HTA Austria
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

HTA-Appendix

Appendix

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1 Introduction

1.1 Disease background

Table 1-1: Differential diagnosis for B-ALL [1]

Malignant disorders	
T cell ALL/LBL	Immunophenotyping is required to distinguish T-ALL/LBL from B-ALL/LBL.
Burkitt lymphoma	Typically, the malignant cells of Burkitt lymphoma (BL) have a different appearance from lymphoblasts in smears. However, there is sufficient overlap that this distinction cannot be made reliably, particularly in cases of BL with extensive marrow involvement.
Other acute leukaemias	B-ALL/LBL lymphoblasts may be difficult to distinguish morphologically from other forms of acute leukaemia, particularly those that are minimally differentiated, including acute myeloid leukaemia (AML), acute undifferentiated leukaemia and mixed phenotype leukaemia.
Other lymphoproliferative disorders	Other lymphoproliferative disorders that may resemble B-ALL clinically and/or morphologically can be distinguished by immunophenotype and/or genetic features, including chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), B prolymphocytic leukaemia, mantle cell lymphoma (MCL), and plasma cell leukaemia.
Chronic myeloid leukaemia (CML) in blast crisis	Morphologically, CML is typically manifested as an expanded population of myeloid cells at various stages of differentiation with the Philadelphia chromosome, t(9;22), and BCR::ABL1 rearrangement. About 10 percent of blast crisis CML may have a dominant population of lymphoblasts, but in this setting, the Philadelphia chromosome is detected in myeloid cells and basophilia may be present.
Small round blue cell tumours	In children, small round blue cell tumours, including Ewing sarcoma and peripheral primitive neuroectodermal tumour, may resemble B-ALL morphologically. These disorders are distinguished by a uniform population of small, round, blue cells with hyperchromatic nuclei and scant cytoplasm, absence of B lymphoid markers and presence of specific characteristic cytogenetic/molecular findings.
Nonmalignant disorders	
Certain non-malignant disorders may resemble B-ALL in a morphologic and/or clinical way. In adults and children, the following disorders may be included in the differential diagnosis: ❖ Human immunodeficiency virus ❖ Infectious mononucleosis ❖ Pertussis ❖ Osteomyelitis ❖ Tuberculosis ❖ Heavy metal toxicity ❖ Thymoma ❖ Autoimmune diseases (including juvenile rheumatoid arthritis in children)	

Abbreviations: ALL…acute lymphoblastic leukaemia, B-ALL…B-cell acute lymphoblastic leukaemia, BCR-ABL1…breakpoint cluster region-ABL proto-oncogene 1, BL…Burkitt lymphoma, CML…chronic myeloid leukaemia, LBL…lymphoblastic lymphoma, MCL…mantle cell lymphoma, Ph…Philadelphia chromosome, T-ALL…T-cell acute lymphoblastic leukaemia

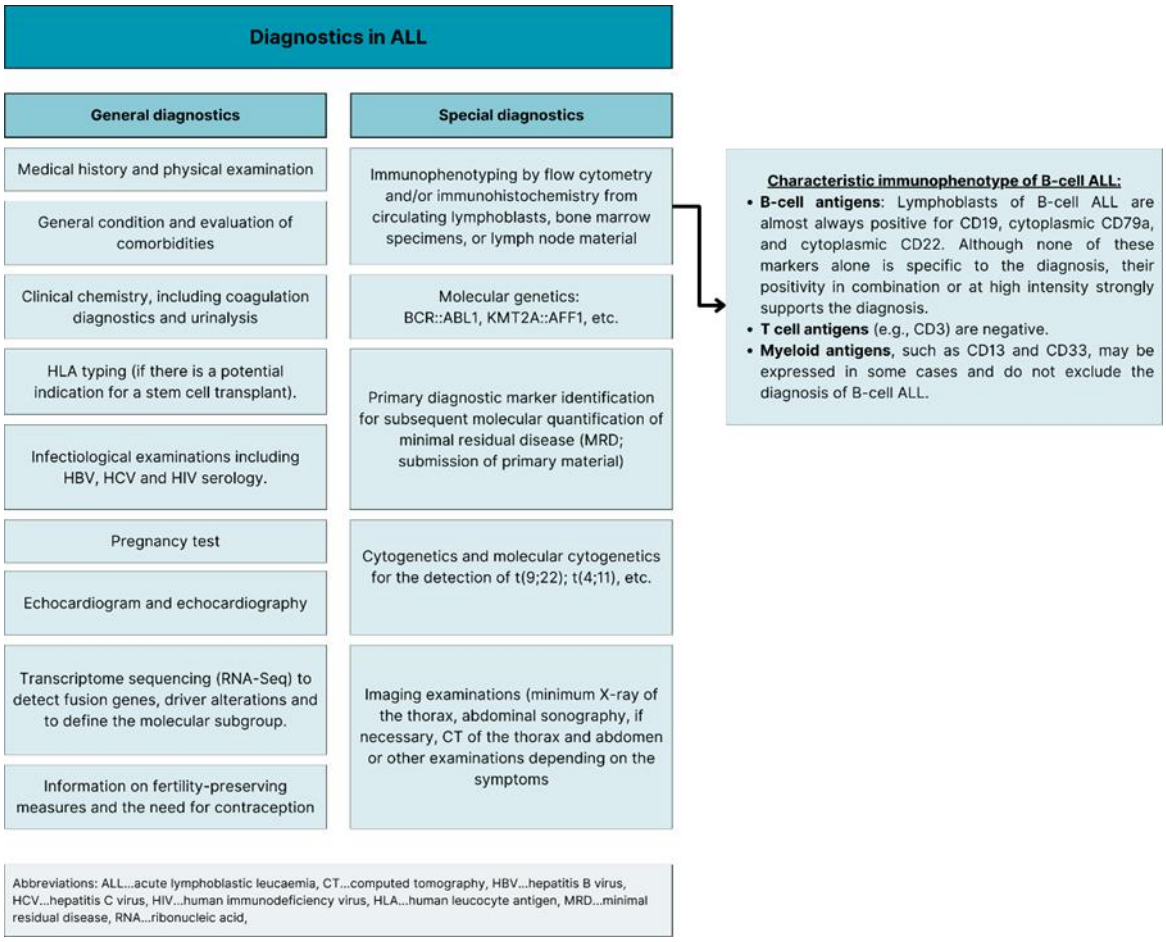

Figure 1-1: Diagnostic steps in ALL [1, 2]

1.2 Standard of care in Austria

No additional tables or figures are provided for this chapter.

1.3 Medicinal product under evaluation

Requirements for companion diagnostics and/or monitoring [3-5]

- Monitoring during and after the infusion, respectively, is required for:
  - Hypersensitivity reactions
  - Cytokine release syndrome (CRS), neurologic toxicities/immune effector cell-associated neurotoxicity (ICANS) and other acute toxicities (daily for at least 14 days at the healthcare facility following the first infusion).
  - *Cytopenias*, including anaemia, neutropenia, and thrombocytopenia (blood count monitoring).
  - *Immunoglobulin levels* (monitoring and management per institutional guidelines)
  - Infection
  - *Secondary malignancies*. Mature T cell malignancies (including CAR-positive tumours) may present as early as weeks following infusion and may include fatal outcomes (lifelong monitoring) required [5].
- Monitoring should be continued for at least four weeks following each infusion. Thus, patients should be instructed to remain within proximity of a healthcare facility for at least four weeks following the first infusion to enable close monitoring [5]. It is recommended that patients remain hospitalised for at least 14 days following infusion [4].
- Patients should avoid driving or engaging in hazardous activities for eight weeks after treatment, as treatment with obe-cel can cause sleepiness, confusion, weakness, and temporary problems with memory and coordination [3, 5].

Monitoring während und nach der Infusion:

Hypersensitivität, CRS, ICANS, Zytopenie, Immunglobinspiegel, Infektionen

Entwicklung sekundärer Malignome möglich, lebenslanges Monitoring notwendig

14 Tage stationärer Aufenthalt empfohlen

für 8 Wochen: potenziell gefährliche Tätigkeiten meiden

2 Scope of assessment

No additional tables or figures are provided for this chapter.

3 Methods

Guiding questions based on the EUnetHTA core model [6]

Table 3-1: Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes, is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table 3-2: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?
A0018	What are the other typical or common alternatives to the current technology?
A0022	Who manufactures the technology?

Abbreviation: CE…European Conformity marking (Conformité Européene)

Table 3-3: Clinical effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect the progression (or recurrence) of the disease or health condition?
D0012	What is the effect of the technology on generic health-related quality of life?

D0013	What is the effect of the technology on disease-specific quality of life?

Table 3-4: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Table 3-5: Economic aspects

Element ID	Research question
E0001	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
A0002	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated costs of the assessed technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s) (outcome identification, measurement and valuation)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?
E0013	What methodological assumptions were made in relation to the technology and its comparator(s)?
E0012	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?

Table 3-6: Organisational, ethical, and social aspects

Element ID	Research question
G0001:	How does the technology affect the current work processes?
G0002	What kind of involvement has to be mobilised for patients/participants, important others, and/or caregivers?
G0101	What are the processes ensuring access to the new technology for patients/participants?
H0200	What are the experiences of living with the condition?
H0100	What expectations and wishes do patients have with regard to the technology, and what do they expect to gain from the technology?
H0006	How do patients perceive the technology under assessment?
H0002	What is the burden on caregivers?

H0202	How are treatment choices explained to patients?
F0010	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?
F0011	What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.?
F0104	Are there any ethical obstacles to evidence generation regarding the benefits and harms of the intervention?
F0005	Is the technology used for individuals who are especially vulnerable?
H0012	Are there factors that could prevent a group or person from gaining access to the technology?

3.1 Search strategy

3.1.1 Cochrane (04.07.2025)

Search name: Aucatzyl	
Search date: 04.07.2025	
ID	Search
#1	("obecabtagene autoleucel") (Word variations have been searched)
#2	(aucatzyl*) (Word variations have been searched)
#3	(auto NEXT 1) (Word variations have been searched)
#4	(cat NEXT 19) (Word variations have been searched)
#5	(cat19) (Word variations have been searched)
#6	(obe-cel*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#9	#7 NOT #8
Total hits: 11	

3.1.2 Embase (04.07.2025)

Search name: Aucatzyl		
Search date: 04.07.2025		
No.	Query Results	Results
#10.	#8 NOT #9	97
#9.	'clinical trial':dtype	533,362
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	104
#7.	'obe-cel*'	17

#6.	cat19	11
#5.	'cat 19'	50
#4.	'auto1 (research code)'	
#3.	'auto 1 (research code)'	
#2.	aucatzyl*	4
#1.	'obecabtagene autoleucel'/exp	48

3.1.3 International HTA database (04.07.2025)

Search name: Aucatzyl	
Search date: 04.07.2025	
Search Step	Search query, "Hits", "Search At"
7	(obe-cel*) OR (cat19) OR ("cat 19") OR ("auto 1") OR (aucatzyl*) OR ("obecabtagene autoleucel"),"0","2025-07-04T18:16:51.000000Z"
6	obe-cel*,"0","2025-07-04T18:16:37.000000Z"
5	cat19,"0","2025-07-04T18:16:06.000000Z"
4	"cat 19","0","2025-07-04T18:15:52.000000Z"
3	"auto 1","0","2025-07-04T18:15:22.000000Z"
2	aucatzyl*,"0","2025-07-04T18:14:53.000000Z"
1	"obecabtagene autoleucel","0","2025-07-04T18:14:23.000000Z"
Total hits: 0	

