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Gesundheitsökonomische Bewertungen immunonkologischer Therapien am Beispiel der CAR-T-Zell-Therapie bei Patienten mit DLBCL

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

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München, 01.08.2023	Mörtl, Bernhard Alexander
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Inhaltsverzeichnis

Abkürzungsverzeichnis

Allo-SZT……..……Allogene Stammzelltransplantation

Auto-SZT……Autologe Stammzelltransplantation

CAR-T……..……chimärer Antigen Rezeptor

BIA…….……..…Budget Impact Analyse

CAR……..……chimärer Antigen Rezeptor

CEA……..Cost-effectiveness Analyse

DLBCL……..…diffus großes B-Zell Lymphom

DRG……...Diagnosis Related Groups

EMA……European Medicines Agency

GKV……...Gesetzliche Krankenversicherung

HDT……...Hochdosis-Therapie

ISPOR…….International Society for Pharmacoeconomics and Outcomes Research

NHL……..…...….Non-Hodgkin Lymphom

NUB ……...Neue Untersuchungs und Behandlungsmethoden

ORR…….Overall Response Rate

OS……..Overall survival

PFS……..…..…Progression-free survival

PTS……..…….……...…Patienten

RKI……..……..…….…Robert Koch Institut

SZT/SCT…….……Stammzell-Transplantat

ZE……..……..…..Zusatzentgelt

1L……..……....Erste Therapielinie

2L……..……..……...Zweite Therapielinie

3L……..……Dritte Therapielinie

Publikationsliste

1.1 Peer reviewed Publikationen:

B. Moertl, M. Dreyling, Ch. Schmidt, E. Hoster, W. Schoel, M. von Bergwelt-Baildon, K. Berger. **Inpatient treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL): A health economic perspective**. Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):474-482. doi: 10.1016/j.clml.2021.12.018.

D. Skalt, B. Moertl, M. von Bergwelt-Baildon, Ch. Schmidt, W. Schoel, V. Buecklein, T. Weiglein, M. Dreyling, K. Berger. **Budget Impact analysis of CAR-T cell therapy for adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) in Germany**. HemaSphere: July 2022 - Volume 6 - Issue 7 - p e736. doi: 10.1097/HS9.0000000000000736

1.2 Wissenschaftliche Kongressbeiträge:

Oral Präsentation:

B. Moertl, M. Dreyling, E. Hoster, Ch. Schmidt, W. Schoel, M. von Bergwelt, K. Berger. **Economic aspects of stem cell transplantation by patients with relapsed diffuse B-cell Lymphoma (DLBCL) in a German tertiary hospital**. The 47th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians - Oral Sessions (O010 – O169). *Bone Marrow Transplant* 56, 21–183 (2021). https://doi.org/10.1038/s41409-021-01342-6

Poster / Abstract Präsentation:

D. Skalt, K. Berger, M. von Bergwelt-Baildon, W. Schoel, Ch. Schmidt, T. Weiglein, M. Dreyling, B. Moertl. **Budget impact analysis of CAR-T-cell therapies for the inpatient treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Germany.** Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie (Hybrid-Kongress), 01.–04. Oktober 2021: Abstracts. Oncol Res Treat 2021;44:1–335. https://doi.org/10.1159/000518417

B. Moertl, M. Dreyling, M. von Bergwelt, W. Schoel, Ch. Schmidt, E. Hoster, K Berger. **Diffuse large B-Cell Lymphoma (DLBCL): Economic aspects associated with treatment beyond 1st line treatment**. Abstractband für die Virtuelle Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie, 09.–11. Oktober 2020: Abstracts. Oncol Res Treat. https://doi.org/10.1159/000510995

Abstract:

B. Moertl, M. Dreyling, E. Hoster, Ch. Schmidt, W. Schoel, M. von Bergwelt, K. Berger. **Inpatient care of patients with early-relapsed diffuse B-cell Lymphoma (DLBCL): an economic perspective.** EHA2021 Virtual Congress Abstract Book, HemaSphere: June 2021 - Volume 5 - Issue - p e566 doi: 10.1097/HS9.0000000000000566

Beitrag zu den Veröffentlichungen

1.3 Beitrag zu Paper I

B. Mörtl war maßgeblich an der Konzeption und Pilotierung des Projekts beteiligt. Die Daten wurden von B. Mörtl in einer von ihm erstellten Datenbank erfasst und statistisch ausgewertet. B. Mörtl fertigte einen Publikations-Entwurf an und arbeitete das Feedback aller Co-Autoren ein. B Mörtl reichte das publikationsreife Manuskript bei der Peer Reviewed Zeitschrift „Clinical Lymphoma, Myeloma and Leukemia“ ein und hat maßgeblich die Einarbeitung und Beantwortung der Reviewer Anmerkungen, in Abstimmung mit den Koautoren übernommen.

1.4 Beitrag zu Paper II

Hr. Mörtl stellte Kostendaten der Standardtherapie (2L und 3L), die im Rahmen der retrospektiven Kostenstudie zu DLBCL Patienten erhoben wurden, zur Verfügung. Er war beteiligt an der Analyse von Kostendaten zur CAR-T-Zell-Therapie. So unterstützte er bei der Erhebung von Behandlungsschritten und Zeiträumen der CAR-T-Zell Patienten. Den Publikationsentwurf hat Hr. Mörtl Korrektur gelesen sowie Feedback gegeben und unterstützte bei der Beantwortung und Anpassung der Reviewer-Anmerkungen des Journals „HemaSphere“.

2. Einleitung

Hämatologische Erkrankungen bilden eine Gruppe von malignen Krebsarten des blutbildenden Systems mit unterschiedlicher Ätiologie sowie individuellen Charakteristika, Behandlungspfaden und Outcomes. Zu den häufigsten Vertretern gehören Non-Hodgkin-Lymphome, Leukämien, Multiple Myelome und Morbus Hodgkin. [1] Europaweit leiden ca. 80 Millionen Menschen an einer hämatologischen Erkrankung [2]. In Deutschland stieg die Zahl der Individuen mit hämatologischen Neubildungen in den letzten 20 Jahren stark an. So waren es im Jahr 1999 noch knapp 45.000 Menschen mit bösartiger hämatologischer Neuerkrankung und im Jahr 2018 bereits 58.000. [3] Für die beiden hämatologischen Entitäten Non-Hodgkin-Lymphom und Leukämie wird ein europaweiter Anstieg der Inzidenzen zwischen dem Jahr 2020 und 2040 von 21 bzw. 25% prognostiziert [4].

Ein Großteil der neuerkrankten Patienten mit hämatologischen Erkrankungen wird konventionell mit Chemotherapeutika bzw. Chemo-Regimen behandelt [5-7]. Stellt sich der gewünschte Behandlungserfolg nicht ein, werden Patienten mit rezidivierter bzw. refraktärer Erkrankung im weiteren Therapieverlauf u.a. mit hochkomplexen Prozeduren, wie Stammzelltransplantationen behandelt [8-11]. Somit liegt die Länge der Therapielinien (in ≥2L) oft bei mehreren Monaten [12]. Für diese Patienten sind lange Krankenhausaufenthalte, ein steigender Ressourcenverbrauch, sowie erhöhte Kosten durch zusätzliche Aufwendungen (z.B.: für die Behandlung von therapieassoziierten Nebenwirkungen) häufig zu beobachten [13-15]. Dies deutet darauf hin, dass hämatologische Erkrankungen mit einer hohen Belastung der Patienten verbunden sind und die Lebensqualität besonders bei Patienten mit einer r/r Erkrankung stark und langfristig eingeschränkt sein kann [16-18].

Mit neuen Behandlungsmöglichkeiten und Therapieansätzen erhofft man sich zeitnahe, vielversprechende Verbesserungen in der Versorgung dieser Patienten. So stehen den Behandlern neben konventionellen Ansätzen auch eine Vielzahl von kürzlich zugelassenen, innovativen Therapien zur Auswahl. [19] In den Jahren 2014 - 2019 wurden weltweit 57 neue Onkologika für 89 Indikationen eingeführt und zugelassen. Davon entfiel die Indikation von 28 Onkologika auf mind. eine hämatologische Krebsart. Für die Therapie von Lymphomen und Leukämien wurden je zwölf Substanzen zugelassen; für das Multiple Myelom vier Substanzen. [20] Ein Beispiel ist die im Jahr 2018 von der EMA zugelassene innovative „Breakthrough“-Therapie mit chimären antigen-Rezeptor T-Zellen, kurz CAR-T-Zellen. Diese kostenintensive Therapie steht als zusätzliche vielversprechende Behandlungsoption u.a. für Patienten mit refrak-

tären / rezidivierten Lymphomen mit mehr als zwei vorausgegangenen Therapielinien zur Verfügung. Die kommerziell vertriebenen CAR-T-Zell-Therapien sind mit hohen Kosten von ca. 320.000 – 350.000€ pro Gabe verbunden [21]. Hinzu kommen Aufwendungen für den stationären Aufenthalt, die Diagnostik und Behandlung von potentiellen Nebenwirkungen, sowie für die Verwaltung [22]. So haben entsprechende Entscheidungsträger neben klinischen Faktoren auch potentiell hohe finanzielle Auswirkungen unter Ihrer Verantwortung.

In Summe wurde die ökonomische Last der hämatologischen Erkrankungen in Europa (31 europäische Länder) bereits im Jahr 2012 auf 23 Mrd. Euro pro Jahr geschätzt [23]. Die Verfügbarkeit und Nutzung möglichst aktueller ökonomischer Informationen sind für nationale Akteure im Gesundheitswesen höchst relevant, um beispielsweise Kosten einer neu-zugelassenen, innovativen Therapiealternative wissenschaftlich und transparent einzuordnen. Anhand spezifischer Daten können neuartige Therapieansätze mit bisherigen Standardtherapien auf wissenschaftlicher Grundlage in Relation gesetzt werden. So liefern Krankheitskostenberechnungen objektive und transparente Erkenntnisse, welche beispielsweise für politische Diskussionen im Hinblick einer optimalen Ressourcenallokation genutzt werden können [24].

Aufgrund der zu erwartenden steigenden Kosten im deutschen Gesundheitssystem kann man davon ausgehen, dass der Druck für ein wirtschaftliches Verordnungsverhalten der Leistungsträger bzw. restriktives Erstattungsverhalten der Kostenträger aufgrund limitierter Budgets steigen wird [25-28]. So bieten neuartige Therapien zwar vielversprechende klinische Ansätze, jedoch müssen Behandler stets abwägen, um im Hinblick auf Kosten und Outcomes der Therapiealternativen die eigene Budgetverantwortung zu beachten. Auch hier könnten evidenzbasierte Informationen zu aktuellen klinischen und patientenberichteten Outcomes, Ressourcenverbräuchen und Kosten der Therapiealternativen bei der Entscheidungsfindung unterstützen. Sowohl im Kontext neuartiger Therapiemöglichkeiten als auch in Bezug auf die entsprechende Standardtherapie, fehlt für Deutschland allerdings meist die benötigte Datengrundlage. International konnte im Bereich der hämatologischen Erkrankungen bereits gezeigt werden, dass innovative Therapien im Vergleich zu Standardbehandlungen kosteneffektiv sein können und die Zahlungsbereitschaft nationaler Kostenträger gegeben ist [29, 30]. Dennoch existieren kaum wissenschaftlich publizierte Informationen zu malignen hämatologischen Erkrankungen in Deutschland, bei denen epidemiologische Entwicklungen, Patientencharakteristika, Behandlungspfade, Ressourcenverbräuche, Hospitalisierungen, Kosten sowie Outcomes einbezogen sind. Um die Verbesserung und Optimierung der Versorgung dieser Patienten auch zukünftig zu unterstützen, muss entsprechende Evidenz mit gesundheitsökonomischen Analysen fortlaufend und intensiver generiert werden.

