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CAR-T Zell-Therapien in Entwicklung - Update

Horizon Scanning

Endbericht

AIHTA Policy Brief Nr.: 006a, 1. Update | ISSN 2710-3234| ISSN online 2710-3242

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CAR-T Cell-Therapies in Development - Update

Horizon Scanning

Wien/Vienna, März/March 2022

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Dieser Bericht soll folgendermaßen zitiert werden/This report should be referenced as follows:

Sehic O, Wild C. CAR-T Zell-Therapien in Entwicklung – Update 2022, AIHTA Policy Brief Nr.: 006a, 1. Update, 2022. Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

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IMPRESSUM

Medieninhaber und Herausgeber:
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Garnisongasse 7/Top20 | 1090 Wien – Österreich
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Für den Inhalt verantwortlich:
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AIHTA Policy Brief Nr.: 006a, 1. Update

ISSN 2710-3234

ISSN online 2710-3242

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Zusammenfassung/Summary

Hintergrund: CAR-T-Zelltherapien werden gemeinhin als "transformative" Therapien bezeichnet und sind mit großen Erwartungen seit ihrer Marktzulassung 2017 (USA) und 2018 (Europa) verbunden. Aufgrund der Hoffnungen, aber auch der enormen Preise wurde 2020 in Kooperation mit der Tirol Kliniken GmbH erstmals ein Horizon Scanning (HS) Dokument zur Unterstützung der Budgetplanung in Krankenhäusern erstellt. Im ersten HS-Bericht (2020) wurden 13 CAR-T Zelltherapien in fortgeschrittenen Stadien identifiziert. Davon wurden inzwischen neben den damals bereits zugelassenen Yescarta® und Kymriah® drei weitere Therapien von der Europäischen Arzneimittelagentur (EMA) zwischen 8/ 2020 und 03/2022 zugelassen: Tecartus® (2020), Abcema® (2021) und Breyanzi® (2022).

CAR-T Zell-Therapien: große Hoffnungen hohe Preise

Horizon Scanning unterstützt Budgetplanung: seit 2018 5 CAR-T Zelltherapien zugelassen

Methoden: Das vorliegende HS-Dokument aktualisiert den früheren Bericht, indem der Status der zehn bereits 2020 beschriebenen erhoben wurde und zusätzliche Therapien, die inzwischen eine spätere Phase der klinischen Prüfung erreichten, hinzugefügt werden.

Monitoring fortgeschrittener Entwicklungen

Ergebnisse:

- Vier Therapien werden für das Hodgkin- und das (aggressive und indolente) Non-Hodgkin-Lymphom untersucht, aber es sind derzeit keine neuen Zulassungen zu erwarten.

NL+NHL: 4 in Entwicklung, aber keine vor baldiger Zulassung

- Sechs Therapien für das multiple Myelom befinden sich in der Entwicklung, von denen eine (Cilta-cel, Carvykti®) im Februar 2022 von der FDA zugelassen wurde und voraussichtlich 2022 von der EMA zugelassen wird. Fünf befinden sich früheren Studienphasen, wovon eine durch Europäische Forschungsgelder gefördert wird; die Entwicklung einer weiteren Therapie wurde eingestellt (Orva-cel), d.h. es wird in einigen Monaten ein Konkurrenzprodukt zu Abcema® zugelassen werden.

MM: 1 vor Zulassung 5 in Entwicklung, aber nicht vor baldiger Zulassung (davon 1 von EC finanziert) 1 eingestellt

- Eine Therapie befindet sich in zwei Studien für akute myeloische Leukämie (AML) in der Entwicklung, aber aufgrund von Hürden bei der Entwicklung von CAR-T-Therapien für AML gibt es keine Änderung des Status seit 2020.

AML: 1 in Entwicklung, aber nicht vor baldiger Zulassung

- Es gibt nur wenige neue Entwicklungen, wie z. B. autologe SLAMF7-CAR-T-Zellen (beim multiplen Myelom), die vielversprechend sein könnten.

wenig neue (technologische) Entwicklungen

Im Gegensatz zu nur wenigen neu entwickelten CAR-T-Zell-Therapien werden bei den bereits zugelassenen Therapien Erweiterungen auf frühere Therapielinien in der jeweiligen Indikation und/oder weitere Indikationen untersucht.

ABER: Indikationserweiterungen der 5 bereits zugelassenen frühere Therapielinien weitere Indikationen

- für alle zugelassenen CAR-T-Zell-Therapien werden Erweiterungen auf frühere (2.) Linien untersucht.
- neue Indikationen für Yescarta® und Kymriah® (R/R follikuläres Lymphom), Kymriah® (R/R Mantelzelllymphom (MCL) und NHL bei Kindern, Jugendlichen und jungen Erwachsenen), Tecartus® (chronische lymphatische Leukämie/kleinzelliges lymphatisches Lymphom (CLL/ SLL), NHL und ALL) und Breyanzi® (CLL/ SLL und MCL, viele von ihnen indolentes NHL - wie FL 1-3a) werden untersucht.

Schlussfolgerung: Innerhalb des nächsten Jahres wird *eine* neue CAR-T-Zell-Therapie für das Multiple Myelom zugelassen werden und Indikationserweiterungen der fünf bereits zugelassenen CAR-T Zell-Therapien auf frühere Therapielinien und neue Indikationen sind zu erwarten Die Herstellung von im Krankenhaus und von allogenen CAR-T Zell-Therapien befinden sich zwar in der Entwicklung, aber noch in den Kinderschuhen.

1 CAR-T Zell-Therapie & Indikationserweiterungen zu erwarten

Executive Summary

Background: CAR-T cell-therapies are commonly indicated as „transformative" therapies referring to the huge expectations associated with them since their market approval in 2017 (USA) and 2018 (Europe). Due to the hope, but also the enormous prices a horizon scanning (HS) document was first published in 2020 in cooperation with Tirol Kliniken GmbH to support budget planning in hospitals. In 2020 13 CAR-T cell-therapies in advanced stages were identified. Of these, in addition to Yescarta® and Kymriah®, that were already approved at that time, three further therapies have since been approved by the European Medicines Agency (EMA) between 8/ 2020 and 03/2022: Tecartus® (2020), Abcema® (2021) and Breyanzi® (2022).

Methods: This HS document updates the earlier report by surveying the status of the ten therapies already described in 2020 and adding additional therapies that have since reached a later phase of clinical testing.

Results:

- Four therapies are under investigation for hodgkin and (aggressive as well as indolent) non-hodgkin lymphoma, but no new approvals are to be expected soon.
- Six therapies are under development for multiple myeloma, of which one (Cilta-cel, Carvykti®) has been approved by FDA in Feb 2022 and is expected to be approved by EMA soon. Five therapies are still in early trial phases, of which one is sponsored by an EC-grant. One therapy development was discontinued (Orva-cel). To conclude, there will be a competitor to Abcema® approved soon.
- one therapy is under development in two trials for acute myeloid leukemia (AML), but due to hurdles in the development of CAR-T therapies for AML, there is no change in the status since 2020. There are very few new developments, such as Autologous SLAMF7 CAR-T Cells, that is based on a new target and could be promising in multiple myeloma.

In contrast to only few newly developed CAR-T cell-therapies, **extensions to the already approved therapies** to earlier therapy line in the respective indication and/or further indications are

- from only last line therapy to earlier (2nd) lines are investigated for all approved CAR-T cell-therapies.
- new indications for Yescarta® and Kymriah® (R/R follicular lymphoma), Kymriah® (R/R mantle cell lymphoma (MCL) and NHL in children, adolescents and young adults), Tecartus® (chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/ SLL), NHL and ALL) and Breyanzi® (CLL/ SLL and MCL, many of them indolent NHL - such as FL 1-3a) are investigated.

Conclusion: Within the next year one new CAR-T cell-Therapy for multiple myeloma will eventually be approved, but further development can be expected with the extension of the five approved CAR-T cell-therapies towards earlier lines of therapy and new indications In-hospital production and allogeneic CAR-T cell-therapies, though in development, are still in their infancy.

CAR-T cell therapies:
high hopes
high prices

horizon scanning supports budget planning:
since 2018
5 CAR-T cell therapies approved
monitoring of advanced developments

NL+NHL:
4 in development, but no approval soon

MM:
1 before approval
5 in development, but no approval soon
1 discontinued

AML:
1 in development, but no approval soon

BUT:
extension of indications of the 5 already approved

earlier lines of therapy
further indications

1 CAR-T cell therapy & extension of indications expected

1 Einleitung

CAR-T Zell-Therapien sind derzeit (vornehmlich) für bösartige hämatologische Erkrankungen (Leukämien, Lymphome) zugelassen oder in Entwicklung, wenngleich sie auch in frühen Phasen für solide Tumore erprobt werden. Dieser Bericht ist ein Update des 2020 – unter der Federführung der Tirol-Kliniken GmbH - vorgelegten Dokuments. Zu den Methoden verweisen wir dorthin: https://eprints.aihta.at/1268/ (S 16).

CAR-T Zell-Therapien derzeit nur für maligne hämatologische Erkrankungen zugelassen

Exkurs zur Einteilung verschiedener bösartige hämatologische Erkrankungen

Unter maligne hämatologische Erkrankungen fallen jene Krebserkrankungen, die das blutbildende System betreffen. Allen voran sind dies Leukämien und Lymphome.

Leukämie als Überbegriff

Leukämie ist der Oberbegriff für verschiedene Krebserkrankungen des blutbildenden Systems und ist auch unter dem Begriff „Blutkrebs“ bekannt. Leukämie ist eine bösartige Erkrankung, bei der es zu einer übermäßigen Produktion unreifer oder abnormaler Leukozyten kommt, die schließlich die Produktion normaler Blutzellen unterdrückt und zu Symptomen im Zusammenhang mit Zytopenien führt. Im ersten Schritt der Blutbildung entstehen aus den Stammzellen die Vorläuferzellen, die sich dann in mehreren Reifungsschritten zu den funktionstüchtigen und reifen Blutzellen entwickeln. Leukämien entstehen, wenn der normale Reifungsprozess der weißen Blutkörperchen (Leukozyten) im Knochenmark durch eine Fehlschaltung bestimmter Kontrollgene unterbrochen ist. Anstelle von reifen, das heißt vollständig entwickelten und somit funktionstüchtigen weißen Blutkörperchen, entstehen mehr oder weniger unausgereifte weiße Blutkörperchen. Diese Zellen sind in der Regel nicht funktionsfähig und haben zudem die Eigenschaft, sich rasch und unkontrolliert zu vermehren[1].

