 2.1 QALYs gained.	ICERs per QALY gained for Tisa-cel were JPY 2,035,071 vs. Blinatumomab, and JPY 2,644,702 vs. Clo-C.	JPY 7.5 million per QALY gained	Tisa-cel I is a cost-effective treatment for R/R B-ALL from a Japanese public healthcare payer's perspective.
Moradi-Lakeh *et al* (2021)[34]	Switzerland, CHF (2018)	3.5% (costs, effects).	Lifetime horizon	• Tisa-cel: CHF 511,939 • Clo-C: CHF 282,388 • Blinatumomab: CHF 285,595 • Salvage chemotherapy: CHF 259,565	• Tisa-cel: 9.64 LYG; 8.29 QALYs gained. • Blinatumomab: 2.75 LYG; and 2.07 QALYs gained. • Clo-C: 2.25 LYG; 1.64 QALYs gained. • Salvage chemotherapy: 0.78 LYG; 0.39 QALYs gained.	Incremental cost per QALY gained for Tisa-cel in pALL was CHF 31,961, CHF 34,530 and CHF 36,419 compared to salvage chemotherapy, Clo-C and blinatumomab.	CHF 100,000–150,000 per QALY gained	Tisa-cel was shown to be dominant (more effective and less costly) over all the comparators.

The review included 12 studies. All articles were conducted in high-income countries (US, Netherland, Spain, Switzerland, Japan). Ten studies addressed r/r pediatric ALL, and two studies evaluated costs/cost-effectiveness of r/r ALL/AML. All studies reported CEA or CUA except two which analyzed cost outcomes. The review assessed CAR-T cell therapy (tisagenlecleucel, tisa-cel) for r/r ALL as the main intervention, with any of these intervention as other comparators: Blinatumomab (Blina); Clofarabine therapy [Clofarabine monotherapy (Clo–M)] or Clofarabine combination therapy (Clo–C; Clofarabine/cyclophosphamide/etoposide); FLA-IDA salvage chemotherapy (Fludarabine/cytarabine/idarubicin).

CAR-T cell therapy was found to be **more cost-effective** compared to the other treatment strategies in nine studies. Willingness-to-pay (WTP) thresholds varied among studies. (Table above). The ICER for CAR-T cell therapy relative to other comparators ranged from **$18,753 to $157,026/QALY gained**.

Median cost (USD 2019) for CAR-T cell therapy in the reported studies was **$561,075** (IQR: $464,335–$612,779), and mean cost was **$577,631** (SD: ± $180,000). *The estimated costs of CAR-T cell therapy included all cost components of treatment and not just the listing price of tisagenlecleucel, calculated over a life-time horizon.* The main cost driver; the drug list price, and other top three cost drivers included adverse events (AE) management (51.6%), inpatient and ICU admissions not attributed to AE (42.1%), and laboratory tests and procedures (3.8%).The next best treatment option is Blinatumomab, followed by Clofarabine therapy, whereas FLA-IDA salvage chemotherapy provides least value for money.[58]

Gye et al (2022) in another SR aimed to identify sources of variability in CEA of CAR-T cell therapies, tisagenlecleucel and axicabtagene ciloleucel, evaluated by health technology assessment (HTA) agencies, focusing on young compared with older patients. A search for HTA evaluations of CAR-Ts tisagenlecleucel (Tisacel) and axicabtagene ciloleucel (Axi-cel) was conducted between May 2020 and July 2020. HTA evaluations in paediatric acute lymphoblastic leukemia (ALL) and adult diffuse large B-cell lymphoma (DLBCL) were included from Australia, Canada, England, Norway, and the United States. Key clinical evidence, economic approach, and outcomes (costs, quality-adjusted life-years [QALYs] and incremental cost-effectiveness ratios) were summarized. For each therapy, only the final assessment that was the basis of the funding recommendation was included; Information was extracted from the base-case analysis after any adjustments had been made by the evaluators or reviewers. Fourteen HTA evaluations were identified and included (5 ALL, 9 DLBCL [4 tisagenlecleucel, 5 axicabtagene]), they were evaluations from these HTA agencies: CADTH, Institute for Clinical and Economic Review, Medical Services Advisory Committee (MSAC) in Australia, NICE, and the Norwegian Medicines Agency (NoMA). The review assessed CAR-Ts tisagenlecleucel (Tisacel) and axicabtagene ciloleucel (Axi-cel) as the intervention of interest, with these as comparators; blinatumomab, Clofarabine, Clofarabine in combination with Etoposide and Cyclophosphamide. These were the main findings from the review.

Table 7: Summary of findings from SR of CEA included in the review

Agency	Comparator	Clinical evidence
CADTH	Blinatumomab	There is uncertainty in the clinical evidence because of the lack of long-term follow up, single-arm trial design, and small patient numbers in the studies.
MSAC Australia	Clofarabine	The estimated health benefit is substantial although the magnitude is uncertain because of noncomparative trials of short duration.
Andrade 2023 (SR of 6 CEA)	Blinatumomab	Tisa-cel shows promising rates of remission although there are clinical uncertainties (because of single-arm studies, small patient numbers, heterogeneous patient characteristics, and short follow up).
NICE	Blinatumomab	Tisa-cel is clinically effective but a lack of comparative data a challenge; clinical evidence beyond 30 months is uncertain because of small patient numbers and differences in trial populations. No robust evidence that tisa-cel is curative.
NorwayMA	Clofarabine & etoposide/ cyclophosphamide	Tisa-cel seems to have superior efficacy compared with the comparator although the relative treatment effect cannot reliably be established because of data limitations.

ICER

All economic models were considered from a healthcare system perspective. In paediatric ALL, ICERs ranged from **$39 146** (NICE) to **$98 450** (MSAC upper range), approximately a 2.5-fold difference.

For Tisa-cel, the highest number of incremental QALYs gained was 10.6 (CADTH) and the lowest was 3.67 (NoMA). Incremental costs ranged from $226 091 (NoMA) to $443 233 (CADTH), where reported. Incremental QALY varied substantially in ALL (3.67 to 10.6 QALYs gained).

Table 10: ICER of Tisa-cel in paediatric ALL from several agency evaluations

Agency	Cost, $			QALYs			Incremental cost-effectiveness ratio, $
	Tisa-cel	Comparator	Incremental	Tisa-cel	Comparator	Incremental	
Tisa-cel, pediatric ALL							
CADTH[42,43]	$611945	$178722	$433223	10.95	0.35	10.60	$40794
ICER[34]	$666754	$337256	$329498	9.28	2.10	7.18	$45871
MSAC[445]	NR	NR	$25643-$364562	4.97	1.27	3.70	$69280-$98450
NICE[32,45,*]	NR	NR	NR	NR	NR	NR	$39146
NoMA[46]	$455898-$522838	$189806	$226091-$333032	7.12-8.06	3.44	3.67-4.62	$72099-$72435

Price

Where reported, prices for CAR-Ts (excluding associated hospital costs or mark-ups) were in the range of **$342,959 to $575,000**. Some agencies specified a requirement for price reductions (10% in ALL). Most recommendations included a requirement for longer-term follow-up data from clinical trials and additional data collection via patient registries for use in the reassessment of cost-effectiveness.

Overall, they highlighted that modelled, long-term treatment benefit in young patients may be associated with greater uncertainty compared with adults because of potential life-long benefits with cell and gene therapies. This reflects the methodological challenges identified by HTA agencies associated with single-arm, short-term studies. In case of potential for a new treatment to be lifesaving, consideration could be given to interim funding arrangements via managed access arrangements, while additional data are generated for use in a subsequent cost-effectiveness review. Further research is needed to identify the most appropriate mechanism for providing timely access to potentially one-time, curative therapies with value for money.[59]

Wang et al. (2022) in a CEA conducted in Singapore evaluated the cost-effectiveness and budget impact of tisagenlecleucel versus salvage chemotherapy regimen (SCR) or blinatumomab (BLN) for the treatment of pediatric and young adult patients with relapsed/refractory B-cell ALL from the Singapore healthcare system perspective. In this study, a three-health state partitioned survival model was constructed to analyze the cost-effectiveness of tisagenlecleucel vs SCR/BLN with/without allogenic hematopoietic stem cell transplantation (allo-HSCT) over a lifetime period. Clinical efficacy for tisagenlecleucel, SCR and BLN were based on pooled data from ELIANA, ENSIGN and B2101J trials, the study by von Stackelberg et al 2011, and MT103-205 respectively. Medical costs from pre-treatment until terminal care, including treatment, side effects, follow-up, subsequent allo-HSCT and relapse, were considered. Incremental cost-effectiveness ratios (ICERs) were estimated as the incremental costs per quality-adjusted life-year (QALY) gain. Additionally, the financial impact of tisagenlecleucel introduction in Singapore was estimated, comparing the present treatment scenario (without tisagenlecleucel) with a future scenario (with tisagenlecleucel), over 5 years. They found in the base-case analysis, tisagenlecleucel treatment demonstrated cost-effectiveness with an ICER of S$45,840 (US$34,762) per QALY (vs SCR) and S$51,978 (US$39,315) per QALY (vs BLN). The estimated budget ranges from S$477,857 (US$361,438) to S$1.4 million (US$1.05 million) annually for the initial 5 years. They highlighted that Tisagenlecleucel is likely to be a cost-effective treatment option with limited budget implications while treating r/r ALL patients who have failed at least 2 lines of prior therapies. [60]

5.2.6 Organizational

The development, manufacture, testing, and clinical assessment of CAR T cells is challenging. Careful design and appropriate testing of the CAR transgene and delivery vector are critical to product safety, specificity, and function. CAR T cell manufacturing involves multiple biological materials and complex multi-step procedures, which are potential sources of variability among product lots. Thus, control of the manufacturing process and appropriate in-process and lot release testing are crucial to ensure CAR T cell safety, quality, and lot-to-lot consistency.[61]

The implementation of this new therapy in a dedicated centre or institution or hospital should not be underestimated. In addition to the training of staff for this new type of therapy, high demands are placed on quality management by both the pharmaceutical industry and the government. [62]

Leukapheresis procedure

The first step in CAR T-cell therapy is leukapheresis for T-cell collection. Procedures that ensure successful collection are necessary for successful manufacturing and treatment, as higher T-cell numbers in the leukapheresis product may be associated with achievement of remission. patient and disease characteristics that is associated with low lymphocyte collection efficiency (defined as the lymphocyte count per product volume divided by the average lymphocyte count per processed peripheral blood volume) include advanced age, diagnosis of ALL and high platelet count prior to leukapheresis. In addition to volume and quality of the leukapheresis product, another important factor in the leukapheresis process is the timing with respect to the patient's disease trajectory and treatment.

Prior to leukapheresis, patients are evaluated for their general suitability to receive CAR T-cell therapy. The factors evaluated include age, Eastern Cooperative Oncology Group performance status (ECOG PS) or Karnofsky/ Lansky performance status, history of prior malignancies, timing of prior alloSCT as it relates to immunosuppression status and graft-versus-host disease (GVHD), prior CD19-directed therapy or CAR T-cell therapy clinical trials or commercial product, active infections and history of central nervous system disease.[63]

Training

CAR-T confers a risk of potentially life-threatening immunological toxicities and comprehensive training of personnel involved in CAR-T delivery, including intensive care unit (ICU) and neurology specialists, is key.[63]

Implementation of CAR-T cells require collaboration across the MDT as areas that previously worked independently now work together to ensure safe delivery of CAR-T cells to patients. For instance, pharmacies are required to work closely with stem cell laboratories, which is novel for most pharmacists and requires specialist training on a per-product basis.

The scope of training required is broad and is delivered across several disciplines. All staff involved with CAR-T cell therapy (e.g. doctors, nurses, pharmacists and laboratory staff working across haematology, intensive care, neurology and pharmacy) should undertake substantial training in order to understand and be able to deliver the product. In particular, haematology wards, intensive care units, on-call pharmacists and hospital emergency departments are required to have knowledge of CAR-T cells and how to manage complications that may arise as a result of CAR-T cell therapy.

To ensure optimal decision-making by physicians, adequate education programmes must be available and must be regularly updated. There is a need to identify knowledge gaps and barriers to address these issues with continuous medical education. Continuous medical education should fill unavoidable knowledge gaps in a rapidly evolving field. The importance of education is also reflected in the JACIE accreditation scheme, the major objective of which is to promote quality medical and laboratory practice in cellular therapy by offering accreditation based on internationally recognized standards. The relevant standards in this scheme require that clinical, collection, and processing facility staff participate in continuous education activities.

Big data registry studies, multistakeholder coalitions, and multidisciplinary educational meetings provide regular updates on the entire CAR-T cell therapy process. Updates on specific topics and the latest scientific developments are also required to provide individualized high-quality patient management. An e-learning platforms and CAR-T cell meetings provide adequate and specific updates in this complex field, but there is also a need to educate the wider medical community, who refer patients to treatment centers. Continuous medical education is necessary, especially because this field is rapidly evolving.[55]

Post-Authorization Safety Surveillance/Registry

CAR-T qualify as GMOs and competent authorities (United States Food and Drug Administration; EMA) mandate LTFU for 15 years. Post-Authorization Safety Studies (PASS) collect data on adverse events via pre-existing or dedicated registries. The EBMT Registry has created a Cellular Therapy Form to register and monitor European CAR-T recipients. Post-marketing pharmacovigilance over 15 years post-infusion is mandated by the European Medicines Agency (EMA) to ensure ongoing evaluation of the efficacy and safety of licensed CAR-T in the real-world setting via the European Society for Blood and Marrow Transplantation (EBMT) registry. [63]

Post-authorization safety studies (PASS) initiative assesses the value of CAR-T in relation to standard-of-care treatments. European Society for Blood and Marrow Transplantation (EBMT) is the co-founder of GoCART, a multi-stakeholder coalition of patient representatives, health care professionals, pharmaceutical companies, regulators, Health Technology Assessment (HTA) bodies and reimbursement agencies, and medical organisations, collaborating to maximise the potential of cellular therapies manufactured from cells and tissues of hematopoietic origin. [63]

Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) is Europe's only official accreditation body in the field of haematopoietic cell transplantation (HCT) and cellular therapy (CT). It promotes high-quality patient care, medical and laboratory practice through a profession-led, voluntary accreditation scheme. FACT-JACIE standards guide accreditation of HCT program activity across the United States and the EU with the aim of improving outcomes. EBMT and JACIE recommend that CAR-T is best delivered from within an accredited HCT program. JACIE facilitate inspections and ensure that programs comply with data submission to the EBMT Registry, with a view to benchmarking purposes. [64]

Patient eligibility

Patient eligibility should be assessed by a CAR-T center multi-disciplinary team including cellular therapy and haematology/oncology disease specialists. Medical history, performance status and CAR-T product should be considered with respect to tolerability. The European Society for Blood and Marrow Transplantation (EBMT)-Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (2022) collaborated to draft best practice recommendations based on the current literature to support health professionals in delivering consistent, high-quality care in this rapidly moving field. [63]

Table 11: Patient eligibility criteria (ESMO Guideline 2022)

Eligibility criteria	EBMT/EHA recommendation
Age limit	No age limit
Performance status	ECOG<2, Karnofsky >60% or Lansky >60%
Life expectancy	> 6 to 8 weeks
High tumour burden	Risk-benefit assessment required
History of malignancy	Absence or active malignancy requiring treatment other than non-melanoma skin cancer or carcinoma in-situ (eg cervix, bladder, breast)
Prior allo-HCT	Not a contraindication
Immunosuppressive treatment	Relative contraindication
Bacterial or fungal infection	Active infection is a contraindication
Viral infection	Viraemia is a contraindication
History of Central Nervous System Involvement	Relative contraindication

Conducting leukapheresis

A pre-leukapheresis checklist and suggested washout periods for pre-leukapheresis therapeutics are highlighted. Leukapheresis procurement in the European Union (EU) must comply with the Tissue and Cell Directives (2004/23/ EC; 2006/17/EC; 2006/86/EC). Accredited, validated leukapheresis testing methods should be compatible with manufacturer's requirements and authorizations. An absolute lymphocyte count (ALC) threshold of $0.2x10^9$ is generally recommended.