2.1 Das diffus großzellige B-Zell Lymphom

2.1.1 Definition

Maligne hämatologische Krebserkrankungen sind eine heterogene Gruppe von Lymphomen, Myelomen und Leukämien [31]. Sie unterscheiden sich entsprechend Ihres Zelltyps, sowie klinischen und molekularen Eigenschaften hinsichtlich Ihrer Prognose und den möglichen Therapieoptionen [32-34]. Diffus großzellige B-Zell Lymphome gelten als häufigste Neoplasie der Non-Hodgkin-Lymphome [35, 36]. Diese heterogene Erkrankung geht von reifen B-Zellen aus und kann mit unterschiedlicher Aggressivität auftreten. Unbehandelt sterben Erkrankte rasch. [31]

2.1.2 Epidemiologie

Die jährliche Inzidenz von DLBCL beträgt etwa sieben Fälle pro 100.000 Einwohner in Deutschland. Das mittlere Erkrankungsalter liegt bei 64 Jahren. Männer sind häufiger betroffen als Frauen. [3]

2.1.3 Behandlung

Mehr als 90% der inzidenten Patienten erhält unabhängig vom Stadium eine Polychemotherapie nach R-CHOP Schema als Erstlinientherapie. Einzig Hochrisiko-Patienten oder sehr alte Patienten werden mit abgewandelten Formen des R-CHOP Protokolls therapiert (z.B: R-mini CHOP Protokoll) [37]. Durch die Kombination von Rituximab, Cyclophosphamid, Hydroxydaunorubicin (Doxorubicin), Oncovin (Vincristin), Predniso(lo)n werden Heilungsraten von ca. 60% der Patienten nach Erstlinientherapie kommuniziert [38]. Bei den übrigen 40% der Patienten kommt es allerdings zu rezidivierten bzw. refraktären Erkrankungsverläufen. Internationale Publikationen zeigen für diese Patienten, trotz zusätzlicher Therapieansätze deutlich reduzierte Überlebensraten [10, 39-41]. So werden in den höheren Therapielinien (≥ 2L) je nach Alter, Allgemeinzustand, Ansprechrate, Zeitpunkt, Krebsstadium etc. verschiedenste Behandlungskonzepte angewendet [42]. In der Zweitlinientherapie kommen meist konventionelle chemotherapeutische Salvage-Regime mit anschließender autologen Stammzelltransplantation zum Einsatz [43]. Die Durchführung einer jeweiligen Therapie (z.B.: Stammzelltransplantation) bei Patienten mit rezidivierten bzw. refraktären Krankheitsverlauf ist von klinischen Faktoren wie Alter, ECOG-Status oder vorhandene Komorbiditäten abhängig. Patienten mit feh-

lendem Ansprechen bzw. progredienter Erkrankung in ≥2L, können von den Ärzten entsprechend der aktuellen Leitlinien mit einer allogenen SZT oder einer CAR-T-Zell-Therapie weiterbehandelt werden. [44]

2.1.4 CAR-T-Zell-Therapie

Im Jahr 2018 sind zwei CAR-T-Zell-Therapien, nämlich Tisagenlecleucel und Axicabtagene Ciloleucel, von der EMA erstmalig zugelassen worden. Sie bieten einen neuartigen Therapieansatz u.a. für stark betroffene DLBCL-Patienten ab Drittlinienbehandlung. [45, 46] Nach Entnahme und Vermehrung der T-Zellen des Patienten werden chimäre Antigenrezeptoren in die Membran der T-Zellen integriert und als CAR-T-Zellen in den Körper des Patienten reinfundiert. Durch die gezielte Bindung an das spezifische Antigen auf der Oberfläche der Krebszellen (z.B.: CD19) soll eine Immunreaktion ausgelöst werden, die einen zytotoxischen Mechanismus der Krebszelle aktiviert [47]. In beiden zulassungsrelevanten Studien führte die Behandlung mit Tisagenlecleucel und Axicabtagene Ciloleucel beispielsweise zu einer ORR von 52 % bzw. 83 %, während Patienten, die mit einer konventionellen Therapie behandelt wurden, eine ORR von 26 % erreichten [40, 48, 49]. Neben den vielversprechenden klinischen Ergebnissen sind CAR-T-Zell-Therapien mit hohen Kosten verbunden. Wie bereits erwähnt, können die alleinigen Therapiekosten mehr als 300.000€ pro Patienten betragen, zuzüglich weiterer Aufwendungen für Hospitalisierung etc. Entsprechende Kosteninformationen sollten stets in einem wissenschaftlichen Rahmen, objektiv und transparent eingeordnet sowie interpretiert werden.

2.2 Gesundheitsökonomie

Aufgrund der prognostizierten demografischen Entwicklung und der damit verbundenen Anstiege hämatologischer/ onkologischer Neuerkrankungen muss man davon ausgehen, dass die Aufwendungen der Gesetzlichen Krankenversicherung (GKV) zukünftig steigen werden. Damit einhergehend, zeichnet sich ein Trend über eine abnehmende Anzahl an Menschen im erwerbsfähigen Alter und damit sinkenden Erlösen ab, was eine mögliche Finanzierungslücke im deutschen Gesundheitssystem zur Folge haben kann [50]. Vor diesem Hintergrund, ist davon auszugehen, dass Entscheidungsträger versuchen werden Einsparpotentiale zu identifizieren und zu nutzen. So soll eine Finanzierungslücke verhindert bzw. möglichst klein gehalten werden. Hierfür benötigt es umfassende Informationen, die eine Einschätzung zu Unter-, Über-

und Fehlversorgung erlauben und Entscheidungsfindungen und Diskussionen hinsichtlich einer optimalen Ressourcenallokation unterstützen. Da Fragen zu Ressourcenallokation unter den Umständen einer Ressourcenknappheit ein Bestandteil gesundheitsökonomischer Betrachtungen sind, ist die Verfügbarkeit bzw. Generierung wissenschaftlicher Evidenz aus diesem Bereich notwendig. Im Rahmen gesundheitsökonomischer Analysen werden verschiedene Konzepte und Methoden angewendet, welche auf die jeweiligen Forschungsziele und deren resultierende Fragestellungen angepasst werden. Beispielsweise können die Erkenntnisse aus Krankheitskostenanalysen für ökonomische Einordnungen im Rahmen initialer Diskussionen oder als Ausgangsbasis für Folgeprojekte genutzt werden. Wie zum Beispiel für die Erstellung einer Budget Impact Analyse, die u.a. auf bereits erhobenen Kostendaten basiert. Anhand dieser Analyse können die finanziellen Auswirkungen einer neueingeführten Therapie auf das Budget der Kostenträger im Vergleich zur Standardtherapie abgeschätzt werden. Dies ermöglicht den Entscheidungsträgern sich frühzeitig mit den Konsequenzen des Einsatzes innovativer Therapien auseinanderzusetzen und Planungen zu optimieren.

2.3 Zielsetzung

Wie lässt sich der Wert innovativer Therapien für die DLBCL-Behandlung im Kontext der bisherigen Standardtherapie darstellen bzw. ökonomisch einordnen, und welche zukünftigen finanziellen Auswirkungen hätte die Etablierung der entsprechenden Therapie auf das Budget der gesetzlichen Krankenkassen in Deutschland?

Es sollen Antworten auf folgende Teilfragestellungen gegeben werden, um die obenstehenden übergeordneten Fragestellungen zu beantworten:

- Welche diagnostischen bzw. therapeutischen Maßnahmen wurden bei der stationären Versorgung von r/r DLBCL Patienten in Linien ≥2L im Bezug zur Standardtherapie vor der Einführung der CAR-T-Zell-Therapie eingesetzt?
- Wie lässt sich die stationäre Versorgung dieser Patienten hinsichtlich Anzahl und Dauer von Krankenhausaufenthalten beschreiben?
- Welcher Ressourcenverbrauch ist im Rahmen der stationären Versorgung entstanden?
- Wie hoch waren die resultierenden Kosten in Kostenträger-Perspektive?
- Wie hoch war die dokumentierte Mortalität bei r/r Patienten in stationärer Versorgung?
- Wie viele Patienten mit DLBCL werden für den Zeitraum 2021-2026 in Deutschland prognostiziert?
- Wie hoch ist dabei der jährliche Anteil an 3L Patienten?
- Welche jährlichen Kosten für die Behandlung dieser Patienten entstehen im Zeitraum 2021-2026 aus Perspektive der gesetzlichen Krankenkassen?
- Wie hoch ist der jährliche Budget Impact des 3L-Therapieanteils der neu eingeführten CAR-T-Zell-Therapie?

3. Zusammenfassung der vorliegenden Arbeiten:

Für Patienten mit r/r DLBCL sind die Behandlungsmöglichkeiten begrenzt und die Prognose ist meist unzureichend. Die CAR-T-Zell-Therapie ist eine vielversprechende innovative, aber ressourcen- und kostenintensive Therapieoption. In Deutschland gibt es nur wenige Informationen zu Diagnose- & Behandlungsmustern, patientenrelevanten Ergebnissen, Ressourcenverbrauch und Kosten für Standardtherapien und innovative Therapien, um die inkrementellen Kosten in Bezug auf den potentiellen klinischen Nutzen innovativer Behandlungsansätze einzuordnen.

Daher wurden im ersten Teil der vorliegenden Dissertation, Daten aus der stationären Routineversorgung hinsichtlich der oben genannten erforderlichen Informationen zur Standardtherapie (DLBCL SOC) ausgewertet. Im anschließenden zweiten Schritt wurde eine Budget-Impact-Analyse (BIA) durchgeführt, um die finanziellen Auswirkungen der CAR-T-Zell-Therapie auf die Budgets der Kostenträger abzuschätzen.

Zur Ermittlung der DLBCL-SOC Daten wurde eine retrospektive Beobachtungsstudie am LMU-Klinikum durchgeführt. Dabei wurden 84 Patienten (47 Männer, 37 Frauen; Durchschnittsalter bei Erstdiagnose 59 Jahre) analysiert und nach Behandlungslinien (L) gruppiert: 2L (n=78), 3L (n=32) und >3L (n=12). Verordnete Behandlungen in 2L waren Chemotherapie zu 56%, Auto-SZT zu 31%, Allo-SZT zu 1%, andere zu 12%. In 3L: 50%, 16%, 6%, 28%, und >3L: 42%, 0%, 33%, 25%. Die durchschnittliche Zahl der Krankenhauseinweisungen und die Dauer des stationären Aufenthalts (Tage) waren: 2L (4, 44), 3L (2, 26) und >3L (5, 63). Die durchschnittlichen Kosten pro Patient lagen bei 44.750€ in 2L, 32.589€ in 3L und 88.668€ bei Patienten in >3L. Die durchschnittlichen Behandlungskosten pro Patient für stammzelltransplantierte Patienten betrugen 55.468 € für eine autologe SZT (n=28) und 131.264 € für eine allogene SZT (n=7). Die dokumentierte Sterblichkeit lag bei 21 % in 2L, 28 % in 3L und 41 % bei den Patienten >3L.

Im zweiten Projekt dieser Dissertation wurde eine Budget-Impact Analyse von CAR-T-Zell-Therapien zur Behandlung von erwachsenen Patienten mit r/r DLBCL in Deutschland erstellt. Dazu wurde ein partitioniertes Überlebensmodell auf Grundlage von allgemeinen Bevölkerungsvorausschätzungen des Statistischen Bundesamtes und Fachliteratur aus peer-reviewed Journals für die Jahre 2021 bis 2026 entwickelt. In einer Szenarioanalyse wurden die Auswirkungen auf das Budget der GKV einhergehend mit der Behandlung von DLBCL-Patienten mit CAR-T-Zellen bereits ab Zweitlinienbehandlung analysiert. In Anbetracht einer Heilungsrate von 60 % bis 70 % bei der Erstlinienbehandlung und einer frühen Sterblichkeitsrate von 2 %

nach einer konventionellen Chemotherapie kamen 38 % bzw. 28 % der Fälle für eine Zweitlinientherapie in Frage. Der Anteil von 28 %, der eine Zweitlinientherapie erhielt, wurde als Minimalpopulation definiert, während der Anteil von 38 % die Maximalpopulation darstellte. Patienten mit fehlendem Ansprechen der 2L Therapie, Patienten mit progredienter Erkrankung nach 2L, sowie transplantationsfähige Patienten, die sich keiner SCT unterziehen konnten, kamen in die 3L Kohorte.

Für den Zeitraum 2021-2026 resultierten 788-867 (Minimalpopulation, min) und 1.068-1.177 (Maximalpopulation, max.) erwachsene r/r DLBCL-Patienten in der Zielpopulation. Die Auswirkungen auf das Budget reichten von 39 Mio. € bzw. 53 Mio. € (min., max.) im Jahr 0 bis 122 Mio. € bzw. 165 Mio. € (min., max.) im Jahr 5. Die Szenarioanalyse ergab eine Auswirkung auf das Budget von 66 Mio. € bzw. 90 Mio. € (min., max.) und 204 Mio. € bzw. 278 Mio. € (min., max.) für Jahr 0 bzw. Jahr 5.

Die individualisierte r/r DLBCL-SOC Behandlung ist mit erheblichen Kosten und einer großen Kostenspanne verbunden. Die Zahl der dokumentierten Todesfälle und die Dauer des Krankenhausaufenthalts zeigen eine enorme Belastung für Patienten und deren Familien. Gezeigte SOC-Ergebnisse, z.B. die ressourcenintensive Behandlung von Risikopatienten, können die Kosten innovativer CAR-T-Zell-Behandlungen teilweise relativieren. Die Analyse zu den Auswirkungen der Etablierung von CAR-T-Zell-Therapien auf das Budget der gesetzlichen Krankenkassen zeigte eine deutliche, aber vertretbare finanzielle Auswirkung aus Sicht der Kostenträger. Die mögliche Gesamtzahl an Patienten mit r/r DLBCL in dritter Linie (895 bis max. 1.337 Patienten) ist begrenzt. So zeigen die durchgeführten Analysen einerseits die bestehenden Herausforderungen, andererseits den Bedarf an weiterführenden wissenschaftlichen Studien auf, um den Wert innovativer Therapien detailliert zu bestimmen und ökonomisch einzuordnen.