übermäßige Produktion unreifer oder abnormaler Leukozyten

Unterdrückung der Produktion normaler Blutzellen

Leukämien werden üblicherweise auch kategorisiert als

- Akut oder chronisch: Bezogen auf den prozentualen Anteil von Blasten oder Leukämiezellen im Knochenmark oder Blut
- Myeloisch oder lymphatisch: Basierend auf der vorherrschenden Abstammungslinie der malignen Zellen

akut oder chronisch, myeloisch oder lymphatisch

Es wird zwischen folgenden Leukämietypen und deren Verteilung unterschieden[2]:

- Akute myeloische Leukämie (AML): 25% von Leukämien — **AML**
- Akute lymphatische Leukämie (ALL): 7% — **ALL**
- Chronische myeloische Leukämie (CML): 9% — **CML**
- Chronische lymphatische Leukämie (CLL): 30% (wird von Leukämiestatistik miterfasst, zählt aber zu den malignen Lymphomen) — **CLL**

[1] https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/leukaemie/definition-und-haeufigkeit.html

[2] https://www.onkopedia.com/de/; https://www.krebsinformationsdienst.de/tumorarten/leukaemien/index.php

- Sonstige Leukämien

Lymphome sind in der Regel bösartige Tumoren des lymphatischen Systems (umgangssprachlich Lymphdrüsenkrebs). Bei malignen Lymphomen entarten die Lymphozyten und beginnen unkontrolliert zu wachsen und sich zu vermehren[3].

Lymphome
HL
NHL
MML

Innerhalb der malignen Lymphome gibt es historisch betrachtet drei große Gruppen: das Hodgkin-Lymphom, die Non-Hodgkin-Lymphome (NHL) und das Multiple Myelom, das zu den sogenannten Plasmazellerkrankungen gehört:

- Hodgkin-Lymphome (HL, Morbus Hodgkin) sind eine eigenständige Lymphomart.
- Non-Hodgkin-Lymphome (NHL)[4] sind alle anderen Lymphomarten – also solche, die nicht als Hodgkin-Lymphom gelten. Man unterscheidet hochmaligne (aggressive) NHL und indolente (niedrigmaligne) NHL. NHL als Überbegriff umfasst rund 30 verschiedene Lymphom-Erkrankungen zusammen. Dazu zählen etwa
  - B-Zell-Lymphomen: 80% aller NHL, davon DLBCL: 31%, PMBCL: 2%
  - Follikuläres Lymphom (FL) : 6%
  - Mantelzell-Lymphom (MCL): 6%
  - Chronische Lymphatische Leukämie/ kleines lymphozytische Lymphom (CLL/SLL) (6%)

NHL:
FL
MCL
DLBCL, PMBCL

aggressive und indolente Formen

Die NHL werden in eine B- (etwa 80%) und eine T-Linie (20 %) unterteilt, je nachdem, ob das NHL von B-lymphatischen oder T-lymphatischen Zellen ausgeht.

- Multiple Myelome (MML, "Knochenmarkkrebs") gehören ebenfalls zu den bösartigen Lymphomen. Sie gehen von reifen B-Lymphozyten, sogenannten Plasmazellen aus. Diese siedeln sich fehlerhaft im Knochenmark an und vermehren sich dort.

[3] https://www.onkopedia.com/de/; https://www.krebsinformationsdienst.de/tumorarten/lymphome/index.php

[4] https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes

2 Zugelassene CAR-T Zell-Therapien

Derzeit sind diese fünf CAR-T Zell-Therapien

5 CAR-T Zell-Therapien zugelassen

zwischen 2018-2022

1. Yescarta®/ Axicabtagene Ciloleucel (EMA Zulassung: September 2018) - Kite Pharma (Gilead)
2. Kymriah®/ Tisagenlecleucel (EMA Zulassung: September 2018) - Novartis
3. Tecartus®/ Brexucabtagen Autoleucel (EMA Zulassung: Dezember 2020) - Gilead
4. Abecma®/ Idecabtagene Vicleucel (EMA Zulassung Juni 2021) - Bristol Myers Squibb
5. Breyanzi®)/ Lisocabtagene Maraleucel (EMA positive CHMP Jänner 2022) - Bristol Myers Squibb

für folgende Indikationen in Europa zugelassen:

DLBCL (Erwachsene): Yescarta® & Kymriah® Breyanzi®

Wiederkehrendes (rezidiviertes) oder nicht (mehr) auf bestimmte Therapien ansprechendes (refraktäres) **diffus großzelliges B-Zell-Lymphom (DLBCL)**, Erwachsene mit mindestens zwei systemischen Vortherapien

- Yescarta®/ Axicabtagene Ciloleucel; Kymriah®/ Tisagenlecleucel; Breyanzi®/ Lisocabtagen maraleucel

PMBCL (Erwachsene): Yescarta® & Breyanzi®

Rezidiviertes oder refraktäres primary mediastinales **großzelliges B-Zell-Lymphom (PMBCL)**, Erwachsene mit mindestens zwei systemischen Vortherapien

- Yescarta®/ Axicabtagene Ciloleucel; Breyanzi®/ Lisocabtagen maraleucel

B-Zell-ALL (KiJu): Kymriah®

Rezidivierte oder refraktäre akute lymphatische **B-Zell-Leukämie (B-Zell-ALL)**, Kinder, Jugendliche und junge Erwachsene bis einschließlich 25 Jahre

- Kymriah®/ Tisagenlecleucel

MCL (Erwachsene): Tecartus®

Wiederkehrendes (rezidiviertes) oder nicht (mehr) auf bestimmte Therapien ansprechendes (refraktäres) **Mantelzell-Lymphom** (MCL), Erwachsene mit mindestens zwei Vortherapien

- Tecartus®/ Brexucabtagen Autoleucel

MML (Erwachsene): Abecma®

Wiederkehrendes (rezidiviertes) oder nicht (mehr) auf bestimmte Therapien ansprechendes (refraktäres) **Multiples Myelom (MML)**, Erwachsene mit mindestens drei systemischen Vortherapien

- Abecma®/ Idecabtagene Vicleucel

FL3B (Erwachsene): Breyanzi®

Follikuläres Lymphom Grad 3B (FL3B), Erwachsene mit mindestens zwei systemischen Vortherapien

- Breyanzi®/ Lisocabtagen maraleucel

3 Therapien in später klinischer Entwicklung

CAR-T Therapien in klinischen Studienregistern

Laut einem rezenten Bericht von IQVIA[5] (vgl. Abbildung 3-1) befinden sich ca. 200 CAR-T Zell-Therapien in der klinischen Entwicklung, davon viele bereits in Phase 2 oder Phase 3 der klinischen Prüfung. Die in Entwicklung befindlichen CAR-T Zell-Therapien im Bereich der Hämatoonkologie finden sich v. a. in folgenden Indikationen:

1. B-Zell Lymphome (BCL: DLBCL, PMBCL)
2. Follikuläres Lymphom (FL)
3. Mantelzelllymphom (MCL)
4. Multiples Myelom (MM)
5. Akute Lymphatische Leukämie (ALL)
6. Chronische Lymphatische Leukämie (CLL)
7. Akute Myeloische Leukämie (AML)

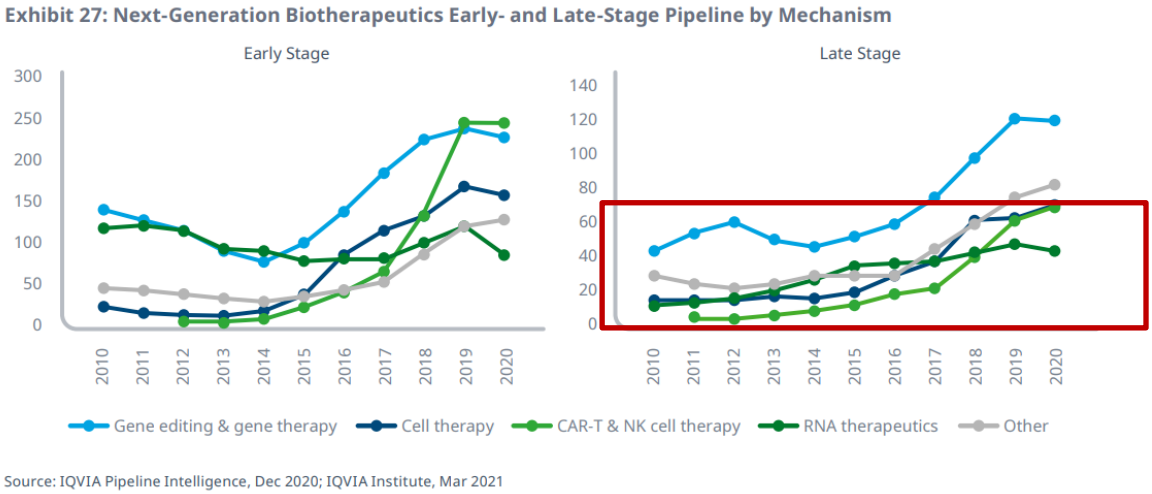

Abbildung 3-1: CAR-T Zell-Therapien (hellgrün) in Entwicklung

Marktanalysten sagen großen Umsatzzuwachs voraus

Neben den CAR-T Zell-Therapien sind Natürliche Killer- (NK-) Zell-Therapien in Entwicklung und nehmen den zweithöchsten Anteil an Zell-Therapien der nächsten Generation ein. Marktanalysten[6] sagen voraus, dass in den nächsten Jahren CAR-T Zell-Therapien mithilfe neuer Konzepte und Technologien sowie anderer Verabreichungsformen heutige Sicherheits- und Wirksamkeitsprofile verändern werden. Es wird ein Umsatzzuwachs von 4 Mrd. $ bis 2027 vorausgesagt (vgl. Abbildung 3-2).