3.1.4 Medline (03.07.2025)

Search name: Aucatzyl	
Search date 03.07.2025	
1	obecabtagene autoleucel.mp. (12)
2	aucatzyl*.mp. (4)
3	auto 1.mp. (2)
4	cat 19.mp. (16)
5	cat19.mp. (3)
6	obe-cel*.mp. (4)
7	1 or 2 or 3 or 4 or 5 or 6 (34)
Total hits: 34	

3.2 Study selection – PRISMA flow chart

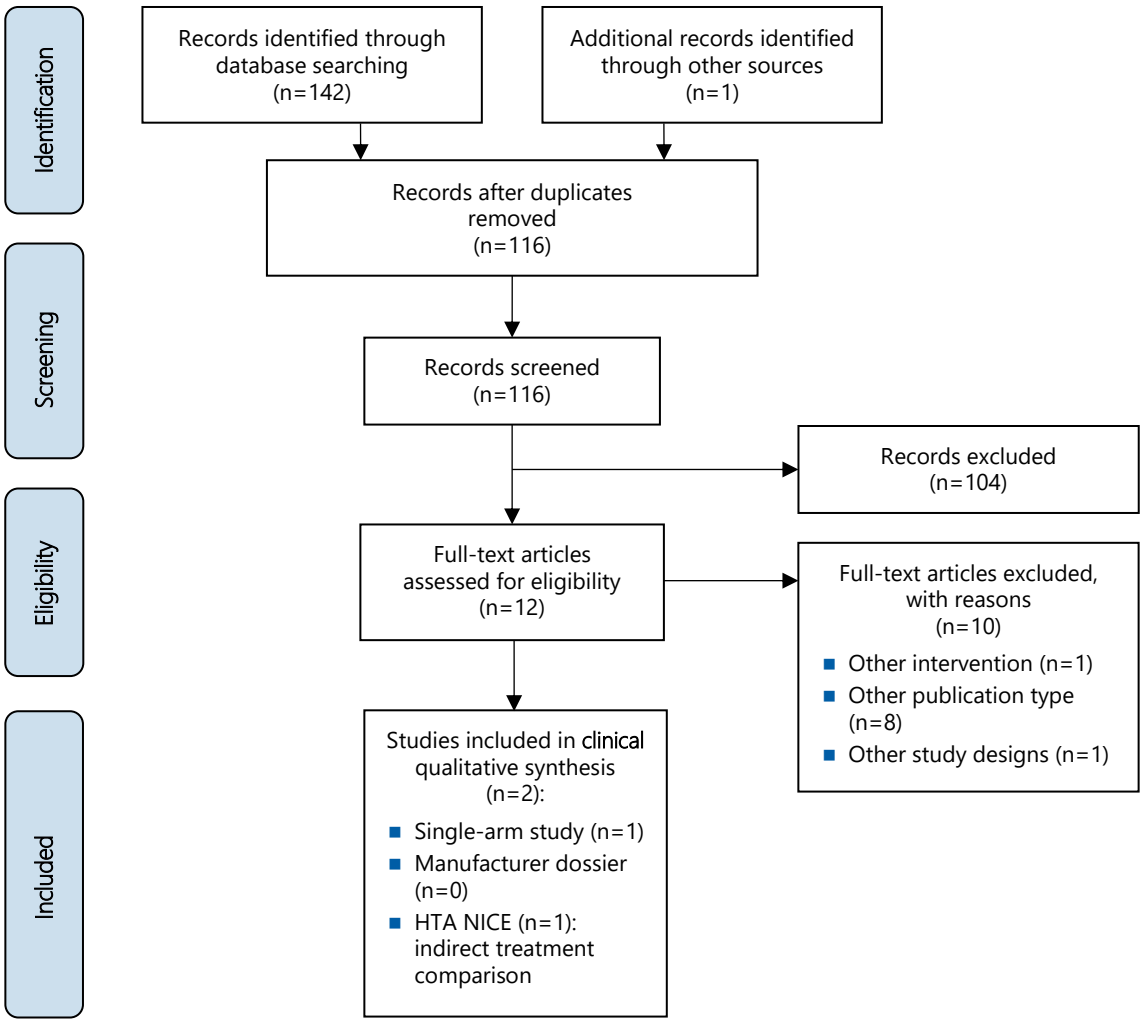

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

Note. The systematic literature search did not identify any economic model for obecel.

Abbreviations: HTA…health technology assessment, NICE…National Institute for Health and Care Ecellence, n…number.

3.3 Organisational, ethical and social assessment

3.3.1 Structured patient questionnaires

Table 3-7: Questions for patients diagnosed with ALL

Question 1	In welcher Rolle füllen Sie den Fragebogen aus? ▪ Einzelne/r Patient:in ▪ Angehörige ▪ Andere
Question 2	In welchem Land befindet sich Ihr Hauptwohnsitz?
Question 3	Sind Sie Mitglied einer Patient:innenorganisation? Wenn ja: ▪ Bei welcher Patient:innenorganisaiton sind Sie Mitglied? ▪ Welche Erkrankung/en wird/werden von der Patient:innenorganisation vertreten? ▪ Welche Rolle haben Sie in der Patient:innenorganisation?
Question 4a	Wie lautet die Diagnose?
Question 4b	In welchem Stadium befindet sie die Erkrankung? Wie würden Sie den Schweregrad aktuell einschätzen?
Question 4c	Welche Symptome haben Sie/hat Ihre Angehöriger/ Ihr Angehöriger derzeit?
Question 4d	Krankheitsgeschichte: ▪ Seit wann leben Sie/ Ihre Angehörige/ Ihr Angehöriger mit der Erkrankung? Wann wurde sie diagnostiziert? ▪ Bitte beschreiben Sie die Behandlungsgeschichte: Wie wurde die Erkrankung festgestellt? Welche Behandlungen wurden bisher durchgeführt?
Question 4e	Zusätzliche Information, die Ihrer Meinung nach für den HTA-Bericht hilfreich wären.
Question 5	Falls zutreffend, wie sind Sie an Informationen zu den Erfahrungen von Patient:innen gelangt? ▪ Persönliche Erfahrungen ▪ Erlebnisse von Patient:innen
Question 6	Was beeinflusst die Erkrankung Ihr tägliches Leben (bzw. das Leben einer Patient/ eines Patienten)?
Question 7	Nur für Patient:innen: Welche Auswirkungen hat die Erkrankung auf Ihr familiäres und soziales Umfeld?
Question 8	Nur für Angehörige: Wie wirkt sich die Erkrankung auf das familiäre und soziale Umfeld aus?
Question 9	Wie geht es Ihnen/ Ihrer Angehörigen/ Ihrem Angehörigen mit der derzeit angewandten Therapie? Falls keine spezifische Therapie zur Verfügung steht, geben Sie das bitte an.
Question 10	Kennen Sie das Medikament Obecabtagene Autoleucel (AUCATZYL®)?
Question 11a	Was würden Sie/ Ihre Angehörige/ Ihr Angehöriger im Allgemeinen von einer neuen Therapie erwarten?
Question 11b	Welche Bedenken haben Sie gegenüber dem neuen Medikament?
Question 12	Für Personen, die Erfahrung mit Obecabtagene Autloeucel (AUCATZYL®) im Rahmen von klinischen Studien haben: Welche Auswirkungen hatte/hat es auf Ihr Leben (positive und negative Auswirkungen)?
Question 13	Bitte geben Sie alles an, was Ihrer Meinung nach für die Bewertung des Arzneimittels durch das zuständige HTA-Team wissenswert sein könnte (z.B. ethische oder soziale Aspekte).
Question 14	Bitte fassen Sie, die aus Ihrer Sicht wichtigsten Punkte, in maximal fünf Aussagen zusammen. Beispiel: ▪ Die größten Herausforderungen eines Lebens mit r/r ALL sind … ▪ Die derzeitigen Therapien/Gesundheitsinterventionen sind ungeeignet, weil … ▪ Die Patient:innen erwarten sich von einer neuen Therapie vor allem …

Abbreviations: ALL…acute lymphoblastic leukaemia, HTA…health technology assessment, r/r…relapsed or refractory

3.3.2 Clinical expert consultations

Table 3-8: Questions for clinical experts

Questions about the population	
Questions about the planned EMA indication for obecabtagene autoleucel (obe-cel, AUCATZYL®) for the treatment of adults (≥ 26 years) with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (r/r B-ALL)	
Question 1	Welches Klassifikationsschema für ALL (Morphologie/Zytogenetik) wird in Österreich angewendet?
Question 2	Gibt es wichtige/klinische-relevante Sub-Populationen hisichtlich der zugelassenen Indikation z.B. Ph+/Ph-?
Questions 3	Bedeutung der Risikostratifizierung nach GMALL (unter anderem MRD-Status, Genetik/Zytogenetik)?
Questions about the number of patients	
Question 4	Wie viele Patient:innen sind in Österreich für Obe-cel geplant?
Questions about the comparator	
Questions about comparator 1: chemotherapy	
Question 5	Welche Chemotherapien/Krebstherapien werden in Österreich für r/r B-ALL angewendet? Z.B. Clofarabine, Cyclophosphamide, Etoposide, Methotrexate, Vincristine, Pegaspargase, Rituximab, Fludarabine, Cytarabine, Idarubicin, Ifosfamide oder Mitoxantrone (laut ELN und NCCN)?
Question 6	Für volle genannte Indikation oder nur für Sub-Population, z.B. Ph+/Ph-?
Question 7	In welchem Setting werden die Chemotherapien in Österreich angewendet: stationär, tagesklinisch, ambulant?
Question 8	Was ist die mediane Behandlungsdauer der angewendeten Chemotherapien?
Question 9	Was sind therapiespezifische und kostenrelevante Begleittherapien beziehungsweise Folgetherapien, z.B. aufgrund von adverse events (AEs)?
Questions about comparator 2 (based on NCCN, ESMO, Onkopedia, ELN guidelines): blinatumomab (Blincyto®)	
Question 10	Wird die Therapie standardmäßig in Österreich für die r/r ALL angewendet?
Question 11	Wenn ja, für die volle Population oder vorzugsweise für Sub-Populationen Ph-/Ph+?
Question 12	Dauerinfusion/Infusionspumpe – wie lange stationär?
Question 13	Mediane Anzahl Behandlungszyklen (1-2? Weitere?)
Question 14	Was sind wichtige therapiespezifische und kostenrelevante Begleittherapien beziehungsweise Folgetherapien, z.B. aufgrund von AEs?
Questions about comparator 3 (based on NCCN, ESMO, Onkopedia, ELN guidelines): IOtuzumab ozogamicin (Besponsa®)	
Question 15	Wird diese Therapie standardmäßig in Österreich für die r/r B-ALL angewendet?
Question 16	Wenn ja, für die volle Population oder vorzugsweise für Sub-Populationen?
Question 17	In welchem Setting: stationär oder tagesklinisch?
Question 18	Was ist die mediane Behandlungszeit? (3-4-Wochen-Zyklen, 3 Zyklen?)
Question 19	Was sind wichtige therapiespezifische und kostenrelevante Begleittherapien beziehungsweise Folgetherapien, z.B. aufgrund von AEs?

