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Austrian Institute for
Health Technology Assessment
GmbH

Obecabtagene autoleucel (AUCATZYL®)

for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia

Health Technology Assessment

Final Report

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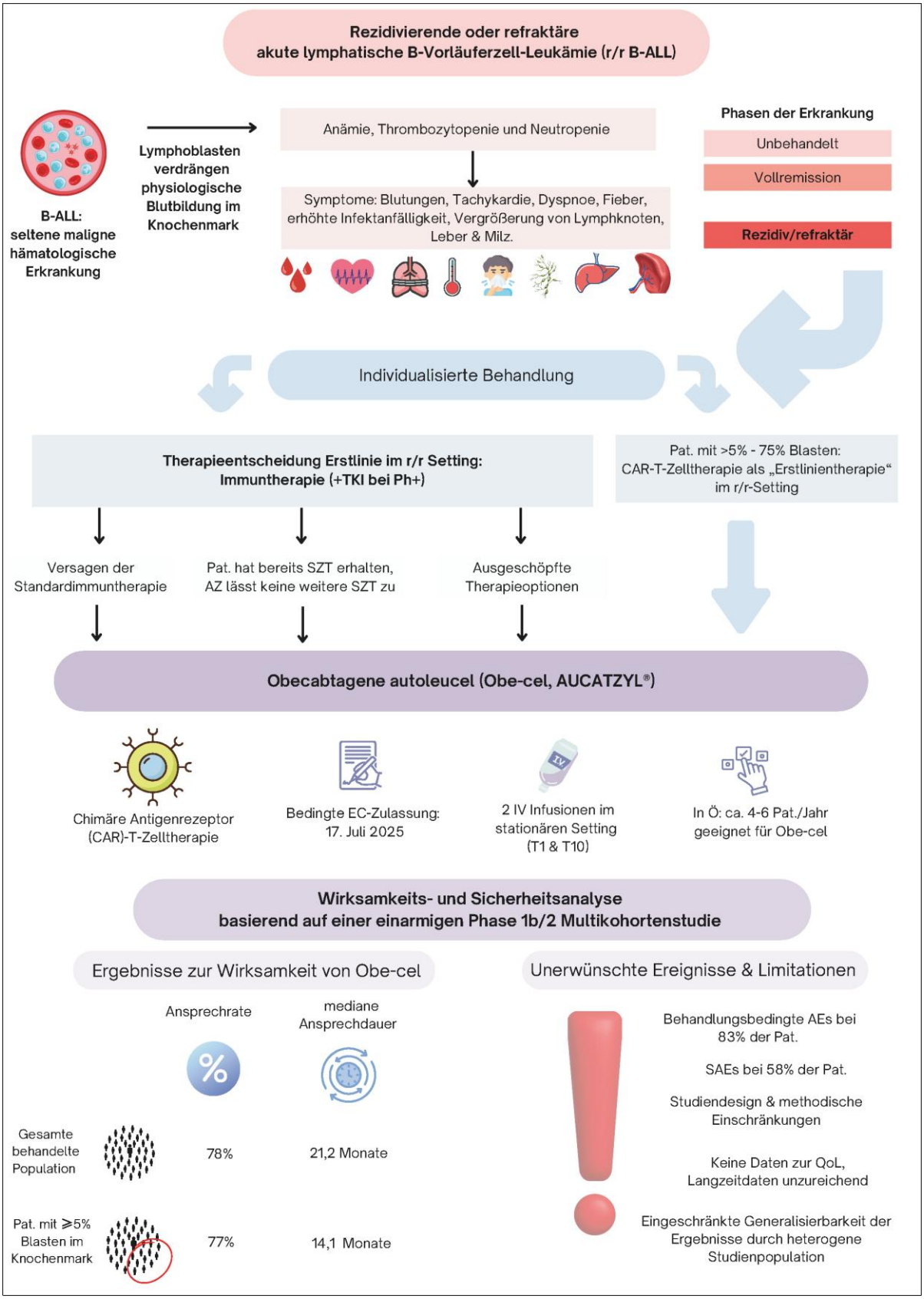
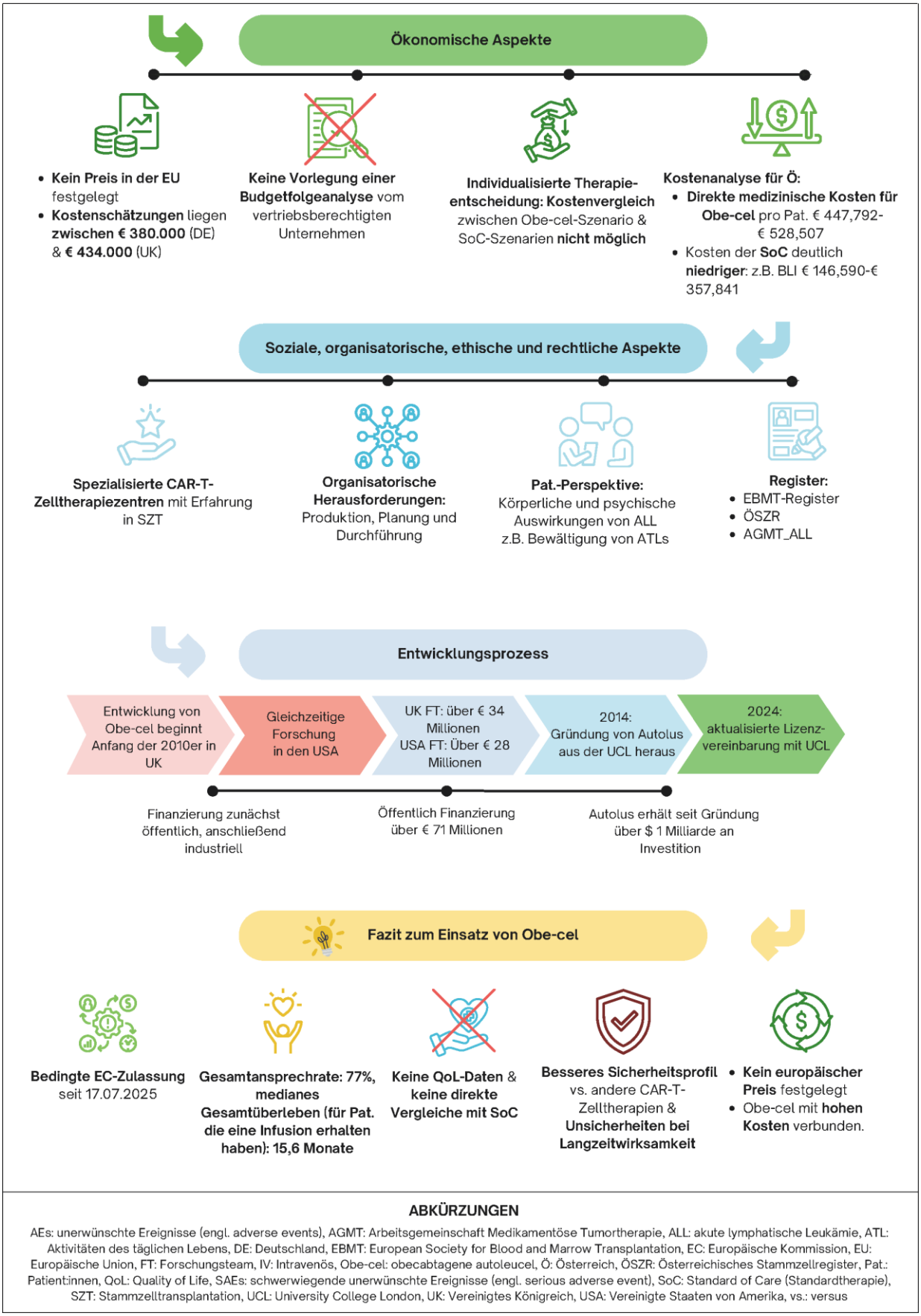




ABKÜRZUNGEN

AEs: unerwünschte Ereignisse (engl. adverse events), AGMT: Arbeitsgemeinschaft Medikamentöse Tumortherapie, ALL: akute lymphatische Leukämie, ATL: Aktivitäten des täglichen Lebens, DE: Deutschland, EBMT: European Society for Blood and Marrow Transplantation, EC: Europäische Kommission, EU: Europäische Union, FT: Forschungsteam, IV: Intravenös, Obe-cel: obecabtagene autoleucel, Ö: Österreich, ÖSZR: Österreichisches Stammzellregister, Pat.: Patient:innen, QoL: Quality of Life, SAEs: schwerwiegende unerwünschte Ereignisse (engl. serious adverse event), SoC: Standard of Care (Standardtherapie), SZT: Stammzelltransplantation, UCL: University College London, UK: Vereinigtes Königreich, USA: Vereinigte Staaten von Amerika, vs.: versus

Zusammenfassung

Der vorliegende Health Technology Assessment (HTA) Bericht evaluiert Obecabtagene Autoleucel (Obecel, Aucatzyl®) zur Behandlung von Erwachsenen ab 26 Jahren mit rezidivierender oder refraktärer akuter lymphatischer B-Vorläuferzell-Leukämie (r/r B-ALL).

Beschreibung der Erkrankung und Behandlungsoptionen

B-ALL, ein Subtyp der akuten lymphatischen Leukämie (ALL), ist eine seltene maligne hämatologische Erkrankung, die durch eine unkontrollierte Proliferation unreifer B-Lymphozyten („Lymphoblasten") charakterisiert ist. Diese Leukämiezellen akkumulieren im blutbildenden Knochenmark und verdrängen die physiologische Blutbildung, was zu Anämie, Neutropenie und Thrombozytopenie führt. Das klinische Bild der B-ALL ist daher geprägt von Symptomen wie Blutungen, Tachykardie, Dyspnoe, Fieber, erhöhter Infektanfälligkeit und Vergrößerungen von Lymphknoten, Leber und Milz. Bei sieben Prozent der Patient:innen manifestiert sich die Erkrankung auch im Gehirn, beispielsweise in Form von Neuropathien oder anderer neurologischer Ausfälle. Die Progression der Erkrankung kann hinsichtlich der Geschwindigkeit sehr unterschiedlich sein, auch ein schnelles Fortschreiten, verbunden mit einem raschen Abfall der körperlichen Leistungsfähigkeit, ist möglich. Für die ALL ist kein klassisches Staging-System verfügbar. Die Phasen der Erkrankung werden in unbehandelt, Vollremission (complete remission, CR; wobei zwischen kompletter morphologischer und kompletter molekularer Remission unterschieden wird), Rezidiv und refraktär unterteilt.

B-ALL tritt vermehrt bei Kindern (75 % der Krankheitsfälle) und Erwachsenen ab 60 Jahren auf. Die Inzidenz liegt bei 1,1/100.000 und betrifft in Österreich ungefähr 42 erwachsene Patient:innen in der für die Indikation relevanten Altersgruppe (≥ 26 Jahre). Für Österreich wird die Anzahl der erwachsenen Patient:innen in der Zielaltersgruppe auf etwa 42 geschätzt, von denen ungefähr 20 Patient:innen eine r/r Erkrankung aufweisen.

Die Therapie verfolgt grundsätzlich einen kurativen Ansatz. Zunächst erfolgt eine Stratifizierung in Standard- und Hochrisikogruppe basierend auf prognostischen Faktoren. Es folgt die (Immun-) Chemotherapie zur Induktion mit dem Ziel einer kompletten Remission (complete remission, CR) und idealerweise auch einer molekularen Remission. Das frühzeitige Erreichen einer MRD-Negativität (measurable residual disease, MRD) ist ein bedeutender, prognostisch günstiger Marker für ein geringeres Risiko eines Rückfalls und ein verlängertes Langzeitüberleben. Bei Hochrisikopatient:innen wird nach Erreichen der ersten Vollremission (CR1) eine allogene Stammzelltransplantation (allo-SZT) als Konsolidierungstherapie empfohlen. Ein klinisch relevanter Unterschied besteht zwischen Philadelphia-Chromosom-positiver (Ph+) und -negativer (Ph-) Erkrankung: Die Ph+ B-ALL betrifft etwa 25 % der Erwachsenen und erfordert zusätzlich zur Chemotherapie den Einsatz von Tyrosinkinase-Inhibitoren (TKI), um den aggressiven Verlauf der Subform zu kontrollieren.

Im r/r-Setting besteht das Behandlungsziel im Erreichen einer zweiten Vollremission (CR2), gefolgt von einer allo-SZT, so diese nicht bereits in der Erstlinie durchgeführt wurde. Zur Standardtherapie in Österreich zählen zielgerichtete Therapien und Immuntherapien, meist bestehend aus Blinatumomab (BLI) oder Inotuzumab Ozagamizin (IO), sowie der zusätzlichen Gabe von Tyrosinkinase-Inhibitoren (TKIs) bei Patien:innen mit Ph+ Erkrankung. Die allo-SZT wird laut klinischen Expert:innen routinemäßig zur Konsolidierung bei jenen Patient:innen angewandt, welche in der Lage sind, eine zweite CR zu erreichen, und stellt bis dato die einzige, etablierte kurative Therapieoption mit nachgewiesener langfristiger Remission dar. Innovative chimäre Antigenrezeptor (chimeric antigen receptor, CAR)-T-Zelltherapien, darunter Brexucabtagene Autoleucel (Brexu-cel) und Obe-cel, stellen einen neuartigen Therapieansatz dar.

Für die Behandlung der r/r B-ALL gibt es in Österreich derzeit (Stand Juli 2025) keine spezifische Leitlinie, laut österreichischen klinischen Expert:innen erfolgt die Behandlung individualisiert mit den genannten Therapiemöglichkeiten.

Überblick über das neue Arzneimittel

Obe-cel ist eine autologe CAR-T-Zelltherapie, bei der Patient:innen-eigene T-Zellen gentechnisch mit einem Anti-CD19-CAR modifiziert werden. Dadurch können die modifizierten T-Zellen CD-19-positive Leukämiezellen gezielt erkennen und angreifen. Die empfohlene Gesamtdosis beträgt 410×10^6 CD19-CAR-positive lebensfähige T-Zellen, die aufgeteilt auf zwei Infusionen (Tag 1 und Tag 10 ± 2 Tage) intravenös in einem spezialisierten CAR-T-Zelltherapiezentrum verabreicht werden. Der komplexe Prozess der CAR-T-Zelltherapie erfordert einen mehrwöchigen Krankenhausaufenthalt der Patientin/des Patienten. Zunächst werden von der betroffenen Patientin/dem betroffenen Patienten durch Leukapherese T-Zellen gewonnen. Während daraus CAR-T-Zellen im Labor produziert werden (Dauer etwa 20 Tage), kann eine Bridging-Therapie notwendig sein, um das zwischenzeitliche Fortschreiten der Erkrankung zu verlangsamen bzw. zu verhindern. Vor der Obe-cel-Infusion erhalten Patient:innen eine lymphodepletive Chemotherapie zur Konditionierung des Immunsystems und hierdurch verbesserten Expansion/Zellteilung des CAR-T-Zellproduktes nach Infusion. Da die Behandlung mit Obe-cel das Risiko für schwerwiegende unerwünschte Wirkungen birgt, insbesondere des Zytokin-Freisetzungssyndroms (cytokine release syndrome, CRS) sowie Neurotoxizitäten, ist die engmaschige Überwachung nach Verabreichung durch ein erfahrenes und geschultes multidisziplinäres Team (mit entsprechenden personellen Ressourcen) notwendig.

Am 22. Mai 2025 erhielt Obe-cel eine positive Bewertung vom Ausschuss für Humanarzneimittel (Committee for Human Medicinal Products, CHMP) der Europäischen Arzneimittelagentur (European Medicines Agency, EMA). Am 17. Juli 2025 erfolgte die bedingte Zulassung von der Europäischen Kommission (EC) für die folgende Indikation: Zur Behandlung von Erwachsenen ab 26 Jahren mit r/r B-ALL.

Wirksamkeit und Sicherheit

Die Wirksamkeit und Sicherheit von Obe-cel wurde in einer multizentrischen, einarmigen, offenen, nichtrandomisierten Phase 1b/2 Multikohortenstudie (FELIX-Studie) bei erwachsenen Patient:innen (≥18 Jahre) mit r/r B-ALL untersucht. Für die primäre Wirksamkeitsanalyse wurde die Kohorte 2A (n=94) herangezogen, während die Gesamtpopulation der infundierten Patient:innen (n=127) für unterstützende gepoolte Analysen diente. In Kohorte 2A (medianes Follow-up: 20,3 Monate) zeigte die Analyse eine Ansprechrate von 77 %, davon 55 % CR, eine mediane Ansprechdauer (duration of response, DOR) von 14,1 Monaten sowie ein ereignisfreies Überleben (event-free survival, EFS) von 9,0 Monaten. Für alle infundierten Patient:innen (medianes Follow-up: 21,5 Monate) betrug das mediane Gesamtüberleben (overall survival, OS) 15,6 Monate. Das OS wurde für Kohorte 2A nicht separat berichtet. Die Ergebnisse zur Lebensqualität wurden in der klinischen Studie nicht erhoben.

Die häufigsten schwerwiegenden unerwünschten Wirkungen (SAEs, Grad ≥ 3) waren febrile Neutropenie (12,6 %), das Immuneffektorzell-assoziierte Neurotoxizitätssyndrom (ICANS, 6,3 %), COVID-19 (6,3 %), Hyperferritinämie (5,5 %) und Sepsis (5,5 %). Zusätzlich trat das Zytokin-Freisetzungssyndrom (cytokine release syndrome, CRS) bei 87 Patient:innen auf; ein CRS ≥ 3 wurde bei drei Patient:innen (2,4 %) beobachtet. Die Erkrankung war mit einer hohen Mortalität assoziiert. Nach der Obe-cel-Infusion verstarben 35 % der Patient:innen, wobei zwei Todesfälle (1,6 %) als behandlungsbedingt eingestuft wurden.

Eine Post-hoc-Analyse nach Knochenmarkblastengehalt vor Durchführung der Lymphodepletion (<5 %, 5–75 %, >75 % Lymphoblasten) zeigte, dass eine niedrigere Tumorlast mit höheren Remissionsraten, besseren Überlebensraten und einer geringeren Häufigkeit eines Rückfalls assoziiert war.

Limitationen der FELIX-Studie betreffen methodische Einschränkungen wie das einarmige, nicht-randomisierte Design, die statistische Analyse zur Wirksamkeit anhand historischer Schwellenwerte und die fehlenden Angaben zur Analyse von Confounding-Faktoren. Die Vertrauenswürdigkeit der Evidenz nach dem GRADE-Ansatz wurde nicht bewertet, da nur eine einzelne Studie in die Evaluation einbezogen wurde. Bis dato ist auch keine offizielle ESMO-MCBS-Bewertung verfügbar. Weitere limitierende Faktoren sind die heterogene Patient:innen-Population und damit verbundene eingeschränkte Generalisier-

barkeit, unzureichende Langzeitdaten sowie die fehlende Evaluierung der Lebensqualität der behandelten Patient:innen.

Ökonomische Aspekte

Da derzeit kein offizieller europäischer Preis für Obe-cel verfügbar ist und auch von Seiten des vertriebsberechtigten Unternehmens kein Preis genannt wurde, wurden für die Kostenübersicht publizierte Obe-cel-Preisschätzungen herangezogen. Diese belaufen sich auf Kosten zwischen € 380.000 (Deutschland) und € 434.000 (UK).

Das vertriebsberechtigte Unternehmen hat zudem keine Budgetfolgenanalyse für Östereich vorgelegt. Aufgrund der individuell anzupassenden Behandlungsalgorithmen in der gegebenen Indikation (r/r B-ALL) und der wenigen zu erwartenden Patient:innen in diesem Setting, ist die Durchführung einer Budgetfolgenanalyse inklusive inkrementeller Kostenvergleiche zwischen Obe-cel-Therapieszenarien und Therapieszenarien ohne Obe-cel wenig aussagekräftig. Stattdessen wurden die direkten medizinischen Kosten von Obe-cel und den möglichen Standardtherapien pro Patient:in separat dargestellt. Auf Basis dieser für den österreichischen Kontext durchgeführten Kostenanalyse belaufen sich die direkten medizinischen Kosten für Obe-cel inklusive notwendiger Zusatzbehandlungen pro Patient:in auf € 461.142 bis € 541.857. Im Vergleich dazu entstehen bei Anwendung der Standardtherapien deutlich niedrigere Kosten: bei BLI zwischen € 132.506 und € 320.519, bei IO zwischen € 85.209 und € 224.968, bei TKIs zwischen € 17.326 und € 69.305, und bei allo-SZT zwischen € 134.590 und € 338.567. Das CAR-T-Zell-Konkurrenzprodukt Brexu-cel liegt mit Kosten zwischen € 408.142 und € 433.152 zwischen Obe-cel und den meisten Standardtherapien.

Aufgrund fehlender Daten sind die Kosten für das Langzeit-Follow-up der behandelten Patient:innen in unserer Analyse nicht berücksichtigt, obwohl sie die direkten Kosten sowohl von der Standardtherapie als auch Obe-cel deutlich erhöhen können. Ebenso werden die direkten medizinischen Kosten von Obe-cel, Brexu-cel und der allo-SZT unterschätzt, da die Angaben zu den in Österreich eingesetzten Bridging-Therapien fehlen. Diese Limitationen führen im Assessment zu einer Unterschätzung der direkten medizinischen Kosten von Obe-cel, Brexu-cel und der allo-SZT.

Soziale, organisatorische, ethische und rechtliche Aspekte

Patient:innen mit r/r B-ALL haben nach bisherigen Behandlungen begrenzte therapeutische Optionen. Gleichzeitig stellt die komplexe Durchführung der CAR-T-Zelltherapie organisatorische Herausforderungen dar, insbesondere im Hinblick auf die Produktion sowie die Planung und Durchführung der Behandlung in spezialisierten CAR-T-Zelltherapiezentren mit Erfahrung in allogenen Stammzelltransplantationen. Die Österreichische Gesellschaft für Hämatologie und Medizinische Onkologie (OeGHO) hat Empfehlungen für die qualitätsgesicherte Durchführung der CAR-T-Zelltherapie in Österreich veröffentlicht.

Außerdem berichten Patient:innen mit ALL von erheblichen Einschränkungen im Alltag, die sowohl körperliche Beschwerden als auch psychische Belastungen wie Zukunftsängste umfassen. Die Behandlung selbst kann die Lebensqualität zusätzlich beeinträchtigen. Zugleich verbinden viele Patient:innen mit innovativen Therapien die Hoffnung auf eine langfristige Remission bei möglichst wenigen Nebenwirkungen.

In Österreich wurde ein nationales CAR-T-Zell-Netzwerk etabliert, um den Zugang zu CAR-T-Zelltherapie bundesweit zu vereinheitlichen. Außerdem wird die Anwendung von CAR-T-Zelltherapien laut klinischen Expert:innen durch begleitende Dokumentation in zwei Registern erfasst: im Register der European Society for Blood and Marrow Transplantation (EBMT) und im Österreichischen Stammzelltransplantationsregister (ASCTR). Zusätzlich besteht das ALL-Register der Arbeitsgemeinschaft Medikamentöse Tumortherapie.

Öffentliche Investition

Die Entwicklung von Obe-cel zur Behandlung erwachsener Patient:innen mit r/r B-ALL begann Anfang der 2010er Jahre am University College London (UCL) in Großbritannien (GB). Gleichzeitig wurden Forschungsarbeiten an der University of Texas MD Anderson Cancer Center sowie am Children's Institute in den Vereinigten Staaten von Amerika (USA) durchgeführt. Die Forschung wurde überwiegend öffentlich mit über € 71 Millionen gefördert und bildet die Grundlage der CAR-T-Zelltherapie.

Die Überführung der akademischen Forschung in die kommerzielle Entwicklung erfolgt über UCL-Business, die Gesellschaft für Technologietransfer der UCL. 2014 wurde Autolus aus der UCL ausgegründet und erhielt eine exklusive Lizenzvereinbarung mit Meilensteinzahlungen und Lizenzgebühren von bis zu £ 106,68 Millionen. Seit der Gründung hat Autolus über $ 1 Milliarde an Investitionen erhalten und hauptsächlich in GB investiert. Zusätzlich ging Autolus strategische Partnerschaften mit BioNTech ($ 250 Millionen, 2024), Blackstone ($ 250 Millionen, 2021) und Moderna (bis $ 60 Millionen, 2021) ein und verfügt über ein umfangreiches Portfolio von 83 Patentfamilien, davon 17 direkt von der UCL lizenziert.

Weitere Entwicklungen

Weitere Entwicklungen umfassen drei laufende klinischen Studien zu Obe-cel. Neben der Nachbeobachtung der FELIX-Studie laufen Studien zu Obe-cel als Konsolidierung in der Erstlinientherapie. Der Abschluss der Studien wird für November 2027 beziehungsweise Mai 2030 erwartet. Außerdem wurden für r/r ALL sieben weitere Therapien in der International Horizon Scanning Initiative (IHSI) Datenbank identifiziert.

Schlussfolgerung

Obe-cel ist eine neuartige innovative CAR-T-Zelltherapie (Advanced Therapy Medicinal Product, ATMP), die eine Erweiterung des Behandlungsspektrums im r/r Setting der B-ALL darstellt. Die FELIX-Studie zeigt, dass Obe-cel bei Patient:innen mit B-ALL im r/r-Setting hohe Ansprechraten erzielt und eine vergleichbare Wirksamkeit zu bestehenden CAR-T-Zelltherapien wie Brexu-cel aufweist. Zusätzlich zeigt die Studie ein günstiges Sicherheitsprofil von Obe-cel mit weniger unerwünschten Ereignissen (AEs) und schwerwiegenden unerwünschten Ereignissen (SAEs), wie etwa dem CRS und der Neurotoxizität verglichen mit den Ergebnissen der ZUMA-3 Studie zu Brexu-cel. Es fehlen direkte Vergleiche zu den Standardtherapien und Ergebnisse zur Lebensqualität.

Trotz der vielversprechenden Ergebnisse bestehen aufgrund des Studiendesigns weiterhin Unsicherheiten hinsichtlich der langfristigen Wirksamkeit. Die Übertragbarkeit der Studienergebnisse auf den österreichischen Kontext ist limitiert und die organisatorischen Herausforderungen, die hohen Kosten und die begrenzten Kapazitäten in spezialisierten CAR-T-Zelltherapiezentren sind zu berücksichtigen.

Obe-cel stellt eine zusätzliche Behandlungsmöglichkeit für Patient:innen mit r/r B-ALL mit klinisch relevanter Wirksamkeit, insbesondere für Patient:innen, die unter den Standardtherapien keine dauerhafte Remission erreichen konnten oder für eine allo-SZT nicht geeignet sind.

Executive summary

This health technology assessment (HTA) evaluates obecabtagene autoleucel (obe-cel, AUCATZYL®) for adult patients (≥26 years of age) with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukaemia (B-ALL).

Disease background

B-ALL is a malignant haematological condition characterised by uncontrolled growth of immature B-cell lymphocytes known as lymphoblasts. B-ALL arises from B-cell lymphocytes. As these leukaemia cells multiply uncontrollably and quickly accumulate in the bone marrow, the production of healthy red blood cells, white blood cells and platelets is decreased, leading to anaemia, neutropenia and thrombocytopenia. B-ALL is most common in children (75% of cases), but there is a second peak of incidence in adults older than 60 years. The overall incidence of ALL is 1.1 per 100,000 inhabitants per year, with an estimated 42 adult B-ALL patients in the target age group in Austria, of whom around 20 patients may have r/r disease.

Treatment follows a curative approach with initial patient stratification into standard-risk and high-risk subgroups based on prognostic factors, and subsequent long-term multiagent chemotherapy aimed at the achievement of complete haematological remission (CR) and ideally also a complete molecular remission (molCR). Early achievement of molCR, also known as measurable residual disease (MRD) negativity, represents the most significant prognostic factor predicting relapse and long-term survival. In a high-risk patient group, consolidation with allogeneic stem cell transplantation (allo-SCT) is recommended after achieving first CR (CR1). A clinically important distinction exists between Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative (Ph-) disease, with Ph+ B-ALL found in approximately 25% of adult patients, requiring additional tyrosine kinase inhibitors (TKIs) to the treatment regimen to control the aggressive features of this subtype. In the r/r setting, the aim is the achievement of second remission (CR2), with subsequent allo-SCT consolidation, which is currently the only established curative option. Current standard of care (SoC) in Austria is represented by targeted therapies and immunotherapeutic agents, consisting mainly of blinatumomab (BLI) and inotuzumab ozagamizin (IO). Chimeric antigen receptor (CAR) T cell therapies, such as brexucabtagene autoleucel (brexu-cel) and obe-cel, represent a novel immunotherapeutic approach in the treatment of r/r B-ALL, potentially leading to a cure without the need for allo-SCT consolidation.

Overview of the new medicinal product

Obe-cel is a genetically modified autologous CAR T-cell therapy consisting of patient's T cells that have been engineered to target CD19 antigen expressed on the surface of B-cells. The total recommended dose of obe-cel is 410×10^6 CD19 CAR-positive viable T cells, administered as a split-dose infusion on Day 1 and Day 10 (± two days). Treatment is delivered in an inpatient setting under the supervision of a physician experienced in anticancer therapies and with a particular expertise in cellular therapeutics. CAR T-cell therapy delivery is a comprehensive process; prior to the infusion of obe-cel, eligible preselected patients undergo extensive screening, a leukapheresis procedure to obtain T cells, and lymphodepleting chemotherapy to condition the immune system, with some patients requiring a bridging therapy between the leukapheresis and lymphodepletion. After the obe-cel infusions, patients require a minimum of two weeks of hospitalisation for monitoring and management of short-term complications, in particular, the cytokine release syndrome (CRS) and the immune effector cell-associated neurotoxicity syndrome (ICANS).

AUCATZYL® received a positive opinion of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on 22 May 2025, and it was approved on 17 July 2025 through a conditional marketing authorisation for the treatment of adults aged 26 years or older with r/r B-ALL.

Clinical effectiveness and safety

One single-arm, open-label, multi-cohort phase 1b/2 clinical trial (FELIX) evaluated the clinical effectiveness and safety of obe-cel in adults (≥18 years) with r/r B-ALL. Overall, it included five cohorts, with the pivotal cohort 2A used for the primary efficacy analysis (n = 94) and the total infused population for a supportive pooled analysis (n = 127). In cohort 2A, at a median follow-up of 20.3 months, obecel demonstrated a 77% overall remission rate (ORR) with 55% achieving CR, a median duration of response (DOR) of 14.1 months and an event-free survival (EFS) of 9.0 months. The median overall survival (OS) for all infused patients at a median follow-up of 21.5 months was 15.6 months (not reported for cohort 2A). Quality of life (QoL) outcomes were not reported in the study.