[5] S 33, https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022

[6] https://clarivate.com/lp/car-t-cell-therapy-pipeline-and-forecast-snapshot/

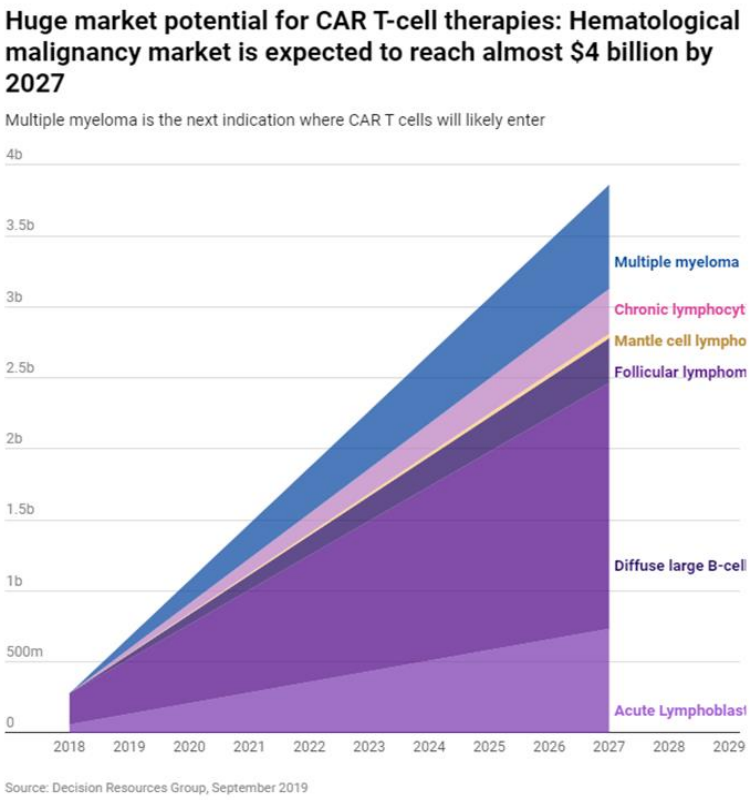

Abbildung 3-2: Vorhersage der Marktentwicklung für CAR-T Zell-Therapien

2020 HSS Bericht: 13 CAR-T Zell-Therapien identifiziert, davon 2022 bereits 3 zugelassen

Im ersten Horizon Scanning Bericht (2020) zur CAR-T Zell-Therapie (https://eprints.aihta.at/1268/) wurden 13 CAR-T Zell-Therapien identifiziert, welche am weitesten in der klinischen Prüfung fortgeschritten waren. Davon sind inzwischen neben den zum damaligen Zeitpunkt bereits zugelassen Therapien Yescarta® und Kymriah®, drei weitere Therapien durch die European Medicines Agency (EMA) zugelassen worden: Tecartus® (2020), Abcema® (2021) und Breyanzi® (2022).

Methode Update Bericht 2022: Überprüfung des Status der 10 nicht zugelassenen und Ergänzung mit weiteren

Für die zehn anderen im Bericht beschriebenen CAR-T Zell-Therapie wurde im Rahmen des vorliegenden Updates (2022) der aktuelle Stand der klinischen Entwicklung recherchiert sowie weitere Therapien, welche inzwischen eine spätere Phase der klinischen Prüfung erreicht haben, ergänzt. In Tabelle 3-1 findet sich eine Übersicht der CAR-T Zell-Therapien in späteren Phasen (Phase 1/ 2 bis Phase 3) klinischer Prüfung.

Nachfolgend werden die entsprechend der jeweiligen hämato-onkologischen Indikation zugeordneten CAR-T Zell-Therapien aus Table 3-1 mit dem aktuellen Stand der klinischen Prüfung beschrieben.

Auswertungen in englische Sprache zur internationalen Verwendung

Zugunsten internationaler Verwendbarkeit des Berichts (z.B. in BeNeLux-AIR, EUnetHTA), werden diese Ergebnisse in englischer Sprache berichtet.

Table 3-1: CAR-T Therapies in development: advanced stages (phase 1/2, 2 or 3) – for approved therapies (extension of indications in Chap. 4)

	CAR-T cell therapy	Target	Oncologicalindica-tion	Pharmaceutical com-pany	Phase; Study-ID: primary completion date, location(s)	EMA/FDA status/others	Comments on Status 03/2022
	Lymphoma: B-cell lymphoma (BCL), Follicular lymphoma (FL) and Acute Lymphoblastic Leukaemia (ALL)						
1	Lisocabtagene Maraleucel (JCAR017, **liso-cel**), **Breyanzi®**)	CD19	DLBCL PMBCL FL3b	Celgene/ BMS	See chapter 4 for extensions of indications	Change to report 2020 (https://eprints.aihta.at/1268/) FDA approval 02/2021 EMA: positive CHMP 01/2022l	
2	CD19-PD1-CART Cells	CD19	BCL B-ALL	Chinese PLA General Hospital National University of Malaysia	Phase 2: NCT04163302: 07/2021, China	n.a.	Study is ongoing, no results available, no new studies registered
3	AUTO3	CD19 CD22	DBCL ALL (adult, pediatric)	Autolus Therapeutics	Phase 1/2: NCT03287817: 11/2024, UK Phase 1/2: NCT03289455: 05/2020, US	FDA: 04/2019 ODD for ALL EMA: -	1 study completed for ALL, 1 study ongoing no phase 2/3 study registered
4	Relmacabtaene autoleucel (JWCAR029, **relma-cel; Carteyva®)**	CD19	DBCL	JW Therapeutics	Phase 2: NCT04089215 12/2022, China Phase 2: NCT04718883 06/2023, China	China/NMPA: approval 09/2021	Phase 2, but only in China Of relevancy for FDA/ EMA?
5	CD30 CAR-T cells (TT11, CART30)	CD30	HL NHL	Tessa Therapeutics	Phase 1/ 2: NCT02259556 10/2018, China Phase 2: NCT04268706 02/2023, US	FDA: 02/2020 RMAT designation EMA: 01/2021 PRIME designation	no change since 2020
	Multiple myeloma (MM)						
1	Idecaptagene (Abcema®)	BCMA	MM	Bristol Myers Squibb (BMS)	See chapter 4 for extensions of indications	Change to report 2020 (https://eprints.aihta.at/1268/) FDA approval 03/2021 EMA approval 06/201	
2	JNJ- 4528 Ciltacabtagene autoleucel (**cilta-cel**, **Carvykti®**)	BCMA	MM	Janssen-Cilag (Johnson & Johnson)	Phase 4: NCT04923893 06/2026, EU, Israel, Japan, US Phase 4; NCT05201781: 08/2036: US Phase 3: NCT05257083: 06/2026:EU Phase 3: NCT04181827: 04/2026, US, EU Phase 2: NCT03758417: 11/2022, China Phase 2: NCT04133636:	FDA ODD: 02/2019 FDA approval 02/2022 EMA PRIME designation: 04/2019 EMA ODD: 02/2020	EMA submission ongoing, **approval expected in 2022**

					05/2022: US, EU, Japan, Israel		
3	Descartes-11	BCMA	MM	Cartesian Therapeutics	Phase 2: NCT04436029: 04/2022, US: Phase 1/2: NCT03994705: 12/2021: US	n.a.	Phase 2 ongoing, no change since 2020
4	BCMA CAR T (CT103A)	BCMA	MM	IASO Bio Innovent Biologics.	Phase 1/2: ChiCTR1800018137: 12/2020, China	FDA: ODD 2022 EMA: - China/NMPA: approval to the investigational new drug (IND)* application for CT103A	Updated clinical data & publications available FDA: ODD granted in 2022
5	BCMA CAR-T (CT053, zevor-cel)	BCMA	MM	Carsgen Therapeutics	Phase 1/2: NCT03975907: 12/2022, China	FDA: 10/2019 granted RMAT designation EMA: 04/2020 positive opinion on OD	Updated Results & publication available
6	P-BCMA-101	BCMA	MM	Poseida Therapeutics	Phase 1/2: NCT03288493: 03/2024, US	FDA: 05/2019 ODD EMA: -	No change since 2020
7	JCARH125 Orvacabtagene autoleucel (orva-cel)	BCMA	MM	Celgene/ JunoTherapeutics	Phase 1/2: NCT03430011: 04/2023, US	FDA: - EMA ODD: 12/2020	Discontinuation of development
8	Autologous SLAMF7 CAR-T Cells	SLAMF7	MM	EC-Grant	Phase 1/2: NCT04499339 03/2024, EU	FDA/ EMA: -	Sponsored by EU-Grant
	Acute myeloid leukemia (AML)						
1	CD123-targeted CART(MB-102)	CD123	AML	Mustang Bio	Phase 1/2: NCT04109482: 03/2023, US Phase 2/3:NCT03631576 08/2021, China	FDA: ODD 07/2019 EMA: -	No change since 2020
	Mantle cell lymphoma (MCL)						
1	Brexucaptagene KTE-X19 (Tecartus®)	CD19	MCL	Gilead	See chapter 4 for extensions of indications	**Change to report 2020** (https://eprints.aihta.at/1268/): FDA approval 10/2021 EMA approval 12/2020	

ALL=acute lymphoblastic leukaemia; AML=Acute myeloid leukemia; B-ALL=B-Acute Lymphoblastic Leukaemia; BCL=B-Cell Lymphoma; BCMA=B-cell maturation antigen; CLL=Chronic lymphocytic leukaemia; DBCL=diffuse-large B cell lymphoma; EMA=European Medicines Agency, FDA=US Food & Drug Administration; FL3b= Follicular lymphoma grade 3B; HL=Hodgkin Lymphoma; IND application=investigational new drug (before phase 1 trial); MM=Multiple myeloma; NHL=Non- Hodgkin Lymphoma; NMPA=National Medical Products AdministrationPRIME=priority medicines designation; RMAT=regenerative medicine advanced therapy; U.S.=United States;

** BLA/MAA means a Biologics License Application ("BLA") submitted to the FDA or a Market Authorization Application ("MAA") submitted to the EMA or MHLW, or any supplemental filing to a BLA or MAA

3.1 Therapies in development: B-Cell Lymphoma (BCL: DLBCL, PMBCL) and acute lymphatic leukaemia (ALL)

3.1.1 Lisocabtagene Maraleucel (JCAR017, liso-cel, Breyanzi®)

Change to report 2020 (https://eprints.aihta.at/1268/): positive CHMP/ EMA-approval for 3 indications.

see Chapter 4

Bristol-Myers Squibb erhielt bereits positive CHMP (01/2022)

3.1.2 CD19-PD1-CART Cells

NO change to report in 2020 (https://eprints.aihta.at/1268/) and entries in clinicaltrials.gov are not up-to- date.