In Europe, to be a CAR-T delivery site, accreditation with Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE is recommended. Accredited, validated leukapheresis testing methods should be compatible with manufacturer's requirements and authorizations. Infectious disease markers must be tested on peripheral blood within 30 days of leukapheresis (with results available on the day of shipment). [63]

Bridging therapy

'Bridging' therapy, administered in the 4 to 6 weeks between leukapheresis and CAR-T administration, aims to reduce disease burden and, in doing so, increase CAR-T efficacy improve intention-to-treat and reduce immunotoxicity. Patient-specific bridging recommendations should be made by a multi-disciplinary team following review of response to prior therapy, overall tumor burden and anatomical sites of disease.[63]

Healthcare setting

Outpatient CAR-T administration can be done safely, provided clear policies, appropriate infrastructure, well-trained staff and capacity for 24/7 hospitalisation in the event of complications are in place. As such facilities are not available in most European centers, they recommend that patients remain hospitalised for at least 14 days following infusion.[63]

Lymphodepleting conditioning (LD) acts to enhance CAR-T proliferation by modulating cytokine and immune pathways. Fludarabine and cyclophosphamide (FC) is widely used.25 Fludarabine dosing is consistent between products and indications (25-30 mg/m^2 /day 3 days) whilst cyclophosphamide schedules differ. LD is administered following CAR-T product release, the week before CAR-T infusion with a minimum of 2 rest days. Where CAR-T infusion is delayed by >4 weeks, repeat LD is recommended. [63]

Infusion

Responsibility for product receipt process varies internationally and nationally. Centres should have regulatory approval for storage of genetically modified organisms (GMOs). Before infusion, patients are medically assessed to ensure they are fit to proceed; identity and consent is confirmed, the prescription reviewed and vital signs and intravenous access (central venous catheter or a newly inserted and pre-tested peripheral cannula) checked at the bedside.Product thawing is carried out in a pharmacy clean room, cell therapy unit or patient bedside, double wrapped in a watertight plastic bag, using thawing devices according to manufacturer's instructions and local regulations (automated thawing device, 37 ± 2C water bath, or dry-thaw method). CAR-T is stable at room temperature for 30-90 min after thawing. CAR-T should be administered rapidly after thawing during working hours by competent medical or nursing personnel. Vital signs should be assessed and recorded before, during and following infusion. Using aseptic non-touch technique, cells in vials are drawn up into a syringe to be administered as a slow bolus. [63]

Global CAR-T Task Force was developed to help identify and address the key challenges in the treatment and management of patients with relapsed or refractory B-ALL destined to undergo treatment with anti CD19 CAR-T such as tisagenlecleucel, commissioned by the American Society for Blood and Marrow Transplant (ASBMT) Practice Guidelines Committee and the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). The Task Force included representatives from ASBMT, EBMT, the International Society of Cell and Gene Therapy (ISCT), and the Foundation for the Accreditation of Cellular Therapy (FACT). [65]

Where and when patients should be referred to

For safe delivery of CAR-T therapy, a robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain-of-custody and chain-of-identity of the cellular product, and facilitate communication to manage potentially severe toxicities. To fulfill these robust requirements for a safe delivery of CAR-T, currently only selected larger institutions are selected for performing CAR-T therapy, and these are typically centers with allo-HCT experience as they are already performing similar process for HCT. They suggested referring patients with induction failure, early relapse after achieving first complete remission, and adult patients with relapsed/refractory B-ALL to CAR-T cell therapy programs to allow discussion of the optimal timing of apheresis and potential of enrollment in CAR-T clinical trials. They suggested prompt referral to a CAR-T center as soon as a patient meets referral criteria (e.g., at the time of relapse, before starting therapy if possible) especially as specified recovery periods from prior therapy are required before leukapheresis.[65]

Optimal strategy to manage bridging chemotherapy and administer lymphodepleting chemotherapy between T-cell collection and infusion of CAR-T

Bridging chemotherapy

Chemotherapy after T-cell collection by leukapheresis is usually required to control disease until the manufacturing of CAR-T is complete. Bridging chemotherapy should focus on disease control rather than remission induction while minimizing organ toxicity or risk of infections. Table below describes various chemotherapy considerations for bridging therapy and how to manage them in relation to CAR-T infusion. The choice of bridging therapy depends on a patient's previous treatment history and should be timed and coordinated closely with the CAR-T manufacturing / treating institution to avoid delays in the infusion of CAR-T therapy. As mentioned above, previous use of blinatumomab is not an absolute contraindication for receiving anti CD19 CAR-T therapy, however to minimize the risk of antigen loss and until more robust data are available, this therapy should ideally be avoided as a bridging chemotherapy. [65]

Table 12: Suggested treatment option for bridging chemotherapy or radiotherapy between leukapheresis and CAR-T therapy

Bridging chemotherapy consideration	Timeline to stop chemotherapy/radiotherapy
Systemic steroid, Hydrea, and Tyrosine Kinase Inhibitor	Stop >3 days prior to tisagenlecleucel infusion
Systemic chemotherapy - Vincristine - 6 mercaptopurine - 6 thioguanine - Methotrexate <25mg/m^2 - Cytosine arabinoside <100mg/m^2/day - Asparaginase (nonpegylated)	Stop >1 weeks prior to tisagenlecleucel infusion (No drug should be administered concomitantly or following lymphodepleting chemotherapy)
CNS disease prophylaxis	
Salvage chemotherapy eg - Cytosine arabinoside >100mg/m^2/day, anthracyclines - Cyclophospamide, methotrexate ≥25mg/m^2	Stop >2 weeks prior to tisagenlecleucel infusion
Radiation therapy at non-CNS site	
Pegylated asparginase	Stop >4 weeks prior to tisagenlecleucel infusion
Anti T cell antibodies CNS directed radiation	Stop >8 weeks prior to tisagenlecleucel infusion

Lymphodepleting chemotherapy

The EBMT & ASBMT (2019) recommended that patients receive fludarabine/cyclophosphamide lymphodepleting chemotherapy prior to tisagenlecleucel infusion as detailed in the package insert of the approved product and stated that adherence to timing between lymphodepleting chemotherapy and CAR-T infusion is important. It may be appropriate for some patients with low lymphocyte counts and/or pancytopenia from disease or prior therapy to forgo lymphodepleting chemotherapy on a risk-benefit basis. [65]

CAR-T a bridging therapy to allo-HCT as definitive relapse therapy

The EBMT & ASBMT (2019) suggested evaluating individual patient factors (quality of available donor, comorbidities), disease related factors (MRD status, and B cell aplasia), and CAR-T related factors (co-stimulatory domain and potential persistence of CAR-T) when considering allo-HCT following anti CD19 CAR-T therapy for a patient who is allo-HCT naïve.[65]

CRS and neurotoxicity management consideration

Because of the risk of CRS and neurological toxicities, KYMRIAH (tisagenlecleucel) is available only through a restricted program under a REMS called the KYMRIAH.Two doses of tocilizumab must be available on site for each patient prior to infusion of CAR-T therapy. Monitoring patients for signs or symptoms of CRS for at least 4 weeks after treatment with tisagenlecleucel is necessary. When patients are treated in the outpatient setting, patients must remain within one to two hours of the hospital and to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS (fever), immediate hospitalization is imperative to allow prompt institution of treatment with supportive care, tocilizumab and/or corticosteroids (as indicated). When managing neurotoxicity, it is important to exclude alternative etiologies, especially infectious causes, stroke or hemorrhage. The extent of work-up (e.g., magnetic resonance imaging, electroencephalogram, cerebrospinal fluid analysis in selected patients) can be tailored to the severity and nature of symptoms. Imaging may also be useful to detect cerebral edema. Patients with a negative work-up may be treated expectantly. Levetiracetam or alternative anti-seizure prophylaxis for patients with a history of seizures or a history of prior neurotoxicity should be considered. Patients with frank CSF leukemia should not receive CAR-T cells until central nervous system (CNS) disease is improving or completely resolved. [65]

Follow-up

A 15-year follow-up is requested as part of the marketing authorization of tisagelecleucel and axicabtagene ciloleucel, both by FDA and EMA. Continental registries such as CIBMTR or EBMT may become essential tools for this endeavor, helping to capture infrequent and delayed events, including the outcome of pregnancies in patients or partners. EBMT and ASBMT recommendation on clinical utilization of CAR-T should be sought in the clinical management of issues revolving around CAR-T and allo-HCT in relapsed/ refractory B-ALL patients. [65]

Guidelines

Published guidelines from ESMO and NCCN provide recommendations for remission induction and consolidation therapies, maintenance therapy, CNS prophylaxis, and age-adopted protocols for standard treatment regimens. Currently, three immunotherapies are FDA approved for the treatment of ALL: i) blinatumomab, ii) inotuzumab ozogamicin, and iii) tisagenlecleucel. [66]

Table 13: FDA-approved cancer immunotherapy agents for ALL

Drug	Type	Mechanism	Approval	Indications
Blinatumomab	Bispecific T cell engager (BiTE)	A "bispecific" antibody with recognition domains for CD3 and CD19 to bring T cells into proximity to tumor cells to promote cytotoxicity	March 2018 July 2017 December 2014	Adults and paediatric patients with B-cell precursor ALL in first or second complete remission with MRD ≥0.1% Relapsed of refractory B-cell precursor ALL in adults and children Philadelphia chromosome-negative relapsed of refractory B-cell precursor ALL
Inotuzumab	Anti-CD22 antibody-drug conjgate	Anti-CD22 antibody-drug conjgated to a DNA-damaging calicheamicin playload that causes apoptotic death	August 2017	Adults with relapsed or refractory B-cell precursor ALL
Tisagenlecleucel	CAR T cell therapy	Genetically modified autologous T cells expressing a chimeric receptor consisting of a CD19-recognition domain and 4-1BB costimulatory domain to enhance expansion and persistence	August 2017	Patients p to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse

CAR, chimeric antigen receptor; FDA, Food and Drug Administration; MRD, minimal/measurable residual disease.

Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline

The Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on immunotherapy for the treatment of acute leukemia recommended:-[1]

- Cell markers at diagnosis and at the time of disease relapse should be performed to identify potential markers that drugs can be used for treatment. Upfront diagnostics for ALL should include the cell markers CD19, CD20, and CD22. CD19+ ALL patients may be eligible for blinatumomab or tisagenlecleucel (patients aged ≤25 years).
- New, experimental drugs should be administered at centers that have proper support, infrastructure, and subspecialties.
- Patients with relapsed B-ALL should receive immunotherapy as a bridging therapy to induce remission prior to allo-HCT.
- Options for patients with relapsed ALL after one line of prior therapy include clinical trial enrollment, treatment with blinatumomab or inotuzumab ozogamicin, or allo-HCT.
- Patients with newly diagnosed B-ALL who are MRD positive after undergoing induction chemotherapy should be offered blinatumomab.
- CAR T cell therapy is strongly recommended for patients with relapsed ALL after second-line and/or third-line therapy.
- For patients with relapsed B-ALL and a high disease burden, inotuzumab ozogamicin should be considered first followed by blinatumomab for persistent disease or MRD positivity.

- Patients should be treated with FDA-approved therapies, if available, with clinical trial enrollment considered at each juncture.
- Patients treated with CAR T cells or blinatumomab should be monitored vigilantly for signs of CRS and neurotoxicity including (but not limited to) fever, hypotension, and altered mental state.
- The management of CRS or neurotoxicity secondary to approved CAR T cell therapy or blinatumomab should follow established guidelines.
- Prior to being treated with immunotherapy, patients and caregivers should be educated about potential AEs and given clear instructions for call parameters for any toxicities.
- Study protocols for new, investigational agents should incorporate QoL assessment using validated tools.

NCCN Guidelines

Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN ALL recommends that patients be treated at a specialized cancer center with expertise in the management of ALL.

For ALL in adults, the NCCN guidelines (version 1.2022) for the treatment of ALL consider Tecartus as an option for AYA and adult patients with relapsed/refractory Ph-negative B-cell ALL. The guidelines also state the role of allogeneic HSCT following treatment with Tecartus is unclear and further study will be required before conclusive recommendations can be made.

The NCCN Guideline for Pediatric Acute Lymphoblastic Leukemia (version 1.2023) recommends tisagenlecleucel (Kymriah®) as a single-agent therapy for Ph-positive B-cell ALL with less than complete response or MRD+ at end of consolidation and Ph-positive TKI intolerant/refractory B-ALL or relapse post-HSCT. Kymriah is also recommended for Ph-negative or Ph-like B-cell ALL that is MRD + after consolidation therapy, as well as relapsed/refractory Ph negative B-cell ALL refractory or ≥ 2 relapses. The guidelines further state the role of allogeneic HSCT following Kymriah is unclear.[66]

Other guidelines

In another guideline recommendation, in patients with relapsed or refractory ALL receiving salvage therapy, MRD should be assessed at least at the time of morphologic remission and at the end of treatment, particularly for patients in first salvage in whom this information has greater predictive importance.[67]

In Malaysia, the National Guidelines for Haemopoietic Stem Cell Therapy Second Edition (2023) served as a guide to all personnel involved in haemopoeitic stem cell transplant to ensure execution of safe and effective procedures and quality of the stem cell transplantation in the country. The guideline highlights important components in CAR-T administration and emphasized that improving access to more affordable CART-cell therapies should be a priority. [68]

CAR-T and other cell-based therapy centers

In general, for CAR-T and cell-based therapy clinical trials, healthcare teams shall follow relevant trial protocols. However, in the setting where commercialized CAR-T therapies are available, this guideline shall apply. CAR-T and other cellular therapies shall be performed in recognised haemopoietic stem cell transplant centres with experience in handling leukapheresis, administration of conditioning regimen and infusion of cellular products. These centres shall have 24-hour facilities for prompt evaluation and treatment of related complications. The centres shall also have timely access to critical care services, in case of life-threatening complications. Immediate access to interleukin-6 inhibitors is mandatory for rapid treatment of CRS. These centres shall have access to determine lymphocyte subsets, immunoglobulin level and CAR-T cell persistence. CAR-T centres are encouraged to participate in national /or international registries to ensure ongoing evaluation of safety and efficacy as well as long-term outcomes, and this centre shall have policies for long-term follow-up and surveillance. [68]

Personnel for CART

The centres shall have experienced physicians/paediatricians who are trained in patient selection, planning of appropriate bridging and lymphodepletion conditioning regimen, thawing and/or infusion of the cellular products and management of ensuing CAR-T-related complications such as CRS and neurotoxicities. The centres shall have a multi-disciplinary team, which consists of trained medical, nursing and pharmacy personnel. Access to other support personnel such as clinical psychologists, social workers, data managers and clinical trial staff is desirable. Informed consent shall be obtained for cell collection, cell infusion and data collection. [68]

Leukapheresis and cell processing facilities

Mononuclear cell collection shall be performed at an accredited apheresis centre. Generation of CAR-T cells shall be performed in ISO5 clean room/ Grade B cGMP facilities to ensure high quality and safe products. The facilities shall have skilled cell culture technologists and relevant supportive staff. An established body shall regulate the cell processing facilities. This process requires significant coordination with manufacturers, including site inspection, transportation and sample tracking.

Indication and compassionate/off-label use

Currently approved indications for CAR-T therapy include:

- Relapsed/Refractory B-Acute Lymphoblastic Leukaemia
- Relapsed/Refractory Diffuse Large B-cell Lymphoma
- Relapsed/Refractory Mantle Cell Lymphoma
- Relapsed/Refractory Multiple Myeloma

This guideline highlighted that there should be a provision for compassionate or off-label usage within the institution in cases of life-threatening malignancies where there is no satisfactory or readily available alternative therapy and where access to or eligibility for clinical trials is not possible, and these shall be performed with appropriate institutional approval. [68]

In Malaysia, registration of cell and gene therapy should follow requirements as stipulated in the guidance document and guidelines for registration of cell and gene therapy products in Malaysia. [69]

Other HTA Agency

The Canadian HTA agency's in its evaluation addressed the policy question of how should the provision of tisagenlecleucel for pediatric and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-cell ALL) and adults with r/r diffuse large B-cell lymphoma (DLBCL) be structured. The recommendation statement for patients with r/r B-ALL was, on the condition that there is a reduction in price, Health Technology Expert Review Panel (HTERP) recommends the provision of tisagenlecleucel to pediatric and young adult patients three to 25 years old with B-cell ALL who are refractory, have relapsed after allogeneic stem cell transplant (SCT), or are otherwise ineligible for allogeneic SCT, or have experienced a second or later relapse. [70]

With regard to implementation of this therapy, HTERP recommends:

– the creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistic support for required travel and short-term relocation.
– the development of clear and transparent eligibility criteria that are acceptable to patients' and clinicians' needs, based on the approved indications.
– the collection of standardized outcomes data in a pan-Canadian registry of patients, which uses a defined set of outcomes and definitions to generate real-world evidence, for consideration in future reassessments to assess longer-term effectiveness, safety, and cost-effectiveness.