Regarding safety, 81.9% of infused patients (104/127) experienced a treatment-emergent adverse event (TEAE) of grade ≥3, the most common being febrile neutropenia (23.6%), anaemia and neutropenia (20.5% each), decreased neutrophil count (19.7%), decreased platelet count and thrombocytopenia (12.6% each), and hyperferritinaemia (10.2%). Considering AEs of special interest, CRS was observed in 87 cases (68.5%), of which 3 (2.4%) developed grade ≥3 CRS; ICANS was observed in 29 cases (22.8%), with grade ≥3 ICANS reported in 9 (7.1%) infused patients. Progressive or relapsed disease was the leading cause of death, accounting for 35% (45/127) of all infused patients' deaths. In two patients, death was attributed to obe-cel in relation to TEAEs (acute respiratory distress syndrome with ongoing ICANS, neutropenic sepsis). In addition, a post-hoc subgroup analysis based on the bone marrow burden before lymphodepletion (<5%, 5–75%, >75% blasts) showed that a lower bone marrow blast burden was associated with better overall remission, survival rates, and reduced relapse incidence compared to higher blast burdens.

Due to the single-arm design, no formal risk of bias assessment, nor Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was performed. Limitations of the FELIX study arise from the single-arm, non-randomised design, small sample size in a heterogeneous population, and insufficient long-term follow-up data. Further uncertainties remain regarding the statistical analysis of efficacy using historical thresholds, and the lack of information on the analysis of confounding factors. To date, no official ESMO-MCBS assessment is available.

Economic aspects

Obe-cel has no set price in Europe yet, and the marketing authorisation holder (MAH) did not propose any price for Austria. Nevertheless, two relevant price submissions from the MAH were identified: €380,000 in Germany, and approximately €430,000 in the UK (reported as £372,000).

The direct medical costs of the obe-cel treatment per patient, including the pre-treatments (bone marrow assessment, leukapheresis and lymphodepleting conditioning) and administration costs, are expected to range from €461,142 to €541,857, depending on the price and length of hospitalisation. Given that the selection of the SoC treatment regimen in the r/r B-ALL indication depends on individual patient characteristics and the available treatments are often used in combination and sequentially (e.g., IO in combination with TKI followed by allo-SCT), a comparative cost analysis was deemed to be of limited value. Nevertheless, SoC treatments are associated with considerably lower per-patient costs: BLI costs range from €132,506 to €320,519, IO from €85,209 to €224,968, TKIs from €17,326 to €69,305, and allo-SCT costs from €134,590 to €338,567. Concerning the competitive CAR T-cell therapy, brexu-cel treatment is estimated to cost between €408,142 to €433,152 per patient.

However, due to data unavailability, our analysis does not include costs associated with long-term follow-up management of treated patients, though they could substantially increase the direct medical costs of both the obe-cel and SoC treatments. In addition, the direct medical costs of obe-cel, brexu-cel and allo-SCT are underestimated due to missing data on bridging therapies used in Austria. These aspects constitute a limitation of the presented economic assessment.

Social, organisational, ethical and legal aspects

Patients with r/r B-ALL have limited therapeutic options after previous treatments. At the same time, the complex implementation of CAR T-cell therapy presents organisational challenges, particularly with regard to production, planning, and implementation of treatment in specialised CAR T-cell therapy centres with experience in stem cell transplantation. The Austrian Society for Hematology and Medical Oncology (OeGHO) has published recommendations for the quality-assured implementation of CAR T-cell therapy in Austria.

From a patient perspective, two surveyed patients reported that the disease has a profound negative impact on the functioning of daily life, as well as on their emotional and psychological well-being. They expressed hopes that the new therapy would be characterised by high effectiveness, especially the potential to induce long-term remission, and minimal to no AEs.

In Austria, the Austrian CAR T-Cell Network was established to standardise access to CAR T-cell therapy nationwide. Furthermore, according to clinical experts, the use of CAR T-cell therapies is recorded through accompanying documentation in two registries: the European Society for Blood and Marrow Transplantation (EBMT) and the Austrian Stem Cell Transplantation Registry (ASCTR). In addition, there is the ALL Registry of the German Association for Drug-Based Tumor Therapy.

Public investment aspect

The development of AUCATZYL® emerged from publicly funded research at the University College London (UCL) and progressed to successful commercialisation through strategic partnerships and continued collaboration between academia and industry. Over €71 million, in public €55 million and philanthropic €16.2 million, funding supported obe-cel's development, with UCL receiving €40 million, University of Texas MD Anderson Cancer Center €28.3 million, and the Children's Research Institute €2.9 million. The identified public research funding contributing to the underlying technology of obe-cel represents an example of how public investment in basic research enables new therapies.

Landscape overview

Efficacy and safety of obe-cel in adult r/r B-ALL population is being further investigated in three ongoing trials, including the active follow-up phase of FELIX trial (NCT04404660) and as consolidation therapy in the first-line setting (NCT07053059). An HTA on obe-cel is currently conducted in England and Wales by the National Institute for Health and Care Excellence (NICE), with a draft guidance document published for consultation in June 2025; final guidance is expected to be released on 15 October 2025.

Additionally, there are seven therapies in development for r/r B-ALL that may expand the treatment algorithm in this patient population, including the paediatric one.

Conclusion

Overall, obe-cel is an advanced therapy medicinal product that can expand the treatment options in r/r B-ALL setting. Its clinical value is particularly significant for patients who have exhausted SoC options without achieving durable remission and those who are contraindicated to allo-SCT. With its lower toxicity, it provides a valuable alternative to currently available CAR T-cell therapy. However, patient selection for obe-cel treatment requires rigorous evaluation of individual benefit-risk profiles and consideration of emerging prognostic factors – particularly tumour burden – by a multidisciplinary team. Implementation involves substantial costs and poses significant organisational and infrastructure challenges. The main benefit of obe-cel is its ability to induce remission with a relevant duration in pretreated B-ALL r/r adult patients, as seen in an open-label, multi-centre, single-arm phase Ib/II study. However, absence of direct comparisons to SoC therapies (BLI, IO, TKIs), unavailability of QoL data, and lack of definitive guidance on optimal sequencing of CAR T therapies in the treatment algorithm, especially in relation to allo-SCT, introduce considerable uncertainty to the presented evidence.

1 Introduction

The objective of this report is to evaluate the clinical effectiveness and safety, as well as the economic and organisational aspects of obecabtagene autoleucel (obe-cel, AUCATZYL®), a chimeric antigen receptor (CAR) T-cell therapy, in adult patients (≥26 years of age) with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (r/r B-ALL).

Obe-cel zur Behandlung von Erwachsenen mit B-Zell-ALL

1.1 Disease background

Overview

B-ALL, a subtype of acute lymphoblastic leukaemia (ALL), is a rare malignancy characterised by the infiltration of the bone marrow and peripheral blood by immature B cells, known as lymphoblasts. The leukaemic blasts displace the regular haematopoietic bone marrow, resulting in bone marrow failure, which is characterised by anaemia, thrombocytopenia, and a variable leukocyte count. Since all other lymphatic and non-lymphatic organs can also be affected, disease symptoms may include lymphadenopathy, hepatomegaly, splenomegaly, or central nervous system (CNS) findings. B-ALL is most common in children (75% of cases), but there is a second peak of incidence in adults older than 60 years [1, 2].

B-Zell-ALL: seltene, maligne, hämatologische Erkrankung

leukämische Blasten verdrängen blutbildendes Knochenmark → Anämie, Thrombozytopenie

Classification

Two current diagnostic and classification schemes can be applied to ALL: the 5th edition of the World Health Organization classification of haematolymphoid tumours (WHO5) and the International Consensus Classification (ICC) of myeloid neoplasms and acute leukaemia. Both categorise ALL according to lymphoid lineage, cytogenetic findings, and molecular features, with modest differences in their categories and labels [3, 4]. WHO5 classification is displayed in Figure 1-1.

Klassifikationen: WHO5 und ICC

A clinically important distinction is between Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative (Ph-) ALL, determined by the presence or absence of the Philadelphia (Ph) chromosome (translocation 9;22) in the bone marrow cells. The t(9;22) results in the expression of the BCR::ABL1 fusion oncogene with persistently increased tyrosine kinase activity, driving the more rapid proliferation of lymphoblasts [6]. It can be detected in approximately 25% of adult ALL patients, and its incidence increases with age; in patients older than 60 years, it is found in about 40–50% of cases [7, 8]. Early identification of Ph+ status is important because it allows for the addition of tyrosine kinase inhibitors (TKIs) that block the activity of the BCR::ABL1 oncoprotein to front-line therapy, significantly improving the prognosis of Ph+ B-ALL patients [9, 10].

Philadelphia-Chromosom bei ca. 25 % der erwachsenen ALL-Pat. nachweisbar

Einsatz von TKIs verbesserte die Prognose bei Ph+ signifikant

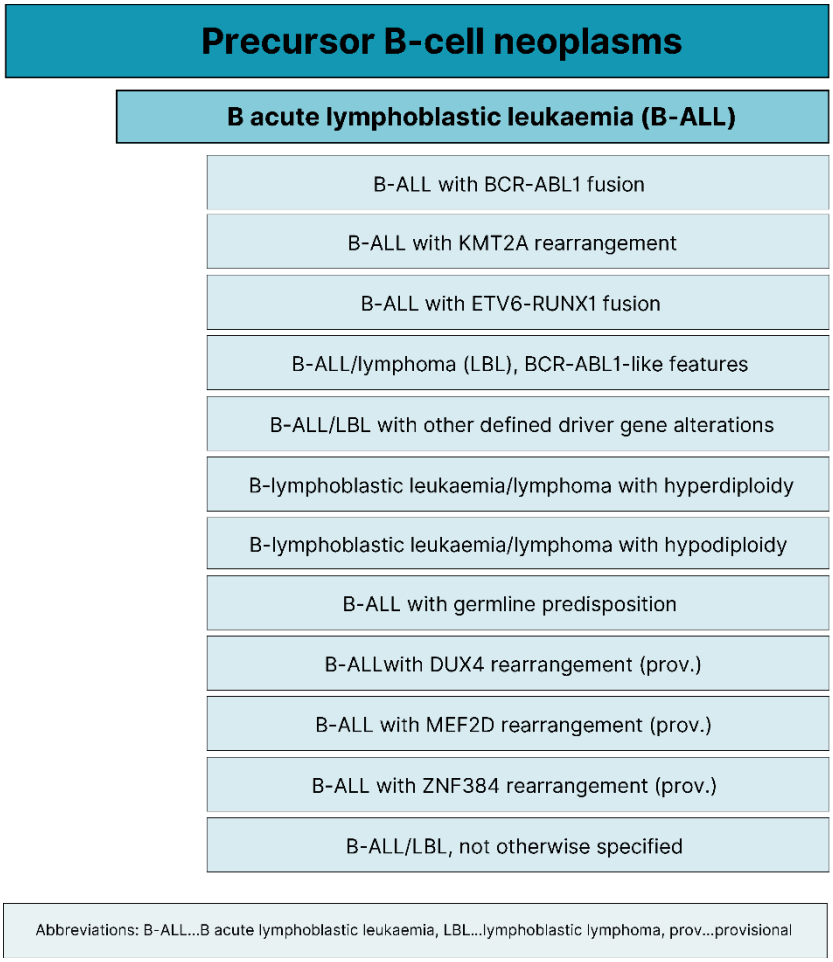


Figure 1-1: Classification of precursor B-cell neoplasms, according to WHO5 [5]

Clinical manifestations and disease course

klinisches Bild durch zunehmende Knochenmarksinsuffizienz geprägt

The clinical picture of ALL results from symptoms attributable to the increasing insufficiency of normal haematopoiesis, as well as to the infiltration of organs. Bone marrow involvement leads to anaemia, thrombocytopenia, and variable white cell counts (leukopenia, leucocytosis, or normal levels). Symptoms can include tachycardia, dyspnoea, fever, bone pain, arthralgia, pale skin, dizziness, increased susceptibility to infection, petechiae, and a tendency towards bleeding and haematoma formation [2, 7].

häufige Symptome: Blutungen, vergrößerte Lymphknoten, Leukozytose

Gehirn bei 7 % der Pat. betroffen

At the time of diagnosis, one-third of patients suffer from infections or haemorrhages. Up to 50% of adult patients suffer from infiltration of the spleen and liver, presenting as splenomegaly and hepatomegaly, while lymphadenopathy from nodal infiltration occurs in nearly 60% of cases. Seven per cent of patients exhibit CNS involvement, which is typically diagnosed as part of a routine examination of the cerebrospinal fluid. However, it may also manifest as cranial neuropathies or meningeal symptoms. Leucocytosis is found in 60% of ALL patients; other extramedullary organ involvement is present in nine per cent of ALL cases. Conversely, the absence of leucocytosis, anaemia, thrombocytopenia, or even the absence of blasts in the blood does not rule out ALL [2, 7].

The progression of disease in B-ALL follows a variable clinical course over time. While some patients present with symptoms that progress slowly over weeks to months, others develop symptoms within days that are accompanied by rapid loss of physical performance [2, 7].

Erkrankung kann sehr rasch fortschreiten

Diagnosis and staging

If B-ALL is suspected, evaluation should include a complete blood count with differential examination of the peripheral smear, immunophenotype of peripheral blood or marrow, and bone marrow examination. Today, complete molecular work-up is also considered standard of care and critical for risk stratification and guidance of treatment decisions. In some cases, an excisional or needle core biopsy of a lymph node is required for the diagnosis of B-ALL [2].

Diagnostik: Untersuchung von Blut und Knochenmark

The detection of lymphoblasts with the characteristic immunophenotype in peripheral blood, bone marrow, or other involved tissue is crucial to establish the diagnosis of B-ALL. A diagnosis of ALL generally requires that ≥20% of the cells in the bone marrow are leukaemic blasts [4, 11]. The detailed diagnostic steps in ALL are described in the appendix.

Nachweis von Lymphoblasten (≥20 %) mit charakteristischem Phänotyp entscheidend für die Diagnose

The differential diagnosis for B-ALL includes numerous malignant conditions (e.g., T-ALL, Burkitt lymphoma, acute myeloid leukaemia) and non-malignant processes (e.g., human immunodeficiency virus infection, infectious mononucleosis)[2]. For detailed information, please see Chapter 1 in the Appendix.

zahlreiche mögliche Differentialdiagnosen

For staging of ALL, there is no classical staging system [10] as in solid tumours (e.g., TNM), since the disease spreads systemically early and does not form localised masses. Instead, it is classified into subtypes based on immunological, genetic, and molecular features relevant for prognosis and therapy (see classification system WHO5 or ICC above). The phases of ALL are categorised as untreated, in remission, relapsed (also called recurrent) or refractory [10]. Within complete remission, morphological remission (blasts <5% in the bone marrow) is distinguished from molecular remission (in those patients with a leukaemia-specific molecular marker/mutation).

kein klassisches Staging-System für ALL verfügbar

Prognosis

Prognostic and predictive factors in adult patients with ALL include patient-related factors (age, Eastern Cooperative Oncology Group/ECOG performance status), disease-related factors (white blood cell counts, immunophenotype, genetics, CNS involvement), and treatment-response factors (measurable residual disease (MRD), time to complete remission (CR), corticosteroid sensitivity, blast cell clearance)[12]. Detailed information on the presence of the Philadelphia chromosome as a predictive factor is provided above.

Prognose u. a. abhängig von Alter, genetischen Faktoren, Ansprechen auf Behandlung

Of these, MRD represents a highly significant prognostic factor at any time during and after therapy. MRD in ALL is defined as the presence of post-therapeutic (chemotherapy, immunotherapy, or radiotherapy) leukaemia cells within the bone marrow and, more rarely, in peripheral blood circulation, detectable by sensitive molecular probe techniques. The early achievement of both complete haematological (morphological) remission (CR) and complete molecular remission (molCR, MRD negativity) characterises a subgroup of ALL patients with a favourable prognosis. In contrast, patients with persistent MRD or molecular recurrence after consolidation have a high recurrence rate, and persistence of MRD is currently the most unfavourable prognostic factor in adult ALL. Further unfavourable prognostic factors are displayed in Figure 1-2. As persistence or MRD indicates resistance to conventional chemotherapy, a change in therapy and the use of targeted therapies should be considered in the event of molecular therapy failure or molecular recurrence [2, 7, 13, 14].

messbare Resterkrankung (MRD): Nachweis leukämischer Zellen nach erfolgter Therapie

hochsignifikanter Prognosefaktor während und nach der Therapie

persistierende MRD gilt als ungünstigster Prognosefaktor

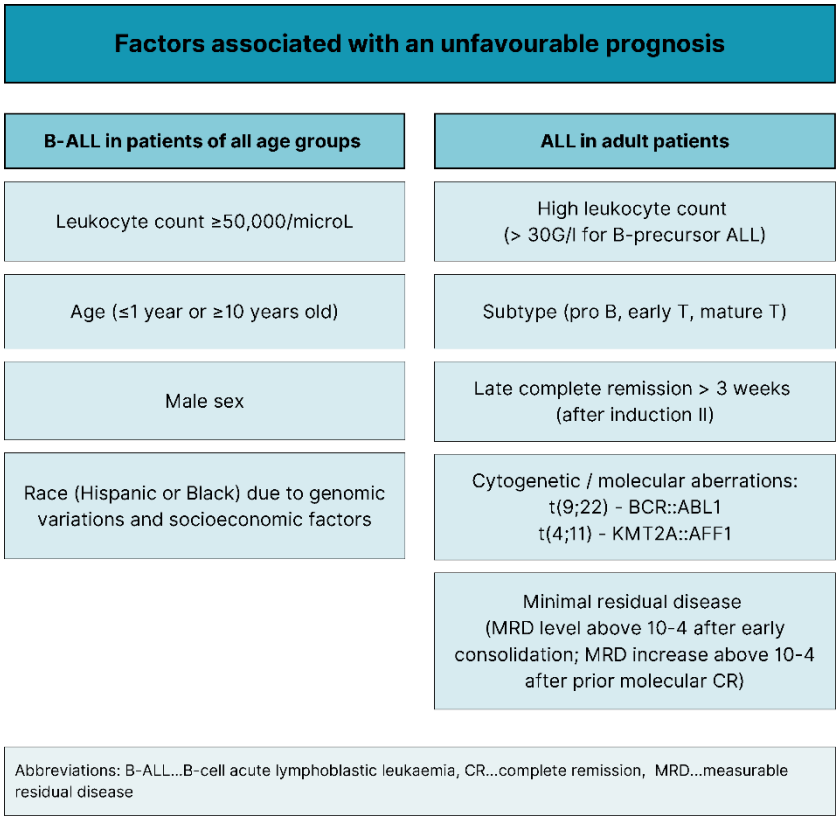


Figure 1-2: Unfavourable prognostic factor in ALL patients[1] [2, 7]

[1] T(9;22) – BCR::ABL1 corresponds to the Philadelphia chromosome, which is an abnormal chromosome that is made when pieces of chromosomes 9 and 22 break off and trade places. The ABL1 gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR::ABL1 fusion gene. The changed chromosome 22 with the fusion gene on it is called the Ph chromosome [15].

Einteilung in Standard- und Hochrisiko-Pat.

Based on the prognostic and predictive factors mentioned above, ALL patients can be stratified into two main risk subsets. Patients without poor prognostic factors and/or with a favourable post-induction MRD response represent approximately 50–60% of all cases and are defined as standard-risk (5-year overall survival >50–60%, and up to 70–80% in selected good-risk subsets). In contrast, patients with any poor prognostic factors and/or poor MRD response are classified as high-risk (5-year overall survival of 40–50%). This distinction is crucial for developing an effective risk-oriented treatment strategy [12].

Epidemiology

Gesamtinzidenz der ALL 1,1/100.000 pro Jahr, mehr als 60 % der ALL-Fälle entsprechen dem B-Zell-Phänotyp betrifft v. a. Kinder oder Pat. >60 Jahre

The overall incidence of ALL is 1.1/100,000 per year, with a slight predominance of males (1.4:1.0) [7]. More than two-thirds of ALL cases are of B-cell phenotype. Incidence of B-ALL demonstrates a bimodal age distribution, with three-quarters of cases occurring in children <6 years old, and a second peak of incidence in adults older than 60 years. The incidence is three times higher in White individuals than in Black individuals. There is an increased incidence of B-ALL in children with Down syndrome and other genetic disorders [2].

keine detaillierten Daten von Statistik Austria verfügbar

In Austria, on average, 375 new cases of B-ALL were registered per year between 2020 and 2022 [16]. However, the proportion of adult patients with B-ALL cannot be directly derived from the published Austrian statistical data.

Ö ALL-Register: 70 neudiagnostizierte Erwachsene pro Jahr

According to an estimate of the Austrian Registry and Biobank study for the collection of clinical data and biomaterial from adult ALL patients (AGMT_ALL Registry), there are approximately 70 newly diagnosed adult patients with ALL in Austria every year [15]. Epidemiological data indicate that 75% of cases present B-cell tumour morphology [20], which results in 60 adult B-ALL patients in Austria.

1.2 Standard of care in Austria

Europäische Leitlinien: Onkopedia, ESMO und ELN

The following European guidelines, intended for the treatment of r/r B-ALL, were identified:

- Onkopedia (2022) [7]
- European Society for Medical Oncology (ESMO) Clinical Practice Guideline (Update 2023) [17]
- European Leukemia Net (ELN) recommendations from a European expert panel: Management of ALL in adults [9].

keine eigene Leitlinie für Ö

Behandlung erfolgt individualisiert

For Austria, no specific guidelines are available for the treatment of adults with r/r B-ALL. According to clinical experts, the treatment is individually tailored to the patient, taking into account prior therapies, patient's condition, time to and extent of relapse, and other factors [18]. This corresponds to the definition of "individualised treatment" as defined by the Member State Coordination Group on Health Technology Assessment (HTA CG) in the Guidance on the scoping process for the purposes of EU Joint Clinical Assessments (JCA) [19]. A treatment algorithm for individualised treatment of adult r/r B-ALL patients, including information from Austrian clinical experts, is presented in Figure 1-3.

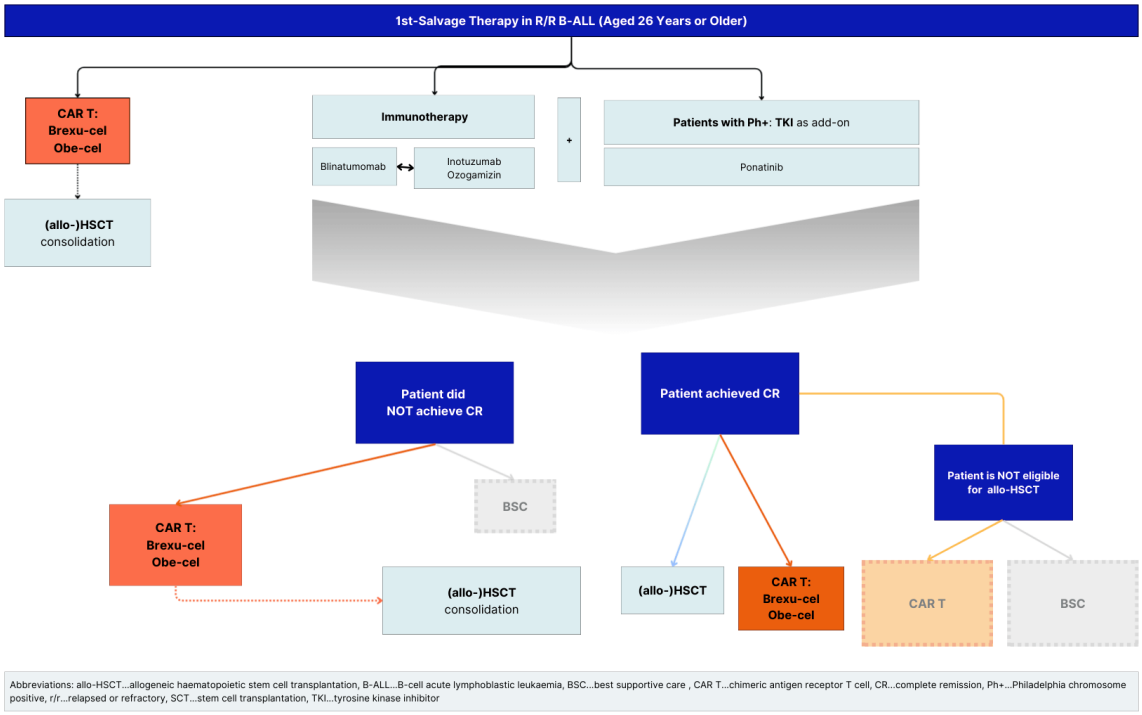


Figure 1-3: Treatment algorithm

Erstlinientherapie: Induktion, Konsolidierung und Erhaltung

primäres Ziel: komplette Remission

The current standard treatment for newly diagnosed B-ALL in the first line generally consists of long-term multiagent (immuno-)chemotherapy delivered over two to three years in three phases: induction, consolidation, and maintenance. The treatment aim is to achieve a CR[2] and ideally also a molCR[3] already with the induction chemotherapy and to subsequently reduce the risk of relapses with consolidation and maintenance therapy. In the standard-risk patient group, a high overall survival (OS) rate can usually be achieved with (immuno)-chemotherapy alone. In contrast, in a high-risk patient group, consolidation with allogeneic stem cell transplantation (allo-SCT) is recommended after achieving first CR (CR1) – however, B-ALL has its peak in adults in the elderly patient cohort, of which many are no longer transplant eligible due to comorbidities or age (>70–75 years). The improvements in chemotherapy protocols as well as the introduction of immunotherapeutic agents to first-line therapy have led to improved outcomes; consequently, the occurrence of r/r B-ALL is now significantly lower [14, 20].

Erreichen einer 2. Remission ist Therapieziel bei rezidivierter und refraktärer B-Zell-ALL

In the treatment of relapsed or refractory cases, the aim is the achievement of second remission (CR2), with subsequent allo-SCT consolidation in those who are transplant eligible. According to clinical experts, early relapsed disease is considered chemotherapy-resistant; therefore, chemotherapy is not the treatment of choice in early r/r setting (within 18–24 months of first-line treatment). SoC in Austria is represented by targeted therapies and immunotherapeutic agents, consisting mainly of blinatumomab and inotuzumab ozagamizin, with the addition of tyrosine kinase inhibitors (TKIs) in patients

[2] CR is defined as <5 per cent lymphoblasts in bone marrow [14].

[3] MolCR/MRD negativity means that the patient is in CR and MRD is not detectable by sensitive molecular probe(s) (sensitivity ≥10−4) [14].

with Ph+ disease. Clinicians confirmed that these immunotherapeutic agents are used in sequence and even repeatedly until the achievement of CR2 and molCR [18]. Of note – response to second-line treatment with achievement of a CR2 is substantially lower than CR1 following first-line treatment. An overview of the targeted therapies used in adults with r/r B-ALL is provided in Table 1-1.

Table 1-1: Overview of targeted therapies used in r/r adult B-ALL (adapted from ESMO [14])

Drug	Drug classification	B-ALL subpopulation
Inotuzumab ozomicin (IO)	Anti-CD22: Immunotherapy, a monoclonal antibody targeting the CD22 antigen on leukaemia cells with a cytotoxic agent (ozogamicin)	overall
Blinatumomab (BLI)	Anti-CD19: Immunotherapy, monoclonal antibody, bi-specific T-cell engager (BiTE) targeting CD19/CD3 antigen	overall
Imatinib, dasatinib, bosutinib, ponatinib	TKIs: Tyrosine kinase inhibitors, target BCR::ABL protein produced by Ph chromosome	Ph+
Brexucabtagene autoleucel (Brexu-cel)	Anti-CD19, CAR T: specific subclass of immunotherapy targeting CD19 antigen (like BLI)	overall

Abbreviations: B-ALL … B cell acute lymphoblastic leukaemia, BiTE … bi-specific T-cell engager, BLI … blinatumomab, CAR … chimeric antigen receptor, IO … inotuzumab ozogamicin, Ph (+) … Philadelphia chromosome (positive), TKIs … tyrosine kinase inhibtors

bis dato: allo-SZT als Standardtherapie

According to clinical experts, allo-SCT remains the only established curative option with proven long-term remission in this indication, and suitable donors are only rarely unavailable in Austrian practice. The optimal prognosis in r/r B-ALL setting is observed in fit patients with standard-risk disease who have not yet undergone allo-SCT and who achieve CR2 with blinatumomab/ inotuzumab ozogamicin and subsequently receive allo-SCT [18].

Ö klinische Exp.: CAR-T-Zelltherapie bisher eher im Bereich der temporären Konsolidierung

Since 2022, there has been one CAR T-cell therapy approved in EU for the treatment of adult patients (≥26 years) with r/r B-ALL, brexucabtagene autoleucel (brexu-cel, TECARTUS®). However, Austrian clinical experts have limited experience with it in the treatment of adult r/r B-ALL patients. In nearly all cases where brexu-cel has been used in Austria to date, it was indicated in patients who had relapsed after a prior allo-SCT consolidation. If possible, CAR T-cell therapy should be administered in well-controlled disease rather than high tumour burden to lower toxicities and improve response to treatment. Therefore, in practice, patients should be pre-induced, preferably by anti-CD22 therapy (inotuzumab ozogamicin) [18].

Positionierung von Obe-cel innerhalb des Behandlungsalgorithmus noch unklar

Although the Austrian experts are divided in their opinion, the prevalent opinion among Austrian clinical experts is that allo-SCT as of now is the treatment of choice after achieving CR2. Whether certain patients will not require an allo-SCT as a consolidation, and how to identify these patients, needs to be determined in the coming years. The fact is that relapse rates of 40–60% within the first year following CAR T-cell therapy have been reported in earlier studies, but allo-SCT as consolidation (particularly 2nd allo-SCTs) are also afflicted with high treatment-related morbidity and mortality as well as post-transplant relapses [18]. However, for patients who are contraindicated to allo-SCT or do not have a suitable donor when achieving remission, CAR T-cell therapy can be a valuable alternative option.

Follow-up

Even after the end of B-ALL treatment, recurrences can still occur up to five years after the initial diagnosis. After that, the probability of recurrence decreases significantly. Therefore, further regular blood count and bone marrow checks are necessary. In the case of Ph+-ALL, MRD monitoring should be performed every three months during the first year after the completion of maintenance therapy and every six months in the following year to detect any molecular recurrences that may occur. MRD checks after relapse therapy and/or SCT are carried out more frequently. They should also include tests for donor cell chimerism (defining the proportion of donor and recipient cells) after SCT [7, 21].

Rückfälle nach erfolgter Therapie bis zu 5 Jahre nach Erstdiagnose möglich, danach nimmt Wahrscheinlichkeit ab

regelmäßige MRD-Kontrollen erforderlich

Control examinations also serve to detect late effects of the therapy. These may include aseptic bone necrosis after cortisone, myelodysplastic syndrome, secondary malignancies, e.g., development of acute myeloid leukaemia, infertility, hormonal disorders, or mental illness. Osteonecrosis occurs more frequently in younger adults. Patients should be questioned explicitly about possible symptoms. If symptoms are present, the indication for a magnetic resonance imaging scan should be considered liberally. Furthermore, bone health tests, such as calcium and vitamin D levels, should be conducted, and intervention should be implemented in the event of deviations. Most ALL patients in long-term remission, particularly those not undergoing an allo-SCT, are considered cured and do not experience any late complications [7]. Allo-SCT per se is afflicted with substantial long-term morbidity and impaired quality of life [18].