CD19-PD1-CART cells are CD19CART which secretes the mutant PD-1Fc fusion protein. Preclinical studies have shown that CD19CART cells secreting mutant PD-1Fc fusion protein have a superior killing effect to CD19CART cells which does not express PD-1 fusion protein. CD19-PD1-CART cells are investigated in 3 studies in Asia.

klinische Entwicklung in Asien (China und Malaysia) – in öffentlichen Spitälern

keine Zulassung oder OD-Status in EU

Regulatory Status: no Designations identified (by FDA or EMA)

Approval status: not approved (by FDA or EMA)

Clinical investigations:

1 Studie: Phase 2

NCT04163302 (Phase 2, China, 30 pts, 07/2019 - 01/2022):

- Single center, non-randomized, open-label, phase 2 study to evaluate the efficacy and safety of CD19-PD1-CART cells therapy for patients with relapsed/refractory B Cell Lymphoma
- Status: Recruiting since 2019 (Last update: 11/ 2019)
- Status: Recruiting since 2021 (Last update: 10/ 2021)

References: n.r.

3.1.3 AUTO3

Change to report 2020 (https://eprints.aihta.at/1268/): Phase 1 completed, results available

Autolus Therapeutics

AUTO3 is a CAR T-cell therapy designed to target CD19 and CD22 simultaneously and developed by Autolus Therapeutics. First results of a phase 1 study (Amelia Study) in paediatricpatients with relapsed/refractory B-cell acute lymphoblastic leukaemia [33] and a phase 1/2 study in patients with relapsed/refractory DLBCL (Alexander Study) were presented at theASH Meeting in November 2019. The FDA has granted orphan drug designation for AUTO3 in ALL in April 2019.

akute lymphoblastische Leukämie (ALL)bei Kindern UND bei Erwachsenen

CD19 und CD22

Regulatory Status:

- FDA granted Orphan Drug Status in 2019
- EMA: n.a.

FDA: Orphan Drug Status

Approval status: not approved (by FDA or EMA)

Clinical investigations:

2 Studien: beide Phase 1/2

NCT03287817 (**ALEXANDER**,Phase 1/2, UK, 73 Pts., 09/2017 - 11/2024)

- Single Arm, Open-label, Multi-centre Study Evaluating the Safety and Clinical Activity of AUTO3, a CAR T Cell Treatment Targeting CD19 and CD22 with Anti PD1 Antibody in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.
- Status: Active, not recruiting (Last update: 11/2021)

adulte ALL

NCT03289455 (**AMELIA**, Phase 1/2, US, 23 Pts., 06/2017- 05/2020)

- Single-Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity Of AUTO3, a CAR T Cell Treatment Targeting CD19 And CD22 in **Paediatric** And **Young Adult** Patients With Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia
- Status: Completed (Last Update 02/2021)

pädiatrische ALL

References:

Ernst M. et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9(9):CD013365. doi: 10.1002/14651858.CD013365.

Cordoba S. CAR T cells with dual targeting of CD19 and CD22 in pediatric and young adult patients with relapsed or refractory B cell acute lymphoblastic leukemia: a phase 1 trial. Nat Med. 2021 Oct;27(10):1797-1805. doi: 10.1038/s41591-021-01497-1.

3.1.4 JWCAR029 (Relmacabtagene autoleucel, Carteyva; relma-cel)

Change to report 2020 (https://eprints.aihta.at/1268/): NEW (since then only phase 1 studies were available), but in 2022 (moved to phase 2). Studies are only in China (FDA and EMA relevant?).

JW Therapeutics basierend auf Plattform von Juno Therapeutics (Bristol Myers Squibb)

JWCAR029 is an autologous anti-CD19 CAR-T cell immunotherapy product developed by JW Therapeutics based on a CAR T cell process platform of Juno Therapeutics (a Bristol Myers Squibb company). The first product of JW Therapeutics, relma-cel was approved by the China National Medical Products Administration (NMPA) in September 2021 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, making it the first CAR-T product approved as a Category 1 biologics product in China. Currently, it is the only CAR-T product in China that has been simultaneously included in the National Significant New Drug Development Program, granted priority review and breakthrough therapy designations. (https://www.prnewswire.com/news-releases/jw-therapeutics-announces-nmpa-approval-of-relmacabtagene-autoleucel-injection-in-china-301369706.html)

B-Zell-Lymphom

Regulatory Status: n.a.

Approval status: not approved (by FDA or EMA)

Clinical investigations:

NCT03355859 (Phase 1, China, 10 Pts., 01/2018 – 03/2022)

- Open-Label Study of JWCAR029, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Adult Subjects With Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL)
- Status: Active, not recruiting (Last Update: 07/2019)

NCT03344367 (Phase 1, China, 20 Pts., 11/2017 – 03/2022)

- Open-Label Study of JWCAR029, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Adult Subjects With Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL)
- Status: Active, not recruiting (Last Update: 07/2019)

NCT04812691 (Phase 1, China, 12 Pts., 07/2020 – 03/2023)

- Open-label, single-arm, multicenter study conducted in adult subjects with primary refractory DLBCL to evaluate the safety, efficacy, pharmacokinetics(PK), pharmacodynamics(PD) of JWCAR029 and collect immune response after JWCAR029 treatment with 2 year follow-up.
- Status: Recruiting (Last Update: 03/2021)

NCT04089215 (Phase 2, China, 82 Pts., 06/2019 – 09/2024)

- Open-label, single-arm, multicenter study in adult subjects with R/R Non-Hodgkins Lymphoma to evaluate the safety, efficacy, pharmacokinetics(PK), pharmacodynamics(PD) of JWCAR029 and collect the patient reported quality of life changes and immune response after JWCAR029 treatment with 2 year follow-up. Two cohorts, A and B. Large B cell lymphoma (LBCL) patients will be enrolled in cohort A and follicular lymphoma patients will be enrolled in cohort B.
- Status: Recruiting (Last Update: 01/2021)

NCT04718883 (Phase 2, China, 59 Pts., 01/2021 – 06/2025)

- Open-label, single-arm, multicenter study conducted in adult subjects with relapsed and refractory (R/R) mantle cell lymphoma (MCL) in China to evaluate the safety, efficacy, pharmacokinetics(PK), pharmacodynamics(PD) of JWCAR029 and immune response after JWCAR029 treatment with 2 year follow-up.
- Status: Recruiting (Last Update: 03/2021)

OD Status unbekannt (FDA/ EMA)

5 Studien (China):

2 Phase 2
3 Phase 1

References:

Ernst M. et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9(9):CD013365. doi: 10.1002/14651858.CD013365.

Ying Z. et al. Relmacabtagene autoleucel (relma-cel) CD19 CAR-T therapy for adults with heavily pretreated relapsed/refractory large B-cell lymphoma in China. Cancer Med. 2021 Feb;10(3):999-1011. doi: 10.1002/cam4.3686.

3.1.5 CD30 CAR-T cells (TT11, CART30)

Tessa Therapeutics
NL und NHL in Kindern

NO change to report in 2020 (https://eprints.aihta.at/1268/).

CD30.CAR-T are CD30-Directed Genetically Modified Autologous T cells developed by Tessa Therapeutics and investigated in adult and paediatric patients with relapsed or refractory CD30 Positive Classical Hodgkin Lymphoma. In February 2020, the FDA granted Regenerative Medicine Advanced Therapy designation for CD30.CAR-T [40]. The RMAT designation is supported by clinical data from two independent CD30 CAR-T Phase 1/2 studies in patients with relapsed or refractory CD30-positive classical Hodgkin lymphoma conducted by Baylor College of Medicine (NCT02917083) and University of North Carolina Lineberger Comprehensive Cancer Centre (NCT02690545). Both studies demonstrated objective response rates of more than 70%, with 18 patients achieving complete response out of 27 patients treated with CD 30 CAR- T with lymphodepleting chemotherapy as of November 2019. The company is now initiating a pivotal Phase 2 clinical study to investigate their autologous CD30.CAR-T cell therapy program.

FDA: RMAT Status
EMA: PRIME

Regulatory Status:

- FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation in 02/2020
- EMA granted PRiority MEdicines (PRIME) designation in 01/2021 (https://www.biospace.com/article/releases/tessa-therapeutics-receives-prime-designation-from-european-medicines-agency-for-cd30-car-t-therapy/)

Approval status: not approved (by FDA or EMA)

3 Studien:

1 Phase 1
1 Phase 1/ 2
1 Phase 2

Clinical investigations:

NCT02917083 (**RELY-30**, Phase 1, US, 66 Pts., 05/2017 – 04/2022)

- Open-label, single-group, dose escalation study of relapsed CD30 expressing lymphoma treated with CD30 CAR T Cells
- Status: Recruiting (Last Update: 11/2021)

NCT04268706 (**CHARIOT**, Phase 2, US, 94 Pts., 02/2021 – 02/2023)

- A two-part, multicenter, open-label, single-arm study to evaluate the safety and efficacy of autologous CD30.CAR-T in adult and pediatric subjects with relapsed or refractory CD30+ classical Hodgkin Lymphoma.
- Status: Recruiting (Last update: 03/2021)

NCT02259556 (Phase 1/2, China, 30 Pts., 10/2014 – 10/2018)

- A single-arm, open-label study of CD30-directed chimeric antigen receptor t (CART30) therapy in relapsed and refractory CD30 positive lymphomas
- Status: Recruiting (Last update: 01/2016)

References:

Ramos CA. et al. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2020 Nov 10;38(32):3794-3804. doi: 10.1200/JCO.20.01342.

Voorhees TJ. et al. Pretherapy metabolic tumor volume associates with response to CD30 CAR T cells in Hodgkin lymphoma. Blood Adv. 2021 Oct 19:bloodadvances.2021005385. doi: 10.1182/bloodadvances.2021005385.

3.2 Therapies in development: Multiple Myeloma

3.2.1 Idecaptagene (Abcema®)

Change to report 2020 (https://eprints.aihta.at/1268/): approved

see chapter 4

3.2.2 JNJ-4528, Ciltacabtagene autoleucel (JNJ-68284528 , LCAR-B38M, Cilta-cel, Carvykti®)

Janssen Pharmaceutical (Johnson & Johnson)

Multiples Myelom

JNJ-68284528 (LCAR-B38M) is an investigational CAR-T therapy for the treatment of patients with relapsed or refractory multiple myeloma developed by Janssen Pharmaceutical (Johnson & Johnson). The design comprises a structurally differentiated CAR- T with two BCMA-targeting single domain antibodies. In December 2017, Janssen entered into an exclusive worldwide license and collaboration agreement with Legend Biotech to develop and commercialize JNJ-68284528 (LCAR-B38M). In May 2018, Janssen initiated a Phase 1b/2 trial (NCT03548207) to evaluate the efficacy and safety of JNJ-68284528 in adults with relapsed or refractory multiple myeloma, informed by the LEGEND-2 study results. The primary completion date for this study is September 14, 2021.