4. Summary of the presented publications

For patients with r/r DLBCL treatment options are limited and prognosis is poor. The CAR-T-cell-therapy is a promising innovative, but resource and cost intensive therapeutic option. In Germany only limited basic information on treatment patterns, patient relevant outcomes, resource use for standard of care exist to put incremental costs and clinical benefits of innovative treatment approaches into perspective. Therefore, in the first part of the hereby presented thesis, data from inpatient routine care were evaluated regarding aforementioned required information on standard of care (DLBCL SOC). In a second step, a budget impact analysis (BIA) has been performed to estimate the financial impact of CAR-T-cell-therapy on German third party payers' budgets.

First, in order to determine the DLBCL SOC data a retrospective single center observational study was conducted. Eighty-four patients (n=47 were male, n=37 female; mean age at initial diagnosis of 59 years) were identified. The patients were analyzed in received treatment lines (L): 2L (n=78), 3L (n=32), and >3L (n=12). The prescribed treatment-shares in 2L were chemotherapy to 56%, auto-SCT to 31%, allo-SCT to 1%, other to 12%. In 3L: 50%, 16%, 6%, 28%, and >3L: 42%, 0%, 33%, 25%, respectively. Mean four hospital admissions were documented in 2L; two admissions in 3L and five for patients in >3L. The mean length of inpatient stay was: 2L: 44 days, 3L: 26 days, and >3L: 63 days. The average costs per patient were €44,750 in 2L, €32,589 in 3L and €88,668 for patients >3L. The mean treatment costs per patient with autologous stem-cell-transplant was €55,468 (n=28) and €131,264 for allogeneic stem-cell transplanted patients (n=7). The documented mortality was 21%, 28%, and 41% for 2L, 3L, and >3L, respectively.

In the second part of the hereby presented work a budget impact model about CAR-T-cell-therapy as a 3rd line treatment option was established, for the years 2021-2026. Therefore, a partitioned survival model based on outcome data from peer-reviewed literature was designed, using a top-down approach based on population forecasts of the Federal Statistical Office, and age-standardized incidences. Additionally, a scenario analysis about the budget impact of treating 2nd line DLBCL patients with CAR-T-cell-therapy was performed. Considering a cure rate of 60% to 70% in 1st line and an early mortality rate of 2% after conventional chemotherapy, 38% and 28% of incident cases were eligible patients for 2nd line therapy, respectively. The proportion of 28% receiving 2nd line therapy was defined as the minimum population, whereas the proportion of 38% was the maximum population. Candidates for the 3rd line were patients with lacking initial response after treatment, patients with progressive DLBCL as well

as transplant-eligible patients not undergoing a SCT. For the period between 2021-2026 a minimum population of 788–867 (min) and a maximum population of 1,068–1,177 (max) adult 3rd line patients were estimated. The budget impact ranged from €39Mio (min) - €53Mio (max) in year 0 to €122Mio (min) - €165Mio (max) in year 5. Within the scenario analysis, a budget impact of €66Mio(min); €90Mio (max) and €204Mio (min); €278Mio (min; max) for year 0 and year 5 resulted.

Individualized r/r DLBCL SOC treatment is associated with significant costs and wide cost ranges. The length of hospitalization and number of documented deaths signal a tremendous burden on patients and families. Shown SOC results e.g. about the considerable resource intensive treatment for risk patients may put the innovative CAR-T-cell information into perspective. The analysis showed a limited number of patients requiring individualized treatment and a significant but reasonable financial impact for third party payers budget. The number of patients with r/r DLBCL in third line (895 to max. 1.337 patients) is limited. The studies present challenges and future needs for data collection to determine comprehensively value of innovative therapies.

5. Paper I

Inpatient treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL): a health economic perspective

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Inpatient treatment of relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL): A health economic perspective

Bernhard Moertl,[1] Martin Dreyling,[1] Christian Schmidt,[1] Eva Hoster,[1,2] Wolfgang Schoel,[3] Michael v. Bergwelt-Baildon,[1] Karin Berger[1,2]

Abstract

Information on treatment patterns, resource-use, costs, and outcomes (eg, overall-survival) from r/r DLBCL patients before CAR-T-cell licencing were collected. This information which is basic to put innovative treatments into perspective, shows a high burden on patients and families, significant economic burden on payers and a huge variability in results as consequence of individual treatment approaches in ≥2 lines of therapy.

Introduction: Patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) require highly individualized therapies. Limited information exists regarding inpatient treatment patterns, outcomes, resource-use, and costs from the perspective of third-party payers in Germany. The aim of this study was to collect and evaluate routine inpatient care data to fill aforementioned gaps. **Methods:** Retrospective single center observational study in a German tertiary teaching hospital. Data were collected from patient records, the hospital-pharmacy database, and claims data. **Results:** Eighty-four patients (47 male; mean age at initial diagnosis, 59 years) were identified and grouped by treatment line (L): 2L (n = 78), 3L (n = 32), and >3L (n = 12). Prescribed treatments in 2L were chemotherapy 56%, auto-SCT 31%, allo-SCT 1%, other 12%; 3L: 50%, 16%, 6%, 28%, respectively, and >3L: 42%, 0%, 33%, 25%, respectively. Mean number of hospital admissions and length of inpatient stay (days) were: 2L (4, 44), 3L (2, 26), and >3L (5, 63). Average cost/patient: 2L = 44,750€, 3L = 32,589€ and >3L = 88,668€. Mean treatment costs per patient for stem-cell-transplanted patients were 55,468€ for autologous SCT (n = 28) and 131,264€ for allogeneic SCT (n = 7). Documented death was 21%, 28%, and 41% for 2L, 3L, and >3L, respectively. **Conclusion:** Individualized DLBCL treatment in patients ≥ 2L is costly and results in a huge variability in resource consumption. The number of documented deaths and length of hospitalization signal a high economic burden on patients and families. A multicenter comprehensive evaluation of health and economic burdens of r/r DLBCL and linkage with other data sources (eg, registries, payers' claims data) is essential.

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Keywords: Hematopoietic stem cell transplant, Costs, Retrospective study, Lymphoma and Non-Hodgkin disease, German hospital data

Introduction

In 2018, global spending on cancer drug treatment reached approximately $150 billion.[1] Since 2014, these costs have grown by at least double digits.[1] Among other reasons for rising costs in cancer care, such as demographic and epidemiological developments, an increasingly debated point is the number of innovative treatments for small patient groups that have partially impressive clinical study results with premium prices attached.[2,3] The increasing costs for hematological and/or oncologic medications raise questions about the value of innovative cancer treatments compared to standard treatments for rational decisions on health care resource allocation.[4] In 2018, 28 (31%) of the 89 global new oncology drug approvals were for non-solid hematological cancers, including 12 (13%) for lymphoma.[1] The diffuse large B-cell lymphoma (DLBCL) is the second most common form of non-Hodgkin's lymphoma in Europe.[5] It has a crude incidence of 3.8/100 000/year.[5] In Germany, with more than 10,000 annual incident cases DLBCL accounts for approximately 16% of all lymphoid neoplasia.[6,7] Between 1999 and 2017, the number of cases in Germany almost doubled.[7] The treatment claim for DLBCL patients is curative, but the outcomes are subject to various individual factors, such as the disease

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state at the beginning of or during treatment.[8-10] Polychemotherapy R-CHOP is recommended as a first-line therapy.[11] The combination of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), and prednisolone as the first line of therapy cured approximately 60% of treated cases.[12-14] Given various modifications, combination changes, doses, and cycle adjustments to the R-CHOP protocol, there is currently no universal treatment standard.[8,15,16] For patients with relapsed or failed first-line treatment, highly patient-customized and risk-adapted approaches are used to select the additional treatment.[9,10,12,17-19] Approximately 40–60% of adult patients with relapsed or refractory r/r DLBCL respond to second-line chemotherapy; 50% of these proceed to autologous stem cell transplantation.[20-25] For patients with relapse after second-line treatment, guidelines recommend additional options, such as allogeneic stem cell transplantation, palliative care, or innovative therapy with chimeric antigen receptor T (CAR-T) cells.[11] The first two commercially available CAR-T-cell therapies were approved in 2018 for adult patients with r/r DLBCL after two or more lines of systemic therapy.[26,27] This study intended to provide basic information for future health economic discussions in the context of innovative DLBCL diagnostic and treatment approaches. Given the lack of information on routine care of patients with r/r DLBCL in Germany, this study focused on treatment patterns, resource use, and costs per line of treatment (LOT) in routine care at a tertiary teaching hospital to provide initial insight.

Study design and patients

This study was designed as a retrospective, non-interventional, single-center observational study conducted in a German tertiary teaching hospital. Given the descriptive, non-interventional study design, only a few inclusion criteria were defined: adult patients (≥18 years), diagnosis of relapsed DLBCL (ICD: C83.3), or failed first-line treatment, and treated between January 1, 2007, and January 1, 2018. Patients must have received at least one line of therapy at the study center. Patients with any additional active malignant disease or high-malignant transformation were excluded from the study. The follow-up duration was two years. The study followed the STROBE-recommendations[28] and was approved by the ethics review board of the Faculty of Medicine, [blinded for review].

Material and Methods

The study cohort for this health economic analysis was identified using an internal clinical-epidemiological database that includes 2 cohorts of patients with malignant lymphomas treated in the hematology and/or oncology (2007,2016). The database provides comprehensive, structured data on patient demographics and clinical characteristics, lines of therapies and diagnostic- and treatment patterns documented by treating physicians. Additional information was obtained from the electronic prescribing system (Zenzy2.4), medical records (digital: hospital information system; analog: hospital archive), and claims data. A database (Microsoft Excel) was developed and pilot-tested for data collection. Costs were determined from a third-party payer perspective by analyzing the administrative claims data.

Diagnostic and treatment patterns

To describe the frequency of diagnostic measures, we focused on computed tomography (CT) and magnetic resonance imaging (MRI) scans because these are the standard imaging diagnostics in the context of lymphoma treatment.[29] Treatment was evaluated in four groups: treatment with autologous stem cell transplant + chemotherapy (auto-SCT), treatment with allogeneic stem cell transplant + chemotherapy (allo-SCT), chemotherapy, and others. The chemotherapy regimens included mostly immunochemotherapy regimens (i-chemo; various chemotherapy combined with rituximab) and chemotherapy (standard chemotherapy or various combined chemotherapy regimens). Others were radiation (radiation; not further specified), operation (eg, resection), immuno-maintenance therapy.

The LOT index date was defined for the initial given anticancer treatment or drug in a single-dose and/or fixed combination (doses can vary; in combinations, < 20% of the pharmaceuticals can be changed during LOT). The LOT end-point was the date of the last given dose in the respective regimen. Prescribed drugs and doses were identified through electronic prescribing software (Zenzy2.4, Dr. Heni Software, Kirchzarten, Germany). Subsequent LOTs were defined as therapy after failure of previous LOT, progression, or relapse. All data were cross-checked with medication data, physicians' letters, and admission and/or discharge dates.

Hospitalization and costs

The number of admissions and inpatient days was extracted from the patient records. Hospital claims and/or controlling data were analyzed for costs. All billed diagnosis-related groups (DRG), additional fees, and fees for new examination and treatment were cumulated per line. Cost per line were not stratified per year or adjusted as the increase of DRGs values is negligible between 2007 and 2021[30,31]. For validation purposes, the indication of fees was cross-checked with the individual patient's record for the context of DLBCL treatment.

Mortality

The date of documented death (dd) or the last contact was extracted from patient records for each patient. Overall survival was calculated per line and shown in Kaplan-Meier curves.

Statistical analysis

Qualitative variables were presented with frequency distributions in 2L, 3L, and >3L. Quantitative variables were expressed as mean, standard deviation (SD), median, and range. All statistical tests were performed using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Under consideration of the study inclusion and exclusion criteria, n = 110 patients were eligible. Because of missing data and high malignant transformations, n = 26 patients were additionally excluded during the analyses. Finally, the analyses were based on 84 patients with r/r DLBCL treatment in ≥ 2L. The mean age at initial diagnosis (ID) was 59 years (median, 61 years; range, 21–97 years;

Table 1 Patient Characteristics (n = 84)

Patient characteristics (n = 84)	
Sex, n (%) Male Female	 47 (56) 37 (44)
Age at ID, years Mean (SD) / Median (Range)	 59 (±15) / 61 (21-97)
Stage of disease at ID[a], n (%)	
I	21 (25)
II	14 (17)
III	21 (25)
IV	28 (33)

Abbreviations: ID = initial diagnosis.
[a] Ann Arbor

Table 2 Treatment of Relapsed / Refractory DLBCL Patients

Regime; n (%)	2L (n = 78)	3L (n = 32)	>3L (n = 12)
chemotherapy	44 (56)	16 (50)	5 (42)
auto-SCT	24 (31)	5 (16)	0 (0)
allo-SCT	1 (1)	2 (6)	4 (33)
other	9 (12)	9 (28)	3 (25)

Abbreviations: 2L = second-line; 3L = third-line; >3L = treatment in >3 lines; DLBCL = diffuse large B-cell lymphoma; auto-SCT = autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant.