Spätfolgen angewandter Therapien: Osteonekrosen, akute myeloische Leukämie, Infertilität, Hormonstörungen, psychische Erkrankungen, etc.

1.3 Medicinal product under evaluation

The medicinal product under evaluation in this HTA is obecabtagene autoleucel (obe-cel, AUCATZYL®), a genetically modified autologous CAR T-cell therapy [22]. Table 1-2 summarises the most important information on this product.

HTA-Bericht zu Obe-cel (AUCATZYL®): CAR-T-Zelltherapie

Table 1-2: Characteristics of the medicinal product [23]

INN	
Product name	AUCATZYL®
Active substance(s)	Obecabtagene autoleucel (obe-cel)
ATC code	L01XL
Pharmacologic class	ATMP
Manufacturer/MAH	Autolus GmbH

Abbreviations: ATC … Anatomical Therapeutic Chemical, ATMP … Advanced Therapy Medicinal Product, INN … International non-proprietary name, MAH … marketing authorisation holder

Obe-cel is a genetically modified autologous CAR T-cell therapy, a type of personalised cancer immunotherapy. It consists of the patient's T cells that have been engineered to express an anti-CD19 CAR. The engagement of anti-CD19 CAR-positive T cells with CD19 protein expressed on the surface of B

Wirkmechanismus: personalisierte Immuntherapie (CAR-T-Zelltherapie)

cells leads to activation of the anti-CD19 CAR-positive T cells and subsequent signalling. This triggers an immunological response in which the T cells release inflammatory cytokines and chemokines, ultimately leading to the destruction of CD19-expressing cells [22, 24].

Regulatory status

EMA: Zulassung durch die EC im Juli 2025

On 22 May 2025, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for AUCATZYL® for the treatment of adults from 26 years of age with r/r B-ALL. On 17 July 2025, the European Commission (EC) approved AUCATZYL® for this indication [25]. AUCATZYL® is an advanced therapy medicinal product; the CHMP positive opinion is therefore based on an assessment by the Committee for Advanced Therapies (CAT). The medicinal product was supported through EMA's PRIority MEdicines (PRIME) scheme. It was granted orphan designation on 13 April 2022 for the treatment of ALL. Following the recent positive CHMP opinion, the Sponsor (Autolus GmbH) requested its withdrawal from the Union Register of orphan medicinal products [22, 26]. EMA regulatory information is summarised in Table 1-3.

Table 1-3: EMA regulatory information on AUCATZYL® [23]

Orphan medicinal product	
Conditional marketing authorisation	yes
Specific obligations of the conditional marketing authorisation	no
Additional monitoring	no
Accelerated approval	no
Exceptional circumstances	no
ATMP	yes
PRIME	yes
Orphan designation status	withdrawn
First approved indication	Treatment of adults from 26 years of age with r/r B cell precursor acute lymphoblastic leukaemia.
Details of ongoing early access programs in the EU (as provided by the MAH)	No information was provided by the MAH.

Abbreviations: ATMP: Advanced Therapy Medicinal Product, EU: European Union, MAH: Marketing Authorisation Holder, PRIME: Priority Medicines, r/r … relapsed or refractory

FDA: Zulassung 11/2024, Indikation enthält keine Altersbeschränkung

The U.S. Food and Drug Administration (FDA) approved obe-cel (also with the trade name "AUCATZYL®") on 8 November 2024 for the treatment of adults with r/r B-ALL. The application has been granted regenerative medicine advanced therapy designation and orphan drug designation [27]. In contrast to EMA's indication, the indication approved by the FDA contains no age specification.

Posology

As shown in Figure 1-4, for the manufacturing of obe-cel, initially, the patient's peripheral blood mononuclear cells are collected by a standard leukapheresis procedure. These cells are then enriched for T cells, activated and transduced with a replication-incompetent lentiviral vector containing the CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, and then formulated into a suspension. These steps are conducted ex-vivo in a laboratory. Obe-cel is cryopreserved in patient-specific infusion bags and thawed prior to infusion. In addition to T cells, obe-cel also contains non-transduced autologous T cells and non-T cells, phosphate-buffered saline, human serum albumin, ethylenediaminetetraacetic acid and 7.5% dimethyl sulfoxide [24]. According to the manufacturer, the production process is successful in 95% of cases and takes, from vein-to-release, about 20 days; however, it is intended to reduce the time to 16 days in the future [28].

Pat.-eigene T-Zellen werden durch Leukapherese gewonnen

Produktion und Vermehrung von CAR-T-Zellen

Prozess dauert ca. 20 Tage

After manufacturing, obe-cel infusion bags, stored in metal cassettes, are supplied directly to the cellular therapy laboratory associated with the infusion centre in the vapour phase of a liquid nitrogen shipper and stored below minus 150°C. Thawing of each infusion bag takes between two and eight minutes and must be continuously monitored [24].

Aufbewahrung bei –150°C, Auftauprozess dauert 2–8 Minuten

The total recommended dose of obe-cel is 410×10^6 CD19 CAR-positive viable T cells, supplied in three to five colour-coded infusion bags (10×10^6, 100×10^6, 300×10^6). The treatment regimen consists of a split-dose infusion to be administered on Day 1 and Day 10 (± two days). The dosage regimen should be determined based on the tumour burden, which is assessed by the percentage of bone marrow blasts from a sample obtained within seven days prior to the start of lymphodepletion [24].

personalisiertes Dosierungsschema, Gesamtdosis wird auf 2 Infusionen (Tag 1 & Tag 10) aufgeteilt

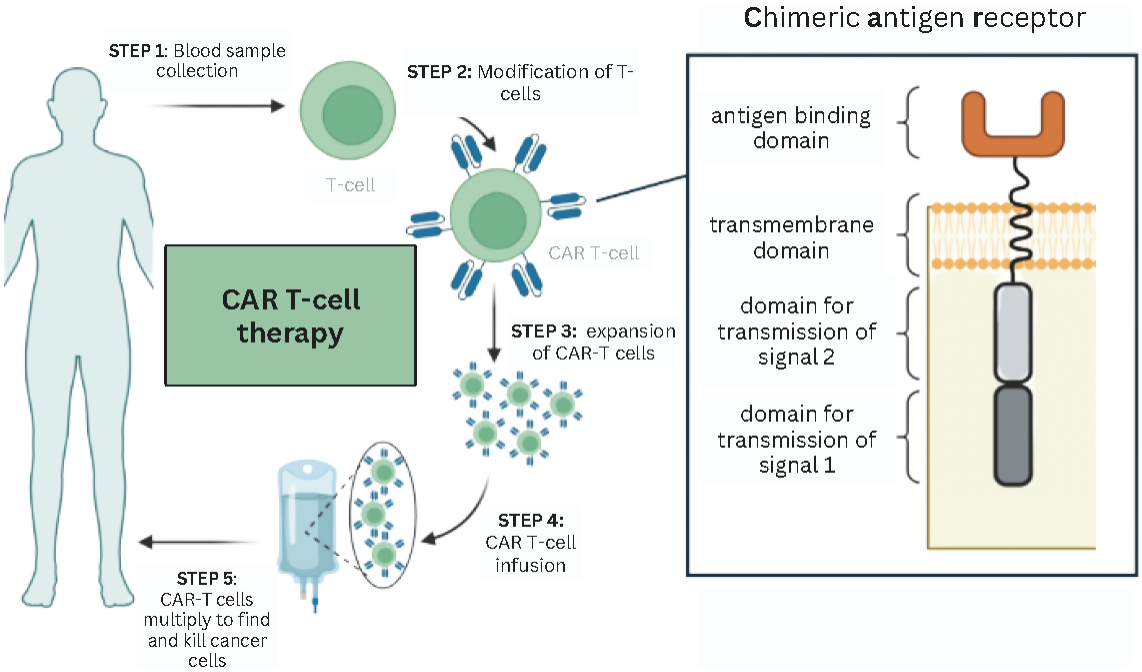


Figure 1-4: Process of CAR T-cell therapy, adapted from [29]

Requirements for diagnostics and monitoring

Administration of CAR T-cell therapy consists of several critical steps, starting with the selection of eligible patients up to long-term follow-up. All necessary steps are presented in Chapter 6 and, again more detailed, in the Appendix. Safe and efficient application of obe-cel therapy requires that at each of these steps, patient's condition is thoroughly evaluated, and appropriate criteria are met before proceeding to the subsequent steps (Figure 1-5).

Obe-cel: umfangreicher Prozess, zahlreiche Schritte erforderlich

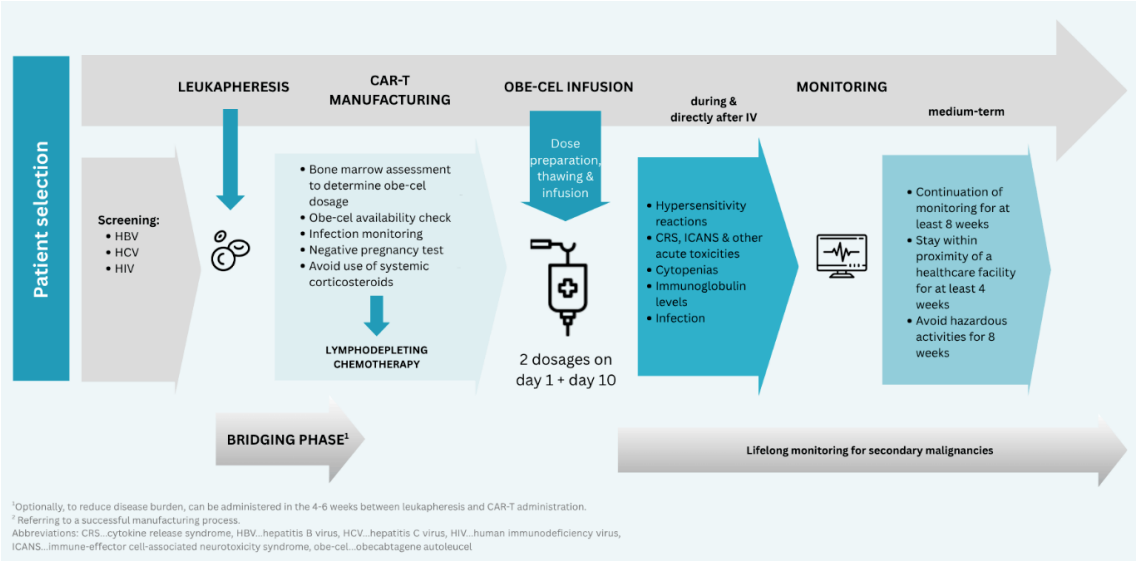


Figure 1-5: Overview of obe-cel treatment procedure [24, 30]. Patient selection criteria are presented in the Appendix.

Use in specific populations

Information on the use of obe-cel in specific populations is presented in Table 1-4.

Anwendung bei Schwangeren, Kindern und Älteren

Table 1-4: Use of obecabtagene autoleucel in specific populations [24]

	Obe-cel is not recommended for use in women who are pregnant or breastfeeding, as there is no information available regarding the presence of the medicinal product in human milk or its effect on the breastfed infant or milk production. It is not known if it has the potential to be transferred to the foetus and cause foetal toxicity. Pregnancy after infusion should be discussed with the treating physician.
	The safety and efficacy of obe-cel have not been established in paediatric patients.
	In patients 65 years of age and older, no overall differences in safety or effectiveness were observed between this patient group and younger patients.

Expected number of patients receiving obe-cel in Austria

Based on the data reported under Epidemiology, there are approximately 60 newly diagnosed adult patients with B-ALL in Austria every year [20, 31]. It is further assumed that 80% of the new adult cases are aged 26 and older [32], which yields approximately 42 patients with B-ALL in the target age group. Of these patients, around 40–50% are assumed to be refractory or in a relapse based on clinical estimates [18], which yields 17–21 patients per year who could be eligible for treatment with obe-cel. Nevertheless, clinicians in Austria expect that from the eligible population, only four to six patients per year would be indicated for treatment with obe-cel.

laut österr. klinischer Expert:innen könnten 4 bis 6 Patient:innen pro Jahr für die Behandlung mit Obe-cel geeignet sein

2 Scope of assessment

This report aims to evaluate the clinical effectiveness, safety, economic and other aspects of obecabtagene autoleucel (obe-cel, AUCATZYL®) for the treatment of adult patients (≥26 years) with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukaemia (B-ALL).

HTA:
Evaluierung von Obe-cel bei rezidivierender oder refraktärer B-Zell-ALL

2.1 Research questions

The following research questions will be answered in this present report:

Clinical domain:

- In adult patients (≥26 years) with r/r B-ALL, is obe-cel more effective and safer compared to the current standard treatment in Austria regarding patient-relevant effectiveness and safety outcomes?

klinische Domäne:
Wirksamkeit und Sicherheit

Non-clinical domains:

- What are the economic, organisational, ethical, social and legal consequences of implementing obe-cel into the Austrian healthcare system?
- What were the key contributions of publicly funded research institutions and private companies in discovering and developing obe-cel as a therapy for adult patients with r/r B-ALL, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

nicht-klin. Domänen:
ökonomische, organisatorische, ethische, soziale und rechtliche Konsequenzen, sowie öffentliche Beiträge zu Entwicklungskosten

2.2 Inclusion criteria

The inclusion criteria for relevant clinical studies are summarised in the PICO table below (see Table 2-1).

Regarding the non-clinical domains, relevant economic literature was included with information about obe-cel prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical, social and legal domains as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

PICO:
Einschlusskriterien für relevante klinische Studien

zusätzlich Literatur für nicht klin. Bereiche berücksichtigt

Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain.

Population	Adult patients (≥ 26 years of age) with r/r B-cell precursor ALL
Intervention	Obecabtagene autoleucel (obe-cel, AUCATZYL®)
Comparator(s)	Full population: ■ Blinatumomab (BLI) ■ Inotuzumab ozogamicin (IO) ■ Allo-SCT ■ Brexucabtagene autoleucel (brexu-cel) Ph+ subpopulation: ■ TKIs (dasatinib, imatinib, ponatinib, nilotinib, bosutinib)
Outcomes	Mortality: ■ OS Morbidity: ■ PFS ■ Overall remission (CR or CR with incomplete haematologic recovery) ■ EFS ■ DOR ■ MRD-negative remission rate ■ RFS ■ Proportion of patients undergoing SCT before leukaemia relapse ■ Proportion of patients in CR/CRi without SCTs or other subsequent therapies at 6, 12 and 24 months following obe-cel infusion ■ Incidence of CD19-negative relapse Patient-reported outcome: ■ QoL Safety ■ AEs ■ AEs of special interest: CRS, ICANS, T-cell malignancies, hypogammaglobulinaemia ■ SAEs ■ TEAEs ■ Death
Study design	■ Randomised controlled trials or meta-analyses ■ If not available: ▪ Non-randomised controlled studies ▪ Indirect treatment comparisons ▪ Observational studies ▪ Single-arm studies
Languages	English, German, Slovak

Abbreviations: AE … adverse event, ALL … acute lymphoblastic leukaemia, CR … complete remission, CRi … complete remission with incomplete haematologic recovery, CRS … cytokine release syndrome, DOR … duration of remission, EFS … event-free survival, ICANS … immune effector cell-associated neurotoxicity syndrome, MRD … measurable residual disease, OS … overall survival, PICO … patient, intervention, comparison and outcome, PFS … progression-free survival, QoL … quality of life, RFS … relapse-free survival, r/r … relapsed or refractory, SAE … serious adverse event,
SCT … stem cell transplantation, TEAE … treatment-related adverse event, TKIs … tyrosine kinase inhibitors

3 Methods

This HTA employed a multi-domain assessment approach following European Network for Health Technology Assessment (EUnetHTA) methodology (see guiding question in the Appendix Chapter 3) to evaluate obe-cel across clinical, economic, organisational, and social dimensions [33]. Methods were tailored to address the three primary research questions identified in Chapter 2, with a data cut-off of 22 July 2025.

Multi-Methoden-Ansatz – EUnetHTA-Leitfragen

Daten-Cut-off: 22. Juli 2025

Systematic literature search and study selection

A systematic literature search was conducted by an information specialist on 3–4 July 2025, across four databases: Medline via Ovid, Embase, the Cochrane Library, and the International Network of Agencies for Health Technology Assessment (INAHTA). The search was limited to English and German sources (see detailed search strategies in Chapter 3 in the Appendix). After deduplication, 115 citations were identified. Additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielded four potentially relevant hits. The manufacturer did not submit a dossier.

1 systematische Literatursuche in 4 Datenbanken: 115 Treffer

& Suche nach laufenden Studien

The study selection process followed a structured approach, where two researchers (AC, MR) independently screened references at the abstract level based on the pre-defined PICO criteria. Full texts were screened in duplicate, with arbitration by a third researcher (SGG) when disagreements arose. One study was ultimately included for clinical qualitative synthesis. However, one relevant reference was identified through an additional manual search and was considered for the effectiveness chapter. The study selection process is presented in the form of a PRISMA flow diagram in Chapter 3 in the Appendix.

Literaturauswahl:

klinische Domäne (n=1)

indirekter Therapievergleich (n=1)

Clinical effectiveness and safety assessment

Data extraction was conducted systematically by one reviewer (AC) and verified by a second reviewer (MR). For the assessment of clinical effectiveness and safety, no formal risk of bias (RoB) tool was applied to the included single-arm study, following the methodological standards for single-arm trials issued by the Member State Coordination Group on Health Technology Assessment. In line with the Guidance on Validity of Clinical Studies, uncontrolled trials are inherently of limited value for evaluating relative effectiveness and therefore do not require a formal RoB assessment [34]. Instead, we conducted a structured descriptive evaluation examining:

syst. Datenerhebung im 4-Augenprinzip

kein RoB-Tool angewendet: einarmige Studie wurde deskriptiv bewertet

- Study design appropriateness for the research question
- Population representativeness and external validity
- Outcome measurement validity and completeness
- Statistical analysis appropriateness
- Potential sources of bias specific to single-arm studies

Evidence synthesis followed a narrative approach due to limited comparative data. Therefore, the strength of evidence was not assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [35].

keine GRADE-Bewertung, da nur eine Studie vorhanden

In addition to the description of the identified single-arm study, an indirect treatment comparison (ITC) was considered. Through manual searching, we identified an indirect treatment comparison from the National Institute for Health and Care Excellence (NICE) technology appraisal [36, 37]. While this report contained confidential data (redacted sections), we included it as supplementary evidence and descriptively summarised the available findings. No formal assessment or quality appraisal was conducted on it.

jedoch indirekter Vergleich von NICE zu Obe-cel identifiziert

In addition, a congress abstract containing an ITC was identified through the systematic search [38]. However, in accordance with our pre-defined inclusion criteria, abstracts were not included in the clinical evidence synthesis.

Kongressabstract mit indirektem Vergleich nicht in Analyse inkludiert

Moreover, the European Society for Medical Oncology – Magnitude of Clinical Benefit Scale (ESMO-MCBS) was not applicable as no scorecards are available for haematological indications [39].

ESMO-MCBS: kein Score für Obe-cel verfügbar

Economic evaluation methods

According to the implementation regulation §4(2), a three-year budget impact analysis, including the gross drug budget impact and additional costs related to administration, should be conducted. However, given the expected low patient number for obe-cel as well as the current representation of individual standard of care (SoC) treatments in the assessed indication, an alternative approach to the budget impact analysis was applied: direct medical costs associated with obe-cel and the SoC treatments were estimated on a per-patient basis. In addition, we accounted for anticipated variation in the costs through minimum (MIN) and maximum (MAX) value ranges, generally associating the MIN scenario with patients necessitating shorter or less complex treatment. For this cost analysis we have made several assumptions:

Alternative zur Budgetfolgenanalyse: Abschätzung der direkten medizinischen Kosten pro Pat. für Obe-cel und Standardtherapien

getroffene Annahmen: ...

- Consideration of published placeholder prices as no official European price is yet available for obe-cel and the marketing authorisation holder did not submit a dossier containing price proposal for Austria.
  ... publizierte Platzhalterpreise
- The patient population estimates were derived from published epidemiological data and Austrian clinical expert input.
  ... Pat. epid. Daten von Exp.-Info
- The cost calculations involved ex-factory prices (Fabrikabgabepreise, FAP, from the Austrian Warenverzeichnis Apothekenverlag) and inpatient treatment cost data from the Austrian procedure- and diagnosis-related groups (PDRG) (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue.
  ... Kostendaten: Fabrikabgabepreise (Warenverzeichnis) bzw. LKF-Katalog (krankenhausbezogen)
- Minor cost categories, as well as costs associated with diagnostics and long-term post-treatment management, were excluded from the analysis due to the individualised diagnostic and monitoring options.
  Diagnostik und Langzeitkosten nicht berücksichtigt

Regarding the international economic evidence, we screened the literature identified through systematic and additional manual searches via Google to identify existing economic evaluations of obe-cel. We identified an abstract of a study describing an economic model comparing the costs associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) among patients treated with obe-cel and brexucel [40]. However, based on our pre-defined inclusion criteria, the abstract was excluded. Nevertheless, through the hand search, we found a preliminary guidance and accompanying committee paper from NICE that presents details of the pharmacoeconomic model submitted by the marketing authorisation holder for reimbursement of obe-cel by England's National Health Service [36, 37].

zusätzliche Handsuche nach ökonomischen Analysen zu Obe-cel

Abstract zu ökonom. Model ausgeschlossen

ökonom. Model von NICE als Anhaltspunkt

Organisational, ethical and social assessment

Data for the organisational, ethical and social aspects were gathered from three sources:

3 Quellen für weitere Perspektiven …

- To better understand the experiences of patients within the Austrian context, we initially searched for relevant patient organisations in Austria, intending to invite patients to complete a questionnaire about their experiences with the disease, current treatment options and hopes for new therapies. However, there are no patient organisations for ALL in Austria, which clinical experts also confirmed [18]. Therefore, we expanded our search to other German-speaking countries (the DACH countries: Germany, Austria and Switzerland). Additionally, we sought to identify patients through clinicians and obtain a statement from a patient organisation representing individuals affected by ALL. The patient questionnaires were completed by two patients diagnosed with acute lymphoblastic leukaemia (ALL), see Chapter 3 in the Appendix for more details.

  … schriftliche Pat.-Befragungen: Schwierigkeiten bei Pat.-Identifikation → keine Ö Pat.-Organisation für ALL Ausweitung der Suche auf DACH-Region, Einbeziehung von Kliniker:innen & Vertreter:innen von Pat.-Organisation

- Expert consultations with six leading clinicians (see Chapter 3 in the Appendix). Expert information was also used for the background and economic chapters. Simultaneously, the clinical experts validated the information we identified.

  … Exp.-Konsultationen

- Systematic literature review and manual search findings.

  … Literaturquellen

Development costs and public contributions

The methodology for assessing development costs and public contributions involved several steps (see Chapter 7 in the Appendix for details):

Entwicklungskosten und öffentliche Beiträge erhoben:

- Identifying product origins through searches for generic/ non-proprietary names and trade names.

  Identifizierung von: generischer oder (nicht) geschützter Bezeichnungen

- Searching for the earliest references to identify basic R&D support and research grants.
- Exploring databases on clinical trials and research funding.

  Produktherkunft & Grundlagenforschung

- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching Securities and Exchange Commission (SEC) reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.

  Finanzierungsrunden, Fusionen & Übernahmen

- Funding amounts were converted to € using the conversion rates as of 17.07.25 from the Austrian National Bank [41].

Supplementary methods

The clinical findings are presented in Chapter 4, the cost analysis in Chapter 5, the extended perspectives in Chapter 6 and the public contributions in Chapter 7 of this report. Each results chapter follows the methodological approach outlined above, with limitations and uncertainties acknowledged.

Verweise zu Ergebnissen

Additionally, we compiled a landscape overview of other therapies in development for r/r B-ALL, using the search terms “relapsed B-cell acute lymphoblastic leukaemia” and “refractory B-cell acute lymphoblastic leukaemia” in the International Horizon Scanning Initiative (IHSI) database [42].

zusätzlicher Überblick zu Leukämie-Therapien in Entwicklung

Furthermore, for the visual presentation of extracted data, selected figures were created using Canva graphic design platform [43].

Abbildungen mit Canva erstellt

4 Clinical effectiveness and safety

4.1 Characteristics of included studies

One clinical study evaluating the clinical effectiveness and safety of obecabtagene autoleucel (obe-cel) in adults with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B-ALL), authored by *Roddie et al.*, was identified [44]. This study was a phase 1b/2, single-arm, interventional, open-label, non-randomised trial (FELIX), with assignment to multiple cohorts, structured as follows:

eine klinische einarmige Phase 1b-2 Studie mit 5 Kohorten wurde identifiziert

Phase 1b:

- *Cohort 1A:* Patients with morphologic disease (≥5% bone marrow blasts[4]) receiving obe-cel infusion.
- *Cohort 1B:* Patients with measurable residual disease[5] (MRD, <5% bone marrow blasts) receiving obe-cel infusion.

Phase 1b: Kohorten mit morphologischer Erkrankung oder messbarer Resterkrankung

Phase 2:

- *Cohort 2A:* Main pivotal cohort for patients with morphologic disease at enrolment.
- *Cohort 2B:* Exploratory cohort for patients with MRD.
- *Cohort 2C:* Exploratory cohort for patients with isolated extramedullary disease (leukaemia manifestations outside the bone marrow).

Phase 2: Kohorten mit morphologischer Erkrankung, messbarerer Resterkrankung oder extramedulärer Beteiligung

Phase 1b evaluated the safety and optimal dosing of obe-cel, while phase 2 assessed its efficacy using the dosing regimen established in phase 1b. Data from both phases were analysed separately and combined into pooled analyses including all the infused patients as supportive evidence. The primary efficacy analysis was conducted for cohort 2A only, though *Roddie et al.* did not justify the choice of this population. This assessment presents results for both cohort 2A and the pooled analysis (referred to as the "total infused population"). The main characteristics of the FELIX trial are summarised in Table 4-1.

Phase 1b testete Sicherheit und Dosierung (n=16), Phase 2 bewertete Wirksamkeit (n=111); primäre Analyse fokussierte auf Kohorte 2A, Gesamtpopulation der behandelten Pat. als unterstützende Analyse

Table 4-1: Main characteristics of the included FELIX trial [44]

Reference/ID	FELIX (AUTO1-AL1)/2019-001937-16 [44]
Study type and design	Phase 1b-2, multicohort, multicentre, open-label study
Study population	Patients ≥18 years of age with relapsed or refractory B-cell acute lymphoblastic leukaemia
Study arms	Single-arm study: ■ Phase 1b: n=16 patients ■ Phase 2: n=111 patients (n=94 patients in Cohort 2A, main pivotal cohort) ■ Total infused population: n=127 (all the patients who received infusion of obe-cel)

[4] Per cent of bone marrow blasts refers to the percentage of immature blood cells in the bone marrow that is used as a marker for disease severity.

[5] MRD refers to minimal amounts of cancer cells that can be detected using highly sensitive techniques such as molecular testing.

Reference/ID	FELIX (AUTO1-AL1)/2019-001937-16 [44]
Study duration, data cut-off and locations	■ Median study follow-up for Cohort 2A: 20.3 months ■ Data cut-off: 7 February 2024 ■ Multiple trial centres in Spain, the UK and the US
Study endpoints	■ Primary endpoint: overall remission (complete remission or complete remission with incomplete haematologic recovery) ■ Secondary endpoints: complete remission, remission duration, event-free survival, MRD-negative remission, overall survival, progression-free survival, relapse-free survival, safety, stem-cell transplantation, and overall remission without stem-cell transplantation or other subsequent therapies
Available documentation	■ CSR: not provided ■ Registry entry: NCT04404660 ■ Sponsoring status: sponsored

Abbreviations: CSR … clinical study report, n … number of patients, UK … United Kingdom, US … United States.

4.1.1 Study population

The FELIX trial [44] defined inclusion and exclusion criteria for adults aged 18 years or older with r/r B-ALL, listed below (seeTable 4-2).

Ein- und Ausschlusskriterien für die FELIX-Studie

Table 4-2: Inclusion and exclusion criteria of the FELIX trial [44]

In- and exclusion criteria of FELIX trial	
Inclusion criteria	Exclusion criteria
■ Age 18 years or older ■ ECOG performance status of 0 or 1 ■ Relapsed or refractory B-ALL ■ Patients with Ph+ ALL are eligible if intolerant to TKI, failed two lines of any TKI, or failed one line of second-generation TKI, or if TKI is contraindicated ■ Documented CD19 positivity within 1 month of screening ■ Phase 1b: Primary Cohort 1A: Presence of ≥5% blasts in BM (bone marrow) at screening ■ Phase 1b: Exploratory Cohort 1B: MRD-positive defined as ≥1e–4 and <5% blasts in the BM at screening ■ Phase 2: Primary Cohort 2A: Presence of ≥5% blasts in BM at screening ■ Phase 2: Cohort 2B: ≥2nd CR or CRi with MRD-positive defined as ≥1e–3 by central ClonoSeQ® NFA testing and <5% blasts in the BM at screening ■ Adequate renal, hepatic, pulmonary, and cardiac function	■ Phase 1b (Cohort 1A and Cohort 1B) and Phase 2 (Cohort 2A and Cohort 2B) B-ALL with isolated EM disease ■ Diagnosis of Burkitt's leukaemia/lymphoma or CML lymphoid in blast crisis ■ History or presence of clinically relevant CNS pathology ■ Presence of active or uncontrolled fungal, bacterial, viral, or other infection requiring systemic antimicrobials for management ■ Active or latent Hepatitis B virus or active Hepatitis C virus ■ Human Immunodeficiency Virus (HIV), HTLV-1, HTLV-2, syphilis positive test ■ Prior CD19 targeted therapy other than blinotumomab. Patients who have experienced Grade 3 or higher neurotoxicity following blinatumomab.

Abbreviations: ALL … acute lymphoblastic leukaemia, B-ALL … B-cell acute lymphoblastic leukaemia, BM … bone marrow, CML … chronic myeloid leukaemia, CNS … central nervous system, CR … complete remission, CRi … complete remission with incomplete haematologic recovery, ECOG … Eastern Cooperative Oncology Group, EM … extramedullary, HIV … human immunodeficiency virus, HTLV-1 … human T-lymphotropic virus type 1, HTLV-2 … human T-lymphotropic virus type 2, MRD … measurable eesidual disease, NFA … next-generation sequencing flow cytometry assay,
Ph+ … Philadelphia chromosome positive, TKI … tyrosine hinase inhibitor

Eligible patients first underwent leukapheresis to collect T cells. During CAR T-cell manufacturing, bridging therapy could be administered to control leukaemia. The manufacturing process to generate obe-cel was the same in all the cohorts.