The initial review by NICE highlighted that NHS England announced coverage for tisagenlecleucel through the Cancer Drug Fund prior to NICE guidance being issued (Sept 2018). NICE guidance recommends tisagenlecleucel for r/r B-cell ALL in people up to 25 years of age if conditions in the managed access agreement (price and data collection) are followed (November 2018). In its recent review (2024), NICE stated that Tisagenlecleucel is recommended, within its marketing authorisation, as an option for people 25 years and under for treating B-cell acute lymphoblastic leukaemia that is: [72]

- relapsed after a transplant, or relapsed for a second or later time, or refractory.
- It is only recommended if the company provides it according to the commercial arrangement. For commercial arrangement, there is a simple discount patient access scheme for tisagenlecleucel. NHS organisations could get the details on the Commercial Access and Pricing (CAP) Portal.

The recent NICE guidance reviews new evidence collected as part of the managed access agreement, which includes evidence from a clinical trial and from people having treatment in the NHS in England. The recommendation is made supported by these factors:[71]

- Usual treatment for B-cell acute lymphoblastic leukaemia that is refractory, relapsed after a transplant, or relapsed for a second or later time in people 25 years and under includes blinatumomab and chemotherapy.
- There are no clinical trials directly comparing tisagenlecleucel with usual treatments. But an indirect comparison suggests that people having tisagenlecleucel live longer than people having blinatumomab or chemotherapy.
- When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tisagenlecleucel is recommended for routine use in the NHS.

The Scottish Medicine Consortium (SMC) Committee considered the benefits of tisagenlecleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as tisagenlecleucel is an orphan medicine, hence, SMC can accept greater uncertainty in the economic case. Tisagenlecleucel was designated an orphan medicinal product for the treatment of B lymphoblastic leukaemia/lymphoma on 29 April 2014 (EU/3/14/1266). It also meets SMC ultra-orphan and end of life criteria for this indication.

The SMC advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is following a full submission considered under the ultra-orphan and end of life process. Tisagenlecleucel (Kymriah®) is accepted for use within NHS Scotland. Indication was for treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. SMC advice takes account of the benefit of Patient Access Schemes (PAS) that improve the cost-effectiveness of tisagenlecleucel and is contingent upon the continuing availability of this PAS in NHS Scotland or a list price that is equivalent or lower.[72]

Tisagenlecleucel is intended for autologous use only. Tisagenlecleucel is to be administered via intravenous infusion. A single dose of tisagenlecleucel contains:

– for patients 50kg and below: 0.2 to 5 x 106 CAR positive viable T cells/kg body weight.
– for patients above 50kg: 0.1 to 2.5 x 108 CAR positive viable T cells (non-weight based).

Lymphodepleting chemotherapy is recommended to be administered before tisagenlecleucel infusion unless the white blood cell count within one week prior to infusion is ≤1,000 cells/microlitre. The recommended lymphodepleting chemotherapy regimen is fludarabine (30mg/m2 intravenously for four days) and cyclophosphamide (500mg/m^2 intravenously for two days starting with the first dose of fludarabine). It is recommended that tisagenlecleucel is infused two to 14 days after completion of the lymphodepleting chemotherapy. The availability of tisagenlecleucel must be confirmed prior to starting the lymphodepleting regimen. To minimise potential acute infusion reactions, it is recommended that patients be premedicated with paracetamol and diphenhydramine (or another H1 antihistamine) approximately 30 to 60 minutes before tisagenlecleucel infusion.

Tisagenlecleucel must be administered in a qualified treatment centre, and should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with tisagenlecleucel. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion.[72]

Reimbursement

The conditions for reimbursement for CAR-T cell therapy are not uniform in Europe. Most European countries use a DRG system for billing hospital services, but the details vary. Nonetheless, the similarity is that expensive therapies, such as CAR-T cell therapy, are initially not included in the DRG system.

Most countries possess instruments to ensure the financing of such expensive therapies outside the DRG system as separate payments. These reimbursement instruments of DRG systems are used in most countries both for short-term financing for innovative and new therapies and as long-term additional fees within the respective DRG system.

One should consider that other significant costs exist in addition to the price of the actual CAR-T cell product, which has been agreed upon with the pharmaceutical industry. In addition to the usual hospitalization costs, the price of the inpatient stay for the administration of CAR-T cells can include the costs for intensive care and expensive medication, such as tocilizumab. These additional costs are generally reimbursed through the established system in each country. However, at least two years are required to integrate the costs of a new therapy or method into the existing DRG.

The special feature of CAR-T cell therapy is that the hospital needs to collect lymphocytes from the patient in advance through apheresis. This initial product for the production of CAR-T cells induces further costs that are usually not reimbursed.

These structural costs (mostly personnel costs) for the hospital must be agreed upon separately with health insurance companies or the government, depending on the state-dependent reimbursement system.A single hospital has a minor impact on the pricing of a CAR-T cell product; this is usually done by negotiation between pharmaceutical companies and government agencies.

In addition to the reimbursement of the CAR-T cell product at the price set by these negotiations, the additional costs of this therapy are reimbursed differently, particularly within Germany. Efforts are being made to centralize these negotiations, but the success of such a centralized negotiation depends on the structures and organization of the numerous health insurance companies in Germany. In Germany, the individual hospital then becomes responsible for the specific reimbursement of costs for each individual patient. In the case of extremely high costs, advanced agreements are usually made between the health insurance and the hospital.[73]

The Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T cells expressing at least one chimeric antigen receptor (CAR) when administered at health care facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for either an FDA approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. [74]

In the absence of published evidence, second infusions of CAR T-cell therapy for relapsed and refractory disease was considered as unproven regardless of product or indication. At the current time there is a lack of adequate published evidence demonstrating efficacy. [75]

Eligibility requirement

The patient's performance status and comorbidities are critical considerations for CAR T-cell therapy eligibility. In an expert panel opinion from the American Society for Transplantation and Cellular Therapy (ASTCT), eligibility evaluation should consider the following:[75]

- Renal function (GFR, Cr)
- Liver function (AST/ALT, bilirubin)
- Cardiac status (LVEF)
- Pulmonary status (dyspnoea, pulse ox)
- Hematologic status (ANC< ALC, platelets)
- Baseline neurologic examination and evaluation
- Presence of autoimmune conditions and use of immunosuppressive agents
- Presence of active or uncontrolled infection

The following are considered contraindications to CAR T-cell therapy regardless of the product:[75]

- Pregnancy
- Members receiving immunosuppressive therapy for an autoimmune disorder
- Any active, uncontrolled infection
- Uncontrolled human immunodeficiency virus (HIV) infection. These patients should be under the management of an HIV specialist and their disease controlled prior to CAR T-cell therapy
- Active hepatitis B or hepatitis C infection for lymphomas
- Active hepatitis B or hepatitis C or CMV infection for multiple myeloma
- Hepatitis B or C infection
- Active graft vs. host disease in members with a history of allogeneic hematopoietic stem cell transplant
- Primary central nervous system lymphoma
- Solid tumors

Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL) when the following criteria are met:[75]

- The member is 25 years of age or younger
- Philadelphia chromosome-negative (Ph-) disease that is refractory or has had 2 or more relapses OR
- Philadelphia chromosome-positive (Ph+) and one of the following:

    - Has refractory disease, including MRD (+) at conclusion of consolidation
    - Less than complete response
    - High-risk genetics
    - Tyrosine kinase inhibitor (TKI) intolerant or refractory (TKIs include dasatinib tablets,imatinib tablets, ponatinib tablets, nilotinib capsules, and bosutinib tablets)
    - Relapse following allogeneic hematopoietic stem cell transplantation

- Member has been treated with two cycles of standard chemotherapy without a complete response or achieved a complete response and experienced multiple relapses following at least two cycles of standard chemotherapy.
- Member has received or will receive adequate standard lymphodepleting chemotherapy or a therapeutically equivalent regimen within two weeks preceding tisagenlecleucel infusion. (The standard is a lymphodepleting chemotherapy regimen of fludarabine 30mg/m^2 intravenously for four days and cyclophosphamide 500mg/m^2 intravenously daily for two days [starting with the first dose of fludarabine] within two weeks preceding infusion).
- A member weighing 50kg or less will receive weight-based dosing at 0.2 to 5.0 x 10^6 CAR positive viable T cells per kg of body weight.
- Member will not be treated with more than 2.5 x 10^8 CAR-positive viable T cells.
- Member does not have active, uncontrolled CNS ALL.
- Member has not received prior treatment with CAR T-cell therapy.
- If the member has had a prior allogeneic HSCT, member does not currently have active GCHD.
- The treating facility is certified under the Kymriah Risk Evaluation and Mitigation Strategy (REMS).

Novel value assessment and payment approaches have been used to facilitate patient access while mitigating high uncertainty in the long-term outcomes of a CAR-T. For instance, Germany has outcome-based rebates that are connected to specific patient outcomes, and Italy has outcome-based stage payment, where payment are made in three instalments and also connected to specific patient outcomes. The UK offers coverage for CAR-T with potential pricing adjustment based on longer term follow-up and post-launch evidence.[76]

In Malaysia, CAR-T therapy has the potential to significantly improve outcomes for patients with B-ALL with careful planning and collaboration among stakeholders. The roles of relevant stakeholders including the Ministry of Health, Healthcare Institutions, Consultant Hematologists, nursing and support staff, pharmaceutical and biotech companies, insurance providers and Patient Advocacy Groups, are important in facilitating the successful integration of CAR-T cell therapy into the Malaysian healthcare system. The locally produced cellular CAR-T products which may be less expensive could be assessed in clinical trials for regulatory consideration.

5.2.7 Social and ethical

No evidence retrieved on social and ethical issues related to CAR-T cell therapy or implication on CAR-T therapy for patients in the treatment of patients with r/r B-ALL. The National Cancer Society Malaysia (NCSM) input was sought on this area, and they supported this review to address the patients unmet need. The institution provided supporting facilities to patients with ALL, namely children's home of hope, dietitian support and play therapy. Together, these services is hoped will ensure that children with cancer, including those with relapse/ refractory ALL, receive not just medical care, but holistic support addressing their physical, emotional, and nutritional needs during challenging time.[77]

Children's Home of Hope (Halfway Home):

- The Children's Home of Hope provides a free, temporary accommodation for children and their families who travel far from their homes to receive treatment. This halfway home helps ease the financial burden on families by offering a comfortable and safe place to stay close to the hospital.
- It is particularly beneficial for long-term treatment like chemotherapy or post-relapse treatments, where frequent hospital visits are needed.

Dietitian Support:

- The NCSM provides access to dietitians who specialize in paediatric oncology. Nutrition is critical in cancer care, and dietitians help create personalized plans to support the immune system, manage side effects of treatment like nausea or mouth sores, and ensure that children receive the appropriate nutrients to maintain strength and energy.
- For children with ALL, particularly those undergoing intensive chemotherapy or who are in relapse, this support helps manage complex nutritional needs.

Play Therapy:

- NCSM employs play therapists to help children cope emotionally with their illness. Play therapy uses therapeutic play to allow children to express feelings, reduce anxiety, and develop coping mechanisms in a non-threatening, child-friendly way.
- This is especially important for children dealing with the fear, pain, and uncertainty of relapsed cancer. Play therapy provides emotional support and contributes to their mental well-being.[77]

5.2.8 Legal

The EU pioneered the development of a specific regulatory framework by defining a specific classification for Advance Therapy Medicinal Product and establishing a centralised approval procedure for them. The cornerstone of this regulation is that marketing authorisation must be obtained prior to the marketing of ATMPs. The evaluation of these products is led by a specialised committee within the European Medicines Agency (EMA), that is, the Committee for Advanced Therapies (CAT), which prepares a draft opinion before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion and authorisation is granted by the European Commission.

Switzerland has not yet issued any specific standalone regulations on ATMPs. Instead, the provisions on ATMPs have been implanted into the existing regulatory framework. The autogenous transplantation of cells has been defined as transplant products. The definition of transplant products was newly regulated in the Ordinance of 16 March 2007 on the Transplantation of Human Organs, Tissues and Cells (the 'TO'). The TO defines that transplant products are products consisting of or containing human organs, tissues or cells, where the organs, tissues or cells: (1) have been substantially processed; or (2) are not intended to perform the same function in the recipient individual as in the donor individual.

As a consequence, and according to Swissmedic's practice, authorisation is required for the entire manufacturing process. Transplant medicinal products that are applied to patients in Switzerland require marketing authorisation. For transplant products that are based on an individual patient's cells and can therefore not be standardised, marketing authorisation is granted for the manufacturing process. For the marketing authorisation and application process, Swissmedic refers mainly to the Therapeutic Products Act (TPA) (general duty of care; requirements for marketing authorisation; requirement of a licence for manufacturing, import, export, wholesale, prescription and dispensing; rules on advertising and granting of financial benefits to HCPs; market surveillance and inspections by Swissmedic, and reporting obligations towards Swissmedic; fees; and criminal sanction).[78]

CHAPTER 6.0

DISCUSSION

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DISCUSSION

This assessment is an extended umbrella review which includes systematic reviews as well as primary studies. The recent network meta-analysis (Cao et al. 2023) compared multiple treatments simultaneously, which is useful and valuable evidence in this review. Our review found CD19 CAR-T cell was superior than blinatumomab and chemotherapy in achieving CR/CR without complete hematologic recovery. The OS rate was higher following CD19 CAR-T compared with blinatumomab, inotuzumab ozogamicin and chemotherapy. The dual CD19/CD22 CAR-T cell demonstrated favourable effectiveness in OS compared with blinatumomab, inotuzumab ozogamicin and chemotherapy; but showed no significant difference from CD19 CAR-T cells.

Other systematic review conducted in pediatric and young adulthood patiens with r/r ALL similarly showed good CR rate of 82%. [38] Other meta-analysis by Hu (2021),79 CD19 CAR-T therapy bridge to HSCT decreased the relapse rate, RR 0.40 (95%CI 0.32 to 0.50) and improved survival, HR 0.37 (95%CI 0.19 to 0.71) in patients with r/r B-ALL. The CD19 CAR-T cell therapy showed inspiring result with survival at one year between 64 to 67.3%. [80,81]

The AE commonly encountered following this intervention is CRS. Any grade of CRS occurred in quite a high proportion in the studies included in this review, ranged from 81 to 92% of patients; while grade 3 or higher CRS demonstrated in smaller group of patients 6% to 27% of cases. Meanwhile, iincidence of any grade CRS occurred in CD22 targeted vs CD19/CD22 targeted was almost comparable from our review. In other study, sequential CD19-22 CAR-T therapy demonstrated safer profile compared with single CD19 CAR-T therapy with only one in four patients develop grade 3 CRS. 82 Despite the incidence of AE, the reported rate of treatment related mortality was relatively low. Overall, optimizing the future design of next generation CAR-T to improve safety profile and lessen toxicity should be prioritized.