Questions about comparator 4: tyrosine kinase inhibitors (TKI)	
Question 20	Welche TKIs werden in Österreich für r/r B-ALL angewendet? Z.B. Dasatinib, Imatinib, Ponatinib, Nilotinib, Bosutinib (laut ESMO & NCCN) oder Kombination von 2 TKIs (Asciminib + Dasatinib; laut NCCN)?
Question 21	Nur für Sub-Populationen Ph+?
Question 22	Orale Gabe – Verordnung extramural?
Question 23	Was ist die mediane Behandlungsdauer?
Question 24	Was sind wichtige therapiespezifische und kostenrelevante Begleittherapien bzw. Folgetherapien, z.B. aufgrund von AEs?
Questions about comparator 5 (based on ESMO, NCCN guidelines): allogenic stem cell transplantation	
Question 25	Wird diese Therapie standardmäßig in Österreich für die r/r B-ALL angewendet?
Question 26	Gilt die allogene Stammzellentransplantation als notwendige/mögliche Folgebehandlung nach CAR-T-Zelltherapien? Was gilt für eine vorherige allogene Stammzellentransplantation und eine anschließende CAR-T-Zelltherapie?
Question 27	Wenn ja, für die volle Population oder vorzugsweise für Sub-Populationen?
Question 28	Wir haben Kosteninformationen von zirka € 180.000 für gesamten Stammzellentransplantationsprozess – valide und auf Hämatoonkologie übertragbar?
Questions about comparator 6 (based on ESMO, NCCN, ELN, NICE guidelines): brexucabtagene autoleucel (Tecartus®)	
Question 29	Wird diese CART-T Zelltherapie in Österreich bei r/r B-ALL angewendet? Registerdaten für CAR-T beziehungsweise ALL (gleiche Indikation wie für Obe-cel)?
Question 30	Klinische Einschätzung von Obe-cel im Vergleich zu Brexu-cel: Gibt es eine Sub-Population, die besonders von Obe-cel profitieren würde, z.B. aufgrund geringerer AEs?
Question 31	Sind Begleitkosten von Brexu-cel vergleichbar mit jenen von Obe-cel (z.B. hinsichtlich Krankenhausaufenthalt und Vortherapien)?
Questions about comparator 7: tisagenlecleucel (Kymriah®)	
Question 32	Anwendung laut Zulassung nur bei Kindern, Jugendlichen und jungen erwachsenen Patient:innen im Alter bis einschließlich 25 Jahren mit r/r B-Zell-ALL ▪ Keine Bedeutung bei geplanter Zulassung von Obe-cel ▪ Laufende Studien bei Erwachsenen mit r/r B-ALL?
Questions about market shares in Austria	
Question 33	Marktanteile der SoC von Slowakei auf Österreich übertragbar? Mit allogener Stammzellentransplantation?
Question 34	Veränderte Marktanteile mit Obe-cel am Markt von Slowakei auf Österreich übertragbar?
Questions about the intervention	
Question 35	Gibt es weitere notwendige Vorbehandlungen oder Voruntersuchungen vor Obe-cel, neben Leukapherese, Knochenmarkuntersuchung, Lymphodepletion mit Fludarabin und Cyclophosphamid?
Question 36	Bekommen Patient:innen eine Überbrückungstherapie? Wann, welche, für wie lange und in welcher Dosierung?
Question 37	Welche Behandlungen von Nebenwirkungen erachten Sie als kosten-relevant, z.B.? ▪ CRS mit Tocilizumab und Vasopressoren (kostenrelevant?) behandelt? ▪ Hypogammaglobulinämie: Mit welchem Immunoglobulin behandelt? Für wie lange?
Question 38	Gibt es noch weitere kostenrelevante Aspekte bei der Behandlung mit Obe-cel?
Question 39	Welche Leitlinien sind für Österreich relevant?

Question 40	Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the EBMT and the JACIE and the EHA? – relevant?
Questions about outcomes	
Question 41	Kritische Endpunkte: ▪ Overall survival ▪ Progression-free survival / event-free survival / relapse-free survival ▪ Overall remission (response) rate ▪ Duration of remission (response) ▪ Quality of life ▪ Serious adverse events and treatment-emergent adverse events
Question 42	MRD-negative remission rate (CR und MRD-) – relevant?
Question 43	Anzahl der Patient:innen, die vor oder nach Obe-cel eine allogene Stamzellentransplantation haben – relevant?
Questions about the additional benefit	
Question 44	Einschätzung des Nutzens anhand der Studienergebnisse Felix Trial im Vergleich zu verfügbaren Therapien.
Question 45	18% der Pat:innen mit Response erhielten eine Transplantation nach Obe-cel, für 33% davon war es 2. SCT.
Question 46	Relevanz/Aussagekraft der indirekten Vergleiche?
Question 47	Vergleich CAR-T zu Brexu-cel?
Questions about the treatment algorithm	
Question 48	Wichtig zu unterscheiden ob vorher SCT?
Question 49	Relevanz CR oder CR/MRD?
Question 50	Unterscheidung 1. oder 2. Relapse?
Question 51	Zeitpunkt Relapse?
Questions about economic aspects	
Question 52	Anzahl Zyklen?
Question 53	Nach allo-SZT max. 4 Spenderlymphozyteninfusion angenommen, basierend auf einer Studie von 2024?
Question 54	Folgende modifizierende Faktoren können für die Einschätzung der Wirtschaftlichkeit zusätzlich herangezogen werden: Schweregrad der Erkrankung, Verfügbarkeit therapeutischer Alternativen, Wirkmechnaismus (anderes CAR-T Konstrukt und Verabreichung in 2 Dosen)?
Questions about selection criteria	
Question 55	Analog andere Indikationen für CAR-T-Zelltherapie (unter anderem Lymphom Selektionskriterien)?
Question 56	Lebenserwartung (Herstellungsprozess dauert 2-4 Wochen)?
Question 57	MRD-Negativität vor Therapie als prognostischer Marker wie bei SCT?
Question 58	Weitere Aspekte?

Abbreviations: AE…adverse event, ALL…acute lymphoblastic leukaemia, B-ALL…B-cell precursor acute lymphoblastic leukaemia, Brexu-cel…brexucabtagene autoleucel, CAR…chimeric antigen receptor, CR…complete remission, CRS…cytokine release syndrome, EBMT…European Society for Blood and Marrow Transplantation, EHA…European Hematology Association, ELN…European LeukemiaNet, ESMO…European Society for Medical Oncology, GMALL…German Multicenter Acute Lymphoblastic Leukemia, JACIE…Joint Accreditation of International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation, MRD…measurable residual disease, NCCN…National Comprehensive Cancer Network, NICE…National Institute for Health and Care Excellence, obe-cel…obecabtagene autoleucel, Ph…Philadelphia, r/r…relapsed or refractory, SoC…standard of care, SCT…stem cell transplantation, TKI..tyrosine kinase inhibitor

4 Clinical effectiveness and safety

4.1 Characteristics of included studies

4.1.1 Study population

Table 4-1: Bridging therapy in the total infused population and by cohort of the FELIX trial [7]

Bridging therapy regimen, n (%)	Phase 1B (n=16)		Phase 2 (n=111)			Total infused population (n=127)
	Cohort A (n=13)	Cohort B (n=3)	Cohort A (n=94)	Cohort B (n=10)	Cohort C (n=7)	
Number of patients with any bridging therapy	13 (100)	3 (100)	88 (93.6)	9 (90.0)	5 (71.4)	118 (92.9)
Chemotherapy alone	10 (76.9)	2 (66.7)	59 (62.8)	5 (50.0)	4 (57.1)	80 (63.0)
Chemotherapy + tyrosine kinase inhibitor therapy	3 (23.1)	0	6 (6.4)	1 (10.0)	0	10 (7.9)
Chemotherapy + Inotuzumab	0	0	8 (8.5)	0	1 (14.3)	9 (7.1)
Inotuzumab alone	0	0	9 (9.6)	0	0	9 (7.1)
Tyrosine kinase inhibitor therapy alone	0	1 (33.3)	3 (3.2)	3 (30.0)	0	7 (5.5)
Corticosteroids alone	0	0	2 (2.1)	0	0	2 (1.6)
Other	0	0	1 (1.1)	0	0	1 (0.8)

Note. Bridging therapies were coded using WHO Drug Global B3 202303.

Abbreviations: n…number, WHO…World Health Organisation.

Table 4-2: Obe-cel exposure in the total infused population and by cohort of the FELIX trial [7]

Obe-cel exposure	**Phase 1B (n=16)**		**Phase 2 (n=111)**			**Total infused population (n=127)**
	Cohort A (n=13)	**Cohort B (n=3)**	**Cohort A (n=94)**	**Cohort B (n=10)**	**Cohort C (n=7)**	
Obe-cel infusions completed/discontinued, n(%)	13 (100)	3 (100)	94 (100)	10 (100)	7 (100)	127 (100)
Total CAR T-cells	409.0	410.0	410.0	409.5	414.0	410.0
($\times 10^6$ cells), median (range)	(10–414)	(405–415)	(10–480)	(323–468)	(391–415)	(10–480)
Patients received both obe-cel doses, n (%)	12 (92.3)	3 (100)	88 (93.6)	10 (100)	7 (100)	120 (94.5)
Patients received dose 1 only, n (%)	1 (7.7)	0	6 (6.4)	0	0	7 (5.5)
Reason for not receiving dose 2, n (%)						
ICANS/CRS	0	0	3 (3.2)	0	0	3 (2.4)
Progressive disease	1 (7.7)	0	1 (1.1)	0	0	2 (1.6)
Manufacturing-related issues	0	0	1 (1.1)	0	0	1 (0.8)
Death	0	0	1 (1.1)	0	0	1 (0.8)

Note: Target dose is 410×10^6 CAR-positive T-cells (±25%)

Abbreviations: CAR T cell…chimeric antigen receptor T-cell, CRS…cytokine release syndrome, ICANS…immune effector cell-associated neurotoxicity syndrome, n…number, Obe-cel…Obecabtagene autoleucel

4.1.2 Baseline characteristics

Table 4-3: Baseline demographics and disease characteristics of participants of the FELIX trial [7]

Baseline demographics and disease characteristics	Phase 1B (n=16)		Phase 2 (n=111)		
	A (n=13)	B (n=3)	A (n=94)	B (n=7)	C (n=7)
Age (years)					

Baseline demographics and disease characteristics	Phase 1B (n=16)		Phase 2 (n=111)		
	A (n=13)	B (n=3)	A (n=94)	B (n=7)	C (n=7)
Mean (SD)	47.7 (17.1)	31.3 (13.1)	48.3 (17.1)	49.4 (15.5)	34.4 (10.3)
Median (range)	46.0 (24–74)	27.0 (21–46)	50.0 (20–81)	46.0 (26–73)	32.0 (23–54)
Age (years) categorised, n (%)					
≥18 to ≤25	1 (7.7)	1 (33.3)	11 (11.7)	0	1 (14.3)
25 to <40	5 (38.5)	1 (33.3)	20 (21.3)	3 (30.0)	5 (71.4)
≥40 to <65	5 (38.5)	1 (33.3)	42 (44.7)	5 (50.0)	1 (14.3)
≥65	2 (15.4)	0	21 (22.3)	2 (20.0)	0
Sex, n (%)					
Male	9 (69.2)	1 (33.3)	47 (50.0)	7 (70.0)	2 (28.6)
Female	4 (30.8)	2 (66.7)	47 (50.0)	3 (30.0)	5 (71.4)
Race, n (%)					
Asian	2 (15.4)	1 (33.3)	10 (10.6)	1 (10.0)	2 (28.6)
Black or African American	0	0	2 (2.1)	0	0
White	9 (69.2)	2 (66.7)	70 (74.5)	9 (90.0)	4 (57.1)
Unknown	2 (15.4)	0	12 (12.8)	0	1 (14.3)
Hispanic or Latino ethnic group, n (%)					
Yes	4 (30.8)	0	29 (30.9)	2 (20.0)	3 (42.9)
No	8 (61.5)	3 (100)	58 (61.7)	8 (80.0)	3 (42.9)
Unknown	1 (7.7)	0	7 (7.4)	0	1 (14.3)
Country, n (%)					
United States	9 (69.2)	1 (33.3)	47 (50.0)	4 (40.0)	5 (71.4)
United Kingdom	4 (30.8)	2 (66.7)	36 (38.3)	5 (50.0)	2 (28.6)
Spain	0	0	11 (11.7)	1 (10.0)	0
Previous therapies					
Number of prior lines of therapy[1]					
Mean (SD)	3.0 (1.3)	3.3 (1.1)	2.2 (1.1)	2.4 (0.7)	2.6 (0.8)
Median (range)	2.0 (2–6)	4.0 (2–4)	2.0 (1–6)	2.5 (1–3)	2.0 (2–4)