Leukapherese und Überbrückungstherapie und

Before receiving obe-cel, patients underwent lymphodepleting chemotherapy to weaken their immune system and create space for the CAR T-cells to expand and function more effectively [44].

lymphodepletierende Chemotherapie als Vorbereitung auf Obe-cel

Based on the bone marrow assessment results, obe-cel was administered using a split-dose approach tailored to each patient's disease burden: patients with >20% bone marrow blasts received 10×10^6 CAR T-cells, whereas those with ≤20% blasts received a higher initial dose of 100×10^6 CAR T-cells. In the absence of severe/unresolved toxicity, a second dose was administered nine days later to achieve a cumulative dose of 410×10^6 CAR T-cells [44].

höhe der Dosis abhängig von Blastenanzahl im Knochenmark; zweite Dosis nur bei Abwesenheit schwerer Toxizitäten

For detailed information on bridging therapy regimens and obe-cel exposure, refer to Chapter 4.1.1 in the Appendix.

4.1.2 Baseline characteristics

The differences in baseline characteristics between cohort 2A and the total infused population are briefly described below (see Table 4-3), with a notable difference in disease burden, where cohort 2A patients had higher bone marrow blast percentages compared to the total infused population. This reflects the inclusion criteria for cohort 2A, which specifically enrolled patients with morphologic disease requiring higher blast counts, while the total infused population included also patients from other cohorts with lower disease burden. Regarding previous treatments, the total infused population demonstrated similar treatment histories compared to cohort 2A. Disease characteristics such as extramedullary disease, Philadelphia chromosome (Ph) status and Eastern Cooperative Oncology Group (ECOG) performance scores were also comparable between the two populations [44].

Baseline-Charakteristika & Unterschiede in den Kohorten, insbesondere bzgl. Krankheitslast & Vortherapien

The baseline characteristics of the patients over all cohorts are presented in Chapter 4.1.2 in the Appendix.

Table 4-3: Baseline demographics of participants in Cohort 2A and in the total infused population in the FELIX trial [44]

Baseline demographics of FELIX trial		
Parameter	Cohort 2A (n=94)	Total infused population (n=127)
Age		
Age [years], median (range)	50.0 (20–81)	47.0 (20–81)
≥65 yr, n (%)	21 (22)	25 (20)
Sex [f/m] (%)		
Male	47 (50)	66 (52)
Female	47 (50)	61 (48)
Race, n (%)		
White	70 (74)	94 (74)
Black	2 (2)	2 (2)

Baseline demographics of FELIX trial		
Parameter	Cohort 2A (n=94)	Total infused population (n=127)
Asian	10 (11)	16 (13)
Unknown	12 (13)	15 (12)
Previous therapies		
Median n of previous lines of therapy (range)[1]	2.0 (1–6)	2.0 (1–6)
Previous use of blinatumomab, n (%)	33 (35)	53 (42)
Previous use of inotuzumab ozogamicin, n (%)	30 (32)	40 (31)
Previous use of blinatumomab and inotuzumab ozogamicin, n (%)	15 (16)	21 (17)
Previous allogeneic stem-cell transplantation, n (%)	36 (38)	56 (44)
Disease characteristics		
Median percentage of bone marrow blasts (range) on morphologic analysis	58.9 (6–100)	40.0 (0–100)
Extramedullary disease, n (%)	19 (20)	29 (23)
Philadelphia chromosome-positive disease, n (%)	25 (27)	36 (28)
ECOG performance-status score, n (%)[2]		
0	35 (37)	50 (39)
1	58 (62)	76 (60)

Note:
[1] *Previous lines of therapy are expected to include also chemotherapy; specific therapy types are not mentioned.*
[2] *ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability. Data were missing for one patient in each group.*

Abbreviations: ECOG...Eastern Cooperative Oncology Group, f ... female, m ... male, n ... number of randomised patients

4.1.3 Sample size

Pat.-Verlauf in der FELIX-Studie

The study enrolment and patient flow for the study population of the FELIX trial [44] are detailed in Table 4-4, showing that 112 patients were included in both the efficacy and safety analyses, with a median follow-up of 20.3 months. The disposition of patients in FELIX trial for all cohorts is presented in Chapter 4.1.3 in the Appendix.

Table 4-4: Disposition of the study population in FELIX trial [44]

Disposition of patients in FELIX trial	
Parameter	Number of patients
Number Screened	217
Number enrolled (ITT population)	153
Number received ≥1 infusion of obe-cel (%)1	127 (83.0%)
Number Withdrawn/Dropout (%)1	26 (17.0%)
Number for Efficacy Analysis (%)1	112 (73.2%)
Number for Safety Analysis (%)1	112 (73.2%)
Median follow-up (months)	20.3

Note: [1] The percentage refers to the total number of patients enrolled (n=153).

4.1.4 Outcomes

Definitions and reporting of efficacy outcomes

mehre Endpunkte zur Wirksamkeit und Sicherheit von Obe-cel evaluiert (u. a. OS, PFS, ORR)

The FELIX study evaluated multiple efficacy and safety endpoints to assess the therapeutic benefit of obe-cel in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia. The study assessed overall survival (OS), progression-free survival (PFS), and overall remission rates (ORR) encompassing both complete remission and complete remission with incomplete haematologic recovery (CR/CRi). Event-free survival (EFS) and duration of remission (DOR) were evaluated among the key temporal outcomes [44].

weitere Endpunkte inkludierten u. a. die Anzahl der Pat. mit MRD-Negativität

The investigators examined MRD-negative remission rates and relapse-free survival (RFS) to understand treatment durability. The study analysed the proportion of patients who underwent stem cell transplantation (SCT) before experiencing leukaemia relapse, as well as the proportion of patients maintaining complete remission or complete remission with incomplete haematologic recovery without requiring stem cell transplantation or other subsequent anticancer therapies at six, twelve, and twenty-four months following obe-cel infusion [44].

Beobachtung der Inzidenz eines CD-19-negativen Rückfalls

Additionally, the research monitored the incidence of CD19-negative relapse as a potential resistance mechanism. Patient-reported outcomes included quality of life (QoL) assessments using validated instruments to capture the patient experience throughout treatment and follow-up [44].

Detailed definitions for each outcome are provided in Chapter 4.1 of the Appendix.

Definitions and reporting of critical and important safety outcomes

Analyse der Nebenwirkungen gemäß CTCAE V 5.0 und ASTCT-Kriterien

In the FELIX trial, safety was assessed through systematic monitoring and documentation of adverse events (AEs) and serious adverse events (SAEs) following obe-cel infusion, including their frequency, severity, and relationship to treatment, as well as recording all deaths and their causes. The severity of AEs was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0. CRS and neurological toxicity were graded according to the American Society for Transplantation and Cellular Therapy/American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation (ASTCT/ASBMT) consensus grading [44].

Study protocol amendments

Protokollanpassungen aufgrund regulatorischer Rückmeldungen (2019–2023)

The protocol underwent nine amendments between 2019 and 2023, primarily following the regulatory feedback from the Medicines and Healthcare products Regulatory Agency (MHRA) and the FDA during initial submissions (versions 1-4). Key changes included expanding patient cohorts to include MRD-positive patients, introducing central laboratory testing, adding interim efficacy analyses, and updating study endpoints and statistical sections per FDA requests [44]. See Chapter 4.1.4 in the Appendix for more details.

4.2 Results on relative effectiveness and safety

The efficacy data from the FELIX trial [44] for cohort 2A and the total infused population are summarised in Table 4-5. The subgroup analysis by bone marrow burden is detailed in Table 4-6. Efficacy data for all study cohorts along with intention-to-treat (ITT) population analyses are in the Appendix Chapter 4.2.1.

Wirksamkeitsergebnisse für Obe-cel für Kohorte 2A & Gesamtpopulation

4.2.1 Clinical efficacy outcomes

OS revealed positive results for all infused patients, with previous allo-SCT showing no impact on survival outcomes. Specific OS data for cohort 2A were not reported in the study.

positive OS Ergebnisse

PFS outcomes were not reported in the study.

PFS nicht berichtet

ORR in cohort 2A reached statistical significance. The total infused population showed similar results to cohort 2A. The ORR for patients with ≥5% bone marrow blasts before lymphodepletion was similar to the total infused population.

stat. sign. ORR in Kohorte 2A

CR were achieved in the majority of cohort 2A patients with statistical significance, with comparable results in the total infused population. Also, the proportion of patients achieving CRi was similar between the two populations.

Mehrheit der Kohorte 2A erreichte CR

EFS differed between populations, with cohort 2A demonstrating shorter median EFS compared to the total infused population. Of the total infused population, 65.4% had EFS by six months, and 49.5% by 12 months. Previous allo-SCT did not affect EFS.

kürzere EFS in Kohorte 2A als in Gesamtpop.

DOR analysis showed variation between populations, with cohort 2A patients experiencing shorter DOR, while the total infused population achieved longer DOR.

kürzere DOR in Kohorte 2A als in Gesamtpop.

Among responders with available MRD data, more than 90% achieved MRD-negative status. Similarly, more than 90% of patients with <5% bone marrow blasts without extramedullary disease achieved MRD-negative remission. For patients presenting with extramedullary disease, the majority achieved clearance of extramedullary manifestations while maintaining <5% bone marrow blasts.

>90 % der Pat. mit Ansprechen erreichten MRD-Negativität

Of the 99 responding patients in the ITT population (n=153), 18 (18%) proceeded to allo-SCT while in remission at a median of 101 days (range, 38 to 421) after obe-cel infusion. For one-third of these patients, this represented a second allo-SCT.

18 % der Pat. mit Ansprechen erhielten SZT

QoL outcomes were not reported in the study. See Table 4-5 for further details.

QoL nicht berichtet

Table 4-5: Efficacy endpoints of the included FELIX trial for cohort 2A and the total infused population [44]

Efficacy outcome measure of FELIX trial		
Outcomes	Cohort 2A (n=94)	Total infused population (n=127)
Median overall survival (OS)	NR	15.6 months (95% CI, 12.9 to not evaluable1)
Overall remission rate (ORR) (proportion of patients achieving CR or CRi)	77% (95% CI, 67–85)	78% (70–85)
Complete remission (CR)	55% (95% CI, 45–66)	57% (95% CI, NR)
Complete remission with incomplete haematologic recovery (CRi)	21% (95% CI, 14–31)	20% (95% CI, NR)
Median event-free survival (EFS)	9.0 months (95% CI, 6.1–15.0)	11.9 months (95% CI, 8.0–22.1)
Median duration of remission (DOR)	14.1 months (95% CI, 8.2 to not evaluable1)	21.2 months (95% CI, 11.6 to not evaluable1)
Overall remission rate (≥5% bone marrow blasts before lymphodepletion)	NA	75% (95% CI, 64–83)
MRD-negative (responders with available MRD data)	NA	94% (95% CI, NR)
MRD-negative remission (<5% bone marrow blasts without extramedullary disease)	NA	96% (95% CI, NR)
Clearance of extramedullary disease and with <5% blasts	NA	71% (95% CI, NR)

Note: [1]Not evaluable, since the response was still maintained.

Abbreviations: CI … confidence interval, MRD … measurable residual disease, NA … not applicable, NR … not reported

Subgroup analysis showed that lower bone marrow blast burdens were associated with better overall remission, survival rates, and reduced relapse incidence compared to higher blast burdens (see Table 4-5). Among the 99 patients who achieved a remission, 31 (31%) experienced morphologic relapse by the data cut-off date. Relapse rates correlated with bone marrow blast burden at lymphodepletion (see Table 4-6). Five patients developed isolated extramedullary relapse, including two with central nervous system involvement, while three patients had concurrent bone marrow and extramedullary disease.

niedrigere Blastenanzahl mit besseren Ergebnissen assoziiert

Table 4-6: Efficacy endpoints for the subgroup analyses by bone marrow burden before lymphodepletion of the FELIX trial [44]

Efficacy outcome measure of FELIX trial			
Outcome	<5% blasts (n=36)	5-75% blasts (n=51)	>75% blasts (n=40)
Overall remission	86% (95% CI: 71–95%)	82% (95% CI: 69–92%)	65% (95% CI: 48–79%)
Overall survival (12 months)	72% (95% CI: 53–84%)	59% (95% CI: 44–71%)	55% (95% CI: 38–69%)
Morphologic relapse1	6/31 pts (19%)	12/42 pts (29%)	13/26 pts (50%)

Note: [1]absolute numbers refer to patients with overall remission (31/36 pts = 86%, 42/51 pts = 82%, 26/40 pts = 65%)

Abbreviations: CI … confidence interval, n … number of patients, pts … patients.

4.2.2 Safety outcomes

Deaths

At data cut-off date, the leading cause of death was progressive or relapsed disease (45 out of 127) [43]. Two deaths (1.6%) were attributed to obe-cel due to acute respiratory distress syndrome/ICANS (0.8%) or neutropenic sepsis (0.8%). Ten deaths (7.9%) occurred in remission either following consolidative allo-SCT or without receiving additional therapy. Progressive or relapsed disease was the leading cause of death, accounting for 35.4% of all infused patients (see Table 4-7).

2 Todesfälle (1,6 %) direkt Obe-cel zugeschrieben

Table 4-7: Deaths of the total infused population of the included FELIX trial [44]

Safety outcome measure of FELIX trial	
Category, n (%)	Total infused population (n=127)
Deaths with progressive or relapsed disease	45 (35.4)
Deaths in remission	10 (7.9)
Following consolditative allo-SCT	5 (3.9)
Without receiving additional therapy	5 (3.9)
Deaths attributed to obe-cel	2 (1.6)
Acute respiratory distress syndrome/ICANS	1 (0.8)
Neutropenic sepsis	1 (0.8)

Abbreviations: allo-SCT … allogeneic stem cell transplant, ICANS … immune effector cell-associated neurotoxicity, n … number of patients

Adverse Events (AEs) and serious adverse events (SAEs)

Across study populations, serious treatment-emergent adverse events (grade ≥3) occurred in similar proportions between cohort 2A and the total infused population (57.4% vs 56%). The most common serious adverse events in both groups were febrile neutropenia (13.8% vs 12.6%), ICANS (6.4% vs 6.3%), COVID-19 (7.4% vs 6.3%), hyperferritinemia (6.4% vs 5.5%), and sepsis (4.3% vs 5.5%). Grade ≥3 CRS occurred only in 3 patients (2.4% of the total infused population).

häufigste schwere Nebenwirkungen (Grad ≥3): febrile Neutropenie, ICANS, COVID-19, Hyperferritinämie, Sepsis

Considering AEs of special interest by blast burden, for the CRS, no grade ≥3 events were reported in patients with <5% blasts, while affecting 4% of patients with 5–75% blasts and 2% of patients with <75% blasts. Similarly, no grade ≥3 ICANS events occurred in patients with <5%, while 8% of patients with 5–75% blasts, and 5% of patients with >75% blasts experienced grade ≥3 ICANS. Febrile neutropenia and infections/infestations of grade ≥3 affected 24% and 52% respectively of the total infused population. AEs of special interest of any grade are depicted in Table 4-8.

Sicherheitsergebnisse variieren je nach Blastenzahl; häufige Nebenwirkungen, febrile Neutropenie (24 % aller Pat.), Infektionen (52 % aller Pat.)

A detailed summary of AEs is in Chapter 4.2.2 in the Appendix.

Table 4-8: Adverse events of special interest stratified by bone marrow blast burden groups and total infused population of the included FELIX trial [44]

Safety outcome measure of FELIX trial								
Adverse Events of special interest	<5% blasts (n=36)		5–75% blasts (n=51)		>75% blasts (n=40)		Total infused population(n=127)	
Grade	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Cytokine release syndrome, n (%)	17 (47)	0	36 (71)	2 (4)	34 (85)	1 (2)	87 (69)	3 (2)
ICANS, n (%)	3 (8)	0	10 (20)	4 (8)	16 (40)	5 (12)	29 (23)	9 (7)
Febrile neutropenia, n (%)	-	-	-	-	-	-	31 (24)	30 (24)
Infections and infestations, n (%)	-	-	-	-	-	-	99 (78)	66 (52)

Abbreviations: ICANS … immune effector cell-associated neurotoxicity syndrome, n … number of participants

4.3 Quality of the evidence

4.3.1 Risk of Bias

No RoB assessment tool was applied to the single-arm FELIX trial. The study faces inherent limitations primarily related to its single-arm, non-randomised, open-label study design. The absence of a control group restricts comparative effectiveness assessment and limits the ability to control for confounding variables. The inability to blind participants to treatment represents another limitation in bias control. Furthermore, the representativeness of the target population might be limited as individuals were selected from clinics.

keine passende RoB-Analyse für einarmige Studien; Schwächen einhergehend mit einarmigen Studiendesign

However, the FELIX trial demonstrated several methodological strengths that support the validity of its findings. The study employed outcome assessment through an independent response review committee, utilised validated measurement instruments following NCCN Clinical Practice Guidelines, and maintained patient follow-up with comprehensive documentation of withdrawals and exclusions. The high treatment participation rate (83.0% of enrolled patients received ≥1 infusion of obe-cel) and consistent treatment delivery across multiple centres further strengthen the study's quality. Additionally, the statistical analysis was appropriate for single-arm studies, applying ITT principles with suitable time-to-event analyses.

Stärken der Studie: unabhängiges Bewertungskomitee, validierte Messinstrumente, angemessene statistische Analyse

The FELIX trial evidence comes from heavily pretreated patients with uncertain generalisability to earlier treatment settings but shows high manufacturing success rates that are compatible with Austria's existing CAR T infrastructure, despite logistical challenges from the 21-day production time and frequent bridging therapy needs. While the study demonstrates promising efficacy and better safety than other CAR T therapies, the evidence is limited by a lack of direct treatment comparisons, uncertain long-term benefits, and potential access constraints due to Austria's limited number of specialised treatment centres offering allo-SCT. The applicability of evidence from the FELIX trial for Austria is detailed in Appendix, Chapter 4.3.1.

Anwendbarkeit: hohe Herstellungserfolgsrate, aber begrenzte Generalisierbarkeit und fehlende Direktvergleiche

4.3.2 Statistical analysis and inconsistencies

In the FELIX trial [44], the statistical analysis employed a hierarchical testing approach in cohort 2A with predefined endpoints:

- Primary endpoint: ORR, defined as CR or CRi.
- Secondary endpoints: CR within three months post-obe-cel infusion, MRD-negative remission, DOR, SCT, sustained remission, (S)AEs and QoL.

statistische Analyse für die Kohorte 2A (n=94)

The primary endpoint (ORR) was deemed to meet at a value of ORR of at least 40%, while the key secondary endpoint (CR) employed a threshold of 20%. These benchmarks were derived from a previous phase 3 trial with blinatumomab [45]. Formal statistical testing was conducted only for these two endpoints for cohort 2A.

Schwellenwert für ORR 40 %, für CR 20 % (aus Phase 3 Studien zu etablierten Therapien)

Several methodological concerns have been raised regarding the statistical approach. The FDA noted that using point estimates from external studies (40% ORR threshold from blinatumomab data) rather than more conservative upper confidence interval bounds fails to adequately account for statistical uncertainty [46]. Additionally, the FDA suggested that CR would have been a more clinically meaningful primary endpoint than ORR. The reliance on historical controls from different patient populations (see Table 4-9) introduces external validity concerns, as baseline characteristics differ between the FELIX [44] and the TOWER [45] studies. Furthermore, the NICE Evidence Assessment Group (EAG) argued that the analysis should include the entire enrolled ITT population from cohorts 1A and 2A, starting from leukapheresis rather than infusion, as excluding the pre-infusion period introduces bias by not capturing treatment delays and bridging therapy complications that are inherent to CAR T therapy but not present in comparator treatments that begin immediately [37].

Bedenken bzgl. Methodik: Punktschätzer statt Konfidenzintervalle ...

... fragwürdige historische Kontrollen ... .

... und möglicher Selektionsbias

The primary analysis included all infused patients from cohort 2A (n=94; modified ITT population). Based on sample size calculations, at least 90 patients were required to achieve 90% power at a one-sided 2.5% significance level. An interim efficacy analysis was conducted after 50 patients completed three months of follow-up. Time-to-event endpoints were analysed using Kaplan-Meier methods, with patients censored at SCT or initiation of new anticancer therapies. Supportive analyses without censoring were also performed [44].

modifizierte ITT-Analyse (n=94) erreichte geplante 90 %-Power; Zensur von Pat. bei Erhalt anderer Therapien, Rückfall, Tod oder SZT

Additionally, a subgroup analysis of bone marrow blasts was conducted by stratifying patients into three groups: <5% blasts, 5–75% blasts, and >75% blasts [44].

Subgruppenanalyse nach Knochenmarksbelastung

For a detailed overview, see Chapter 4.3.2 in the Appendix or study protocol, of the FELIX study [44].

umfassender statistischer Analyseplan in FELIX-Studienprotokoll

4.4 Indirect treatment comparison

1 indirekter Vergleich vom vertriebsberechtigten Unternehmen für NICE identifiziert

indirekte Vergleiche via MAIC basierend auf 4 Studien

In addition to the FELIX trial, we identified an indirect treatment comparison (ITC) of obe-cel versus standard of care submitted by the marketing authorisation holder (MAH) to the National Institute for Health and Care Excellence (NICE) and reported in the published appraisal documents [36, 37]. Comparators comprised blinatumomab (BLI) and inotuzumab ozogamicin (IO) for Ph- B-ALL and ponatinib (PON) and IO for Ph+ B-ALL. Brexucabtagene autoleucel (brexu-cel) was not considered a relevant comparator due to its reimbursement via a separate access scheme in the UK. The MAH conducted matching-adjusted indirect comparisons[6] (MAIC) considering the following studies [37]:

- FELIX for obe-cel (Phase 1b/2: n=94; Ph-: n=69; Ph+: n=25) [44]
- INO-VATE for IO (Phase 3 controlled trial: n=164) [47]
- TOWER for BLI (Phase 3 controlled trial: n=271, Ph- patients) [45]
- PACE for PON (Phase 2 single-arm trial: n=32, Ph+ patients) [48]

4.4.1 Methods

systematischen Suche nach relevanten Studien durch Unternehmen

Gewichtung für die Analyse basierend auf Baseline-Charakteristika

Matching limitiert durch fehlende kontrollierte Daten

MAIC-Analyse (Obe-cel vs. IO und BLI) für OS und EFS

naiver Vergleich für PON

Ergebnisse jedoch vertraulich

The MAH has conducted a systematic literature search for the treatment of r/r B-ALL patients 26 years and older. Reasons for exclusion comprised not reporting of relevant outcomes or other settings and populations [37].

Due to the absence of individual patient data[7] in comparator studies and the uncontrolled design of FELIX, only unanchored population-adjusted indirect comparisons were feasible. The MAIC process involved reweighting individual patient data from the FELIX study (n=94) using propensity score weighting to align baseline characteristics with those reported in the comparator studies. For each comparison, weights were applied to FELIX data to match the baseline distribution of prognostic factors and treatment effect modifiers reported in the INO-VATE, TOWER, and PACE studies. The quality and reliability of this matching process were assessed through the effective sample size (ESS). However, the matching was significantly limited by missing data in the comparator studies [37]. The MAIC analyses estimated the relative effectiveness of obe-cel compared with IO and BLI for OS and EFS. For ponatinib, naïve unadjusted comparison was implemented due to poor study overlap and small sample size. The MAIC and naïve comparison results were considered confidential by the MAH [37].

[6] MAICs adjust individual patient data from one study to match aggregate baseline characteristics of another, enabling indirect comparison of treatments in the absence of direct comparative trials.

[7] Only aggregated data (e.g., mean values, percentages) are available hindering a precise adjustment)

4.4.2 Study and patient characteristics

The three comparator studies identified for the indirect treatment comparison differed in design, patient populations, and available baseline characteristics. Table 4-9 summarises the key study features and patient demographics across INO-VATE [47], TOWER [45] and PACE [48].

Table 4-9: Study and patient characteristics of the comparator studies

Study	INO-VATE [47]	TOWER [45]	PACE [48]
Study design	Phase 3 open-label controlled trial	Phase 3 open-label controlled trial	Phase 2 open label single-arm trial
Intervention/Comparison	IO/intensive chemotherapy	BLI/chemotherapy	PON
Total n of patients (Intervention vs Comparison)	326 (164 vs 162)	376 (271 vs 105)	32
Primary endpoints	PFS, OS	EFS, OS	PFS, OS
Median age in yrs	46.5	41.0	62
% of pts receiving previous therapy	1 prior line: 67.7% 2 prior lines: 31.1%	1 prior line: 42% 2 prior lines: 33.6% 3 prior lines: 16.6% > 3 prior lines: 7.8%	TKI exposure: ≤2: 37.5% ≥3: 37.5%
% of pts receiving previous SCT	17.7%	34.7%	28.1%
ECOG performance status	0: 37.8% 1: 49.4% 2: 12.8%	0: 35.4% 1: 49.4% 2: 15.1%	0: 31.9% 1: 42.6% 2: 25.5%
% of pts with bone marrow blasts <50%	32.3%	25.5%	NR

Note: in the TOWER study only Ph- pts, and in the PACE study only Ph+ pts were inlcuded

Abbreviations: BLI … blinatumomab, ECOG … Eastern Cooperative Oncology Group, EFS … event-free survival, IO … inotuzumab ozogamicin, n … number, NR … not reported, OS overall survival, PON … ponatinib, PFS … progression-free survival, pts … patients, SCT … stem cell transplantation, TKI … tyrosine kinase inhibitor, yrs … years

4.4.3 Efficacy results

ereignisfreies Überleben: bessere Ergebnisse nach Obe-cel verglichen mit IO, BLI und PON

In the modified ITT population[8], while unadjusted[9] hazard ratios significantly favoured obe-cel over IO for EFS, adjusted results lost statistical significance. For Ph- patients, both adjusted and unadjusted hazard ratios showed significantly better results for obe-cel over BLI. Similarly, in Ph+ patients, obe-cel achieved statistically significant advantages over PON in both ad-

[8] The modified ITT includes all patients who received at least one infusion of treatment, rather than all enrolled patients. This excludes patients who were enrolled but never received the intervention due to manufacturing failures, death, or other reasons before treatment.

[9] An unadjusted analysis refers to raw, direct comparisons of outcomes between groups without statistical correction for patient differences, compared to the adjusted analysis, where differences like age, prior treatments and disease severity are mathematically corrected.

justed and unadjusted analyses. While specific numerical results remain confidential, the analysis consistently demonstrated favourable EFS outcomes for obe-cel across all comparisons. [37].

höhere Gesamtüberlebensrate nach Obe-cel-Infusion

OS results were similar to EFS findings: The unadjusted comparison in the modified ITT population showed significant benefits for obe-cel versus IO, though adjusted results were non-significant [37]. In Ph- population, statistically significant advantages were demonstrated for obe-cel over BLI in both analyses. For Ph+ patients, while unadjusted comparisons significantly favoured obe-cel over PON, adjusted results were not statistically significant.

Daten zur Lebensqualität, jedoch vertraulich

In addition, NICE also received confidential QoL data, indicating an effect of obe-cel in improving patients' health-related quality of life (HRQoL) within 24 months. This outcome was not part of the ITC [37].

4.4.4 Separate safety analysis

EAG kritisierte unvollständige Erfassung schwerer Nebenwirkungen

For the AEs, the MAH derived the incidence from individual comparator trials [37]. However, the EAG contracted by NICE raised concerns about the MAH's AE reporting, noting the exclusion of critical events such as ICANS. The EAG preferred, including all grade 3 or higher treatment-emergent AEs for the total infused population from the clinical study report.

besseres Sicherheitsprofil von Obe-cel verglichen mit anderen CAR-T-Zelltherapie und Immuntherapien

Based on the safety comparison, NICE concluded that obe-cel has an improved safety profile over existing CAR T cells and immunotherapies in ALL [37]. A separate safety comparison with brexu-cel based on the data from the ZUMA-3 trial (not included in the ITC) showed that after brexu-cel infusion, grade ≥3 CRS and grade ≥3 ICANS occurred in 23.6% and 25.5% of participants, respectively, in contrast to 2.4% and 7.1% of patients treated with obe-cel in the FELIX trial [49]. Immunotherapies also present significant toxicities. For example, veno-occlusive disease grade ≥3 occurred in nine per cent of patients after treatment with IO [47], and five per cent of patients experienced grade ≥3 CRS after receiving BLI [45].

4.4.5 Conclusion

NICE bewertet MAIC-Ergebnisse als stark unsicher aufgrund der kleinen Stichprobe

NICE concluded that the unanchored MAIC analysis demonstrated favourable outcomes for obe-cel compared to established therapies (IO, BLI, and PON) in terms of EFS and OS. However, the analysis revealed significant methodological limitations, particularly regarding population overlap between studies. This refers to the fundamental differences in patient characteristics between the FELIX study and comparator trials – when populations are too dissimilar in terms of age, disease severity, or treatment history, statistical adjustments cannot adequately balance these differences, making indirect comparisons unreliable. The ESS was critically small when matched to PON, indicating poor baseline characteristics overlap, unstable results and a high uncertainty [36].

5 Price comparisons, treatment costs and budget impact

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) were unable to identify a price for obe-cel for the countries queried (EU-14, Norway and the United Kingdom).

GÖG: kein Obe-cel-Preis identifiziert für EU, UK & Norwegen

For Austria, the marketing authorisation holder (MAH) did not submit a dossier; therefore, no price information is available. Given the absence of manufacturer submissions, we employed complementary approaches to assess the economic aspects of obe-cel reimbursement: (1) international economic evidence from the National Institute for Health and Care Excellence (NICE), and (2) Austrian cost comparison analysis as an alternative to budget impact analysis.

kein Dossier vom Unternehmen für Ö eingereicht, daher Analyse internationaler Ergebnisse & eigene Kostenanalyse für Ö

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmacoeconomic model

The MAH did not submit any dossier, nor any pharmacoeconomic model for obe-cel for Austria.

kein Model für Ö übermittelt

5.1.2 Economic evaluation based on published pharmacoeconomic model

We identified a pharmacoeconomic evaluation of Obe-cel in an HTA report [37] from the NICE, describing an economic analysis submitted by the MAH. An External Assessment Group (EAG), represented by the Birmingham Centre for Evidence and Implementation Science, was tasked by NICE to prepare an assessment of this analysis.

pharmakoökonomische Model vom Unternehmen bewertet durch NICE (UK, 2025)

Characteristics of the economic evaluation and applied model

The pharmacoeconomic cost-utility analysis (CUA) from the MAH implemented a partitioned-survival model to estimate the long-term costs and outcomes of treatments for relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B-ALL). The model was based on a payer's perspective from the National Health Service (NHS) England and Personal Social Services (PSS), considering direct healthcare costs.

Kosten-Nutzwertanalyse, Zahlerperspektive des NHS-Englands und des PSS

The model included three mutually exclusive health states: event-free, post-event, and death, where 'event' represented either treatment failure or morphological relapse.