SD ±15 years); 56% (n = 47) were men. Following the Ann-Arbor classification at initial diagnosis, 21 patients (25%) were diagnosed with stage I, 14 (17%) had stage II, 21 (25%) had stage III, and 28 (33%) had stage IV. The mean time between ID and second-line start was 29 months (median, 11; range, 0–223; SD, ±38). Patient characteristics are shown in Table 1. The analysis was driven chronological in lines of therapy (LOT) per patient. Given the lack of recorded costing information, some patients were excluded from the cost analysis for the respective treatment lines. This underlines the importance of a complete and comprehensive dataset for research.

Diagnostic and treatment patterns

Patients in the 2L treatment had a mean of 3.4 CTs (median 3; range 0–13; SD ± 3) and 1.1 MRI procedures (median 0; range 0–11; SD ± 2). The 3L cohort had a mean of 3 CT scans (median 2; range 0–8; SD ± 2) and 1 MRI scan (median 0, range 0-6; SD ± 2). Patients in treatment line >3 received 4.8 CTs on average (median 2.5; range 1-14; SD ± 4) and 1.8 MRIs (median, 1; range, 0-5; SD, ± 5).

A treatment overview is presented in Table 2. We identified 78 patients in the 2L treatment group, 32 in the 3L group, and 12 in the >3L group. Forty-four patients (56%) in 2L received chemotherapy-based chemotherapy, 24 (31%) received an autologous stem cell transplant (auto-SCT), 9 (12%) received other treatment (including radiation in 9 cases), and one patient underwent allogeneic transplantation (allo-SCT).

In the 3L group, 16 patients (50%) received chemotherapy, 7 (22%) received stem cell transplantation (n = 5 auto-SCTs, n = 2 allo-SCTs), and 9 (28%) received other treatments (including radiation in 6 cases). In the >3L cohort, 5 patients received chemotherapy (42%), 4 (33%) received allo-SCT, and 3 (25%) received other treatments (including radiation in 2 cases). For six patients who received prior external treatments, the number of received treatment lines was derived from external medical reports, but these were not considered in the analysis. More detailed information on the >3L cohort is presented in Supplementary Table 1.

Hospitalization

The total hospitalization period in the 2L group was 44 days (median: 46; range 0–132; ± 3) with a mean of four admissions (median, 4; range, 0–13; SD, ± 3). In the 3L group, the mean inpatient stay was 26 days (median 25; range 0–58; SD ± 17) with a mean of 2 admissions (median 2; range 0–4; SD ± 1). The >3L cohort had a mean of 63 days' inpatient (median 66; range 17–123; SD ± 36) and 5 admissions (median 3; range: 1–12; SD ± 3).

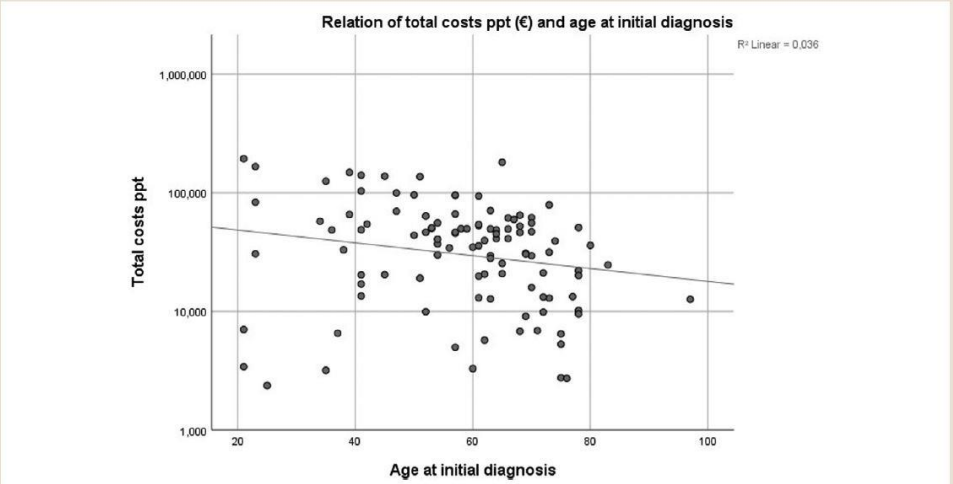
Costs

The mean costs for 2L patients (n = 71 pts with available costing-data) were 44,750€ (median 42,449; range 2,750–166,082; SD ± 32,290); 3L (n = 28) had mean costs of 32,589€ (median 26,644; range 2,368–148,528; SD ± 30,319) and the >3L cohort (n = 10) had mean costs of 88,668€ (median 78,024; range 2,716–193,824; SD ± 68,213). Patients with ≥ 3L (n = 32) had mean costs of 56,224€ (median 33,798; range 2,368–206,327; SD ± 55,990). The average cost for the patients across all lines was 60,885€ (median 48,536; range 2,368–214,173; SD ± 49,073). The correlation between age (at ID) and log-transformed total costs is shown in a linear regression model (Figure 1).

Mortality

A total of 30 deaths (36%) were documented; 22 patients (26%) died within two years after ID and 8 (10%) died more than two years after ID. Sixteen patients died during or after 2L (20%); 9 (28%) died during or after 3L, and 5 (42%) died during or after

Figure 1 Relation of total costs ppt (€) and age at ID (years) Ppt = per patient.



>3L. Kaplan-Meier curves are shown in Figure 2 and in the supplementary Supp_Figure 1-4.

Treatment >3L:

The average age (at ID) of the >3L cohort (n = 12) was 58 years (median 60; range 21–77; SD ± 16). Nine patients were male (75%), and the Ann-Abor stage (at ID) distribution was I-II, n = 7 (58%) and III-IV, n = 5 (42%). For hospitalization in previous treatments, we found an average hospitalization period of 40 days (median 47; range 5–84; SD ± 3) in 2L treatment with a mean of four admissions (median 5; range 1-8; SD ± 3). The average cost for >3L pts in the 2L treatment was 31,207€ (median 28,700; range 2,750–64,679; SD ± 28,382). Average hospitalization for 3L patients was 23 days (median 24; range 8–25; SD ± 12) with a mean of 3 admissions (median 3; range 1-4; SD ± 1). The resulting costs were 21,720€ (median 15,167; range 5,281–46,523; SD ± 15,349). The >3L patients had a mean inpatient stay of 63 days (median 66; range 17–123; SD ± 36), with a mean of 5 admissions (median 3, range 1-12; SD ± 3), resulting in a mean cost of 88,668€ (median 78,024; range 2,716–193,824; SD ± 68,213).

Subgroup analysis: autologous and/or allogeneic transplanted patients

Across all treatment lines, 37 patients received a stem cell transplant. The distribution of transplanted patients is shown in Figure 3. The mean inpatient stay for patients with autologous stem cell transplant (n = 30) was 35 days (median 29; range 9–132; SD ± 22). Patients with allogeneic SCT (n = 7) had an average of 47 inpatient days (median 52; range 17–82; SD ± 22). The resulting average costs are shown in Figure 4. Twenty-five patients (32%) received an auto-SCT during 2L treatment and were followed up and analyzed for their subsequent disease process (treatment, hospitalization, relapse, documented death, and costs). After second-line treatment, 13 of 25 patients (52%) were in complete remission (CR; including at 2 year follow up); there was 1 documented death (dd), and 11 patients received further treatment. The mean cost in 2L was 56,448€ (median 54,183; range 30,562–99,527; SD ± 17,658). Eleven patients received a 3L; 6 were in CR, and three died; 2 patients received >3L treatments (1 CR; one dd). The average total cost for the 3L cohort was 54,105€ (median 40,969; range 9,939–148,528; SD ± 42,632). Two patients received >3L treatment resulting in mean costs of 65,705€ (range 32,820–98,591; SD ± 32,885).

Discussion

To the best of our knowledge, this is the first German study describing treatment, resource use, costs, and mortality in routine care for patients with r/r DLBCL in Germany. The average costs ppt were nearly 45,000€ in 2L, 33,000€ for 3L and 89,000€ in >3L. The results demonstrated that treating patients in the prera of innovative or personalized therapies was highly individual, resource- and cost-intensive. Stem cell transplants were identified as the main cost drivers with mean costs for an autologous stem cell transplant of 55,500€ per patient and an allogeneic stem cell transplant of 131,300€ per patient. The documented patients' burden in terms of mortality, number and length of hospitalization was significant. The highest rate of admissions and length of inpatient stay were documented for the >3L cohort with a mean of 5 admissions and 63 days' inpatient. In terms of mortality, the highest rate of documented death in respective lines of therapy was 42% for the

Figure 2 Kaplan-Meier curves for 2L, 3L & >3L patients auto-SCT = autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant.

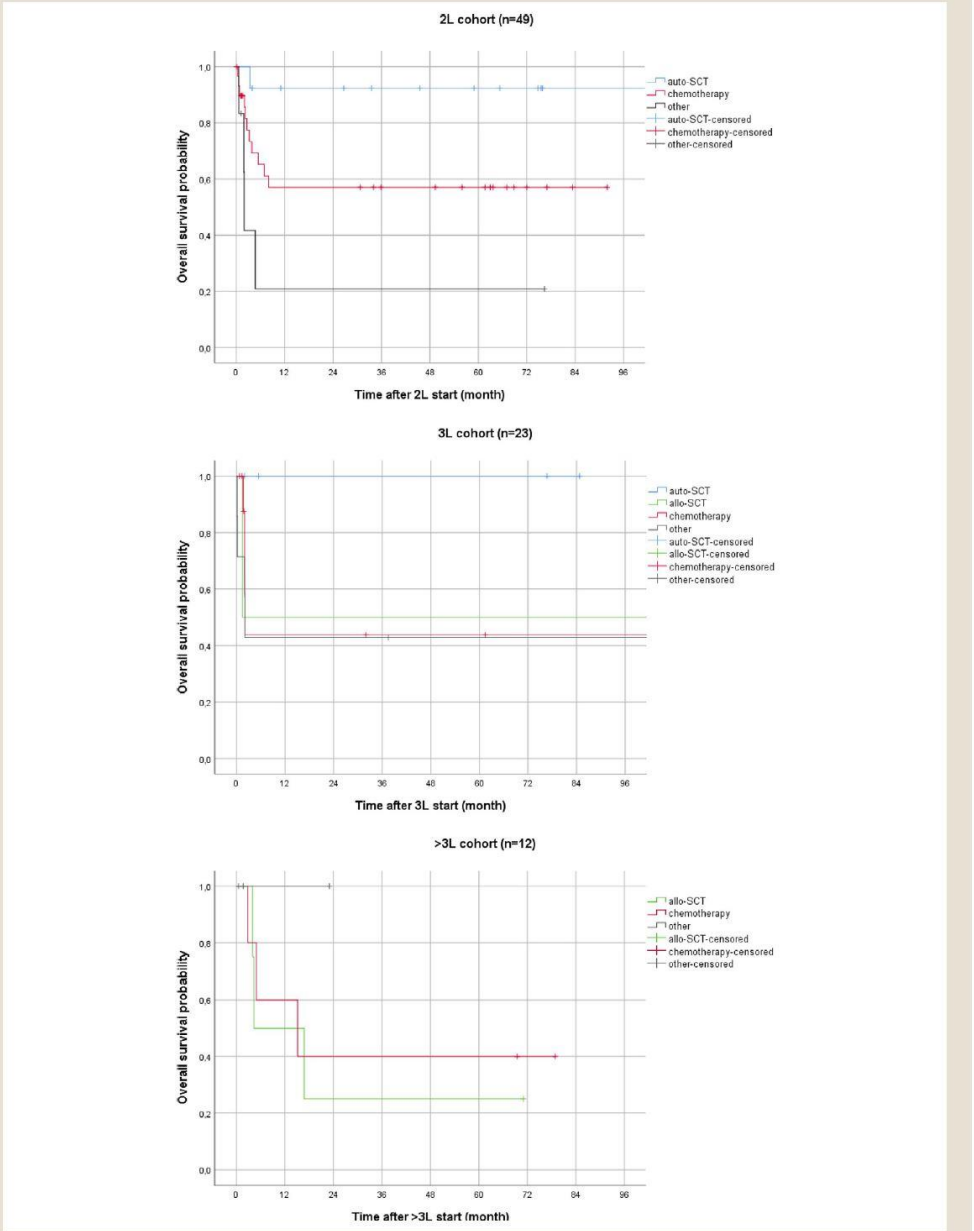


Figure 3 Treatment in context of SCT; n (Pat.) auto-SCT: autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant.