Baseline demographics and disease characteristics	Phase 1B (n=16)		Phase 2 (n=111)		
	A (n=13)	B (n=3)	A (n=94)	B (n=7)	C (n=7)
Number of prior lines of therapy categorized, n (%)					
1	0	0	29 (30.9)	1 (10.0)	0
2	7 (53.8)	1 (33.3)	36 (38.3)	4 (40.0)	4 (57.1)
3	2 (15.4)	0	17 (18.1)	5 (50.0)	2 (28.6)
≥4	4 (30.8)	2 (66.7)	12 (12.8)	0	1 (14.3)
Refractory to all prior lines of anti-cancer therapy, n (%)	0	0	12 (12.8)	1 (10.0)	0
Refractory to first-line therapy, n (%)	2 (15.4)	1 (33.3)	24 (25.5)	2 (20.0)	3 (42.9)
Relapsed to first-line therapy within 12 months, n (%)	7 (53.8)	1 (33.3)	41 (43.6)	8 (80.0)	3 (42.9)
Refractory to last prior line of therapy, n (%)	8 (61.5)	1 (33.3)	51 (54.3)	4 (40.0)	2 (28.6)
Previous blinatumomab, n (%)	7 (53.8)	2 (66.7)	33 (35.1)	5 (50.0)	6 (85.7)
Previous IOtuzumab ozogamicin, n (%)	4 (30.8)	1 (33.3)	30 (31.9)	3 (30.0)	2 (28.6)
Previous blinatumomab and IOtuzumab ozogamicin, n (%)	2 (15.4)	1 (33.3)	15 (16.0)	2 (20.0)	1 (14.3)
Previous blinatumomab or IOtuzumab ozogamicin, n (%)	9 (69.2)	2 (66.7)	48 (51.1)	6 (60.0)	7 (100)
Previous allo-SCT, n (%)	7 (53.8)	2 (66.7)	36 (38.3)	7 (70.0)	4 (57.1)
Disease characteristics					
BM blasts (%) by morphology					
Mean (SD)	65.7 (28.4)	1.3 (1.1)	53.4 (33.2)	1.6 (1.6)	0.7 (1.2)
Median (range)	80.0 (20–95)	2.0 (0–2)	58.9 (6–100)	1.5 (0–5)	0.0 (0–3)
BM blasts (%) by morphology categorized, n (%)					
<5%	0	3 (100)	0	9 (90.0)	7 (100)
≥5 to ≤20%	1 (7.7)	0	28 (29.8)	1 (10.0)	0
20 to ≤75%	5 (38.5)	0	32 (34.0)	0	0
>75%	7 (53.8)	0	34 (36.2)	0	0

Baseline demographics and disease characteristics	Phase 1B (n=16)		Phase 2 (n=111)		
	A (n=13)	B (n=3)	A (n=94)	B (n=7)	C (n=7)
Extramedullary disease presence, n (%)					
Absent	10 (76.9)	3 (100)	75 (79.8)	10 (100)	0
Present	3 (23.1)	0	19 (20.2)	0	7 (100)
ECOG performance status[2], n (%)					
0	4 (30.8)	2 (66.7)	35 (37.2)	5 (50.0)	4 (57.1)
1	9 (69.2)	1 (33.3)	58 (61.7)	5 (50.0)	3 (42.9)
Missing	0	0	1	0	0
CD19 status (by flow cytometry), n (%)					
Positive	13 (100)	3 (100)	94 (100)	10 (100)	7 (100)
Mixed population (positive + negative)	0	0	0	0	0
CNS disease history, n (%)					
CNS1[3]	13 (100)	2 (66.7)	81 (86.2)	9 (90.0)	7 (100)
CNS2[4]	0	1 (33.3)	2 (2.1)	0	0
Unknown	0	0	11 (11.7)	1 (10.0)	0

Note. [1]Previous lines of therapy are expected to include also chemotherapy; specific therapy types are not mentioned. [2]Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Data were missing for one patient in each group, [3] CNS1 indicates no lymphoblasts in cerebrospinal fluid regardless of the white-cell count, [4]CNS2 indicates a white-cell count of less than 5 per microliter in cerebrospinal fluid with the presence of lymphoblasts.

Abbreviations: allo-SCT…allogeneic stem cell transplant, BM…bone marrow, CD19…cluster of differentiation 19, CNS…Central Nervous System, ECO…Eastern Cooperative Oncology Group, f…female, m…male, n …number, SD…standard deviation

4.1.3 Samples size

Table 4-4: Disposition of patients of the FELIX trial [7]

Parameter	Phase 1B		Phase 2		
	Cohort A	Cohort B	Cohort A	Cohort B	Cohort C
Number screened, n	217				
Number enrolled, n	153				
Number received ≥1 infusion of obe-cel, n (%)	127 (83.0%)				
Number withdrawn/dropout, n (%)	26 (17.0%)				
Number for efficacy analysis, n (%)	21 (13.7%)	3 (2.0%)	112 (73.2%)	10 (6.5%)	7 (4.6%)
Number for safety analysis, n (%)	21 (13.7%)	3 (2.0%)	112 (73.2%)	10 (6.5%)	7 (4.6%)
Median follow-up[1], months	21.5				

Note. The median duration of follow-up from the first obe-cel infusion to the data-cutoff date in all the patients who received at least one infusion.

Abbreviations: NR...not reported

4.1.4 Outcomes

Table 4-5: Definitions of efficacy outcomes of the FELIX trial [7]

Outcome	Definition
Overall Survival (OS)	Time from the first obe-cel infusion to the date of death due to any reason. Patients who had not died at the data cut-off were censored at the date of last contact [7].
Progression-Free Survival (PFS)	Time from first obe-cel infusion to date of progressive disease, or date of death due to any reason [7].
Overall Remission Rate (ORR)	Proportion of patients with complete remission (CR) or complete remission with incomplete haematologic recovery (CRi). The ORR was assessed by an independent response review committee (IRRC) [7]. The morphological CR/CRi definition was based on the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, requiring <5% bone marrow blasts, absence of extramedullary disease, adequate blood count recovery, and independence from supportive care such as platelet transfusions and granulocyte colony-stimulating factors [8].
Event-Free Survival (EFS)	Time from first obe-cel infusion to the earliest of treatment failure, morphological relapse, or death due to any reason. Treatment failures include patients who died from underlying disease or received new non-protocol anticancer therapy without achieving at least one assessment of CR or CRi [7].
Duration of Remission (DOR) or relapse-free survival (RFS)	Time from first documented CR or CRi after obe-cel infusion to the earliest of morphological relapse or death due to any reason. Assessed in patients who achieved CR or CRi [7].
MRD-Negative Remission Rate	Proportion of patients achieving CR or CRi while simultaneously being MRD-negative in the bone marrow by central assessment. MRD-negativity was

Outcome	Definition
	defined as having fewer than one leukaemia cell per 10,000 cells (10^{-4} or <0.01% threshold), indicating measurable residual disease below the detection limit of conventional methods [9].
Proportion of Patients Undergoing SCT	Proportion of patients undergoing stem cell transplantation (SCT) prior to leukaemia relapse, representing patients who received consolidative allo-SCT while in remission [7].
Proportion of Patients in CR/CRi Without SCT or Other Subsequent Therapies	Proportion of patients in CR/CRi without allo-SCT or other subsequent therapies at six, twelve and 24 months following obe-cel infusion [7].
CD19-Negative Relapse	Disease recurrence with loss of CD19 expression on leukaemic blasts, representing a potential resistance mechanism to CD19-targeted CAR-T therapy [10].
Quality of Life (QoL)	Patient-reported outcome measured by different scores such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EuroQol (EQ-5D-5L) and the Visual Analogue Scale (VAS) [11].

Abbreviations. CAR-T…Chimeric Antigen receptor T-cell, CR…Complete Remission, CRi…Complete Remission with incomplete hematologic recovery, DOR…Duration of Remission, EFS…Event-Free Survival, EORTC QLQ-C30…European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L…EuroQol 5-Dimension 5-Level, IRRC…Independent Response Review Committee, MRD…Measurable Residual Disease, NCCN…National Comprehensive Cancer Network, obe-cel…Obecabtagene Autoleucel, ORR…Overall Remission Rate, OS…Overall Survival, PFS…Progression-Free Survival, QoL…Quality of Life, SCT…Stem Cell Transplantation, VAS…Visual Analogue Scale.

Table 4-6: Study protocol amendments of the FELIX trial [7]

Version	Date and scope of amendment
Original protocol	04.11.2019 – EU Clinical Trial Application
1.1	02.01.2020 – Amendment following regulatory authority feedback (MHRA, UK).
2.0	19.12.2019 – not submitted and not implemented.
3.0	02.01.2020 – US IND Submission.
4.0	24.04.2020 – Amendment following regulatory authority feedback (FDA, US).
5.0	10.12.2020 – Amendment to include and additional cohort of patients in morphological remission with MRD-positive disease and increase the overall number of patients in Phase Ib.
6.0	28.04.2021 – Amendment to include central laboratory testing for B-cell aplasia and modify the management of bridging therapy and washout period.
7.0	23.02.2022 – Amendment to include additional efficacy interim analysis and expand Cohort IIB (patients with MRD-positive disease).
8.0	01.06.2022 – Amendment to alter Phase IIb NGS screening cut-off and changing into central testing per FDA request; correct the oversight for not updating the eligibility in the synopsis in ver 6 to 7 change.
9.0	23.10.2023 – Updates to study endpoints and statistics section as requested by Health Authority (FDA).