Characteristic of patients and products appear do influence the outcomes of CAR-T cell therapy. Worse survival was observed in patients with morphologic disease before treatment. 36 The co-stimulatory domain used in CAR-T cell product played role on the long-term outcome, with 4-1BB co-stimulatory domain have a more sustained response compared with CD28 domains, which was described possibly related to difference in differentiation and persistence of T cells. Another product characteristic influencing CAR-T cell therapy was the quality of starting material used to manufacture the product. Patients age, has been said may impact the quality of the starting material; with adults potentially having worse outcomes compared to paediatric and young adult patients. Besides, the use of low-dose cyclophosphamide lympohodepletion before CAR-T infusion was demonstrated to be beneficial in improving patients overall survival. [36]

It is important to note that the CR rate was not affected by any of the common poor-risk factors, indicating that CAR-T therapy may be able to defy conventional poor-risk factors (prior transplant history, prior regimens, conditioning regimens). Instead, disease burden and Ph positivity appeared to affect responses. Higher disease burden was associated with higher rate of CRS and neurotoxicity. Higher peak CAR-T cell expansion was noted to be associated with deeper responses (higher MRDnegative CR rate) but at the expense of higher rate of and more

severe neurotoxicity and CRS. The study suggests that both higher disease burden and higher peak CAR-T cell expansion are independent predictors of severe neurotoxic effects. The study again confirmed the phenomenon that lower disease burden is associated with better long-term survival in ALL. Great efforts should be made to achieve the lowest disease burden (MRD-negative CR) prior to CAR-T therapy as well as to alloSCT.[83]

There were differences in sample sizes, CAR constructs, and study center participations, as well as primary end points in the studies included, explaining reason of variation in the results collected. Recognizing the benefit demostrated bt CAR-T therapy, so as to address their unmet needs, several international guidelines; ESMO, NCCN, EBMT, SITC recommended the use of Tisa-cel for r/r ALL patients. The need for effective lymphodepleting chemotherapy, pharmacovigilance monitoring post-infusion, and education to patients and caregiver's prior treatment is highlighted clearly in these documents.

This review covers both paediatric and adult patients, while two of the SR of cost-effectiveness focused on paediatric and young adult population. Another SR was broader, covering use of CAR-T in paediatric and adult patients with hematologic and solid malignancy. Our findings from review of these economic evaluation papers following cost-utility analysis conducted in various countries from payer, provider and societal perspective found that CAR-T therapies were expensive with estimated incremental cost-effectiveness ratio (ICER) of CAR-T therapies ranged from: $9,424 to $4,124,105 per QALY in adults; and $20,784 to $243,177 per QALY in paediatric patients. The evidences demonstrated that Tisagenlecleucel is expensive therapy than conventional alternatives, generated more QALYs than comparators, but their cost-effectiveness was uncertain; dependent on model assumptions, patient population (patient age at onset) and analytic time horizon. However, CAR-T was likely to be cost-effective compared to the other treatment strategies in few countries, depending on the threshold applied. The appraisal of SR of EE used CHEERS checklist (Andrade et al 2023, Soliman et al 2022), with the recent review by Thavorn et al. (2024) used Phillip checklist. Most studies used PSM in simulating long term cost and outcomes, and often compared CAR-T therapy with standard of care, while some studies did not include relevant comparator such as blinatumomab, or inotuzumab ozogamicin. Assumptions on long-term benefit for CAR-T was tested in scenario analysis to extrapolate the long-term remission and durability of treatment effect. The recent SR by Thavorn et al included 47 studies on blood cancer, 12 studies in review by Soliman (2022), and six studies in review by Andrade (2023). In the review by Andrade, studies included used Markov, Microsimulation and Decision Tree model, with most time horizon covered until end of life. Cost of CAR-T emerged as key driver as reported in many of the primary studies, however determining the precise cost remains challenging as often it is not revealed and subjected to negotiation.[57]

Some barriers to the widespread adoption of CAR-T cell therapies has been acknowledged, such as the high cost associated with manufacturing these cells and clinical infrastructure considerations. The different strategies adopted across Asia to implement CAR-T cell therapy, included the patient assistance programs, close engagement with funders, cost-effectiveness studies, on-site manufacturing of CAR-T cells, and joint ventures between local partners and foreign pharmaceutical companies. Other barriers described was patient-centered factors such as the limited number of treatment centers and out-of-pocket costs such as travel, lodging, and meal expenses. From the provider's perspective, there are logistics, staff time, resource constraints, and reimbursement uncertainties.[115]

Limitations

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles. We included recent SR and few non-randomised trial in the review of clinical effectiveness and SR of CEA in review of cost-effectiveness. However, some of the SR on effectiveness included mix primary studies, where most of them are early clinical studies and the rest are not documented. In addition, primary studies addressing other relevant and recent outcome may have been excluded. Another limitation was the methodological quality of the included studies, such as heterogeneity of the SR and risk of bias. Included studies with high risk of bias may affect methodological quality of this review. Most of the included studies in the review were single-arm, open-label trials, lacking in directly comparing CAR-T with other interventions, comparator such as salvage chemotherapy or other immunotherapy. There is lack of long-term follow-up data available as studies are ongoing. Long-term data, data from comparative studies, and real world evidence are needed. Lack of comparative information for CAR-T cell versus salvage chemotherapy or other comparators, information on patient subgroups, patients' prior therapy, long-term effects, need for re-treatment) limits certainty in the results. The NMA included in this review consisted of the recent list of trials. However, the indirect comparison and ranking of treatment were done using pooled data from a mix of patient's adults and children. Some review included broad population group i.e. patients with haematological malignancy, hence precise effect of the intervention in specific patient group is subtle. There was no access to individual patient data for analysis, hence we could not examine the influence of individual patient characteristic with the outcomes of this review. The longest patient's follow-up was 42 months in this review, therefore more long-term studies to ascertain that effectiveness of CAR-T cell therapy in this patient group is sustained would be beneficial. Studies exploring on patients perception, expectations, experience would be informative and meaningful to add more value in the future CAR-T utilization among patients. Other outcomes such as health related quality of life (HRQoL) measures following this intervention are important given to document its further benefit, hence studies evaluating HRQoL measures in future would be required.

CHAPTER 7.0

PART B: ECONOMIC EVALUATION

CHAPTER 7.0

PART B: ECONOMIC EVALUATION

Despite its transformative potential, CAR-T therapy availability in Malaysia for B-ALL patients with relapsed or refractory disease may be limited compared to more established healthcare settings. Currently, access to CAR-T therapy in Malaysia is limited for research purposes and some being offered by private healthcare facilities in collaboration with private laboratories specialising in cell and gene therapy.[84,85] This disparity raises critical considerations regarding accessibility, cost-effectiveness, and the integration of novel therapies into local healthcare frameworks.

Since prognosis for younger patients with refractory or relapsed B-cell acute lymphoblastic leukaemia (r/r B-ALL) is generally poor, CAR-T cell therapy offers one of the few viable options that has potential for significant long-term survival gains. Hence, this following CEA focuses on this population as it intends to not only maximizes the clinical and economic returns on investment but also aligns with societal and ethical imperatives to provide life-saving care where it will yield the greatest long-term impact.

Objectives:

i. To assess the cost-effectiveness (CE) of chimeric antigen receptor T-cell (CAR-T) therapy in comparison to standard treatment in treating paediatric and young adults aged 25 years old and younger with r/r B-ALL in Malaysia.
ii. To estimate the incremental cost-effectiveness ratio (ICER) of CAR-T therapy in comparison to standard treatment for r/r B-ALL among patients aged 25 years old and younger in Malaysia.

7.1 METHODS

7.1.1 Analytical Overview and Model Structure

A cohort-based partitioned survival model (PSM) (**Figure 6**) consisting of three mutually exclusive health states: event-free (EF), progressive disease (PD) and death was developed using Microsoft Excel 2019. It followed a hypothetical cohort of paediatric with r/r B-ALL over a lifetime horizon through a four-week cycle. A one-off treatment with CAR-T cell therapy was compared with salvage chemotherapy regimen (SCR) and bi-specific T-cell engager (BiTE), with or without allogeneic haematopoietic stem cell transplantation (allo-HSCT).

As for the CAR-T cell therapy arm, the PSM was preceded by a decision-tree analysis to account for a number of eligible patients who did not proceed to the infusion for reasons reported by Maude et al. (2018)[20]. Patients who did not receive CAR-T infusion due to adverse events or manufacturing failure will be assumed to eventually receive SCR with similar efficacy and costs as those in the SCR arm.

The initial age assumed for patients entering the cohort simulation was 12 years old, based on gender proportion derived from published local data.[86]

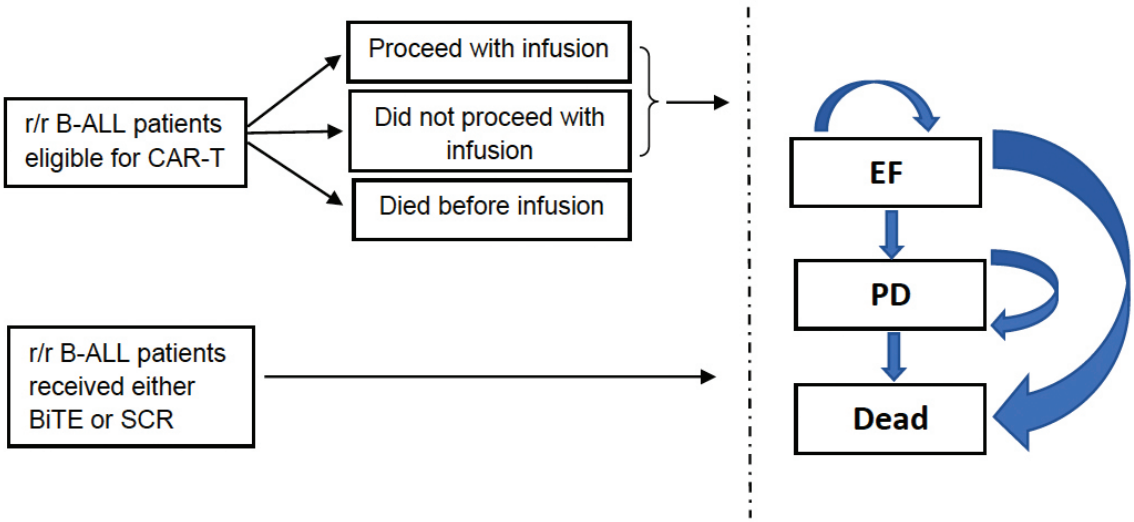


Figure 6: Model structure

r/r B-ALL: relapsed/refractory B-cell acute lymphocytic leukaemia; CAR-T: chimeric antigen receptor T-cell;BiTE: bispecific T-cell engager; SCR: salvage chemotherapy; EF: event-free; PD: progressive disease

All simulated patients began at EF state and then would either remain in their current state or redistribute to PD or death states during each cycle based on the estimated survival probabilities. After disease progression, it was assumed patients were not offered next alternative treatment and would receive best supportive care until death. Based on previously published CE reports and with the agreement of the experts, this analysis assumed no cure, instead patients who remained alive after year 5 were considered as long-term survivors and would have the same mortality risk as B-ALL long-term survivors and did not experience additional relapse.[87]

The described model was analysed independently for each treatment arm in estimating the total costs, life years (LYs) and quality-adjusted life-years (QALYs) gained. Subsequently, the ICERs were estimated for CAR-T cell complete therapy in comparison to SCR and BiTE separately. In absence of explicit national CE/ICER threshold, one time of gross domestic product (GDP) per capita of Malaysia in 2023 (MYR 54,612/QALY) was used to guide the threshold at which CAR-T therapy considered to be cost-effective.[88] This analysis was conducted from the perspective of MOH and an annual three per cent discount rate was applied to both costs and benefits.[89]

7.1.2 Survival Estimation Inputs

Based on the body of evidence reported in the Part A of this report, most of the trials on CAR-T therapy were single arms with very limited data on comparative effectiveness to other competitive treatments available. Hence, individual survival curves were extracted from relevant literature. The overall survival probabilities for the SCR arm were estimated from the published Kaplan-Meier (KM) curve reported by von Stackelberg et al. (2011).[91] Similar type of survival curve was extracted from a landmark trial reported by von Stackelberg et al. (2016)[92] on blinatumomab to represent the BiTE arm. As there were no available EFS curves for both the SCR and BiTE arms, the survival probability for the curves was estimated by assuming its cumulative hazard function was proportional to that of their corresponding OS, with the ratio obtained from the study by Kuhlen et al. (2018).[93]

The benefits seen with the CAR-T cell therapy arm was estimated based on the survival curves reported for tisagenlecleucel which is a CD19-targeted CAR-T cell that have been approved by the FDA.[94] Fitting of appropriate survival curves to the summary survival data were based on method described by Hoyle and Henley (2011).[95] Firstly, the data points from the EFS and OS curves were extracted using DigitizeIt, a plot digitizer software.[96] A web-based application, Shiny, then was used to generate pseudo-individual patient data to reconstruct these KM curves by utilising the extracted data points earlier.[97]

Seven parametric survival distributions (exponential, Weibull, log-normal, log-logistic, gamma, generalised gamma and Gompertz) were applied on the reconstructed KM curves. The best-fitting model for each curve was determined by comparing the calculated Akaike information criterion (AIC) and Bayesian information criterion (BIC) values (as shown in **Table 13**) as well as visual inspection approach. The five-year survival probabilities for both EFS and OS curves were subsequently estimated by fitting the selected parametric distributions. Beyond year five, it was assumed that no additional patients would experience relapse/progression. An age- and genderstratified standardized mortality ratio was then applied to project the proportion of longterm survivors over a lifetime horizon.[99,108]

Table 13: Selected parametric survival distribution parameters

Intervention	EFS		OS	
	Model	Parameter	Model	Model
CAR-T cell therapy	Generalized Gamma	AIC: 304.26	Gompertz	AIC: 294.17
		BIC: 311.36		BIC: 298.91
		Loglik: -149.12		Loglik: -145.0844
BiTE	NA; estimated from OS	Cumulative HR: 0.88	Generalized Gamma	AIC: 331.37
				BIC: 338.11
				Loglik: -162.68
SCR	NA; estimated from OS	Cumulative HR: 0.88	Generalized Gamma	AIC: 256.72
				BIC: 262.51
				Loglik: -125.36

EFS: event-free survival; OS: overall survival; CAR-T: chimeric antigen receptor T-cell; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; Loglik: loglikelihood; NA: not available; HR: hazard ratio

7.1.3 Cost and Utility Inputs

This analysis only considered direct medical costs which included drug acquisition cost, drug administration cost, hospitalisation costs, routine monitoring and follow-up visit cost as well as management cost of serious treatment-related adverse events (sAEs) of grade 3 and 4. Additionally, allo-HSCT cost was also included and reported as total costs that included cost of procedure, follow-up visits and management of sAEs.

The cost of CAR-T therapy in the base case analysis was based on the average price from reference countries provided by the Pharmaceutical Services Programme. All eligible patients for the therapy were assumed to have undergone leukapheresis and pre-treatment cost was calculated with the assumption that the bridging chemotherapy and lymphodepleting chemotherapy regimen adopted in this analysis were as similar as to those reported in ELIANA trial.[20]

In the base case analysis, a modified UK ALLR3 regimen practiced in one of the MOH tertiary centre was used to calculate treatment cost related to the SCR arm. All patients in EF state in the SCR treatment were assumed to have received full course of the prescribed regimen and completed 104 weeks of maintenance chemotherapy if they did not proceed with allo-HSCT. Likewise, patients in the EF state in the BiTE arm were assumed to have completed an average number of five treatment cycles of blinatumomab.[92] The drug costs for all treatment arms were calculated based on the recommended dose for a patient with an assumed body weight of 42 kilogram and body surface area (BSA) of 1.23m^2 on average. In the BiTE arm, an equal number of patients was assigned to receive the dose according to their BSA or body weight. Additionally, the drug costs calculated specifically for tocilizumab and intravenous immunoglobulin (IVIg) to manage cytokine release syndrome (CRS) and B-cell aplasia, respectively, were based on the duration reported in the literature.[20,87]

Hospitalisation costs were obtained from the MOH casemix data[98] and used as a proxy for estimating the cost associated with drug administration as well as for managing treatment-related sAEs. The probabilities of sAEs for each treatment strategy were taken from published literature.[20,92,100,102,110,111] For ease of calculation, costs for managing all sAEs included in this analysis were assumed to be incurred during the first cycle. Moreover, patients were assumed to receive their treatment in inpatient setting as to monitor for sAEs based on the duration advised by the products' manufacturer and published literature.[99,100] All cytokine-release syndrome (CRS) cases reported for CAR-T cell therapy and BiTE were assumed to require admission into intensive care unit (ICU).[87,101]

The cost for the routine monitoring during EF and PD health states included laboratory investigation and specialist clinic visit. The latter cost was assumed to be double of that EF state cost estimated for patients treated with SCR/BiTE in the first year, across all intervention arms. End-of-life cost was not included as it was assumed those who were in terminal stage would be discharged home. All cost inputs were inflated to 2023 according to the Malaysian consumer price index when necessary.[101]

The health utility values associated with EF and PD states for those with r/r B-ALL were taken from published literature.[102] The associated QALYs then was calculated by multiplying the survival time in each state and its corresponding health utility values. Disutility values were also applied to certain parameters were appropriate.[103-105] The admission into ICU for CRS or non-CRS event were assumed to result in health state utility of zero.[87,60] **Table 14** lists the key parameters inputted in the PSM model.