In addition, a phase 3 randomized study comparing JNJ-68284528 versus pomalidomide, bortezomib and dexamethasone or daratumumab, pomalidomide and dexamethasone in subjects with relapsed and lenalidomide-refractory multiple myeloma was initiated in June 2020 by Janssen Research & Development, LLC (NCT04181827).

Regulatory Status:

FDA: OD Status, Breakthrough Designation
EMA: PRIME

- FDA: In February 2019, the FDA granted Janssen an Orphan Drug Designation (OSS) for JNJ-4528. In December 2019, Janssen announced receipt of a Breakthrough Therapy Designation from the FDA.
- EMA: In April 2019, JNJ-68284528 was granted PRIME designation by the EMA.
- EMA: Janssen Submits Marketing Authorisation Application: 04/2021

FDA: Zulassung 2/2022
EMA: Zulassung bald erwartet

Approval Status: FDA approval in Feb 2022

Clinical Investigations:

8 Studien:

2 Phase 4
2 Phase 3
2 Phase 2
2 Phase 1/2

NCT05257083 (**CARTITUDE-6,** Phase 3, EU, 750 Pts., 06/2022 – 06/2026)

- Randomized Study Comparing Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Ciltacabtagene Autoleucel Versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Autologous Stem Cell Transplant (ASCT) in Participants With Newly Diagnosed Multiple Myeloma Who Are Transplant Eligible.
- Status: Not yet recruiting (Last Update: 02/2022)

NCT04923893 (**CARTITUDE-5,** Phase 4, US, EU, Israel, Japan, 650 Pts., 08/2021 – 06/2026)

- Participants who had previously received treatment with cilta-cel in a Janssen-sponsored clinical study (example, NCT04923893, NCT04181827, NCT04133636, and NCT03548207) in the global development program will be enrolled into this study once the individual's participation in the particular interventional study has ended. Participants will not receive any treatment in this study and will be followed-up at least once per year on delayed adverse events for up to 15 years after receiving the last dose of cilta-cel.
- Status: Recruiting (Last Update: 01/2022)

NCT05201781 (Phase 4, US, 228 Pts, 02/2022 – 08/2036)

- A Long-term Study for Participants Previously Treated With Ciltacabtagene Autoleucel. There will be no treatment administered during the study and the data obtained from this study will help to assess whether there will be long-term cilta-cel-related toxicities. The study will consist of 2 phases: within the first 5 years after receiving the last dose of cilta-cel and Year 6 to 15 years after last dose of cilta-cel. Safety evaluations will include a review of adverse events, laboratory test results, and physical examination findings (including neurological examination). The duration of the study is up to 15 years after last dose of cilta-cel and participants will be followed at least once per year.
- Status: Not yet recruiting (Last Update: 01/2022)

NCT03758417 (**CARTIFAN-1,** Phase 2, China, 130 Pts., 01/2019-11/2022)

- Open-Label Study of LCAR-B38M CAR-T Cells, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against BCMA in Chinese Subjects With Relapsed or Refractory Multiple Myeloma
- Status: Recruiting (Last Update: 01/2022)

NCT04181827 (**CARTITUDE-4**, Phase 3, US, EU, Israel, Japan, 419 Pts., 06-2020 - 04/2026)

- Open-Label. Randomized Study Comparing JNJ-68284528 Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects With Relapsed and Lenalidomide-Refractory Multiple
- Status: Active, not recruiting (Last Update: 01/2022)

NCT03090659 **(LEGEND-2,** Phase 1/2, China, 100 Pts., 10/2015 - 12/2021)

- Open-Label Clinical Study of Legend Biotech BCMA-chimeric Antigen Receptor Technology in Treating Relapsed/Refractory (R/R) Multiple Myeloma Patients
- Status: Active, not recruiting (Last Update: 09/2021)

NCT03548207 (**CARTITUDE-1**, Phase 1/2, US, Japan, 113 Pts., 06/2018-02/2022)

- Open-Label Study of JNJ-68284528, A Chimeric Antigen Receptor T-Cell (CAR-T) Therapy Directed Against BCMA in Subjects With Relapsed or Refractory Multiple Myeloma. Participants will be followed for at least 2 years after study drug infusion, with long-term 15 year follow-up on a separate study. The study will evaluate safety, biomarkers, pharmacokinetic/pharmacodynamic evaluations and efficacy.
- Status: Active, not recruiting (Last Update: 01/2022)

NCT04133636 **(CARTITUDE-2,** Phase 2, US, EU, Japan, Israel, 11/2019 – 05/2022)

- Phase 2, multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA in Subjects With Multiple Myeloma
- Status: Active, not recruiting (Last Update: 01/2022)

References:

Cohen AD. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies, Blood Cancer J, . 2022 Feb 24;12(2):32. doi: 10.1038/s41408-022-00629-1.

Manier S. et al. Current state and next-generation CAR-T cells in multiple myeloma, Blood Rev, 2022 Jan 21;100929. doi: 10.1016/j.blre.2022.100929.

Merz M. et al. Adjusted Comparison of Outcomes between Patients from CARTITUDE-1 versus Multiple Myeloma Patients with Prior Exposure to PI, Imid and Anti-CD-38 from a German Registry, Cancers (Basel), 2021 Nov 29;13(23):5996. doi: 10.3390/cancers13235996.

Zhao WH, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol. 2018 Dec 20;11(1):141. doi: 10.1186/s13045-018-0681-6.

Weisel K, et al. Comparative Efficacy of Ciltacabtagene Autoleucel in CARTITUDE-1 vs Physician's Choice of Therapy in the Long-Term Follow-Up of POLLUX, CASTOR, and EQUULEUS Clinical Trials for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. Clin Drug Investig. 2022 Jan;42(1):29-41. doi: 10.1007/s40261-021-01100-y.

Martin T, et al.. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma. Curr Med Res Opin. 2021 Oct;37(10):1779-1788. doi: 10.1080/03007995.2021.1953456. Epub 2021 Jul 23. Erratum in: Curr Med Res Opin. 2021 Oct 6;1-12.

Berdeja JG, et al.. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021 Jul 24;398(10297):314-324. doi: 10.1016/S0140-6736(21)00933-8. Erratum in: Lancet. 2021 Oct 2;398(10307):1216.

3.2.3 Descartes-11

Cartesian Therapeutics

Multiples Myelom

2 Studien:

Phase 1/2
Phase 2

NO change to report in 2020 (https://eprints.aihta.at/1268/).

Descartes-11 s an autologous CD8+ anti-BCMA CAR T-cell therapy being developed by Cartesian Therapeutics. In June 2020, Cartesian Therapeutics initiated phase 2 trial (NCT04436029) to evaluate efficacyof Descartes-11 in patients with high-risk multiple myeloma who have residual disease following induction therapy.

Regulatory Status: n.a.

Approval status: not approved (by FDA or EMA)

Clinical investigations:
NCT04436029 (Phase 2, US, 30 Pts., 06/2020-04/2022)

- Open-Label Descartes-11 Consolidation Treatment in Patients With High-Risk Multiple Myeloma Who Have Residual Disease After Induction Therapy
- Status: Recruiting (Last Update: 02/2021)

NCT03994705 (Phase 1/2, US, 25 Pts. 08/2019 – 12/2021)

- Safety Study of Descartes-11 in Patients With Relapsed/Refractory Multiple Myeloma
- Status: Completed (Last Update: 03/2022)

References: n.r.

3.2.4 BCMA CAR T (CT103A)

Iaso Biotherapeutics
Multiples Myelom

zugelassen in China

1 Studie:
Phase 1/2

Change to report in 2020 (https://eprints.aihta.at/1268/): **FDA ODD status granted, phase 1/2 started**

CT103A is a novel BCMA-targeting CAR-T with a lentiviral vector containing a CAR structure with a fully human scFv, CD8a hinger, and transmembrane, 4-1BB co-stimulatory and CD3z activation domains developed by Iaso Biotherapeutics and investigated in patients withrelapsed/refractory multiple myeloma (ChiCTR1800018137).

The National Medical Products Administration (NMPA) in China has granted approval to the investigational new drug (IND) application for CT103A, for the treatment of relapsed/refractory multiple myeloma in October 2019.

Regulatory Status: FDA Grants Orphan Drug Designation (ODD), 02/2022

Approval status: not approved (by FDA or EMA)

Clinical investigations:
NCT05066646 (FUMANBA-1, Phase 1/2, 132 Pts. China, 04/2020 – 10/2022)

- A single-arm, open-label, multicenter study to evaluate the efficacy and safety of CT103A in subjects with relapsed and refractory Multiple Myeloma
- Status: Recruiting (Last update: 11/2021)

References:

Que Y. et al. Anti-BCMA CAR-T Cell Therapy in Relapsed/Refractory Multiple Myeloma Patients With Extramedullary Disease: A Single Center Analysis of Two Clinical Trials. J.Front Immunol. 2021 Oct 29;12:755866. doi: 10.3389/fimmu.2021.755866.

Wang D. et al. A phase 1 study of a novel fully human BCMA-targeting CAR (CT103A) in patients with relapsed/refractory multiple myeloma. J.Blood. 2021 May 27;137(21):2890-2901. doi: 10.1182/blood.2020008936.

3.2.5 BCMA CAR-T (Zevor-cel, CT053)

CARsgen Therapeutics
Multiples Myelom

Change to report in 2020 (https://eprints.aihta.at/1268/)**: Phase 1/2 trial started.**

CT053 are fully human anti-BCMA autologous chimeric antigen receptor T-cells for the treatment of multiple myeloma developed by CARsgen Therapeutics. CT053 recently received positive EMA opinion on orphan drug designation in April 2020. In October 2019, the U.S. Foodand Drug Administration has granted its Regenerative Medicine Advanced Therapy (RMAT) designation to the investigational therapy CT053 for the treatment of relapsed or refractory multiple myeloma. The designation follows a recently granted orphan drug designation by theFDA and priority medicines (PRIME) eligibility from the European Medicines Agency. It was based on data from an ongoing Phase 1 clinical trial (NCT03975907) in people with heavily pre-treated multiple myeloma [30].