Abbreviations: EU…European Union, FDA…Food and Drug Administration, IND…Investigational New Drug, MHRA…Medicines and Healthcare products Regulatory Agency, MRD…measurable residual deisease, NGS…Next-Generation Sequencing, UK…United Kingdom, US…United States

4.2 Results on relative effectiveness and safety

4.2.1 Clinical efficacy outcomes

Table 4-7: Response rates according to cohort and total infused population for the FELIX trial [7]

Response rate	Phase 1b (N=16)		Phase 2 (N=111)			Total infused population (N=127)
	Cohort A (n=13)	Cohort B (n=3)	Cohort A (n=94)	Cohort B (n=10)	Cohort C (n=7)	
CR/CRi, n (%)	9 (69,2)	2 (66,7)	72 (76,6)	10 (100,0)	6 (85,7)	99 (77,95)
95% CI, %	39-91	9-99	67-85	69-100	42-10o	70-85
CR, n (%)	6 (46)	2 (67)	52 (55)	9 (90)	4 (57)	73 (57)
CRi, n (%)	3 (23)	0	20 (21)	1 (10)	2 (29)	26 (20)

Abbreviations: CI…confidence interval, CR…complete remission, CRi…complete remission with incomplete haematologic recovery

Table 4-8: Response rates for all enrolled patients (intention-to-treat population) and by cohort for the FELIX trial [7]

Response rate	Phase 1B (n=24)		Phase 2 (n=129)			All patients enrolled (N=153)
	Cohort A (n=21)	Cohort B (n=3)	Cohort A (n=112)	Cohort B (n=10)	Cohort C (n=7)	
Infused, n (%)	13 (61.9)	3 (100)	94 (83.9)	10 (100)	7 (100)	127 (83.0)
CR/CRi, n (%)	9 (42.9)	2 (66.7)	72 (64.3)	10 (100)	6 (85.7)	99 (64.7)
95% CI, %	21.8-66.0	9.4-99.2	54.7-73.1	69.2-100	42.1, 99.6	56.6, 72.3
CR, n (%)	6 (28.6)	2 (66.7)	55 (49.1)	9 (90.0)	5 (71.4)	77 (50.3)
CRi, n (%)	3 (14.3)	0	17 (15.2)	1 (10.0)	1 (14.3)	22 (14.4)

Abbreviations: CI…confidence interval, CR…complete remission, CRi…complete remission with incomplete haematologic recovery

4.2.2 Safety outcomes

Table 4-9: Serious treatment-emergent adverse events grade ≥3 (occurring in ≥5% of all infused patients) for the total infused population and by cohort for the FELIX trial [7]

Serious TEAE	Phase 1B (n=16)		Phase 2 (n=111)			Total infused population (N=127)
	Cohort A (n=13)	Cohort B (n=3)	Cohort A (n=94)	Cohort B (n=10)	Cohort C (n=7)	
Number of patients with any serious TEAE, n (%)	6 (46.2)	2 (66.7)	54 (57.4)	5 (50.0)	4 (57.1)	71 (55.9)
Febrile neutropenia, n (%)	0	1 (33.3)	13 (13.8)	2 (20.0)	0	16 (12.6)
ICANS, n (%)	1 (7.7)	0	6 (6.4)	1 (10.0)	0	8 (6.3)
COVID-19, n (%)	0	0	7 (7.4)	1 (10.0)	0	8 (6.3)
Hyperferritinaemia, n (%)	0	0	6 (6.4)	0	1 (14.3)	7 (5.5)
Sepsis, n (%)	1 (7.7)	0	4 (4.3)	0	2 (28.6)	7 (5.5)

Abbreviations: TEAE…treatment-emergent adverse events, COVID-19…coronavirus disease 2019, ICANS…immune effector cell-associated neurotoxicity syndrome

Table 4-10: Treatment-emergent adverse events grade ≥3 (occurring in ≥5% of all infused patients) for the total infused population and by cohort for the FELIX trial [7]

TEAE	Phase 1B (n=16)		Phase 2 (n=111)			Total infused population (N=127)
	Cohort A (n=13)	Cohort B (n=3)	Cohort A (n=94)	Cohort B (n=10)	Cohort C (n=7)	
Number of patients with any TEAE, n (%)	9 (62.9)	3 (100)	78 (83.0)	7 (70)	7 (100)	103 (81.9)
Febrile neutropenia, n (%)	2 (15.4)	1 (33.3)	25 (26.6)	2 (20.0)	0	30 (23.6)
Anemia, n (%)	3 (23.1)	0	19 (20.2)	1 (10.0)	3 (42.9)	26 (20.5)
Neutropenia, n (%)	1 (7.7)	0	19 (20.2)	2 (20.0)	4 (57.1)	26 (20.5)
Neutrophil count decreased, n (%)	1 (7.7)	2 (66.7)	19 (20.2)	1 (10.0)	2 (28.6)	25 (19.7)
Platelet count decreased, n (%)	2 (15.4)	0	12 (12.8)	1 (10.0)	1 (14.3)	16 (12.6)
Thrombocytopenia, n (%)	1 (7.7)	1 (33.3)	14 (14.9)	0	0	16 (12.6)
Hyperferritinemia, n (%)	0	0	12 (12.8)	0	1 (14.3)	13 (10.2)
ICANS, n (%)	1 (7.7)	0	7 (7.4)	1 (10.0)	0	9 (7.1)
Pneumonia, n (%)	1 (7.7)	0	6 (6.4)	1 (10.0)	1 (14.3)	9 (7.1)
White blood cell count decreased, n (%)	0	1 (33.3)	8 (8.5)	1 (10.0)	1 (14.3)	11 (8.7)
Sepsis, n (%)	2 (15.4)	0	4 (4.3)	0	2 (28.6)	8 (6.3)
Hypokalemia, n (%)	1 (7.7)	0	7 (7.4)	0	0	8 (6.3)
COVID-19, n (%)	0	0	7 (7.4)	1 (10.0)	0	8 (6.3)

TEAE	Phase 1B (n=16)		Phase 2 (n=111)			Total infused population (N=127)
	Cohort A (n=13)	Cohort B (n=3)	Cohort A (n=94)	Cohort B (n=10)	Cohort C (n=7)	
Respiratory failure, n (%)	2 (15.4)	0	5 (5.3)	0	0	7 (5.5)

Abbreviations: TEAE…treatment-emergent adverse events, COVID-19…coronavirus disease 2019, ICANS…immune effector cell-associated neurotoxicity syndrome

4.3 Quality of evidence

4.3.1 Risk of Bias

Table 4-11: Summary table characterising the applicability of the included study [7]

Domain	Description of applicability of evidence
Population	The FELIX study comprised adults aged 18 years and over with relapsed or refractory CD19-positive B-cell ALL. Of the 153 patients enrolled in the study, 127 received at least one infusion and were therefore evaluable for analysis. The study population had a median age of 47 years with a notably wide age range (20-81 years), with an equal distribution between males (52%) and females (48%). The patient population was characterised by a high degree of pre-treatment, with a median of two previous lines of therapy (range one to six). Notably, 52% of patients were refractory to their last line of therapy. The data indicate that almost half of the patients (44%) had previously undergone allo-SCT, and a significant proportion had received targeted therapies, including BLI (42%) and IO (31%). The disease characteristics included Ph+ disease in 28% of patients and EMD in 23%. **Applicability**: It is important to note that this group represents a particularly treatment-resistant population, who has already undergone at least one therapy and have limited further treatment options. Generalisability to less heavily pretreated patient populations remains uncertain.
Intervention	The intervention consisted of obe-cel, a form of autologous 4-1BB-ζ anti-CD19 CAR T cell therapy that uses an intermediate-affinity CAR with fast binding off-rate. The therapeutic intervention was administered using a bone marrow burden-adjusted split-dose regimen after lymphodepletion. The initial dose consisted of either 10×10^6 CAR T cells (59.8% of patients) or 100×10^6 CAR T cells (40.2% of patients), with 94.5% of patients receiving both planned doses. The median time from leukapheresis to product release was 21 days. The majority of patients (92.9%) received bridging therapy, which mainly was chemotherapy-based. **Applicability**: The manufacturing success rate (95.4%) is high and therefore reliable. In addition, Austria has already developed several specialised centres and a good process for CAR T cells, which means that integration of obe-cel in clinical practice would be possible. Nevertheless, the duration of the production of the drug (21 days) is long and still requires high organisational aspects, particularly given that 93% of patients required bridging therapy with associated mortality risks during this waiting period.
Comparators	The FELIX study was a single-arm study without a control group. Instead, previously study data and predefined thresholds were used for statistical testing, with an overall remission threshold of ≤40% and a CR threshold of ≤20%, both based on previous BLI experience. No indirect comparisons with potential alternative therapies have been identified. According to clinical experts, direct comparators are also difficult to define with precision, as multiple treatment options exist and are applied in a highly patient-specific manner. **Applicability:** The lack of a direct comparator limits the ability to assess relative efficacy compared to current standard treatments. According to clinical experts, ALL treatment is generally highly patient-specific with considerable variation in treatment approaches. Consequently, the positioning of CAR T cell therapy is also highly patient-specific, as it varies significantly between individual patients based on their specific clinical circumstances.

Domain	Description of applicability of evidence
Outcomes	The primary outcomes showed an overall remission rate (CR or CRi) of 77% (95% CI 67-85) in cohort 2A. Secondary efficacy outcomes included a complete remission rate of 55% (95% CI 45-66), median event-free survival of 11.9 months (95% CI 8.0-22.1) and median OS of 15.6 months (95% CI 12.9-not evaluable). The 6-month and 12-month EFS rates were 65.4% and 49.5%, respectively, while the 12-month overall survival rate was 61.1%. Safety outcomes demonstrated a favourable profile with grade ≥3 CRS occurring in only 2.4% of patients and grade ≥3 ICANS in 7.1% of patients. Treatment-related deaths occurred in 2 patients (1.6%). **Applicability**: The study demonstrates high response rates with notably lower severe toxicity rates compared to other CAR T therapies. Although obe-cel showed clinical efficacy in the study, evidence on long-term treatment durability is still limited, and only minimal information was provided regarding patient-reported outcomes and quality of life.
Setting	The FELIX study was a phase 1b-2 multicenter study conducted at 34 sites across three countries: Spain, the UK, and the US. Treatment required inpatient management, with 15.7% of patients requiring ICU admission. **Applicability**: The multi-centre international design supports broader generalisability of findings. However, the requirement for specialised CAR T treatment centres may limit accessibility within the Austrian healthcare system, where only nine certified CAR T cell therapy centres are available.

Abbreviations: ALL…acute lymphoblastic leukaemia, allo-SCT…allogeneic stem cell transplantation, BLI…blinatumomab, CAR…chimeric antigen receptor, CD19…cluster of differentiation 19, CI…confidence interval, CR…complete remission, CRi…complete remission with incomplete hematologic recovery, CRS…cytokine release syndrome, EFS…event-free survival, EMD…extramedullary disease, ICANS…immune effector cell-associated neurotoxicity syndrome, ICU…intensive care unit, IO…inotuzumab ozogamicin, obe-cel…obecabtagene autoleucel, OS…overall survival, Ph+…Philadelphia chromosome-positive, UK…United Kingdom, US…United States

4.3.2 Statistical analysis and inconsistencies

Table 4-12: Statistical analysis in the FELIX trial [7]

Statistical analysis	Sequential testing procedure for cohort 2A
Primary endpoint: overall remission	
H^0 for primary endpoint	≤ 40% overall remission
Primary threshold	> 40% overall remission[1]
Key secondary endpoint: complete remission	
H^0 for secondary endpoint	≤ 20% complete remission
Secondary threshold	> 20% complete remission[1]
Timing of interim analysis	After 50 patients from Cohort 2A had received obe-cel infusion and were followed for 3 months or withdrawn before the month 3 visit
Statistical method	Alpha-spending approach according to Lan–DeMets (O'Brien–Fleming)
Follow-up analysis	If null hypothesis was not rejected in the interim analysis, endpoints were to be retested in the primary analysis according to the pre-specified alpha-spending plan
Type I error control analysis	Familywise type I error controlled at the one-sided 2.5% level throughout testing sequence
Other secondary endpoints	All other pre-specified endpoints and analyses for other cohorts were summarised descriptively
Statistical analysis for time-to-event endpoints	Kaplan–Meier method

Statistical analysis	Sequential testing procedure for cohort 2A
Censoring criteria	Patients receiving new non-protocol anticancer therapies (e.g., stem cell transplantation) were censored for duration of response and event-free survival analyses

Note. [1]The thresholds are based on phase 3 study with blinatumomab .[12]

Abbreviations: H^0...null hypothesis.

5 Price comparisons, treatment costs and budget impact

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmaco-economic model

No dossier nor pharmaco-economic model were submitted by the marketing authorisation holder.