7.1.4 Sensitivity Analysis

One-way sensitivity analysis (OWSA) was performed to determine key drivers that have the biggest influence on the ICER generated in the base case analysis. Each relevant parameter was varied one-by-one according to its estimated range based on the reported 95% CI or estimated minimum-maximum range from referenced source if available, or by varying it over a range of ±20 per cent of the base case value. The results of the sensitivity analyses for both comparisons were presented as tornado diagrams.

Probabilistic sensitivity analysis (PSA) using 1,000 iterations of Monte-Carlo simulations was also conducted in which model parameters were varied using specific distribution as listed in **Table 14**. The results of the uncertainties in the estimates were visualised through a scatterplot from which the mean probabilistic ICER was estimated. Additionally, the probability of CAR-T therapy being more cost-effective than SCR or BiTE were evaluated under different cost-effectiveness thresholds (CET) based on the estimated net monetary benefit (NMB) calculated from the PSA values.

7.1.5 Scenario Analysis

Several scenario analyses were performed to further assess how different assumptions, inputs and clinical or economic conditions would have affected the estimated ICER in the base case analysis. These include parameters identified from the sensitivity analysis as well as the structural assumption applied in the base case model. Similar to the base case analysis, the results were presented separately for the comparison between CAR-T cell and SCR, as well as CAR-T cell and BiTE.

Table 14: Model parameters

Parameter	Item	Base case value	PSA Distribution	Source
Direct medical costs				
Pre-treatment cost, per patient (MYR):	Leukapheresis	630	Gamma	Fees Act 1951, 2014[106]
	Bridging chemotherapy	191.99		Regimen: Carey, 2022[87] Cost: Pharmacy Services Programme
	Lymphodepleting chemotherapy	1,472.01		Regimen: EMA, 2024[99] Cost: Pharmacy Services Programme
Intervention cost, per patient (MYR):	BiTE (average per cycle)	187,646.86	Gamma	Pharmacy Services Programme
	SCR	16,301.06		
	IV reconstitution & administration	107.05		Lee, 2016[107]
	Tocilizumab (for CRS)	2,150.57		Cost: Pharmacy Services Programme Duration: Maude, 2018[20]; von Stackelberg, 2016[92]; Carey, 2022[87]
	IVIg (for B-cell aplasia)	26,040.00		
	Allo-HSCT	100,000		Clinicians' advice; assumed total cost inclusive of procedures, 12 months follow-up after transplant and management of AEs
Hospitalisation cost for treatment administration, per patient (MYR):	[a]Bridging chemotherapy	1,891.68	Cost: Gamma; LOS: Log-normal	Cost: MOH Casemix[98] LOS: [a]Maude, 2018[20]; [b]EMA, 2024[99]; [c]NPRA,2024[100]; dlocal hospital's regimen
	[a]Lymphodepleting chemotherapy	6,357.36		
	[b]CAR-T cell therapy	9,458.40		
	[c]BiTE	16,079.28		
	[d] SCR (induction phase)	19,072.08		
	SCR (consolidation phases)	128,736.54		
	SCR (maintenance phase, total)	162,112.68		

Parameter	Item	Base case value	PSA Distribution	Source
Pre-treatment cost, per patient (MYR):	CAR-T cell therapy	17,750.18	Gamma	Cost: MOH Casemix[98] LOS: CRS and non-CRS requiring ICU (CAR-T)[99]; CRS (BiTE)[100]; Febrile neutropenia[87]; Others - assumption, based on average LOS from MOH Casemix
	BiTE	14,796.95		
	SCR	8,204.66		
Cost of EF state per patient per cycle for BiTE and SCR (MYR):	0 – 12 months	693.33	Gamma	Cost: Fees Act 1951, 2014[106] Frequency and type of tests: Clinicians' advice
	13 – 24 months	288.33		
	25 – 60 months	88.33		
	Beyond 60 months	44.17		
Cost of EF state per patient per cycle for CAR-T (MYR):	0 – 12 months	723.33	Gamma	
	13 – 24 months	308.33		
	25 – 60 months	98.33		
	Beyond 60 months	49.17		
Clinical effectiveness				
Decision-tree inputs for CAR-T cell therapy arm:				
Proportion of eligible patients (%):	Received CAR-T infusion	83.68	Dirichlet	Maude, 2018[20]
	Did not receive infusion	0.56		
	Died prior to infusion	8.00		
	Received bridging chemotherapy	87.00	Beta	
	Received lymphodepleting chemotherapy	96.00		
Mortality rate:				
Standardised mortality ratio	Base case analysis	9.1	Gamma Not varied	MacArthur, 2007[108] Fidler, 2016[109]
	Scenario analysis	15.5		
Gender	Male	0.55	Dirichlet	MOH National Cancer Registry[86]

Parameter	Item	Base case value	PSA Distribution	Source
Transplant rate:				
Proportion of patients underwent subsequent allo-HSCT (%)	CAR-T cell	50	Beta	Clinicians' advice
	BiTE	0.69		Carey, 2022[87]
	SCR	0.62		von Stackelberg, 2011[90]
Health state (dis)utility values				
Base case analysis	EF state	0.8	Beta	NoMA, 2018[102]
	PD state	0.63		
Scenario analysis	EF state beyond year 5	0.9	Not varied	Kwon, 2018[103]
Disutility	Leukapheresis/ BT/ LDC	- 0.2	Normal	Kwon, 2018[103]
	Cytokine-release syndrome	-. 0.8		Carey, 2022[87]
	Non-CRS ICU admission	- 0.8		
	Febrile neutropenia	-. 0.15		
	Other sAEs	- 0.15		
	Allo-HSCT (0 – 3 months)	- 0.2		Forsythe, 2018[104]
	Allo-HSCT (4 – 12 months)	- 0.13		Felder-Puig, 2006[105]

MYR: Malaysia Ringgit; CAR-T: chimeric antigen receptor T-cell; BiTE: bispecific T-cell engager; SCR: salvage chemotherapy; IV: intravenous; CRS: cytokine release syndrome; IVIg: intravenous immunoglobulin; allo-HSCT: allogeneic haematopoietic stem cell transplant; LOS: length of stay; sAEs: serious adverse events; EF: event-free; ICU: intensive care unit; AE: adverse events; PD: progressive disease; BT: bridging chemotherapy; LDC: lymphodepleting chemotherapy

7.2 RESULTS

7.2.1 Base case

The outcomes for the base case analysis are displayed in **Table 15**. In the treatment of paediatric and young adult patients with r/r B-ALL, CAR-T cell therapy demonstrated significant improvements in health outcomes compared to BiTE and SCR. Specifically, CAR-T cell therapy yielded an additional 7.95 LYs and 5.82 QALYs when compared to BiTE, and an additional 10.63 LYs and 7.94 QALYs compared to SCR.

The incremental cost per patient for CAR-T cell therapy compared to BiTE was around MYR 1,055,300 resulting in ICER of approximately MYR 132,700 per LY and MYR 181,400 per QALY. In comparison, when CAR-T was evaluated against SCR, the incremental cost was around MYR 1,172,300 leading to an ICER of MYR 110,250 per LY and MYR 147,600 per QALY.

Given these findings, while CAR-T cell therapy provides substantial clinical benefits, its ICER against BiTE and SCR exceeds the CET of MYR 55,000. Hence, the economic burden of CAR-T therapy may pose challenges for its adoption in clinical practice, despite its potential to significantly improve survival and quality of life for patients.

Table 15: Summary of costs and outcomes results in base case analysis

Strategy	Total cost (MYR)	Progression-free LYs	Overall LYs	QALYs	*ICER (MYR/QALY)
CAR-T cell	1,355,831	9.2	11.7	8.8	-
BiTE*	300,502	3.6	3.8	2.9	181,392
SCR*	183,508	1.0	1.1	0.8	147,623

**CAR-T cell in comparison to other treatment strategy*
CAR-T: chimeric antigen receptor T-cell; SCR: salvage chemotherapy; BiTE: bispecific T-cell engager; MYR: Malaysian Ringgit; LY: life years; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio

7.2.2 Sensitivity Analysis

The tornado diagrams illustrated parameters that have remarkable impact on the ICER estimation in the base case scenario. In the comparison between CAR-T cell therapy and BiTE, as presented in **Figure 7**, three main parameters identified were cost of CAR-T cell therapy and health utility values associated with event-free state and proportion of patients successfully infused with CAR-T cell. Similarly, cost of CAR-T cell therapy affects its ICER relative to SCR the most (**Figure 8**). As expected, lower CAR-T cell therapy cost would likely drive the ICER closer to the threshold value. On the contrary, higher value associated with the EF and PD states would reduce the generated ICER values hence, increasing the likelihood of CAR-T cell to be cost-effective.

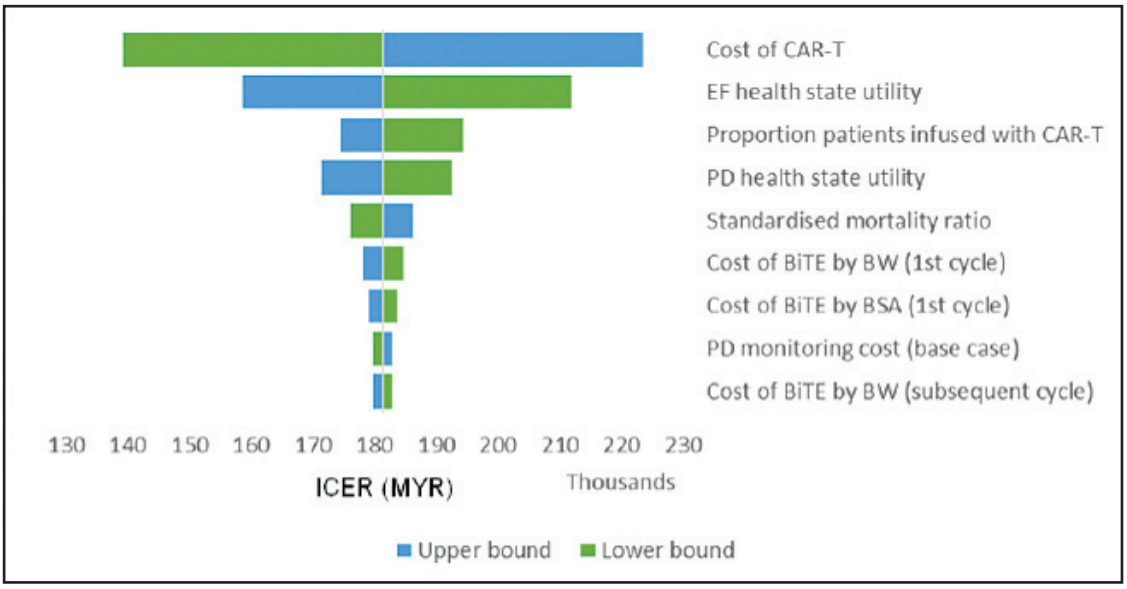


Figure 7: One-way sensitivity analysis for CAR-T vs BiTE

CAR-T: chimeric antigen receptor T-cell; BiTE: bispecific T-cell enganger; EF: event-free; PD: progressive disease BW: body weight; BSA: body surface area

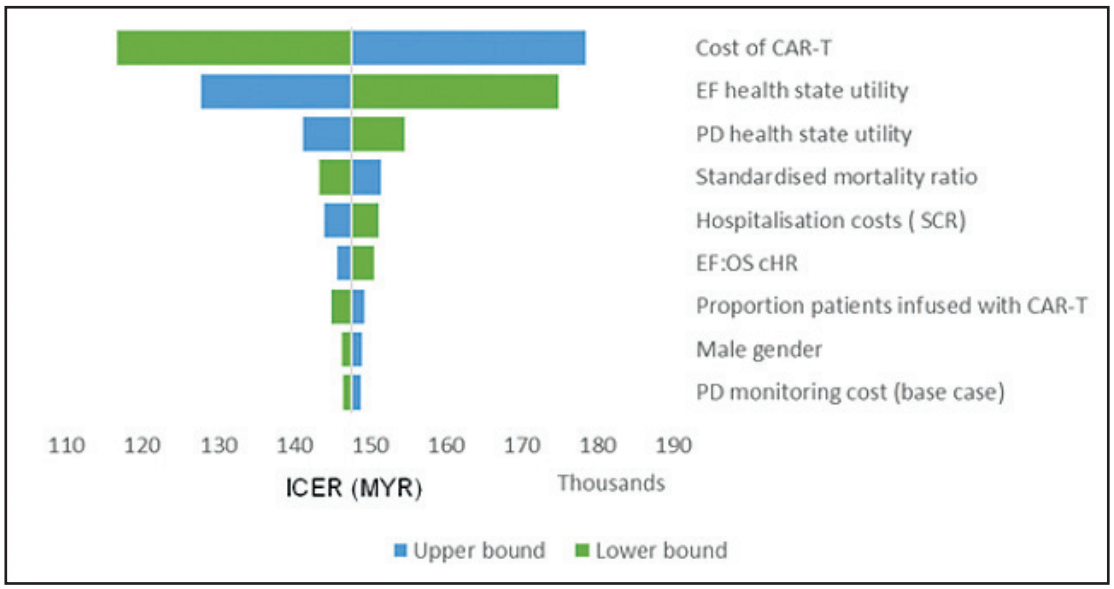


Figure 8: One-way sensitivity analysis for CAR-T vs SCR

CAR-T: chimeric antigen receptor T-cell; BiTE: bispecific T-cell enganger; EF: event-free; PD: progressive disease; SCR: salvage chemotherapy; OS: overall survival; cHR: cumulative hazard ratio

Figure 9 shows the results of the conducted PSA displayed on a cost-effectiveness plane. Majority of dots were above the threshold line, suggesting that in most simulations, the cost per QALY for CAR-T exceeded MYR 55,000, meaning it is unlikely to be cost-effective at this threshold. The graph suggests that while CAR-T cell therapy may offer more QALYs than BiTE, it often comes at a higher incremental cost, exceeding the CET in most cases. The mean ICERs estimated for CAR-T cell therapy against BiTE and SCR were MYR 182,833 and MYR 148,785, respectively. This could indicate that from a cost-effectiveness standpoint, CAR-T cell therapy may not be justifiable at the set threshold of MYR 55,000 per QALY gained.