3 Gesundheitszustände: eventfrei, post-Event, Tod

The population was derived from the FELIX study [44] investigating obe-cel in phase 1b for safety (cohorts 1A, 1B) and phase 2 for efficacy (cohorts 2A, 2B). Specifically, the modified intention-to-treat (mITT) population from the FELIX cohort 2A study served as the basis for all comparisons, which included patients who had received at least one obe-cel infusion. Patients who were alive at three years were assumed to be cured, and this cure assumption was applied to all treatment arms in the model.

Felix-Studie (Obe-cel): Population (mITT, Kohorte 2A) als Vergleichsbasis; Heilungsannahme (3 Jahre) in allen Behandlungsarmen

For the comparative clinical data, the MAH utilised an indirect treatment comparison (ITC) of obe-cel with inotuzumab ozogamicin (IO), blinatumomab (BLI) and ponatinib (PON) (see Chapter 4.4.).

ITC (MAIC/naiv) von Obe-cel vs. IO, BLI, PON

In the base case scenario, the MAH used a bottom-up costing approach for obe-cel administration, including hospitalisation and intensive care unit (ICU) costs, based mainly on predicted resource use derived from the FELIX clinical trial data.

Kostenansatz (bottom-up) für Obe-cel, basierend auf Ressourcennutzung in der FELIX-Studie

For the model, it was assumed that patients in the comparator arms could receive subsequent allogeneic stem cell transplant (allo-SCT) after treatment failure and excluded this possibility for the obe-cel arm. Additionally, immunoglobulin (IG) costs for hypogammaglobulinaemia adverse events (AEs), which were assumed to be zero in the comparator arms, were slightly higher for obe-cel.

Modellannahmen: Allo-SZT nach Therapie-versagen nur für Komparatoren; IG-Kosten höher für Obe-cel

A discount rate of 3.5% per cycle was applied for both costs and outcomes expressed as quality-adjusted life years (QALYs). In addition, the MAH assumed that obe-cel met the criteria for a 1.7 severity modifier, applied in NICE assessments for life-threatening or severely debilitating conditions, adjusting the weight of incremental QALYs across all analyses regardless of population and comparator. The use 1.7 severity modifier resulted in an increase of willingness-to-pay (WTP) threshold from £30,000 to £50,000.

3,5 % Diskontsatz für Kosten und QALYs; für Obe-cel: 1,7 Schweregrad-Modifikator – erhöhter WTP (£ 50.000)

A detailed characterisation of the pharmacoeconomic model is in Chapter 5 of the Appendix.

Limitations of the pharmacoeconomic model

The EAG described several issues with the submitted pharmacoeconomic model from the MAH. The key limitations are described here:

EAG identifiziert Limitationen des Modells:

- The EAG preferred an ITT population from both cohorts 1A and 2A. Furthermore, they argued that the FELIX trial may not accurately reflect the NHS population due to its lower proportion of people aged 65 and above and the exclusion of individuals with an ECOG performance status of 2 or higher, compared to NHS patients.

  EAG: ITT (1A/2A) bevorzugt; FELIX-Studie nicht repräsentativ für NHS (Alter, ECOG)

- The EAG preferred the latest NHS England CAR T-cell tariff cost of £60,462, which includes comprehensive costs for leukapheresis, delivery, in-hospital AEs, monitoring, and training, compared to the MAH's bottom-up costing approach.

  EAG bevorzugt NHS CAR-T-Zelltherapie-Tarif (£60.462) inkl. umfassender Kosten vs. MAH Bottom-up-Ansatz

- The EAG challenged the MAH's assumption that no obe-cel patients would receive allo-SCT, arguing that obe-cel has dual potential as both curative therapy and bridging therapy to allo-SCT. The EAG estimated that approximately 10% of patients would receive obe-cel as bridging therapy to allo-SCT.

  MAH-Annahme zu allo-SZT; Obe-cel als kurative/Überbrückungstherapie (ca. 10 %)

- According to the EAG, the proportion of people who had intravenous (IV) IG and the duration of treatment were underestimated. Thus, the EAG requested the MAH to update the scenarios accordingly.

  IV IG-Anteil und Behandlungsdauer unterschätzt

- The EAG preferred a standard per-year discount rate of 3.5% instead of MAH's per-cycle discount rate.
- The MAH's base case scenario failed to capture the utility impacts of allo-SCT. Therefore, the EAG adjusted utility values in the post-event health state using time-dependent utilities from previous technology appraisals better to reflect the changes in post-transplant quality of life.
- For modifying the weight of QALYs, the EAG reported a 1.2 severity modifier to be more appropriate.

jährlichen Diskontsatz (3,5 %) statt MAH-zyklischem Satz

MAH-Basis-Szenario ohne allo-SCT-Nutzen

EAG: 1,2 Schweregrad-Modifikator für QALYs angemessener

Additionally, both the MAH and the EAG implemented the cure assumption rate of three years, explained above. The NICE committee criticised this since it was questionable to assume that people who had experienced disease events could be considered "cured" and share the same standardised mortality ratio (SMR) as people who remained "event-free".

MAH/EAG: 3-Jahres-Heilungsannahme; NICE-Kritik (Frage zur „Heilung" nach Ereignissen, gleiches SMR)

The summary of MAH's and EAG's base case assumptions is depicted in Chapter 5 of the Appendix.

Results of the economic evaluation and applied model

The base case results from the MAH were presented using the list price for all comparators, as well as both the list price and confidential discounted Patient Access Scheme (PAS) price for obe-cel. Incremental costs were deemed confidential and therefore redacted from the NICE-HTA report; however, incremental QALYs were reported.

MAH-Basis-Szenario: Listenpreise vs. PAS-Preis; inkrementelle Kosten vertraulich – inkrementelle QALYs berichtet

Regarding the incremental QALYs, in the MAH model (using a severity modifier of 1.7), obe-cel generated an additional 2.88 QALYs compared to IO in the overall population ([35], p. 178). In the Ph- sub-population, obe-cel resulted in an additional 5.08 QALYs compared to BLI and an additional 2.15 QALYs compared to IO. In the Ph+ subpopulation, when compared with PON, obe-cel produced an additional 11.04 QALYs.

inkrementelle QALYs: Gesamt: +2,88 vs. IO; Ph- +5,08 vs. BLI, +2,15 vs. IO; Ph+ +11,04 vs. PON

Details of the incremental costs analysis were deemed confidential; consequently, the resulting incremental cost effectiveness ratios (ICERs) are not publicly available. Nevertheless, the expected cost outcomes in relation to each comparator were reported in terms of cost savings/additional costs and are displayed in Table 5-1 below.

Kosten (MAH-Modell): Obe-cel Listenpreis führt zu Einsparungen vs. IO und Mehrkosten vs. PON/BLI

PAS-Preis: Einsparungen vs. IO, Mehrkosten vs. BLI/PON

ICER vertraulich

Table 5-1: Base case results of the marketing authorisation holder model

Base-case results using obe-cel list price (£372,000)	
Obe-cel vs IO in full population	Additional costs*
Obe-cel vs IO in Ph- population	Additional costs*
Obe-cel vs IO in Ph+ population	Cost savings*
Obe-cel vs BLI in Ph- population	Additional costs*
Obe-cel vs PON in Ph+ population	Additional costs*
Base-case results using obe-cel Patient Access Scheme (PAS) price	
Obe-cel vs IO in full population	Cost savings*
Obe-cel vs IO in Ph- population	Cost savings*
Obe-cel vs IO in Ph+ population	Cost savings*
Obe-cel vs BLI in Ph- population	Additional costs*
Obe-cel vs PON in Ph+ population	Additional costs*

** ICERs of the MAH model were confidential.*
Abbreviations: ICERs … incremental cost effectiveness ratios, MAH … marketing authorisation holder

Due to the identified limitations of the MAH model (explained above), the EAG re-ran the MAH's base case analysis utilising adjusted conservative assumptions. This re-analysis led to different overall results. A reduction in QALYs gained by obe-cel treatment was observed across all comparisons. Detailed results are presented in Chapter 5 of the Appendix. In addition, the EAG's base case analysis using the PSA price resulted in an ICER exceeding the WTP threshold of £30,000 per QALY gained across all populations and against all comparators.

EAG angepasste Annahmen:
ICER über £ 30.000/QALY Zahlungsbereitschaft für alle Populationen und Vergleiche

The deterministic sensitivity analysis of the MAH model showed that the most sensitive parameters were the proportion of IO patients receiving allo-SCT, the IO allo-SCT cost per cycle, the allo-SCT initial treatment cost, the OS standard parametric coefficients, the EFS standard parametric coefficients, the SMR, the proportion of PON patients receiving allo-SCT, and the EFS flexible parametric coefficients.

zahlreiche Parameter mit Einfluss auf finalen ICER

Conclusion on the pharmacoeconomic model

In conclusion, based on the EAG's assessment of the MAH's submitted pharmacoeconomic model, NICE emphasised essential uncertainties in the clinical effectiveness and the modelling. It noted that more evidence was needed to generate robust cost-effectiveness estimates. Overall, it could not be concluded that obe-cel would be cost-effective and hence NICE did not recommend obe-cel for r/r B-ALL in their draft guidance.

NICE-Fazit (basierend auf EAG): Obe-cel nicht kosteneffektiv, daher von NICE für r/r B-ALL nicht empfohlen

Moreover, the transferability of the NICE pharmacoeconomic model results to the Austrian context is significantly limited due to fundamental healthcare system differences. The UK-specific payer perspective (NHS England and Personal Social Services) differs substantially from Austrian healthcare financing and reimbursement mechanisms. Additionally, the model's population characteristics and treatment assumptions may not represent Austrian epidemiological patterns and clinical practices. Finally, Austria lacks an established willingness-to-pay threshold, making ICER interpretations problematic, unlike the UK's defined £30,000–£50,000 per QALY thresholds. These limitations necessitate substantial model adaptations with Austrian-specific cost inputs, treatment pathways, and utility values rather than direct extrapolation of UK results for meaningful Austrian healthcare decision-making.

UK-Modell nicht auf Ö Kontext übertragbar

The detailed results of the MAH's and EAG's CUA are presented in the Appendix Chapter 5.

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the manufacturer

The MAH submitted neither a dossier, nor a budget impact analysis (BIA) for obe-cel.

keine Budgetfolgen-Analyse eingereicht

5.2.2 Austrian cost analysis

Eligible patients and per-patient costs

In Austria, there are approximately 42 adult patients with B-ALL ≥26 years of age, of which clinicians estimate that around 40–50% might be refractory or in a relapse [18], which would result in 17 to 21 patients per year who could be eligible for obe-cel treatment. However, the number of indicated patients for obe-cel treatment is expected to be initially lower and rise only gradually, based on the practical clinical experience with the treatment: from one to five patients indicated in the first years up to a maximum of 10 patients in the subsequent years.

individuelle B-ALL-Therapieentscheidung → eventuell nur 1 Pat. für das 1. Jahr für Obe-cel ausgewählt

Given that the selection of a specific SoC treatment regimen in this indication depends on individual patient characteristics (see a detailed description of the B-ALL SOC in Chapter 1.2) and considering the small eligible patient population for CAR T-cell therapy, this Austrian cost analysis provides per-patient estimates of direct medical costs. The analysis covers obe-cel and each identified SoC treatment used in Austrian clinical practice for adult r/r B-ALL.

individualisierte Therapieentscheidungen und einzelne geeignete Pat. → Analyse zeigt Kosten pro Pat.

The per-patient costs are presented as minimum costs and maximum costs. The reduced costs, corresponding to the minimum (MIN) scenario, are anticipated for patients with low disease burden who do not require bridging interventions and experience no treatment-related serious adverse events necessitating ICU admission. In contrast, elevated costs, corresponding to the maximum (MAX) scenario, are expected when managing patients who develop complications during any treatment phase.

präsentierte Kostenspanne von minimal bis maximal

Direct medical costs of the obe-cel treatment

The total cost of obe-cel treatment shall encompass all the crucial elements of CAR T-cell therapy delivery: leukapheresis, bridging therapy, lymphodepleting conditioning, obe-cel acquisition costs and inpatient hospitalisation, as well as the costs related to long-term follow-up [30]. Below, we report the details of deriving the direct medical costs of obe-cel treatment.

direkte medizinische Kosten einer Obe-cel-Therapie

Acquisition cost of obe-cel (AUCATZYL®)

Currently, there is no Austrian list price proposal for obe-cel available from the MAH. Nevertheless, we identified two relevant MAH price estimates: €380,000 in Germany, excluding value-added tax (VAT) [50] and approximately €430,000 in the UK[10] [37].

geschätzte internationale Listenpreise für Obe-cel: € 380.000 (Deutschland) bis € 430.000 (UK)

Hospitalisation costs

The duration of hospitalisation is determined by the expected onset and duration of AEs following the obe-cel infusion, i.e., the short-term complications that arise within 28 days after the treatment. Most AEs can be resolved at a haemato-oncological unit. However, potentially life-threatening AEs of grade ≥3, particularly CRS and ICANS, require the transfer to the ICU [30]. For the MIN cost scenario, we assumed 14 days of hospitalisation in a haemato-oncological unit based on the FDA drug information [24], and no ICU stay. Conversely, for the MAX inpatient cost scenario, we adopted a more conservative assumption based on NICE's assessment, applying a 24-day hospital stay duration unit [37], with 5.5 of these days spent in the ICU, reflecting the median duration of an ICU stay in the FELIX study [44]. Furthermore, we added five days of hospitalisation at a haemato-oncological unit arising from a prior lymphodepleting procedure to both scenarios. As a result, the hospitalisation costs range from MIN of €50,730 to MAX €81,445.

Obe-cel-Krankenhauskosten je nach Aufenthaltsdauer: zwischen € 50.730 und € 81.445

Pre-treatment costs

All patients who receive obe-cel treatment must undergo prior bone marrow assessment, leukapheresis, and lymphodepleting conditioning consisting of fludarabine (30 mg/m^2/day intravenously (IV) for four days) and cyclophosphamide (500 mg/m^2/day IV for two days) [24]. This results in total pre-treatment costs of €30,412 (*no variations to be expected*).

Vorbehandlungskosten betragen € 30.412

Bridging therapy costs

Between leukapheresis and lymphodepletion, bridging therapy is needed for most patients awaiting obe-cel infusion. In the FELIX trial, some form of bridging therapy was used in 92.9% of infused patients. The therapeutic agents used for bridging purposes in the trial included vincristine, cyclophosphamide, methotrexate, mercaptopurine, cytarabine, fludarabine, ponatinib, IO, and dexamethasone; the choice depended on the investigator's preference and local practice [37]. However, the Austrian clinical experts could not reliably determine which agents would be most likely used in clinical practice; therefore, considering bridging therapy costs in this analysis was not possible. Nevertheless, in the published MAH model submission to NICE, it was revealed that the cost of bridging therapy in the UK is assumed to vary from £4,242 to £6,284 [37].

aufgrund der individualisierten Therapieentscheidungen, Kosten für Überbrückungstherapien nicht berücksichtigt

für UK: Kosten zwischen £ 4.242 und £ 6.284 geschätzt

Long-term management costs

Longer-term side effects of a CAR T-cell therapy include an increased risk of infection in some patients with hypogammaglobulinaemia and prolonged B-cell aplasia. Patients with recurrent infections often receive immunoglobulin replacement therapy administered IV every month, typically in a hospital setting. However, similar to the NICE committee [37], we could not reliably

ebenso keine langfristigen Folgekosten berücksichtigt

[10] Reported as £372,000 price for NICE, converted to € on 23.07.2025 using European Central Bank rate, rounded upwards to nearest thousand.

determine the average duration of IG therapy; therefore, we did not consider these costs in the analysis.

The overall direct medical costs of an obe-cel treatment in Austria (excluding bridging therapy and follow-up treatment costs) are expected to range from MIN €461,142 to MAX €541,857. The breakdown of the costs is detailed in Table 5-2.

Obe-cel Gesamtkosten pro Pat. (exkl. Kosten von Überbrückungstherapie & Folgekosten):
€ 461.142 bis € 541.857

Table 5-2: Direct medical costs of obe-cel treatment per patient

Cost items	MIN	MAX
Obe-cel acquisition cost per patient		
AUCATZYL® list price estimations	€380,000	€430,000
Obe-cel administration costs per patient	€50,730	€81,445
Hospitalisation at a haemato-oncological unit, including the treatment of acute AEs[1]	€50,730	€62,745
ICU hospitalisation costs[2]	-	€18,700
Pre-treatment costs per patient	€30,412	€30,412
Bone marrow assessment (LKF data)	€10,345	€10,345
Leukapheresis (LKF data)	€18,046	€18,046
Lymphodepleting conditioning (based on EFP)	€2,021	€2,021
Bridging therapy	Not included due to lack of data	
Post-treatments per patient		
Long-term AE management: outpatient immunoglobulin IV after obe-cel	Not included due to lack of data	
Total direct medical costs of obe-cel treatment (excl. briding therapy and follow-up costs) per patient	€461,142	€541,857

Notes:

[1] *Cost estimation for an inpatient stay (1 night) based on LKF-data.*

[2] *Cost estimation for an ICU stay (1 night) based on LKF-data.*

Abbreviations: AE … adverse events, EFP … ex-factory price, ICU … intensive care unit, IV … intravenous, LKF … Leistungsorientierte Krankenanstaltenfinanzierung, NA … not applicable, obe-cel … obecabtagene autoleucel

Direct medical cost of the Austrian standard of care options for patients with r/r B-ALL

Brexucabtagene autolecel (brexu-cel)

Brexu-cel is the only other CAR T-cell product approved in the EU for the treatment of patients with the same indication as obe-cel [22].

2. in Europa zugelassene CAR-T-Zelltherapie: Brexu-cel

Acquisition cost

According to the hospital association of Vienna, the official list price of TECARTUS® in Austria is €327,000.

offizieller Ö Listenpreis für Tecartus®: € 327.000

Hospitalisation costs

Equivalent to obe-cel, the MIN hospitalisation costs for brexu-cel are €50,730, assuming a 14-day stay in a haemato-oncological department and no ICU stay. In contrast, the MAX inpatient costs were based on the results from the ZUMA-3 trial, the pivotal trial for brexu-cel in the B-ALL indication [51], which reported a median duration of hospitalisation of 22 days and five ICU days. This setting results in hospitalisation costs of € €75,740. Five additional days of hospitalisation at a haemato-oncological unit were added to both scenarios to account for the lymphodepleting procedure stay.

Brexu-cel-Krankenhauskosten je nach Aufenthaltsdauer: zwischen € 50.730 und € 75.740

However, a less favourable toxicity profile of brexu-cel in comparison to obe-cel should be considered. In the ZUMA-3 trial, CRS occurred in 89% of patients (24% with grade ≥3), with a median duration of 7.5 days in the ICU [51]. By contrast, in the FELIX trial, CRS occurred in 68.5% of patients (2.4% with grade ≥3), with a median duration of 5 days in the ICU [52]. Consequently, the MAX cost scenario arising from the need for prolonged hospitalisation is more likely to be observed in patients treated with brexu-cel than with obe-cel.

Krankenhauskosten pro Pat. unterschätzen den gesamten Kosteneffekt nach Brexu-cel, da ca. ¼ der Pat. an Grad ≥3 CNS leiden

Pre-treatment costs

Given the standardisation of CAR T-cell therapy management, we assumed that the same pre-treatment applies to both brexu-cel and obe-cel (€30,412).

Vorbehandlungskosten betragen € 30.412

Bridging therapy and long-term AE management

Similar to obe-cel, as there are no Austrian data about bridging therapies before and follow-up treatments after brexu-cel, we did not include these costs in the analysis.

Kosten von Überbrückungstherapien & Nachbehandlungen nicht berücksichtigt

Based on all these cost categories, the overall direct medical costs per patient for brexu-cel treatment (excluding bridging therapy and follow-up treatment costs) are expected to range from €408,142 to €433,152. Disaggregated cost breakdown is available in Table 5-3.

Brexu-cel Gesamtkosten pro Pat. (exkl. Kosten von Überbrückungstherapie & Folgekosten): € 408.142 bis € 433.152

Table 5-3: Cost of brexu-cel treatment per patient

Cost items	MIN	MAX
Acquisition cost per patient		
Brexu-cel official list price Austria	€327,000	€327,000
Administration costs per patient	€50,730	€75,740
Hospitalisation at a haemato-oncological unit, including the treatment of acute AEs[1]	€50,730	€58,740
ICU hospitalisation costs[2]	-	€17,000
Pre-treatment costs per patient	€30,412	€30,412
Bone marrow assessment (LKF data)	€10,345	€10,345
Leukapheresis (LKF data)	€18,046	€18,046
Lymphodepleting conditioning (based on EFP)	€2,021	€2,021
Post-treatments per patient		
Long-term AE management: outpatient immunoglobulin IV after brexu-cel	not considerable because no data	
Total direct medical costs of brexu-cel treatment (excl. briding therapy and follow-up costs) per patient	€408,142	€433,152

Notes:

[1] *Cost estimation for an inpatient stay (1 night) based on LKF-data.*
[2] *Cost estimation for an ICU stay (1 night) based on LKF-data.*
Abbreviations: AE … adverse events, EFP … ex-factory price, ICU … intensive care unit, IV … intravenous, LKF … Leistungsorientierte Krankenanstaltenfinanzierung, brexu-cel … brexucabtagene autoleucel

Blinatumomab (BLI)

direkte medizinische Kosten von BLI

The total cost of BLI treatment presented encompasses the cost categories of immunotherapies, including the acquisition and administration costs. According to the clinical expert, cost-relevant AE management is rare; thus, these costs were not considered in the analysis.

Acquisition costs

höhere Dosierung ab der 2. Hälfte des 1. Zykluses

The dosing used for the acquisition costs of BLI was extracted from the Blincyto® summary of product characteristics [53]. Each treatment cycle comprises 28 days of continuous infusion followed by a 14-day treatment-free interval. Dosing is 9µg/day for the first seven days of cycle 1, then 28µg/day for the remainder of the cycle and all subsequent cycles.

Produktkosten abhängig von der Zyklusanazahl: € 105.243 (2 Zyklen) bis € 279.726 (5 Zyklen)

Patients with r/r B-ALL are initially treated for two cycles, with patients achieving CR after two treatment cycles being eligible for up to three additional consolidation cycles based on an individual benefit-risk assessment. Hence, two cycles, applicable to non-responders and corresponding to 38 vials (17 in cycle 1 plus 21 in cycle 2), served as the basis for calculating MIN acquisition cost of BLI. In contrast, five cycles, applicable to responders and corresponding to 101 vials (17 in cycle 1, plus 84 in subsequent ones), served as the basis for calculating MAX acquisition costs [22]. Consequently, drug acquisition costs of BLI, derived from ex-factory prices (Fabrikabgabepreise, FAP), range from €105,243 to €279,726.

Administration costs

Administrationskosten (10 Tage stationär, danach tagesklinisch) variieren zwischen € 16.917 und € 30.449

Concerning the administration costs, patients are assumed to be administered on an inpatient basis for the first 10 days of the first cycle; after that, BLI is administered intravenously on an outpatient basis via a home-infusion pump, for which a new bag is required every three days [37]. Patients visit the daycare clinic for every bag change. As a result, the administration costs of BLI are expected to range from €16,917 to €30,449, with fixed first-cycle administration costs (inpatient + outpatient) of €10,151.

BLI-Gesamtkosten pro Pat.: € 132.506 bis € 320.519

Overall, the direct medical costs per patient treated with BLI are expected to range from €132,506 (2 cycles) to €320,519 (5 cycles), see Table 5-4 for detailed presentation.

Table 5-4: Direct medical costs of blinatumomab treatment per patient

Costs items	MIN	MAX
Acquisition costs of blinatumomab per patient	€105,243	€279,726
First cycle (based on EFP)	€47,083	€47,083
Subsequent cycles (based on EFP; MIN: 1, MAX: 4)	€58,161	€232,643
Drug administration costs per patient	€16,917	€30,449
Hospitalisation at oncological unit – first cycle[1]	€5,923	€5,923
Hospital outpatient clinic – first cycle[2]	€4,228	€4,228
Hospital outpatient clinic – subsequent cycles[2]	€6,765	€20,297

Costs items	MIN	MAX
Pre-treatment costs per patient		
Bone marrow assessment (LKF data)	€10,345	€10,345
Cost-relevant long-term AEs	NA	NA
Total direct medical costs of BLI treatment per patient	€132,506	€320,519

Notes:
[1] *Cost estimation for an inpatient stay (1 night) based on LKF-data.*
[2] *Cost estimation for a day at the hospital outpatient clinic based on LKF-data.*
Abbreviations: AE … adverse events, BLI … blinatumomab, EFP … ex-factory price, LKF … Leistungsorientierte Krankenanstaltenfinanzierung, NA … not applicable

Inotuzumab ozogamicin (IO)

direkte medizinische Kosten von IO

The total cost of IO treatment presented encompasses the cost categories of immunotherapies, including the acquisition and administration costs. According to the clinical expert, cost-relevant AE management is rare; thus, these costs were not considered in the analysis.

Acquisition costs

Dosierung von IO abhängig von der Ansprechrate

The dosing of IO used for the cost calculation was taken from the recommended posology of Besponsa® [54]. In the first cycle, 1.8mg/m² is delivered in total, split as 0.8mg/m² (day 1), 0.5mg/m² (day 8), and 0.5mg/m² (day 15) over 3 weeks (extendable to four weeks for CR/CRi or toxicity recovery). Subsequent cycles depend on response: CR/CRi patients receive 0.5mg/m² on days 1, 8, and 15, while non-responders continue the original 0.8/0.5/0.5mg/m² regimen.

Produktkosten abhängig von der Behandlungsdauer: € 69.790 bis € 199.400

The possible treatment duration is two to six cycles, with two recommended for patients proceeding to allo-SCT. Any patient who does not achieve a CR/CRi within three cycles should discontinue treatment [54]. Based on these assumptions, drug acquisition costs of IO can range from €69,790 to €199,400, with the fixed first-cycle component amounting to €39,880 (calculated using FAP).

Administration costs

Administrationskosten (tagesklinisch) liegen zwischen € 5.074 und € 15.223

In Austria, IO is administered in outpatient hospital clinics, resulting in administration costs arising only in relation to IV infusions. Depending on the number of cycles, total administration costs can range from €5,074 to €15,223, with one cycle component amounting to €2,537 [37].

IO-Gesamtkosten pro Pat.: € 85.209 bis € 224.968

Overall, the direct medical costs per patient related to IO treatment are expected to be MIN €85,209 vs MAX €224,968 (see Table 5-5-5).

Table 5-5: Cost of inotuzumab ozogamicin treatment per patient

Cost items	MIN	MAX
Acquisition cost of inotuzumab ozogamicin per patient	€69,790	€199,400
First cycle (based on EFP)	€39,880	€39,880
Subsequent cycles (based on EFP; MIN: 1 with CR, MAX: 5 with no CR)	€29,910	€159,520
Administration costs per patient	€5,074	€15,223
Hospital outpatient clinic – first cycle[1]	€2,537	€2,537

Cost items	MIN	MAX
Hospital outpatient clinic – subsequent cycles (MIN: 1, MAX: 5)[2]	€2,537	€12,685
Pre-treatment costs per patient		
Bone marrow assessment (LKF data)	€10,345	€10,345
Cost-relevant long-term AEs	NA	NA
Total direct medical costs of IO treatment per patient	€85,209	€224,968

Notes:

[1] *Cost estimation for an inpatient stay (1 night) based on LKF-data.*

[2] *Cost estimation for a day at the hospital outpatient clinic based on LKF-data.*

Abbreviations: AE … adverse events, CR … complete response, IO … inotuzumab ozogamicin, EFP … ex-factory price, LKF … Leistungsorientierte Krankenanstaltenfinanzierung, NA … not applicable

Tyrosine kinase inhibitor treatment for PH+ patients

häufigste TKI in Ö: Ponatinib

For patients with Ph+ r/r B-ALL, a tyrosine kinase inhibitor (TKI) is a routine part of treatment, typically as an add-on to immunotherapy [55]. Clinical experts confirmed that the most commonly used TKI in r/r B-ALL is the third-generation TKI ponatinib (PON) [20]. It is administered orally at a dose of 45mg per day, and a pack containing 30 x 45mg tablets costs €5,775.46.

According to summary of product characteristics of Iclusig®, discontinuation should be considered if a complete haematologic response has not occurred by 90 days [56]. Hence, for the MIN acquisition cost of TKI treatment, we assume that the Ph+ patients are treated with PON for three months. For the MAX acquisition cost, we assume that Ph+ patients are treated with PON for the whole year.

Produktkosten der TKI liegen je nach Behandlungsdauer zwischen € 17.326 und € 69.305

Given the outpatient administration of TKIs and their primary use as add-on treatment in the r/r setting, additional administrative and follow-up treatment costs were not considered in the analysis. Consequently, the overall per-patient cost of TKI treatment ranges from €17,326 to €69,305. Table 5-6 presents the TKI costs in detail.

Table 5-6: Cost of TKI treatment per patient

Cost items	MIN	MAX
Drug acquisition cost per patient		
Ponatinib	€17,326	€69,305
Administration costs	NA	NA
Costs of relevant long-term AEs	NA	NA
Total direct medical costs of TKI treatment per patient	€17,326	€69,305

Abbreviations: AE … adverse event, NA … not available, TKI … tyrosine kinase inhibitor

Allogeneic stem-cell transplantation

Großteil der Pat. benötigt eine Konsolidierung der allo-SCT

bei älteren Pat. wird eine reduzierte Intensität der allo-SCT angewendet

The allo-SCT process generally consists of conditioning pre-treatment, followed by an infusion of healthy stem cells from either a related or unrelated donor. The conditioning therapy involves high doses of chemotherapy and/or immunotherapy agents with optional radiation therapy, and it is employed to achieve a lower MRD load (or MRD negativity) before the transplant [17]. Reduced-intensity allo-SCT may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy and/or radiation used in preparation for a standard transplant [20].

Kosten für die allo-SZT liegen zwischen € 134.590 und € 212.243, abhängig von der Art des Spenders und der Intensität des Verfahrens

The lowest and highest cost allo-SCT procedures in the Austrian LKF catalogue represent our MIN and MAX scenarios. The least costly option corresponds to allo-SCT with reduced conditioning therapy without implant purchase (related donor), costing €134,590. Conversely, the most complicated and thus costly instance of allo-SCT implements high-dose/aplastic conditioning therapy with implant purchase (unrelated donor), resulting in a cost of €212,243.[11]

[11] It remains unclear from the LKF data which services are included in the costs. Thus, e.g., follow-up costs might need to be added on top.