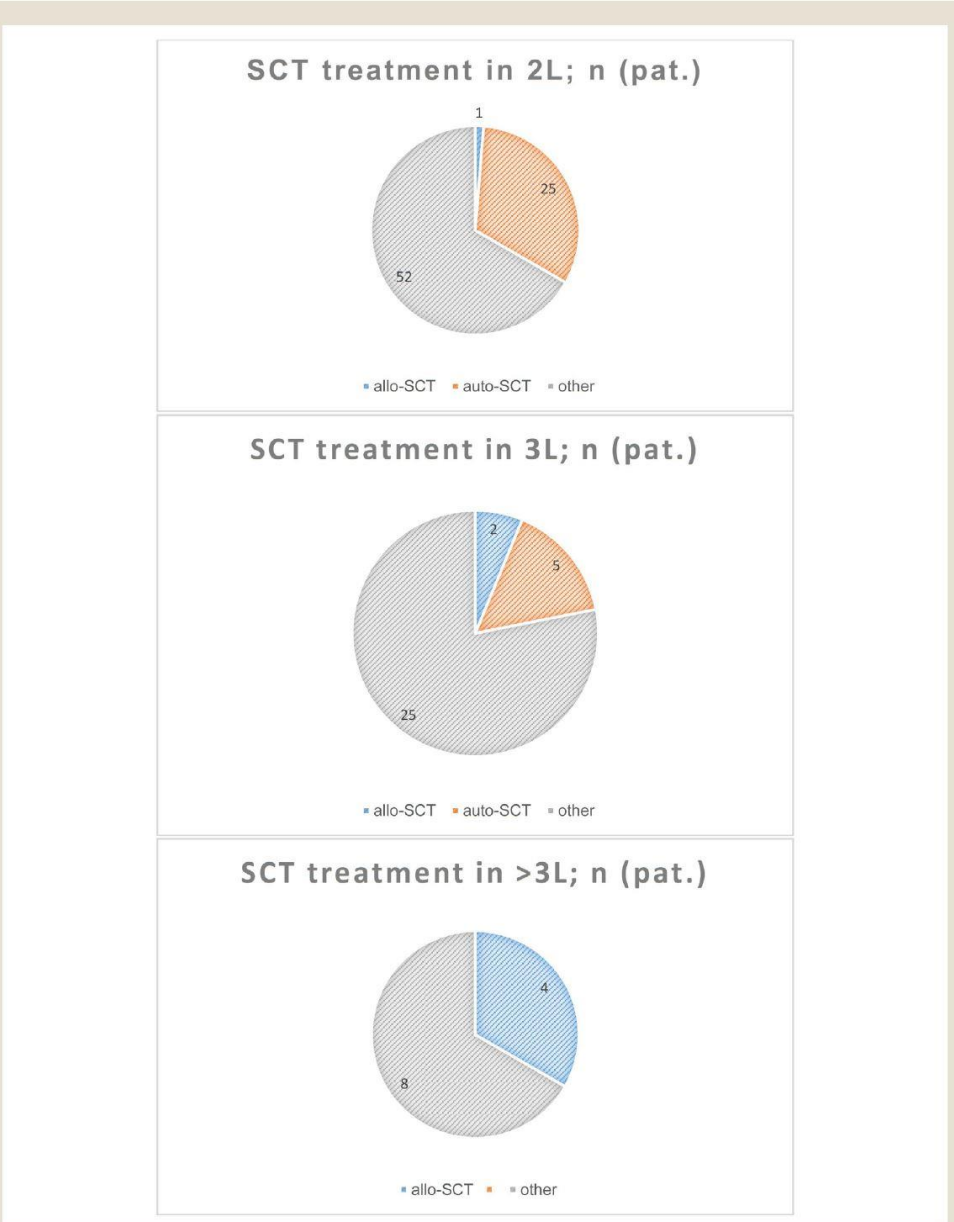
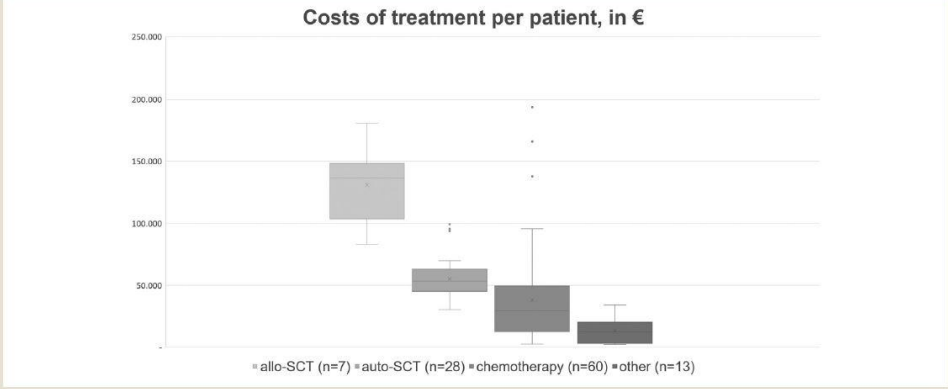


Figure 4 Total treatment costs ppt; in € auto-SCT = autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant.



>3L cohort. In the overall survival probability analysis, the autologous SCT cohort showed promising outcomes for transplanted patients in the respective treatment lines. Therefore, an additional subgroup analysis was performed to provide detailed information on stem cell transplanted patients.

In terms of patient characteristics, the study cohort was comparable to data presented in previously published economic studies in DLBCL-care. The mean age of patients with r/r-DLBCL at ID was 59 years, and 56% were male. The Ann-Arbor distribution at ID in this study was stage I + II, n = 35 (42%) and stage III + IV, n = 49 (58%). Tkacz et al. showed a mean age at 1L of 61 years and sex distribution of 56% males[32]. Costa S. et al. documented 53% of patients in stage III-IV (Ann-Abor) at initial diagnosis[33]. The slight differences may because the differing inclusion and exclusion criteria of the referred studies.

The shown results for Germany were generally consistent with previous international research that evaluated treatment patterns of r/r-DLBCL patients. Morrisson et al. reported that 57% of all 2L treatments in the US are based on chemo-regimens, with 33% for 3L patients[34]. For DLBCL patients in Japan, Tsutsué et al. reported approximately 50% for chemo-based therapies in 2L, 41.6% in 3L, and 35% in >3L[35]. We attribute the higher shares for chemotherapies in ≥2L to the fact for differently defined treatments in this study, eg, only rituximab-based chemotherapies. Given the important role of stem cell transplants in DLBCL treatment, this study ran an additional subgroup analysis and found that auto- and allo-SCT distribution in 2L was 32% (auto: 31; allo:1); 3L was 22% (16; 6) and >3L was 33% (0; 33). Purdum et al. reported a 28% SCT rate in the two years after first-line relapse[36]. Tkacz et al. showed SCT percentages of 13% in 2L and 9% in 3L[32]. One reason for these higher percentages might be that only inpatient treatments were included in this study. Further, the study setting was at a national center of excellence, which may have resulted in a higher proportion of patients with poorer health status in the study cohort. The individuality in SCT rates and their impact on resource use and costs will be discussed in a later section.

Besides the individual treatment, the number and length of inpatient stay had a strong impact on the patients burden. The results showed a mean hospitalization period of 44 days in 2L, 26 days in 3L, and 63 days in >3L. As mentioned before, the comparable literature, eg, in terms of hospitalization in German DLBCL-care, was strongly limited. Tkacz et al. documented an increasing trend in hospitalization within higher treatment lines: 23 days for 2L; 27 days for 3L; and 36 days for >3L[32]. Due to the specific characteristics of the respective health care systems, comparability between our results and international data is limited. One reason for the divergent 3L results may be that the lowest SCT rates were documented for the 3L cohort.

This study was conducted as a cost analysis on DLBCL-patients in ≥2 lines of treatment with a strong focus on treatment patterns, resource use, and costs. However, more comprehensive information, eg, on clinical outcomes, is needed to assess the value of future therapies in DLBCL care. In this context, the rate of documented death and the overall survival were analyzed to give initial insights. First, the results on death rates signal a high patient burden. Second, the results can give first impressions for future health economic research in Germany. The shown rate of documented death were fairly consistent with previously published data[37]. In terms of the performed survival analyses, the shown association of SCT with higher survival rates has been suggested in earlier publications[34,38].

The main objective of this study was to give a first idea about the cost dimensions for German third-party payers. From an international point of view, only a limited number of cost analyses in r/r-DLBCL care have been published. The existing literature poses a challenge in terms of interpretation as well as the comparability of results in costs owing to the specific features of the respective health care systems. Tkacz et al. showed that for 2L patients, the mean total costs for patients receiving transplants were approximately 2.7

times higher than for those without transplants (93% auto-SCT).[32] Similar to our findings, the published data had a huge range because of the high degree of individualized therapies. Additionally, Khor et al. reported data about the impact on total costs of using a single additional drug for treatment[40]. One possible explanation for the low costs in 3L is the high rate of radiation and the low SCT rate. Covering these varying costs between individual patient treatments with fixed DRG rates (in Germany) is challenging for decision-makers, physicians, and stakeholders. SCTs had a major cost impact in r/r DLBCL treatment. International studies also reported a huge impact of SCT treatments on costs[36,41]. Mayerhof et al. reported that the average cost ppt for an allogeneic transplant was approximately 230,000€ from the German third-party payer perspective. Over 80% of these costs resulted from inpatient care alone. Average direct costs of 107,500€ (81% for hospital care) were reported for patients with autologous transplants.[42] One reason for the lower costs in our results could be the different methodological setting. The costs in our study were not reported longitudinally and only describe the inpatient costs per treatment line. The regression analysis on age and costs showed a trend of higher costs for patients with lower age at ID. Banega et al. reported comparable results of higher costs across all cancer sites for patients aged below 65 than those aged 65 or older[39]. . In terms of rising DLBCL prevalence in Germany, comprehensive care for patients in ≥2L leads to high costs for health systems and places pressure on public budgets. The results can be used as a baseline for future economic studies, eg, in the context of innovative DLBCL therapies in Germany.

Certain factors limit our findings. A larger patient sample would have improved the possibility of identifying and controlling statistical outliers. This study was conducted at a single center and based on inpatient information, that might limit the results' generalizability and representativeness. So far, published real-world data on German r/r-DLBCL treatment patterns, resource use and cost of care are limited. Therefore, the study focused on a comparison with international data. A future multicenter study with outpatient data could lead to stronger evidence and increased generalizability. In addition, this study could not show patients' disease course; for example, some patients were admitted to the participating hospital after previous therapies in other hospitals and/or departments or through professionals not affiliated with this hospital. The reported mortality corresponds to the quality of data documentation and thus might be underestimated.

Conclusion

A DLBCL diagnosis is a huge burden for patients and their families. Treating this aggressive lymphoma is resource intensive and costly, and for patients with failed 1L therapy, it is associated with an uncertain prognosis. Patients with relapsed and/or refractory disease require additional intensive therapies, including stem cell transplantation, resulting in increased per patient fees and financial strain on hospitals and third-party payers. Comprehensive cost estimates are currently limited and depend on the treatment modalities for individual patients. Advancements in DLBCL treatment and surveillance, including innovative therapies such as CAR-T, have the potential to improve outcomes. However, given high initial treatment costs, a substantial increase in healthcare expenditure is expected. DLBCL prevalence is likely to increase with the aging population, and identifying cost-effective first-line therapies and surveillance modalities for DLBCL will require continued economic evaluation to limit the significant financial burden placed on third-party payers, patients, and hospitals.

Clinical practice points

- Patients with relapsed or refractory (r/r) DLBCL require highly individualized therapies. According to current German guidelines, treatment in ≥2 lines of therapy consists of stem cell transplant options, various (immuno)-chemotherapy regimens, CAR ("chimeric antigen receptor")-T-cell products or palliative care. Limited information exists regarding treatment patterns, outcomes and resource use and/or costs in clinical routine inpatient care. In the last years, cost intensive innovative therapies eg, CAR-T-cells have been launched for DLBCL treatment in >2 lines of therapy. Yet, payers are facing rising costs and request evidence to demonstrate value and rational treatment decisions in the context of limited budgets. Therefore, the need for proven evidence of costs relative to benefits and the budget for new treatments for use has become imperative. So far evidence to estimate and discuss comprehensively the value of innovative therapies like CAR-T-cells in terms costs and benefits is missing. As a first step we collected information on treatment patterns, resource use, costs, and outcomes from r/r DLBCL patients before CAR-T-cell licencing at a German tertiary teaching hospital. This information which is basic to put innovative treatments into perspective shows significant treatment costs and a huge variability of costs as consequence of individual treatment approaches in patients with treatment lines ≥ 2L. Number of hospitalizations, length of hospital stay and documented mortality are signals for a high burden to patients and families. An additional output of this paper is the depiction of data that is required for evidence generation in this area.