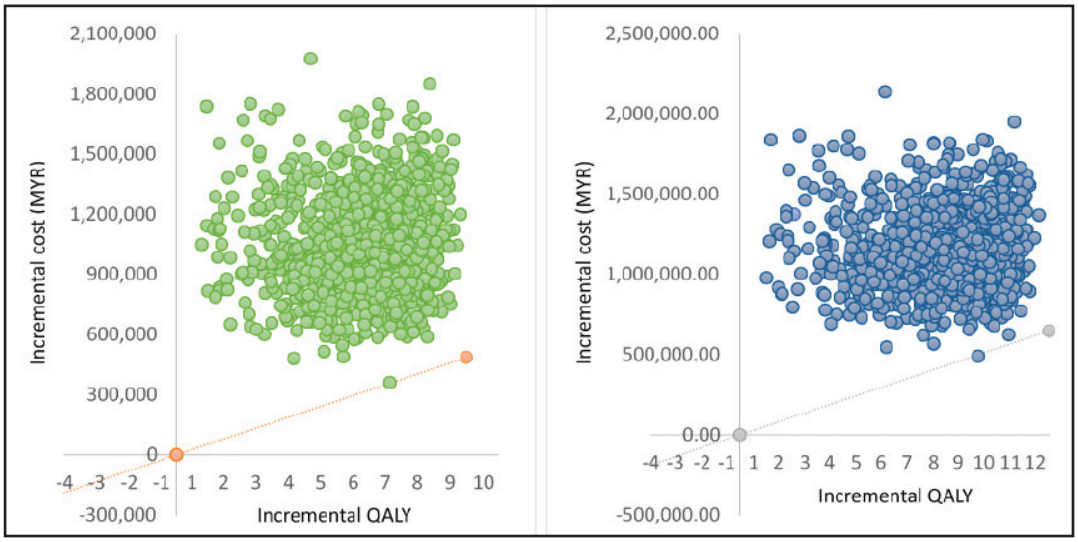
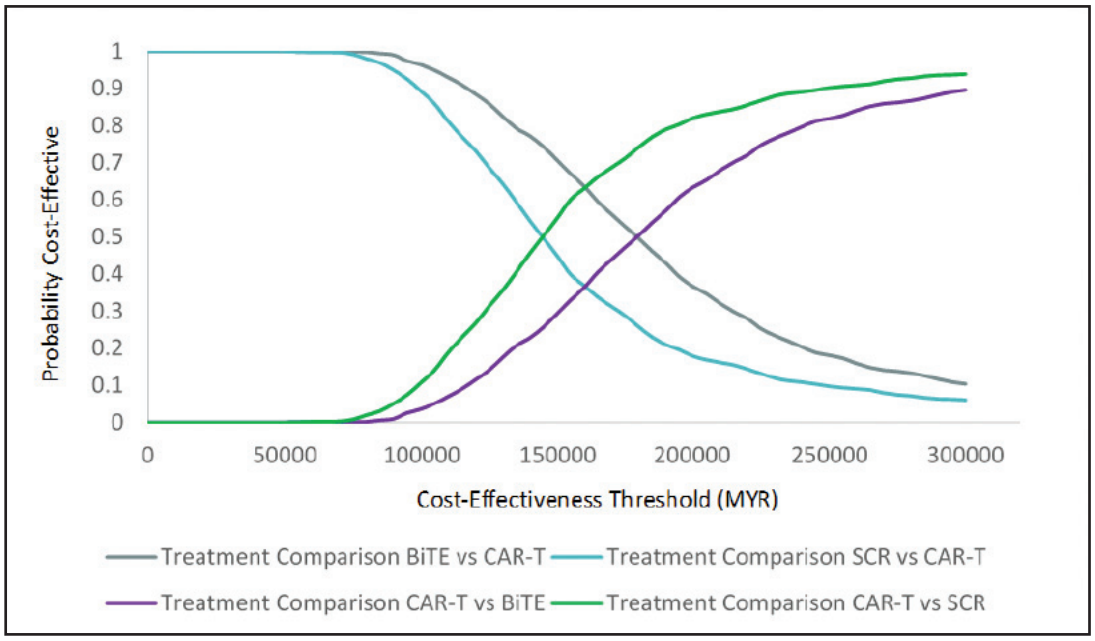


Figure 9: Cost-effectiveness plane A) CAR-T vs BiTE; B) CAR-T vs SCR

CAR-T: chimeric antigen receptor T-cell; BiTE: bispecific T-cell enganger; SCR: salvage chemotherapy

The CEAC as shown in **Figure 10** illustrates the relative cost-effectiveness probabilities for multiple treatment comparisons under varying CETs. BiTE shows a high probability of being cost-effective compared to CAR-T cell therapy at lower CET values, suggesting it is a favourable option under budget-constrained scenarios. However, as the CET rises, CAR-T cell therapy gains a higher probability of being cost-effective relative to BiTE. At CET of approximately MYR 180,000 (3.3 times the base case CET), CAR-T cell therapy starts surpassing BiTE as a more cost-effective choice, though this comes at much higher thresholds. The graph indicates that CET must be increased to approximately 4.5 times the base case threshold for CAR-T cell therapy to achieve a 90% probability of being cost-effective compared to BiTE.

In the comparison between CAR-T cell therapy and SCR, SCR maintains a cost-effectiveness advantage at lower CET values. However, CAR-T cell therapy becomes progressively more competitive, and by a CET of around MYR 150,000 (2.7 times the base case CET), CAR-T cell therapy reaches a higher probability of being cost-effective compared to SCR. This trend continues, indicating that CAR-T cell therapy becomes a more favourable option as the CET increases further. At CET of MYR 300,000, it has approximately 94% probability to be cost-effective compared to SCR.



MYR: Malaysian Ringgit

Figure 10: Cost-effectiveness acceptability curve (CEAC) for comparison between treatment strategies

7.2.3 Scenario Analysis

As presented in **Table 16**, several scenarios have shown positive impact on the base case ICERs, but none except in one scenario, presented CAR-T cell therapy as a cost-effective option. As CAR-T cell therapy is a high-cost treatment, only a substantial reduction in its cost to about one third of the base case cost would yield cost-effective when compared to BiTE and SCR. It was observed at this markedly reduced cost, the ICERs of CAR-T cell therapy relative to BiTE and SCR did not differ much. In addition, applying a reduced discount rate of 1.5% on all the benefits accrued over the simulation time across all treatment strategies has led to considerable decrease in estimated ICERs and greater benefits in both comparisons.

Besides, improvement in health outcome was seen in Scenario 3 and 4. The additional QALYs gain came at lower ICER value for both comparisons in the former, however, marginal increase in the ICER was noted in the latter when comparing CAR-T cell therapy to SCR. In contrast, the shorter the duration of the model simulation, the higher the ICERs and the lesser the benefits would be generated for both comparisons. Interestingly, using a different definition for long-term survivors would have exerted opposite effect on the benefits and ICERs estimated for CAR-T cell therapy relative to BiTE and SCR.

Table 16: Scenario analysis

Scenarios:	Interventions	LYs gained	QALYs gained	Incremental cost (MYR)	ICER (Cost/ QALY)
Base case	CAR-T vs BiTE	7.95	5.82	1,055,329	181,392
	CAR-T vs SCR	10.63	7.94	1,172,323	147,623
Scenario 1: CAR-T price reduction e.g. ~MYR 500,000	CAR-T vs BiTE	7.95	5.82	246,502	42,369
	CAR-T vs SCR	10.63	7.94	363,497	45,773
Scenario 2: Lower discount rate (benefit in all arms)	CAR-T vs BiTE	10.41	7.69	1,055,329	137,289
	CAR-T vs SCR	13.88	10.43	1,172,323	112,381
Scenario 3: Higher HSUV for long-term survivors	CAR-T vs BiTE	7.95	6.26	1,055,329	168,663
	CAR-T vs SCR	10.63	8.58	1,172,323	136,693
Scenario 4: 100% eligible patients infused with CAR-T	CAR-T vs BiTE	10.22	7.51	1,311,836	174,574
	CAR-T vs SCR	13.07	9.76	1,456,477	149,236
Scenario 5: Alternative PD state cost	CAR-T vs BiTE	7.95	5.82	1,033,038	177,560
	CAR-T vs SCR	10.63	7.94	1,148,572	144,632
Scenario 6: Lower subsequent allo-HSCT rate for CAR-T	CAR-T vs BiTE	7.95	5.50	1,034,523	177,816
	CAR-T vs SCR	10.63	7.94	1,151,518	145,003
Scenario 7: Long-term survivor beyond year 3	CAR-T vs BiTE	7.40	5.50	1,043,626	189,709
	CAR-T vs SCR	10.77	8.17	1,161,388	142,131
Scenario 8: Higher SMR	CAR-T vs BiTE	7.25	5.34	1,047,307	196,147
	CAR-T vs SCR	9.72	7.29	1,163,456	159,497
Scenario 9: Time horizon over 30 years	CAR-T vs BiTE	6.61	4.76	1,050,352	220,744
	CAR-T vs SCR	8.87	6.54	1,169,718	178,774
Scenario 10: Time horizon at 20 years	CAR-T vs BiTE	5.10	3.64	1,043,872	286,642
	CAR-T vs SCR	6.89	5.05	1,160,347	229,841

LY: life years; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; MYR: Malaysian Ringgit; CAR-T: chimeric antigen receptor T-cell; BiTE: bispecific T-cell engager; HSUV: health state utility values; PD: progressive disease; allo-HSCT: allogeneic haematopoietic stem cell transplant; BW: body weight; SMR: standardised mortality ratio

7.3 DISCUSSION (ECONOMIC EVALUTION)

The base case analysis demonstrates that, while CAR-T cell therapy offers substantial clinical benefits for paediatric and young adult patients with r/r B-ALL, its high-cost results in ICERs that exceed the set CE threshold (MYR 55,000 per QALY). This outcome raises important considerations for healthcare decision-makers, particularly in middle-income countries with constrained budgets. The finding echoes the results of the systematic review presented in Part A showing that the magnitude of clinical benefit often contrasts with the therapy's prohibitive cost.

The high acquisition and administration costs associated with CAR-T cell therapy remain a substantial barrier to its cost-effectiveness, particularly in middle-income countries like Malaysia. This aligns with findings by Choi et al. (2022), who emphasize that the initial treatment cost, combined with additional expenses for monitoring adverse events like CRS and other serious AEs that require admission int intensive care unit (ICU), contributes to the overall financial burden. With regards to the product itself, the personalised production process requiring extensive infrastructure and specialised personnel pose as one of the challenges that plays a significant contribution to the high cost of CAR-T cell therapy.[113] These costs may be mitigated through the establishment of on-site manufacturing facilities; however, additional factors such as facility infrastructure expenses, staffing requirements, and costs associated with release testing and quality control must be carefully considered, as they can contribute significantly to the final cost of the product.[114]

Currently, as CAR-T cell therapy poses significant financial burden, there is a growing interest in alternative pricing models that link reimbursement to actual clinical outcomes. Drummond et al. (2023) emphasize the importance of outcome-based agreements and managed entry schemes, which align costs with therapeutic effectiveness, thus ensuring that healthcare systems only bear the expenses that correspond to verified patient benefits. Similarly, it has been argued that value-based pricing could make CAR-T cell therapy more accessible by balancing its high upfront costs with longer-term patient outcomes. These models could provide a viable pathway for middle-income countries to adopt CAR-T cell therapy by reducing economic risk and ensuring that payments reflect real-world efficacy. By connecting reimbursement to the value delivered, these adaptive pricing strategies hold promise for enhancing access to CAR-T cell therapy while managing financial constraints in resource-limited healthcare settings.[113,116] As the long-term affordability of CAR-T cell therapy is contingent upon strategic pricing and reimbursement frameworks, substantial cost adjustments would be necessary to bring CAR-T cell therapy within Malaysia's CET as reflected in Scenario 1 of this analysis.

Furthermore, the survival benefits associated with CAR-T cell therapy, while noteworthy, are complicated by uncertainties in long-term outcomes, as observed in both clinical practice and trials. Nukala et al. (2021) emphasizes that while CAR-T cell therapy yields substantial response rates for relapsed or refractory cancers, limited follow-up data and variability in long-term remission outcomes introduce uncertainty in cost-effectiveness estimates. This aligns with findings in the present analysis, where survival gains are apparent yet complicated by a lack of comparative, head-to-head data against standard treatments.[117]

The scenario analyses also have shown the impact of extending the time horizon in evaluating cost-effectiveness of therapies with curative potentials such as CAR-T cell therapy. Although longer time horizons allow for the inclusion of more long-term benefits, they do not ensure the cost-effectiveness of high-cost interventions, as shown in this CEA. Nevertheless, while the time horizon selected should be sufficient to capture all relevant costs and health outcomes, merely extending it may not offset substantial upfront costs, especially in resource-constrained settings.[118] This consideration is crucial in paediatric oncology, where long-term survival is a key outcome, yet immediate financial constraints cannot be overlooked. Policymakers in middle-income countries like Malaysia must balance the potential future health benefits against current economic limitations to ensure sustainable healthcare decisions.

Finally, reducing the discount rate applied to future health benefits (Scenario 7) produced the lowest ICER observed, suggesting that lower discount rates improve the cost-effectiveness profile for treatments with long-term benefits, such as CAR-T cell therapy. Discounting is a standard practice in CEAs to reflect societal preference for present versus future health outcomes, but it can disproportionately disadvantage therapies that yield prolonged survival gains.[119] Nevertheless, even with reduced discounting, the generated ICER for CAR-T cell therapy in Scenario 2 remained above the CET, indicating that further measures, such as cost-sharing models or selective subsidization, would likely be required to enable sustainable adoption.

Limitation

There are several limitations that may have directly or indirectly influenced the outcome estimated in this evaluation. Although this CEA has attempted to incorporate as much input relevant to Malaysian population as accessible, the use of CAR-T cell therapy for the treatment of r/r B-ALL among paediatric and young adults in Malaysia, especially in the MOH setting is very limited. Additionally, traditional survival modelling techniques applied to estimate long-term survival outcomes (up to five years), along with the use of cumulative hazard ratio to estimate EFS curves, may generate less accurate predictions compared to more advanced extrapolation techniques, such as mixture cure models and spline-based model.[120] The no-cure model with a lifetime horizon assumed in the base case may also overestimate costs if some patients achieve long-term remission, impacting long-term ICERs. Furthermore, the use of a single ICER threshold does not account for the potential variability in societal willingness-to-pay (WTP) for high-cost treatments in Malaysia. Hence, the results presented in this CEA should be interpreted with cautious. Future studies could improve upon this analysis by incorporating more robust comparative, localized data to refine estimates and exploring tiered thresholds that reflect the diverse perspectives within Malaysia's healthcare system. Though beyond the scope of this analysis, a broader societal perspective might capture additional costs and benefits, such as option value, caregiver impacts and productivity gains.[116]

CHAPTER 8.0

CONCLUSION (OVERALL)

CHAPTER 8.0
CONCLUSION (OVERALL)

Based on the above review, there was good level of evidences on CAR-T cells to be used in the management of patients with r/r B-ALL.

This review showed overall CAR-T cells appeared beneficial in achieving CR/CRi and improving in OS, compared to Blinatumomab, Inotuzumab ozogamicin, and standard chemotherapy in patients with r/r B-ALL.CAR-T cells. CAR-T cells demonstrated ability to achieve MDR negative CR, best complete response with low incidence of relapse.

CD19 CAR T-cells was superior in achieving CR/CRi compared with: Blinatumomab (OR=8.32, 95% CI: 1.18 to 58.44) and Standard chemotherapy (OR=16.4, 95% CI: 2.76 to 97.45). Multiple treatment comparison showed CD19 CAR-T rank the highest with SUCRA of 88.2%, followed by dual CD19/CD22 CAR-T, sequential CD19-22 CAR-T, Inotuzumab Ozogamicin, Blinatumomab and standard chemotherapy. CR rate ranges from 81% to 93% at day 30.

The MRD negative Complete Remission achieved 81% (ranged from 64% to 87%), at 4 weeks post-infusion. The MRD negative CR rate was higher (70%) with anti CD19 or anti CD-22, compared to dual anti-CD19/22 (64%).

CD19 CAR T-cells and dual CD19/CD22 CAR T-cells significantly improved 1-year OS rate vs Blinatumomab, Inotuzumab ozogamicin, and standard chemotherapy. Network comparison showed Dual CD19/CD22 CAR-T rank the highest with SUCRA of 99.3%, followed by CD19 CAR T, Blinatumomab, Inotuzumab izogamicin and standard chemotherapy.

- The 1-year OS rates ranged from 58% to 84%; 2-year OS and 5-year OS were 56.5% and 44.1% respectively. The median OS was 36.2 months (95% CI 28.9, NR).
- The 1-year EFS rates following CAR-T cell therapy ranged from 46% to 76%, 2-year and 5-year were 42.1% and 35%. The Median EFS was 13.3 months (95% CI 12.2 to 17).
- Best Complete Response is higher following CD22, and CD19/CD22 CAR-T cells in patients with r/r ALL (75% and 90%) vs NHL (64% and 47%).
- Incidence of relapse is lowest following anti-CD22 (24%), and in terms of costimulatory domain, relapse is lowest with CD28ζ domain (16%).