FDA: RMAT Status
EMA: OD Status

Regulatory Status:

- EMA: 04/2020 positive opinion on orphan designation
- FDA: 10/2019 granted Regenerative Medicine Advanced Therapy (RMAT) designation

Approval status: not approved (by FDA or EMA)

2 Studien:

Clinical investigations:

Phase 1
Phase 1/2

NCT03975907 (**LUMMICAR STUDY 1,** Phase 1/2, China, 62 Pts., 06/2019 – 12/2022)

- Open Label, Clinical Trial to Evaluate the Safety and Efficacy of Fully Human Anti-BCMA Chimeric Antibody Receptor Autologous T Cell （CAR T）in Patients With Relapsed and/or Refractory Multiple Myeloma
- Status: Recruiting (Last Update: 11/2020)

NCT03915184 (**LUMMICAR STUDY 2,** Phase 1/2, US/CAN, 105 Pts., 09/2019 – 12/2024)

- A single-arm, open label, multi-center, clinical trial to evaluate the safety and efficacy of autologous chimeric antigen receptor-B-cell maturation antigen (CAR-BCMA T cell; zevor-cel/CT053) in patients with relapsed and or refractory Multiple Myeloma.
- Status: Recruiting (Last update: 02/2022)

References:

Manier S. Current state and next-generation CAR-T cells in multiple myeloma, Blood Rev, 2022 Jan 21;100929. doi: 10.1016/j.blre.2022.100929.

Hyde A. Results from the LUMMICAR-2 study of CT053, a human BCMA-specific CAR-T therapy for patients with RRMM, Feb 17, 2021, https://multiplemyelomahub.com/medical-information/results-from-the-lummicar-2-study-of-ct053-a-human-bcma-specific-car-t-therapy-for-patients-with-rrmm

3.2.6 P-BCMA-101

Poseida Therapeutics
Multiples Myelom

NO Change to report 2020 (https://eprints.aihta.at/1268/)

P-BCMA-101 is a CAR-T cell product targeting B Cell Maturation Antigen (BCMA). P-BCMA-101 is produced using the piggyBac® DNA Modification System instead of the viral vector that is used with most CAR-T cells, requiring only plasmid DNA and mRNA. P-BCMA-101 is developed by Poseida Therapeutics which received FDA orphan drug designation for P-BCMA-101 for the treatment of multiple myeloma in May 2019. A pivotal Phase 2 study has recently been designed and initiated (PRIME; NCT03288493) in r/r multiple myeloma (MM) patients who have received at least 3 prior lines of therapy [25].

FDA: OD Status

Regulatory Status:

- FDA: 05/2019 orphan designation granted

Approval status: not approved (by FDA or EMA)

1 Studie
Phase 1/2

Clinical investigations:

NCT03288493 (Phase 1/2, US, 220 Pts., 09/2017 – 03/2024)

- Open-Label, Multicenter, Phase 1 Study to Assess the Safety of P BCMA-101 in Subjects With Relapsed / Refractory Multiple Myeloma (MM) Followed by a Phase 2 Assessment of Response and Safety (PRIME)
- Status: Active, not recruiting (Last Update: 01/2022)

References:

Manier S. Current state and next-generation CAR-T cells in multiple myeloma, Blood Rev, 2022 Jan 21;100929. doi: 10.1016/j.blre.2022.100929.

3.2.7 JCARH125 Orvacabtagene autoleucel (orva-cel)

Juno Therapeutics (Celgene, Bristol Myers Squibb)

Change to report 2020 (https://eprints.aihta.at/1268/):

On February 11, 2021, it was announced that Bristol Myers Squibb (BMS) was abandoning further development on Orvacabtagene Autoleucel - a BCMA CAR T cel-therapy originally developed by Juno Therapeutics[7].

[7] https://www.biospace.com/article/bristol-myers-squibb-abandon-s-orva-cel-program/

Regulatory Status:
EMA: 12/2020 orphan designation granted

Abbruch der Weiterentwicklung

Approval status: not approved (by FDA or EMA)

Clinical investigations:
NCT03430011 (**EVOLVE**, Phase 1/2, US, 169 Pts., 02/2018 – 04/2023)

1 Studie
Phase 1/2

- Open-label, multicenter, Phase 1/2 study to determine the safety and efficacy of JCARH125 in adult subjects with relapsed and/or refractory multiple myeloma. The safety and tolerability of JCARH125 in subjects who receive prophylactic treatment with anakinra will be evaluated in a separate Phase 1 cohort. The antitumor activity of JCARH125 in subjects who have been previously treated with BCMA-directed therapy will be evaluated in separate Phase 2a cohorts.
- Status: Active, not recruiting (Last Update: 06/2021)

References:

Teoh PhJ. et al. CAR T-cell therapy in multiple myeloma: more room for improvement, Blood Cancer J, 2021 Apr 29;11(4):84. doi: 10.1038/s41408-021-00469-5.

3.2.8 Autologous SLAMF7 CAR-T Cells

Change to report 2020 (https://eprints.aihta.at/1268/)**: NEW**

The CARAMBA project and the CARAMBA-1 clinical trial are supported by the European Union in the Horizon 2020 research and innovation program: https://www.caramba-cart.eu/

EC - F & E CARAMBA Projekt

Clinical development of chimeric antigen receptor (CAR)-T-cell therapy has been enabled by advances in synthetic biology, genetic engineering, clinical-grade manufacturing, and complex logistics to distribute the drug product to treatment sites. A key ambition of the CARAMBA project is to provide clinical proof-of-concept for virus-free CAR gene transfer using advanced Sleeping Beauty (SB) transposon technology. SB transposition in CAR-T engineering is attractive due to the high rate of stable CAR gene transfer enabled by optimized hyperactive SB100X transposase and transposon combinations, encoded by mRNA and minicircle DNA, respectively, as preferred vector embodiments. This approach bears the potential to facilitate and expedite vector procurement, CAR-T manufacturing and distribution, and the promise to provide a safe, effective, and economically sustainable treatment. As an exemplary and novel target for SB-based CAR-T cells, the CARAMBA consortium has selected the SLAMF7 antigen in multiple myeloma. SLAMF7 CAR-T cells confer potent and consistent anti-myeloma activity in preclinical assays in vitro and in vivo. CARAMBA is the first clinical trial with virus-free CAR-T cells in Europe, and the first clinical trial that uses advanced SB technology worldwide.

Regulatory Status:
Approval status: not approved (by FDA or EMA)

Clinical investigations:
NCT04499339 (**CARAMBA-1**, Phase 1/2, EU, 38 Pts., 07/2020 – 03/2024)

1 Studie
Phase 1/2

- an open-label, non-randomized, multicenter clinical trial which combines a phase I dose-escalation part with a phase IIa dose-expansion part to assess feasibility, safety and anti-myeloma activity of SLAMF7 CAR-T cells. MA-directed therapy will be evaluated in separate Phase 2a cohorts.
- Status: Recruiting (Last Update: 10/2021)

References:

Prommersberger S. et a. CARAMBA: a first-in-human clinical trial with SLAMF7 CAR-T cells prepared by virus-free Sleeping Beauty gene transfer to treat multiple myeloma, Gene Ther 2021 Sep;28(9):560-571. doi: 10.1038/s41434-021-00254-w.

3.3 Therapies in development: Acute myeloid leukemia (AML)

Since there seems to be – according to the literature – some hurdles in the development of CAR-T therapies for AML, none of the products are already in an advanced stage.

3.3.1 CD123-targeted CART(MB-102)

Mustang Bio

Akute Myeloische Leukämie

NO Change to report 2020 (https://eprints.aihta.at/1268/)

MB-102 is a CAR T-cell therapy that is produced by engineering patient T cells to recognize andeliminate CD123-expressing tumours and is developed by Mustang Bio Inc. CD123 is widely expressed on bone marrow cells of patients with myelodysplastic syndrome and hematologicmalignancies, including in 75-89% of AML patients and over 90% in blastic plasmacytoid dendritic cell neoplasm (BPDCN) patients. MB-102 has shown promising response rates in earlysmall populations of these patients in an investigator-sponsored Phase 1 clinical trial (NCT02159495). On July 24, 2019, Mustang announced that the FDA granted Orphan Drug Designation to MB-102 for the treatment of AML. The FDA also previously granted Orphan Drug Designation to MB-102 for the treatment of BPDCN. In August 2019, the U.S. Food and Drug Administration (FDA) has approved the Company's IND application to initiate a multi-centre Phase 1/2 clinicaltrial of MB-102 (CD123 CAR T) in acute myeloid leukaemia (AML), blastic plasmacytoid dendritic cell neoplasm (BPDCN) and high-risk myelodysplastic syndrome (MDS) [32].

Regulatory Status:

FDA: OD Status

- FDA: 07/2019 Orphan drug designation granted

Approval status: not approved (by FDA or EMA)

Clinical investigations:

2 Studien:
Status unbekannt

NCT04109482 (Phase 1/2, US, 44 Pts., 02/2020-03/2023)

- Open Label, Multicenter Trial to Assess the Safety and Efficacy of MB-102 in Patients With Relapsed or Refractory Blastic Plasmacytoid Dendritic Cell Neoplasm

1 Phase 2/3
1 Phase 1/2

- Status: Recruiting (Last Update: 02/2021)

NCT03631576 (**STPHI_0001**, Phase 2/3, China, 08/2018 - 08/2021)

- Open Label study of CD123/CLL1 CAR-T Cell Therapy for Relapsed and Refractory Acute Myeloid Leukemia
- Status: Unknown (Last Update: 01/2020)

References:

Mardiana Sh. et al. CAR T Cells for Acute Myeloid Leukemia: State of the Art and Future Directions. Front Oncol. 2020; 10: 697. doi: 10.3389/fonc.2020.00697

Marofi F. et al. Novel CAR T therapy is a ray of hope in the treatment of seriously ill AML patients, Stem Cell Res Ther. 2021; 12: 465. doi: 10.1186/s13287-021-02420-8

4 Extension of Indications for approved CAR-T cell therapies

In March 2022, five CAR-T cell therapies have been approved by EMA, six by the FDA. Additional to new CAR-T cell therapies in development (see chapter 3) our search in clinicaltrials.gov resulted in several ongoing clinical trials for CAR-T cell therapies in either additional indications or in their use in earlier lines (see Tables 4-1 to 4-4).