5.1.2 Economic evaluation based on published pharmaco-economic models

Table 5-1: Summary of marketing authorisation holders' and External Assessment Group's base case assumptions

Assumption	MAH base case	EAG base case
Modelled population	Cohort IIA (mITT)	Cohorts IA and IIA (ITT)
Cure point and standardised mortality ratio (SMR)	3 years (3.0)	3 years (3.0)
Follow-up costs of allo-SCT	Costs aligning with brexucabtagene autoleucel	Normalise patient distribution across follow-up periods in each cycle
Approach to CAR T-cell infusion cost calculations	Bottom-up costing using UK-specific FELIX trial data	Using tariff costs for CAR T infusion and monitoring
Source of AEs incidence	Grade ≥3 AEs in FELIX mITT population	Include TEAEs (Grade ≥3) for all infused patients
Allo-SCT utility effects	Exclude	Include
Discount factor	Per-cycle discount factor	Per-year discount factor
Severity modifier across populations	1.7	1.2

Abbreviations: AE…adverse event, allo-SCT…allogeneic stem cell transplant, CAR T…chimeric antigen receptor T-cell, EAG… External Assessment Group, ITT…intention-to-treat, MAH…manufacturing authorisation holder, mITT…modified intention-to-treat, SMR…standard mortality ratio, TEAE…treatment-emergent adverse event

Table 5-2: Characteristics of the economic evaluation of obe-cel

Author, year [reference]	Country	Intervention and comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Utility values	Severity modifier	Discount rate	Model assumptions and limitations
NICE HTA report	UK	obe-cel vs IOtuzumab, blinatumomab and ponatinib	Adults with relapsed/refractory B - cell acute lymphoblastic leukaemia (ALL)	Model-based cost-utility analysis (CUA)	Partitioned-survival model with three states: event-free, post-event and death	NHS England and Personal Social Services (PSS) perspective for a horizon of a lifetime	life years gained (LYG), QALYs	1.7 severity weight applied to QALYs for all populations	3.5% per cycle for costs and utilities	Cure assumption: People alive three years after treatment are considered cured. Allo-SCT rates: Company assumed 0% allo-SCT after obe-cel; NICE assumed ~10% would have allo-SCT. Population generalisability: patients from the FELIX trial are representative of the patients in NHS practice. Limitations: ■ Likely underestimated proportion and duration of immunoglobulin therapy. ■ Limited data on the appropriate proportion having allo-SCT after obe-cel. ■ Unclear how costs of bridging therapies are captured.

										■ Insufficient evidence that FELIX better reflects NHS population than the comparator studies.

Abbreviations: allo-SCT…Allogeneic Stem Cell Transplant, CUA… cost-utility analysis, HTA…Health Technology Assessment, LYG… life years gained, NHS…National Health Service, NICE…National Institute for Health and Care Excellence, PSS… Personal Social Services , QALYs…Quality-Adjusted Life Years, UK…United Kingdom

Table 5-3: Main results of the included economic evaluation of obe-cel[1]

Author, year [reference]	Country	Incremental costs (base-case)	Incremental effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses
NICE HTA report [13]– MAH's model	UK	NR With discounted confidential PAS obe-cel price: Overall population: ■ IO – cost savings Ph- population: ■ IO – cost savings ■ BLI- additional costs Ph+ population: ■ IO – cost savings ■ PON- additional costs	■ vs IO: 2.88 QALYs in the overall population ■ vs IO: 2.15 QALYs in Ph- population ■ vs BLI: 5.08 QALYs in Ph- population ■ vs PON: 11.04 QALYs in Ph+ population	Results using discounted confidential PAS obe-cel price: Overall population: ■ IO – dominant ICER Ph- population: ■ IO – dominant ICER ■ BLI- under £30,000 Ph+ population: ■ IO – dominant ICER ■ PON- under £30,000 Results using list price: redacted	Cost-effective threshold of £50,000 per QALY gained (due to severity modifier)	Deterministic sensitivity analysis: 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. Probabilistic sensitivity analysis: A total of 1,000 Monte Carlo simulations were plotted over time for each model population using the patient access scheme discount and the 1.7 severity modifier, to demonstrate the convergence of the population-specific ICERs.
NICE HTA report [13]– EAG's revised model	UK	NR	■ vs IO: 1.51 QALYs in the overall population	Results using discounted confidential PAS obe-cel price: Overall population: ■ IO – over £30,000	Cost-effective threshold of £30,000 per QALY gained	Results of probabilistic sensitivity analysis, one-way sensitivity analysis and scenario analysis are not reported.

[1] The detailed results of the economic evaluation of the MAH for the UK were confidential; here we present all the results that are publicly available.

			■ vs IO: - QALYs in Ph- population ■ vs BLI: 1.09 QALYs in Ph- population ■ vs PON: 1.33 QALYs in Ph+ population	Ph- population: ■ IO – over £30,000 ■ BLI- over £30,000 Ph+ population: ■ IO – over £30,000 ■ PON- over £30,000 Results using list price: redacted		

Abbreviations: allo-SCT…Allogeneic Stem Cell Transplant, BLI…blinatumomab, EAG…External Assessment Group, EFS…event-free survival, HTA…Health Technology Assessment, ICER… incremental cost-effectiveness ratio, IO…IOtuzumab, NICE…National Institute for Health and Care Excellence, NR…not reported, OS…overall survival, PAS…Patient Access Scheme, Ph+/-… Philadelphia chromosome-positive/negative, PON…ponatinib, QALY…Quality-Adjusted Life Year, SMR…standard mortality ratio

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the manufacturer

No dossier and BIA were submitted by the marketing authorisation holder

6 Extended perspectives

6.1 Stakeholder perspectives

- Patient selection
  - A CAR T centre should assess patient eligibility in a multi-disciplinary team, including cellular therapy and haematology/oncology disease specialists. The following criteria should be considered:
    - Eastern Cooperative Oncology Group (ECOG) PS <2
    - Life expectancy >6-8 weeks
    - Tumour burden
    - History of malignancy
    - Prior allogeneic hematopoietic cell transplantation (allo-HCT)
    - Prior treatments directed toward the antigenic target of chimeric antigen receptor (CAR) T (e.g. bispecific antibodies/prior CAR T)
    - Immunosuppressive treatment
    - Bacterial, fungal or viral infections
    - History of central nervous system (CNS) involvement [4].

  An overview of eligibility criteria is presented in .

Kriterien für die Selektion geeigneter Pat.

- Before leukapheresis:
  - *Screening* for hepatitis B virus, hepatitis C virus and human immunodeficiency virus should be performed [5].

Infektionsscreening vor Leukapherese

- Bridging therapy:
  - Aiming to reduce disease burden, it is administered between four and six weeks between leukapheresis and CAR T administration.
  - Patient-specific bridging recommendations should be made by a multidisciplinary team, considering the response to prior therapy, overall tumour burden, and anatomical sites of disease.
  - Bridging is broadly split into: high-dose chemotherapy, low-dose chemotherapy, radiotherapy and novel agents/approaches. Recommended washout periods have to be considered.
  - Bridging can be omitted if the CAR T 'vein-to-vein' time is short and the disease burden is low [4].

"Bridging-Therapie" kann zur Reduktion der Krankheitslast eingesetzt werden

Zeitpunkt zwischen Leukapherese und CAR-T-Infusion

- Prior to the infusion:
  - *Bone marrow assessment* must be available from a sample obtained within seven days before starting lymphodepleting chemotherapy treatment. It will be used to determine the obe-cel dosage regimen, based on a bone marrow blast of >20% or ≤20%.
  - The availability of obe-cel must be confirmed before initiating lymphodepleting chemotherapy treatment.
  - The prophylactic use of systemic corticosteroids should be *avoided,* as they may interfere with the activity of obe-cel.
  - *Monitoring* for signs and symptoms of infection.
  - *Negative pregnancy test* in sexually active females of reproductive potential.

vor der Infusion: Untersuchung des Knochenmarks

Prüfung der Verfügbarkeit

Gabe systemischer Kortikoide vermeiden

Ausschluss von Infekten

negativer Schwangerschaftstest

- *Lymphodepleting chemotherapy regimen*, consisting of fludarabine 30 mg/m² per day, intravenously (IV) for four days and cyclophosphamide 500 mg/m² per day IV for two days starting with the first dose of fludarabine (total dose: fludarabine 120 mg/m²; cyclophosphamide 1000 mg/m²) is administered before the infusion of obe-cel. Obe-cel is infused three days (± one day) after completion of lymphodepleting chemotherapy treatment (Day 1), allowing a minimum 48-hour wash-out [5].

Lymphodepletion: Fludarabin + Cyclophosphamid

- Directly before the infusion:
  - Dose preparations and thawing of obe-cel.
  - *Premedication* with acetaminophen should be performed approximately 30 minutes before the obe-cel infusion to minimise the risk of an infusion reaction [5].

unmittelbar vor der Infusion: Auftauen + Prämedikation

Eligibility criteria	EBMT/EHA recommendations	Comments
Age limit	No age limit	Decision should be based on physical condition rather than age, although ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children. Real-world CAR-T data suggest that 5.9% of treated patients with B-ALL were <3 years old and 53.5% of treated patients with NHL were >65 years old and that CR rates were comparable in both groups to the rest of the population.
Performance status	ECOG <2, Karnofsky >60% or Lansky >60%	Although patients with ECOG >1 were treated outside clinical trials, it was associated with significantly decreased OS and PFS.
Life expectancy	>6-8 weeks	Requires careful consideration in terms of risk–benefit ratio.
High tumour burden	Risk–benefit assessment required	High tumour burden in B-ALL and LBCL is a risk factor for treatment failure and greater toxicity and careful consideration of the individual risk–benefit ratio is required.
History of malignancy	Absence of active malignancy requiring treatment other than non-melanoma skin cancer or carcinoma *in situ* (e.g. cervix, bladder, breast).	Requires careful consideration of the risk–benefit ratio.
Prior allo-HCT	Not a contraindication	Not a contraindication when off immunosuppression but in ALL may increase risk of CAR-T-associated toxicity
Prior treatments directed toward antigenic target of CAR-T, e.g. bispecific antibodies/prior CAR-T	Not a contraindication, but antigen-negative escape should be excluded at relapse post-targeted therapy and before CAR-T especially in B-cell ALL	Reduced CD19 expression may not decrease the efficacy of anti-CD19 CAR-T in B-ALL; however, prior treatment with blinatumomab may impair efficacy.[73] A second infusion of anti-CD19 CAR T cells may be feasible and can induce remission in a subset of patients.[74] In MM, re-treatment with anti-BCMA CAR-T is possible[75]
Immunosuppressive treatment	Relative contraindication	Any systemic immunosuppressive treatment may impair the efficacy of CAR-T. Intermittent topical, inhaled, or intranasal corticosteroids are permitted
Bacterial or fungal infections	Active infection is a contraindication	Infection should be treated and well controlled such that the patient should be stable before leukapheresis. In most cases, active infection requires only a temporary deferral
Viral infection	Viremia is a contraindication. Treatment should be delayed in cases of positive COVID-19 PCR.[69]	Active viral infection should prompt deferral of initiation of CAR-T therapy until the infection is controlled. Some latent infections e.g. HIV, are a contraindication to manufacturing for several (but not all) commercial and trial CAR-T products. When proceeding to CAR-T in cases of latent HBV, HCV or HIV infections, prophylactic anti-viral treatment is required. Asymptomatic patients testing positive for COVID-19 by qPCR may proceed to CAR-T manufacture, but this is done at risk and at the physician's discretion. Before proceeding, feasibility should be checked with the CAR-T manufacturer well in advance of leukapheresis
History of central nervous system (CNS) involvement	Relative contraindication	Requires careful consideration of the risk–benefit ratio. LBCL: for ZUMA-1[78] and Juliet 4, CNS involvement was an exclusion criterion, but in Transcend-world,[76] controlled SCNSL was permitted on study. MCL: on ZUMA-2,[79] CNS involvement was an exclusion. B-ALL: on ELIANA,[1] active CNS involvement was an exclusion. Real-world evidence (RWE) on CAR-T for CNS involvement in DLBCL is emerging: suggesting that it is well tolerated and has potential efficacy.[76,80-82] MM: CNS involvement was an exclusion in KarMMa study[77]

Figure 6-1: Patient eligibility criteria for CAR T [4]

Abbreviations: B-ALL…B-cell acute lymphoblastic leukaemia, CAR…chimeric antigen receptor, COVID-19…coronavirus disease 2019, CR…complete remission, DLBCL…diffuse large B-cell lymphoma, ECOG…Eastern Cooperative Oncology Group, HBV…hepatitis B virus, HCT…haemotopoietic cell transplantation, HCV…hepatitis C virus, HIV…human immunodeficiency virus, LBCL…large B-cell lymphoma, MCL…mantle cell lymphoma, MM…multiple myeloma, NHL…non-Hodgkin lymphoma, OS…overall survival, PFS…progression-free survival, qPCR…quantitative polymerase chain reaction, SCNSL…secondary central nervous system lymphoma, RWE…real-world evidence

6.2 Patient's perspective

No additional tables or figures are provided for this subchapter.