Similarly, in patients with r/r ALL with CNSL, CAR-T cells demonstrated ability to achieve 87.5% CR/Cri and 72.9% MRD negative CR at day-30. The median OS was 16.0 months, with median EFS of 8.7 months. The 6-month OS rate was 72% (95%CI: 55.6 to 86.1) and EFS rate was 53.3% (95%CI: 36.5 to 68.1).

Safety

Tisagenlecleucel received regulatory aprroval from USFDA, EMA, Health Canada, Ministry of Health Welfare, Japan. Tisagenlecleucel was designated an orphan medicinal product for the treatment of B lymphoblastic leukaemia/lymphoma (2014) (EU/3/14/1266).

Following CAR-T cell therapy, CRS was reported in 81 to 92% of patients, with higher grade CRS (>3) occurred in 6% to 27% of cases. Incidence of any grade CRS occurred in CD22 targeted and CD19/CD22 targeted was almost comparable. Any grade neurotoxicity occurred in 30 to 37% of cases, while severe ICANS were reported in 3% to 14% of patients whom underwent CAR-T cell therapy. Higher neurotoxicity was reported with anti-CD22 than anti-CD19/CD22 [0.83 (95% CI: 0.60 to 0.98)] and [0.77 (95% CI: 0.71 to 0.83)],respectively. Other reported AE includes infection: 12.2%, Graft vs Host Disease: 23.4%, and all cause 30-days mortality 1%.

Cost-effectiveness

Cost-utility analysis conducted in various countries from payer and provider perspective estimated the incremental cost-effectiveness ratio (ICER) for CAR-T therapies ranged from: $9,424 to $4,124,105 per QALY in adults; and $20,784 to $243,177 per QALY in paediatric patients. The evidence demonstrated that Tisagenlecleucel is expensive therapy than conventional alternatives, generated more QALYs than comparators, but their cost-effectiveness was uncertain. However, CAR-T was likely to be cost-effective compared to the other treatment strategies (studies such as in Switzerland, Japan, Singapore), with varied WTP thresholds. Median cost (USD 2019) for CAR-T cell therapy in the reported studies was $561,075, with the list drug price as the main cost driver.

Organizational

Patient eligibility should be assessed by a CAR-T center multidisciplinary team (MDT) including cellular therapy and haematology/oncology disease specialists. Patients should be evaluated for their general suitability to receive CAR T-cell therapy prior to leukapheresis; for factors such as age, Eastern Cooperative Oncology Group performance status (ECOG PS), history of prior malignancies, active infections and history of central nervous system disease.

Implementation of CAR-T cells require collaboration across the MDT and comprehensive training of personnel involved in CAR-T delivery including haematology, intensive care, neurology, pharmacy and laboratory. In addition to the training, high demands are placed on quality management by both the pharmaceutical industry and the government. The relevant standards in accreditation scheme in cellular therapy require that clinical, collection, and processing facility personnel participate in continuous education activities to ensure high quality patient care, medical and laboratory practice.

Post-marketing pharmacovigilance over a defined period post-infusion is mandated to ensure ongoing evaluation of the efficacy and safety of licensed CAR-T in the real-world setting via dedicated registry. Registries such as Center for International Blood & Marrow Transplant Research (CIBMTR) or European Society for Blood and Marrow Transfusion (EBMT) may become essential tools for this endeavour, to capture infrequent and delayed events.

Given the complexity of ALL treatment regimens and the required supportive care measures, patients should be treated at a specialized cancer centre with expertise in managing ALL. CAR-T is best delivered from within an accredited haematopoietic cell transplantation (HCT) program. In Europe, to be a CAR-T delivery site, accreditation with Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE is recommended.

For safe delivery of CAR-T therapy, a robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain-of-custody and chain-of-identity of the cellular product, and facilitate communication to manage potentially severe toxicities. To fulfill these robust requirements for a safe delivery of CAR-T, only selected larger institutions are identified for performing CAR-T therapy, these are typically centers with allo-HCT experience. Centres should have regulatory approval for storage of genetically modified organisms (GMOs). Before infusion, patients are medically assessed to ensure they are fit to proceed; identity and consent is confirmed. ESMO guideline recommend that patients remain hospitalised for at least 14 days following infusion.

The European Society for Blood and Marrow Transplantation (EBMT) and American Society for Blood and Marrow Transplantation (ASBMT) suggested referring patients with induction failure, early relapse after achieving first complete remission, and adult patients with relapsed/refractory B-ALL to CAR-T cell therapy programs to allow discussion of the optimal timing of apheresis and potential of enrollment in CAR-T trials. Prompt referral to a CAR-T center should be made as soon as a patient meets referral criteria (e.g., at the time of relapse, before starting therapy if possible) especially as specified recovery periods from prior therapy are required before leukapheresis.

Chemotherapy after T-cell collection by leukapheresis is usually required to control disease until the manufacturing of CAR-T is complete. Bridging chemotherapy should focus on disease control rather than remission induction while minimizing organ toxicity or risk of infections.

The EBMT & ASBMT (2019) recommended that patients receive fludarabine/cyclophosphamide lymphodepleting (LD) chemotherapy to enhance CAR-T proliferation the week before CAR-T infusion with a minimum of 2 rest days. Where CAR-T infusion is delayed by >4 weeks, repeat LD is recommended.

The Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on immunotherapy for the treatment of acute leukaemia recommended;

- New, experimental drugs should be administered at centers that have proper support, infrastructure, and subspecialties.
- CAR-T cell therapy is strongly recommended for patients with relapsed ALL after second-line and/or third-line therapy.
- Patients treated with CAR-T cells or blinatumomab should be monitored vigilantly for signs of CRS and neurotoxicity including (but not limited to) fever, hypotension, and altered mental state. The management of CRS or neurotoxicity secondary to approved CAR-T cell therapy should follow established guidelines.
- Prior to being treated with immunotherapy, patients and caregivers should be educated about potential AEs and given clear instructions for call parameters for any toxicities.

The US Centers for Medicare & Medicaid Services (CMS) covers autologous treatment for cancer with T cells expressing at least one chimeric antigen receptor (CAR) when administered at health care facilities enrolled in the FDA risk evaluation and mitigation strategies and when used for FDA approved indication. Tisagenlecleucel (Kymriah®) is considered medically necessary for the treatment of refractory or second or later relapsed B-cell precursor acute lymphoblastic leukemia (ALL) when the identified criteria's are met.

The Malaysia National Guidelines for Haemopoietic Stem Cell Therapy Second Edition (2023) highlighted that CAR-T therapies shall be performed in recognised haemopoietic stem cell transplant centres with experience in handling leukapheresis, administration of conditioning regimen and infusion of cellular products. The centres shall have experienced physicians/ paediatricians who are trained in patient selection, planning of appropriate bridging and lymphodepletion conditioning regimen, product infusion and management of ensuing CAR-T-related complications. Mononuclear cell collection shall be performed at an accredited apheresis centre. Generation of CAR-T cells shall be performed in ISO5 clean room/Grade B cGMP. CAR-T centers are encouraged to participate in national/or international registries to ensure ongoing evaluation of safety, efficacy and long-term outcomes. This guideline also pointed that improving access to more affordable CART-cell therapies should be a priority.

In Malaysia, registration of cell and gene therapy should follow requirements as stipulated in the guidance document and guidelines for registration of cell and gene therapy products in Malaysia.

Social, Ethical

No evidence on social or ethical issues or implication on CART-T cell therapy for patients with r/r B-ALL. The Malaysia National Cancer Society input was sought and they support this assessment to address the patients unmet need, and provide supporting facilities to patients with ALL such as children's home of hope, dietition support and play therapy. Together, these services ensure that children with cancer, including those with relapse/refractory ALL, receive not just medical care but holistic support addressing their physical, emotional, and nutritional needs during challenging time.

Legal

The EU pioneered the development of a specific regulatory framework by defining a specific classification for Advance Therapy Medicinal Product and establishing a centralised approval procedure for them. The cornerstone of this regulation is that marketing authorisation must be obtained prior to the marketing of ATMPs. The autogenous transplantation of cells has been defined as transplant products. For transplant products that are based on an individual patient's cells and can therefore not be standardised, marketing authorisation is granted for the manufacturing process.

Economic Evaluation

The CEA from the perspective of Malaysia's MOH highlights both the clinical benefits and economic challenges of CAR-T cell therapy. While CAR-T cell therapy provides an estimated gain of six to eight additional QALYs for pediatric and young adult patients with r/r B-ALL, its high costs result in ICERs that exceed the acceptable threshold by 2.7 to 3.3 times. Consequently, CAR-T cell therapy is not a cost-effective alternative compared to current options like BiTE and SCR. Scenario analyses indicate that a significant reduction in CAR-T pricing could greatly enhance its cost-effectiveness.

The findings from the CEA, together with insights from the broader literature, highlight the complexities of adopting CAR-T cell therapy in middle-income settings like Malaysia. The adoption of this advanced therapy could be more feasible with substantial cost reductions and more flexible thresholds. In addition, policy initiatives, such as risk-sharing agreements, value-based pricing, or cost-sharing frameworks, could be explored to ensure continued assessments of its value, as well as to mitigate CAR-T's financial burden and facilitate access without overextending MOH budgets. An investment in research to evaluate the real-world outcomes of CAR-T cell therapy in local settings could also yield data which would help validate model assumptions and refine ICER estimates, making the case for CAR-T cell therapy adoption in Malaysia more precise.

CHAPTER 9.0

RECOMMENDATION

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Based on current evidence, CAR-T cell therapy could be used in the treatment of paediatric and young adults, as well as adult patients with B-cell ALL that relapse and/or refractory, either never achieve remission, relapse for a second or later time, or relapse after a transplant.

CAR-T cell therapy should be delivered in a qualified treatment centre, best within an accredited haematopoietic cell transplantation (HCT) program, to fulfil the robust requirements for its safe delivery.

Collection of standardized outcomes data post-infusion in registry of patients is encouraged to ascertain its long-term benefit and safety.

Due to high cost of currently approved CAR-T, competitive options may be explored.

In view of the current therapeutic gap in these patients, a committee refining patient selection criteria and access could be established to facilitate CAR-T cell therapy adoption in the local context.

CHAPTER 10.0

REFERENCES

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REFERENCES

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CHAPTER 11.0

APPENDICES

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APPENDICES

APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomisation.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

1.0 BACKGROUND INFORMATION

1.1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is rapidly progressing form of leukemia, defined by high percentage of blast in the blood, bone marrow and by the predominant lineage of malignant cells.[1] The disease is resulted from deregulation in various pathways in the cell cycle, characterized by uncontrolled proliferation of malignant cells and arrest in normal lymphoid progenitor cell development thereby inhibiting homeostatic hematogenous and immune functions.[2] It is the most common type of cancer in pediatric patients, accounting for 26% of childhood cancer; and the most common form of childhood leukemia representing 75% to 80% of acute leukemias, while ALL represents approximately 20% of all leukemias among adults.[3,4] Its age-adjusted incidence rate in the United States is 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths estimated in 2021. The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years.[5] The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and the second peak around the age of 50.[6] In Malaysia, the incidence and mortality of leukemia was 3.8% and 5.2% respectively (2022).[7] It is the sixth most common cancer in Malaysia with a total of 4273 cases registered (2012 to 2016) compared to 4573 cases (2007 to 2011). Majority of them were from 0 to 14 years. The lifetime risk was 1 in 307 (male) and 1 in 388 (female). [8]

ALL can be classified as B-cell precursor ALL (B-ALL), which occurs in 85% of diagnosed patients and T-cell ALL (T-ALL), accounting for the remaining 15% of cases, according to the 2017 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, based on the immunophenotype assessment. B-cell ALL is primarily diagnosed in children, with three quarter of cases were diagnosed in children less than six years.[9]

The progress of ALL treatment is reflected by the increase in the 5-year overall survival (OS) from 57% (1970s) to up to 96% in the most recent studies, depending on clinical and cytogenic features; and the 5-year event free survival (EFS) reaches 92%.[10,11] Nevertheless, the estimated 5-year survival rates in Asia range widely between 44.3% and 80%.[12] Despite significant advances in treatment, the relapse rate remains high (15 to 20% of children).[13] Patients with relapse or refractory (r/r) B-ALL have a much lower cure rate with an estimated 20% overall 5-year survival.[13] In adults, ALL is much less frequent representing 0.2% of all cancers. Prognosis is less encouraging with ALL, with an expected 5-year OS between 20% and 40%, despite complete remission (CR) rates of 85% to 90%. [14] Adults with r/r ALL historically have a poor prognosis, with cure rate below 40%. After relapse, the reported overall survival was only about 7%.[15]

Complexity of ALL treatment regimens involve risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative ALL; and supportive care consideration.[16] Standard risk was assigned to patients age one to less than ten years and with WBC count less than 50x109 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk. Very high risk was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of BCR-ABL1 fusion protein; hypodiploidy; BCR-ABL1–like or Ph-like ALL; iAMP21; or failure to achieve remission with induction therapy.[17]

Standard treatment paradigms for acute leukemia have centered on high-intensity induction chemotherapy to achieve complete remission (CR) followed by allogeneic hematopoietic cell transplant (allo-HCT) in certain patients to eradicate residual disease.[1] The treatment regimens are typically intense involving many chemotherapeutic agents that carry a multitude of toxicity risks.[18] The first-line treatment of pediatric ALL is conducted in phases; induction, consolidation, intensification (reinduction, delayed intensification in some protocols), and remission maintenance therapy. Induction of remission is based on steroid therapy accompanied by cytostatic administration. Consolidation of remission and maintenance therapy in most protocols is based on systemic and intrathecal cytostatic administration. Commonly used cytostatic are methotrexate, daunorubicin, doxorubicin, vincristine, cytarabine, cyclophosphamide, thioguanine, and 6-mercaptopurine, and the entire therapy usually takes about two to three years. However, despite the highly toxic intensified therapies, durable remission is difficult to achieve.[9]

Radiation is used to treat ALL in selected groups of patients. Formerly, craniospinal irradiation was a crucial departure point in the treatment of leukemia. Currently, its eligibility depends on a specific central nervous system (CNS) status at diagnosis. CNS irradiation is used to control CNS recurrence, which commonly given in high-risk ALL patients with CNS status 3.19 For patients with high-risk features in first complete remission (CR1), refractory or relapsed disease; treatment option remains allogenic hematopoietic stem cell transplantation (HSCT). Most children, prior to allogenic HSCT, receive conditioning that include total body irradiation, following which could impacting their adult life with condition such as hypothyroidism, delayed puberty and infertility.[9] Side effects such as Graft versus Host Disease (GvHD) in allogeneic HSCT are common. Hematopoietic Stem Cell Transplantation (HSCT) presents significant limitations and outcome of the consolidation treatment is patient dependent, therefore, using alternative method to address these challenges is crucial.[20]

The introduction of safer therapies has become a priority in the management of hematological pediatric patients. Genetic characterization of ALL has revolutionized treatment approaches with targeted therapies such as Tyrosine Kinase Inhibitors (imatinib, dasatinib, nilotinib) for ALL patients with Philadelphia chromosome, and Janus Kinase inhibitor (ruxolitinib) by targeting and blocking JAK proteins.[9] The advent of cancer immunotherapy offers additional options beyond standard regimen. Targeted immunotherapy utilizing antibodies, antibody–drug conjugates (ADCs), immunotoxins, bi-specific antibody T cell engagers (BiTEs), and chimeric antigen receptor (CAR)-T cells have changed the treatment landscape for relapsed and high-risk B-ALL. [1]

Advances in harnessing the immune system in cancer treatment have defined the past decade of progress in oncology. Development of CAR-T cell therapy represents a breakthrough in ALL therapeutics and transformed treatment paradigm for r/r B-ALL in children and young adults.[21] CAR-T cell therapy is an individualized cell-based gene therapy that harness the natural function of body's T lymphocytes. T cells are genetically engineered to express a specific CAR, designed to recognize a specific tumor associated antigen, allowing the T-cells to actively target and selectively kill cells expressing that antigen (e.g.CD19).[22]

Various CAR designs are being studied, with CD19 being the most commonly targeted antigen, and CD28 and 4-1BB being the most widely used co-stimulatory domain.[23] CD19 CAR-T cell has demonstrated complete remission rate as high as 90% in r/r B-ALL patients.[24] The USFDA approved Tisagenlecleucel (Kymriah) for pediatric and young adults up to 25 years with r/r B-ALL in 2017 incorporates the 4-1BB co-stimulatory domain, while Brexucabtagene autoleucel (Tecartus) which incorporates the CD28 co-stimulatory domain, was approved for patients ≥18 years with r/r B-ALL (2021).[25]

CAR-T cells are a cellular immunotherapy with remarkable efficacy in treating multiple hematologic malignancies, however they are associated with high prices that are prohibitively expensive for many countries.[26] In Malaysia, however as of now, there is no CAR-T cells being registered with the National Pharmaceutical Regulatory Agency (NPRA), and they are not available in the MOH formulary. Addressing the feasibility of CAR-T cell as therapy with better efficacy and lower toxicity to achieve durable remission is pivotal and timely to meet the increasing needs of patients with r/r ALL in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use CAR-T cells in the management of r/r ALL patients in Malaysia as requested by a pediatric Hemato-Oncologist from Hospital Tunku Azizah, Kuala Lumpur.