In addition, donor lymphocyte infusions (DLI) are a widely employed strategy to increase the graft-versus-tumor (GvT) effect of allo-SCT and/or to sustain donor engraftment following the allo-SCT. It can be indicated for some patients treated in Austria for prophylactic, pre-emptive and/or therapeutic use after allo-SCT [57]. In line with Serpenti et al. [58], we assumed the median number of four DLIs in the MAX cost scenario, which resulted in post-treatment costs of €126,324.

MAX-Szenario: anschließend 4 Spenderlymphozyten-Infusionsbehandlung (DLI) kosten zusätzlich € 126.324

Furthermore, like obe-cel and standard-of-care treatments, allo-SCT incurs additional costs during the post-transplant follow-up phase, including long-term monitoring and treatment of complications such as graft-versus-host disease. Due to data unavailability, we could not include these costs in our analysis, though they could substantially increase the direct medical costs of allo-SCT treatment.

Based on all these cost categories, the overall per-patient direct medical costs for allo-SCT treatment in Austria can range from €134,590 to €338,567 (see Table 5-7).

allo-SZT-Gesamtkosten pro Pat.: € 134.590 bis € 338.567

Table 5-7: Cost of allogeneic stem cell transplantation per patient[12]

Cost items	MIN	MAX
Allo-SCT procedure	€134,590	€212,243
DLI procedure (MIN: 0; MAX: 4)	NA	€126,324
Total direct medical costs of allo-SCT treatment per patient	€134,590	€338,567

Abbreviations: allo-SCT … allogeneic stem-cell transplantation, DLI … donor lymphocyte infusion, NA … not available

Comparison of costs

Figure 5-1 presents a graphical comparison of the presented total direct medical per-patient costs arising from obe-cel and the SoC treatments indicated for r/r B-ALL patients in Austria. As shown, obe-cel is associated with the greatest per-patient expenditure under both the MIN and MAX scenarios, followed by brexu-cel. Allo-SCT under the MAX scenario (with subsequent DLI treatment) represents the third most costly option, followed by MAX per-patient costs of BLI and IO therapies. TKI treatment, used mostly as an add-on treatment, is the least costly option.

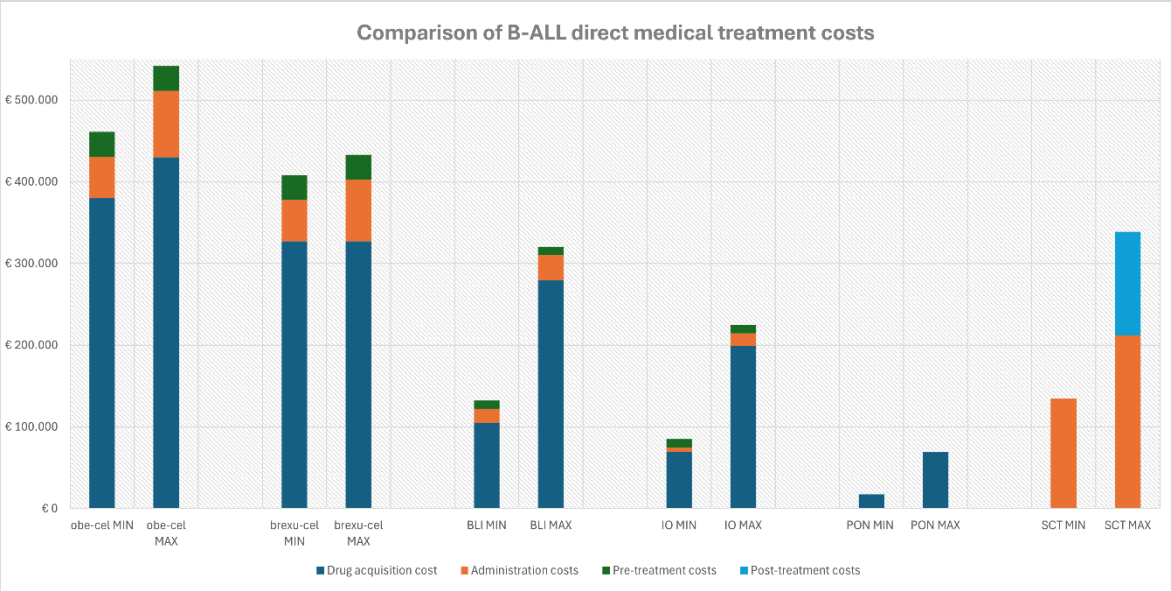
die höchsten per-Pat.-Kosten für CAR-T-Zelltherapien

Indirect costs

Standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs, which constitutes a limitation of the analysis.

keine indirekten Kosten berücksichtigt

[12] Exact composition of allo-SCT procedures covered by the given LFK code is not known



Abbreviations: BLI … blinatumomab, brexu-cel … brexucabtagene autoleucel, IO … inotuzumab ozogamicin, obe-cel … obecabtagene autoleucel, PON … ponatinib, SCT … allogeneic stem-cell transplantation

Figure 5-1: Comparison of B-ALL direct medical treatment costs by procedure.

6 Extended perspectives

To complement the clinical and economic aspects of the health technology assessment (HTA), this chapter examines extended perspectives, including stakeholder perspectives, patient perspectives, and additional ethical and social aspects.

erweiterte Perspektiven

6.1 Stakeholder perspectives

Haematological oncology is a rapidly evolving and complex field, with ongoing advancements in diagnostic and therapeutic measures. The introduction of obecabtagene autoleucel (obe-cel) for relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukaemia (B-ALL) brings significant shifts for various stakeholders.

B-ALL:
komplexe Diagnostik & Behandlungsmöglichkeiten

Organisational aspects

Chimeric antigen receptor (CAR) T cell therapy not only requires experienced and specially trained healthcare staff, but also contingency resources to manage complications [59]. The complexity of CAR T-cell therapy has led to increased attention on strategies for safe delivery:

Komplexität der CAR-T-Zelltherapie macht sichere Anwendungsstrategien erforderlich

In Austria, the Austrian Society of Haematology and Medical Oncology (Österreichische Gesellschaft für Hämatologie und Medizinische Onkologie, OeGHO) has published national recommendations and structural requirements to ensure the quality-assured implementation of CAR T-cell therapy, including careful selection of patients for treatment, personnel qualifications and structural requirements [59]. Although originally developed for CAR T-cell therapies in other indications, particularly lymphoma, these recommendations have proven a valuable framework for the implementation of CAR T-cell therapy in ALL. An overview of the requirements for CAR T-cell therapy centres in Austria is provided in Figure 6-1.

Ö: OeGHO-Empfehlung für qualitätsgesicherte Durchführung der CAR-T-Zelltherapie, ursprünglich entwickelt für andere Indikationen

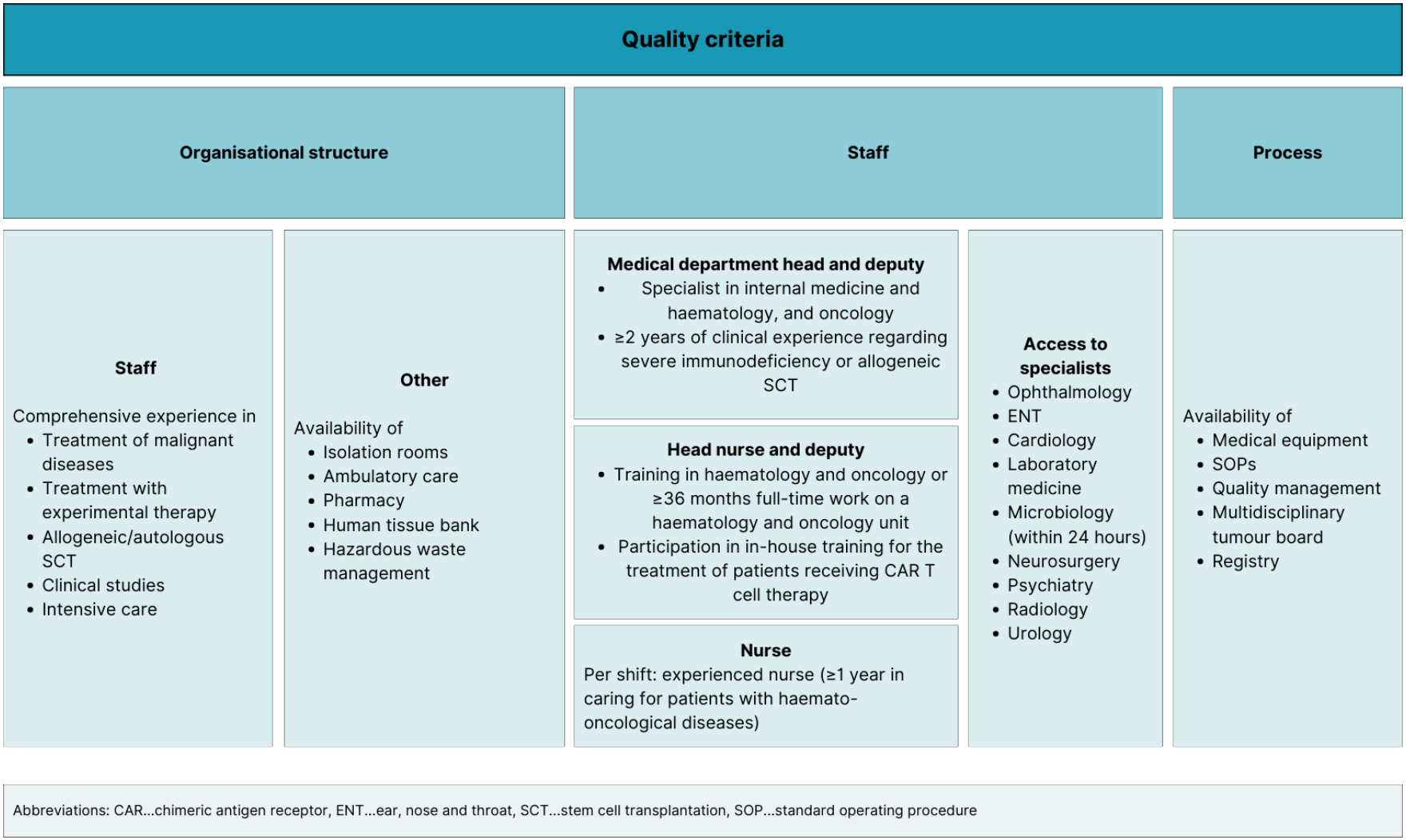


Figure 6-1: Overview of quality criteria for CAR T-cell therapy treatment centres [59]

Health delivery process and management

Referral and patient evaluation

Überblick über den Behandlungsablauf mit Obe-cel: komplexe Behandlung, sorgfältige Pat.-Selektion durch multidisz. Tumorboard

The administration of CAR T-cell therapy involves several critical steps, ranging from selecting eligible patients to conducting long-term follow-up [24]. Patient eligibility should be assessed by a multidisciplinary tumour board, as recommended by the OeGHO for other indications and other expert bodies [30, 59]. Key considerations include the patient's general health status, tumour burden, and medical history, including prior treatments [30]. This approach could also be applied to CAR T-cell therapy in ALL.

basierend auf EBMT, JACIE, EHA Best Practice und Zulassungsinformation von Obe-cel

Figure 6-2 illustrates an overview of this comprehensive process, including the primary diagnostic and monitoring requirements. It is based on the best practice recommendations for CAR T-cell therapy from the European Society for Blood and Marrow Transplantation (EBMT), the Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT (JACIE) and the European Hematology Association (EHA). Additionally, the prescribing information of obe-cel has also been incorporated [24, 30]. A detailed description of the outlined steps is provided in the Appendix.

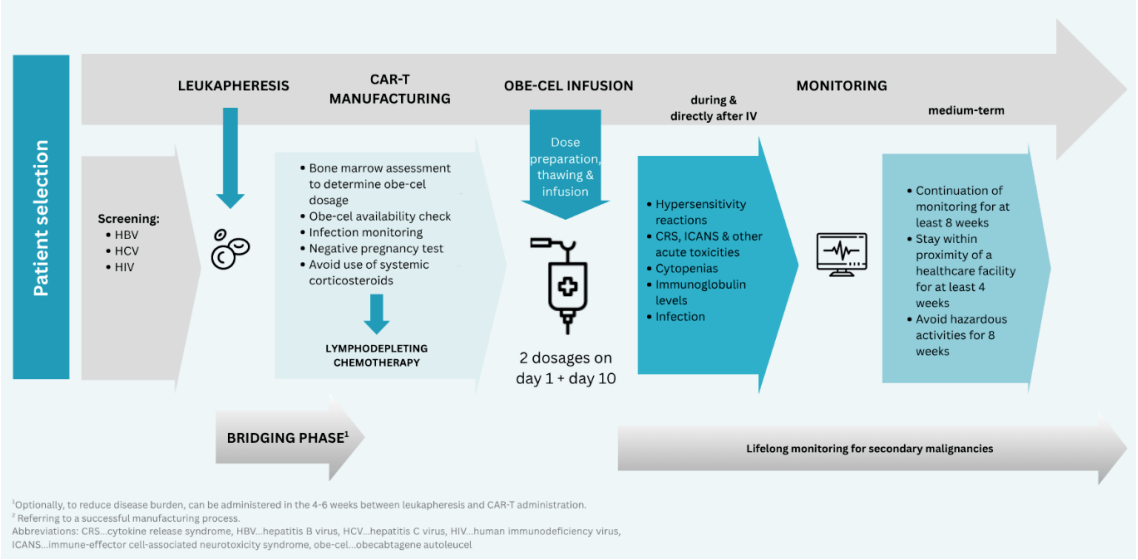


Figure 6-2: Overview of obe-cel treatment procedure [24, 30]. Patient selection criteria are presented in the Appendix.

Ö CAR-T-Zell-Netzwerk: geregelten Zugang zu CAR-T-Zelltherapie in Ö (ursprünglich für andere Indikationen)

The Austrian CAR T-Cell Network was established in 2019 [60] to enable timely and easy access to CAR T-cell therapies, initially focusing on lymphoma [61]. The network is also suitable for supporting CAR T-cell therapy applications in ALL. As of 2025, Austria has nine certified CAR T-cell therapy centres, located across several federal states see Figure 6-3.

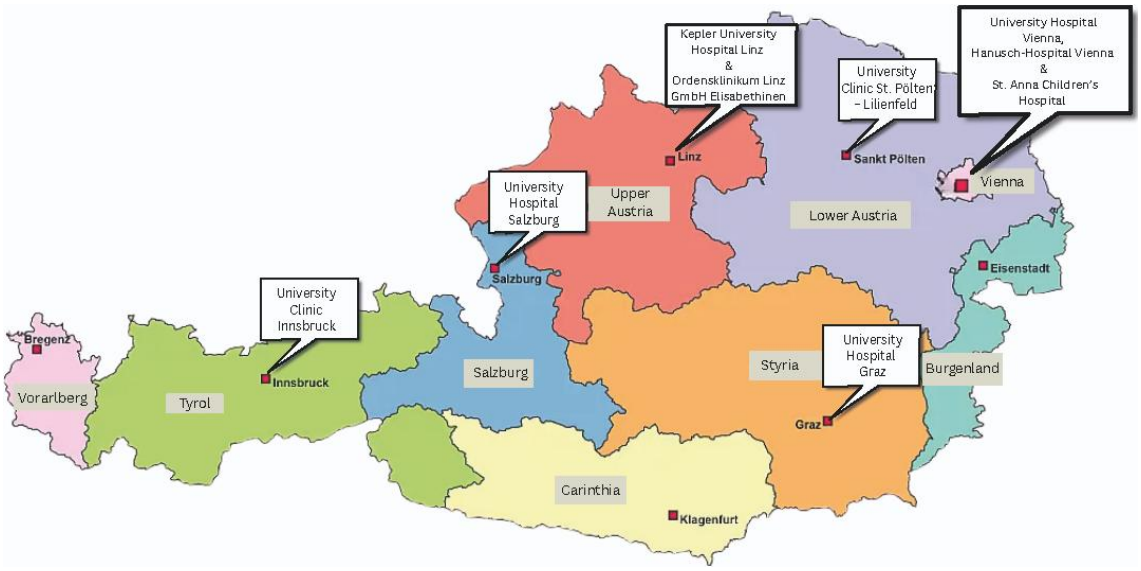


Figure 6-3: CAR T-cell therapy centres [62] (the map of Austria was adapted from [63])

Initially, treatment with obe-cel should be offered in centres that have experience in CAR T-cell therapy and allogeneic stem cell transplantation (allo-SCT). Early clinical use is expected to involve complex decisions regarding whether to proceed with allo-SCT or CAR T-cell therapy. Additionally, the administration of CAR T-cell therapy after allo-SCT represents donor-derived CAR T-cell therapy and carries uncertain risks regarding graft-versus-host disease exacerbation concerning the administration of CAR T-cell therapy following allo-SCT. As the number of eligible patients is expected to be limited, clinical experts recommend concentrating care in a select number of specialised centres [18].

Exp. empfehlen Obe-cel vorerst in spez. Zentren mit CAR-T- & SZT-Erfahrung

Manufacturing and logistics

Complex shipping logistics and transport processes require specialised infrastructure, including qualified and experienced healthcare staff, properly equipped laboratories and close coordinated collaboration between the manufacturer, the transport provider, and the laboratory of the treatment centre [64]. Additional information on the treatment process can be found under "Posology" in Chapter 1.3.

komplexe Logistik & Transportprozesse

There is a growing demand for resources to support SCT, cell therapies, and CAR T treatments. As advanced therapy medicinal products (ATMPs) continue to reach the market, there is a corresponding need for specialised healthcare staff, improved infrastructure, and enhanced overall treatment capacity [18].

steigender Ressourcenbedarf: Personal, Infrastruktur & Kapazitäten

Treatment and consecutive requirements

Patients are hospitalised for a minimum of 10–14 days following infusion to monitor and promptly manage potential toxicities [18, 30]. If AEs occur, patients may require admission to the intensive care unit (ICU) for specialised care (*this information was also used for the Austrian cost analysis, see Chapter 5.2.2*) [65].

Klinikaufenhalt von min. 2 Wochen für Obe-cel IVs

After hospital discharge, patients are advised to remain in proximity to a healthcare facility for at least four weeks following the obe-cel infusion. Additionally, patients are monitored for at least four weeks following the second dose of obe-cel [24]. It is also recommended that a caregiver, trained to recognise delayed complications, be continuously present [30].

nach Entlassung: 28 Tage in der Nähe einer Klinik, Betreuung durch eingeschulte Angehörige empfohlen

6.2 Patient's perspective

Impact of the disease and treatments

Patients living with ALL often experience reduced quality of life (QoL) due to challenges associated with their symptoms and treatments [66].

reduzierte Lebensqualität durch Symptome & Therapie

Crawford and colleagues (2023) conducted a social media review of patients living with ALL to examine self-reported information on experiences with their symptoms and effects on health-related QoL (HRQoL). Their findings highlighted several key areas of concern. Many patients reported the impact on their daily lives, emotional and psychological well-being, and relationships. Patients reported an impact on their ability to work (39%) and difficulties with daily tasks, such as grocery shopping or household chores (22%). Additionally, patients expressed feeling anxious related to fears of relapse (10%), uncertainties about the future (10%), and feeling lonely (5%). Some even reported feeling betrayed by their own body (5%), with one patient stating, "I felt a deep anger towards my body; I felt betrayed by it." Regarding relationships, patients reported that their medical condition affected their relationships (63%), noting improvement (12%) or deterioration (10%) [66].

Analyse basierend auf soziale Medien zeigt Auswirkungen u. a. auf Arbeitsfähigkeit (39 %), Aktivitäten des tägl. Lebens (22 %), Zukunftsängste (10 %) & zwischenmenschliche Beziehungen (63 %)

Regarding the Austrian context, no patient experiences were available. However, insights were drawn from two patients from Germany who completed the questionnaire. Both were members of a patient organisation. The characteristics of the participants in this study are described in Table 6-11.

2 Pat. haben Fragebögen ausgefüllt

Table 6-1: Characteristics of participants of the structured patient questionnaires (n=2) conducted by the AIHTA

Patient characteristics	Total number of patients (n=2)
Sex	
Female	1
Male	1
Median age	68
Diagnosis (self-reported)	
ALL	2
Role	
Patient	2
Carer	0
Member of patient organisation	
Yes	2

Abbreviations: AIHTA … Austrian Institute for Health Technology Assessment, ALL … acute lymphoblastic leukaemia, n … number

After receiving SCT over 20 years ago, both patients have been in remission and no longer receive treatment. One patient is symptom-free, while the other is experiencing polyneuropathy. Given their long-term remission, they reported no impact on their daily routine, family life, or work ability [67]. As this information is based on only two patients who have not received treatment for over 20 years, it cannot be considered representative of the r/r population [18].

beide Pat. seit über 20 Jahren in Remission, keine Auswirkungen auf den Alltag

Expectations and wishes regarding the new therapy

A discrete choice experiment (DCE)[13] was conducted in the United Kingdom (UK) involving patients with r/r ALL; it was designed to explore patients' treatment preferences in the r/r setting. The results for relative attributed importance of patients diagnosed with ALL (23% of the respondents) range from mode of administration (2.1%), QoL during treatment (8.1%), QoL during response (10.4%), duration of response (13.3%), to chance of response (66.1%). Mott and colleagues (2024) suggest that these findings may be attributed to patients with ALL being more recently diagnosed and either currently undergoing treatment or having recently undergone a transplant, compared to respondents with other types of leukaemia. As a result, they remember their treatment experience more vividly, leading them to prioritise achieving remission [69].

66 % der Pat. erhoffen sich ein Ansprechen auf die Therapie

Furthermore, during the draft guidance consultation on obe-cel for treating r/r B-ALL published by the National Institute for Health and Care Excellence (NICE), patients reported that CAR T-cell therapy is associated with a shorter recovery time compared to other available treatment options. They also expressed the belief that earlier access could have prevented many long-term AEs, even though it can result in a weakened immune system [36].

Pat. berichten über kürzere Regenerationszeit & denken, dass rascherer Zugang langfristige Nebenwirkungen vermeiden könnte

The two patients interviewed by the AIHTA (see Table 6-1) shared both expectations and concerns about the new therapy. They hoped for high effectiveness, minimal to no AEs, and no long-term complications. However, they also voiced concerns, particularly about the potential risk of disease recurrence, the likelihood of experiencing multiple AEs, and the possibility of long-term effects [67].

Erwartung der beiden befragten Pat.: hohe Wirksamkeit, geringe bzw. keine Nebenwirkungen, keine Spätfolgen

[13] A discrete choice experiment (DCE) is a quantitative research method used to explore participants' preferences without asking them directly. The participants are presented with several alternative hypothetical scenarios and are asked to rank their preferences [68].

6.3 Further ethical and social aspects

Social impact

Even before the introduction of novel therapies, including CAR T-cell therapy, Kumari and colleagues (2018) examined the burden of caregiving and its effects on patients with ALL. The age of patients ranged from 14 to 65 years, with a mean age of 26. Most patients (71.7%) reported having restricted activity, and only 28.3% were employed. Most caregivers were parents (58.3%), followed by spouses (28.3%), and, on average, they spent 14.1 hours per day providing care. The most frequently reported burden among caregivers was financial, which showed a significant correlation with lower levels of social support. Notably, half of the caregivers reported experiencing only a moderate level of social support [70]. Although the HTA report focuses on adults, the burden is comparable across different age groups.

Betreuung durch Angehörige: finanzielle Belastung & wenig soziale Unterstützung

To help patients with chronic illnesses and their families, the Austrian-based online platform "selpers" – a compound word formed from "self" and "help" – was established [71]. Among other resources, selpers developed the "CAR T-Coach" for patients and their families throughout the CAR T-cell therapy process. The programme is organised into five modules and addresses the following topics: understanding CAR T-cells, preparation for CAR T-cell therapy, treatment during CAR T-cell therapy, post-treatment, and resources for families navigating CAR T-cell therapy [72].

selpers: Ö digitale Plattform für Pat. und ihre Angehörigen, Mission: gratis Hilfe zur Selbsthilfe; CAR-T-Coach bietet Informationen für Pat. & Angehörige

Autonomy, justice and equity

Healthcare providers working with patients with ALL often face difficult and complex situations [73]. In navigating these challenges, they are guided by the four fundamental principles of ethics: beneficence, nonmaleficence, autonomy, and informed consent [74]. Farroni and colleagues suggest four strategies to mitigate ethical dilemmas in practice by:

- Allowing an open communicative environment and setting reasonable expectations, aligned with the patient's values and goals.
- Establishing trigger events to communicate with patients, such as significant changes in therapy response.
- Addressing goals of care early and repeatedly, including transition care.
- Integrating multidisciplinary perspectives, including hospital ethicists or ethics committees, into routine discussions for a greater understanding of the patient's beliefs, values, and expectations [73].

Versorgung v. ALL-Pat. oft herausfordernd & komplex → Orientierung an 4 ethischen Grundprinzipien Vermeidung v. ethischen Herausforderungen bei der Behandlung von ALL durch z. B. angemessene Zielsetzung & Integration von multidiszipl. Perspektiven

Furthermore, the use of novel therapies, such as CAR T-cell therapy, introduces not only new treatment options but also significant ethical complexities. Imbach and colleagues (2018) outlined key ethical considerations relevant to the development and commercialisation of CAR T-cell therapy, focusing on three phases: pre-market, post-market, and cross-cutting issues throughout all phases, see Figure 6-4 [75].

ethische Herausforderungen bei Entwicklung & Kommerzialisierung von CAR-T-Zelltherapie

Moreover, regarding equitable access, an analysis conducted at the University of Chicago suggests that certain aspects of a patient's socioeconomic status do not impact overall survival (OS) if care is available in specialised treatment centres for ALL [76]. In Austria, the establishment of the Austrian CAR T-Cell Network aimed to address these disparities by coordinating and standardising care across CAR T-cell therapy treatment centres nationwide [61].

Einführung des Ö CAR-T-Zell-Netzwerkes: für fairen & bundesweit einheitlichen Zugang zu CAR-T-Zelltherapie

In addition to the ethical imperatives, obtaining informed consent is essential, with no other legal requirements identified regarding obe-cel.

Einverständniserklärung von Pat. – keine zusätzlichen rechtlichen Aspekte identifziert.

Ethical considerations		
Pre-market phase	**Post-market phase**	**Cross-cutting**
• Conducting ethical clinical trials • Navigating the pre-approval process	• Ensuring equitable access • Transitioning to front-line treatment	• Minimising harms to research participants and patients • Managing expectations and minimising hype

Figure 6-4: Ethical considerations relevant to CAR T-cell therapy, adapted from [75]

6.4 Registries and documentation of the application

In the statement of the OeGHO, the EBMT Registry and the Austrian Stem Cell Transplantation Registry (ASCTR) are mentioned [59]. The EMBT Registry was established in 1974, and as of July 2025, 14,538 CAR T-cell therapies were documented by EBMT members [77]. Participating centres are also invited to the CAR T Data Collection Initiative that supports post-authorisation safety studies mandated by the European Medicines Agency (EMA) [78]. However, the registry does not contain information on the QoL [77].

EBMT-Register & ASCTR
EBMT-Register: 14,538 CAR-T-Zelltherapien dokumentiert, keine Info zu Lebensqualität

Additionally, the Austrian Group for Medical Tumor Therapy (Arbeitsgemeinschaft Medikamentöse Tumortherapie, AGMT) established the AGMT_ALL Registry in 2012 to systematically collect clinical data and biomaterial from patients aged 18 years or older who are diagnosed with ALL. The registry documents a wide range of information, utilising both retrospective and prospective study designs [79]. Figure 6-5 gives an overview of the registry.

AGMT_ALL Register

Currently, ALL patients in Austria are recorded in the EBMT registry and the ASCTR, and those receiving obe-cel could also be documented there [18].

Obe-cel könnte auch in EBMT & ASCTR Registern vermerkt werden

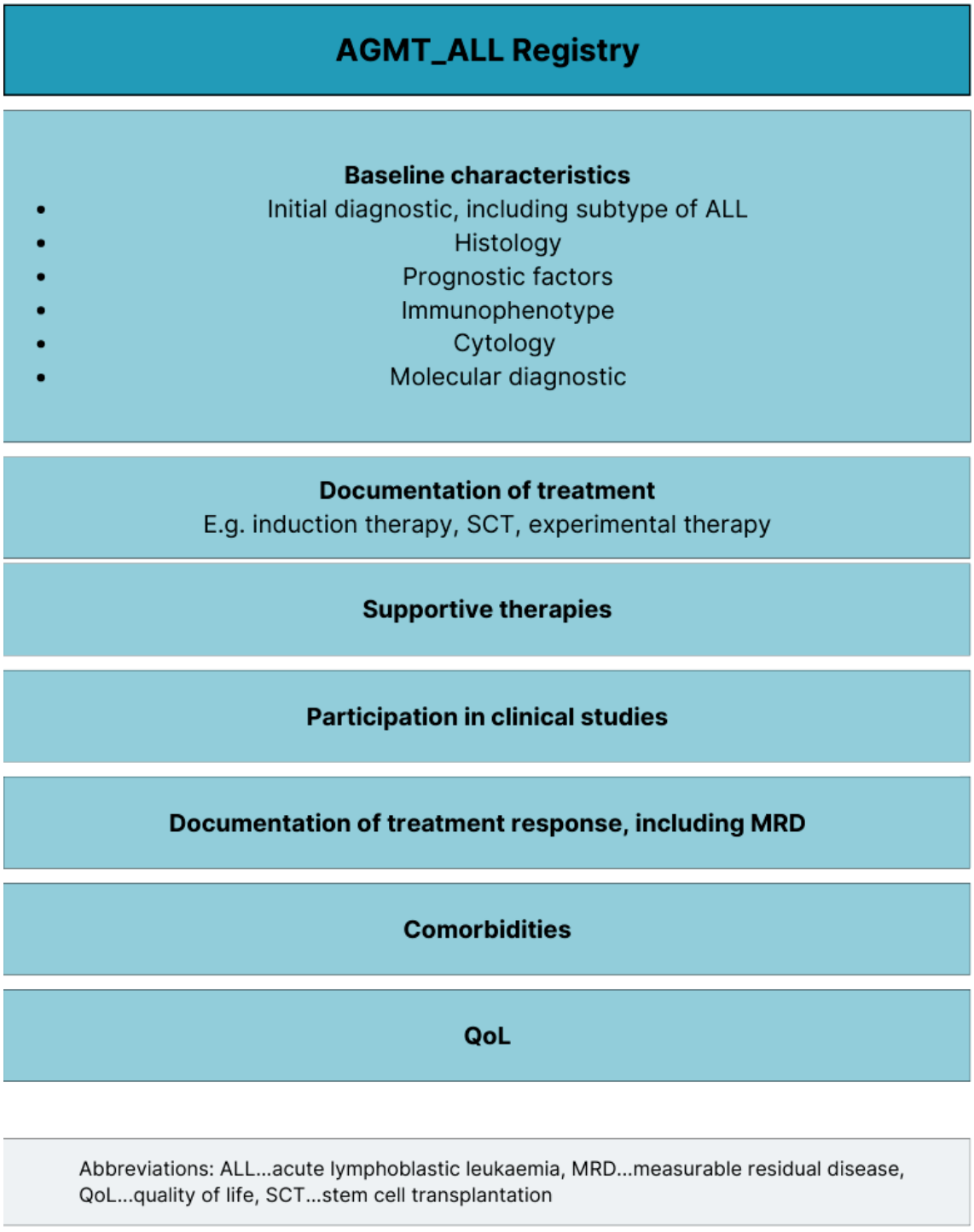


Figure 6-5: AGMT_ALL Registry [79]

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licences

keine Entwicklungskosten von AUCATZYL® publiziert

Autolus Therapeutics (Autolus, see sub chapter "Company structure and financials") has not published the total amount of research and development (R&D) expenses attributed to obecabtagene autoleucel (obe-cel). Table 7-1 provides a short overview of obe-cel.