EU: 5 zugelassene CAR-T Therapien

USA: 6 zugelassene CAR-T Therapien

Table 4-0: CAR-T Therapies: approved therapies

	CAR-T cell therapy	Oncological indication	Pharmaceutical company	Date of EMA/FDA approval
1	Yescarta® (Axicabtagene Ciloleucel)	R/R DLBCL (adult) R/R PMBCL (adult)	Kite Pharma (Gilead)	FDA approval 10/2017 EMA approval 09/2018
2	Kymriah® (Tisagenlecleucel)	R/R DLBCL (adult) B-ALL (< 25 y)	Novartis	FDA approval 08/2017 EMA approval 08/2018
3	Tecartus® (Brexucaptagene; TE-X19)	R/R MCL (adult)	Gilead	FDA approval 10/2021 EMA approval 12/2020
4	Abcema® (Idecaptagene)	R/R MM (adult)	Bristol Myers Squibb	FDA approval 03/2021 EMA approval 06/2021
5	Breyanzi® (lisocabagene maraleucel; liso-cel)	R/R DLBCL (adult) R/R PMBCL (adult) R/R FL3b (adult	Celgene (Bristol Myers Squibb)	FDA approval 02/2021 EMA: CHMP 01/2022
6	Carvykti® (Ciltacabtagene autoleucel; cilta-cel)	R/R MM (adult)	Janssen Biotech	FDA approval 2/2022 EMA: submitted

B-ALL=B-Cell Acute Lymphoblastic Leukaemia; BCL=B-Cell Lymphoma; DBCL=diffuse-large B cell lymphoma; EMA=European Medicines Agency, FDA=US Food & Drug Administration; FL3b= Follicular lymphoma grade 3B; MM=Multiple myeloma; R/R= relapsed/refractory

4.1 Yescarta®/ Axicabtagen-ciloleucel

Yescarta® is approved for treating two types of blood cancer in adult patients whose blood cancer has returned or has stopped responding to previous treatment (Relapsed/refractory (R/R)).

zugelassen

R/R DLBCL
R/R PMBCL

- diffuse large B-cell lymphoma (DLBCL);
- primary mediastinal large B-cell lymphoma (PMBCL).

Additional Indications:

FDA Zulassung für NHL (FL) sowie Studien zu 1st/2nd-line DLBCL

- Yescarta® is investigated in two trials for R/R Non-Hodgin Lymphoma (Phase 1/ 2 and Phase 2: follicular lymphoma) and FDA approval of Yescarta® for R/Refractory Follicular Lymphoma in 03/2021 (ZUMA-5)

Earlier lines:

- Yescarta® is investigated in a clinical trial as 2nd line (ZUMA-7) and 1st line therapy for DLBCL

(see Table 4-1)

References:

Ernst M, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9(9):CD013365. doi: 10.1002/14651858.CD013365.

Locke FL, et al.. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17; 386(7):640-654. doi: 10.1056/NEJMoa2116133.

Jacobson CA, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022 Jan; 23(1):91-103. doi: 10.1016/S1470-2045(21)00591-X.

*Table 4-1: List of ongoing clinical trials for **Axicabtagen-ciloleucel**/ Yescarta® (Kite/Gilead)*

	NCT Number	Conditions	Phase	Status	Start Date - Primary Completion Date	Locations
1	NCT02926833 (ZUMA-6)	R/R DLBCL	1/2	Active, not recruiting	09/2016 - 02/2019	US
2	NCT02348216 (ZUMA-1)	R/R NHL	1/2	Active, not recruiting	04/2015 - 09/2020	US, CA, Israel, EU
3	NCT03391466 (ZUMA-7)	2nd line DLBCL	3	Active, not recruiting	01/2018 - 01/2023	US, AUS, CA, Israel, EU, CH, UK
4	NCT03105336 (ZUMA-5)	R/R NHL (FL)	2	Active, not recruiting	06/2017 - 02/2022	US, France
5	NCT03761056 (ZUMA-12)	1st Line DLBCL	2	Active, not recruiting	01/2019 - 05/2021	US, AUS, CA, France
6	NCT03704298 (ZUMA-11)	R/R DLBCL	1/2	Active, not recruiting	11/2018 - 05/2021	US

DLBCL=Diffuse Large B-Cell Lymphoma; FL= Follicular lymphoma; NHL= Non-Hodgkin Lymphoma; R/R= relapsed/ refractory

4.2 Tisagenlecleucel/ Kymriah® (Novartis)

zugelassen

R/R B-ALL ≤ 25 Jahre
R/R DLBCL

Kymriah® is approved for treating two types of blood cancer in patients whose blood cancer has returned or has stopped responding to previous treatment (Relapsed/refractory (R/R)).

- B-cell acute lymphoblastic leukaemia (ALL), in children and young adults up to 25 years of age whose cancer did not respond to previous treatment, has come back two or more times, or has come back after a transplant of stem cells;
- Diffuse large B-cell lymphoma (DLBCL) in adults whose cancer has come back or did not respond after two or more previous treatments.

Additional Indications:

Indikationsausweitung

- Kymriah® is investigated in a trial (phase 2) for the treatment of R/R mantle cell lymphoma (MCL)
- Kymriah® is investigated in a trial (phase 2) for the treatment of R/R follicular lymphoma (FL): ELARA Trial: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7508,
- Kymriah® is investigated in three trials (2 phase 2, 1 phase 3) for the treatment of R/R non- hodgkin lymphoma (NHL) in children, adolescents and adults.

R/R MCL
R/R FL
R/R NHL

Earlier lines:

frühere Therapielinien & erneute Therapie: B-ALL ≤ 25 Jahre

- Kymriah® is investigated as Re-Treatment Paediatric/ young adult with ALL,
- Kymriah® is investigated as 1st line Paediatric/ young adult B-ALL who are Minimal Residual Disease Positive at the End of Consolidation Therapy
- Kymriah® is investigated as 2nd line therapy in aggressive B-Cell Lymphoma (but did not prove to be superior to standard of care: BELINDA trial in Bishop): https://ascopost.com/news/december-2021/belinda-study-second-line-tisagenlecleucel-equivalent-to-standard-of-care-for-relapsed-or-refractory-aggressive-b-cell-non-hodgkin-lymphoma/

2nd line DLBCL

see Table 4-2

References:

Ernst M, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9(9):CD013365. doi: 10.1002/14651858.

Fowler NH, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022 Feb;28(2):325-332. doi: 10.1038/s41591-021-01622-0.

Bishop MR, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):629-639. doi: 10.1056/NEJMoa2116596.

Schuster SJ, et al. Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7508

*Table 4-2: List of ongoing clinical trials for **Tisagenlecleucel / Kymriah® (Novartis)***

	NCT Number	Conditions	Phase	Status	Start Date – Primary Completion Date	Locations
1	NCT04225676	Re-Treatment ALL (<25 y)	2	Completed	10/2020 - 10/2022	US
2	NCT04094311	B- ALL DBCL	3	Recruiting	11/2019 - 03/2022	CA, Japan
3	NCT04234061	R/R MCL	2	Active, not recruiting	04/2020 - 09/2027	AUS
4	NCT03876769	1st line B-ALL (<25 y) with MDR+ at End of Consolidation Therapy	2	Recruiting	06/2019 - 04/2027	US, CA, EU, UK
5	NCT03568461 (ELARA)	R/R FL	2	Active, not recruiting	11/2018 - 11/2020	US, AUS, EU, Japan, UK
6	NCT04161118	R/R DLBCL	2	Recruiting	05/2021 - 06/2024	Germany
7	NCT03610724	R/R DLBCL (<25 y)	2	Recruiting	02/2019 - 07/2021	US, CA, AUS, Japan, EU, UK
8	NCT03570892 (BELINDA)	2nd DLBCL	3	Active, not recruiting	05/ 2019 - 10/2026	US, AUS, Brazil, China, Japan, Hong Kong, Singapur, Taiwan, CH, EU, UK

B-ALL= B-cell acute lymphoblastic leukaemia, DLBCL=Diffuse Large B-Cell Lymphoma; FL= Follicular lymphoma; MCL= Mantle cell lymphoma; NA=not available; NHL= Non-Hodgkin Lymphoma; MRD+=Minimal Residual Disease positive; R/R= relapsed/refractory

4.3 Brexucabtagen Autoleucel/ Tecartus® (Gilead)

Tecartus® is approved for

zugelassen

- treating adults with mantle cell lymphoma (MCL) whose blood cancer has returned or has stopped responding to previous treatment (Relapsed/refractory (R/R)).

R/R MCL

Additional Indications:

Indikationsausweitung

- Tecartus® is investigated in two trials for R/R chronic lymphocytic leukaemia (CLL) and R/R small lymphocytic lymphoma (SLL),
- Tecartus® is investigated in one trial (phase 1/ 2) for R/R non-hodgkin lymphoma (NHL),
- Tecartus® is investigated in two trials (phase 1/2) for acute lymphoblastic leukaemia (ALL)

R/R CLL/ SLL
R/R NHL
RR ALL

Earlier lines:

- For now, Tecartus® seems not to be investigated for earlier lines treating mantle cell lymphoma (MCL), though ZUMA-2 has 3 cohorts, of which might be 2nd line therapy

ev. 2nd line

see Table 4-3:

References:

Shah BD, 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 Aug 7;398(10299):491-502. doi: 10.1016/S0140-6736(21)01222-8.

Wang M, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020b Apr 2;382(14):1331-1342. doi: 10.1056/NEJMoa1914347.

*Table 4-3: List of ongoing clinical trials for **Brexucabtagen Autoleucel**/ Tecartus® (Gilead)*

	NCT Number	Conditions	Phase	Status	Start Date – Primary Completion Date	Locations
1	NCT03624036 (ZUMA-8)	R/R CLL R/R SLL	1	Active, not recruiting	11/2018 - 02/2021	US, Italy
2	NCT02625480 (ZUMA-4)	ALL (pediatric) R/R NHL	1/2	Recruiting	02/2016 - 08/2023	US, Canada, EU
3	NCT02614066 (ZUMA-3)	ALL (adult)	1/2	Active, not recruiting	03/2016 - 09/2020	US, Canada, EU
4	NCT04880434 (ZUMA-2)	R/R MCL	2	Recruiting	04/2021 - 07/2024	US, EU
5	NCT02601313 (ZUMA-2)	R/R MCL	2	Active, not recruiting	11/2015 - 07/2019	US, EU

ALL= acute lymphoblastic leukaemia; CLL= Chronic Lymphocytic Leukemia; MCL= Mantle Cell Lymphoma; NHL= Non-Hodgkin Lymphoma; SLL= Small Lymphocytic Lymphoma; R/R= relapsed/refractory

4.4 Idecabtagene Vicleucel/ Abecma® (Bristol Myers Squibb)

Abecma® is approved for

zugelassen

- treating adults with multiple myeloma (MM) when the cancer has come back and has not responded to treatment (Relapsed/refractory (R/R)).

