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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report: Appendices

Title	The CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B cell acute lymphoblastic leukaemia, diffuse large B cell lymphoma and primary mediastinal B cell lymphoma
Authors	Konstance Nicolopoulos, Magdalena Moshi, Ming Min, Danielle Stringer, Thomas Vreugdenburg Royal Australasian College of Surgeons
Technology	Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Yescarta®)
Type of Technology	Medical services
Date	9 July 2024

Conflict of Interest: The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

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1 Appendix A: Systematic search results

1.1 Summary of bibliographic database search results

Table 1 Summary of bibliographic database search results

Database	Results
OVID—Medline & Embase (combined)	2,608
Cochrane Library—CENTRAL	9
EconLit	1
HTA agency websites	45
International HTA Database	33
Records identified through pearling	6
Total	**2,702**

Table 2 Summary of clinical trial registry search results

Database	Results
ClinicalTrials.gov	50
EU Clinical trials registry	15
Total	**65**

1.2 Literature sources and search strings

Table 3 Search strategy – Ovid (Medline and Embase)

PICO domain	#	Search term	Results
Intervention terms	1	Tisagenlecleucel*.tw.	1,593
	2	Kymriah*.tw.	663
	3	Axicabtagen*	2,453
	4	Yescarta*	557
	5	axi-cel*	803
	6	CART-19.tw.	119
	7	CAR19.tw.	310
	8	CART 19.tw.	119
	9	"ctl 019".tw.	92
	10	ctl019.tw.	245
	11	Receptors, Antigen, T cell.sh.	26,425
	12	Receptors, Chimeric Antigen.sh.	3,925
	13	Immunotherapy, Adoptive.sh.	13,301
Intervention 1	**14**	**1 OR 2 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**	**40,675**
Intervention 2	**15**	**3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**	**41,285**
Population 1	16	B cell acute lymphoblastic leukaemia.tw.	538
	17	B cell acute lymphoblastic leukemia.tw.	5,622
	18	acute lymphocytic leukaemia.tw.	923
	19	acute lymphocytic leukemia.tw.	8,992
	20	B cell ALL.tw.	2,494
	21	Precursor B cell lymphoblastic leukemia-lymphoma.sh.	2,903
	22	**16 OR 17 OR 18 OR 19 OR 20 OR 21**	**19,892**
Population 2	23	Diffuse large B cell lymphoma.tw.	46,848
	24	DLBCL.tw.	33,430
	25	lymphoma, large B cell, diffuse.sh.	23,400
	26	Lymphoma, Non-Hodgkin.sh.	36,414
	27	Lymphoma, B cell.sh.	16,202
	28	**23 OR 24 OR 25 OR 26 OR 27**	108,876
Population 3	29	Primary mediastinal large B cell lymphoma.tw.	1,102
	30	MPMBCL.tw.	3
	31	PBCL.tw.	396
	32	PMBCL.tw.	873
	33	mediastinal neoplasms.tw.	365
	34	**29 OR 30 OR 31 OR 32 OR 33**	2,426
	35	14 AND 22	934

	36	(14 OR 15) AND 28	2,220
	37	15 AND 34	110
Combined search	**38**	**35 OR 36 OR 37**	3,002
Limits	**39**	**Limit 38 to human, publication from 1 January 2010**	**2,608**

Table 4 Search strategy – The Cochrane Library

PICO domain	#	Query	Results
Intervention terms	1	(Tisagenlecleucel*):ti,ab,kw	37
	2	(Kymriah*):ti,ab,kw	1
	3	(Axicabtagen*):ti,ab,kw	55
	4	(Yescarta*):ti,ab,kw	1
	5	(Axi-cel*):ti,ab,kw	38
	6	(CART-19):ti,ab,kw	7
	7	(CAR19):ti,ab,kw	1
	8	(CART 19):ti,ab,kw	152
	9	(ctl 019):ti,ab,kw	2
	10	(ctl019):ti,ab,kw	15
Combined search	**11**	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10**	**233**
Limit	**12**	**Limit to Cochrane reviews**	**9**

Table 5 Search strategy – Econlit

PICO domain	#	Query	Results
Intervention terms	1	TX Tisagenlecleucel*	0
	2	TX Kymriah*	0
	3	TX Axicabtagen*	0
	4	TX Yescarta*	0
	5	TX Axi-cel*	0
	6	TX CART-19	0
	7	TX CAR19	0
	8	TX CART 19	0
	9	TX ctl 019	0
	10	TX ctl019	0
	11	TX car t-cell therapy	1
Combined search	**12**	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11**	**1**

Table 6 Search strategy – International HTA Database

PICO Domain	#	Query	Results
Intervention terms	1	Tisagenlecleucel	9
	2	Kymriah	5
	3	Axicabtagen*	8
	4	Yescarta	4
	5	CAR T*	22
	6	CAR-T*	13
Combined search	**7**	**1 OR 2 OR 3 OR 4 OR 5 OR 6**	**33**

Table 7 Search strategy – Clinicaltrials.gov

PICO Domain	#	Query	Results
Intervention terms	1	Tisagenlecleucel	-*
	2	Axicabtagene*	-*
	3	Yescarta	-*
	4	Kymriah	-*
Combined search	**5**	**1 OR 2 OR 3 OR 4**	**50**

Notes:
* Individual search term results unavailable

Table 8 Search strategy – EU Clinical trials registry

PICO Domain	#	Query	Results
Intervention terms	1	Tisagenlecleucel	-*
	2	Axicabtagene*	-*
	3	Yescarta	-*
	4	Kymriah	-*
Combined search	**5**	**1 OR 2 OR 3 OR 4**	**15**

Notes:
* Individual search term results unavailable

Table 9 HTA agency websites

Global	
INAHTA HTA Database	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Singapore	
Agency for Care Effectiveness (ACE)	ace-hta.gov.sg
Spain	

Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR)	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html

Source:
Based on INAHTA members list[1]

2 Appendix B: List of included effectiveness/safety studies

2.1 Systematic reviews/meta-analyses (k=0)

Nil

2.2 Randomised controlled trials (k=0)

Nil

2.3 Non-randomised studies of interventions (k=4; n=4)

2.3.1 B-ALL treated with tisa-cel

1. Ragoonanan D, Bhar S, Mohan G, et al. A multicenter study of ICU resource utilization in pediatric, adolescent and young adult patients post CAR-T therapy. *Frontiers in Oncology* 2022;12:1022901.

2.3.2 LBCL treated with axi-cel

2. Mian A, Wei W, Winter AM, et al. Outcomes and factors impacting use of axicabtagene ciloleucel in patients with relapsed or refractory large B-cell lymphoma: results from an intention-to-treat analysis. *Leukemia & lymphoma* 2021;62(6):1344-52.
3. Neelapu SS, Locke FL, Bartlett NL, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. *Blood advances* 2021;5(20):4149-55.

2.3.3 LBCL treated with tis-cel

4. Maziarz RT, Zhang J, Yang H, et al. Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma. *Blood Advances* 2022;6(8):2536-47.

2.4 Single-arm studies (k=31; n=23)*

***Note:** Pasquini 2020 was included in both the B-ALL and LBCL groups, but has only been counted once in the total number of publications and included studies reported in subheading 2.4.

2.4.1 B-ALL (k=10; n=7)

ELIANA (k=3; n=1)

1. Laetsch TW, Maude SL, Rives S, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. *Journal of Clinical Oncology* 2023;41(9):1664-69.
2. Laetsch TW, Myers GD, Baruchel A, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. *The Lancet Oncology* 2019;20(12):1710-18.
3. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine* 2018;378(5):439-48.

ENSIGN (k=2; n=1)

4. Mueller KT, Grupp SA, Maude SL, et al. Tisagenlecleucel Immunogenicity in Relapsed/Refractory Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma. *Blood advances* 2021
5. Novartis Pharmaceuticals. A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell Acute Lymphoblastic Leukemia: ClinicalTrials.gov; 2019 [cited Pearling Screened TIAB]. Available from: https://clinicaltrials.gov/study/NCT02228096?term=NCT02228096&rank=1&tab=history accessed July 17 2023].

Independent (k=5; n=5)

6. Ghorashian S, Jacoby E, De Moerloose B, et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study. *The Lancet Haematology* 2022;9(10):e766-e75.
7. Moskop A, Pommert L, Baggott C, et al. Real-world use of tisagenlecleucel in infant acute lymphoblastic leukemia. *Blood Advances* 2022;6(14):4251-55.
8. Pasquini MC, Hu Z-H, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood advances* 2020;4(21):5414-24.
9. Ravich JW, Huang S, Zhou Y, et al. Impact of High Disease Burden on Survival in Pediatric Patients with B-ALL Treated with Tisagenlecleucel. *Transplantation and cellular therapy* 2022;28(2):73.e1-73.e9.
10. Dourthe ME, Rabian F, Yakouben K, et al. Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia. *Leukemia* 2021;35(12):3383-93. doi: https://dx.doi.org/10.1038/s41375-021-01281-7.

2.4.2 LBCL (k=22; n=17)

JULIET (k=3; n=1)

1. Maziarz RT, Waller EK, Jaeger U, et al. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. *Blood Advances* 2020;4(4):629-37.
2. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New England Journal of Medicine* 2019;380(1):45-56.
3. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *The Lancet Oncology* 2021;22(10):1403-15.

NCT03601442 (k=1; n=1)

4. Riedell PA, Hwang W-T, Nastoupil LJ, et al. Patterns of Use, Outcomes, and Resource Utilization among Recipients of Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B Cell Lymphomas. *Transplantation and cellular therapy* 2022;28(10):669-76.

ZUMA-1 (k=4; n=1)

5. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *The Lancet Oncology* 2019;20(1):31-42.
6. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Molecular therapy: the journal of the American Society of Gene Therapy* 2017;25(1):285-95.
7. Neelapu SS, Jacobson CA, Ghobadi A, et al. 5-Year Follow-Up Supports Curative Potential of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1). *Blood* 2023
8. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. *New England Journal of Medicine* 2017;377(26):2531-44.

ZUMA-9 (k=1; n=1)

9. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2020;38(27):3119-28.

Independent (k=13; n=13)

10. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nature Medicine* 2022;28(10):2145-54.
11. Baird JH, Epstein DJ, Tamaresis JS, et al. Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. *Blood advances* 2021;5(1):143-55.
12. Benoit A, B Boies M-H, Dery N, et al. CAR T-Cells for the Treatment of Refractory or Relapsed Large B-Cell Lymphoma: A Single-Center Retrospective Canadian Study. *Clinical lymphoma, myeloma & leukemia* 2023;23(3):203-10.
13. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. *Blood* 2022;140(4):349-58.
14. Gauthier J, Gazeau N, Hirayama AV, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. *Blood* 2022;139(26):3722-31.
15. Grana A, Gut N, Williams K, et al. Safety of Axicabtagene Ciloleucel for the Treatment of Relapsed or Refractory Large B-Cell Lymphoma. *Clinical Lymphoma, Myeloma and Leukemia* 2021;21(4):238-45.
16. Melody M, Gandhi S, Saunders H, et al. Incidence of thrombosis in relapsed/refractory B-cell lymphoma treated with axicabtagene ciloleucel: Mayo Clinic experience. *Leukemia & lymphoma* 2022;63(6):1363-68.
17. Pannait L, Wu QV, Voutsinas J, et al. Predictors of cytopenias after treatment with axicabtagene ciloleucel in patients with large B-cell lymphoma. *Leukemia & lymphoma* 2022;63(12):2918-22.
18. Pasquini MC, Hu Z-H, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood advances* 2020;4(21):5414-24.
19. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood advances* 2020;4(13):2871-83.
20. Sesques P, Ferrant E, Safar V, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. *American Journal of Hematology* 2020;95(11):1324-33.
21. Sim AJ, Jain MD, Figura NB, et al. Radiation Therapy as a Bridging Strategy for CAR T Cell Therapy With Axicabtagene Ciloleucel in Diffuse Large B-Cell Lymphoma. *International Journal of Radiation Oncology Biology Physics* 2019;105(5):1012-21. doi: https://dx.doi.org/10.1016/j.ijrobp.2019.05.065.
22. Yagi Y, Kanemasa Y, Sasaki Y, et al. [Tisagenlecleucel for relapsed/refractory diffuse large B-cell lymphoma: real-world data from single institute experience]. *[Rinsho ketsueki] The Japanese journal of clinical hematology* 2022;63(10):1363-72.

3 Appendix C: List of included economic studies

3.1 Cost-effectiveness studies (k=18)

1. Cher BP, Gan KY, Aziz MIA, et al. Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective. *Journal of Medical Economics* 2020;23(11):1321-29.
2. Choe JH, Abdel-Azim H, Padula WV, et al. Cost-effectiveness of Axicabtagene Ciloleucel and Tisagenlecleucel as Second-line or Later Therapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *JAMA Network Open* 2022;5(12):e2245956.
3. Hillis C, Vicente C, Ball G. The Cost Effectiveness of Axicabtagene Ciloleucel Versus Best Supportive Care in the Treatment of Adult Patients with Relapsed or Refractory Large B-Cell Lymphoma (LBCL) After Two or More Lines of Systemic Therapy in Canada. *PharmacoEconomics* 2022;40(9):917-28.
4. Li N, Zheng B, Cai H, et al. Cost-effectiveness analysis of axicabtagene ciloleucel vs. salvage chemotherapy for relapsed or refractory adult diffuse large B-cell lymphoma in China. *Supportive Care in Cancer* 2022;30(7):6113-21.
5. Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2018;36(32):3192-202.
6. Lin JK, Muffly LS, Spinner MA, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma. *Journal of Clinical Oncology* 2019;37(24):2105-19.
7. Maria J, Santasusana R, De Andres Saldana A, et al. Cost-effectiveness analysis of tisagenlecleucel in the treatment of relapsed or refractory B-cell acute lymphoblastic Leukaemia in children and young adults in Spain. *ClinicoEconomics and Outcomes Research* 2020;12:253-64.
8. Moradi-Lakeh M, Yaghoubi M, Seitz P, et al. Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland. *Advances in Therapy* 2021;38(6):3427-43.
9. Qi CZ, Bollu V, Yang H, et al. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United States. *Clinical Therapeutics* 2021;43(8):1300-19.e8.

10. Roth JA, Sullivan SD, Lin VW, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *Journal of medical economics* 2018;21(12):1238-45.
11. Sarkar RR, Gloude NJ, Schiff D, et al. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *Journal of the National Cancer Institute* 2019;111(7):719-26.
12. Thielen FW, van Dongen-Leunis A, Arons AMM, et al. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *European Journal of Haematology* 2020;105(2):203-15.
13. Wakase S, Teshima T, Zhang J, et al. Cost Effectiveness Analysis of Tisagenlecleucel for the Treatment of Adult Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma in Japan. *Transplantation and Cellular Therapy* 2021;27(6):506.e1-06.e10.
14. Wakase S, Teshima T, Zhang J, et al. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia in Japan. *Transplantation and Cellular Therapy* 2021;27(3):241.e1-41.e11.
15. Wang XJ, Wang YH, Li SCT, et al. Cost-effectiveness and budget impact analyses of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma from Singapore's private insurance payer's perspective. *Journal of Medical Economics* 2021;24(1):637-53.
16. Wang XJ, Wang YH, Ong MJC, et al. Cost-Effectiveness and Budget Impact Analyses of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia from the Singapore Healthcare System Perspective. *ClinicoEconomics and Outcomes Research* 2022;14:333-55.
17. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. *JAMA Pediatrics* 2018;172(12):1161-68.
18. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. *JAMA network open* 2019;2(2):e190035.

3.2 HTAs with an economic evaluation component (k=10)

1. Bisaillon R, Mombo NN, Beha S, et al. Avis: tisagenlecleucel pour le traitement de la leucémie lymphoblastique aiguë récidivante ou réfractaire. Canada: Institut national d'excellence en sante et en services sociaux (INESSS), 2019.

2. CADTH. Tisagenlecleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report. CADTH Optimal Use Report [Internet]. 2019 [cited 2022 31 October]; vol. 8(no. 3e). Available from: https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma.
3. CADTH. Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report. CADTH Optimal Use Report [Internet]. 2019 [cited 2022 31 October]; vol. 8(no. 3f). Available from: https://www.cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma.
4. CADTH. Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report. CADTH Optimal Use Report [Internet]. 2019 [cited 2022 31 October]; vol. 9(no. 1d). Available from: https://www.cadth.ca/axicabtagene-ciloleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma.
5. Mombo NN, Bisaillon R, Beha S, et al. Avis: tisagenlecleucel pour le traitement du lymphome diffus à grandes cellules B récidivant ou réfractaire. Canada: Institut national d'excellence en sante et en services sociaux (INESSS), 2019.
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4 Appendix D: List of included ELSO studies

4.1 Ethical considerations (k=2)

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4.2 Legal consideration (k=0)

Nil

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4.4 Social considerations (k=0)

Nil

5 Appendix E: List of excluded studies at full text

5.1 Incorrect comparator (k=3)

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5.3 Incorrect language (k=0)

Nil

5.4 Incorrect outcome (k=18)

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5.6 Incorrect publication status (k=0)

Nil

5.7 Incorrect publication type (k=55)

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5.9 Trial data not included in analysis (k=12)

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5.10 Unable to extract data (k=0)

Nil

6 Appendix F: Minimum clinically important differences and improvements for outcomes of interest

A non-systematic targeted search was conducted to identify minimum clinically important difference (MCID), minimum important change (MIC), minimum important difference (MID) and minimum clinically important improvement (MCII) related to the outcomes of interest (see ***Section 5.4***). It was planned to use the identified MCIDs and MIDs (***Table 10***) as a guide, not as a complete assessment of the literature. The MCIDs and MIDs generally relate to health-related and cancer-specific quality of life (i.e. PedQL, EQ-5D VAS, FACT-G, FACT-Lym, SF-36). The applicability of these MID and MCID measures to the current HTA report is currently uncertain. Differences in population demographics, diagnosis and interventions exist, so caution must be taken when extrapolating these measures to the outcomes reported.

Table 10 Minimum clinically important differences/improvements for outcomes of interest

Outcome measure	MIC/MID/MCII/MCID	Study type	Population demographics	Author, year
HRQoL				
PedQL 4.0	MCID: 4.36	Clinimetric assessment	Paediatric population	Varni et al. 2003[2]
EQ-5D VAS	MID: 7–10	Clinimetric assessment	Cancer patients	Pickard et al. 2007[3]
FACT-G total score	MCID: 3–7	Clinical study (NRSI)	Cancer patients	Maziarz et al. 2020[4]
FACT-Lym subscale	MCID: 2.9–5.4	Clinical study (NRSI)	Lymphoma patients	Maziarz et al. 2020[4]
FACT-Lym trial outcome index	MCID: 5.5–11	Clinical study (NRSI)	Lymphoma patients	Maziarz et al. 2020[4]
FACT-Lym total score	MCID: 6.5–11.2	Clinical study (NRSI)	Lymphoma patients	Maziarz et al. 2020[4]
SF-36: bodily pain	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: general health	MID: 2	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: mental health	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: physical functioning	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: role emotional	MID: 4	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: role physical	MID: 4	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: social functioning	MID: 4	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: vitality	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]

SF-36: physical health total score	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]
SF-36: mental health total score	MID: 3	Clinimetric assessment	General and NHL populations*	Swigris et al. 2020[5]

Abbreviations:

EQ-5D = EuroQol 5-dimension questionnaire, **FACT-G** = Functional Assessment of Cancer Therapy – General, **FACT-Lym** = Functional Assessment of Cancer Therapy – Lymphoma, **HRQoL** = health-related quality of life, **MCID** = minimum clinically important difference, **MCII** = minimum clinically important improvement, **MIC** = minimum important change, **MID** = minimum important difference, **NHL** = non-Hodgkin's lymphoma, **NRSI** = non-randomised studies of interventions, **PedQL** = Paediatric Quality of Life Inventory, **SF-36** = 36-item short form health survey, **VAS** = visual analogue scale.

Notes:

* SF-36 has become the standard tool for both general and disease-specific populations, including NHL patients, as per Maziarz et al. 2020.[4]

7 Appendix G: Economic evidence tables

7.1.1 Applicability assessment

Table 11 Applicability assessment of the existing economic evidence using NICE's appraisal checklist items

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	***Overall Judgement***
tisa-cel in adults with r/r DLBCL								
Cher 2020	Yes	Yes	Partly. Singaporean healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Choe 2022	Partly. ≥2 prior therapies combined with 1 prior therapy.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Lin 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Moradi-Lakeh 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	***Directly applicable***
Qi 2021	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Wakase 2021a	Yes	Yes	Partly. Japanese healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Wang 2021	Yes	Yes	Partly. Singaporean healthcare setting	Yes	Yes	Yes	Yes	*Partly applicable*
tisa-cel in children or young adults with r/r B-ALL								
Lin, 2018	Yes	Yes	Partly, United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	***Overall Judgement***
Maria, 2020	Yes	Yes	Partly. Spanish healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Moradi-Lakeh 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	***Directly applicable***
Sarkar 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Thielen 2020	Yes	Yes	Partly. Dutch healthcare setting	Yes	Yes	Yes	Yes	*Partly applicable*
Wang, 2022	Yes	Yes	Partly. Singaporean healthcare setting.	Yes	Yes	Unclear if outcomes are discounted	Yes	*Partly applicable*
Wakase 2021b	Yes	Yes	Partly. Japanese healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2018	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Axi-cel in adults with DLBCL								
Hillis 2022	Partly. DLBCL combined with other LBCLs.	Yes	Partly. Canadian healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Li 2022	Yes	Yes	Partly. Chinese healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Lin 2019	Yes	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Roth 2018	Partly. DLBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2019	Partly. DLBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Axi-cel in adults with PMBCL								
Hillis 2022	Partly. PMBCL combined with other LBCLs.	Yes	Partly. Canadian healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	***Overall Judgement***
Roth 2018	Partly. PMBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*
Whittington 2019	Partly. PMBCL combined with other LBCLs.	Yes	Partly. United States healthcare setting.	Yes	Yes	Yes	Yes	*Partly applicable*

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **DLBCL** = diffuse large B cell lymphoma, **LBCL** = large B cell lymphoma, **PMBCL** = primary mediastinal B cell lymphoma, **QALY** = quality-adjusted life year.

7.1.2 Assessment against the CHEERS reporting checklist

Table 12 CHEERS checklist items for the existing Swiss study

Item	Section	Topic	Y/N	Comments
1	Title	Title	Y	Title specifies intervention (tisa-cel), target populations (B-ALL, DLBCL), and setting.
2	Abstract	Abstract	Y	
3	Introduction	Background and objectives	Y	
4	Methods	Health economic analysis plan	N	
5		Study population	Y	
6		Setting and location	Y	
7		Comparators	Y	
8		Perspective	Y	
9		Time horizon	Y	
10		Discount rate	Y	
11		Selection of outcomes	Y	
12		Measurement of outcomes	Y	
13		Valuation of outcomes	Y	
14		Measurement and valuation of resources and costs	Y	
15		Currency, price, data, and conversion	Y	
16		Rationale and description of model	Y	PSM, a typical approach in oncology and has been used in prior submissions to NICE and CADTH.
17		Analytics and assumptions	Y	During B-ALL model development, clinical experts were consulted to evaluate efficacy inputs and long-term extrapolation from a clinical perspective. The assumption that DLBCL patients are cured after year 3 was, according to the authors, validated by NICE submission of tisa-cel, with this approach being preferred by the NICE committee.
18		Characterising heterogeneity	N	
19		Characterising distributional effects	N	
20		Characterising uncertainty	Y	
21		Approach to engagement with patients and others affected by the study	Partial	Authors note the Swiss clinical experts were consulted on various issues. Engagements with patients or payers were not described.
22	Results	Study parameters	Y	
23		Summary of main results	Y	
24		Effect of uncertainty	Y	
25		Effect of engagement with patients and others affected by the study	Y	Swiss clinical experts provided input regarding comparators, diagnostic and therapeutic procedures, clinical evidence, and costs, which were used to inform the models.
26	Discussion	Study findings, limitations, generalisability and current knowledge	Y	

Item	Section	Topic	Y/N	Comments
27	Other relevant information	Source of funding	Y	
28		Conflicts of interest	Y	

Abbreviations:
B-ALL = B-cell acute lymphoblastic leukaemia, **CADTH** = Canadian Agency for Drugs and Technologies in Health, **CHEERS** = Consolidated Health Economic Evaluation Reporting Standards, **DLBCL** = diffuse large B cell lymphoma, **NICE** = National Institute of Health and Care Excellence, **PSM** = partitioned survival model, **tisa-cel** = tisagenlecleucel

7.1.3 Limitations assessment

Table 13 Limitations assessment of the existing Swiss economic evidence using NICE's appraisal checklist items

Checklist question	Response	Comments
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Decision tree captures discontinuations prior to infusion for CAR T-cell therapies. PSM health states built around PFS or EFS, progressive disease and death.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime horizon is used.
2.3 Are all important and relevant outcomes included?	Yes	EFS/PFS, disease progression, OS, long-term survival, AEs, costs, QALYs, LYs
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Derived from well-conducted clinical trials and published studies. However, concern regarding applicability of the data as comparative evidence for the populations of interest.
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Derived from pooled IPD of single-arm clinical trials. Estimates of relative effect are based on indirect treatment comparisons, introducing significant uncertainty.
2.6 Are all important and relevant costs included?	Yes	Pre-treatment leukapheresis, bridging chemotherapy and lymphodepleting costs for tisa-cel, drug and procedure acquisition costs, associated drug administration costs, associated hospitalisation and ICU costs, AE costs, subsequent SCT costs, other follow-up and monitoring costs, and terminal care costs.
2.7 Are the estimates of resource use from the best available source?	Partly	Resource use is based on clinical trial data and verified with clinical experts.
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	The funder of the study is Novartis, Switzerland.
Overall Judgement	Potentially serious limitations – the study fails to meet ≥1 quality criteria, and this could change the conclusions about cost effectiveness.	

Abbreviations:
AE = adverse event; **CAR** = chimeric antigen receptor; **EFS** = event-free survival; **ICU** = intensive care unit; **IPD** = individual patient data; **LY** = life year; **NICE** = National Institute of Health and Care Excellence; **OS** = overall survival; **PFS** = progression-free survival; **PSM** = partitioned survival model; **QALY** = quality-adjusted life year; **SCT** = stem cell transplantation; **tisa-cel** = tisagenlecleucel.

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7.1.4 Overview of existing HTAs with an economic evaluation component

Table 14 Summary of existing HTAs with an economic evaluation component

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
NICE, UK			
NICE TA554[6]	B-ALL that is refractory, in relapse post-transplant, or in second or later relapse, in people up to age 25 years. Mean age of the cohort at model entry of 12 years.	**Intervention**: tisa-cel Those discontinuing prior to infusion were assumed to receive either blinatumomab or salvage chemotherapy. *Note: the review group considered the assumption that tisa-cel patients not receiving the infusion receive comparator therapies is problematic, as these patients have faced a significant delay in treatment and include a proportion of patients who do not receive infusion due to AEs.* **Comparator**: Blinatumomab or salvage chemotherapy (FLA-IDA). **Subsequent therapies**: subsequent allogenic SCT after intervention or comparator therapies.	**About**: company submission from Novartis **Analysis**: incremental cost per QALY gained **Model**: hybrid decision tree and 3-state PSM was used. The decision tree accounted for patients who are assigned for tisa-cel treatment but did not receive the infusion. The PSM included the following states: EFS, relapsed/progressed disease, and death. 1-month cycle length. **Data sources (efficacy)**: OS and EFS for tisa-cel arm derived from pooled analysis of IPD from 3 trials (ELIANA, ENSIGN and B2101J).[7-9] IPD data were not available for the comparators; the model therefore had to rely on published summary data. OS and EFS for tisa-cel were extrapolated using an MCM approach. This approach was also used for blinatumomab. For salvage chemotherapy, a standard parametric survival approach was used. *Note: the review group notes that a central feature of the company's model is the concept of cure.* **Time horizon**: lifetime horizon (88 years). **Discount**: costs and effects were both discounted at 3.5% p.a. **Results**: **Company's base-case (deterministic),** when provided with the confidential PAS discount, the ICERs were £18,392 (CHF23,424) and £25,404 (CHF32,354) per QALY gained, respectively. The mean probabilistic ICERs were £20,046 (CHF25,530) and £27,066 (CHF34,471) per QALY gained. The probability of tisa-cel being the most cost-effective treatment option is 90% at the £50,000 per QALY gained threshold and 65% at the £30,000 per QALY gained threshold. **ERG corrected company base-case** addressed a calculation error, which increased the ICER from £18,392 (CHF23,424) per QALY to £20,864 (CHF26,572) per QALY, and from £25,404 (CHF32,354) to £28,806 (CHF36,687) per QALY. **ERG alternative base-case (probabilistic)** suggests that the ICER for tisa-cel is £29,501 (CHF37,572) and £48,265 (CHF61,470) per QALY. **Further exploratory analyses on the ERG's base-case** also explored uncertainties regarding the uptake of SCT in patients receiving CAR T and the duration of IVIG use. The ICERs based on this exploratory analysis ranged between £23,900 (CHF30,439) per QALY and £46,133 (CHF58,755) per QALY compared with blinatumomab and between £41,274 (CHF52,566) per QALY and £65,229 (CHF83,075) per QALY compared with salvage chemotherapy.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
NICE TA559[10] **Note**: this guidance has been updated and replaced by NICE TA872 (published 28 February 2023).[11] In the updated guidance, the company's economic model used the same approach as in the original appraisal.	Adult patients with r/r DLBCL, PMBCL and transformed follicular lymphoma who are ineligible for autologous SCT.	**Intervention:** axi-cel. **Comparator:** BSC, defined as a blended comparator of the following options: GEM, GEM-P, RGCVP and RVP. All were assumed to share the same safety and efficacy profile with each other and with the regimens used in SCHOLAR-1. **Subsequent therapies:** subsequent SCT (all allogenic in base case) after intervention or comparator. *Note: review group highlights that the potential impact of SCT on HRQoL was not formally captured.*	**About:** Company submission from Kite, a Gilead Company **Analysis:** Incremental cost per QALY gained **Model**: 3-state PSM (pre-progression, post-progression, and death). 1-month cycle length. *Note: the review group noted that use of data for the modified ITT population (for axi-cel) implies model entry for patients receiving axi-cel occurs from the timepoint of infusion (not leukapheresis).* **Data source (efficacy):** IPD from modified ITT population from ZUMA-1 trial for OS and PFS of axi-cel.[12,13] MCM used for OS; standard parametric curve used for PFS (for axi-cel). IPD from SCHOLAR-1 study for OS of comparator (extrapolated using standard parametric curve). PFS derived from OS, assuming the same ratio between OS and PFS as observed in ZUMA-1. **Time horizon:** Lifetime horizon (44 years). **Discount:** 3.5% p.a. for costs and effects. **Results**: **Company base-case results without PAS**: axi-cel was associated with an ICER of £67,323 (CHF85,742) per additional QALY gained. Results showed that the probability of axi-cel being more cost-effective compared to BSC is 0.43%, given a WTP threshold of £50,000 (CHF63,680) per QALY. **ERG results** were confidential. **Conclusions**: The ERG considered the company's economic submission to meet the requirements of the NICE reference case. However, the ERG identified a number of key uncertainties: 1. The uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC; 2. The use of the mITT population for axi-cel; 3. Significant uncertainties remain concerning the company's base-case OS extrapolation for axi-cel; 4. The inclusion of additional structural assumptions related to cure; 5. Uncertainties surrounding the HRQoL and costs of AEs associated with axi-cel (specifically for B-cell aplasia and CRS); 6. Uncertainty surrounding post-treatment SCT; 7. Uncertainty surrounding broader infrastructure and training requirements; 8. Uncertainty surrounding whether the criteria are met relating to the application of end-of-life considerations and the appropriate discount rate. **Updated result from TA872**: the committee concluded that the most plausible probabilistic ICER was below £50,000 per QALY gained.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
NICE TA567[14]	Adult patients with r/r DLBCL who have failed 2 or more lines of systemic therapy. Mean age of the cohort at model entry is 54 years.	**Intervention**: tisa-cel. **Comparator:** salvage chemotherapy, including R-GEMOX, R-GDP, or pixantrone monotherapy (generally considered to be palliative). **Subsequent therapies:** SCT after tisa-cel; model assumes no patients treated with a comparator therapy would receive SCT. *Note: review group's clinical advisor noted patients could be given a non-cross-resistant salvage therapy with a view to possible autologous SCT.*	**About**: Company submission from Novartis **Analysis**: Incremental cost per QALY gained **Model**: A hybrid decision tree and 3-state PSM was used. The decision tree accounted for patients assigned to tisa-cel who did not receive the infusion (tisa-cel arm only). The PSM included the following states: PFS, progressed disease, and death. A 1-month cycle length was considered. **Data sources (efficacy)**: OS and PFS for tisa-cel arm derived from pooled analysis of IPD from JULIET and Schuster et al. (2017), extrapolated using MCMs.[15,16] Pseudo-IPD from the Eyre et al. (2016) UK observational study was used for the comparator, extrapolated using a standard parametric approach.[17] Patients were considered to be long-term survivors after 2 years. *Note: the review group considered data from the CORAL extension studies to be relevant. The review group considered the assumption of long-term survivorship reasonable, but that a 5-year time point may be more appropriate.* **Time horizon**: Lifetime horizon (46 years). **Discount**: Costs and effects were both discounted at 3.5% p.a. **Results**: **Company's cost-effectiveness results (deterministic):** With the PAS discount applied to tisa-cel, the corresponding ICERs were £47,684 (CHF60,730), £47,526 (CHF60,529) and £44,648 (CHF56,863) per QALY gained versus [R-]Gem-Ox, [R-]GDP and pixantrone monotherapy, respectively, which is below the WTP threshold of $50,000 (CHF63,680) per QALY. Tisa-cel was found to represent a cost-effective use of NHS resources. **Company's revised base-case corrected by the ERG**: ERG identified an error on how the cost and utility of long-term survivors had been programmed in the company's model and resulted in an ICER of £46,173 (CHF58,806) per QALY for tisa-cel vs GDP. **The key uncertainties addressed by the ERG scenario analyses relate to**: 1. Extrapolation of OS for tisa-cel; 2. Additional structural assumptions associated with cure and its timing; 3. OS evidence source used for salvage chemotherapy and the uncontrolled nature of the comparisons; 4. Relevant patient population. **ERG's alternative base case (tisa-cel vs GDP)**: Using data from PIX301, the ICER varied between £49,964 (CHF63,634) and £62,345 (CHF79,402) per QALY depending on whether the survival for tisa-cel is modelled with the MCM or the one knot spline model for 5 years, followed by general population mortality. Using data from the CORAL extension study, the ICER varied between £67,568 (CHF86,054) and £93,862 (CHF119,542) per QALY depending on whether the survival for tisa-cel is modelled with the MCM or the one knot spline model for 5 years, followed by general population mortality.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
CADTH, Canada			
Optimal Use Report, Vol.9 Issue 1D[18]	Adult patients with LBCL (median age 58 years) that is refractory or has relapsed after 2 or more lines of systemic therapy and who are ineligible for autologous SCT or relapsed after autologous SCT.	**Intervention:** axi-cel. **Comparator:** BSC, defined as a combination of salvage mono-chemotherapies, specifically, gemcitabine, etoposide and cyclophosphamide. *Note: The clinical expert consulted by CADTH raised concerns as to whether the salvage chemotherapy regimens used in SCHOLAR-1 adequately reflect current contemporary practice.*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model**: 3-state PSM that included the following health states: progression free, progressed disease, and death. *Note: Methodological concerns remain with the use of a PSM. The use of mixture cure rates in the PSM limits transparency, given that there is no explicitly defined state of cure in PSM. CADTH noted the estimated cure fraction used is highly uncertain.* **Data sources (efficacy)**: OS and PFS for axi-cel arm derived from IPD from ZUMA-1 using an MCM.[12] OS for the comparator was derived by fitting a parametric survival model on selected IPD from SCHOLAR-1.[13] PFS for the comparator was derived from OS, by applying a time-dependent HR. *Note: The clinical expert consulted by CADTH considered a 5-year cure point to be appropriate.* **Time horizon**: Lifetime horizon (44 years). **Discount**: 1.5% p.a. for costs and effects. **Results**: **Manufacturer's submission**: The manufacturer reported that the associated ICUR was $84,030 (CHF61,787) per QALY for axi-cel compared with BSC. Axi-cel is cost-effective nearly 90% of the time under a $100,000 (CHF73,530) per QALY WTP threshold. **CADTH Revised Base Case**: The ICUR of axi-cel compared with BSC is estimated to be $226,131 (CHF166,275) per QALY gained. The probability that axi-cel is cost-effective was 0% at a WTP threshold of $50,000 (CHF36,765) per QALY. **Limitations identified with the Manufacturer's Economic Submission**: 1. Lack of head-to-head comparative efficacy and safety of axi-cel, salvage chemotherapy and tisa-cel; 2. Generalisability of the patient population; 3. Approach to model cured patients inappropriate; 4. Inappropriate modelling and distributional assumptions in estimating OS; 5. Approach to censoring due to subsequent treatment or retreatment; 6. Inconsistencies in modelling the pre-infusion and infusion period; 7. Uncertainty in PFS in the comparators; 8. Uncertainty around the costs of tisa-cel; 9. Long-term costs and implementation costs underestimated.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
Optimal Use Reort, Vol. 8. No. 3e[19]	Adult patients with r/r DLBCL who are ineligible for or relapse after autologous SCT. (Average age of 54 years at model entry)	**Intervention:** tisa-cel. **Comparator:** salvage chemotherapy (assumed to consist of rituximab, gemcitabine, cisplatin and dexamethasone). *Note: CADTH noted that it is unclear whether the salvage chemotherapy regimens used in the SCHOLAR-1 trial represent standard practices in Canada (specific salvage chemotherapies used in the included evidence is NR). CADTH felt it would have been more appropriate to derive PFS and OS from the LY-12 and CORAL studies, which included treatments widely available in Canada (R-GDP, R-ICE and R-DHAP).*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM which included the following health states: progression free, progressed disease, and death. Cycle length of 1 month. **Data sources (efficacy)**: OS and PFS for tisa-cel derived by fitting parametric curves to pooled IPD from JULIET and Schuster et al. (2017).[15,16] For salvage chemotherapy, the OS data were based on a parametric survival model fitted using SCHOLAR-1, while PFS was derived from OS based on the assumptions of a constant cumulative HR between OS and PFS. *Note: CADTH noted that the impact of subsequent SCT was only partially accounted for.* **Time horizon:** 20 years. **Discount**: 1.5% p.a. for costs and effects. **Results**: **Manufacturer's base case**: The manufacturer reported that the ICER of submitted tisa-cel vs salvage chemotherapy is CA$143,018 (CHF105,188) per QALY. **CADTH reanalysis suggested** an ICUR of CA$211,870 (CHF155,828) per QALY. The probability that tisa-cel is cost-effective was 0% at a WTP threshold of CA$50,000 (CHF36,774) per QALY and 1.8% at a WTP threshold of CA$100,000 (CHF73,549) per QALY. **Limitations identified with the Manufacturer's Economic Submission**: 1. Lack of head-to-head comparative efficacy and safety of tisa-cel and salvage chemotherapy; 2. Salvage chemotherapy regimens used in the SCHOLAR-1 study were not specified; 3. Total cost of tisa-cel was underestimated; 4. Impact of subsequent SCT was partially accounted in the model; 5. Probabilistic and uncertainty analyses were based on unjustified assumptions of variation; 6. Model parameters were assumed to be independent; 7. Heterogeneity of patient characteristics impacting treatment effectiveness was not considered; 8. Reference case is non-probabilistic; 9. Lack of consistency in the use of PFS definitions.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
Optimal Use Report, Vol. 8 No. 3f[20]	Paediatric and young adult patients (3–25 years of age) with r/r B-ALL. The modelled patients were assumed to be, on average, 12 years of age (SD 5.2 years) at model entry.	**Intervention**: tisa-cel. **Comparator**: salvage chemotherapy. *Note: CADTH had concerns around the generalisability of OS data from the von Stackelberg et al. (2011) study to Canadian patients. Moreover, CADTH noted that the impact of subsequent SCT was only partially captured. Only costs and disutility were accounted for; potential impacts of SCT in delaying progression and improving patient survival were not considered.*	**About**: Manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM that included the following health states: event free, progressive disease, and death. Cycle length of 1 month. EFS defined as the earliest among death, relapse and treatment failure. **Data sources (efficacy)**: OS and EFS for tisa-cel derived by fitting parametric curves to pooled IPD from ELIANA, ENSIGN, and B2101J.[7-9] For salvage chemotherapy, the OS data were based on parametric survival model fitted to data from the curative arm of the von Stackelberg et al. (2011) study.[21] EFS for the comparator was estimated from OS by assuming a constant HR between OS and EFS over time. From year 5 onwards, the predicted OS based on the literature of ALL long-term survivors was applied to both arms. *Note: CADTH suggested it was inappropriate to pool data from ELIANA, ENSIGN, and B2101J trials due to differences in cell doses and study designs.* **Time horizon:** 70 years. **Discount**: 1.5% p.a. for costs and effects. **Results**: **The manufacture's probabilistic analysis** showed an ICER of CA$42,093 (CHF30,959) per QALY gained, when comparing tisa-cel with salvage chemotherapy. The PSA results revealed that at a WTP threshold of CA$50,000 (CHF36,774) per QALY gained, the probability of tisa-cel being cost effective was 85.9%; this probability increased to 100% if the WTP value was CA$80,000 (CHF58,839) per QALY gained. **CADTH revised base case**: an ICUR of CA$53,269 (CHF39,179) per QALY. The probability that tisa-cel was cost-effective was 44.2% and 99.1% at a WTP threshold of CA$50,000 (CHF36,774) and CA$100,000 (CHF73,549) per QALY, respectively. Uncertainties included: 1. Comparative effects relative to salvage chemotherapy; 2. Impact of potential delays to receive tisa-cel; 3. Likely rate of manufacturing failure in practice; 4. Information on the use of tisa-cel in different stages of therapy; 5. Lack of longer-term clinical evidence for tisa-cel; 6. Impact on capacity constraints at health care facilities (and potential opportunity costs for delay of treatment for other patients). **Conclusions**: The manufacturer's model was unnecessarily complex and lacked transparency.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
INESSS, Canada			
None provided[22]	Adults with r/r DLBCL.	**Intervention:** tisa-cel. **Comparator:** salvage chemotherapy.	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM that included the following health states: PFS, progressive disease, and death. *Note: INESSS felt it would have been relevant to model a decision tree for the tisa-cel arm to consider the fact that certain patients selected will not receive the therapy.* **Data sources (efficacy)**: JULIET and Schuster et al. (2017) for tisa-cel,[15,16] SCHOLAR-1 for comparator,[13] with safety data for salvage chemotherapies from the literature. After 39 months it was assumed the probability of death in the tisa-cel arm was equal to OS data from SCHOLAR-1. *Note: INESSS did not retain the study by Schuster et al. (2017); only the JULIET study was considered. Probabilities of death between the 2 arms were set equal after 24 months. Safety data for the comparator was taken from LY-12 study. INESSS felt use of SCHOLAR-1 to estimate deaths may overestimate long-term OS of patients receiving salvage chemotherapy.* **Time horizon:** 20 years. **Discount:** 1.5% p.a. for costs and effects. **Results**: **Scenarios proposed by INESSS**: Compared to salvage chemotherapy, tisa-cel incurred an ICUR of CA$174,814 (CHF128,541) per QALY gained for Scenario 1 (parametric distributions), and CA$288,346 (CHF212,021) per QALY gained for Scenario 2 (based on the lower limit of the confidence interval). **No ICUR data available according to the manufacturer.** **Conclusions**: INESSS considered that the submitted and available evidence was too immature to confidently recognise the therapeutic value of this therapy. However, they did recognise the severity of the disease and the significance of the unmet need. The members of the deliberative committee are of the opinion that this therapy should be available for r/r DLBCL patients, but only with coverage conditions that take into account the high degree of uncertainty regarding the situation. Uncertainties included long-term clinical benefits and safety of tisa-cel.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
None provided[23]	Children and young adults with r/r B-ALL.	**Intervention:** tisa-cel **Comparator**: salvage chemotherapy; and in sensitivity analyses: clofarabine monotherapy, clofarabine based regimens and blinatumomab. *Note: INESS felt, regarding the comparison with salvage chemotherapy—von Stackelberg et al. (2011)—comparisons with tisa-cel data are difficult as recruitment took place >20 years ago, in which time clinical practice (e.g. with regard to SCT) has evolved. Only the clofarabine-based regimen and blinatumomab were retained.*	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM that included the following health states: event free, progressive disease, and death. *Note: INESSS felt it would have been relevant for a decision tree to be modelled for the tisa-cel arm to take into account the patients who do not receive an infusion.* **Data sources (efficacy)**: for tisa-cel, OS and PFS from B2202, B2205J and B2101J; for the comparator, OS from Hijiya et al. (2011) for clofarabine-based regimen and von Stackelberg et al. (2016) for blinatumomab.[24,25] PFS for comparators derived from OS curves. After 5 years, patients still alive were assumed to be cured. *Note: INESSS felt it was not appropriate to combine data from studies B2202, B2205J and B2101J, and retained data from B2202 only.* **Time horizon:** 70 years. **Discount:** 1.5% p.a. for costs and effects. **Results**: **Cost-Utility Analysis submitted by Manufacturer**: Data unavailable. **Scenarios proposed by INESSS:** **Scenario 1**: Resulting ICUR is CA$53,552 (CHF39,377) per QALY gained compared to the clofarabine-based regimen and CA$62,074 (CHF45,643) per QALY gained compared to blinatumomab. **Scenario 2 (lower limit of the confidence interval)**: Resulting ICUR is CA$92,805 (CHF68,240) per QALY gained compared to the clofarabine-based regimen and CA$108,241 (CHF79,590) per QALY gained compared to blinatumomab. **Conclusions**: INESSS recognised that this therapy should be administered to patients with r/r B-ALL for an economic burden mitigation measure.

HTA identifier	Population	Intervention and comparator(s)	Summary of the economic evidence considered
None provided[26]	Adults with r/r LBCL.	**Intervention**: axi-cel. **Comparator:** salvage chemotherapies.	**About**: manufacturer's submission **Analysis**: Incremental cost per QALY gained **Model:** 3-state PSM. **Data sources (efficacy):** Survival data for axi-cel and salvage chemotherapy derived from an unanchored adjusted indirect comparison of data from ZUMA-1 and SCHOLAR-1.[12,13] This data were extrapolated using: for axi-cel, both parametric models and MCMs (given the potentially curative nature of axi-cel); for the comparator, only parametric models (*according to experts consulted, salvage chemotherapy cannot be considered curative).* **Time horizon**: lifetime (44 years) used by manufacturer; *INESSS used a 20-year horizon in their update.* **Discount**: 1.5% p.a.for costs and effects. **Results**: **According to the manufacturer**, the ICUR is unknown. **INESS**: The ICUR of axi-cel compared to salvage chemotherapies would range from CA$156,000 (CHF114,707) per QALY gained, recognising that the therapy is curative, to CA$350,000 (CHF257,356) per QALY gained otherwise. The results of the probabilistic analysis showed there is a probability of <1% that the ratio is below CA$100,000 (CHF73,530) per QALY. This same probability reaches 56% for a ratio of <CA$200,000 (CHF147,060)/QALY. **Conclusions**: INESS felt it was still too early to definitively attribute an incremental therapeutic value to axi-cel when compared to salvage chemotherapy or tisa-cel. INESS stated there is considerable uncertainty regarding axi-cel's long-term safety, mainly with respect to neurologic toxicities and to potential treatment-related sequelae, including, but not limited to, risk of a second cancer and neurological sequelae.

Abbreviations:

AE = adverse event, **ALL** = acute lymphoblastic leukaemia, **axi-cel** = axicabtagene ciloleucel, **B-ALL** = B-cell acute lymphoblastic leukaemia, **BSC** = best supportive care, **CADTH** = Canadian Agency for Drugs and Technologies in Heath, **CAR T** = chimeric antigen receptor T cell, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B cell lymphoma, **EFS** = event free survival, **ERG** = evidence review group, **GDP** = gross domestic product, **GEM** = gemcitabine and methylprednisolone, **GEM-P** = gemcitabine, methylprednisolone, and cisplatin, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **ICER** = incremental cost-effectiveness ratio, **ICUR** = incremental cost-utility ratio, **INESSS** = Institut National d'Excellence en Santé Sociaux, **IPD** = individual patient data, **ITT** = intention to treat, **IVIG** = intravenous immunoglobulins, **LBCL** = large B cell lymphoma, **MCM** = mixture cure model, **mITT** = modified intention-to-treat, **NICE** = National Institute for Health and Care Excellence, **NR** = not reported, **OS** = overall survival, **PAS** = patient access scheme, **PFS** = progression free survival, **PMBCL** = primary mediastinal B cell lymphoma, **PSM** = partitioned survival model, **QALY** = quality-adjusted life year, **RGCVP** = rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone, **r/r** = relapse or refractory, **R-GDP** = rituximab, gemcitabine, dexamethasone, cisplatin, **R-GEMOX** = rituximab, gemcitabine, oxaliplatin, **RVP** = rituximab, vinblastine, and prednisolone, **SCT** = stem cell transplantation, **SD** = standard deviation, **tisa-cel** = tisagenlecleucel, **WTP** = willingness to pay.

7.1.5 Questions for clinical experts regarding the comparator therapies

Question
The draft HTA protocol on CAR T cell therapies identifies a range of 'standard care' alternatives to CAR T. It will not be possible to model the clinical or cost-effectiveness for all possible treatment options in each patient group; for the purposes of conducting the evaluation, we need to narrow down this list to the most important or commonly used comparators. The following is a list of potential comparators to CAR-T therapy, when given in the **third-line** setting. We ask that you identify the one or two **most relevant** or **most commonly used** comparators, based on your experience: ***Paediatric ALL:*** • Blinatumomab • Inotuzumab • Chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Tyrosine kinase inhibitor • Palliation • Other (please specify) ***Adult DLBCL:*** • Salvage chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Salvage chemotherapy followed by high-dose therapy and autologous SCT (if selected, please specify which chemotherapy regimen/(s) would be most commonly prescribed) • Palliation • Other (please specify) ***Adult PMBCL:*** • Salvage chemotherapy (if selected, please specify which regimen/(s) would be most commonly prescribed) • Salvage chemotherapy followed by high-dose therapy and autologous SCT (if selected, please specify which chemotherapy regimen/(s) would be most commonly prescribed) • Palliation • Other (please specify)

7.1.6 Additional economic studies

Table 15 Evidence table for the additional economic studies

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Badaracco, 2023[27]	United States, healthcare system	2020, US$	This study used clinical and economic inputs informed from secondary literature to estimate costs associated with grade 1–2 or grade ≥3 CRS or NEs in patients with r/r LBCL treated in the third- or later-line setting. Average per patient costs were estimated separately for liso-cel, axi-cel and tisa-cel.	Weighted average per-patient costs for CRS or NE management: $18,718 (CHF17,398), $47,665 (CHF44,304) and $42,538 (CHF39,538) for liso-cel, axi-cel and tisa-cel, respectively. Weighted average per-patient cost per CRS event: $8,213 (CHF7,634), $20,442 (CHF19,001) and $26,009 (CHF24,175). Weighted average per-patient cost per NE was $10,505 (CHF9,764), $27,223 (CHF25,303) and $16,528 (CHF15,363).	Per-patient costs for CRS or NE management were shown to differ between CAR T therapies owing to differences in incidence rates and symptom severity. These findings highlight the economic implications of differences in safety among CAR T-cell therapies.
Broder, 2020[28]	United States, healthcare payer	2019, US$	This study generated an evidence-based list of r/r DLBCL treatment-related neurologic AEs (across CAR T-cell therapy, high-intensity cytotoxic therapy, low-intensity cytotoxic therapy, targeted therapy). A retrospective cohort claims analysis—across 3 databases—was then undertaken to estimate rates of neurologic AEs and total healthcare costs for patients with and without neurologic AEs within 30 days of treatment.	A final list of 11 neurologic AEs consistent with ICANS were defined for the retrospective claims analysis. Of 11,098 patients (≥18 years) with r/r DLBCL, 299 (2.7%) had ≥1 neurologic AE, including 43/118 (36.4%) after CAR T-cell therapy. For patients who received CAR T-cell therapy, mean healthcare costs of $419,662 (CHF409,420) and $276,353 (CHF269,608) for those with or without NE were reported. Mean healthcare costs stratified by NE occurrence were also reported for high-intensity cytotoxic therapy, low-intensity cytotoxic therapy, targeted therapy regimens (data NR).	The study confirmed that patients with NE have higher healthcare costs than patients without NE. This is true regardless of treatment type, but the difference is greatest in patients receiving CAR T-cell therapy.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Chacim, 2022[29]	Portugal; healthcare provider	2019, €	This study estimated costs associated with CAR T-cell therapy among 20 adult patients with r/r DLBCL (n=14), PMBCL (n=3) or TFL (n=3) who underwent leukapheresis with the intent to receive CAR T-cell therapy (axi-cel [n=13] or tisa-cel [n=7]) between May 2019 and February 2021 (follow-up until March 2021) in IPO-Porto. Total medical costs and costs per activity reported across all patients.	Median total costs for treated patients: €355,165 (CHF387,894), or €10,667 (CHF11,650) when excluding CAR T-cell drug costs. CAR T-cell drug costs accounted for 97.0% of overall medical costs. Excluding CAR T-cell acquisition costs, inpatient care and diagnostic-therapeutic procedures accounted for 57% and 38% of total cost/patient, respectively.	This study highlights the heavy economic burden of CAR T cell therapy driven by drug acquisition costs.
Foglia, 2023[30]	Italy; hospital	2019, €	This study evaluated the cost and organisational impacts of using CAR T vs BSC for treatment of DLBCL patients in third-line therapy over 3 years. Cost and resource data from 47 third-line lymphoma patients were collected from 2 Italian hospitals. Mean cost per patient was reported.	BSC pathway required fewer resources compared to CAR T (excluding therapy cost), with BSC costing €29,558.41 (CHF32,282.29) and CAR T costing €71,220.84 (CHF77,784.03), resulting in a 58.5% cost difference.	This study highlights the necessity for specific reimbursement tariffs at both the hospital and NHS levels, as there is currently no consensus on appropriate compensation for hospitals that offer CAR T therapy at added risks and costs.
Huguet, 2021[31]	France; National Health Insurance	Costing year NR, €	This study assessed the cost of hospital stay for CAR T infusion. Data on 485 hospital stays collected from the French Medical Information Systems Program (PMSI) between January 2019 and December 2020 were categorised into 3 groups: tisa-cel for ALL (n=44), tisa-cel for DLBCL (n=139), and axi-cel (n=302). Average costs per hospital stay for CAR T infusion were estimated separately for the 3 groups.	Mean (95% CI) costs per hospital stay: • tisa-cel in ALL: €372,400 (CHF395,360) (€360,045–€384,754) (CHF 382,244–408,476) • tisa-cel in DLBCL: €342,903 (CHF364,045) (€339,188–€346,617) (CHF360,101–367,988) • axi-cel: €366,562 (CHF389,162) (€364,457–€368,667) (CHF 386,928–391,397) CAR T cell therapy expenses accounted for >80% of these costs with €303,916.9 (CHF 322,654.9) for tisa-cel and €333,867 (CHF 354,452) for axi-cel.	This research contributes important original data, as there is limited information available about the costs of hospitalisation for CAR T cell treatments.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Jakobs, 2022[32]	Germany; healthcare payer	2021, €	This study evaluated the expected costs and benefits along the efficiency frontier of third-line treatments for DLBCL, including 17.7% (n=11) in BSC, 22.6% (n=14) in allogeneic SCT, 27.4% (n=17) in axi-cel and 32.3% (n=20) in tisa-cel. Costs were retrieved from the university hospitals Cologne and Hamburg-Eppendorf. Clinical benefits of allogeneic SCT, CAR T (tisa-cel and axi-cel) and BSC (in terms of median OS) were derived from a systematic literature review in PubMed. Median values of costs and benefits (measured as median OS) were reported.	Median OS varied from 6.3 months in BSC to 23.5 months in CAR T (axi-cel). Median (range) real-world treatment costs: • BSC: €26,918 (CHF28,941) (0–66,468) (CHF 0–71,464) • CAR T (axi-cel): €340,458 (CHF366,046) (316,272–502,096) (CHF 340,042–539,832) • CAR T (tisa-cel): €310,496 (CHF 333,832) (294,113–557,423) (CHF 316,218–599,318) Allogeneic SCT: €73,829 (CHF79,378) (61,337–133,280) (CHF 65,947–143,297)	Shown by the efficiency frontier, CAR T (axi-cel) and allogeneic SCT were the most efficient interventions in terms of survival benefit and cost. This study suggests that innovative treatments (e.g. CAR T) should be priced based on their efficiency compared to other appropriate options.
Keating, 2022[33]	United States; the primary payer varied across databases (commerical insurance, Medicare or Medicare supplemental insurance)	2019, US$	This study retrospectively investigated the HCRU, costs, and safety of CAR T therapy as the third-line treatment for adult patients with r/r DLBCL, using data from 3 US commercial claims databases. All HCRU and mean inpatient, outpatient, pharmacy and total costs per patient were assessed within the first 3 months after CAR T infusion. HCRU and costs were stratified by groups of patients experiencing AEs of interest, such as CRS and NEs.	Within the first 3 months after CAR T cell infusion: • Mean total inpatient hospital days ranged from 17 to 22 days; slightly longer in patients who experienced CRS (18 to 23 days; n=155) or NEs (20 to 25 days; n=125); longer for patients with severe CRS or NE. • 14% to 19% of patients were admitted to the emergency room, and 20% to 37% were readmitted as inpatients. • Mean total costs of care ranged from $379,627 (CHF370,362) to $525,772 (CHF512,940) across databases.	This study demonstrates the high costs associated with CAR T therapy in the real-world setting. In particular, costs and HCRU were increased in the presence and increasing severity of AEs, such as CRS or NEs.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Lyman, 2020[34]	United States; health care practitioner	2018, US$	This study created a decision-tree model using inputs from secondary literature to estimate total cost of CAR T cell administration and acute AE management in different settings (i.e. academic inpatient hospital vs non-academic specialty oncology network). Hypothetical adult patients with r/r LBCL who received CAR T cell therapy were evaluated. Average per patient costs were reported and compared.	Average total cost of care: • Academic hospital inpatient setting: $454,611(CHF433,972) (95% CI, $452,466–$458,267) (CHF431,924–437,462) • Nonacademic specialty oncology network setting: $421,624 (CHF402,482) (95% CI, $417,204–$422,325) (CHF 398,263–403,152) • Difference of $32,987 (CHF31,489). After excluding the CAR T cell acquisition cost, hospitalisation and office visit costs were $53,360 (CHF50,937) (65.3% of total cost) and $23,526 (CHF22,458) (48.4% of total cost), respectively.	The cost difference was mainly due to hospitalisation and office visit costs. This study suggests that CAR T cell therapies with outpatient options available could potentially reduce the total costs.
Maziarz, 2022[35]	United States; no perspective indicated	2020, US$	This study compared non-CAR T costs, HRU, and rates of AEs associated with tisa-cel and axi-cel for the treatment of r/r DLBCL during the infusion encounter and follow-up periods. Data were extracted from the Premier Healthcare Database from 2017 to 2020 (tisa-cel n=33; axi-cel n=86).	Infusion encounter: • Mean inpatient LOS: Tisa-cel: 11.3 days; Axi-cel: 18.3 days. • Non-CAR T costs: Tisa-cel: $27,594.8 (CHF25,649.0); Axi-cel: $51,378.3 (CHF47,755.4). Monthly followups: • Mean inpatient LOS: Tisa-cel: 3.9 days; Axi-cel: 6.9 days. • Non-CAR T costs: Tisa-cel: $28,777.3 (CHF26,748.1); Axi-cel: $46,575.7 (CHF43,291.4). Grade ≥3 CRS rates within the 1-month period post-infusion: Tisa-cel: 6.1% (n=2); Axi-cel: 15.1% (n=13).	Average inpatient LOS and non-CAR T costs during both the infusion phase and the follow-up phase were shown to differ between CAR T therapies. Although rates of AEs and AE treatments were found to be comparable between the 2 CAR T therapies, significant differences in HRU and costs were highlighted.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Ring, 2022 [36]	Switzerland; University Hospital Zurich	Not applicable. Comparative costs were reported in percentages.	This paper compared resource consumption and costs associated with CAR T treatment (n = 1,041 processes) vs high-dose chemotherapy followed by autologous SCT (n = 1,535 processes) for r/r BCL patients. A process model was developed using the ClipMedPPM software. Single-centre data at University Hospital Zurich were collected from 1 March 2020 to 30 November 2020.	• Total treatment costs, including production cost: 63% higher, for CAR T vs ASCT. When excluding production cost, 29% lower. • Average overall treatment time: CAR T 30 days; ASCT 48 days. Therapeutic interventions: 3 cycles of salvage therapy for ASCT vs 1 cycle of bridging therapy for CAR T.	This study underscores the potential benefits of CAR T therapy in terms of cumulative time investment and resource utilisation in Switzerland.
Snyder, 2021 [37]	United States; national level	2020, US$	This study estimated the travel-related economic burden associated with different site-of-care options for patients with r/r DLBCL who receive CAR T as third- or later-line therapy. GIS methods were employed to quantify travel-related economic burden across 3 site-of-care scenarios.	Total national estimated costs associated with traveling and weighted mean costs per patient across 3 site-of-care scenarios: • Academic hospitals only: $21,122,871 (CHF19,633,396), $5368 (CHF4,989) • Academic and community multispecialty hospitals only: $17,099,482 (CHF15,893,716), $4512 (CHF4,194) Any specialised treatment facility: $14,661,012 (CHF13,627,194), $3738 (CHF3,474)	The study highlights the potential economic benefits of expanding access to CAR T cell therapy administration sites beyond academic hospitals, which could substantially reduce travel-related costs and improve access to therapy for patients with r/r DLBCL.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Yang, 2020, ALL [38]	United States; hospital	2019, US$	This study estimated the economic impact of tisa-cel treatment for paediatric r/r ALL, including various cost components from pretreatment to infusion and post-infusion periods, using an economic model. Average per patient costs were reported.	Overall per-patient costs (leukapheresis to 2 months post infustion): $612,779 (CHF597,823). This included: • list price of tisa-cel: $475,000 (CHF463,407) • tisa-cel administration cost: $143 (CHF140) • AE management: $70,968 (CHF69,236) • inpatient and ICU admissions not attributed to AEs: $57,952 (CHF56,538) • laboratory tests and procedures: $5,209 (CHF5,082) • medical professional visits: $1,780 (CHF1,737) • lymphodepleting drugs and their administration: $1,727 (CHF1,685). Costs incurred during the pretreatment, infusion, and follow-up periods were $29,002, $476,659 and $107,118, (CHF28,294, 465,026 and 104,504) respectively.	The cost of care not attributable to the list price of tisa-cel accounted for 22.5% of the total costs. AE management and inpatient and ICU admissions were the main drivers of these additional costs.

Study ID	Setting; perspective	Currency, costing year	Study Overview	Findings	Conclusion/relevance
Yang, 2020, DLBCL[39]	United States; hospital	2019, US$	This study assessed the economic impact of tisa-cel treatment in adult patients with r/r DLBCL. Cost estimates were based on health resource utilisation and safety data from the JULIET trial. An economic model using a fee-for-service approach was employed to assess the total costs from leukapheresis to 2 months post-infusion. Average per patient costs were reported.	Overall per-patient costs: $437,927 (CHF427,239). Disaggregated overall costs included: • list price of tisa-cel: $373,000 (CHF363,896) • administration cost: $143 (CHF140) • additional cost of care: $64,784 (CHF63,203). Additional cost of care included: • AE management: $30,594 (CHF29,847) (47.2%) • inpatient (unrelated to AEs) and ICU admissions (unrelated to CRS): $24,285 (CHF23,692) (37.5%) • lab tests and procedures: $5,443 (CHF5,310) (8.4%) • lymphodepleting drugs and administration: $3,052 (CHF2,978) (4.7%) • medical professional visits: $1,410 (CHF1,376) (2.2%). Costs incurred during the pretreatment, infusion and follow-up periods were $12,363, $374,395 and $51,169 (CHF12,061, CHF365,257, CHF49,920), respectively.	Total cost of tisa-cel treatment was estimated in this analysis, with additional cost of care only accounting for a small proportion (14.8%). The largest cost component was the list price and administration cost of tisa-cel infusion. The main drivers of the additional cost were AE management (47.2%) and inpatient/ICU costs (37.5%).

Abbreviations:
AE = adverse event, **ALL** = acute lymphoblastic leukaemia, **ASCT** = autologous stem cell transplant, **BSC** = best supportive care, **CAR T** = chimeric antigen receptor T-cell, **CHF** = Swiss franc, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B-cell lymphoma, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **ICU** = intensive care unit, **LBCL** = large B-cell lymphoma, **LOS** = length of stay, **NE** = neurologic event, **NR** = not reported, **OS** = overall survival, **r/r** = relapse or refractory, **tFL** = transformed follicular lymphoma, **US** = United States.

7.1.7 Survival outcomes

7.1.7.1 Tisa-cel for B-ALL

7.1.7.1.1 Overall survival

Figure 1 Kaplan-Meier curve with fitted standard parametric distributions, OS for tisa-cel in the treatment of r/r B-ALL

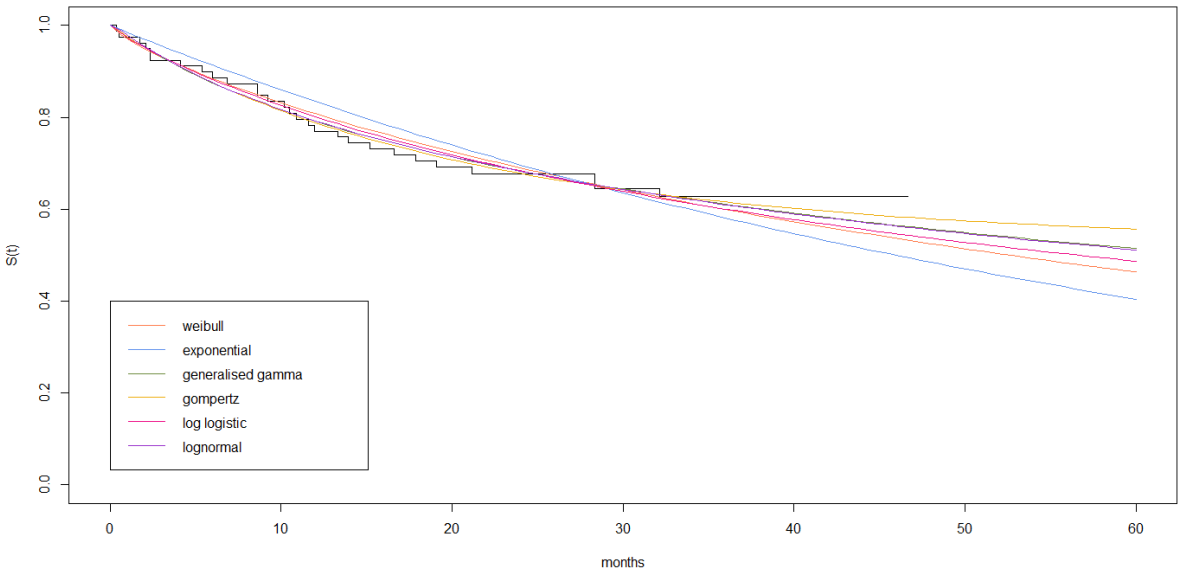

Figure 2 Kaplan-Meier curve with fitted spline-based models, OS for tisa-cel in the treatment of r/r B-ALL

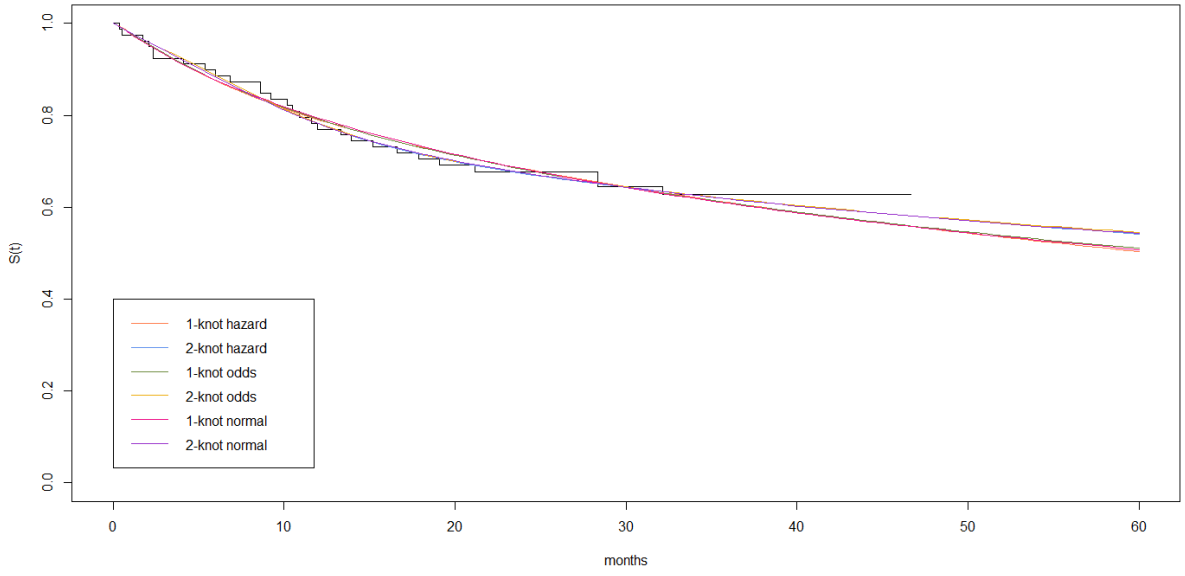

Table 16 Model fit statistics for survival curves, OS for tisa-cel in r/r B-ALL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	293.0978	297.8367	46.3%
Exponential	292.8983	295.2678	40.5%
Generalised gamma	293.8154	300.9237	51.4%
Gompertz	**291.5393**	296.2782	55.7%
Log logistic	292.3491	297.0880	48.7%
Lognormal	**291.8190**	296.5579	51.2%
Spline models			
1-knot hazard	294.0609	301.1693	50.4%
2-knot hazard	294.8308	304.3086	54.2%
1-knot odds	293.9396	301.0480	51.0%
2-knot odds	294.9359	304.4137	54.5%
1-knot normal (probit)	293.8069	300.9152	50.8%
2-knot normal (probit)	294.8715	304.3493	54.3%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.1.2 Event-free survival

Figure 3 Kaplan-Meier curve with fitted standard parametric distributions, EFS for tisa-cel in the treatment of r/r B-ALL

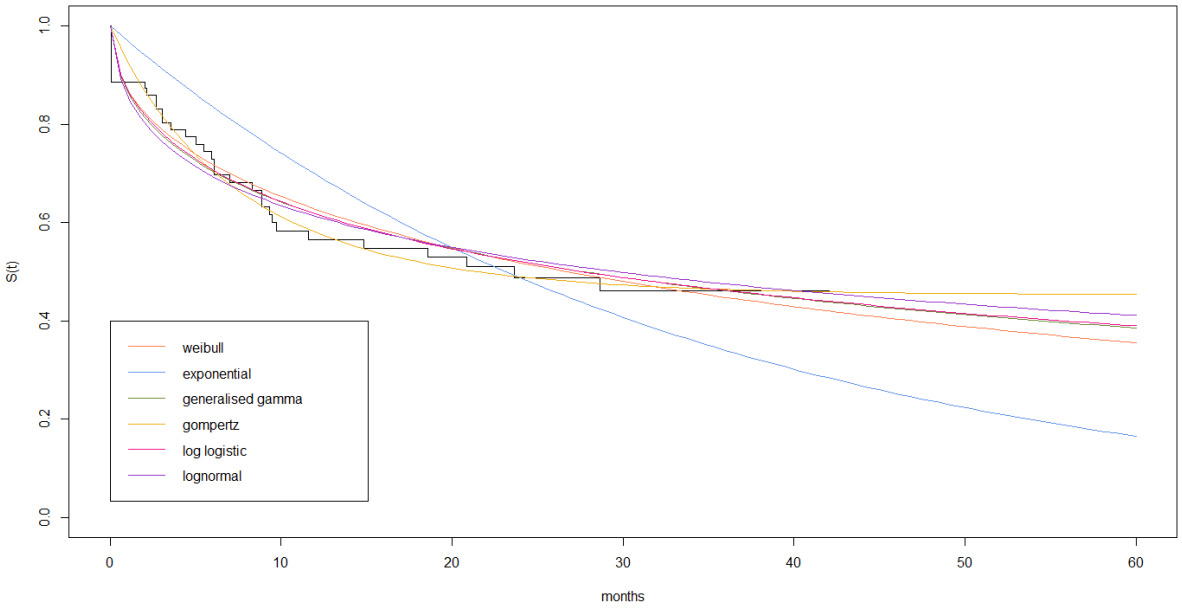

Figure 4 Kaplan-Meier curve with fitted spline-based models, EFS for tisa-cel in the treatment of r/r B-ALL

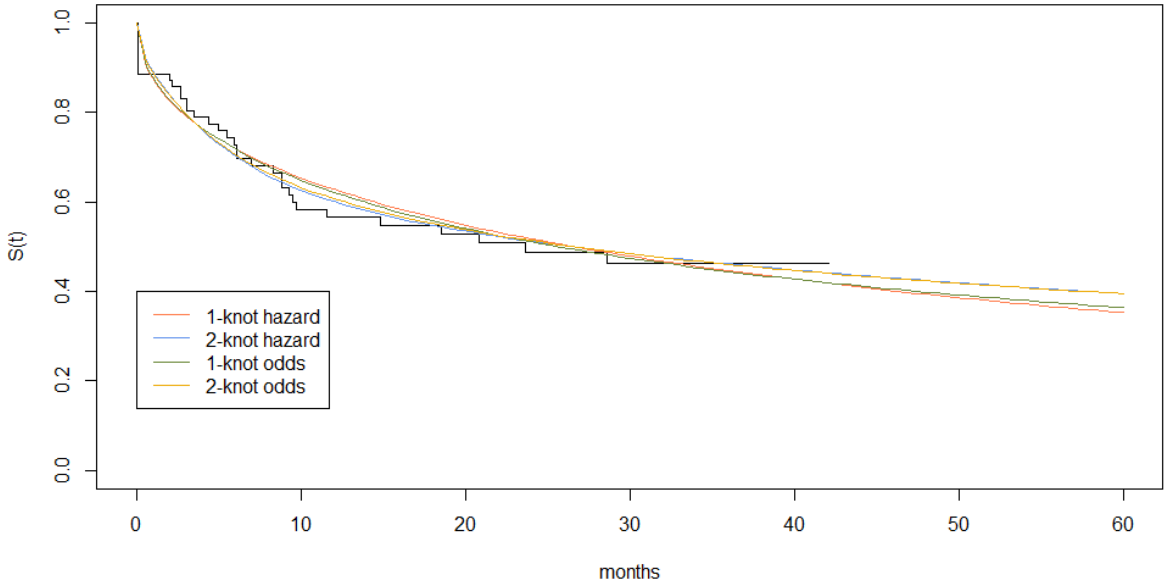

Table 17 Model fit statistics for survival curves, EFS for tisa-cel in r/r B-ALL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	290.0153	294.7542	35.5%
Exponential	317.5441	319.9135	16.6%
Generalised gamma	291.6751	298.7835	38.6%
Gompertz	298.7966	303.5385	45.4%
Log logistic	**289.8626**	294.6015	39.0%
Lognormal	**289.9590**	294.6979	41.1%
Spline models			
1-knot hazard	292.0089	299.1172	35.3%
2-knot hazard	292.4260	301.9038	39.6%
1-knot odds	291.2881	298.3965	36.4%
2-knot odds	292.6413	302.1191	39.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.2 Axi-cel for LBCL

7.1.7.2.1 Overall survival

Figure 5 Kaplan-Meier curve with fitted standard parametric distributions, OS for axi-cel in the treatment of r/r LBCL

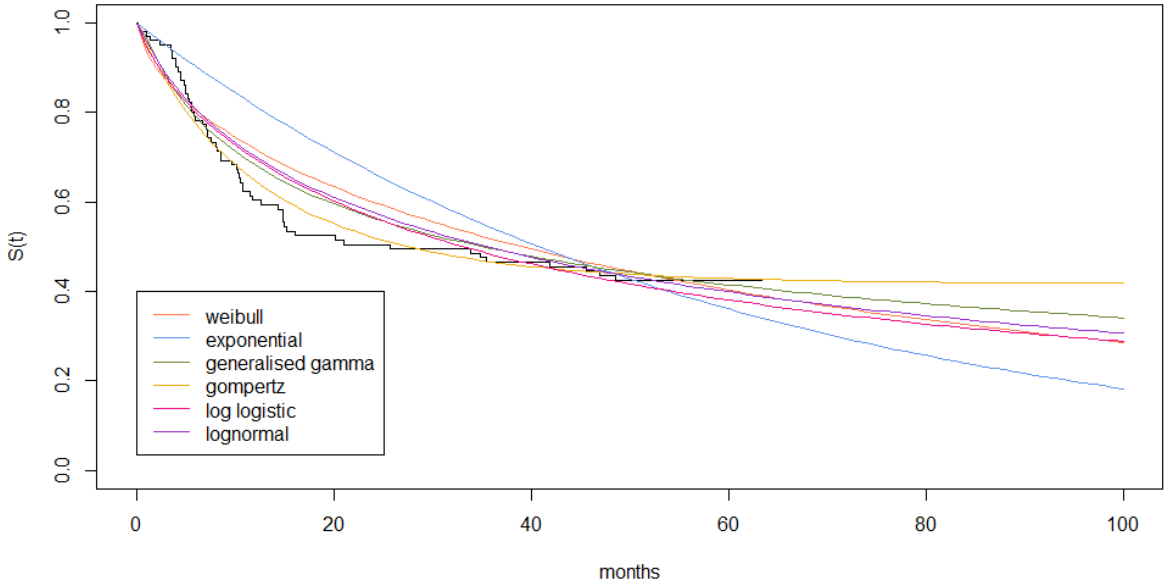

Figure 6 Kaplan-Meier curve with fitted spline-based models, OS for axi-cel in the treatment of r/r LBCL

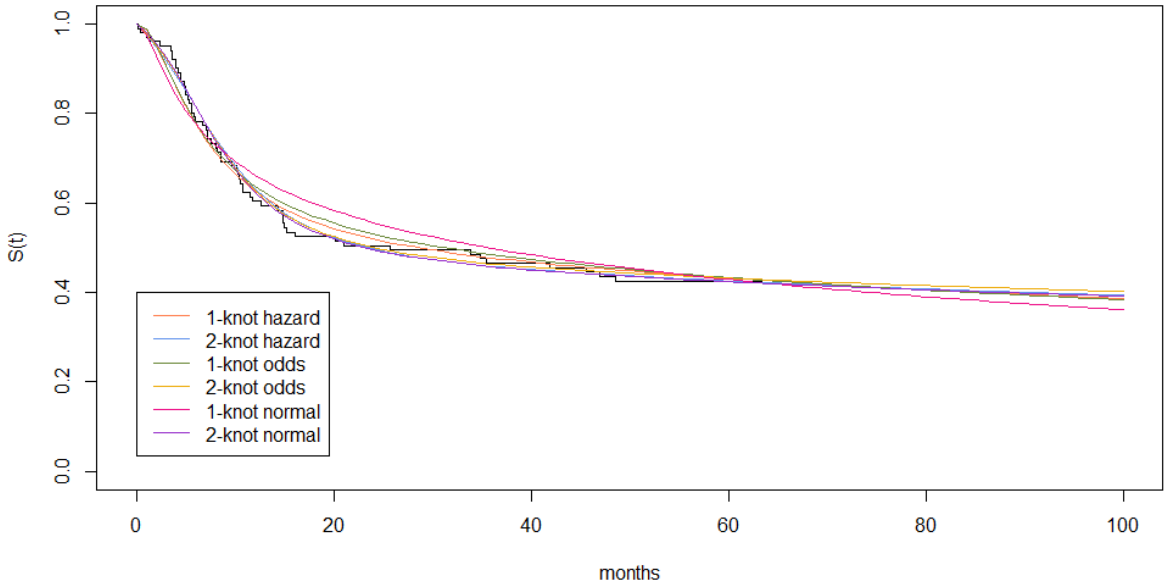

Table 18 Model fit statistics for survival curves, OS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			

Distribution	AIC	BIC	5-year survival probability
Weibull	573.34	578.57	40.4%
Exponential	590.88	593.50	36.1%
Generalised gamma	**561.28**	569.12	41.5%
Gompertz	**550.25**	555.48	42.9%
Log logistic	565.14	570.37	38.1%
Lognormal	**562.29**	567.52	39.9%
Spline models			
1-knot hazard	550.57	558.41	43.2%
2-knot hazard	**546.18**	556.64	42.6%
1-knot odds	551.92	559.76	43.4%
2-knot odds	**545.16**	555.62	43.3%
1-knot normal (probit)	559.42	567.27	42.9%
2-knot normal (probit)	**544.92**	555.38	42.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.2.2 Progression-free survival

Figure 7 Kaplan-Meier curve with fitted standard parametric distributions, PFS for axi-cel in the treatment of r/r LBCL

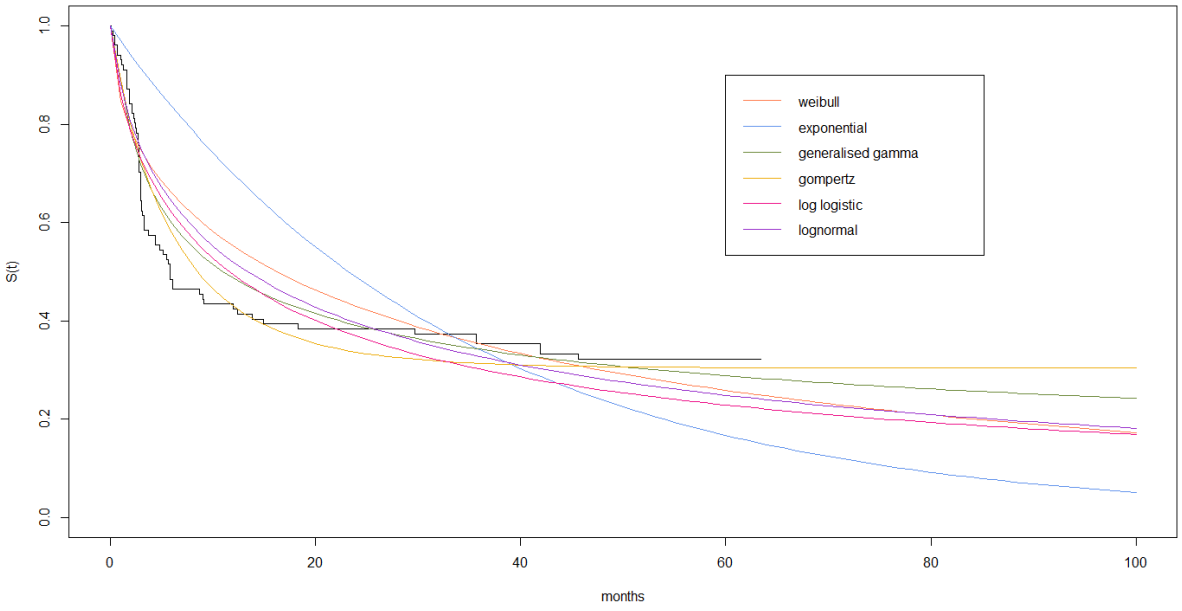

Figure 8 Kaplan-Meier curve with fitted spline-based models, PFS for axi-cel in the treatment of r/r LBCL

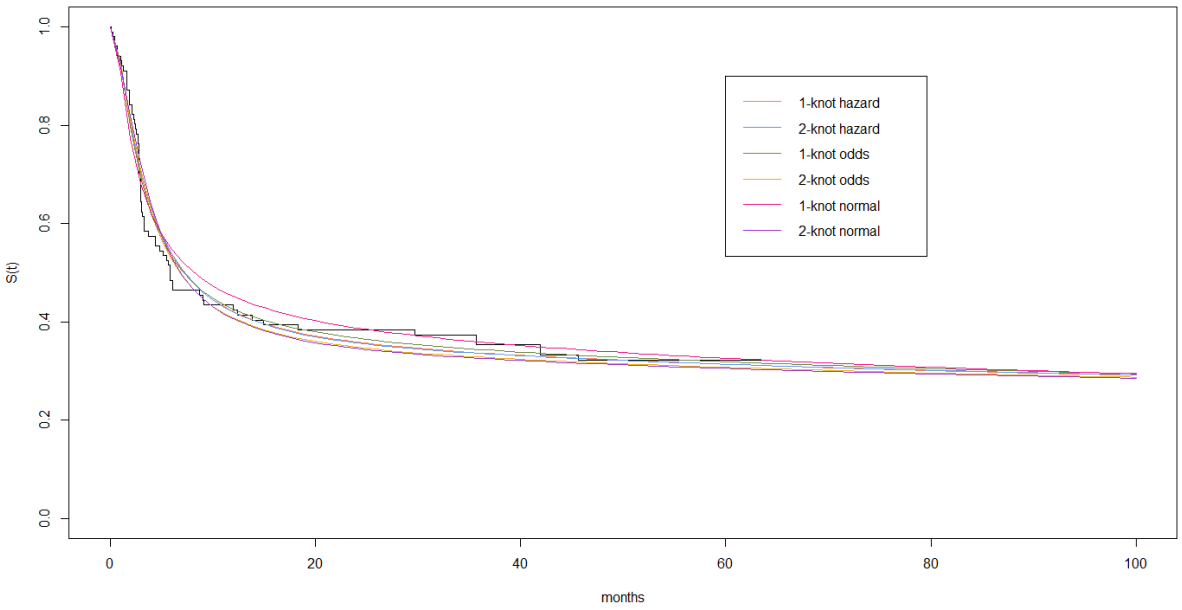

Table 19 Model fit statistics for survival curves, PFS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	560.16	565.39	25.9%
Exponential	615.76	618.37	16.7%
Generalised gamma	527.18	535.02	28.9%
Gompertz	525.41	530.64	30.5%
Log logistic	544.43	549.66	22.9%
Lognormal	540.48	545.71	24.9%
Spline models			
1-knot hazard	**510.51**	518.36	31.4%
2-knot hazard	512.64	523.10	31.4%
1-knot odds	**510.24**	518.08	31.9%
2-knot odds	510.70	521.16	30.7%
1-knot normal (probit)	516.91	524.76	32.6%
2-knot normal (probit)	510.85	521.31	30.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.3 Tisa-cel for LBCL

7.1.7.3.1 Overall survival

Figure 9 Kaplan-Meier curve with fitted standard parametric distributions, OS for tisa-cel in the treatment of r/r DLBCL

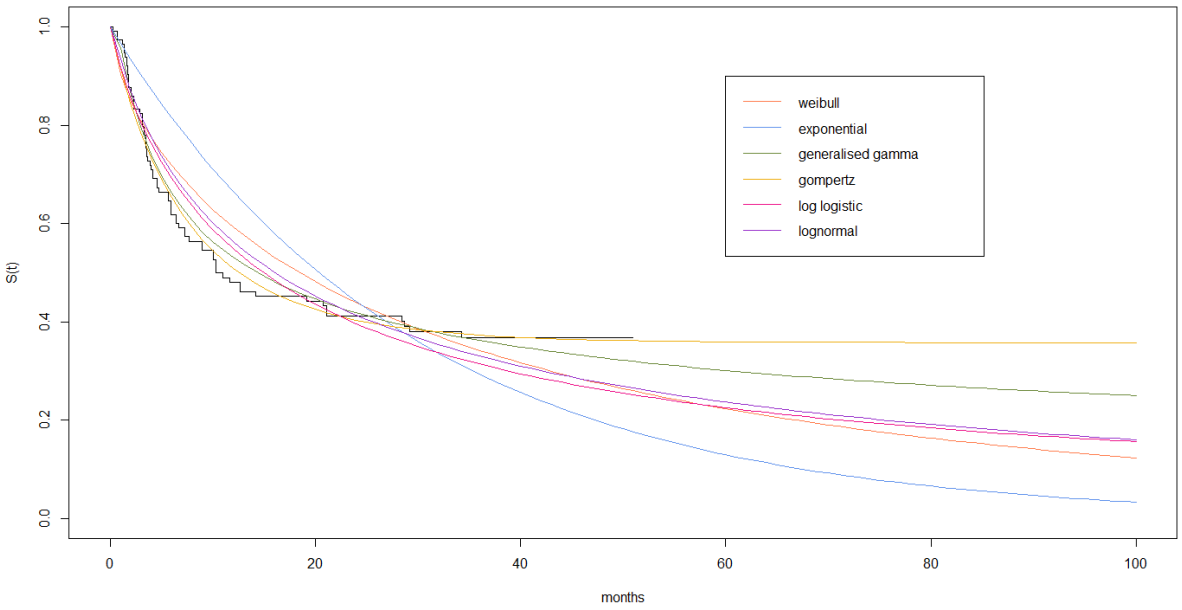

Figure 10 Kaplan-Meier curve with fitted spline-based models, OS for tisa-cel in the treatment of r/r DLBCL

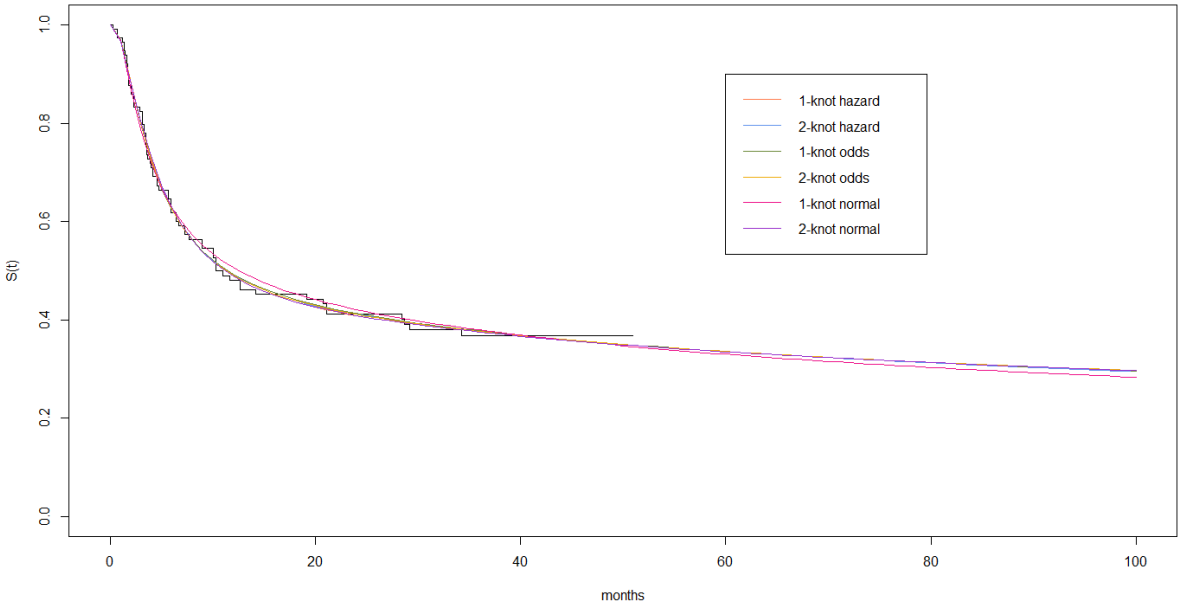

Table 20 Model fit statistics for survival curves, OS for tisa-cel in r/r DLBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	588.12	593.61	22.3%

Distribution	AIC	BIC	5-year survival probability
Exponential	606.58	609.32	13.0%
Generalised gamma	559.23	567.46	30.1%
Gompertz	561.95	657.44	35.9%
Log logistic	575.96	581.45	22.6%
Lognormal	570.93	576.42	23.7%
Spline models			
1-knot hazard	**553.06**	561.20	33.6%
2-knot hazard	555.06	566.04	33.6%
1-knot odds	**552.99**	561.22	33.6%
2-knot odds	555.03	566.01	33.6%
1-knot normal (probit)	554.75	562.99	33.0%
2-knot normal (probit)	555.47	566.45	33.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.3.2 Progression-free survival

Figure 11 Kaplan-Meier curve with fitted standard parametric distributions, PFS for tisa-cel in the treatment of r/r DLBCL

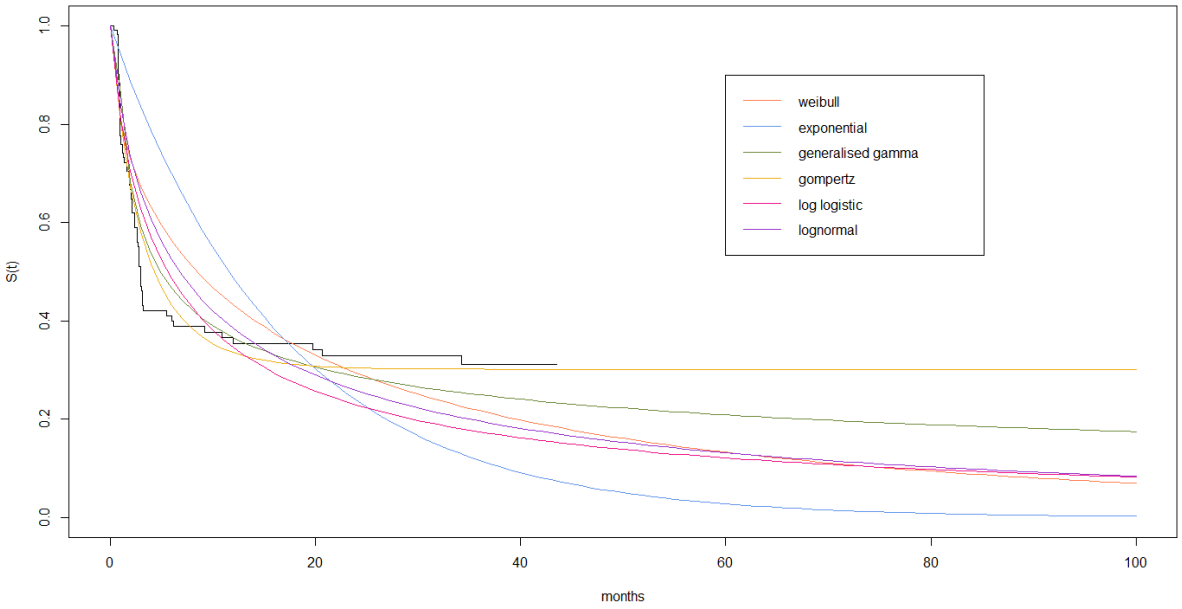

Figure 12 Kaplan-Meier curve with fitted spline-based models, PFS for tisa-cel in the treatment of r/r DLBCL

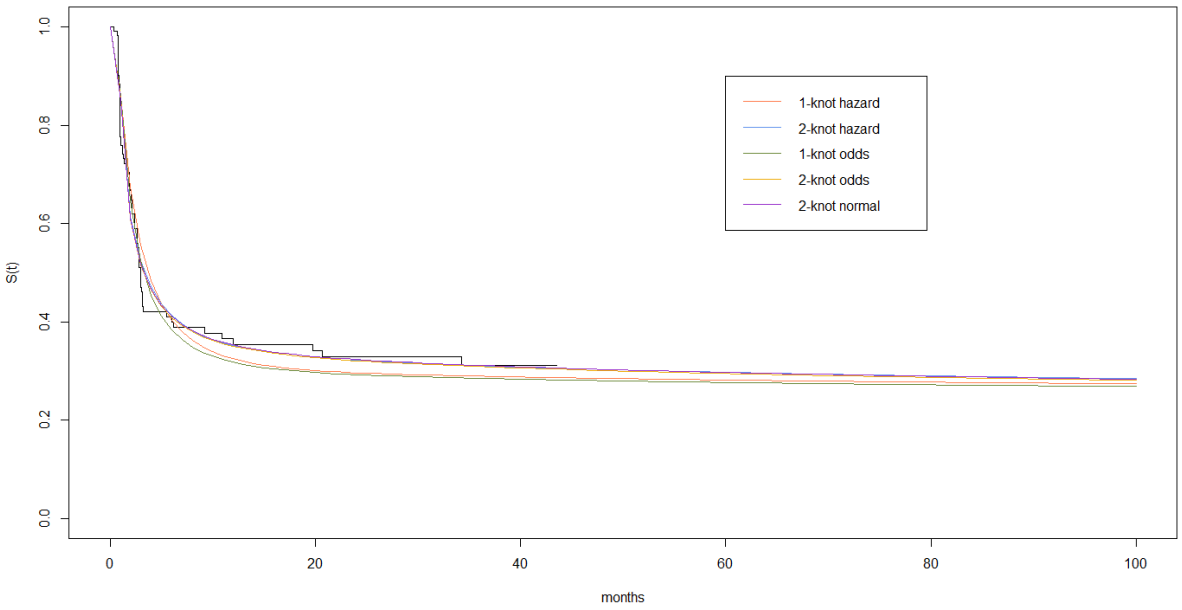

Table 21 Model fit statistics for survival curves, PFS for tisa-cel in r/r DLBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	491.99	497.48	13.3%
Exponential	544.13	546.87	2.8%
Generalised gamma	411.49	419.73	20.9%
Gompertz	440.60	446.90	30.1%
Log logistic	469.34	474.83	12.1%
Lognormal	464.38	469.87	13.2%
Spline models			
1-knot hazard	415.56	423.79	28.2%
2-knot hazard	**401.78**	412.76	29.7%
1-knot odds	408.84	417.08	27.7%
2-knot odds	400.26	411.24	29.5%
2-knot normal (probit)	**399.01**	409.98	29.7%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.4 Blinatumomab for B-ALL

7.1.7.4.1 Overall survival

Figure 13 Kaplan-Meier curve with fitted standard parametric distributions, OS for blinatumomab

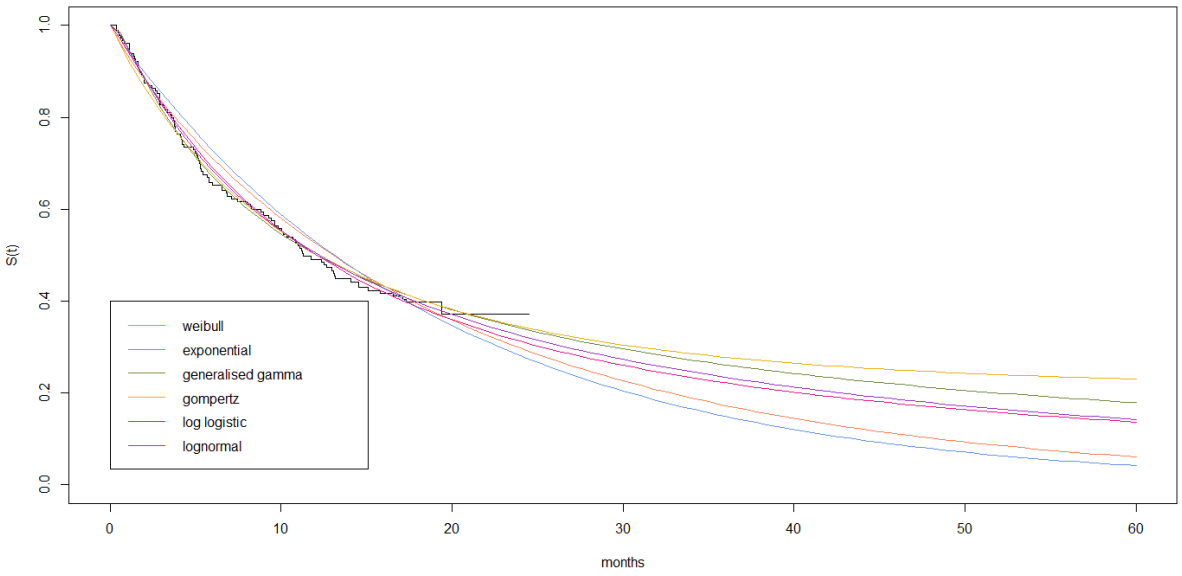

Figure 14 Kaplan-Meier curve with fitted spline-based models, OS for blinatumomab

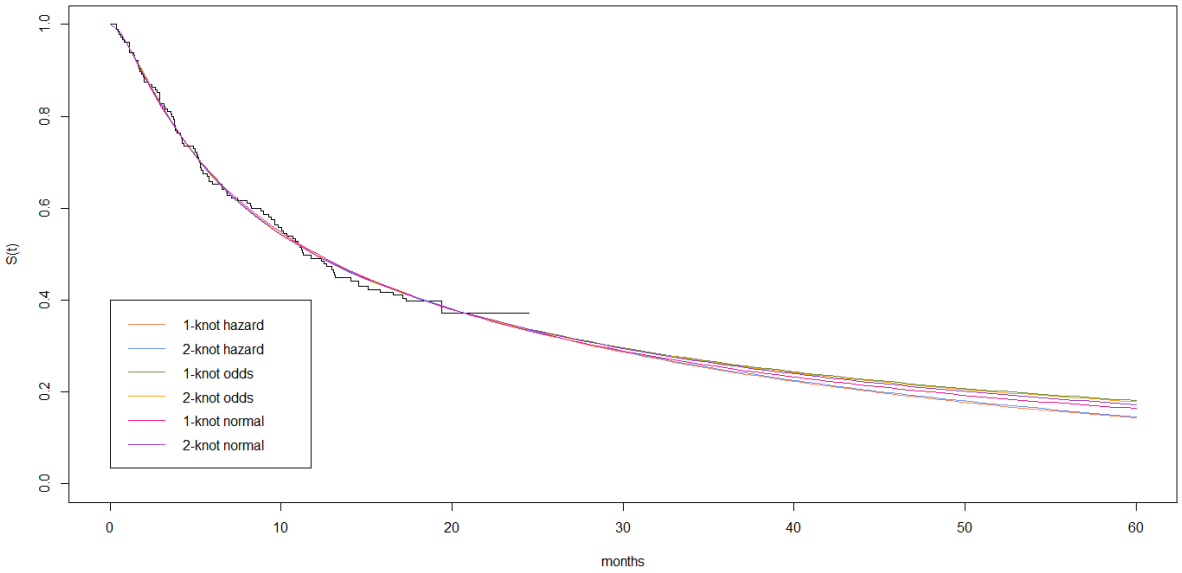

Table 22 Model fit statistics for survival curves, OS for blinatumomab

Distribution	AIC	BIC	5-year survival probability
Parametric			

Distribution	AIC	BIC	5-year survival probability
Weibull	814.40	820.78	6.1%
Exponential	813.53	816.72	4.2%
Generalised gamma	**804.91**	814.49	17.9%
Gompertz	808.60	814.99	23.0%
Log logistic	807.30	813.69	13.7%
Lognormal	**803.93**	810.32	14.2%
Spline models			
1-knot hazard	806.10	815.68	14.4%
2-knot hazard	808.16	820.93	14.7%
1-knot odds	**805.69**	815.26	18.1%
2-knot odds	807.72	820.49	17.9%
1-knot normal (probit)	**805.22**	814.80	16.4%
2-knot normal (probit)	807.13	819.90	17.3%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.5 Historical control for LBCL

7.1.7.5.1 Overall survival

Figure 15 Kaplan Meier curve with fitted standard parametric distributions, OS for historical control in LBCL

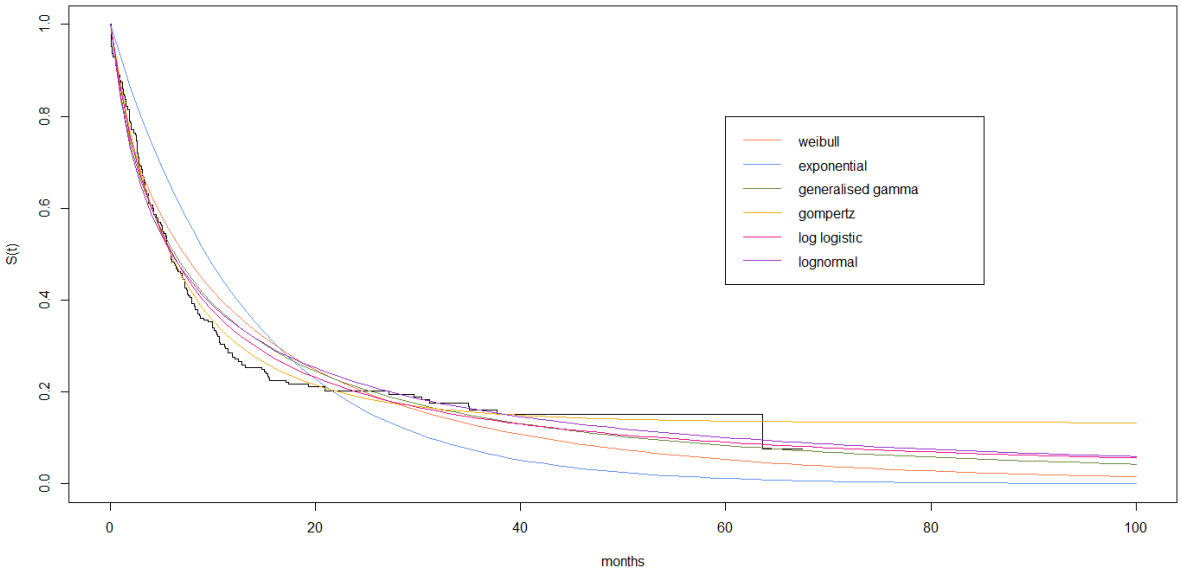

Figure 16 Kaplan-Meier curve with fitted spline-based models, OS for historical control in LBCL

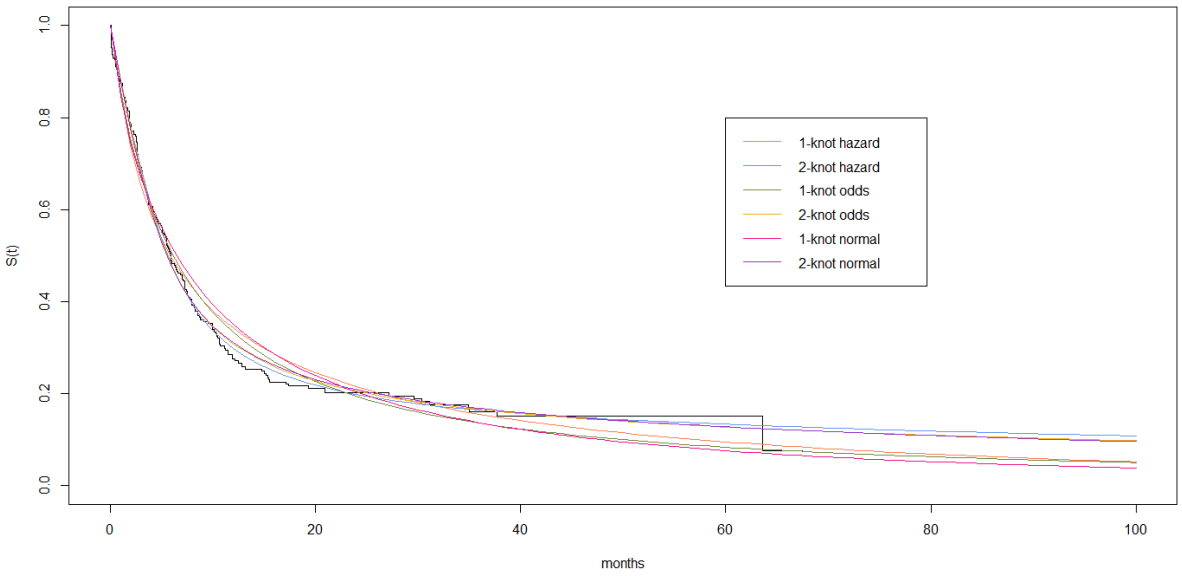

Table 23 Model fit statistics for survival curves, OS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	1,396.41	1,403.57	5.3%
Exponential	1,451.52	1,455.10	1.2%
Generalised gamma	1,383.46	1,394.21	8.4%
Gompertz	**1,367.16**	1,374.32	13.7%
Log logistic	1,373.70	1,380.87	9.1%
Lognormal	1,383.32	1,390.49	10.1%
Spline models			
1-knot hazard	1,382.07	1,392.83	9.5%
2-knot hazard	**1,363.51**	1,377.85	13.4%
1-knot odds	1,375.47	1,386.22	8.4%
2-knot odds	1,365.92	1,380.25	12.8%
1-knot normal (probit)	1,381.44	1,392.19	7.6%
2-knot normal (probit)	1,365.89	1,380.22	12.8%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.6 Polatuzumab for LBCL

7.1.7.6.1 Overall survival

Figure 17 Kaplan-Meier curve with fitted standard parametric distributions, OS for polatuzumab in LBCL

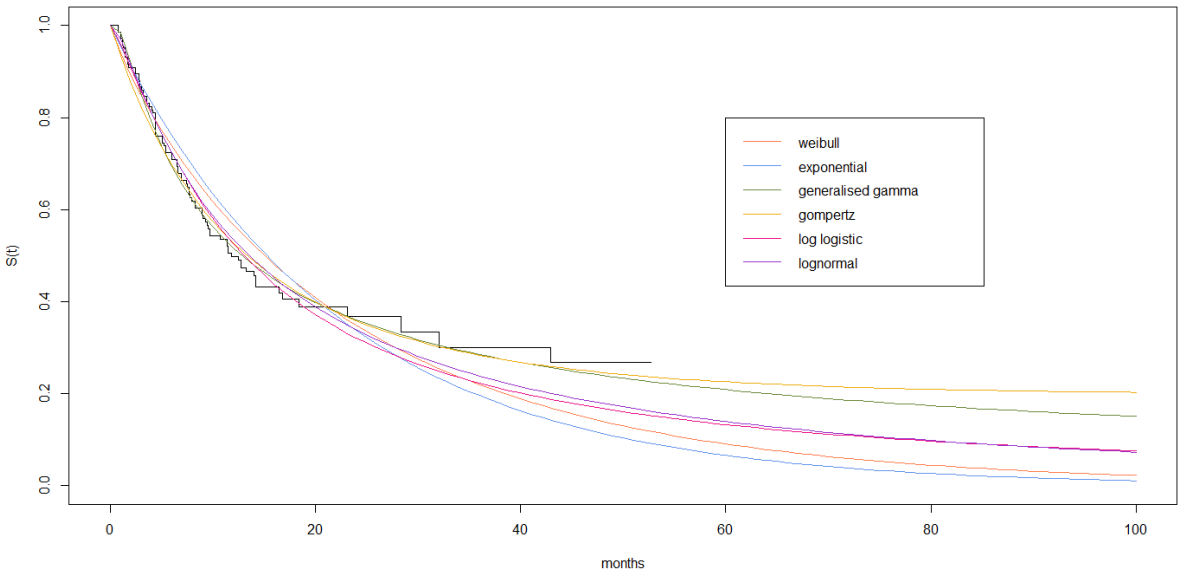

Figure 18 Kaplan-Meier curve with fitted spline-based distributions, OS for polatuzumab in LBCL

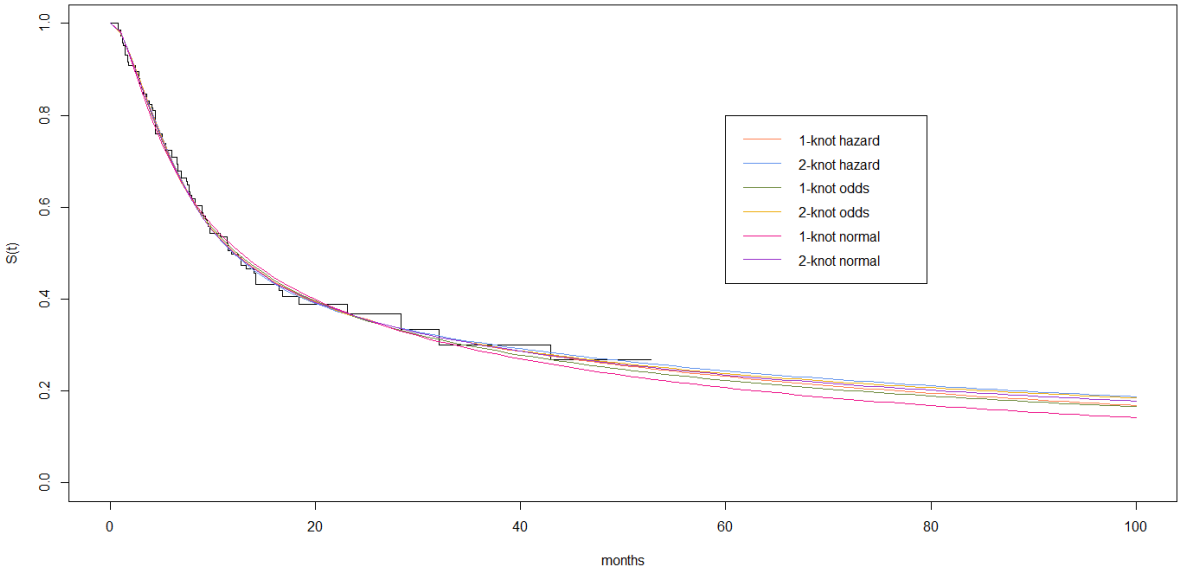

Table 24 Model fit statistics for survival curves, OS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	690.29	696.26	9.1%
Exponential	689.84	692.83	6.6%

Distribution	AIC	BIC	5-year survival probability
Generalised gamma	**670.98**	579.93	20.9%
Gompertz	679.80	685.77	22.6%
Log logistic	677.68	683.65	13.3%
Lognormal	674.03	680.00	14.0%
Spline models			
1-knot hazard	672.09	681.04	23.2%
2-knot hazard	673.68	685.61	24.4%
1-knot odds	672.25	681.20	22.3%
2-knot odds	673.86	685.80	23.8%
1-knot normal (probit)	671.82	680.77	20.7%
2-knot normal (probit)	672.72	684.66	23.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.6.2 Progression-free survival

Figure 19 Kaplan-Meier curve with fitted standard parametric distributions, PFS for polatuzumab in LBCL

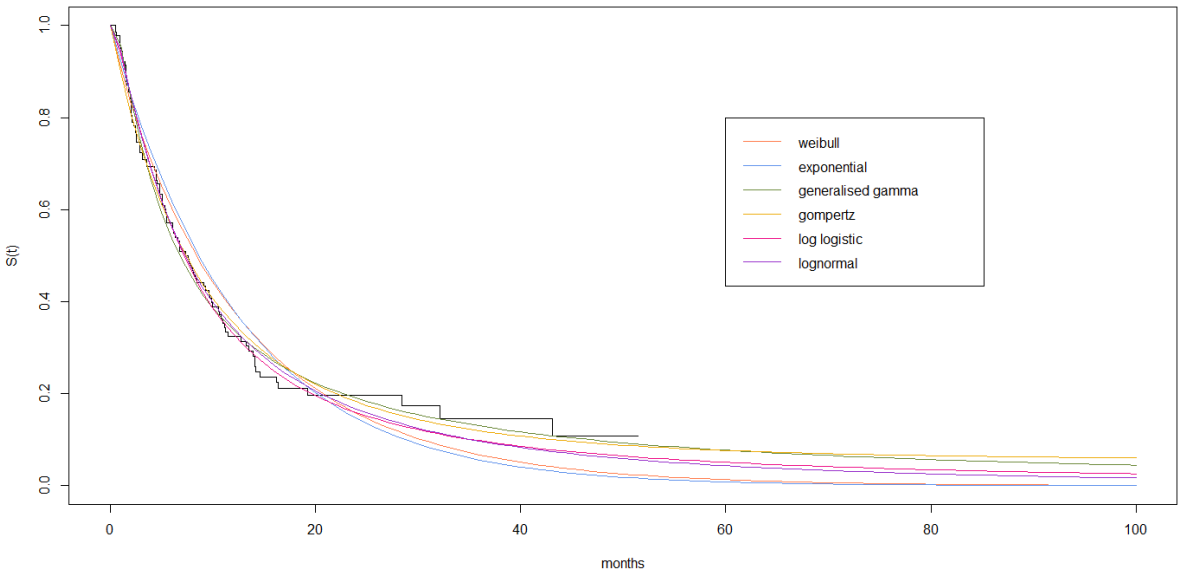

Figure 20 Kaplan-Meier curve with fitted spline-based distributions, PFS for polatuzumab in LBCL

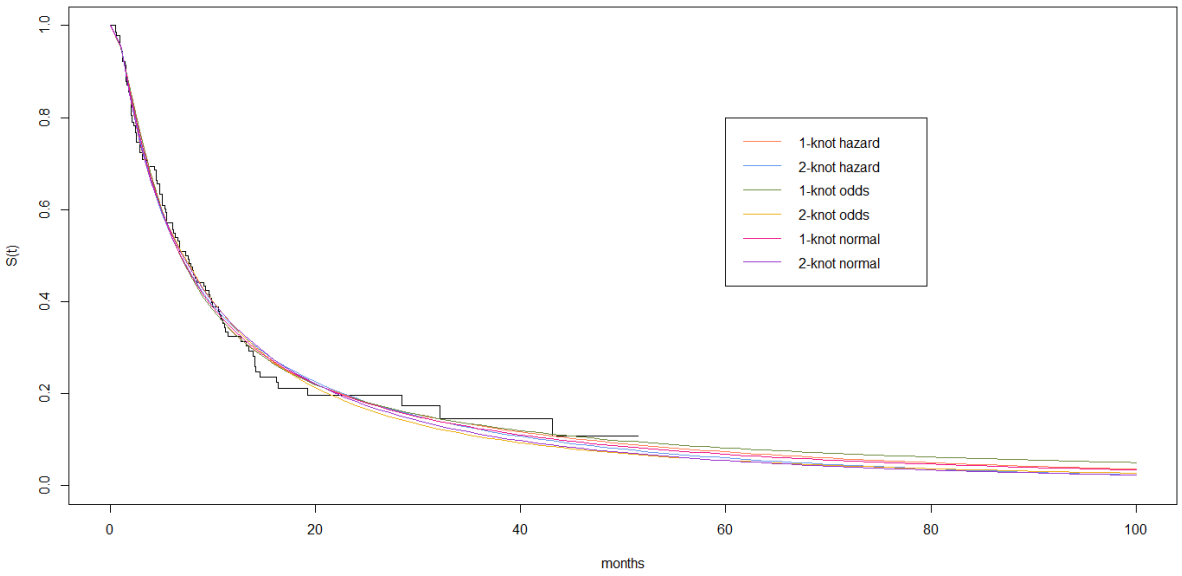

Table 25 Model fit statistics for survival curves, PFS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	715.47	721.43	1.3%
Exponential	714.28	717.26	0.8%
Generalised gamma	**695.79**	704.74	7.7%
Gompertz	707.14	713.11	7.7%
Log logistic	700.07	706.04	5.1%
Lognormal	**696.73**	702.70	4.3%
Spline models			
1-knot hazard	699.52	708.47	7.4%
2-knot hazard	699.77	711.70	6.0%
1-knot odds	699.21	708.16	8.2%
2-knot odds	698.01	709.95	5.5%
1-knot normal (probit)	**696.75**	705.70	6.8%
2-knot normal (probit)	697.69	709.63	5.5%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.7 Pembrolizumab for PMBCL

7.1.7.7.1 Overall survival

Figure 21 Kaplan-Meier curve with fitted standard parametric distributions, OS for pembrolizumab in PMBCL

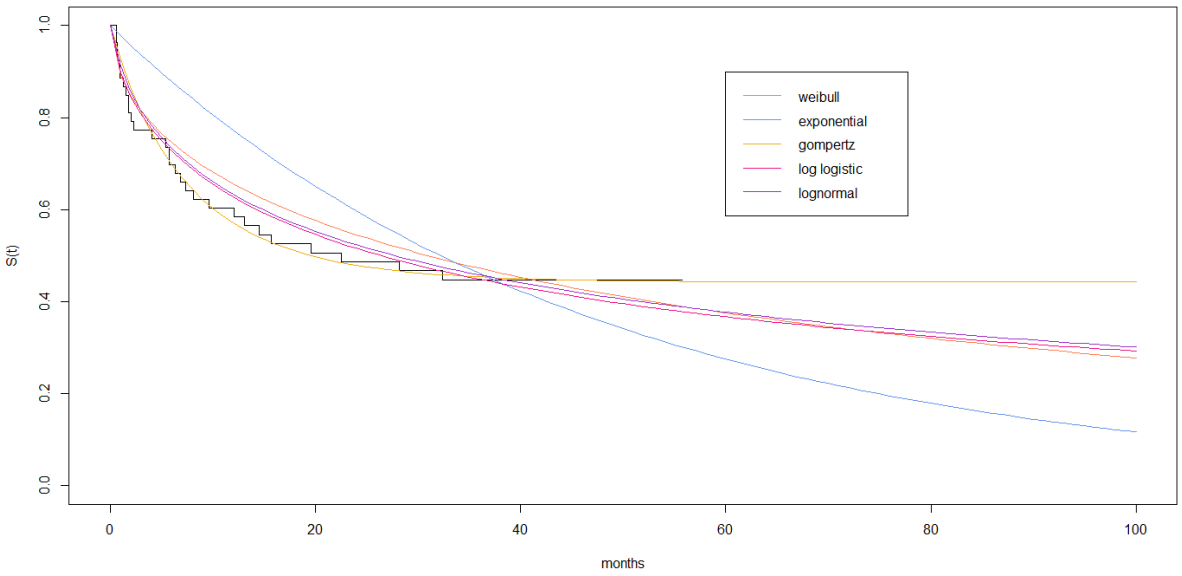

Figure 22 Kaplan-Meier curve with fitted spline-based distributions, OS for pembrolizumab in PMBCL

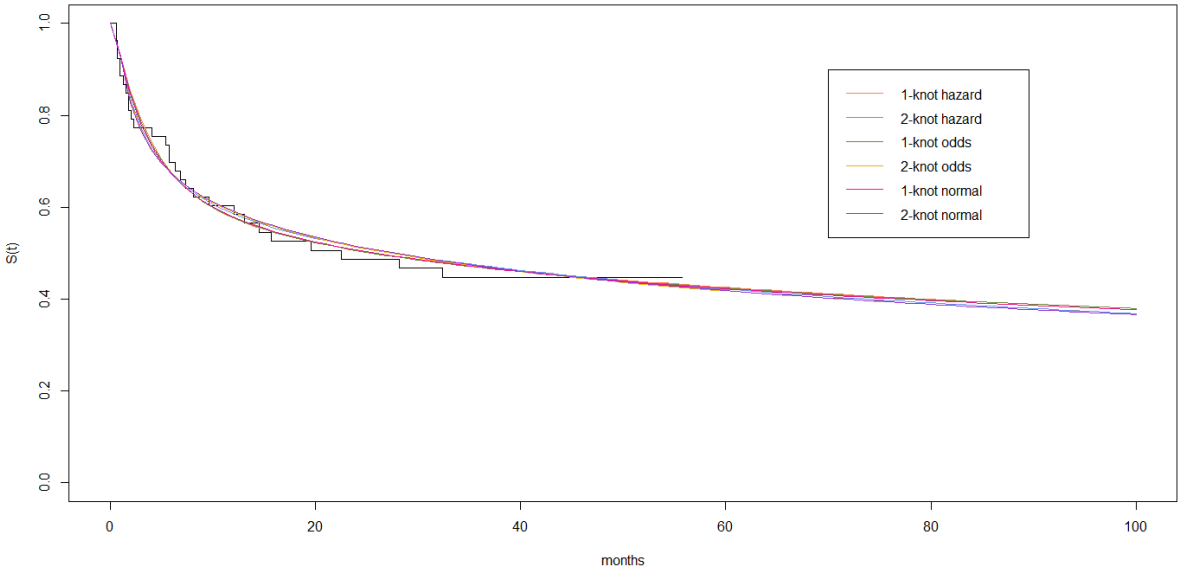

Table 26 Model fit statistics for survival curves, OS for pembrolizumab in PMBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	264.77	268.71	37.6%
Exponential	282.72	284.69	27.5%

Distribution	AIC	BIC	5-year survival probability
Gompertz	**254.29**	258.23	44.4%
Log logistic	261.24	265.18	36.7%
Lognormal	258.78	262.72	37.7%
Spline models			
1-knot hazard	257.21	263.12	42.6%
2-knot hazard	258.00	265.88	42.2%
1-knot odds	256.83	262.74	42.4%
2-knot odds	257.59	265.47	43.0%
1-knot normal (probit)	**255.58**	261.49	42.3%
2-knot normal (probit)	256.57	264.45	41.8%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

7.1.7.7.2 Progression-free survival

Figure 23 Kaplan-Meier curve with fitted standard parametric distributions, PFS for pembrolizumab in PMBCL

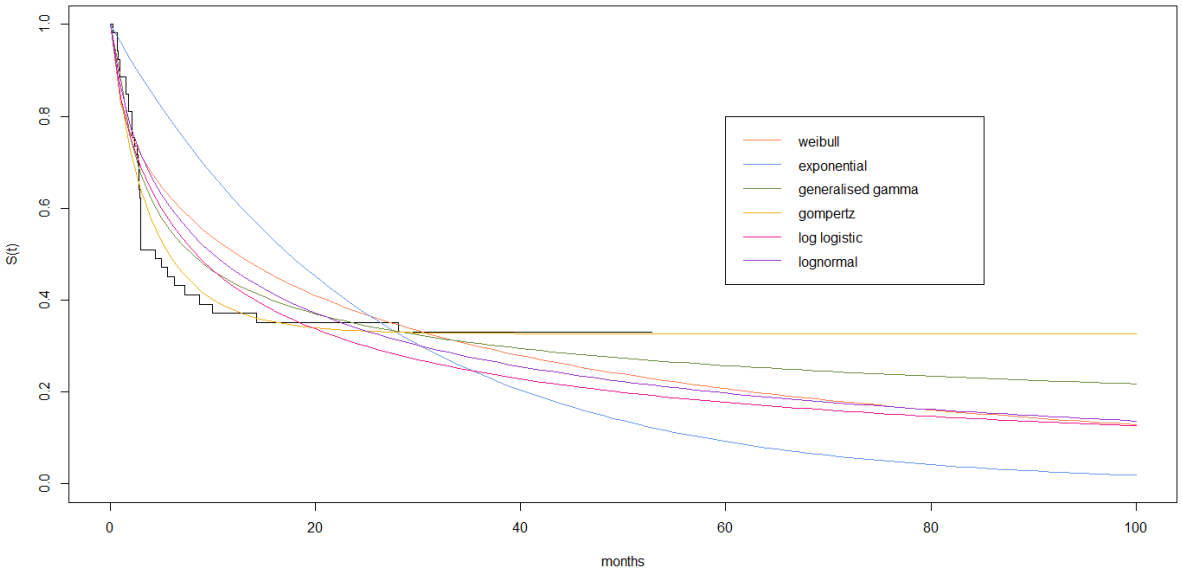

Figure 24 Kaplan-Meier curve with fitted spline-based distributions, PFS for pembrolizumab in PMBCL

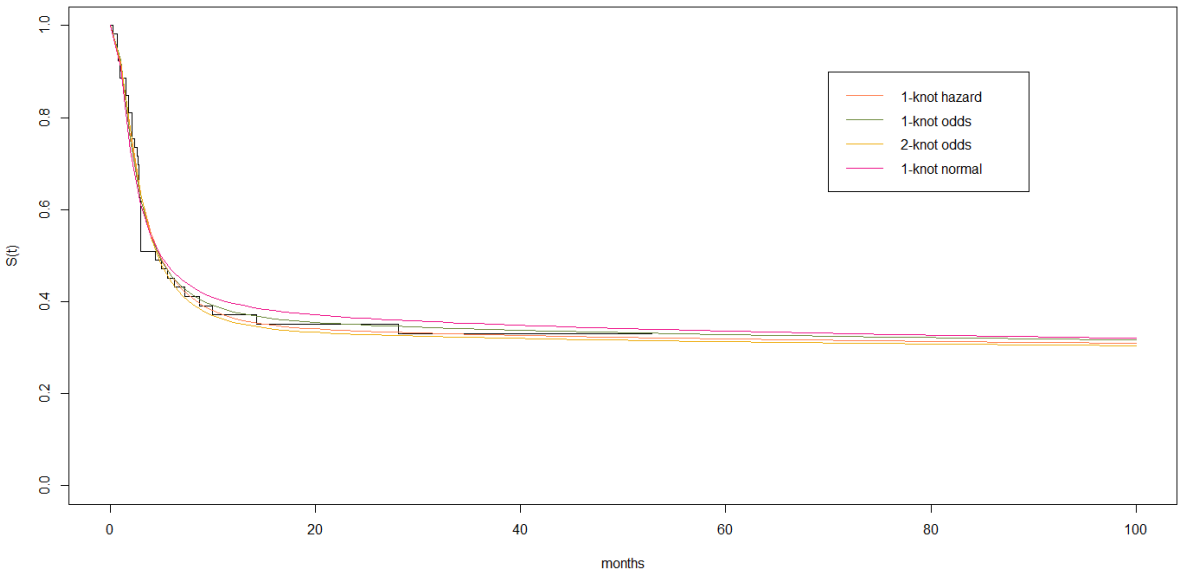

Table 27 Model fit statistics for survival curves, PFS for axi-cel in r/r LBCL

Distribution	AIC	BIC	5-year survival probability
Parametric			
Weibull	269.94	273.88	20.8%
Exponential	297.81	299.78	9.2%
Generalised gamma	245.17	251.09	25.8%
Gompertz	**239.29**	243.23	32.7%
Log logistic	259.59	263.53	17.8%
Lognormal	257.61	261.55	19.8%
Spline models			
1-knot hazard	**232.24**	238.15	31.9%
1-knot odds	232.44	238.35	32.8%
2-knot odds	232.61	240.50	31.3%
1-knot normal (probit)	235.07	240.98	33.6%

Abbreviations:
AIC = Akaike's information criterion; **BIC** = Bayesian information criterion.

8 Appendix H: Clinical practice recommendations and guidelines

Table 28 Summary of clinical guidelines and recommendations regarding tisa-cel and axi-cel in the populations of interest

Author, Date, Country	Recommendation (Strength of Recommendation)*
Technology Appraisal Guidelines	
National Institute for Health and Care Excellence (NICE) 2018[40] UK	**Tisa-cel for treating r/r B-ALL in people up to age 25 years** *Recommendation:* Tisa-cel therapy is recommended for use within the NHS Cancer Drugs Fund as an option for treating r/r B-ALL in people age up to 25 years, only if the conditions of the 'managed access agreement' are followed.
NICE 2019[41] UK	**Tisa-cel for treating r/r DLBCL after ≥2 systemic therapies** *Recommendation:* Tisa-cel therapy is recommended for use within the NHS Cancer Drugs Fund as an option for treating r/r DLBCL in adults after ≥2 systemic therapies, only if the conditions of the 'managed access agreement' are followed.
NICE 2023[42] UK	**Axi-cel for treating r/r DLBCL after first-line chemoimmunotherapy** *Recommendation:* Axi-cel is recommended for use within the NHS Cancer Drugs Fund as an option for treating DLBCL in adults when AutoSCT is suitable if it: (i) has relapsed within 12 months after first-line chemoimmunotherapy, or (ii) is refractory to first-line chemoimmunotherapy. It is recommended only if the conditions of the 'managed access agreement' are followed.
NICE 2023[11] UK	**Axi-cel for DLBCL and PMBCL after ≥2 systemic therapies** *Recommendation:* Axi-cel is recommended within its marketing authorisation as an option for treating r/r DLBCL or PMBCL in adults after ≥2 systemic therapies. Axi-cel is only recommended if provided according to the 'commercial arrangement'.†
Clinical Practice Guideline and Consensus-based Recommendations	
European Society for Blood and Marrow Transplantation (EBMT), the Joint Accreditation Committee of ISCT (International Society for Cell & Gene Therapy) and EBMT (JACIE), the European Haematology Association (EHA) 2022[43] Europe	**Management of adults and children receiving CAR T therapy** This document was created by CAR T experts from various disciplines. Recommendations are based on current literature and consensus view of the authors. Given the absence of RCT evidence, recommendations were not graded. **Patient eligibility:** • Eligibility assessment should be done by a multidisciplinary team, considering medical history, performance status and tolerability. Criteria should assess: age limit, performance status, life expectancy, high tumour burden, history of malignancy, prior alloSCT, prior CAR T, immunosuppressive treatments, bacteria/fungal/viral infections, CNS involvement. **Screening tests:** • Screening tests should be conducted to determine patient eligibility and fitness. Tests should include, but are not limited to: disease confirmation,

	haematology, bilirubin, AST/ALT, creatine clearance, Hep B/C, HIV, COVID-19, cardiac function, CNS imaging, lumbar puncture, fertility. **Work-up and carrying out leukapheresis:** • Leukapheresis procurement must comply with relevant directives and regulations. • Washout periods prior to leukapheresis will vary depending on the prior therapy received by the patient. • CAR T product prescription and scheduling are coordinated with manufacturing facilities. • Storage and handling guidelines for leukapheresis samples should be followed as provided by the manufacturer. • Infectious disease markers and microbial contamination should be tested prior to leukapheresis. **Bridging therapy:** • Patient-specific bridging recommendations are determined by a multidisciplinary team considering prior therapy response, tumour burden and disease sites. • Bridging therapy options include: high-dose chemotherapy, low-dose chemotherapy, radiotherapy, novel agents/approaches. **In/outpatient administration:** • Outpatient CAR-T administration can be considered if conditions are met (see publication); however, in many European centres, where such facilities might be unavailable, it is recommended that patients remain hospitalised for a minimum of 14 days after CAR T infusion. **Lymphodepletion (LD) conditioning:** • Common LD regimens include fludarabine and cyclophosphamide; bendamustine has been tested as an alternative to fludarabine. • LD should be given a week before infusion, with ≥2 rest days. If CAR T is delayed by 4 weeks, patients may require repeat LD. • Potential LD complications may include pancytopenia, infection, neurotoxicity, haemorrhagic cystitis, etc. **Thawing and infusion:** • Patients assessed for fitness, and consent given before CAR T infusion. • Vital signs, pre-medication (paracetamol, antihistamine), and IV access should be checked before infusion. • CAR T product thawing should follow manufacturer's instructions. • Infusion conducted by trained personnel, during which vitals are monitored. • Infusion reactions are rare, if these occur, they are treated symptomatically; corticosteroids should only be administered if patient is critically unwell. **Complications:** • Short-term complications (administration to 28 days) may include tumour lysis syndrome (TLS), infection, CRS, microphage activation syndrome, ICANS, cardiovascular toxicities. Management of such complications is outlined in the text. • Medium-term complications (>day 28 to day 100) may include delayed TLS, CRS or ICANS, infection, B-cell aplasia, hypogammaglobulinemia, GVHD, delayed cytopenias, immunosuppression. Management of such complications is outlined in the text. • Long-term complications (>100 days) may include prolonged cytopenia, hypogammaglobulinemia, infection, neurological complications, pulmonary toxicities and secondary malignancies. Long-term follow up and testing is crucial. Tests and schedule are outlined in the text.

German Cancer Society (Deutsche Krebsgesellschaft [DKG]), German Cancer Aid (Stiftung Deutsche Krebshilfe [DKH]), Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF]) 2022[44] Germany	**Treatment in DLBCL patients with ≥2 recurrence with primarily curative intent:** *Consensus-based recommendation:* In the case of primarily curative therapy intentions, CAR T cell therapy should be carried out in patients with ≥2 recurrence or progression of DLBCL if this was not carried out in the second-line therapy. **(Strong consensus)**
	Treatment in r/r PMBCL patients: *Consensus-based recommendation:* Patients with r/r PMBL after 2 prior systemic therapies should be treated with anti-CD19 CAR T cell therapy. **(Strong consensus)**
	Second-line therapy for high-dose-capable patients with early recurrence with curative intention: *Consensus-based recommendation:* High-dose capable patients with early relapse should receive anti-CD19 CAR T cell therapy with axi-cel or lisocabtagene maraleucel. **(Strong consensus, Grade B evidence)**
Cancer Care Alberta 2023[45] Canada	**Treatment of r/r DLBCL (patients fit for intensive therapy):** *Recommendation:* r/r DLBCL <12 months from completion of R-CHOP chemotherapy – when publicly funded, patients should be referred for CAR T cell therapy as second-line therapy. In lieu of CAR T therapy, patients should receive platinum-containing salvage chemotherapy: (i) relapse 3–12 months: consider RDICEP over RGDP, particularly if non-rapid progression and normal lactate dehydrogenase (ii) refractory disease: RGDP or RgemOx. Those with less than PR can proceed to CAR T therapy, while those with chemo-sensitive disease can proceed with high dose therapy autoSCT. *Recommendation:* r/r DLBCL after ≥2 lines of therapy – patients should be referred for CAR T cell therapy. All patients with r/r LBCL, tFL, or PMBCL after ≥2 lines of systemic therapy, with ECOG 0–2, adequate organ function and absence of infections should be considered for CAR T cell therapy. Patients must have failed standard therapies (i.e. RCHOP first line and platinum-containing salvage chemotherapy) to be considered for CAR T therapy. Axicabtagene ciloleucel (funded only after 2 prior lines of therapy)
National Comprehensive Cancer Network (NCCN) 2023[46] USA	**Treatment of r/r B-ALL** **Ph+ B-ALL (adolescents, young adults and adults)** *Recommendation:* Tisa-cel recommended in patients <26 years of age with refractory B-ALL or ≥2 relapses and following therapy that has included 2 tyrosine kinase inhibitors. **(Category 2A)** **Ph- B-ALL (adolescents, young adults and adults)** *Recommendation:* Tisa-cel recommended in patients <26 years of age with refractory B-ALL or ≥2 relapses. **(Category 2A)**
National Comprehensive Cancer Network (NCCN) 2023[47] USA	**Treatment of DLBCL patients with relapse >12 months or refractory disease** *Recommendation:* In those with intentions to proceed to transplantation, consider anti-CD19 CAR T therapy if PR achieved to second-line therapy. Axi-cel and tisa-cel are suggested treatment regimens as third-line and subsequent therapy. **(Category 2A)**
	Treatment of r/r PMBCL *Recommendation:* Manage as per r/r DLBCL. Tisa-cel is not FDA-approved for r/r PMBL. **(Category 2A)**
NHS Northern Cancer Alliance 2019[48]	**Treatment of DLBCL patients with second relapse**

UK	*Recommendation:* Patients should be referred for consideration of CAR T therapy.
Oncology Group for the Treatment and Study of Lymphomas (GOTEL), Spanish Society of Medical Oncology (SEOM) 2023[49] Spain	**Treatment of r/r DLBCL** *Recommendation:* Currently, the use of CAR T therapy in first recurrence of DLBCL is not yet justified, although this recommendation may be modified in the near future. **(Category 2C)** *Recommendation:* Patients who do not respond or who relapse after high-dose chemotherapy could be candidates for CAR T therapy. **(Category 3A)**
Royal Marsden (RM) Partners, South East London Cancer Alliance, North Central and East London Cancer Alliance 2020[50] UK	**Treatment of relapsed DLBCL** *Recommendation:* For patients not achieving a complete or very good partial response to salvage therapies (i.e. R-GDP, R-DHAP, R-ESHAP, R-ICE, R-IVE, R-GemP, R-Gem-Ox), consideration should be given to treatment with licenced CD19 CAR T products (axi-cel, tisa-cel), if patients fulfil NHS Cancer Drugs Fund eligibility criteria, or clinical trials incorporating other novel agents including alternative CAR T therapies.
British Society for Haematology (BSH) 2019[51] UK	**Treatment of r/r PMBCL** *Recommendation:* 'There are many new emerging therapeutic agents, such as brentuximab vedotin, agents directed at the PDCD1 (PD-1)/CD274 (PD-L1) axis and CD19 CAR T therapy, which may have a role in salvage therapy in the future, but currently the evidence for their use in PMBCL is sparse… Participation in a clinical trial should be considered.'
Society for Immunotherapy of Cancer (SITC) 2020[52] USA	**Treatment of DLBCL** *Consensus-based recommendation:* In transplant-eligible patients who receive salvage therapy and exhibit PR, the panel did not reach consensus on a preferred consolidation regimen. Options include anti-CD19 CAR T cell therapy or autoSCT. *Consensus-based recommendation:* There was consensus that the third-line treatment for DLBCL in fit patients should be anti-CD19 CAR T cell therapy (axi-cel or tisa-cel).
	CAR-T specific considerations *Consensus-based recommendation:* There was consensus that ICI and CAR T cell therapy are both acceptable after a patient has received autoSCT. The panel did not reach consensus on the subject of whether ICIs or CAR T cell therapy should be administered prior to autoSCT. *Consensus-based recommendation:* There was consensus that CAR T cell therapy is safe and could be considered following alloSCT, if the patient does not have active GVHD or require immunosuppression. Caution should also be exercised for patients with a history of severe GVHD.
	Patient considerations for immunotherapy in the treatment of lymphoma *Consensus-based recommendation:* The panel did not reach consensus on the subject of whether patients with active bacterial infections should receive ICI therapy. There was consensus that patients with active bacterial infections should not receive CAR T therapy, autoSCT or alloSCT. *Consensus-based recommendation:* The panel did not reach consensus on the subject of whether patients with active viral infections should receive ICI therapy or autoSCT. There was consensus that patients with active viral infections should not receive CAR T therapy or alloSCT. *Consensus-based recommendation:* There was consensus that patients with active inflammatory disorders should not receive CAR T cell therapy. *Consensus-based recommendation:* There was consensus that the extended time needed for cell therapy manufacturing and high financial burden are likely to impair clinical trials of cell-based therapies, such as CAR T cell therapy.

American Society of Clinical Oncology (ASCO) 2021[53] USA	**Management of immune-related adverse events in patients treated with CAR T therapy** *Consensus-based recommendations*: 'It is recommended that clinicians manage toxicities as follows: (i) Management of short-term toxicities associated with CAR T begins with supportive care for most patients, but may require pharmacologic interventions for those without adequate response. (ii) Management of patients with prolonged or severe CAR T–associated CRS includes treatment with tocilizumab with or without a corticosteroid. On the basis of the potential for rapid decline, patients with moderate to severe ICANS should be managed with corticosteroids and best supportive care. Steroids should be rapidly tapered once symptoms improve to Grade 1.'

Abbreviations:

AlloSCT = allogenic stem cell transplant, **AutoSCT** = autologous stem cell transplant, **axi-cel** = axicabtagene ciloleucel, **B-ALL** = B cell acute lymphoblastic leukaemia, **CAR T** = chimeric antigen receptor T cell, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B cell lymphoma, **ECOG** = Eastern Cooperative Oncology Group, **FDA** = Food and Drug Administration, **GVHD** = graft-versus-host disease, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **ICI** = immune checkpoint inhibitor, **LBCL** = large B cell lymphoma, **NHS** = National Health Service, **Ph** = Philadelphia chromosome, **PMBCL** = primary mediastinal B cell lymphoma, **PR** = partial response, **r/r** = relapsed or refractory, **tFL** = transformed follicular lymphoma, **tisa-cel** = tisagenlecleucel, **UK** = United Kingdom, **USA** = United States of America.

Notes:

***** Strength of recommendation only included if provided by publication. See below for key to recommendations per publication description.

† The contents of the 'commercial access agreement' is redacted as these are confidential.

Key:

Grade B: body of evidence can be trusted to guide practice in most situations.[44]

Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[46]

Category 2C: evidence from ≥1 well-designed clinical trial, without randomisation; from cohort or case controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results from uncontrolled experiments. Poor evidence to support a recommendation.[49,54]

Category 3A: evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. Good evidence to support a recommendation for use.[49,54]

9 Appendix I: Ongoing clinical trials

Appendix I includes a table of ongoing, withdrawn and terminated clinical trials that meet the inclusion criteria for this assessment. The aim of this table is to outline upcoming evidence, in order to determine if new evidence that may affect the results of this assessment is likely to be published in the near future. Additionally, clinical trials that have been withdrawn, terminated or prematurely ended are listed to capture whether reported treatment effects are biased due to early stoppage.

Table 29 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID; Country	Study design; follow-up	Indication; Sample size (estimated/ enrolled)	Intervention; Comparator	Relevant outcomes	Recruitment status; Expected completion date
NCT05541341 Brazil	Cohort study 15 years	DLBCL B-ALL n=200 (estimated)	Tisa-cel Nil	ORR EFS OS SAE and AE CRS and ICANS	Not yet recruiting December 2038
NCT05108805 USA	Cohort study 6 weeks	LBCL DLBCL n=25 (enrolled)	Axi-cel Nil	Hospitalisation CRS	Active, not recruiting December 2024
NCT03876769 USA, Belgium, Canada, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, UK	Cohort study 8 years	B-ALL who are minimal residual disease positive at the end of consolidation therapy n=120 (estimated)	Tisa-cel Nil	Disease-free survival OS CRR HRQoL	Recruiting October 2027
NCT03642626 USA	Case-control study 100 days	B-ALL DLBCL Multiple myeloma n=240 (estimated)	Tisa-cel Axi-cel Tecarus Abecma Breyanzi Nil	CRR ORR EFS OS Treatment-related mortality CRS/ICANS	Recruiting June 2028
NCT04290000 France	Cohort study 15 years	B-cell lymphoma (LBCL) B-ALL n=300 (estimated)	Axi-cel Tisa-cel Nil	OS	Recruiting March 2040
NCT04914091 France	Cohort study 6 months	DLBCL n=70 (estimated)	Axi-cel Tisa-cel Nil	HRQoL	Recruiting April 2023

Trial registry ID; Country	Study design; follow-up	Indication; Sample size (estimated/ enrolled)	Intervention; Comparator	Relevant outcomes	Recruitment status; Expected completion date
NCT05041309 USA, Canada, France, Germany, Israel, the Netherlands	Cohort study 15 years	DLBCL n=700 (estimated)	Axi-cel Nil	Late-onset AEs Late-onset SAEs OS	Enrolling by invitation March 2041
NCT04608487 USA	Cohort study 2 years	Primary/secondary CNS lymphomas (LBCL) n=18 (enrolled)	Axi-cel Nil	TRAEs CRR OS PFS	Active, not recruiting June 2025
NCT05077527 USA	Cohort study 2 years	HIV associated B-cell NHL (DLBCL, PMBCL) n=20 (estimated)	Axi-cel Nil	Infections CRS CRR EFS	Not yet recruiting January 2027
NCT02445222 Australia, Austria, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Norway, Singapore, Spain, Sweden, Switzerland, Taiwan, UK, USA	Cohort study 15 years	B-cell NHL n=1,400 (estimated)	Tisa-cel Nil	Delayed AEs EFS OS	Recruiting February 2036

Abbreviations:
AE = adverse event, **autoSCT** = autologous stem cell transplantation, **Axi-cel** = axicabtagene-ciloleucel, **B-ALL** = B cell acute lymphoblastic leukaemia, **CR** = complete response, **CNS** = central nervous system, **CRR** = complete response rate, **CRS** = cytokine release syndrome, **DLBCL** = diffuse large B cell lymphoma, **HGBCL** = high-grade B cell lymphoma, **HIV** = human immunodeficiency virus, **HRQoL** = health-related quality of life, **ICANS** = immune effector cell-associated neurotoxicity syndrome, **ID** = identification, **LBCL** = large B cell lymphoma, **n** = number of patients, **NHL** = Non-Hodgkin's lymphoma, **ORR** = overall response rate, **OS** = overall survival, **RCT** = randomised controlled trial, **SAE** = serious adverse event, **Tisa-cel** = tisagenlecleucel, **TRAEs** = treatment-related adverse events, **UK** = United Kingdom, **USA** = United States of America.

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