Table 7-1: AUCATZYL® overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
University College London	Autolus Therapeutics (formerly Autolus Limited)	Spin-out in 2014: From University College London and Martin Pule as scientific founder License agreement 2014: Exclusive license agreement for T-cell programming modules developed by Martin Pule's team License agreement 2024: Updated licensing agreement between Autolus Limited and UCL	Over €71 million direct and indirect public and philanthropic contributions.	Basic, preclinical and clinical research

Abbreviations: UCL … University College London

Basic research and clinical development

Entwicklungsgeschichte von Obe-cel

The development of AUCATZYL® (obe-cel) for the treatment of relapsed/refractory B-cell acute lymphoblastic leukaemia (r/r B-ALL) emerged from research at the University College London (UCL), as shown in Chapter 7 in the Appendix. The fundamental chimeric antigen receptor (CAR) T cell research began at the UCL Cancer Institute under the leadership of Martin Pule in the early 2010s, who developed innovative T-cell programming modules and CAR T technologies that would form the basis of Autolus's therapeutic platform [80].

parallel zu UCL, Forschung an der University of Texas MD Anderson Cancer Center und The Children's Research Institute

Parallel to UCL, researchers at the University of Texas MD Anderson Cancer Center, primarily Catherine Bollard, studied cord blood transplantation which is highly relevant for obe-cel. Furthermore, a research project "Next Generation T-cell therapies for childhood cancers" (NexTGen) aims at contributing to the broader CAR T field. The Children's Research Institute, University of Texas MD Anderson Cancer Center and the UCL are involved in NexTGen[81].

7.2 Public contributions to drug development

Public research funding

Chapter 7 in the Appendix demonstrates extensive public research funding for CAR T development at UCL and collaborating institutions. We identified over €71 million in direct and indirect public (together €55 million) and philanthropic (€16.2 million) funding specifically for CAR T research that contributed to Autolus's technology platform. The largest funding amount of €40 million can be attributed to UCL, followed by €28.3 million for the University of Texas MD Anderson Cancer Center and €2.9 million for the Children's Research Institute (for the individual sources see Chapter 7 in the Appendix).

über € 71 Mio. öffentliche und philanthropische Gelder flossen in die CAR-T-Forschung, die Autolus Technologie ermöglichte – davon € 40 Mio. an die UCL

Martin Pule's research at the UCL received public contributions from national and supranational public institutions: the European Commission (EC) provided substantial support through both the Seventh Framework Programme (€5.9 million for the Advanced T-cell Engineered for Cancer Therapy/ATECT project, 2013–2018) and Horizon Europe (€6 million for CARs for Advanced Therapies/CARAT, 2015–2019). United Kingdom (UK) funding bodies made significant contributions: the National Institute for Health and Care Research (NIHR) Invention for Innovation (i4i) programme provided €3.3 million for phase I/II CAR19 studies, the Welcome Trust invested €2.3 million in CAR T-cell therapy for central nervous system (CNS) lymphoma, and the Medical Research Council (MRC) contributed over €2.7 million through various grants including a major Developmental Pathway Funding Scheme (DPFS) grant of €2.1 million for allogeneic CAR T-cell therapy development. Additionally, a philanthropic organisation also contributed: The Mark Foundation for Cancer Research and Cancer Grand Challenges supported the development of novel immunotherapies for childhood tumours, contributing €13.9 million to advance this research area.

Martin Pules CAR-T-Forschung an der UCL erhielt über € 34 Mio. Förderung:
€ 11,9 Mio. von der EU,
€ 8,3 Mio. von britischen Förderern und
€ 13,9 Mio. von Stiftungen

Catherine Bollard at the University of Texas MD Anderson Cancer Center received substantial funding of €28.3 million from the National Cancer Institute (NCI) between 2011 and 2022. The NexTGen project, involving UCL and the Children's Research Institute, received combined funding of over €7 million from the NCI between 2022 and 2024 [81].

Catherine Bollard erhielt € 28,3 Mio. vom NCI, das NexTGen-Projekt weitere € 7 Mio. (2022–2024)

The translation from academic research to commercial development occurred through UCL Business (UCLB), UCL's technology transfer company. In 2014, Autolus was spun out from UCL with an exclusive license agreement for T cell programming modules developed by Martin Pule's team. This initial agreement involved 1.5 million ordinary shares, management fees of £120,000, and structured milestone payments totalling up to £104.5 million. The agreement was subsequently amended, with the updated 2024 terms including up to £106.68 million in milestone payments, of which £10 million has been paid following obe-cel's U.S. Food and Drug Administration (FDA) approval. UCLB retains low to mid-single digit royalties on product sales and revenue sharing on sublicenses (not further disclosed).

UCL-Ausgründung Autolus (2014) mit Exklusivlizenz: bis zu £ 106,68 Mio. Meilensteinzahlungen plus Lizenzgebühren

Strategic partnerships with pharmaceutical companies have been crucial to Autolus's development. In 2024, BioNTech entered a $250 million upfront collaboration, gaining exclusive licenses to certain target binders and options for additional technologies. Blackstone Life Sciences provided $250 million in 2021 to support obe-cel through pivotal trials. Moderna licensed Autolus's targeting technology in 2021 with up to $60 million in milestone payments. We visualised the most relevant development milestones for the development of obe-cel in Figure 7-1.

strategische Partnerschaften: BioNTech ($ 250 Mio., 2024), Blackstone ($ 250 Mio., 2021) und Moderna (bis $ 60 Mio., 2021)

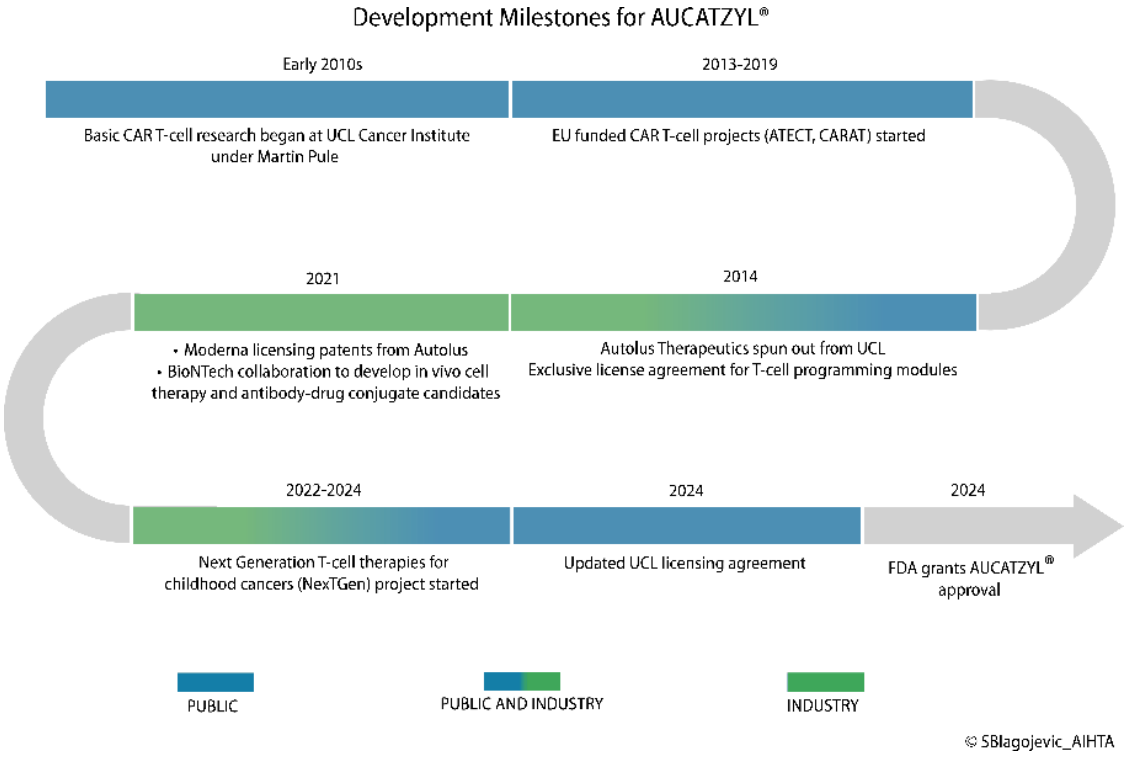


Figure 7-1: Development milestone for AUCATZYL®

Company structure and financials

Autolus was founded as a spin-out from UCL in 2014, with Martin Pule as the scientific founder and UCLB providing commercialisation support. Since its inception, the company has raised over $1 billion in investment, with most invested in the UK, including the development of a manufacturing facility (The Nucleus in Stevenage) [80].

Autolus hat über $ 1 Mrd. an Investitionen bekommen

The company's further financing reflects investor confidence in its CAR T platform. Initial funding came from Syncona with a $45 million Series A financing in 2015 [82], followed by a £40 million Series B from Woodford Investment Management and Perceptive Bioscience in 2016 [83], and a $80 million Series C in 2017 led by Syncona with participation from Nextech Invest, Arix Bioscience, and Woodford [84]. The company went public in 2018 with a $150 million initial public offering (IPO) [85], followed by a $100.8 million follow-on offering in 2019 [86]. Venture capital was the most important type of investor for Autolus.

Finanzierungsrunden: Series A-C ($ 165 Mio., 2015-2017), IPO ($ 150 Mio., 2018), Follow-on ($ 100,8 Mio., 2019). Hauptinvestor: Venture Capital

Patents

The UCL research group, led by original patent holder Martin Pule, developed crucial innovations in receptor design that have become the foundation of Autolus's technology portfolio. These innovations include new suicide genes, novel receptor types, strategies to target T-cell lymphomas, and methods for CAR targeting of multiple antigens simultaneously, all which UCL patented and ultimately licensed to Autolus. As of December 31, 2024, Autolus has built a patent portfolio comprising 83 patent families, with 17 of these originating directly from UCL, reflecting the strong publicly financed academic foundation underlying the company's leading technology [87].

UCL-Forscher Martin Pule entwickelte CAR-T-Schlüsseltechnologien; Autolus besitzt 83 Patentfamilien, davon 17 direkt von der UCL lizenziert

8 Landscape overview

8.1 Ongoing studies on obecabtagene autoleucel

3 laufende Studie zu Obe-cel identifiziert

Abschluss bis November 2027 bzw. Mai 2030 erwartet

Three ongoing clinical studies and programs evaluating obecabtagene autoleucel (obe-cel) treatment were identified via ClinicalTrials.gov, all sponsored by Autolus [88]. These include the pivotal FELIX study (NCT04404660), a phase 1b/2 trial currently in the active follow-up phase. The overall completion was anticipated by May 2025, though individual participating centres have varying reporting timelines (e.g., Spanish centres: May 2028) [89]. Another identified phase 2 study (NCT07053059), which is not yet recruiting, plans to assess obe-cel as consolidation therapy in newly diagnosed high-risk B-ALL patients. It has an estimated enrolment of 30 patients and completion targeted for May 2030 [90]. Additionally, an expanded access program (NCT06799221) provides out-of-specification obe-cel for adult ALL patients [91]. Further details are provided in the Appendix (Chapter 8).

8.2 Treatments of ALL in development

7 Therapien in der Pipeline für r/r B-ALL

Through the International Horizon Scanning Initiative (IHSI) database [26], we found a total of seven distinct therapies in developement (brexucabtagene autoleucel/brexu-cel; azd0486; vnx-101; lisocabtagene maraleucel/liso-cel; ucart22; inotuzumab ozogamicin/IO; azercabtagene zapreleucel/azer-cel) for eight specific ALL indications. Specifically, the already authorised brexu-cel is also in the development for the second line or later treatment of r/r B-ALL in adults and elderly and as a third line or later treatment of r/r B-ALL in children, adolescents and adults up to 21 years of age. IO, that is already authorised, is also investigated as a monotherapy for treatment of r/r CD22-positive B-ALL in infants and toddlers over 1 year of age, children and adolescents. The expected European Commission (EC) decision times for some of the marketing authorisations is as follows: brexu-cel (January 2027), ucart22 (July 2029), and IO (November 2025). See Chapter 8 in the Appendix for details.

9 Discussion

This health technology assessment (HTA) report evaluates obecabtagene autoleucel (obe-cel, AUCATZYL®), a novel chimeric antigen receptor (CAR) T cell orphan drug, that was approved on 17 July 2025 through a conditional marketing authorisation for the treatment of adults from 26 years of age with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (r/r B-ALL) [23].

Obe-cel als neue CAR-T-Zelltherapie bei Pat. mit r/r B-ALL

Based on the European Medicines Agency (EMA) approval, treatment guidelines and clinical experts' input, the following key research questions were defined for this report:

1. In patients ≥26 years with r/r B-ALL, is obe-cel more effective and safer compared to the current standard treatment (SoC) in Austria?
2. What are the economic, organisational, ethical, social and legal consequences of implementing obe-cel into Austria?
3. What were the key contributions of publicly funded research institutions and private companies in developing obe-cel?

3 Forschungsfragen:

1. Wirksamkeit & Sicherheit von Obe-cel vs. Standardtherapie
2. Implementierungsfolgen im Ö Gesundheitssystem
3. Beitrag öffentlicher Forschungsgelder

R/r B-ALL in adult patients is a rare disease, and its complex treatment algorithm is individually tailored to each patient, while no specific guideline is available in Austria. Nevertheless, the guidelines identified in the literature include Onkopedia [7], the European Society for Medical Oncology (ESMO) Clinical Practice Guideline [14] and the European Leukemia Net (ELN) recommendations from a European expert panel [9]. Available targeted therapies like blinatumomab (BLI), inotuzumab ozogamycin (IO), tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome positive (Ph+) patients are used and can be followed by allogeneic stem cell transplantation (allo-SCT) [14], the only established curative option with proven long-term remission [18]. Additionally, for patients ≥26 years, another CAR T-cell therapy, brexucabtagene autoleucel (brexu-cel, TECARTUS®) is available on the market [92], although the experience with it in Austria is limited.

B-ALL als seltene Erkrankung mit komplexer Behandlung

derzeitige Behandlungsoptionen: BLI, IO, TKIs, allo-SZT, Brexu-cel

mehrere Leitlinien – genaue Positionierung im Algorithmus unklar

For effectiveness and safety, a phase 1b/2, single-arm, interventional, open-label, non-randomised, multi-cohort clinical study (FELIX trial), evaluating the clinical effectiveness and safety of obe-cel in adults (≥18 years) with r/r B-ALL was identified. Included patients were heavily pretreated, with a median of two previous therapies and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (38%) or 1 (61%) [44].

Phase 1b/2 Studie: Sicherheit und Wirksamkeit von Obe-cel

In the comparison of the results from separate studies, obe-cel (FELIX) [44] showed comparable efficacy to the competing CAR T therapy brexu-cel (ZUMA-3) [51], with overall remission rates (ORR) of 77% vs 73%, complete remission (CR) rates of 55% vs 56%, median duration of response (DOR) of 14.1 vs 12.8 months, and median overall survival (OS) of 15.6 vs 18.2 months at median follow-up of 21.5 vs 16.4 months, respectively. Interestingly, CR and DOR remained consistent after two years [93] and three years [49] of ZUMA-3 follow-up, with an improved median OS of 25.6 months. Of note, while the previous therapy burden was comparable between ZUMA-3 and FELIX patients, ZUMA-3 population had a significantly higher bone marrow blast burden and lower frequency of extramedullary disease.

Wirksamkeitsergebnisse:

ähnliche Ergebnisse zu OR und DOR zwischen Obe-cel und Brexu-cel

bessere Ergebnisse zu OS für Brexu-cel

In contrast, the conventional targeted therapies, such as BLI and IO, reached an OS of only 3–6 months [94, 95], and CR rates usually ranged between 30–80% with durable responses remaining rare without subsequent allo-SCT [96, 97]. In an indirect treatment comparison (ITC), obe-cel was generally superior to BLI, IO and a TKI, ponatinib (PON); however, the National Institute for Health and Care Excellence (NICE) advised considerable caution in interpreting these results due to methodological limitations [37]. An additional ITC [38], only available in abstract form, demonstrated improvements in ORR and event-free survival (EFS) with obe-cel compared to BLI, IO, or chemotherapy. However, these findings should be interpreted cautiously, given the undisclosed methodology and unclear peer review status.

indirekter Vergleich von Obe-cel mit BLI, IO & Chemotherapie: bessere Ergebnisse zu ORR & EFS für Obe-cel; Ergebnisse unsicher → intransparente Methoden

Moreover, among patients in the FELIX study who responded to obe-cel, 18% proceeded to allo-SCT while in remission [44], suggesting a need for further treatment for some patients. Furthermore, quality of life (QoL) results from the FELIX study were only reported in abstract form for 70 out of 94 patients, showing initial deterioration post-infusion, followed by a later recovery that exceeded baseline values [40]. These preliminary abstract findings should be interpreted with caution.

18 % der Pat. in der FELIX-Studie benötigten SZT nach Obe-cel; Lebensqualität-Daten zu Obe-cel nur in Abstract-Form verfügbar

Concerning safety results, obe-cel demonstrated a significantly lower rate of severe adverse events (SAEs) in the FELIX study [44] compared to brexu-cel in the ZUMBA-3 trial [49, 93], presumably due to a reduction of excessive T cell activation [98]. Grade ≥3 cytokine release syndrome (CRS) occurred in 2.4% of obe-cel patients versus 24% with brexu-cel, while grade ≥3 immune cell-associated neurotoxicity syndrome (ICANS) was observed in 7.1% versus 25%, respectively. Conversely, grade ≥3 febrile neutropenia was more frequent with obe-cel (23.6% vs 13%), whereas grade ≥3 anaemia was lower (20.5% vs 45%). Additionally, two treatment-related deaths occurred with both obe-cel and brexu-cel [44, 51]. Based on these data, the safety profile of obe-cel is more favourable than that of brexu-cel with comparable clinically relevant advantages, which could guide the selection among CAR T-cell therapies.

weniger schwerwiegende AEs bei Obe-cel vs. Brexu-cel

vermutete Ursache: reduzierte T-Zell-Überaktivierung

mögliche Hilfestellung bei der Therapiewahl

The FELIX study [44] faces several constraints that impact its clinical interpretation. Internal validity concerns include the single-arm design, which inherently limits comparative efficacy claims and creates dependence on historical controls with associated uncertainties. The historical thresholds from the TOWER study [48] comparing BLI versus chemotherapy have methodological issues, with the U.S. Food and Drug Administration (FDA) review [46] noting that using point estimates (40% ORR, 20% CR) from BLI data, rather than the more conservative upper bounds of confidence intervals (CI), inadequately accounts for statistical uncertainty. Additionally, dropouts from manufacturing failures or patient deterioration may introduce selection bias by systematically excluding certain subgroups. Due to the single-arm design, no formal risk of bias or Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment were performed. Limitations based on external validity arise from population differences between the FELIX, TOWER and ZUMA-3 studies, raising concerns about the appropriateness of the historical comparisons. Furthermore, applicability to the Austrian context faces additional constraints despite some favorable characteristics. The study population represents heavily pretreated, treatment-resistant patients with limited therapeutic options, making generalisability to less pretreated populations uncertain.

limitierte vergleichende Wirksamkeitsaussagen aufgrund des Studiendesigns der FELIX-Studie

& keine Bewertung des Verzerrungsrisikos & kein GRADE-Assessment möglich

While the therapeutic potential of obe-cel with its favourable safety profile compared to existing CAR T therapies is acknowledged, there are concerns regarding long-term efficacy, as the data do not support durable remissions [18]. This limited durability is evidenced by the 18% rate of subsequent allo-SCT in the FELIX study [44]. Moreover, although the benefit of obe-cel in patients ≥70 years remains unclear, it could expand treatment eligibility for patients who would otherwise be limited to palliative care [98].

trotz günstiger Sicherheitsbilanz von Obe-cel im Vergleich zu anderen CAR-T-Zelltherapien Unsicherheit zu Langzeitwirksamkeit

The current standard of care for r/r B-ALL in Austria centers on allo-SCT, which has demonstrated good results with a substantial proportion of patients achieving long-term remission through donor-derived immunity and the availability of donor lymphocyte infusion for subsequent relapses. However, some patients experience transplant failure, are ineligible for allo-SCT, lack compatible donors, or are not fit enough to tolerate the procedure, creating a significant unmet medical need for alternative therapeutic approaches [18]. CAR T-cell therapy, particularly obe-cel, represents a promising treatment option for this patient population that has exhausted conventional therapeutic options. Clinical data indicate obe-cel's value in providing crucial bridging time to allo-SCT and as a potential consolidation therapy for transplant-ineligible patients. However, patient selection remains critical – candidates must be fit enough to tolerate CAR T therapy, and obe-cel should not be offered to patients in full relapse due to bridging period challenges. The most appropriate positioning of obe-cel in the treatment algorithm of r/r B-ALL is currently unclear and remains under discussion. While some guidelines mention its potential role, the limited clinical evidence, lack of long-term data, and scarce experience with CAR T therapy in adult B-ALL patients make the optimal treatment pathway less well defined. In Austria, it is debated whether obe-cel could be considered as an early option in highly selected patients, or whether allo-SCT should remain the preferred initial strategy [18]. Real-world experience and additional trial data, including durability of remission results from the ongoing follow-up of the FELIX trial [89], will be crucial in defining the optimal positioning of obe-cel therapy and may significantly influence treatment decision-making for adult r/r B-ALL patients in the future.

mögliche Erweiterung der Behandlungsoptionen für Pat., die bisher nur palliativ versorgt werden würden

aktuelle Einordnung von Obe-cel im Behandlungsschema unklar → Daten mit längerem Follow-up notwendig

Concerning a health economic evaluation (HEE) of obe-cel, the marketing authorisation holder (MAH) did not submit any data, and no cost-effectiveness evaluation (CEA) was found for Austria. Instead, a HEE was identified in the HTA report from NICE [36, 37], which described a partially confidential pharmacoeconomic cost-utility analysis (CUA) from the MAH. The analysis, based on a payer's perspective, modelled the costs and outcomes of obe-cel versus IO, BLI and PON across Ph+, Ph-, and the full population. While the MAH claimed that obe-cel was cost-effective in all the comparisons conducted, NICE re-ran the analysis utilising adjusted conservative assumptions, resulting in the incremental cost-effectiveness ratios (ICERs) that exceeded the willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life year (QALY) gained across all populations and against all comparators. In conclusion, in the draft guidance consultation document, NICE did not recommend obe-cel, noting that uncertainties in both clinical effectiveness and economic modelling prevented demonstration of cost-effectiveness, high-lighting the need for more robust analysis.

keine Kosteneffektivitäts-bewertung zu Obe-cel liegt für Ö vor

HTA-Bericht von NICE: keine Empfehlung für Obe-cel wegen Unsicherheiten in klin. Wirksamkeit & ökonom. Modell → robustere Analysen notwendig

Furthermore, a US-American economic model published as an abstract [40] showed that obe-cel was associated with a cost saving of $18,619 per patient for CRS and $36,133 per patient for ICANS relative to brexu-cel.

weiteres Model (Abstrakt): Kosteneinsparungen durch Obe-cel bei CRS & ICANS vs. Brexu-cel

In addition, no budget impact analysis (BIA) has been submitted by the MAH. Due to the complex individualised treatment algorithm, we conducted an Austrian cost overview of obe-cel and SoC used, showing costs per patient. Several uncertainties affected our calculations, beginning with the absence of an obe-cel price submission from the MAH. Consequently, we relied solely on extrapolations from foreign list prices (Germany and the UK). Although the price of the competing CAR T-cell therapy brexu-cel is established in Austria, obe-cel can be expected to be priced higher due to a more favourable toxicity profile. Our analysis was also constrained by unclear CAR T best practices, specifically regarding bridging therapy selection (clinician discretion in Austria) and long-term AE management durations. Additionally, unavailable indirect cost data restricted our assessment to direct medical costs only. All these limitations could have resulted in an underestimation of the presented per-patient treatment costs.

keine BIA-Daten vom MAH → keine formale BIA vom AIHTA – stattdessen eine Ö Kostenübersicht für Obe-cel & SoC

Brexu-cel-Listenpreis für Ö, Obe-cel eventuell teurer

indirekte Kosten in Ö nicht verfügbar

Nevertheless, utilising minimum and maximum cost scenarios, our cost analysis demonstrated that obe-cel is associated with the highest treatment costs, ranging from €461,142 to €541,857. In comparison, SoC showed considerably lower costs: BLI ranged from €132,506 to €320,519, IO from €85,209 to €224,968, PON from €17,326 to €69,305, and allo-SCT from €134,590 to €338,567. The competing CAR T therapy brexu-cel resulted in costs from €408,142 to €433,152, positioning it between obe-cel and SoC alternatives. However, patients treated with obe-cel are less likely to experience prolonged hospitalisations and associated maximum costs compared to those receiving brexu-cel. Also, unlike obe-cel, allo-SCT incurs additional costs during the follow-up phase including the treatment of graft-versus-host disease, which was not accounted for in the calculations. Importantly, treatment selection should consider both clinical outcomes and budget implications.

MIN.-MAX.-Szenarien: Obe-cel am teuersten: € 461.142 – € 541.857

Brexu-cel höhere Wahrscheinlichkeit der MAX. Kosten: € 433.152 → SoC wesentlich kostengünstiger

The CAR T-cell network was established in Austria in 2019 in the context of the first CAR T-cell therapies for lymphoma. Since then, several more CAR T-cell products have been approved, and more centres have been set up across Austria. The recommendations must now be reassessed regarding expanding indications and the increasing resource requirements – both personnel and structural – for cell therapies, including CAR T and stem cell transplantation. Given the complex manufacturing processes, and intensive care requirements, a comprehensive national concept is required from an organisational perspective. Furthermore, with the anticipated increase in such therapies, in-house cell therapy production and the establishment of dedicated manufacturing capacity within hospitals should be considered for Austria, as already established in other countries. Austria has national recommendations to ensure the implementation of CAR T-cell therapy [50] and currently has nine certified CAR T-cell therapy centres operating at full capacity. A good manufacturing practice laboratory should be considered to be established, which would produce CAR T products locally, potentially reducing shipping times and treatment delays. It can be expected that the system burden will increase with the increased number of CAR T-cell products, and this should be taken into account before the implementation. However, with a 95.4% manufacturing success rate, obe-cel shows promise for Austrian implementation, where established CAR T infrastructure would support clinical integration despite the logistical challenges of the 21-day production time-

organisatorische Aspekte:

nationale Empfehlungen für CAR-T-Zelltherapie

ca. 23. Tage für Herstellung und Transport von Obe-cel

9 zertifizierte CAR-T-Zelltherapiezentren in Ö

pot. Herstellung von Obe-cel im Inland

neue CAR-T-Zelltherapie-Generationen möglicherweise in wenigen Tagen hergestellt

line and the need for bridging therapy in 93% of patients with its associated mortality risks.

From the perspective of ALL patients (n=2), the disease profoundly affects their daily lives, emotional and psychological well-being, and their ability to work and manage daily tasks, and is often accompanied by anxiety and fear [66]. Additionally, while multiple therapeutic options exist, these treatments often impose a substantial burden through AEs and prolonged hospitalisations, including those caused by CAR T-cell therapies with a limited duration of remission. Moreover, the absence of dedicated ALL patient organisations in Austria compounds these challenges by limiting access to peer support, advocacy resources, and information networks [99]. Required caregiving for ALL patients represents further strain on society, including a financial burden due to informal care [70].

Pat. im Alltag eingeschränkt

Behandlung durch viele Krankenhausaufenthalte und Nebenwirkungen geprägt

Regarding equitable access, socioeconomic factors may not impact overall survival when specialised treatment centres are available [76]. The Austrian CAR T-Cell Network was established to address access disparities by coordinating and standardising care across CAR T-cell therapy centres nationwide [61]. At the beginning of treatment, obe-cel should be offered in a limited number of geographically distributed centres with expertise in allo-SCT and CAR T-cell therapy to gain sufficient experience, given the limited number of patients [99].

Obe-cel könnte zu Beginn in 3 CAR-T-Zelltherapiezentren in Ö zur Verfügung stehen

Austria has established a registry infrastructure that already captures ALL patients [60, 83]. To maximise real-world evidence generation, documentation of new treatments such as obe-cel should be systematically incorporated into these existing frameworks and should be mandatory.

Daten zu ALL Pat. im Register zu dokumentieren

The development of AUCATZYL® emerged from publicly funded research at the University College London (UCL) and progressed to successful commercialisation through strategic partnerships and continued collaboration between academia and industry. Over €71 million, in public €55 million and philanthropic €16.2 million, funding supported obe-cel's development, with UCL receiving €40 million, University of Texas MD Anderson Cancer Center €28.3 million, and the Children's Research Institute €2.9 million. The identified public research funding contributing to the underlying technology of obe-cel represents an example of how public investment in basic research enables new therapies.

öffentliche Forschungsgelder von € 71 Mio. für Herstellung von Aucatzyl®

Several critical evidence gaps limit the comprehensive evaluation of obe-cel in r/r B-ALL. First, the FELIX trial lacks long-term follow-up data (≥3 years) necessary to assess durability of remission. Second, the single-arm study design prevents direct comparison with current standard of care options, relying instead on historical controls that create uncertainties. Finally, quality of life data remain insufficient, with only preliminary abstract form results available. These gaps collectively hinder definitive treatment recommendations and optimal patient selection, emphasising the need for extended follow-up studies and robust comparative effectiveness research to establish obe-cel's precise therapeutic role. The three ongoing studies that are evaluating obe-cel [89-91] in B-ALL patients are expected to provide additional evidence on long-term efficacy and safety, including first-line setting. More robust quality of life data are also expected. Additionally, currently there are seven therapies in development for r/r B-ALL that may expand the treatment algorithm in this patient population, including the paediatric one.