R/R multiple myeloma

Additional Indications:

- For now, Abecma® is not investigated for any other indications than multiple myeloma (MM).

keine weiteren Indikationen, aber

Earlier lines:

- Abecma® is investigated as 2nd line therapy in patients with relapsed and refractory multiple myeloma (KarMMa-3, Phase 3).
- Abecma® is investigated in 12 clinical trials (of which 1 phase 3 and 3 phase 2) for multiple myeloma (MM) in earlier treatment lines.

frühere Therapielinien

see Table 4-4

References:

Martin T, et al.. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma. Curr Med Res Opin. 2021 Oct;37(10):1779-1788. doi: 10.1080/03007995.2021.1953456.

*Table 4-4: List of ongoing clinical trials for **Idecabtagene Vicleucel** / Abecma® (Bristol Myers Squibb)*

	NCT Number	Conditions	Phase	Status	Start Date - Primary Completion Date	Locations
1	NCT02658929 (bb2121)	MM	1	Active, not recruiting	12/2015 - 07/2019	US
2	NCT03651128 (KarMMa-3)	MM	3	Recruiting	10/2018 - 05/2022	US, CA, EU, Japan, CH, UK
3	NCT03601078	MM	2	Recruiting	12/2018 - 08/2022	US, EU, UK
4	NCT04855136	MM	1/2	Recruiting	06/2021 - 11/2024	US, Spain
5	NCT04637269	MM	1	Recruiting	11/2020 - 11/2021	China
6	NCT03361748	MM	2	Active, not recruiting	12/2017 - 11/2024	US, CA, EU, Japan
7	NCT04196491	MM	1	Recruiting	05/2020 - 01/2025	US
8	NCT02786511	MM		Completed	04/2016 - 10/2025	US
9	NCT04727008	MM	1	Not yet recruiting	06/2021 - 12/2022	China
10	NCT03274219	MM	1	Active, not recruiting	08/2017 - 12/2022	US
11	NCT05032820	MM	2	Not yet recruiting	10/2021 - 04/2023	US

bb2121=advancement of Idecabtagene Vicleucel; MM= multiple myeloma

4.5 Lisocabtagene Maraleucel (JCAR017, liso-cel, Breyanzi®)

Breyanzi® is approved for treating patients whose cancer has returned or has stopped responding to previous treatment (Relapsed/refractory (R/R)) in three indications of Non-Hodgkin Lyphoma:

zugelassen

DLBCL
PMBCL
FL3b

- diffuse large B-cell lymphoma (DLBCL)
- primary mediastinal large B-cell lymphoma (PMBCL)
- follicular lymphoma grade 3B (FL3b)

Additional Indications:

Indikationsausweitung
CLL & SLL
iNHL: FL 1 bis 3a + MZL

- Breyanzi® is investigated R/R chronic lymphocytic leukemia (CLL) and R/R small lymphocytic lymphoma (SLL).
- Breyanzi® is investigated indolent NHL (follicular lymphoma grade 1 to 3a) and mantle cell lymphoma (MCL)

Earlier lines:

2nd line Therapie

- Breyanzi® is investigated in the R/R large B-cell lymphoma (DLBCL) in the outpatient setting.
- Breyanzi® is investigated as 2nd line DLBCL.

see Table 4-5

References:

Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020 Sep 19;396(10254):839-852. doi: 10.1016/S0140-6736(20)31366-0.

Ernst M, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9(9):CD013365. doi: 10.1002/14651858.CD013365.

Maloney DG, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol. 2021 Sep 8;14(1):140. doi: 10.1186/s13045-021-01144-9.

Siddiqi T. et al. Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. Blood. 2021 Oct 26; blood.2021011895. doi: 10.1182/blood.2021011895.

Westin JR, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: Observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol. 2021 Oct 1;96(10):1295-1312. doi: 10.1002/ajh.26301.

*Table 4-5: List of ongoing clinical trials for **Lisocabtagene Maraleucel** /Breyanzi® (Celgene/ Bristol Myers Squibb)*

	NCT Number	Conditions	Phase	Status	Start Date - Primary Completion Date	Locations
1	NCT02631044 (TRANSCEND-NHL001)	R/R DLBCL	1	Recruiting	01/2016 - 12/2022	US
2	NCT03484702 (TRANSCENDWORLD)	R/R DLBCL PMBCL FL3b	2	Recruiting	04/2018 - 03/2024	EU
3	NCT03744676 (TRANSCEND-OUT-REACH-007)	R/R DLBCL outpatient	2	Active, not recruiting	11/2018 - 10/2023	US
4	NCT03483103 (TRANSCEND-PILOT-017006)	2nd line DLBCL	2	Active, not recruiting	03/2018 - 12/2022	US
5	NCT03331198 (TRANSCEND-CLL-004)	R/R CLL R/R SLL	1/2	Recruiting	11/2017 - 12/2025	US
6	NCT04245839 (TRANSCEND-FL)	iNHL: R/R FL(1-3a) R/R MCL	2	Recruiting	07/2020 - 04/2024	EU, US
7	NCT03575351 (TRANSFORM)	2nd line DLBCL	3	Active, not recruiting	10/2018 - 12/2023	US
8	NCT03483103 (TRANSCEND-PILOT-017006)	2nd line DLBCL	2	Active, not recruiting	07/2018 - 12/2022	US

CLL= Chronic lymphocytic leukemia; DLBCL= FL1-3a= follicular lymphoma grade 1 to 3a; iNHL= indolent Non-hodgkin leuphoma; MCL= Mantle cell lymphoma PMBCL= R/R= SLL= Small lymphocytic lymphoma; R/R= relapsed/refractory

5 Summary and Conclusion

CAR-T cell therapies are commonly indicated as „transformative“ therapies referring to the huge expectations associated with them since their market approval in 2017 (USA) and 2018 (Europe). Due to the hope, but also their enormous prices a horizon scanning (HS) document was first launched 2020 (https://eprints.aihta.at/1268/) in cooperation with Tirol Kliniken GmbH to support budget planning in hospitals. The present HS document intended to update the earlier report in monitoring changes like proceeding to more advanced stages in the clinical development and ev. moving towards market authorization, but also to identify additional, new therapies under development.

CAR-T Zell Therapien oft auch als “transformative” bezeichnet

HSS zur Budgetplanung im Krankenhaus

Update: seit 2020 3 CAR-T Therapien zugelassen

Of the 13 CAR-T cell-therapies identified as more advanced in 2020, three have been approved since then: Tecartus®, Abcema® and Breyanzi®.

The remaining 10 CAR-T cell-therapies and two additional ones are still in more (or less) advanced stages of development (see table 3-1):

derzeit 12 in etwas fortgeschritteneren Stadien

- Four therapies are under investigation for hodgkin and (aggressive as well as indolent) non-hodgkin lymphoma, of which one is approved in China only (relma-cel), for another therapy a Phase 2 study in China and Malaysia only is ongoing, but no new studies are registered and two therapies hold FDA or EMA (orphan drug, RMAT, PRIME) designations, but are still in phase 1/2. **No new approvals are to be expected soon.**

NHL+ ALL: keine Zulassungen in naher Zukunft

- Six therapies are under development for multiple myeloma, of which one (Cilta-cel, Carvykti®) has been approved by FDA in Feb 2022 and is expected to be approved by EMA in 2022. Five therapies are still in early trial phases, of which one is sponsored by an EC-grant. One therapy development was discontinued (Orva-cel). **To conclude, there will be a competitor to Abcema® approved soon, but no further approval are to be foreseen soon.**

MM: ciltacel von FDA 2022 zugelassen, EMA: bald erwartet

AML: keine Zulassungen in naher Zukunft

- one therapy is under development in two trials for acute myeloid leukemia (AML), that holds a (orphan drug) designation by FDA, but due to hurdles in the development of CAR-T therapies for AML, **there is no change in the status since 2020.**
- there are **very few new developments**, such as Autologous SLAMF7 CAR-T Cells, that is based on a new target and could be promising in multiple myeloma.

In contrast to only few newly developed CAR-T cell-therapies, **extensions to the already approved therapies** to earlier therapy line in the respective indication and/or further indications are

Indikations-erweiterungen der 5 zugelassenen CAR-T Therapien: frühere Therapielinien in zahlreichen Studien

- from only last line therapy to earlier (2nd) lines are investigated for all approved CAR-T cell-therapies.

  for new indications of Yescarta® and Kymriah® (R/R follicular lymphoma), Kymriah® (R/R mantle cell lymphoma (MCL) and NHL in children, adolescents and young adults), Tecartus® for chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/ SLL), NHL and ALL; Breyanzi® for CLL/ SLL and MCL, many of them indolent NHL (such as FL 1-3a).

zusätzliche Indikationen: Erprobung für indolente NHL

Forschung an allogenen "off-the-shelf" CAR-T Therapie

Phase 1

As described in the HS-report 2020 manufacturing a personalized CAR-T product takes time and is not always successful. To address that issue, the design of off-the-shelf CAR-T strategies is being pursued by multiple groups. Only recently (08/2021) the FDA granted an orphan drug designation to the allogeneic CAR T-cell therapy ALLO-715 (and in 4/2021 Regenerative Medicine Advanced Therapy (RMAT)) for the treatment of patients with multiple myeloma, based on data from ongoing phase 1 UNIVERSAL trial (NCT04093596)[8] and presented at ASH in 12/2021.[9] The development of allogeneic CAR T-cell therapy is still in a very early stage.

ebenso erst Phase 1 "point-of-care in-hospital production"

Also numerous academic medical centres are trying to produce CAR-T cell-therapy as a point-of-care in-hospital production: these efforts are also still in phase 1 or with only preliminary results. Experts envision a future in which a hybrid model of onsite and commercially produced therapies allow them the flexibility to provide treatments tailored toward their patients' needs[10]. Miltenyi[11] is the leading company in this field.

Schlussfolgerung: 2022 CAR-T bei MM

Indikations-erweiterungen

Conclusion: Within the next year one new CAR-T cell-Therapy for multiple myeloma will eventually be approved, but further development can be expected with the extension of the five approved CAR-T cell-therapies towards earlier lines of therapy and new indications In-hospital production and allogeneic CAR-T cell-therapies, though in development, are still in their infancy.

[8] https://www.onclive.com/view/fda-grants-car-t-cell-therapy-allo-715-orphan-drug-status-for-multiple-myeloma

[9] https://ash.confex.com/ash/2021/webprogram/Paper145572.html

[10] https://www.healio.com/news/hematology-oncology/20211014/pointofcare-manufacturing-offers-treat-it-when-you-need-it-approach-to-cart

[11] https://www.miltenyibiotec.com/

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