1.2 TECHNOLOGY DESCRIPTION

CAR-T cell therapies use genetically modified, autologous T cells to target and destroy cancer cells. The therapy involves expressing engineered receptors (known as CARs) in a patient's immune cells (i.e. a T cell), to direct their action to specific cancer cells.[27]

The concept of using CAR-T cell to target tumour surface antigen was described in the late 1980s. The first-generation CAR-T, which included only the receptor component CD3z as an intracellular domain showed limited efficacy. The subsequent second-generation CAR-T then have the addition of co-stimulatory domain derived from either CD28 or 4-1BB. A viral vector is used to deliver the genetic material; which include the targeting antibody-based variable region, a transmembrane domain, a co-stimulatory domain, and the CD3z signaling domain into the patients' T cell. The third generation CAR-T contain additional costimulatory domains, aiming to improve proliferation, cytokine secretion, and in-vivo persistence.[27] (**Figure 1**)

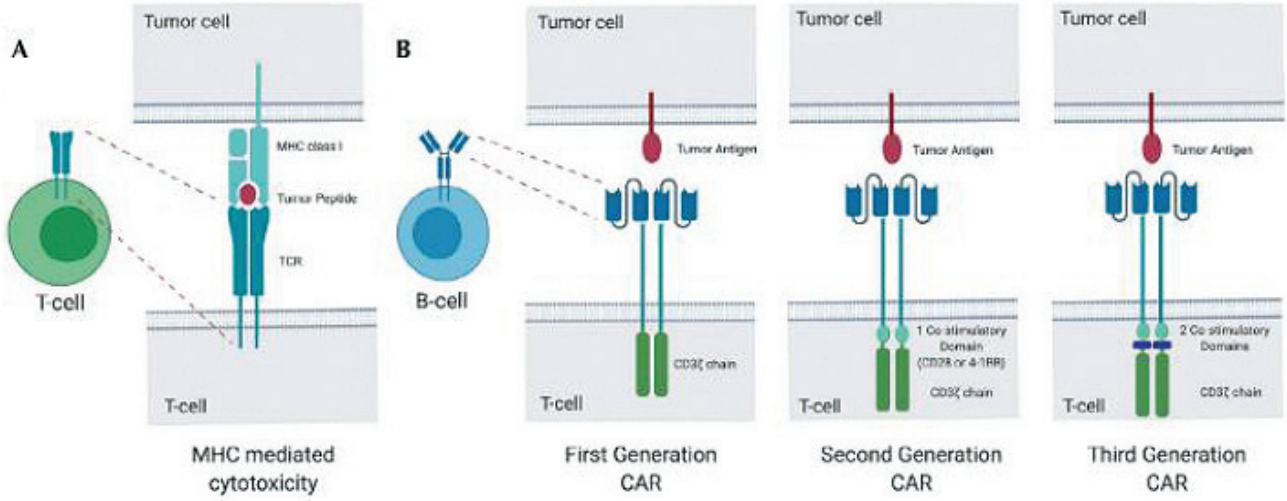

Figure 1: Mechanism of action for CAR-T cell therapy.

(A) Cytotoxicity mediated by T cell receptor of the major histocompatibility complex of a cell-surface antigen (B) Cytotoxicity through direct targeting of a cell-surface antigen by a CAR-T cell. (Source: Wall DA & Krueger J 2020)

The USFDA and Health Canada have approved two constructs for CAR-T production; Tisagenlecleucel, a-41BB based construct for R/R ALL in children and R/R B-cell lymphoma in adults; and Axicabtagene ciloleucel which uses the CD28 costimulatory construct for the treatment of R/R B-cell lymphoma in adults.Since the first CAR-T cell therapy was approved by the USFDA in 2017, (tisagenlecleucel (tisa-cel) for the treatment of B-ALL3), there are now six CAR-T cell therapies approved in the United States for the treatment of hematologic malignancies (**Table 1**). [27]

Table 1: List of USFDA approved CAR T-Cell

Generic Name	Brand Name	Approved Indication	Approval Date	Approved via Accelerated Approval	Acronym for Pivotal Trial	List Price in March 2023 (WAC, USD)
Tisagenlecleucel (tisa-cel)	Kymriah	R/R pediatric and young adult (<25) B-cell ALL	August 30, 2017	No	ELIANA	$543,828
		R/R adult DLBCL, HGBL, transformed DLBCL	May 1, 2018	No	JULIET	$427,048
		R/R FL	May 27, 2022	No	ELARA	$427,048
Axicabtagene ciloleucel (axi-cel)	Yescarta	R/R DLBCL	October 18, 2017	No	ZUMA-1	$424,000
		R/R FL	April 2, 2021	Yes	ZUMA-5	$424,000
Lisocabtagene maraleucel (liso-cel)	Breyanzi	R/R DLBCL, HGBL, transformed DLBCL, PMBL, FL grade 3B	February 5, 2021	No Yes	TRANSCEND-NHL-001	$447,227
Brexucabtagene autoleucel (brexu-cel)	Tecartus	R/R MCL	July 24, 2020	Yes	ZUMA-2	$424,000
		Adult R/R B-cell All	October 1, 2021	No	ZUMA-3	$424,000
Idecabtagene vicleucel (ide-cel)	Abecma	R/R MM	March 26, 2021	No	KarMMA	$427,255
Ciltabtagene vicleucel (cilta-cel)	Carvykti	R/R MM	February 28, 2022	No	CARTITUDE-1	$465,000

NOTE: List prices (WACs) include rebates and other confidential discounts, but these discounts are typically modest for oncology products (on average 2%).[4] Source: FDA Cellular and Gene Therapy Products website, Office of Tissues and Advanced Therapies and Red Book (Micromedex). Abbreviation: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; FL, follicular lymphoma HGBL, high-grade B-cell lymphoma: MCL, mantle-cel lymphoma: MM, multiple myeloma: PMBL, primary mediastinal B-cel lymphoma: R/R. relapse

Production and administration of CAR T cell therapies

The process of producing CAR-T cell therapies is presented in **Figure 2**. The first step is leukapheresis, which involves harvesting the patient's T cells from peripheral blood. Protocol requirements can vary, but a circulating CD3 count of at least 150/mm^3 is needed to reliably collect a number of T-cells sufficient for manufacturing. Any apharesis platform can be used for cell collection, example of commonly used platform is Spectra Optia system.[28]

In the current CAR-T cell therapies, harvested T cells are sent to a specialist or certified laboratory to be genetically modified to express a CAR specific to CD19 B lymphocytes (i.e. cancerous cells). This is accomplished using either viral or non-viral methods. Transduction involves the use of viral vectors to deliver ribonucleic acid (RNA) into the patient's T cells. The RNA is subsequently reverse transcribed and integrated into the T cells' deoxyribonucleic acid (DNA), facilitating receptor expression; additional methods to insert RNA/DNA include chemical transfection, electroporation and the use of nanoparticles.[28]

After selection of modified cells, the cells are cultured (grown in expanded numbers) until there are enough of them for clinical use. The CAR-T cells are generally returned to the hospital for infusion into the patient three to four weeks after leukapheresis. [29]

In the meantime, patients may receive bridging chemotherapy to control their disease while the CAR-T cells are being manufactured. The optimal chemotherapy regimen for bridging depends on the patient's treatment history and prior toxicities. Drugs commonly used for bridging regimens include steroid, vincristine, mercaptopurine, methotrexate, low dose cytosine arabinoside, cyclophosphamide, etoposide and asparaginase. It is important that enough time be allowed between drug dosing and CAR-T infusion, the washout time, so as to not impair CAR-T function.[27]

To promote persistence and expansion of the CAR-T after infusion, lymphodepleting chemotherapy is given the week before the CAR-T infusion. Patients typically receive lymphodepleting chemotherapy with fludarabine, cytarabine, cyclophosphamide or bendamustine in different combinations depending on the indication. For patients with low cell or lymphocyte count, CAR-T could be infused without prior lymphodepleting chemotherapy. To decrease potential reactions to the CAR-T infusion, patients are pre-medicated with antihistamines prior to the infusion (30 to 60 minutes). Finally, patients receive the CAR-T cells as a one-off intravenous infusion, and are then monitored for adverse events in the in-patient setting. [30]

Therapy with CAR-T has unique toxicities that require coordinated management by multiple teams. Major acute toxicities include cytokine release syndrome (CRS), neurologic toxicity, tumour lysis syndrome and cytopenia. Four grades of CRS (depending of the presence of fever, degree of hypoxia and hypotension) standardize the reporting of CRS. The dose of CAR-T cells administered to patients is dependent on the patients' diagnosis, body weight, and type of therapy (i.e. Axi-cel, Tisa-cel).[30]

Contraindications to tisa-cel include known hypersensitivity to tisa-cel or any of the excipients (e.g. dimethyl sulfoxide, dextran 40, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium).[31] For safe delivery of CAR-T therapy, a robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain of custody and chain of identity of the cellular product, and facilitate communication to manage potentially severe toxicities.[32]

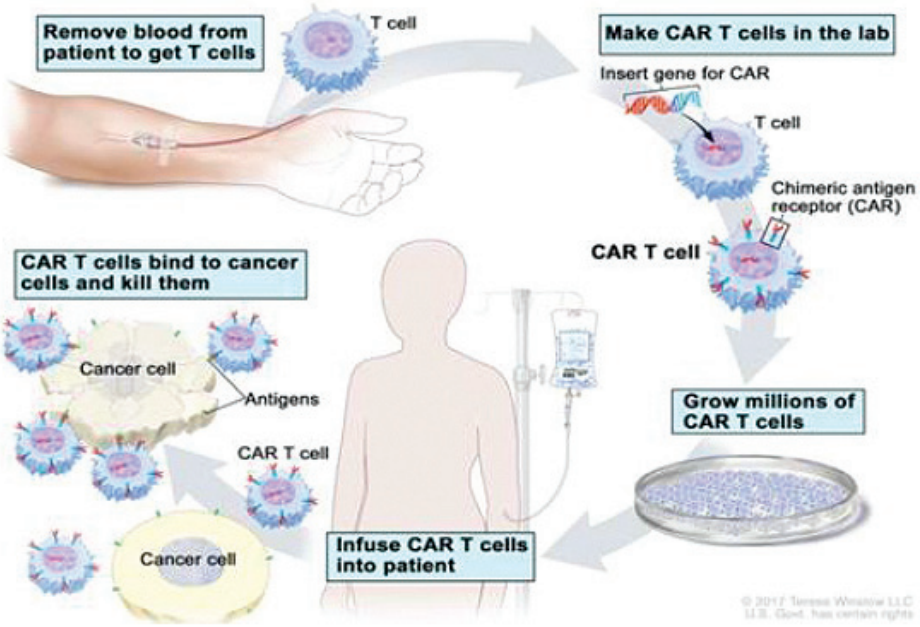

Figure 2: CAR-T process (Source; National Cancer Institute)

2.0 POLICY QUESTION:

Should CAR-T cell therapy be used as a standard treatment option for patients with relapse or refractory B-cell Acute Lymphoblastic Leukemia in Malaysia?

3.0 OBJECTIVES:

Should CAR-T cell therapy be used as a standard treatment option for patients with relapse or refractory B-cell Acute Lymphoblastic Leukemia in Malaysia?

3.1 The following are the objectives of this review:

i. To assess the comparative effectiveness and safety of CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.
ii. To evaluate the economic, organizational, social, ethical and legal implications of CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.

3.2 The following are the research questions of this review:

i. How effective and safe are the CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia?
ii. How cost-effective are the CAR-T cell therapy in the treatment of patients with relapsed or refractory Acute Lymphoblastic Leukemia?
iii. What are the organizational, social, ethical and legal implications of CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia?

4.0 METHODS:

4.1 Search Strategy

Electronic databases will be searched for published literatures pertaining to CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.

4.1.1 Databases are as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the references of the related articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix

4.2 Inclusion and exclusion criteria

Population Problems	Patients with relapse or refractory B-cell Acute Lymphoblastic Leukemia (ALL)
Intervention	CAR-T cell therapy [(including Tisagenlecleucel (tisa-cel) and Brexucabtagene autoleucel (brexu-cel)]
Comparators	• Standard care • Chemotherapy
Outcomes	i. Effectiveness • Overall survival (OS) • Progression free survival (PFS) • Overall response rate (ORR) • Complete response rate (CRR) • Quality of life (QoL) • Treatment free interval ii. Safety • Adverse events • Treatment discontinuation iii. Economic outcomes • Cost-effectiveness • Cost-utility • Cost-benefit • Costs, budget impact • Any other measure of economic outcome iv. Organizational, social, ethical and legal implications
Study designs	HTA reports, systematic review with or without meta-analysis, randomised controlled trial (RCT), non-randomised trial, and economic evaluation studies
Setting	Hospitals
English full text articles	

4.2.2 Exclusion criteria

a. Animal study
b. Laboratory study
c. Design: Narrative review, cohort, case-control, cross-sectional
d. Non-English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The methodology quality of all retrieved literatures will be assessed using the relevant checklist according to study design using Cochrane Risk of Bias tool.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

a. Details of methods and study population characteristics.
b. Details of interventions and comparators.
c. Details of individual outcomes for effectiveness, safety and economic evaluation associated with CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia.

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness of CAR-T cell therapy in the treatment of patients with relapse or refractory Acute Lymphoblastic Leukemia will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment if there is available data from similar outcome and study design.

5.0 REPORT WRITING

6.0 REFERENCES

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APPENDIX 3: SEARCH STRATEGY

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Database: Ovid MEDLINE(R) ALL <1946 to September 28, 2024>
Search Strategy:

1. RECEPTORS, CHIMERIC ANTIGEN/
2. chimeric adj2 antigen receptor*.tw.
3. chimeric adj1 immunoreceptor*.tw.
4. artificial adj3 t cell receptor*.tw.
5. artificial adj2 t-cell receptor*.tw.
6. chimeric adj3 t cell receptor*.tw.
7. chimeric adj2 t-cell receptor*.tw.
8. T-LYMPHOCYTES/
9. t adj1 cell*.tw.
10. t adj1 lymphocyte*.tw.
11. (thymus-dependent or thymus dependent) adj1 lymphocyte*.tw.
12. IMMUNOTHERAPY, ADOPTIVE/
13. adoptive adj2 cellular immunotherapy*.tw.
14. adoptive adj1 immunotherap*.tw.
15. car adj2 t-cell therap*.tw.
16. car t cell therapy.tw.
17. chimeric antigen receptor therapy.tw.
18. or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. LEUKEMIA/
20. leuk?emia*.tw.
21. leucocyth?emia*.tw.
22. 19 or 20 or 21
23. 18 and 22
24. limit 23 to (english language and humans)
25. limit 24 to “systematic review”
26. limit 25 to “RCT”
27. limit 23 to “systematic review” and “RCT” and “economic evaluation”
28. limit 27 to yr=“2013 -Current”

APPENDIX 4: EVIDENCE TABLE

Available upon request to the author.

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ISBN: 978-629-7842-09-7