3 laufende Studien zu Obe-cel, 7 weitere Therapien für r/r B-ALL in Entwicklung

In conclusion, obe-cel demonstrated clinically meaningful efficacy in heavily pretreated r/r B-ALL patients with a favourable safety profile compared to existing CAR T therapies. However, evidence remains limited by single-arm study design and short follow-up. High acquisition costs represent significant budget impact, though superior safety may reduce total treatment costs. Price negotiations should target costs comparable to existing treatments to support Austrian healthcare implementation and reimbursement. Austria has adequate infrastructure for safe obe-cel delivery through existing CAR T networks, with initial restriction to experienced centres. Implementation requires mandatory registry participation, comprehensive outcomes monitoring, and reassessment after two years based on follow-up data. Currently, limited number of patients are eligible for CAR T-cell therapy but may expand as evidence grows. Successful implementation necessitates rigorous indication assessment through coordinated interdisciplinary tumour board decisions and close coordination with SCT-centres to optimise patient selection and treatment timing.

potenzieller Nutzen von Obe-cel in r/r B-ALL mit geringer Toxizität …

… aber:
Evidenzqualität limitiert,
hohe Kosten,
unklare Positionierung im Algorithmus und
Registerpflicht notwendig

10 References

[1] Orphanet. Precursor B-cell acute lymphoblastic leukemia. 2025 [cited 08.07.2025]. Available from: https://www.orpha.net/de/disease/detail/99860?name=all&mode=name.

[2] Advani AS, Aster JC and UpToDate. Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma. 2022 [cited 08.07.2025]. Available from: https://www.uptodate.com/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-b-cell-acute-lymphoblastic-leukemia-lymphoma?search=precursor%20acute%20lymphoblastic%20leukemia&topicRef=4484&source=see_link.

[3] Zhang Y, Le Beau MM, Aster JC and UpToDate. Classification, cytogenetics, and molecular genetics of acute lymphoblastic leukemia/lymphoma. 2024 [cited 08.07.2025]. Available from: https://www.uptodate.com/contents/classification-cytogenetics-and-molecular-genetics-of-acute-lymphoblastic-leukemia-lymphoma?search=precursor%20acute%20lymphoblastic%20leukemia&topicRef=4686&source=see_link#H3402544092.

[4] Arber D. A., Orazi A., Hasserjian R., Thiele J., Borowitz M. J., Le Beau M. M., et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405. DOI: 10.1182/blood-2016-03-643544.

[5] World Health Organization (WHO). WHO Classification of Tumours. Haematolymphoid Tumours. 2025 [cited 07.07.2025]. Available from: https://whobluebooks.iarc.fr/structures/haematolymphoid/.

[6] Ravandi F. and Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23(5):1043-1063, vi. DOI: 10.1016/j.hoc.2009.07.007.

[7] Gökbuget N, Baldus C, Brüggemann M, Hauswirth AW and et al. Onkopedia Leitlinien. Akute Lymphatische Leukämie (ALL). 2022 [cited 08.07.2025]. Available from: https://www.onkopedia.com/de/ onkopedia/guidelines/akute-lymphatische-leukaemie-all/@@guideline/html/index.html.

[8] Haider MZ and Anwer F. StatPearls. Genetics, Philadelphia Chromosome. 2023 [cited 08.07.2025]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560689/.

[9] Gökbuget N., Boissel N., Chiaretti S., Dombret H., Doubek M., Fielding A., et al. Management of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024;143(19):1903-1930. DOI: 10.1182/blood.2023023568.

[10] Canadian Cancer Society. Staging acute lymphoblastic leukemia. 2025 [cited 08.07.2025]. Available from: https://cancer.ca/en/cancer-information/cancer-types/acute-lymphoblastic-leukemia-all/staging.

[11] American Cancer Society. Tests for Acute Lymphocytic Leukemia (ALL). 2025 [cited 2025-07-08]. Available from: https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/detection-diagnosis-staging/how-diagnosed.html.

[12] Gökbuget N., Boissel N., Chiaretti S., Dombret H., Doubek M., Fielding A., et al. Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024;143(19):1891-1902. DOI: 10.1182/blood.2023020794.

[13] Kruse A., Abdel-Azim N., Kim H. N., Ruan Y., Phan V., Ogana H., et al. Minimal Residual Disease Detection in Acute Lymphoblastic Leukemia. Int J Mol Sci. 2020;21(3). Epub 20200205. DOI: 10.3390/ijms21031054.

[14] Hoelzer D., Bassan R., Dombret H., Fielding A., Ribera J. M., Buske C., et al. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v69-v82. Epub 20160407. DOI: 10.1093/annonc/mdw025.

[15] National Cancer Institute (NIC). NCI Dictionary of Cancer Terms. Philadelphia chromosome. 2025 [cited 2025-08-20]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/philadelphia-chromosome.

[16] Statistik Austria. Krebserkrankungen in Österreich. 2024 [cited 10.07.2025]. Available from: https://www.statistik.at/fileadmin/publications/Krebs-2024_Webversion-barrierefrei_Rev1.pdf.

[17] Hoelzer D., Bassan R., Boissel N., Roddie C., Ribera J. M., Jerkeman M., et al. ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol. 2024;35(1):15-28. Epub 20231011. DOI: 10.1016/j.annonc.2023.09.3112.

[18] Personal communication with clinical experts. July/August 2025. 2025.

[19] Member State Coordination Group on Health Technology Assessment (HTA CG). Guidance on the scoping process. 2024 [cited 24.07.2025]. Available from: https://health.ec.europa.eu/document/download/7be11d76-9a78-426c-8e32-79d30a115a64_en?filename=hta_jca_scoping-process_en.pdf.

[20] Leukemia and Lymphoma Society. Acute Lymphoblastic Leukemia in Adults. 2024 [cited 10.07.2025]. Available from: https://www.lls.org/sites/default/files/2024-05/PS33_AdultALL_2024_FINAL.pdf.

[21] Bader P K. H., Bacigalupo A. Documentation of Engraftment and Chimerism After HCT. 2024 Apr 11. In: Sureda A, Corbacioglu S, Greco R, et al., editors. The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies [Internet]. 8th edition. Cham (CH): Springer; 2024. Chapter 21. [cited 16.07.2025]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK608246/; DOI: 10.1007/978-3-031-44080-9_21.

[22] European Medicines Agency (EMA). New treatment for adults with acute lymphoblastic leukaemia. 2025 [cited 08.07.2025]. Available from: https://www.ema.europa.eu/en/news/new-treatment-adults-acute-lymphoblastic-leukaemia.

[23] European Medicines Agency (EMA). Medicines. Aucatzyl.: 2025 [cited 08.07.2025]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/aucatzyl.

[24] U.S. Food and Drug Administration (FDA). Aucatzyl®. Prescribing information. 2024 [cited 08.07.2025]. Available from: https://www.fda.gov/media/183463/download.

[25] European Commission (EC). Union Register of medicinal products for human use. Product information. Aucatzyl.: 2025 [cited 2025-08-11]. Available from: https://ec.europa.eu/health/documents/community-register/html/h1951.htm.

[26] International Horizon Scanning Initiative (IHSI). 2025 [cited 08.07.2025]. Available from: https://ihsi-horizonscandb.ecri.org/.

[27] U.S. Food and Drug Administration (FDA). FDA approves obecabtagene autoleucel for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. 2024 [cited 08.07.2025]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-obecabtagene-autoleucel-adults-relapsed-or-refractory-b-cell-precursor-acute.

[28] Autolus Inc. AUCATZYL manufacturing process. [cited 08.07.2025]. Available from: https://www.aucatzylhcp.com/about-aucatzyl/manufacturing/.

[29] St. Anna Kinderkrebsforschung. CAR-T-Zelltherapie. [cited 08.07.2025]. Available from: https://kinderkrebsforschung.at/car-t-zelltherapie/.

[30] Hayden P. J., Roddie C., Bader P., Basak G. W., Bonig H., Bonini C., et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Annals of Oncology. 2022;33(3):259-275. DOI: 10.1016/j.annonc.2021.12.003.

[31] Arbeitsgemeinschaft medikamentöse Tumortherapie gemeinnützige GmbH. AGMT_ALL Registry. 2019 [cited 10.07.2025]. Available from: https://agmt.at/wp-content/uploads/2019/04/AGMT_ALL_Register_Poster_OeGHO_2019_web.pdf.

[32] National Institute for Value and Technologies in Healthcare (NIHO). Liečivo brexukabtagÈn autoleucel (Tecartus) na liečbu pacientov vo veku 26 rokov a starších s recidivuj˙cou alebo refraktÈrnou ak˙tnou lymfoblastickou leukÈmiou (ALL) B-bunkov˝ch prekurzorov.: 2023 [cited 10.07.2025]. Available from: https://niho.sk/en/publikovane-projekty/.

[33] EUnetHTA Joint Action 2. Work Package 8. HTA Core Model® version 3.0. 2016 [cited 03.07.2025]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf.

[34] Member State Coordination Group on Health Technology Assessment. Guidance on Validity of Clinical Studies. 2024 [cited 17.07.2025]. Available from: https://health.ec.europa.eu/document/download/9f9dbfe4-078b-4959-9a07-df9167258772_en?filename=hta_clinical-studies-validity_guidance_en.pdf.

[35] Guyatt G., Oxman A. D., Akl E. A., Kunz R., Vist G., Brozek J., et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. Epub 20101231. DOI: 10.1016/j.jclinepi.2010.04.026.

[36] National Institute for Health and Care Excellence. Obectabagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia 2025 [cited 18.07.2025]. Available from: https://www.nice.org.uk/guidance/gid-ta11496/documents/draft-guidance.

[37] National Institute for Health and Care Excellence. Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]. 2025 [cited 16.07.2025]. Available from: https://www.nice.org.uk/guidance/gid-ta11496/documents/committee-papers.

[38] Topp M. S., Shah B. D., Jabbour E., Park J. H., Shaughnessy P., Logan A. C., et al. Comparison of Obecabtagene Autoleucel (obe-cel) Versus an External Control Arm (ECA) in Adult Patients (pts) with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (R/R B-ALL). 2025. p. S121.

[39] ESMO. ESMO-MCBS Scorecards. 2025 [cited 06.08.2025]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards.

[40] Logan A. C., Shah B. D., Pantin J., Jabbour E., Park J. H., Shaughnessy P., et al. An Economic Model Comparing the Costs Associated with Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Among Patients Treated with Chimeric Antigen Receptor (CAR) T-Cell Therapies for Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (R/R B-ALL). 2025. p. S226-S227.

[41] Österreichische Nationalbank. Wechselkurse. 2025 [cited 17.07.2025]. Available from: https://www.oenb.at/Statistik/Standardisierte-Tabellen/zinssaetze-und-wechselkurse/Wechselkurse.html.

[42] International Horizon Scanning Initiative (IHSI). 2025 [cited 05.06.2025]. Available from: https://ihsi-horizonscandb.ecri.org/.

[43] Canva. 2025 [cited 17.07.2025]. Available from: https://www.canva.com/.

[44] Roddie C., Sandhu K. S., Tholouli E., Logan A. C., Shaughnessy P., Barba P., et al. Obecabtagene Autoleucel in Adults with B-Cell Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2024;391(23):2219-2230. DOI: https://dx.doi.org/10.1056/NEJMoa2406526.

[45] Kantarjian H., Stein A., Gokbuget N., Fielding A. K., Schuh A. C., Ribera J. M., et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2017;376(9):836-847. DOI: 10.1056/NEJMoa1609783.

[46] U.S. Food and Drug Administration (FDA). BLA 125813/0 Clinical Review and Evaluation AUCATZYL (obecabtagene autoleucel) – Statistical Review. 2024 [cited 08.07.2025]. Available from: https://www.fda.gov/media/184204/download.

[47] Kantarjian H. M., DeAngelo D. J., Stelljes M., Liedtke M., Stock W., Gokbuget N., et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019;125(14):2474-2487. Epub 20190328. DOI: 10.1002/cncr.32116.

[48] Cortes J. E., Kim D. W., Pinilla-Ibarz J., le Coutre P. D., Paquette R., Chuah C., et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018;132(4):393-404. Epub 20180322. DOI: 10.1182/blood-2016-09-739086.

[49] Shah B. D., Cassaday R. D., Park J. H., Houot R., Logan A. C., Boissel N., et al. Three-year analysis of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. Leukemia. 2025;39(5):1058-1068. Epub 20250319. DOI: 10.1038/s41375-025-02532-7.

[50] Deutsche Gesellschaft für Hämatologie und medizinische Onkologie e.V. N. U.-u. B. N. A. Obecabtagene-autoleucel. 2025 [cited 15.07.2025]. Available from: https://www.dgho.de/arbeitskreise/a-g/drg-gesundheitsoekonomie/nub-2025/atmp-1-obecabtagen-autoleucel_dgho_stand-2025-04-15_final.pdf/view.

[51] Shah B. D., Ghobadi A., Oluwole O. O., Logan A. C., Boissel N., Cassaday R. D., et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491-502. Epub 20210604. DOI: 10.1016/S0140-6736(21)01222-8.

[52] Roddie C.; Sandhu K. T., E. et al. Protocol for Obecabtagene autoleucel in adults with B-cell acute lymphoblastic leukemia. New England Journal of Medicine. 2024(391):2219-2230. DOI: DOI: 10.1056/NEJMoa2406526.

[53] European Medicines Agency (EMA). Blincyto. Summary of product characteristics. 2025 [cited 23.07.2025]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto.

[54] European Medicines Agency (EMA). Besponsa. Summary of product characteristics.: 2024 [cited 23.07.2025]. Available from: https://www.ema.europa.eu/en/documents/product-information/besponsa-epar-product-information_en.pdf.

[55] Österreichischen Gesellschaft für Hämatologie und Medizinische Onkologie (OeGHO). Qualitätsgesicherte Durchführung der CAR-T-Zelltherapie in Österreich. 2019 [cited 17.07.2025]. Available from: https://www.oegho.at/fileadmin/Benutzer/qualitaetskriterien-car-t-zentren-final.pdf.

[56] European Medicines Agency (EMA). Iclusig. Summary of product characteristics. 2025 [cited 23.07.2025]. Available from: https://www.ema.europa.eu/en/documents/product-information/iclusig-epar-product-information_en.pdf.

[57] Pagliuca S., Schmid C., Santoro N., Simonetta F., Battipaglia G., Guillaume T., et al. Donor lymphocyte infusion after allogeneic haematopoietic cell transplantation for haematological malignancies: basic considerations and best practice recommendations from the EBMT. Lancet Haematol. 2024;11(6):e448-e458. DOI: 10.1016/S2352-3026(24)00098-X.

[58] Serpenti F., Fidanza C. A., Barbullushi K., Cavallaro F., Tagliaferri E., Goldaniga M., et al. Donor Lymphocyte Infusions in Acute Lymphoblastic Leukemia: A Single-Center Retrospective Analysis. Blood. 2024;144. DOI: https://doi.org/10.1182/blood-2024-207699.

[59] Die CAR-T-Zellplattform der Österreichischen Gesellschaft für Hämatologie und Medizinischen Onkologie (OeGHO). Qualitätsgesicherte Durchführung der CAR-T-Zelltherapie in Österreich. 2019 [cited 08.07.2025]. Available from: https://www.oegho.at/fileadmin/Benutzer/qualitaetskriterien-car-t-zentren-final.pdf.

[60] Rudzki J. D. Update zur CAR-T-Zelltherapie für Zuweiser: Patientenselektion für die CAR-T-Zelltherapie. 2021 [cited 18.07.2025]. Available from: https://innere-med-1.meduniwien.ac.at/fileadmin/content/OE/innere-med-1/dokumente/Haema/Div_For_Car_T-Cell_Network_150621-ES.pdf.

[61] Jäger U. Österreichisches CAR-T-Zell-Netzwerk – eine Standortbestimmung. 2022 [cited 17.07.2025]. Available from: https://car-t-cell.com/aktuelles/oesterreichisches-car-t-zell-netzwerk-eine-standortbestimmung.

[62] Die Plattform zur CAR-T-Zelltherapie. CAR-T-Zelltherapie in Österreich und Deutschland. [cited 07.07.2025]. Available from: https://car-t-cell.com/zentren.

[63] World Map Blank. Karte von Österreich mit Bundesländern und Städten [PDF]. 2023 [cited 24.07.2025]. Available from: https://statics.teams.cdn.office.net/evergreen-assets/safelinks/2/atp-safelinks.html.

[64] Perica K., Curran K. J., Brentjens R. J. and Giralt S. A. Building a CAR Garage: Preparing for the Delivery of Commercial CAR T-Cell Products at Memorial Sloan Kettering Cancer Center. Biol Blood Marrow Transplant. 2018;24(6):1135-1141. Epub 20180301. DOI: 10.1016/j.bbmt.2018.02.018.

[65] Khan A. N., Asija S., Pendhari J. and Purwar R. CAR T-cell therapy in hematological malignancies: Where are we now and where are we heading for? Eur J Haematol. 2024;112(1):6-18. Epub 20230807. DOI: 10.1111/ejh.14076.

[66] Crawford R., Sikirica S., Morrison R., Cappelleri J. C., Russell-Smith A., Shah R., et al. The Patient Experience of Acute Lymphoblastic Leukemia and Its Treatment: Social Media Review. JMIR Cancer. 2023;9:e39852. Epub 20230501. DOI: 10.2196/39852.

[67] Patient involvement. 2025.

[68] York Health Economics Consortium (YHEC). Discrete Choice Expertiment (DCE). 2016 [cited 28.07.2025]. Available from: https://yhec.co.uk/glossary/discrete-choice-experiment-dce/.

[69] Mott D. J., Hitch J., Nier S., Pemberton-Whiteley Z. and Skedgel C. Patient Preferences for Treatment in Relapsed/Refractory Acute Leukemia in the United Kingdom: A Discrete Choice Experiment. Patient Prefer Adherence. 2024;18:1243-1255. Epub 20240617. DOI: 10.2147/PPA.S442530.

[70] Kumari R., Kohli A., Malhotra P., Grover S. and Khadwal A. Burden of caregiving and its impact in the patients of acute lymphoblastic leukemia. Ind Psychiatry J. 2018;27(2):249-258. DOI: 10.4103/ipj.ipj_75_18.

[71] selpers. Presseaussendung vom 25. April 2024. 2024.

[72] selpers. CAR-T Coach by selpers. 2023 [cited 16.07.2025]. Available from: https://selpers.com/car-t-coach/.

[73] Farroni J. S., Thompson P. A., Arif D., Cortes J. E. and Gallagher C. M. Ethical Issues in Patients with Leukemia: Practice Points and Educational Topics for the Clinical Oncologist and Trainees. Journal of Clinical Research & Bioethics. 2017;08(05). DOI: 10.4172/2155-9627.1000314.

[74] Varkey B. Principles of Clinical Ethics and Their Application to Practice. Med Princ Pract. 2021;30(1):17-28. Epub 20200604. DOI: 10.1159/000509119.

[75] Imbach K. J., Patel A. and Levine A. D. Ethical Considerations in the Translation of CAR T-Cell Therapies. Cell and Gene Therapy Insights. 2018;4(4):295-307. DOI: 10.18609/cgti.2018.030.

[76] Johnston H., Youshanlouei H. R., Osei C., Patel A. A., DuVall A., Wang P., et al. Socioeconomic determinants of the biology and outcomes of acute lymphoblastic leukemia in adults. Blood Adv. 2024;8(1):164-171. DOI: 10.1182/bloodadvances.2023011862.

[77] European Society for Blood and Marrow Transplantation (EBMT). The EBMT Registry. 2025 [cited 10.07.2025]. Available from: https://www.ebmt.org/registry/ebmt-registry.

[78] European Society for Blood and Marrow Transplantation (EBMT). CAR T Data Collection Initiative. 2025 [cited 10.07.2025]. Available from: https://www.ebmt.org/registry/ebmt-car-t-data-collection-initiative?_gl=1*zty1pu*_up*MQ..*_ga*NDAxMjI4NDI3LjE3NTIxMzMxOTU.*_ga_3WD8VFX5KR*czE3NTIxMzMxOTUkbzEkZzAkdDE3NTIxMzMxOTUkajYwJGwwJGgw.

[79] Austrian Group Medical Tumor Therapy (AGMT). AGMT_ALL Registry. [cited 24.07.2025]. Available from: https://www.agmt.at/all-registry/?lang=en.

[80] University College London. UCL spinout Autolus gains UK licence for cancer therapy. 2025 [cited 13.08.2025]. Available from: https://www.ucl.ac.uk/news/2025/apr/ucl-spinout-autolus-gains-uk-licence-cancer-therapy.

[81] RePorter. Improving Cord Blood Transplantation. 2025 [cited 14.08.2025]. Available from: https://reporter.nih.gov/search/4Z9Y9mQunEOfZSHtDmB9nA/project-details/9134065.

[82] Carroll J. The CAR T brain war: Scientific trailblazer inspires a $45M biotech startup. Journal. 2015. Epub Epub Date. Original Publication.

[83] Reynolds J. Autolus Limited secures £40 million funding – Woodford Investment Management and Perceptive Bioscience complete Series B financing. Journal. 2016. Epub Epub Date. Original Publication.

[84] Wilson J. AUTOLUS LIMITED: Autolus Secures US$80 million Series C Funding. Journal. 2017. Epub Epub Date. Original Publication.

[85] Taylor P. IPO bonanza continues with $150M listing for CAR T player Autolus. Journal. 2018. Epub Epub Date. Original Publication.

[86] Bonanos P. Autolus follows up CAR T data with $101M raise. Journal. 2019. Epub Epub Date. Original Publication.

[87] Autolus Therapeutics plc. Form 10-K: ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934. 2024.

[88] U.S. National Library of Medicine and ClinicalTrials.gov. 2025 [cited 08.07.2025]. Available from: https://clinicaltrials.gov/.

[89] U.S. National Library of Medicine and ClinicalTrials.gov. A Study of CD19 Targeted CAR T-Cell Therapy in Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia (ALL). 2024 [cited 11.07.2025]. Available from: https://clinicaltrials.gov/study/NCT04404660.

[90] U.S. National Library of Medicine and ClinicalTrials.gov. Phase 2 Study Assessing the Clinical Activity and Safety of Obecabtagene Autoleucel as a Consolidation in Patients With Newly Diagnosed High-risk B-cell Acute Lymphocytic Leukemia (ALL). 2025 [cited 11.07.2025]. Available from: https://clinicaltrials.gov/study/NCT07053059?cond=Acute%20Lymphoblastic%20Leukemia&intr=Obecabtagene%20autoleucel%20%5C(obe-cel%5C)&rank=1.

[91] U.S. National Library of Medicine and ClinicalTrials.gov. Expanded Access Program for OOS Obe-cel. 2025 [cited 11.07.2025]. Available from: https://clinicaltrials.gov/study/NCT06799221.

[92] European Medicines Agency (EMA). Tecartus. Summary of product characteristics.: 2025 [cited 23.07.2025]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus.

[93] Shah B. D., Ghobadi A., Oluwole O. O., Logan A. C., Boissel N., Cassaday R. D., et al. Two-year follow-up of KTE-X19 in patients with relapsed or refractory adult B-cell acute lymphoblastic leukemia in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study. J Hematol Oncol. 2022;15(1):170. Epub 20221210. DOI: 10.1186/s13045-022-01379-0.

[94] Kantarjian H. M., DeAngelo D. J., Stelljes M., Martinelli G., Liedtke M., Stock W., et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. New England Journal of Medicine. 2016;375(8):740-753. Epub 20160612. DOI: 10.1056/NEJMoa1509277.

[95] Gokbuget N., Kelsh M., Chia V., Advani A., Bassan R., Dombret H., et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016;6(9):e473. Epub 20160923. DOI: 10.1038/bcj.2016.84.

[96] Molina J. C. and Shah N. N. CAR T-cells better than BiTEs. Blood Adv. 2021;5(2):602-606. DOI: 10.1182/bloodadvances.2020003554.

[97] Pasvolsky O., Kebriaei P., Shah B. D., Jabbour E. and Jain N. Chimeric antigen receptor T-cell therapy for adult B-cell acute lymphoblastic leukemia: state-of-the-(C)ART and the road ahead. Blood Adv. 2023;7(14):3350-3360. DOI: 10.1182/bloodadvances.2022009462.

[98] Yared J. A., Fromowitz A., Kocoglu M., Hardy N., Atanackovic D. and Rapoport A. P. Obecabtagene autoleucel, a novel CD19-directed CAR T-cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia: the future for reducing toxicity and T-cell exhaustion? Journal. 2025. Epub Epub Date. Original Publication. DOI: https://dx.doi.org/10.1080/17474086.2025.2523551.

[99] Personal communication with clinical experts. July 2025. 2025.

List of abbreviations

AE	adverse event
AGMT	Austrian Group Medical Tumor Therapy
AIHTA	Austrian Institute for Health Technology Assessment GmbH
ALL	acute lymphoblastic leukaemia
allo-SCT	allogeneic stem cell transplant
ASBMT	American Society for Blood and Marrow Transplantation
ASCTR	Austrian Stem Cell Transplantation Registry
ASTCT	American Society for Transplantation and Cellular Therapy
ATECT	Advanced T-cell Engineered for Cancer Therapy
ATMP	advanced therapy medicinal product
Autolus	Autolus Therapeutics
Azer-cel	azercabtagene zapraleucel
B-ALL	B-cell acute lymphoblastic leukaemia
BCR::ABL1	breakpoint cluster region-ABL proto-oncogene 1
BIA	budget impact analysis
BLI	blinatumomab
BM	bone marrow
Brexu-cel	brexucabtagene autoleucel
CAR	chimeric antigen receptor
CARAT	CARs for Advanced Therapies
CAR T	chimeric antigen receptor T-cell
CAT	Committee for Advanced Therapies
CD19	cluster of differentiation 19
CEA	cost-effectiveness analysis
CG	clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CML	chronic myeloid leukaemia
CNS	central nervous system
COMP	Committee for Orphan Medicinal Products
COVID-19	Coronavirus Disease 2019
CR	complete remission
CR1	first complete remission
CR2	second complete remission
CRi	complete remission with incomplete haematologic recovery
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CUA	cost-utility analysis
DACH	Germany, Austria and Switzerland
DCE	discrete choice experiment
DLI	donor lymphocyte infusion
DOR	duration of remission
DPFS	Developmental Pathway Funding Scheme
DRG	Diagnosis Related Groups
DUX4	double homeobox 4
EAG	Evidence Assessment Group
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECB	European Central Bank
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EHA	European Hematology Association
EKO	Ethikkommission Oberösterreich
ELN	European Leukemia Network
EM	extramedullary
EMA	European Medicines Agency
ENT	ear, nose and throat
EORTC Q.-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ESMO	European Society for Medical Oncology

ESMO-MCBS..... European Society for Medical Oncology Magnitude of Clinical Benefit Scale
ESS ..... effective sample size
ETV6-RUNX1 – ETS variant 6-runt related transcription factor 1
EU ..... European Union
EUnetHTA..... European Network for Health Technology Assessment
f..... female
FDA ..... U.S. Food and Drug Administration
GMP ..... good manufacturing practice
GÖG..... Austrian Public Health Institute (Gesundheit Österreich GmbH)
GRADE..... grading of recommendations assessment, development and evaluation
GvT..... graft-versus-tumour
HBV..... hepatitis B virus
HCV..... hepatitis C virus
HEE..... health economic evaluation
HIV ..... human immunodeficiency virus
HLA..... human leucocyte antigens
HRQoL ..... health-related quality of life
HSCT..... haematopoietic stem cell transplantation
HTA..... health technology assessment
HTLV ..... human T-lymphotropic virus type
ICANS..... immune effector cell-associated neurotoxicity
ICC ..... International Consensus Classification
ICER..... incremental cost effectiveness ratio
ICU..... intensive care unit
ID ..... identification
IG..... immunoglobulin
IHSI ..... International Horizon Scanning Initiative
INAHTA..... International Network of Agencies for Health Technology Assessment
INN..... international nonproprietary name
IO ..... inotuzumab ozogamicin
IPO ..... initial public offering
IRRC..... independent response review committee
ITC..... indirect treatment comparison
ITT..... intention-to-treat
IV..... intravenous(ly)
IV IG..... intravenous immunoglobulin
i4i..... Invention for Innovation
JACIE ..... Joint Accreditation Committee ISCT-EBMT
JCA..... joint clinical assessment
KMT2A ..... lysine methyltransferase 2A
LBL..... lymphoblastic lymphoma
Liso-cel..... lisocabtagene maraleucel
LKF..... Leistungsorientierte Krankenanstaltenfinanzierung
m..... male
MAH..... marketing authorisation holder
MAIC..... matching adjusted indirect comparison
MAX ..... maximum
MEF2D..... myocyte enhancer factor 2D
MHRA..... Medicines and Healthcare products Regulatory Agency
MIN ..... minimum
mITT..... modified intention-to-treat
molCR ..... molecular complete remission
MRC ..... Medical Research Council
MRD..... measurable residual disease
n ..... number
NA..... not applicable
NCCN..... National Comprehensive Cancer Network
NCI ..... National Cancer Institute
NCI CTCAE..... National Cancer Institute Common Terminology Criteria for Adverse Events
NCT ..... National Clinical Trial
NexTGen..... Next Generation T cell Therapies for Childhood Cancers
NFA..... next-generation sequencing flow cytometry assay
NHS..... National Health Service
NICE ..... National Institute for Health and Care Excellence

NIHR ..... National Institute for Health and Care Research
NR ..... not reported
NUB ..... Neue Untersuchungs- und Behandlungsmethoden
Obe-cel ..... obecabtagene autoleucel
OeGHO ..... Austrian Society for Haematology and Medical Oncology (Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie)
ORR ..... overall remission rate
OS ..... overall survival
PAS ..... Patient Access Scheme
PFS ..... progression-free survival
Ph- ..... Philadelphia chromosome-negative
Ph+ ..... Philadelphia chromosome-positive
Ph ..... Philadelphia chromosome
PICO ..... patient, intervention, comparison and outcome
PON ..... ponatinib
PPRI ..... Pharmaceutical Pricing and Reimbursement Information
PRIME ..... PRIority Medicines
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Prov ..... provisional
PSS ..... Personal Social Services
Pts ..... patients
QALY ..... quality-adjusted life year
QoL ..... quality of life
R&D ..... research and development
REMS ..... Risk Evaluation and Mitigation Strategies
RFS ..... relapse-free survival
RNA ..... ribonucleic acid
RoB ..... risk of bias
r/r ..... relapsed or refractory
SAE ..... serious adverse event
SCT ..... stem cell transplantation
SD ..... standard deviation
SEC ..... Security and Exchange Commission
SMR ..... standardised mortality ratio
SoC ..... standard of care
SOP ..... standard operating procedure
TEAE ..... treatment-emergent adverse events
TKI ..... tyrosine kinase inhibitor
UCL ..... University College London
UCLB ..... University College London Business
UK ..... United Kingdom
US ..... United States
VAS ..... Visual Analogue Scale
VAT ..... Value Added Tax
WHO ..... World Health Organisation
WHO-ICTRP ..... World Health Organisation International Clinical Trials Registry Platform
WHO5 ..... 5th edition of the World Health Organization classification of haematolymphoid tumours
WTP ..... willingness-to-pay
ZNF384 ..... zinc finger protein 384

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