6.3 Further ethical and social aspects

No additional tables or figures are provided for this subchapter.

6.4 Registries and documentation of the application

No additional tables or figures are provided for this subchapter.

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licenses

No additional figures or tables are provided for this sub-chapter.

7.2 Public contributions to drug development

Table 7-1: *Financing, patent deals, licensing, funding rounds of all companies involved in the development of Aucatzyl®*

Type of financing	Details on collaboration, financing, public funding	Year	Amount	Funders/ Investors/ Acquiror	Source
Autolus Therapeutics (spin-out from University College London in 2014)					
General information	Autolus Therapeutics was founded by Martin Pule, based at UCL Cancer Institute, and with the support of UCLB, UCL's commercialisation company, was spun out in 2014. It has since raised over $1B, with most of this invested in the UK, including the development of a state-of-the-art manufacturing facility, The Nucleus in Stevenage, employing 450 people.	2025	Raised over $1B of investment	n.a.	https://www.ucl.ac.uk/news/2025/apr/ucl-spI-Out-autolus-gains-uk-licence-cancer-therapy

Licensing information	Continuous cooperation between UCL and Autolus Therapeutics: Company amended licensing agreement of 2014 in 2024 for the T-cell technology from UCLB.	2024	Equity (1.8 million + shares) + £120,000 management fee + cash for amendments (£2 million total) Up to £106.68 million in milestone payments (clinical, regulatory, commercial, sales) £10 million regulatory milestone already paid for obe-cel FDA approval Low to mid-single digit royalties on product sales Revenue sharing on sublicenses (decreasing over time) UCLB retains academic research rights	UCL (through its commercialization company UCLB)	https://www.sec.gov/Archives/edgar/data/1730463/000173046325000019/autl-20241231.htm
Patent information	As of December 31, 2024, Autolus Therapeutics has a patent portfolio of 83 patent families, of which 17 patent families originated from UCLB	2024	n.a.	UCL/ UCLB	https://www.sec.gov/Archives/edgar/data/1730463/000173046325000019/autl-20241231.htm
General pricing information	Aucatzyl® will go for $525,000, a list price that "reflects the clinical evidence and benefit" of the treatment. Competitors Gilead's Tecartus, meanwhile, is priced lower at around $460,000, while Novartis' Kymriah is priced at around $580,000 per treatment, William Blair analysts pointed out in a note to clients.	2024	Estimated price: $525,000	n.a.	https://www.fiercepharma.com/pharma/autolus-readies-its-aucatzyl-car-t-go-after-heavy-hitter-competition-after-landing-fda

Collaboration	Now, the German biotech has brought British company Autolus Therapeutics on board in an intriguing $250 million upfront collaboration. In addition, BioNTech gains an exclusive license to use certain target binders identified by UK-based Autolus as well as the option to license additional binders or cell programming technologies to support the German biotech's own in vivo cell therapy and antibody-drug conjugate (ADC) candidates. Autolus will be eligible to receive milestone payments from any resulting drugs.	2024	$250 million	BioNTech	https://www.fiercebiotech.com/biotech/bion-tech-pays-autolus-250m-manufacturing-car-t-expertise-wide-ranging-collab
Collaboration	Autolus Therapeutics has found a deep-pocketed supporter of its CD19 CAR T therapy. Having seen Autolus' stock halved over the past year, Blackstone Life Sciences has stepped in with a $250 million package to support the British biotech through to a pivotal readout and beyond. The first phase of the deal will see Blackstone pay $50 million upfront and make a $100 million investment in Autolus. Beyond that, Blackstone is on the hook for up to $100 million in payouts tied to obe-cel development and regulatory milestones.	2021	$250 million	Blackstone Life Sciences	https://www.fiercebiotech.com/biotech/black-stone-bets-autolus-cd19-car-t-250m-deal-clear-ing-path-to-pivotal-readout-2022
Collaboration/ Licensing	The 2021 deal commits Moderna to up to $60 million in milestones, split evenly between development and sales events, per product, plus royalties in the low to mid-single digits on net sales. While the sums are relatively small, Martin Pule, CSO at Autolus, framed the deal as a validation of the technology.	2021	$60 million	Moderna	https://www.fiercebiotech.com/bio-tech/moderna-says-yes-autolus-licensing-tar-geting-technology-immuno-oncology-project

Follow-on $150 million offering	Days after announcing the first response rates from a phase I/II trial of CAR T cell therapy AUTO1, Autolus raised $100.8 million in a follow-on offering.	2019	$100.8 million	n.a.	https://www.biocentury.com/article/301764/autolus-follows-up-car-t-data-with-101m-raise
IPO	Biotech IPOs continue to come thick and fast this week, with UK T-cell therapy specialist Autolus the latest to list with an impressive $150 million raise.	2018	$150 million	n.a.	https://www.fiercebiotech.com/ipo-bonanza-continues-150m-listing-for-car-t-player-autolus
Series C financing	AUTOLUS LIMITED: Autolus Secures $80 million Series C Funding	2017	$80 million	Syncona, Nextech Invest, Arix Bioscience, Woodford Investment Management	https://www.globenewswire.com/news-release/2017/09/26/1132588/0/en/AUTOLUS-LIMITED-Autolus-Secures-US-80-million-Series-C-Funding.html
Series B financing	Autolus Limited secures £40 million funding – Woodford Investment Management and Perceptive Bioscience complete Series B financing	2016	£40 million	Woodford Investment Management and Perceptive Bioscience	https://www.fiercebiotech.com/biotech/autolus-limited-secures-£40-million-funding-–-woodford-investment-management-and-perceptive
Series A financing	Autolus is getting started with $45 million in startup cash from Syncona. Christian Itin, the former CEO at Micromet, is taking over as chairman of the newly minted biotech. Micromet was bought out by Amgen back in 2012 for $1.2 billion, largely so it could get its hands on BLI, a BiTE.	2015	$45 million	Syncona	https://www.fiercebiotech.com/biotech/car-t-brain-war-scientific-trailblazer-inspires-a-45m-biotech-startup

Licensing agreement (amended in the following year, for the most up-to-date licensing information check "Licensing agreement 2024"	In September 2014, we entered into an exclusive license agreement with UCLB, the technology-transfer company of UCL, for the development and commercialisation rights to certain T cell programming modules.	2014	1,497,643 ordinary shares of Autolus Therapeutics company licensed T-cell technology from UCLB with: £120,000 management fee + equity/cash for amendments (£1.65 million + total) Up to £104.5 million in milestone payments (regulatory, commercial, sales) Low to mid-single-digit royalties on product sales Revenue sharing on sublicenses (decreasing over time) Option to buy out UCLB's rights after reaching sales threshold	UCL/UCLB	https://www.sec.gov/Archives/edgar/data/1730463/000173046318000005/autolus20fdoc.htm#s738C4D9ABE6D5D178D739BAC938F7C5D
University College London					
Basic research funding	NexTGen	2022-2024	$3,627,871	NCI	https://reporter.nih.gov/search/HE6ks61mc0ie-yhHwLhHDTw/project-details/10631014
Basic research funding	The Mark Foundation for Cancer Research Awards ~$12 million to Cancer Grand Challenges Team Developing Novel Immunotherapies for Childhood Solid Tumors	2022	$12 million	The Mark Foundation for Cancer Research	https://themarkfoundation.org/2022/06/the-mark-foundation-for-cancer-research-awards-12-million-to-cancer-grand-challenges-team-developing-novel-immunotherapies-for-childhood-solid-tumors/
Basic and applied research funding	ATECT	2013-2018	€5,931,151	EC (Seventh Framework Programme)	https://cordis.europa.eu/project/id/602239/reporting
Applied research funding	Large-scale production of lentiviral vectors	2015-2018	£1.8 million	Innovate UK / BBSRC Consortium	https://www.ucl.ac.uk/medical-sciences/divisions/cancer/our-research/ucl-car-t-programme/martin-pule
Applied research funding	Phase I/II study of CAR19 in r/r ALL (PI Martin Pule)	2015-2018	£3.9 million	NIHR i4i	https://www.ucl.ac.uk/medical-sciences/divisions/cancer/our-research/ucl-car-t-programme/martin-pule

Basic and applied research funding	CARs for Advanced Therapies	2015-2019	€5,989,158.75	EC (Horizon Europe)	https://cordis.europa.eu/project/id/667980
Basic and applied research funding	CAR T cell therapy of CNS lymphoma. PI Martin Pule	2016-2020	£2.7 million	Wellcome Trust. Health Innovation	https://www.ucl.ac.uk/medical-sciences/divisions/cancer/our-research/ucl-car-t-programme/martin-pule https://www.washingtonpost.com/health/2022/08/05/childrens-cancer-research-gains/ (Note: We were unable to verify the exact number.)
Basic and applied research funding	A protein-based method for allogeneic CAR T cell therapy PI Martin Pule	2019-2024	£2,507,997	MRC DPFS grant	https://www.ukri.org/publications/competitive-funding-decisions-data-2015-to-2020/ https://www.ucl.ac.uk/medical-sciences/divisions/cancer/our-research/ucl-car-t-programme/martin-pule
Basic and applied research funding	CD21 CAR T cell therapy for T-ALL PI Martin Pule	2019-2022	£680,000	MRC Project grant	https://www.ucl.ac.uk/medical-sciences/divisions/cancer/our-research/ucl-car-t-programme/martin-pule (Note: We were unable to verify the numbers.)
The University of Texas MD Anderson Cancer Center					
Basic research funding	Improving cord blood transplantation PI Catherine Bollard	2011-2022	$24,444,013	NCI	https://reporter.nih.gov/search/4Z9Y9mQunEOfZSHtDmB9nA/project-details/9134065
Children's Research Institute					
Basic research funding	NexTGen	2022-2024	$2,528,270	NCI	https://reporter.nih.gov/search/4Z9Y9mQunEOfZSHtDmB9nA/project-details/10627010