Author contribution

The manuscript was prepared according to the ICMJE Recommendations.

Disclosures

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.12.018.

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6. Paper II

Budget impact analysis of CAR-T cell therapy for adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) in Germany

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Budget Impact Analysis of CAR T-cell Therapy for Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma in Germany

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ABSTRACT

The aim was to assess the incremental costs of chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel, tisagenlecleucel) compared with standard of care in adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) from the German third-party payer perspective. A budget impact model was established over a 6-year period. Estimation of the third-line population: partitioned survival model based on outcome data from peer-reviewed literature, a top-down approach based on population forecasts, and age-standardized incidences. Cost data were derived from the controlling department of a tertiary hospital and a German cost-of-illness study. In the scenario analysis, the budget impact of treating second-line DLBCL patients was calculated. One-way deterministic sensitivity analyses were conducted to test the robustness of the model. For the period 2021-2026, 788-867 (minimum population, min) and 1,068-1,177 (maximum population, max) adult third-line r/r DLBCL patients were estimated. The budget impact ranged from €39,419,562; €53,426,514 (min; max) in year 0 to €122,104,097; €165,763,001 (min; max) in year 5. The scenario analysis resulted in a budget impact of €65,987,823; €89,558,611 (min; max) and €204,485,031; €277,567,601 (min; max) for years 0 and 5, respectively. This budget impact analysis showed a significant but reasonable financial burden associated with CAR T-cell therapy for a limited number of patients requiring individualized care. Further, this study presents challenges and future needs in data acquisition associated with cost analysis in personalized medicine. For comprehensive economic discussions, complementary cost-effectiveness analyses are required to determine the value of innovative therapies for r/r DLBCL.

INTRODUCTION

In the last 40 years, there has been an increase in malignant neoplasms of lymphoid hematopoietic and related tissues (C81-C96) among both children and adults in Germany.[1] Especially, since 2001, incident cases of non-Hodgkin lymphoma (NHL) have risen by 16.9% and 35.6% for women and men, respectively.[2] Among NHL cases, diffuse large B-cell lymphoma (DLBCL) is the most common subtype, with an age-standardized incidence rate of 7 per 100,000 in Europe and the United States.[3–5] As a first-line therapy, rituximab-based chemotherapy (R-CHOP), which is curative for 60%–70% of patients, is suggested.[6,7] In cases of relapsed or refractory disease (r/r), salvage chemotherapy followed by high-dose (chemo) therapy (HDT) and autologous stem-cell transplantation (ASCT) is recommended.[6,8] Transplant-ineligible patients and those who relapse after ASCT have a poor prognosis and limited treatment options.[9,10]

Since 2018, 2 chimeric antigen receptor (CAR) T-cell therapies, namely tisagenlecleucel (tisa-cel; Kymriah) and axicabtagene Ciloleucel (axi-cel; Yescarta), have been approved. They provide a new therapeutic approach for patients with r/r DLBCL and acute lymphoblastic leukemia (r/r ALL) after ≥2 lines of therapy.[11] After extracting and reproducing the patient's T cells in a laboratory, CARs are integrated into the T-cell membrane and reinfused as CAR T-cells into the patient's body. Upon binding to the antigen CD19+ at the surface of malignant cells, a specific immune reaction can be induced, activating a cytotoxic mechanism to destroy the CD19+ cancer cells.[12] In both pivotal studies, treatment with tisacel (JULIET) and axicel (ZUMA-1) resulted in overall response rates (ORR) of 52% and 83%, respectively, whereas patients treated with conventional therapy (SCHOLAR-1) achieved an ORR of 26%.[9,13,14]

A 2-year follow-up reported an ORR and CR of 83% and 54% in ZUMA-1 versus 34% and 12% for SOC in SCHOLAR-1. In addition, the 2-year survival rate was 54% for CAR T-cell therapy compared with 20% for SOC indicating an improvement in clinical outcomes for patients treated with CAR T-cells.[15]

Despite promising clinical outcomes, CAR T-cell therapies are associated with high costs. The reimbursement of axi-cel and tisa-cel for a single infusion amounts to €282,000 and €275,000 in Germany, respectively.[16] However, this sum does not include

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additional costs incurred for other aspects, for example, hospitalization and managing adverse events (AEs). Several cost-effectiveness analyses (CEAs) for treating r/r DLBCL patients with tisa-cel and axi-cel have been conducted to assess their economic value in the United States. Results indicated that CAR T-cell therapies seemed to be mostly cost-effective and did not exceed the willingness-to-pay threshold at a certain probability. However, these findings were highly dependent on the chosen time period and clinical outcomes, such as long-term remission and survival of CAR T patients.[17–19]

Budget impact analyses (BIA) take on a complementary role to CEAs[20] by outlining how the impact on the payer's budget will change if a new intervention is added to the current mix of treatments and then distributed in routine care.[20,21] As personalized therapies such as CAR T-cell therapies are initially associated with significant costs, questions on the future economic impact of innovative therapies for payers are increasingly prominent. A corresponding BIA will provide a clearer idea of the potential economic burden for third-party payers in Germany. Peer-reviewed literature on BIAs is limited, and no analysis on the financial burden of CAR T-cells in German statutory health insurance has been published so far.

The objective of this study was to estimate the incremental costs of treating adult r/r DLBCL patients with axi-cel and tisa-cel in an inpatient setting in comparison to the standard of care (SOC) from the German statutory health insurance perspective. Specifically, the development of the proportion of r/r DLBCL patients treated with CAR T-cells over a 6-year time period was investigated.

METHODS

Model design

A budget impact model and a 3-state partitioned survival model were used to assess the relevant target population. Inpatient costs of the 2 treatment strategies were compared: standard therapy in the third-line and CAR T-cell treatment. The time period included a baseline year (2021; year 0) and 5 subsequent years (2022–2026; years 1–5) with annual cycles. This BIA was developed according to the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) principles of good practices for budget impact analysis.[20,22] Additionally, national methodological recommendations provided by the Institute for Quality and Efficiency in Health Care (IQWiG) were considered.[21] The resulting model structure is presented in **Figure 1**. All calculations were performed using Microsoft Excel 2016.

Model parameters

Target population

Adult patients (≥18 y) diagnosed with DLBCL (ICD-10: C83.3) who had been treated with at least 2 systemic therapies were included in the model.[6] In this analysis, the eligible population was a yearly cohort estimated using an epidemiological top-down approach.

First-line patient population

For the assessment of German incident DLBCL cases per year, the annual German population was identified for the respective time period (6 y) based on general population forecasts by the Federal Statistical Office of Germany (Destatis).[23] Therefore, a moderate development of fertility, life expectancy, and migration (G2-L2-W2) was assumed.[23] The latest DLBCL age-standardized incidence rate (2017) was extracted from the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch-Institute (RKI) (**Table 1**). A growing incidence rate per year was assumed due to an increase in German age-standardized incidence rates for DLBCL in recent years.[5] Therefore, an average annual growth rate of 2% was calculated based on the reported age-standardized incidence rates from 2009 to 2017 (**Table 1**).

Second-line patient population

Considering a cure rate of 60%–70% in first-line patients and an early mortality rate of 2% after conventional chemotherapy, 28% (minimum population, min), to 38% (maximum population, max) of incident cases were eligible patients for second-line therapy (**Table 1**).

Third-line patient population

To gather information on clinical outcomes, for example, response rates and survival probabilities in second-line standard therapy, a literature search in PubMed with the following MeSH terms was conducted: "lymphoma, large B-cell, diffuse," "adult," "adolescent," "stem cell transplantation*," "transplantation, autologous," "salvage therapy*," "oxaliplatin," "overall survival," and "progression-free survival." **Table 1** presents the clinical parameters that were extracted from the CORAL and ORCHARRD studies, as well as additional references that were considered for transplant-ineligible patients. These input variables were embedded in a simplified therapy algorithm (**Figure 2**) based on the German DLBCL guideline.[6] With each treatment option (chemotherapy and HDT/ASCT, if eligible), the proportion of patients with overall responses was determined. Additionally, the percentage of patients who died after stem-cell transplantation (SCT) (5%) was considered in the calculation (**Table 1**). To assess the number of third-line patients by means of 1-year survival probabilities, a 3-state partitioned survival model was used. The number of surviving patients with progressive disease or relapse was estimated by post-progression survival (PPS). PPS results from the difference between overall survival (OS) and progression-free survival (PFS). Patients in the death state were estimated using OS probability. Candidates for the third-line were patients with no initial response after treatment, patients with progressive disease, and transplant-eligible patients who did not respond to SCT. According to the chosen cost perspective, the percentage of people covered by statutory health insurance (88%) was applied to the eligible r/r DLBCL population (**Table 1**).

Treatment regimens

Standard therapy for third-line patients consisted of chemotherapy, allogeneic SCT, and ASCT. The choice of current treatment patterns was based on a single-center retrospective study of r/r DLBCL patients conducted at the LMU Hospital.[29] The new intervention included 2 approved CD19+ CAR T-cell therapies for r/r DLBCL, namely axicabtagene Ciloleucel and tisagenlecleucel.

Market share

CAR T-cell therapy was supposed to replace the current treatment, and the proportion of patients treated with CAR T-cells was assumed to increase over time. Within the CAR T therapy group, the annual distribution of axi-cel and tisa-cel was constant at 50% each, as no specific preferences regarding treatment with 1 of the 2 CAR T-cell therapies were assumed. The proportion of patients treated with CAR T-cells at baseline was assumed to be 16.5% (**Table 1**). For the following 5 years, an average annual growth rate of 23% was applied (**Table 1**). The percentages of patients treated with CAR T-cells were 20%, 25%, 31%, 38%, and 47% for the years 2022–2026, respectively.

Costs

In this analysis, only inpatient costs were considered. CAR T-cell therapy is intended for exclusive use in qualified clinical facilities, which is assumed to be in inpatient settings.[32,33] Charges for inpatient treatment with CAR T-cells and SOC were derived from codes for diagnosis related groups (DRG), new diagnostic and treatment methods regulation (NUB), and

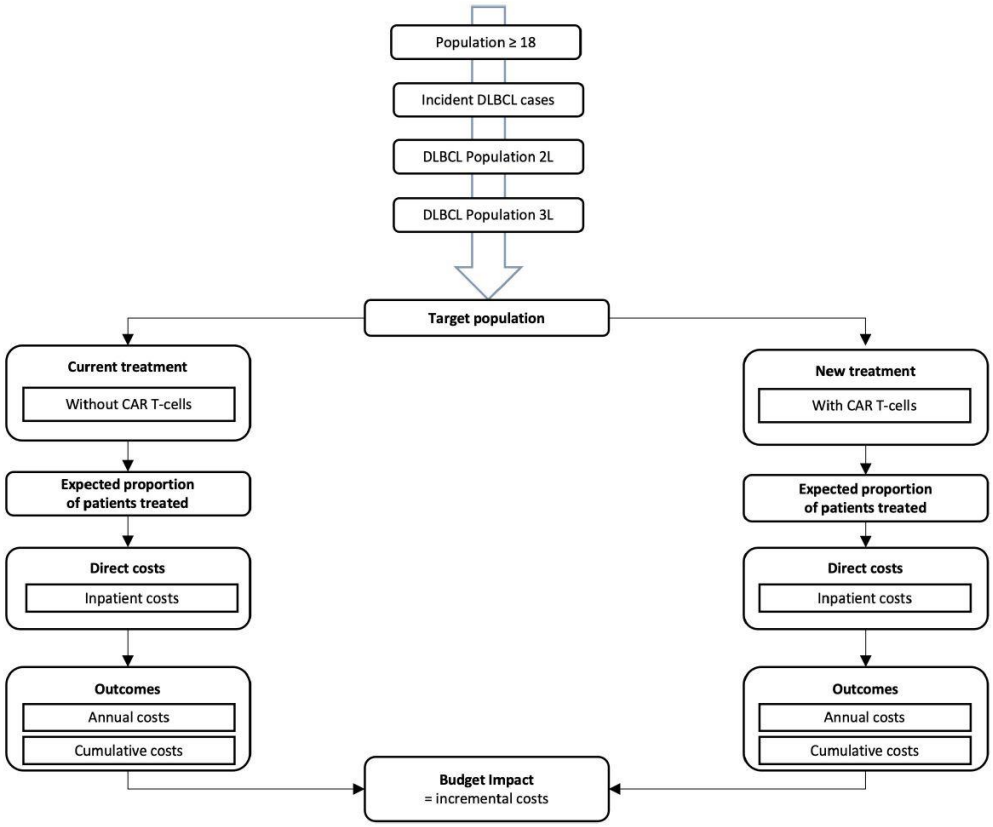


Figure 1. Budget impact model structure of r/r DLBCL patients treated with CAR T-cells over a 6-y time horizon from the perspective of the German statutory health insurance. 2L = Second-line; 3L = Third-line; cumulative costs = aggregated costs over the 6-y time horizon; CAR = chimeric antigen receptor; r/r DLBCL = relapsed or refractory diffuse large B-cell lymphoma.

"Zusatzentgelte" (ZE) from the Medical Controlling at the LMU Hospital (aG-DRG billing).

The mean costs for standard therapy were selected from a single-center retrospective cost study assessing the costs of DLBCL patients treated with ≥third-line standard care (Table 1). Costs for CAR T-cell therapy were based on administrative hospital claims data (Table 1). Patients were analyzed from the leukapheresis up to the end of the CAR T associated inpatient stay at the department. The mean inpatient stay was 22 days post CAR T-cell retransfusion. The cutoff points were discharge (eg, relocation to another hospital); getting further DLBCL-treatment unrelated to CAR T-cell therapy. Costs per patient were separately assessed for treatment with axi-cel and tisa-cel. The mean costs per patient for SOC and CAR T-cell therapy were multiplied by the respective calculated share of the patient population. The resulting costs per year were considered to be independent of each other.

Further, the costs of tocilizumab were more precisely assessed for the subsequent sensitivity analysis as tocilizumab served as a proxy for the costs of managing possible AEs of CAR T-cell therapies. In addition, no discounting was applied as this BIA was conducted over a short period of time with no means to determine the net present value of the budget impact.[20,22] Table 1 presents the mean costs per patient for axi-cel and tisa-cel.

Model output

Relevant outcomes were the incremental costs of CAR T-cell therapies compared with those of standard treatment. The budget impact was assessed annually and cumulatively (aggregated over a 6-y period).

Analyses

Base case analysis

The budget impact of r/r DLBCL third-line patients treated with CAR T-cells represented the base case.

Scenario analysis

In the scenario analysis, the budget impact of CAR T-cell therapy in second-line patients was assessed. Even though treatment with CAR T-cells is currently approved for ≥third-line, there are ongoing phase III trials testing the efficacy of axi-cel and tisa-cel in patients relapsing after first-line therapy.[34,35] The target population consisted of second-line DLBCL patients covered by statutory health insurance. Salvage chemotherapy, HDT,

Table 1.
Model Input

Parameter	Value	Sources
Epidemiology		
Standardized incidence rate (per 100,000)	7.4	[5]
Average annual growth rate (for incidence rate)	2%	[5]a
Statutory insurance coverage	88%	[24]
Treatment and survival		
Cure rate first-line	60% – 70%	[6]
ASCT eligible	50%	[25]
Salvage ORR	63%	[26]
Salvage PFS	50%	[26]
Salvage OS	71%	[26]
ASCT rate	35%	[27]
ASCT ORR	70.50%	[27]
ASCT PFS	65.50%	[28]
ASCT OS	84%	[28]
Salvage ORR (transplant ineligible)	61%	[10]
Salvage PFS (transplant ineligible)	26%	[10]
Salvage OS (transplant ineligible)	49%	[10]
Early mortality conventional chemotherapy	2%	Based on experts
Early mortality ASCT	5%	[25]b
Unit costs (mean values) in €		
Tisagenlecleucel	345,485	LMU Hospital controlling[a]
Axicabtagene ciloleucel	373,324	LMU Hospital controlling[a]
Standard therapy second-line	44,750	[29]
Standard therapy third-line	56,224	[29]
Market share		
Proportion treated with CAR T-cells (baseline)	16.50%	[30]
Average annual growth rate	23%	[31]c

[a]Own calculation based on data in "Sources."
[b]Confirmed by experts.
[c]Estimation of the growth rate based on German CAR T-cell market projections.
ASCT = autologous stem-cell transplantation; CAR = chimeric antigen receptor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

and ASCT are the standard treatments according to the German DLBCL guidelines.[6] For the estimation of patients treated with CAR T-cells, the same market share at baseline (16.5%) and average annual growth rate (23%) were applied equal to the base case (**Table 1**). The mean costs for standard therapy were extracted from the retrospective cost study for second-line DLBCL patients (**Table 1**). The cost of CAR T-cell treatment remained equal to the base case values.

Sensitivity analysis

A 1-way deterministic sensitivity analysis was conducted to test the robustness of the model by varying the following model parameters: the proportion of patients treated with CAR T-cells at baseline (market share at year 0), the corresponding average annual growth rate for the market share, and costs for both CAR T-cell therapies, standard therapy for third-line patients, and tocilizumab for axi-cel and tisa-cel, respectively. An increase and decrease of values by 20%, according to standard modelling practices, were applied. The variation of population parameters, such as clinical outcomes, was not included, as uncertainty has already been presented by specifying a minimum and maximum population. The impact of the parameter variation was illustrated in the form of a tornado diagram. Relevant outcomes of the sensitivity analyses were the cumulative budget impacts (min, max).

RESULTS

Base case analysis

Target population

In first-line therapy, 5,158–5,680 patients with newly diagnosed DLBCL were treated during the period 2021–2026. The numbers of patients in second-line therapy were estimated to be 1,444–1,590 (min) and 1,960–2,158 (max). The calculated third-line target population amounted to 788–867 (min) and 1,068–1,177 (max). **Figure 3** presents a top-down overview of the annual population size from the first to the third-line. For detailed information on the top-down approach and the calculation of the third-line population, see the Suppl. Appendix. During the period 2021–2026, the numbers of patients treated with CAR T-cells increased from 130 to 402 (min) and from 176 to 546 (max), respectively.

Budget impact

At baseline, the total cost of CAR T-cell therapy was €83,724,074; €113,473,746 (min; max) compared with €44,304,512; €60,047,232 (min; max) when treated with standard therapy. At year 5, the total cost of CAR T-cell therapy was €170,850,035; €231,938,649 (min; max) compared with €48,746,208; €66,175,648 (min; max) without the introduction of CAR T-cells (Suppl. Appendix). The budget impact ranged from €39,419,562, €53,426,514 (min; max) in 2021 to €122,104,097; €165,763,001 (min; max) in 2026 (**Figure 4**). The cumulative budget impact for CAR T-cell therapy was €447,992,998; €608,059,242 (min; max) over the 6-year time period.

Scenario analysis

The eligible second-line patient population covered by the statutory health insurance was estimated to be 1,271–1,399 (min) and 1,725–1,899 (max) during the period 2021–2026. Considering the resulting market uptake, 210–650 (min) and 284–882 (max) patients were treated with CAR T-cells in the respective time period. The total cost of introducing CAR T-cells ranged from €122,865,073; €166,752,361 (min; max) at baseline to €267,090,281; €362,547,851 (min; max) in year 5 (Suppl. Appendix). The increased population resulted in a higher annual budget impact from €65,987,823; €89,558,611 (min; max) in year 0 to €204,485,031; €277,567,601 (min; max) in year 5 (**Figure 4**). The scenario analysis reported a 68% higher cumulative budget impact of €750,629,900; €1,018,838,624 (min; max) compared with the base case.

Sensitivity analysis

Deterministic sensitivity analyses showed that the cumulative budget impact was most sensitive to the variation in market share at baseline, average growth rate of the market share, and costs of axi-cel and tisa-cel. It remained robust in the case of variation in tocilizumab costs. The variation and outcomes for each parameter are presented in a tornado diagram in **Figure 5** for the minimum and maximum target populations.

DISCUSSION

In this study, the budget impact of treating third-line r/r DLBCL patients with CAR T-cells compared with the SOC in an inpatient setting was assessed from the third-party payer perspective. Thus far, no budget impact analysis from the German statutory health insurance perspective has been published based on real-life inpatient cost data of CAR T-cell therapies. The number of DLBCL patients in third-line therapy eligible for CAR T-cell therapy was estimated at 788–867 (min) and 1,068–1,177 (max) in years 0 and 5. The incremental costs for CAR T-cell therapy ranged from €39 to €53 million (min; max) in 2021 and from €122 to €166 million (min; max) in 2026. The cumulative budget impact over the 6-year time period was €448 million; €608 million (min; max).

The annual incremental costs in years 0 and 5 amounted to 0.7%; 1% (min; max) and 2.3%; 3.1% (min; max), respectively, of the German statutory health insurance expenses in 2019 on antineoplastic agents (approximately €5.3 billion).[36]

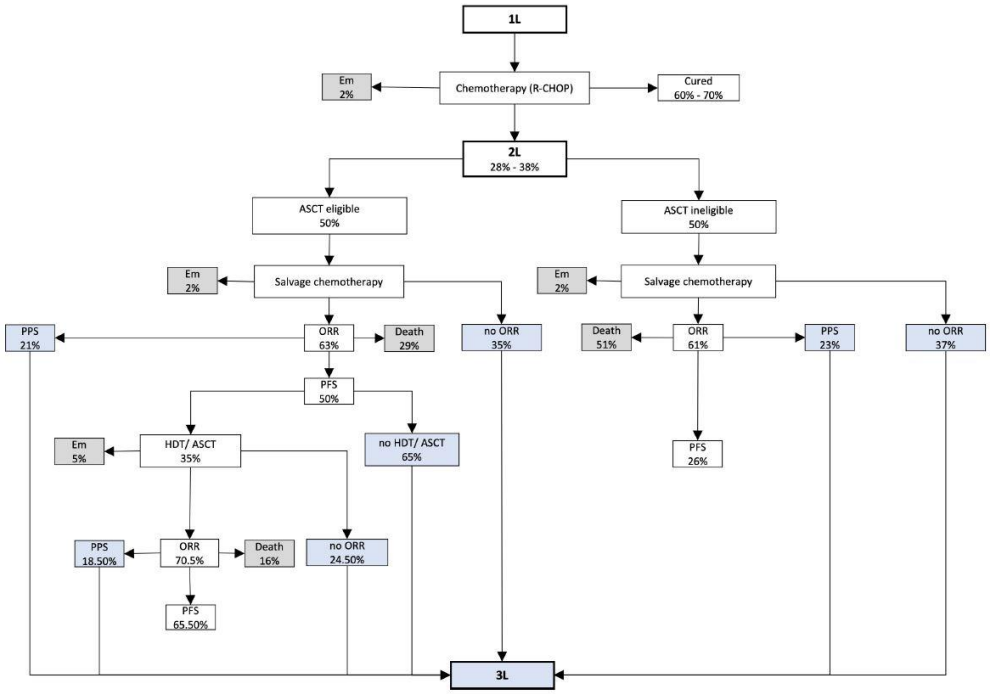


Figure 2. Therapy algorithm for the calculation of the third-line DLBCL population. 1L = First-line; 2L = Second-line; 3L = Third-line ASCT = autologous stem-cell transplantation; DLBCL = diffuse large B-cell lymphoma; Em = Early mortality; HDT = high-dose (chemo) therapy ORR = overall response rate; PFS = progression-free survival PPS = postprogression survival; R-CHOP = Rituximab—cyclophosphamide, doxorubicin, vincristine, prednisolone.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Population 1L	5,158	5,264	5,368	5,468	5,575	5,680
Range (min - max)						
Population 2L	1,444 – 1,960	1474 – 2,000	1,503 – 2,040	1,531 – 2,078	1,561 – 2,119	1,590 – 2,158
Population 3L	895 – 1,214	913 – 1,239	931 – 1,263	948 – 1,287	967 – 1,312	985 – 1,337
Target population (statutory insured)	788 – 1,068	803 – 1,090	819 – 1,111	834 – 1,133	851 – 1,155	867 – 1,177

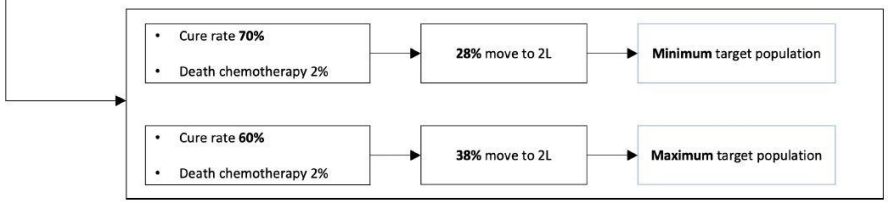


Figure 3. Top-down calculation of the DLBCL target population. 1L = First-line, 2L = Second-line; 3L = Third-line; DLBCL = diffuse large B-cell lymphoma.

Compared with other budget impacts in Germany, treatment of r/r multiple myeloma patients with 3 intravenous (carfilzomib, lenalidomide, dexamethasone [KRd]; elotuzumab, lenalidomide, dexamethasone [ERd]; daratumumab, lenalidomide, dexamethasone [DRd]) and 1 oral therapy (ixazomib, lenalidomide, dexamethasone [IRd]) indicated 1-year budget impacts of €551, €163, €584, and €95 million, respectively. Although therapy costs are not as high as for CAR T-cells, these results clearly exceed our base case budget impact of €39 million for the first year.[37]

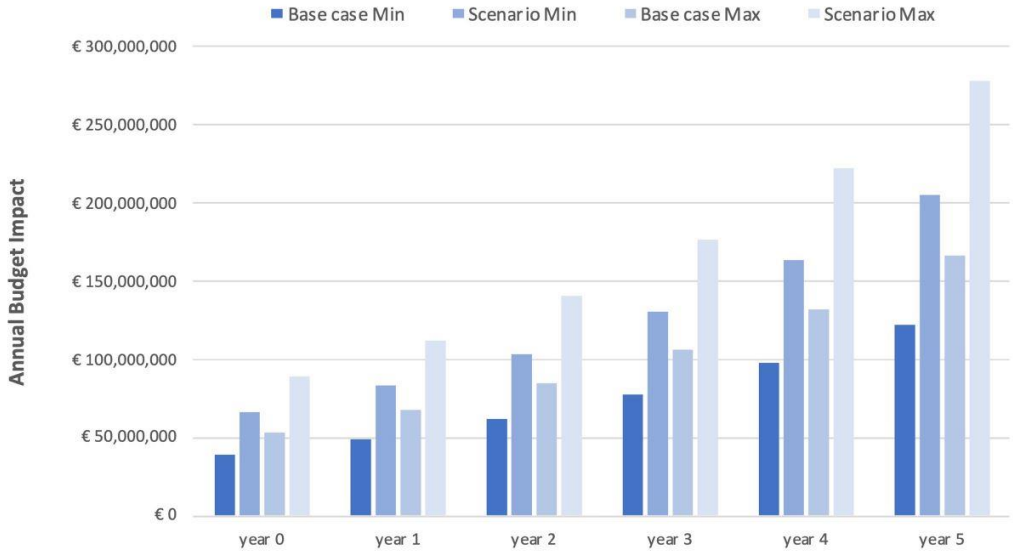
Incremental costs of alternative therapies should be interpreted in the context of the patient population size, the chosen SOC, treatment settings, and lines of therapy. Further options for comparison are limited because only a few BIAs are published for Germany.

From an international point of view, only a limited number of BIAs for CAR T-cell therapies have been published. The existing literature poses a challenge in terms of interpretation as well as the comparability of results owing to the various approaches employed for model structure and methodology across different studies.

The economic report of the Canadian Agency for Drugs and Technologies in Health (CADTH) reported a 3-year cumulative budget impact of $387 million for introducing tisa-cel into routine care, presenting a similar cost dimension, although our analysis was carried out over a 6-year time period.[38] In an economic analysis of CAR T-cell therapies for the treatment of hematological cancers in the former EU-5 (France, Germany, Spain, Italy, and the United Kingdom) and the Netherlands, the eligible patient population for Germany ranged from 996 in 2019 to 1,050 in 2029, which aligns with our calculated target population. Although this analysis attempted to portray the incremental costs of CAR T-cell therapies, no adequate BIA was conducted.[39]

Although assessing the value of CAR T-cell therapies is not the focus of budget impact analyses, their promising clinical outcomes for r/r DLBCL patients should be taken into consideration when interpreting the calculated incremental costs. Studies on 5-year outcomes for r/r DLBCL patients treated with CAR T-cell therapies have reported an ORR of 58%, with 46% of patients being in CR. In terms of survival, the study documented a PFS of 31% at 5 years.[40] A retrospective observational study compared the outcomes of CAR T-cell therapies with alternate treatment methods and showed an ORR of 72% compared with 32% in the control group. Patients previously treated with 2 lines of therapy achieved a median PFS of 6.4 months (mo) when treated with CAR T-cells compared with 2.3 mo for conventional therapy.[41]

In this BIA, we also performed a scenario analysis to assess the financial burden of CAR T-cell therapies in second-line treatment. Clinical trials evaluating CAR T-cell therapy in second-line for DLBCL or follicular lymphoma (FL) patients showed positive results.[34,35,42] For example, the ZUMA-7 study reported an ORR of 83% for CAR T-cell versus 50% for SOC. The CR was 65% versus 32%. In terms of survival, patients treated with CAR T-cell therapy had a longer median EFS (8.3 mo versus 2 mo).[35] The target population was estimated to be 1,271; 1,725 (min; max) in 2021 and 1,399; 1,899 (min; max) in 2026. The annual budget impact was calculated at approximately €66 million; €90 million (min; max) in year 0 and €204 million; €278 million (min; max) in year 5. In this case, the budget impact was 1.2% and 1.7%



Minimum Population (Costs in €)						
Base Case	39,419,562	49,409,020	61,984,015	77,636,682	97,439,621	122,104,097
Scenario	65,987,823	82,825,361	103,917,411	130,137,117	163,277,157	204,485,031
Maximum Population (Costs in €)						
Base Case	53,426,514	67,068,283	84,083,322	105,470,457	132,247,665	165,763,001
Scenario	89,558,611	112,392,163	140,991,499	176,704,370	221,624,379	277,567,601

Figure 4. Annual budget impact in base case and scenario analysis for the minimum and maximum population.

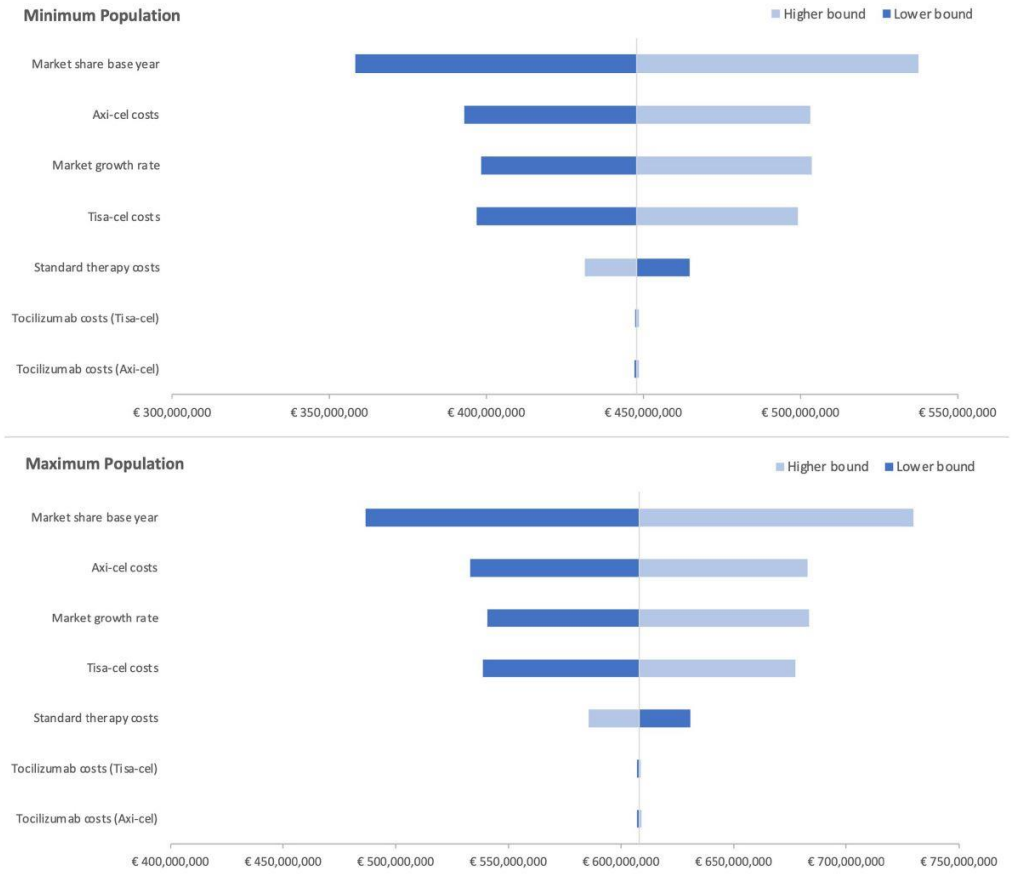


Figure 5. Tornado diagram of the minimum and maximum population with cumulative budget impact as outcome parameter.

(min; max) and 3.8% and 5.2% (min; max) of the costs for antineoplastic agents from the German statutory health insurance perspective at baseline and in year 5, respectively.[36] Due to a greater patient population, the calculated budget impact represents a larger and thus considerable cost indicator. The interpretation depends on the clinical outcomes of CAR T-cell therapies, which must also be taken into consideration to ensure sufficient interpretation.

The calculated budget impact of CAR T-cell therapies seems to represent a manageable cost factor for German third-party payers. Unfortunately, transparency in the budget impact of innovative therapies in Germany is limited to allow a comprehensive comparison. No threshold exists to interpret the severity of the budget impact in the context of German third-party payers' financial burden.

This budget impact analysis has several limitations. Throughout the process of data collection for suitable input variables, we were confronted with a lack of epidemiological data, comprehensive treatment patterns, and cost data in Germany. The scope of this study was on the inpatient treatment only. Future analyses on outpatient treatment pattern and costs would complement this first budget impact analysis. Additionally, this budget impact only focused on a limited time frame, which is why potential future cost savings, and the development of long-term expenditures could not be analyzed when combined with CEAs. Costs over a longer follow-up period (including long-term toxicity management) are missing and should also be considered in subsequent analyses.

In summary, the results of this BIA provide a first picture of the potential impact of innovative therapies in hematology/oncology. Lately, BIAs have become an increasingly important tool for evaluating the financial impact of new health technologies.[22] This kind of model calculation may help to rationalize decisions for budget holders through methodological approaches and provide a foundation for further decisions in terms of resource allocation by decision-makers.[20,22] However, due to limited data on peer-reviewed real-world data budget impacts and lack of comparison possibilities within the German healthcare system, it is difficult to assess the financial burden of CAR T-cell therapies. Published budget impact analyses in the context of innovative therapies in hematologic diseases are limited so far. Thus, no further adequate comparisons could be added to the discussion to put our results into perspective. Future efforts in economic analyses, for example, BIAs referring on diagnostic and treatment approaches in haematological

malignancies, based on standardized and harmonized methods could support in rational decision making.

This raises the question of what is needed to ensure a comprehensive BIA. Although principles of good practices for BIAs from the ISPOR exist, they only present general recommendations. Moreover, they are not adopted equally due to different needs for data collection, methodological approaches, and reporting methods when conducting BIAs.[20] Therefore, clear and structured national recommendations should be developed and applied in the future.[22] Further, innovative therapies are on the rise and present new treatment options, for example, for patients with rare disease.[43] Besides the much-discussed CAR T-cell therapies, other gene therapies are equally challenging for the respective budget holder.[44] For instance, Onasemnogene Abeparvovec for treating spinal muscular atrophy (SMA) has a price of about €2 million per patient. An established budget impact analysis by the Institute for Clinical and Economic Review (ICER) showed that the set threshold of $991 million was not exceeded, reaching 45%, if the entire eligible US patient population of 215 incident SMA type I patients per year. Over a 5-year time period, the per-patient budget impact was about $950,000 compared with the best supportive care Nusinersen.[45]

Even if innovative therapies cannot be exactly compared in terms of financial burden, they face the same challenges in terms of assessment and reimbursement. New potential payment models and reimbursement policies need to be discussed exclusively for such personalized therapies, as current assessment strategies cannot be applied to therapies with unknown future value (in the long term) and average high costs per patient.

CONCLUSION

We conducted a budget impact analysis for treating r/r DLBCL patients with axi-cel and tisa-cel in Germany from a third-party payer's perspective.

In the context of expenses for antineoplastic agents and national budget impacts in Germany for cancer therapies, for example, multiple myeloma, our documented budget impact of CAR T-cell therapies seems to be reasonable for a limited number of patients. Internationally viewed, other documented BIAs of CAR T-cell therapies presented comparable cost dimensions. For a better interpretation of the results, updated assessment policies and reimbursement strategies are needed for such innovative therapies. This study may provide general guidance for future reimbursement strategies for personalized medicine. Subsequent collection of epidemiological data, information on treatment patterns, and costs from outpatient and inpatient settings is needed to assure comprehensive budget impact analyses in the future. Additionally, further investigations, for example, CEAs that describe the value of CAR T-cell therapies, need to be taken into consideration including clinical outcomes of innovative therapies.

AUTHOR CONTRIBUTIONS

DS and BM have been involved throughout the process of data collection, data analysis, interpretation of results as well as drafting and writing up the final version of the article. CS, WS, VB, and TW supported as clinicians on the data collection in the clinical department of the LMU. MD supported as clinical expert on lymphoma and has been involved in data collection as well as critical interpretation of results. KB contributed to the development of the conceptional study design, data collection, data analyses, critical interpretation of results, and writing the draft as well as the final version of the article. All authors were involved in critically reviewing the article and gave approval of the version to be published.

DISCLOSURES

MD is an editor for HemaSphere. The remaining authors have no conflicts of interest to disclose.

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