Abbreviations: ADC… antibody-drug conjugate, ALL…acute lymphoblastic leukaemia, ATECT…Advanced T-cell Engineered for Cancer Therapy, B…billion, BBSCR…Biotechnology and Biological Sciences Research Council, BLI…blinatumomab, BiTE…bispecific T-cell engager, CAR…chimeric antigen receptor, CD19…cluster of differentiation 19, CEO…chief executive officer, CNS…central nervous system, CSO…chief scientific officer, DPFS…Developmental Pathway Funding Scheme, EC…European Commission, FDA…US Food and Drug Administration, i4i…Invention for Innovation, IPO…initial public offering, MRC…Medical Research Council, n.a….not applicable, NCI…National Cancer Institute, NexTGen…Next Generation T Cell for Childhood Cancers, NIHR…National Institute for Health and Care Research, obecabtagene autoleucel…obe-cel, PI…principal investigator, r/r…relapsed or refractory, UCL…University College London, UCLB…University College London Business, UK…United Kingdom

Table 7-2: Search terms used to identify the development history and public contributions of AUCATZYL®

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	AUCATZYL, obecabtagene autoleucel	n.a.	Yes	Earliest mention – 06/2025	Active substance, Medical speciality, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorisation, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorisation issued
https://adisinsight.springer.com/			Yes		Alternative names
https://pubmed.ncbi.nlm.nih.gov/			Yes		Development history
https://clinicaltrials.gov/			Yes		Clinical trials
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://trialsearch.who.int/			Yes		
https://cordis.europa.eu/			Yes		
https://reporter.nih.gov/			Yes		Basic research. Authors selected based on literature found on PubMed
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm			Yes		Patent information and associated references
https://competition-cases.ec.europa.eu/search			No		Funding amounts
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		

https://eic.ec.europa.eu/index_en	AUCATZYL, obecabtagene autoleucel, Anti-CD19 CAR T cell therapy, AUTO 1, CAT19, CD19 CAR T-cells, CD19CAT-41BBZ CAR T-cells, obe-cel, Autolus Limited, Autolus Therapeutics, Martin Pule, University College London, Farzin Farzaneh, Catherine Bollard, University College London Car T, University College London Leukaemia		No		
https://www.eib.org/en/index			No		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			No		
https://www.sbir.gov/			No		Project funding for companies involved in the development
https://www.nsf.gov/			No		SME, national, regional, local, international, supranational funding
https://www.ukri.org/			Yes		
https://foerderportal.bund.de/			No		
https://www.health-holland.com/			No		
https://www.bpifrance.com/			No		
https://www.inserm.fr/en/home/			No		
https://innovationsfonden.dk/da			No		
https://lundbeckfonden.com/en			No		
https://www.ucc.ie/en/apc/			No		
https://www.amractionfund.com/about			No		
https://www.gatesfoundation.org/			No		
			No		
https://www.google.com/			Yes		Patent information
https://www.forbes.com/			No		n.a.
https://www.reuters.com/			No		
https://www.science.org/			No		
https://www.cafepharma.com/			No		Collaborations, funding, financing, Series A-C funding, patent information, acquisitions
https://www.livescience.com/			No		
https://www.biospace.com/			No		
https://www.bioworld.com/			No		
https://www.biopharmadive.com/			No		
https://pharmaphorum.com/			No		
https://pharmatimes.com/			No		
https://pharmafile.com/			No		

https://www.fiercepharma.com/			Yes		
https://www.fiercebiotech.com			Yes		
https://www.biocentury.com			Yes		
https://www.businesswire.com/			No		
https://www.businessinsider.com/			No		
https://www.statnews.com/			No		
https://finance.yahoo.com			No		
https://www.globenewswire.com			Yes		
https://www.sec.gov/			Yes		

Abbreviations: CAR…chimeric antigen receptor, CD19…cluster of differentiation 19, n.a….not applicable, PRIME…priority medicines, SME…small and medium-sized enterprise

8 Landscape overview

8.1 Ongoing studies on obecabtagene autoleucel

Table 8-1: List of ongoing studies

Title	Trial ID	Other IDs	Phase	Status	Intervention/ Comparison	Start and Estimated study completion date	Sponsor	Additional information
An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating the Safety and Efficacy of AUTO1, a CAR T Cell Treatment Targeting CD19, in Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia	NCT04404660	EUCTR2019-001937-16	Phase 1b/2	Active, not recruiting	Obe-cel/ n.a.	03.06.2020-25.05.2025	Autolus Limited	All centres (including centres in Spain and UK)
		CTIS2024-512903-38-00				01.12.2021-26.05.2028		Spanish centres only
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 Leukaemia (ALL)	NCT07053059	2025-0580 NCI-2025-04660	Phase 2	Not yet recruiting	Obe-cel/ n.a.	01.12.2025-31.05.2030	M.D. Anderson Cancer Center and Autolus Limited	Estimated enrollment 30
Expanded Access Program (EAP) for Obecabtagene Autoleucel (obe-cel) Out-of-specification (OOS) in Adult Patients with Acute Lymphoblastic Leukaemia	NCT06799221	AUTO1-OS1	n.a.	available	Obe-cel/ n.a	n.a. (submitted on 23.01.2025)	Autolus Limited and Iqvia Proprietary Limited	n.a.

Abbreviations: ALL…acute lymphoblastic leukaemia, CAR…chimeric antigen receptor, CD19…cluster of differentiation 19, EAP…Extended Access Progam, n.a.…not applicable, obe-cel…obecabtagene autoleucel, OOS…Out-of-specification, UK…United Kingdom

8.2 Treatments in development in r/r B-ALL

Table 8-2: Landscape overview for relapsed or refractory B cell lymphoblastic leukaemia

Indication	Active ingredient	NCT Number	Developer	Estimated EC decision
Brexu-cel				
Brexu-cel monotherapy for second line or later treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia in adults and elderly	brexu-cel	NCT02614066	Gilead Sciences	N/A
Brexu-cel				
Brexuc-cel monotherapy for third line or later treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia in children, adolescents and adults up to 21 years of age following conditioning chemotherapy regimen of fludarabine and cyclophosphamide	brexu-cel	NCT02625480	Gilead Sciences	January 2027
Azd0486				
Azd0486 monotherapy for second line or later treatment of relapsed or refractory Acute lymphoblastic leukaemia in adolescents, adults and elderly	Azd0486	NCT06137118	AstraZeneca	N/A
Vnx-101				
Vnx-101 monotherapy for first line or later treatment of relapsed or refractory CD19-positive B-cell acute lymphoblastic leukaemia in adolescents, adults and elderly who are ineligible or declined CAR T therapy or failed to respond or relapsed after such therapy	Vnx-101	NCT06533579	Vironexis Biotherapeutics	N/A
Liso-cel				
Liso-cel monotherapy for second line treatment of relapsed or refractory CD19-positive B-cell acute lymphoblastic leukaemia in infants, toddlers, children, adolescents and adults up to 25 years of age	liso-cel	NCT03743246	Bristol Myers Squibb	N/A
Ucart22				
Ucart22 monotherapy for salvage treatment of relapsed or refractory CD22+ B-cell Acute lymphoblastic leukaemia in adolescents, adults and elderly following a lymphodepletion regimen	Ucart22	NCT04150497	Cellectis	July 2029
IO				
IO monotherapy for treatment of relapsed/refractory CD22-positive B-	IO	2016-000227-71 (only	Pfizer	November 2025

Indication	Active ingredient	NCT Number	Developer	Estimated EC decision
cell precursor Acute lymphoblastic leukaemia in infants and toddlers over 1 year of age, children and adolescents		EudraCT Number available)		
Azer-cel				
Azer-cel monotherapy for second line treatment of relapsed/refractory CD19-positive B-cell acute lymphoblastic leukaemia in adults and elderly following fludarabine and cyclophosphamide lymphodepletion	azer-cel	NCT03666000	Imugene	N/A

Abbreviations: azer-cel…azercabtagene zapreleucel, brexu-cel…brexucabtagene autoleucel, CAR…chimeric antigen receptor, CD19…cluster of differentiation 19, EC…European Commission, IO… inotuzumab ozogamicin, liso-cel…lisocabtagene maraleucel, N/A…not available, NCT…National Clinical Trial

9 Discussion

No additional tables or figures are provided for this chapter.

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List of abbreviations

ADC	antibody-drug conjugate
AE	adverse event
AIHTA	Austrian Institute for Health Technology Assessment
ALL	acute lymphoblastic leukaemia
allo-HCT	allogeneic hematopoietic cell transplantation
allo-SCT	allogeneic stem cell transplant
AML	acute myeloid lymphoma
ATECT	Advanced T-cell Engineered for Cancer Therapy
B	billion
B-ALL	B-cell precursor acute lymphoblastic leukaemia
BBSCR	Biotechnology and Biological Sciences Research Council
BCR-ABL1	breakpoint cluster region-ABL proto-oncogene 1
BiTE	bispecific T cell engager
BL	Burkitt lymphoma
BLI	blinatumomab
BM	bone marrow
Brexu-cel	brexucabtagene autoleucel
CAR	chimeric antigen receptor
CARAT	CARs for Advanced Therapies
CAR T cell	chimeric antigen receptor T-cell
CD19	cluster of differentiation 19
CE	European Conformity marking
CEO	chief executive officer
CI	confidence interval
CLL	chronic lymphocytic leukemia
CML	chronic myeloid lymphoma
CNS	Central Nervous System
COVID-19	coronavirus disease 2019
CR	complete remission
CRi	complete remission with incomplete hematologic recovery
CSO	chief scientific officer
CRS	cytokine release syndrome
CUA	cost-utility analysis
DOR	duration of remission
DPFS	Developmental Pathway Funding Scheme
DLBCL	diffuse large B-cell lymphoma
EAG	External Assessment Group
EAP	Extended Access Program
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EHA	European Hematology Association
ELN	European LeukemiaNet
EMD	extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ESMO	European Society for Medical Oncology
EU	European Union
f	female
FDA	US Food and Drug Administration
GMALL	.German Multicenter Acute Lymphoblastic Leukemia
H0	null hypothesis
HBV	hepatitis B virus
HCV	hepatitis C virus

HCT	haematopoietic cell transplantation
HIV	human immunodeficiency virus
HTA	health technology assessment
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IND	Investigational New Drug
IO	inotuzumab ozogamicin
IPO	initital public offering
IRRC	Independent Response Review Committee,
ITT	intention-to-treat
IV	intravenous
i4i	Invention for Innovation
JACIE	Joint Accreditation of International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation
LBCL	large B-cell lymphoma
LBL	lymphoblastic lymphoma
Liso-cel	lisocabtagene maraleucel
LYG	life years gained
m	male
MAH	marketing authorisation holder
MCL	mantle cell lymphoma
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intention-to-treat
MM	multiple myeloma
MRC	Medical Research Council
MRD	measurable residual disease
n	number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NHL	non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NR	not reported
N/A	not available
n.a.	not applicable
NCI	National Cancer Institute
NCT	National Clinical Trial
NexTGen	Next Generation T Cell for Childhood Cancers
NIHR	National Institute for Health and Care Resarch
obe-cel	obecabtagene autoleucel
OOS	out-of-specification
ORR	overall remission rate
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome-positive
Ph-	Philadelphia chromosome-negative
PI	principal investigator
PON	ponatinib
PRIME	priority medicines
PS	performance status
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
qPCR	quantitative polymerase chain reaction
r/r	relapsed or refractory
RWE	real-world evidence
SAE	serious adverse event
SCNSL	secondary central nervous system lymphoma
SCT	stem cell transplantation
SD	standard deviation

SLL ..... small lymphocytic lymphoma
SME ..... small and medium-sized enterprise
SMR ..... standard mortality ratio
SoC ..... standard of care
T ALL ..... T-cell acute lymphoblastic leukemiaTEAE 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
WHO ..... World Health Organisation

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH