Online Appendix for Ph.D. dissertation

Dissertation title: Current Challenges in Health Technology Assessment. Assessing costs and cost-effectiveness of novel treatments in haemato-oncology

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Appendix description: This online Appendix contains supplemental material to some of the Chapters presented in the Ph.D. dissertation by W.F. Thielen with the title "Current Challenges in Health Technology Assessment. Assessing costs and cost-effectiveness of novel treatments in haemato-oncology.", to obtain the degree of Doctor from the Erasmus University Rotterdam. The dissertation can be read without this online Appendix and therefore the here presented supplements are not part of the printed version of the dissertation. This reduced the ecological footprint of the dissertation and improves the readability of its printed version.

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Appendices for Chapter 2

Title of Chapter in dissertation: How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3)

Appendix 2A - Databases for detecting economic evaluations.

Basic databases	
The Excerpta Medica database (Embase)[a], Ovid[b]	
Web link	Embase.com
Dates covered	1974 – onwards
Access	Limited/ licensed
Searching	Search string is indexed with controlled vocabulary (Emtree)
Content	A major biomedical and pharmaceutical database
Type of studies	Various
Host / Sponsor	Elsevier Publishers B.V.; OVID/ Wolters Kluwer
Additional links	
Medline[a], Ovid[b], PubMed[b], ProQuest[b]	
Web link	gateway.ovid.com/autologin.html
Dates covered	1946-onwards
Access	Licensed
Searching	Search strings indexed with controlled vocabulary (MESH)
Content	Encompasses information from Index Medicus, Index to Dental Literature, and International Nursing, allied health, biological and physical sciences, humanities and information science as they relate to medicine and health care, communication disorders, population biology, and reproductive biology.
Type of studies	Various
Host / Sponsor	U.S. National Library of Medicine OVID/Wolters Kluwer PubMed
Additional links	Medline Database Guide: http://ospguides.ovid.com/OSPguides/medline.htm
CRD; NHS Economic Evaluation Database (NHS EED) (Internet)	
Web link	http://www.crd.york.ac.uk/CRDWeb
Dates covered	1994 - end 2014 Bibliographic records were published until 31st March 2015.
Access	Open

Searching	Terms
Content	NHS EED (NHS Economic Evaluation Database) focuses primarily on the economic evaluation of health care interventions. NHS EED provides links to HEED full abstract records only (from 2000 forward), so although a search of NHS EED will retrieve all full abstract records from both databases, it will not retrieve bibliographic records of partial economic evaluations, methodology studies or reviews of economics studies that are held in HEED only.
Type of studies	Economic evaluations
Host / Sponsor	National Institute of Health research (NHS)
Additional links	
Econlit (EBSCO)	
Web link	https://www.aeaweb.org/econlit/index.php
Dates covered	1886-onwards
Access	Limited / licensed
Searching	Terms
Content	An academic literature database with articles, abstracts and citations with a focus on economics and to a lesser extent business administration
Type of studies	400 major journals as well as articles in collective volumes (essays, proceedings, etc.), books, book reviews, dissertations and working papers licensed from Cambridge University Press. Various publications are available in full text.
Host / Sponsor	EBSCO, Inc.
Additional links	Tutorial for searches http://support.ebsco.com/training/flash_videos/adv_guided/adv_guided.html
Web of Science	
Web link	http://ipscience.thomsonreuters.com/product/web-of-science/
Dates covered	1900 - onwards
Access	Licensed
Searching	Terms
Content	A citation indexing database that consists of seven online databases across 50 disciplines
Type of studies	Various
Host / Sponsor	Thomson Reuters
Additional links	

[a] Database, [b] Platform

Specific databases	
Guidelines	
International Guidelines Library (GIN)	
Web link	http://www.g-i-n.net/library/international-guidelines-library
Dates covered	August 2013-onwards
Access	Open
Searching	terms
Content	Contains guidelines, evidence reports and related documents, which were developed or endorsed by the organisational members.
Type of studies	Guidelines, systematic reviews and HTA reports
Host / Sponsor	Guidelines International Network
Additional links	
National Guideline Clearinghouse	
Web link	http://www.guideline.gov/
Dates covered	NA
Access	Open
Searching	Terms (disease/condition, treatment/intervention, organization type, intended users, clinical specialty, strength of the evidence, recommendations, age / sex of target population)
Content	Free accessible, public resource for evidence-based clinical practice guidelines in all clinical fields.
Type of studies	Guidelines, systematic reviews and HTA reports
Host / Sponsor	NGC is an initiative of the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services.
Additional links	Tutorial for searches: http://www.guideline.gov/videos.aspx?source=ngchelps
Nursing	
Cumulative Index to Nursing & Allied Health Literature (CINAHL)	
Web link	http://www.cinahl.com/
Dates covered	1937 – onwards
Access	Limited / licensed
Searching	Terms; indexed with controlled vocabulary (CINAHL-headings)

Content	Provides access to English-language nursing journals, publications from the American Nurses' Association and the National League for Nursing, and journals from 17 allied health disciplines. Also covers consumer health, health sciences librarianship, chiropractic, and health services administration literature.
Type of studies	Various
Host / Sponsor	EBSCO
Additional links	Tutorial for searches: http://support.ebsco.com/training/flash_videos/cinahl_basic/cinahl_basic.html http://support.ebsco.com/training/flash_videos/cinahl_advanced/cinahl_advanced.html
Education	
The ERIC database	
Web link	http://www.eric.ed.gov/
Dates covered	1964 – onwards
Access	Limited / licensed
Searching	Terms
Content	Contains abstracts of documents and journal articles on education research and practice. If full texts are available, links are included.
Type of studies	Abstracts of documents and journal articles on education research and practice
Host / Sponsor	U.S. Department of Education, Institute of Education Sciences (IES)
Additional links	
Occupational therapy	
Occupational Therapy Systematic Evaluation of Evidence (OTseeker)	
Web link	http://www.otseeker.com/
Dates covered	2003 – onwards
Access	Open
Searching	Terms
Content	Contains abstracts of systematic reviews, randomised controlled trials and other resources relevant to occupational therapy interventions
Type of studies	Randomised controlled trials, systematic reviews (critically appraised)
Host / Sponsor	Department of Occupational Therapy, The University of Queensland
Paediatrics	
Pediatric Economic Database Evaluation (PEDE)	

Web link	http://pede.ccb.sickkids.ca/pede/search.jsp
Dates covered	January 1980 – December 2014
Access	Open
Searching	Terms
Content	Contains full economic evaluations citations and about 1,656 health state utility weights from cost-utility studies
Type of studies	Full economic evaluations
Host / Sponsor	Canadian Institutes of Health Research, Ontario Ministry of Health and Long-term Care Drug Innovation Fund and more

Physiotherapy	
Physiotherapy Evidence Database (PEDro)	
Web link	http://www.pedro.org.au/
Dates covered	1929 – onwards
Access	Open
Searching	Terms
Content	A free database of randomized trials, systematic reviews and clinical practice guidelines in physiotherapy. For each trial, review or guideline, PEDro provides citation details, abstracts and links to the full text, where possible. All trials are independently assessed for quality.
Type of studies	Randomised controlled trials, systematic reviews and evidence-based clinical practice guidelines (critically appraised)
Host / Sponsor	Centre for Evidence-Based Physiotherapy at The George Institute for Global Health
Additional links	Tutorial for searches: http://www.pedro.org.au/english/search-help/

Psychology	
PsycINFO®[a], Ovid[b]	
Web link	http://www.apa.org/psycinfo/
Dates covered	1800s – onwards
Access	Licensed
Searching	Terms, indexed with controlled vocabulary from APA's Thesaurus of Psychological Index Terms®
Content	Contains peer-reviewed literature in behavioural science and mental health with citations and summaries dating as far back as the 1600s.
Type of studies	Abstracts of journal articles, book chapters, books, and dissertations
Host / Sponsor	The American Psychological Association (APA)
Additional links	

Global health topics	
GlobalHealth.gov	
Web link	http://www.globalhealth.gov/index.html
Dates covered	Not mentioned
Access	Open
Searching	Terms
Content	Contains global health topics (more specific: Communicable, Diseases, Disabilities Global Health Security, Global Water Supply and Safety, Health Diplomacy, Lesbian, Gay, Bisexual, and Transgender Global Health, Maternal and Child Health, Non-Communicable Diseases)
Type of studies	Documents
Host / Sponsor	United States Department of Health and Human Services (HHS)
Additional links	
Various	
European Health for All Database	
Web link	http://www.euro.who.int/en/what-we-do/data-and-evidence/databases/european-health-for-all-database-hfa-db2
Dates covered	Not mentioned
Access	Open
Searching	Terms (allows queries for country, intercountry and regional analyses)
Content	Provides a selection of core health statistics covering basic demographics, health status, health determinants and risk factors, and healthcare resources, utilization and expenditure in the 53 countries in the WHO European Region.
Type of studies	Data
Host / Sponsor	World Health Organization, regional office for Europe
Additional links	

[a] Database, [b] Platform

Optional databases	
CRD Health Technology Assessment Database (HTA)	
Web link	http://www.crd.york.ac.uk/CRDWeb
Dates covered	1994 – onwards
Access	Open
Searching	Terms

Content	Focusses on completed and ongoing health technology assessments from around the world. It is a source for identifying grey literature, as much of the information it contains is generally available only directly from individual funding agencies. Database content is supplied by the 52 members of the International Network of Agencies for Health Technology Assessment (INAHTA) and 20 other HTA organisations around the world. All new content is checked, proofread and published on the database by the in-house team at CRD.
Type of studies	Completed and ongoing health technology assessments
Host / Sponsor	National Institute of Health research (NHS)
Additional links	
CRD Canadian Agency For Drugs and Technologies in Health (CADTH), HTA Database Canadian Search Interface	
Web link	http://www.crd.york.ac.uk/PanHTA/
Dates covered	1994 – onwards
Access	Open
Searching	Terms
Content	Health technology assessment producers from Ontario, Quebec, Alberta, and the pan-Canadian agency CADTH have partnered with the National Institute for Health Research's Centre for Reviews and Dissemination to create a common repository and search tool for Canadian HTA reports within the existing international HTA Database.
Type of studies	Completed and ongoing health technology assessments
Host / Sponsor	National Institute of Health research (NHS)
Additional links	
Research funding (UK), including HTA	
Web link	http://www.nets.nihr.ac.uk/programmes
Dates covered	NA
Access	Open
Searching	Terms
Content	Holds information on various research programmes, namely: Efficacy and Mechanism Evaluation (EME) Programme, Health Services and Delivery Research (HS&DR) Programme, Health Technology Assessment (HTA) Programme, Public Health Research (PHR) Programme, Systematic Reviews (SR) Programme, NIHR Clinical Trials Unit (CTU) Support Funding
Type of studies	Guidelines and Guidance

Host / Sponsor	National Institute of Health Research
Additional links	

Science Citation Index (SCI) (Web of Science)

Web link	http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/social-sciences-citation-index.html
Dates covered	1997 – onwards
Access	Licensed
Searching	Hand selection of relevant articles
Content	Social Sciences Citation Index®, (via Web of Science™ Core Collection) provides access to the bibliographic and citation information.
Type of studies	Various
Host / Sponsor	Thomson Reuters
Additional links	

National Institute for Health and Clinical Excellence (NICE) Guidance

Web link	http://guidance.nice.org.uk/
Dates covered	NA
Access	Open
Searching	Terms
Content	Provides national guidance and advice for improving health and social care.
Type of studies	Guidelines, Guidance and HTA reports
Host / Sponsor	National Institute for Health and Clinical Excellence
Additional links	

Google scholar

Web link	https://scholar.google.com/
Dates covered	Not mentioned
Access	Open
Searching	Terms
Content	Aims to rank documents on the basis of weighing the full text of each document, where it was published, who it was written by, as well as how often and how recently it has been cited in other scholarly literature.
Type of studies	Articles, theses, books, abstracts and court opinions, from academic publishers, professional societies, online repositories, universities and other web sites
Host / Sponsor	Google Inc.
Additional links	

Cost-Effectiveness Analysis (CEA) Registry

Web link	https://research.tufts-nemc.org/cear4/Home.aspx
Dates covered	2006 – onwards
Access	Open (basic search), limited (advanced search)
Searching	Terms (conditions, publication year, ICER ratios, Interventions)
Content	Contains cost-utility analyses on a wide variety of diseases and treatments and consists of three main files: Article, Ratio and Utility Weight.
Type of studies	Articles
Host / Sponsor	Tufts Medical Center
Additional links	Tutorial for searches: https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/Tutorial.aspx
International Clinical Trials Registry Platform (ICTRP)	
Web link	http://apps.who.int/trialsearch/Default.aspx
Dates covered	Not mentioned
Access	Open
Searching	Terms
Content	Aims to facilitate the prospective registration of the WHO Trial Registration Data Set on all clinical trials, and the public accessibility of that information.
Type of studies	Clinical trials (also referred to as interventional trials) interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care.
Host / Sponsor	World Health Organization
Additional links	
ClinicalTrials.gov	
Web link	http://www ClinicalTrials.gov
Dates covered	2008 – onwards
Access	Open
Searching	Terms (conditions and interventions)
Content	Provides information on publicly and privately supported clinical studies on a wide range of diseases and conditions
Type of studies	Clinical trials
Host / Sponsor	U.S. National Institutes of Health
Additional links	
The International Standard Randomised Controlled Trial Number ISRCTN registry	
Web link	http://www.isrctn.com/

Dates covered	2000 – onwards
Access	Open
Searching	Terms (trial status, condition, recruitment country, age)
Content	Contains the basic set of data items to describe a study at inception, as per the requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors' (ICMJE) guidelines. All study records in the database are freely accessible and searchable and have been assigned an ISRCTN ID.
Type of studies	Clinical trials (observational and interventional trials)
Host / Sponsor	WHO, NHS, NIHR
Additional links	

Campbell collaboration	
Web link	http://www.campbellcollaboration.org/index.as
Dates covered	2004 – onwards
Access	Open
Searching	Terms
Content	A peer-reviewed online monograph series of systematic reviews prepared under the editorial control of the Campbell Collaboration on social science, crime and justice, education, international development and social welfare
Type of studies	Systematic reviews
Host / Sponsor	Major sponsors at present include the Norwegian Directorate of Health and the Norwegian Ministry of Education and Research.
Additional links	

Cochrane Library of Systematic Reviews (CDSR)[a], Wiley Online Library[b]	
Web link	http://cochranelibrary.com/
Dates covered	Not stated
Access	Licensed, (open access end 2016)
Searching	Terms (browsing possible with advanced search, by topic or in updated or new reviews)
Content	Holds information on the effectiveness of health care on the grounds of evidence-based medicine.
Type of studies	Systematic reviews, Cochrane controlled trials, abstracts of reviews of effects
Host / Sponsor	Supported by national governments, international governmental and non-governmental organizations, universities, hospitals, private foundations, and personal donations
Additional links	

Centre of Research and Dissemination (CRD); Database of Abstracts of Reviews of Effects (DARE)	
Web link	http://www.crd.york.ac.uk/CRDWeb
Dates covered	1994 – end 2014
Access	Open
Searching	Terms
Content	DARE was focused primarily on systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services.
Type of studies	Systematic reviews (critically appraised)
Host / Sponsor	National Institute of Health Research
Additional links	

Optional websites		
Conference proceedings		
Name	Content	Web link
HTAi	HTAi is a global scientific and professional society for all those who produce, use, or encounter HTA. It also provides access to a variety of Resources including the International Journal of Technology Assessment in Health Care (IJTAHC).	http://www.htai.org/
ISPOR	ISPORs mission is to increase the efficiency, effectiveness, and fairness of health care to improve health.	http://www.ispor.org/
iHEA	The International Health Economics Association (iHEA) was formed to increase communication among health economists, foster a higher standard of debate in the application of economics to health and health care systems, and assist young researchers at the start of their careers.	https://www.healtheconomics.org/
SMDM	The Society for Medical Decision Making's (SMDM) aims to improve health outcomes through the advancement of proactive systematic approaches to clinical decision making and policy-formation in health care by providing a scholarly forum that connects and educates researchers, providers, policy-makers, and the public.	http://smdm.org/
GIN	The Guidelines International Network (GIN) mission is to lead, strengthen and support collaboration in guideline development, adaptation and implementation.	http://www.g-i-n.net/

Cochrane Colloquia	Colloquia are designed to bring people together in one place to discuss, develop and promote our work, and to shape the organisation's future direction.	https://colloquium.cochrane.org/
Grey literature		
International	The International Journal on Grey Literature	http://www.greynet.org/thegreyjournal.html
The Netherlands	GLIN (Grey Literature in the Netherlands) contains titles of publications of governmental and other public institutions, of universities and other scientific institutions and of theses, published in The Netherlands since 1982.	Only through Dutch university websites
Free access to full papers		
List to free access journals	http://highwire.stanford.edu/lists/freeart.dtl http://www.freefullpdf.com/ http://www.researchgate.net/	

Appendix 2B – Example of reporting on databases and search strategies

Date of search: _____

Name of database	URL	Search strategy used	No. of total hits
MEDLINE (via PubMed)	http://www.ncbi.nlm.nih.gov/pubmed	((("ketogenic diet"[MeSH Terms] OR ("ketogenic"[TIAB] AND "diet"[TIAB]) OR "ketogenic diet"[TIAB] OR (ketogen*[TIAB] AND diet[TIAB]) OR "diet therapy"[MeSH] OR "diet therapy"[TIAB]) AND ((epilepsy[MeSH] OR epilepsy[TIAB] OR epileps*[TIAB] OR epilept*[TIAB]) OR (seizures[MeSH] OR seizures[TIAB] OR seizure[TIAB]) OR (convulsion OR convulsions[TIAB])))) AND ("2000/01/01"[PDat] : "3000"[PDat]) AND (English[lang]) AND (cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp] OR cost benefit analys*[Title/Abstract] OR cost-benefit analysis[MeSH Term] OR health care costs[MeSH:noexp])	16
…	…	…	…

...	...	...	...
Total			**...**

Appendices for Chapter 3

Title of Chapter in dissertation: Cost of Healthcare for Paediatric Patients with Sickle Cell Disease. An analysis of resource use and costs in a European country

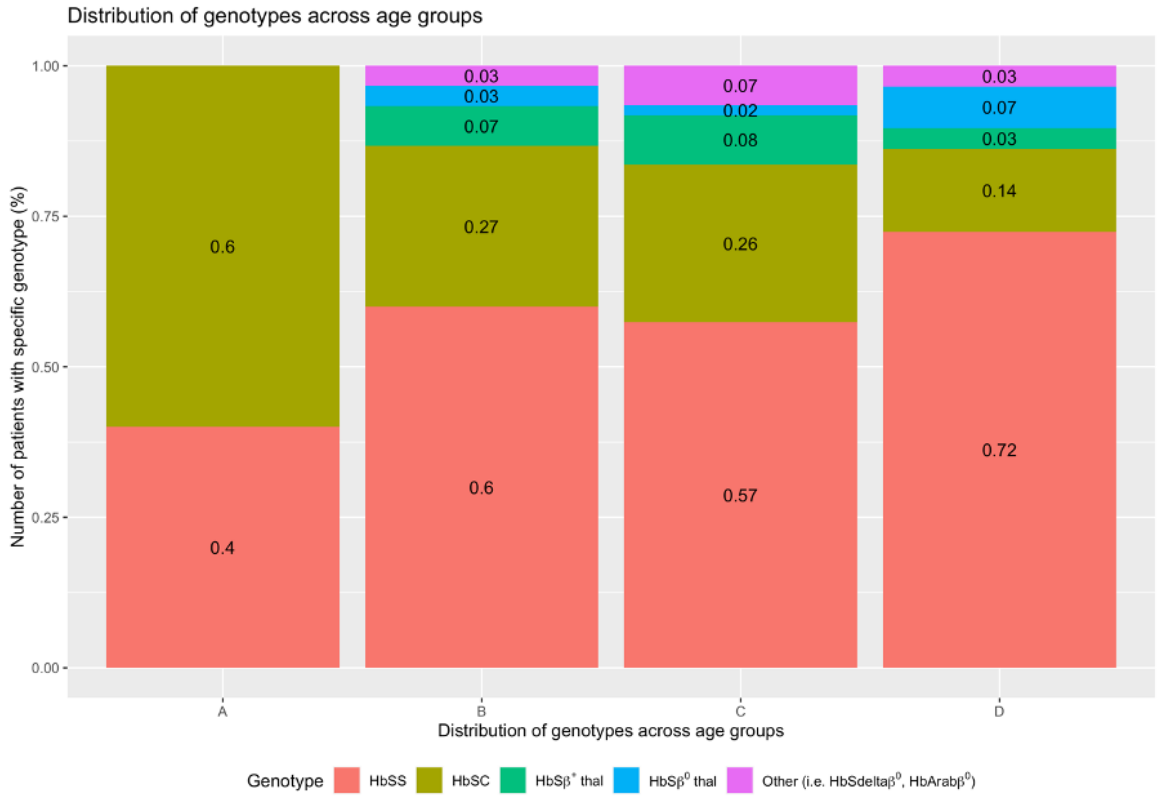
Appendix 3A – Loaded R packages

Loaded R packages included:

- openxlsx
- lubridate
- cbsodataR
- Hmisc
- Tidyverse

Appendix 3B – Distribution of genotypes across age groups

For the following figure, respective age groups of patients were determined on 2016-12-31 (the last day of the follow-up period).



Abbreviations; HbSβ⁺ thal: HbSβ⁺ thalassemia, HbSβ⁰ thal: HbSβ⁰ thalassemia

Appendix 3C – Distribution of inpatient care across age groups

	Age group			
Type of inpatient care	**A**	**B**	**C**	**D**
Inpatient care	37.8%	60.1%	20.5%	49.9%
Inpatient care at local hospital	62.2%	39.3%	67.0%	33.5%
Intensive care unit	0%	0%	12.2%	15.8%
Day care	0%	0.5%	0.2%	0.8%

Appendices for Chapter 4

Title of Chapter in dissertation: Second-line treatment for acute graft-versus-host disease with mesenchymal stromal cells: A decision model

Appendix 4A - Data extraction form

Patient characteristics
Age
Sex
Original diagnosis
aGvHD grade and organ involvement stages before treatment
Time of
HSCT
First MSC infusion
First response evaluation
Death, last follow-up or end of study
Response after first response evaluation
aGvHD grade (0-IV)
Response category (e.g. complete response, mixed response, partial response etc.)
Chronic GvHD
Adverse events
Relapse or adverse events of underlying haematological disease
MSC
Origin (e.g. bone-marrow)
Dosage (number of MSCs x 10^6/kg recipient body weight)
Frequency of administration

Appendix 4B - Detected phase II trials

Author (year)	**Type of MSC**	**Number of patients with aGvHD II-IV**	**Time of inclusion**	**MSC dose (x 10^6 per kg)**	**Definition response**
Ringdén (2006)[1]	Bone marrow	8		0.7 – 9	CR: disappearance of all symptoms of acute GvHD
Fang (2007)[2]	Human adipose-tissue-derived mesenchymal stem cells (AMSC)	6	2002 - 2005	1.0	CR: complete resolution of GvHD PR: decrease in organ stage by at least one stage NR: progressive worsening requiring introduction of additional GvHD treatment
Le Blanc (2008)[3]	Bone marrow	55	2001 - 2007	0.4 – 9 (median 1.4)	CR: loss of all symptoms of aGvHD PR: improvement of at least one grade SD: no change in GvHD PD: worsening of GvHD
Müller (2008)[4]	Bone marrow	2	2004 - 2005	0.4 – 3.0	Not defined
Von Bonin (2009)[5]	Bone marrow	13	2007	0.6 – 1.1 (median 0.9)	MR: improvement in staging of one organ with no change in others PR: decrease in staging but no resolution of all signs CR: resolution of all signs OR: CR+PR+MR
Lucchini (2010)[6]	Bone marrow	4	2008 - 2009	1.0-3.7	CR: complete disappearance of all signs and symptoms pf GvHD PR: GvHD improvement of at least 1 stage in single organ scoring, or 1 grade in overall GvHD scoring, if more than 1 organ was involved

					SD: no change in GvHD staging and grading PD: worsening of GvHD, intended as either involvement of new organs or worsening of the previously involved organs
Pérez-Simon (2011)[7]	Bone marrow	10	2007 - 2009	0.6 – 2.0	Not defined
Prasad (2011)[8]	Bone marrow	12	2005 - 2007	2.0 – 8.0	CR: resolution of aGvHD in all evaluable involved organs PR: decrease of at least 1 GvHD stage in any 1 organ system without a worsening in any other organ system MR: a decrease of at least 1 GvHD stage in any 1 organ system or worsening in other organs system NR: no change in any organ system or worsening in 1 or more organ system without improvement in any other organ system
Herrmann (2012)[9]	Bone marrow	12	2007 - 2010	1.7 – 2.3	CR: loss of all symptoms and signs of aGvHD PR: at least an improvement of one grade or more
Ball (2013)[10]	Bone marrow	37	2005 - 2009	0.9 – 3.0 (median 2.0)	CR: disappearance of all symptoms due to aGvHD PR: improvement of at least one overall grade NR: no change in aGvHD grade and/or progressive worsening of aGvHD
Muroi (2013)[11]	Bone marrow	14	2009 - 2010	2	CR: complete resolution of aGvHD PR: a decrease in organ stages of aGvHD NR: no change in aGvHD PG: progressive worsening of aGvHD MR: mixture of a decrease and increase in organ stages of aGvHD

Introna (2014)[12]	Bone marrow	31	2009 - 2012	0.8 – 3.1	CR: absence of signs and symptoms of GvHD PR: decrease of at least 1 grade as compared with day 0 NR: no change in GVHD scoring
Kurtzberg (2014)[13]	Bone marrow	75	Not mentioned	2	CR: Resolution of aGVHD in all involved organs Responders at day 28: additional improvement in at least 1 organ of at least 1 stage without worsening in any other organ between day +28 and day +100. Patients who maintained a CR after day +28 were considered responders as well. Patients who had a PR at day +28 but experienced no change in organ staging between day +28 and day +100 were considered nonresponders.
Sánchez-Guijo (2014)[14]	Bone marrow	25	2011 - 2012	2-8 (median 1.1)	CR: absence of signs or symptoms of aGvHD PR: a decrease of at least 1 grade from the day of the first MSC dose NR: no change in the GvHD grade Response = CR or PR
Te Boome (2015)[15]	Bone marrow	48	2009 - 2012	0.9-2.5 (median 1.8)	CR: resolution of GvHD in all involved organs (overall grade 0) at day 28 after first infusion of MSCs Non-CR: No complete resolution of GvHD (overall grade ≠ 0) in all involved organs at day 28 after first infusion of MSCs

Appendix 4C - AIC/BIC values for the parametric survival fit

Distribution	**CR (n=115)**				**nCR (n=119)**			
	AIC	***#***	***BIC***	***#***	***AIC***	***#***	***BIC***	***#***
Exponential	533.63	6	536.38	4	1059.40	6	1062.20	6
Weibull	531.26	4	536.75	5	1056.20	5	1061.80	5
Log normal	525.12	2	530.61	2	1028.00	2	1033.60	2
Log-logistic	529.26	3	534.75	3	1032.70	3	1038.30	3
Gompertz	531.56	5	537.05	6	1040.70	4	1046.20	4
Generalised gamma	518.00	1	526.00	1	986.00	1	994.00	1

AIC: Akaike's Information Criterion, BIC: Bayes Information Criterion, #: Rank

Appendices for Chapter 5

Title of Chapter in dissertation: Cost-Effectiveness of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-cell acute Lymphoblastic Leukemia. A societal view

Appendix 5A - General remarks

All conversion rates are taken from oanda.com and based on the exchange rate on 2019-01-01.

Appendix 5B - Dosing schedules for tisagenlecleucel and comparator treatments

Treatment	Dosing schedule	Distribution of patients per cycle or number of cycles	Source
Tisagenlecleucel (intervention)			
Lymphodepleting regimen			ELIANA trial[16]
Regimen 1		94.67%	
Fludarabine	30 mg/m^2 intravenous (IV) daily for 4 doses		
Cyclophosphamide	500 mg/m^2 IV daily for 2 doses		
Regimen 2		1.33%	
Cytarabine	500 mg/m^2 IV daily for 2 days		
Etoposide	150 mg/m^2 IV daily for 3 days		
Tisagenlecleucel	One time infusion	100%	
Clofarabine monotherapy			Jeha et al. 2006[17]
Clofarabine	30 mg/m^2 daily (5 doses)	2 cycles	
Clofarabine combination monotherapy			Hijiya et al. 2011[18]
Induction		100% (1 cycle)	
Clofarabine	40 mg/m2 daily for 5 days		

Cyclophosphamide	440mg/m2 daily for 5 days		
Etoposide	100mg/m2 daily for 5 days		
Consolidation		32% (cycle 2), 8% (cycle 3)	
Clofarabine	40 mg/m2 daily for 4 days		
Cyclophosphamide	440mg/m^2 daily for 4 days		
Etoposide	100mg/m^2 daily for 4 days		
Blinatumomab			von Stackelberg 2016[19]
Blinatumomab cycle 1	5 mcg/m^2/day Day 1-7; 15 mcg/m2/day Day 8-28	96%	
Blinatumomab cycle 2	15 mcg/m^2/day Day 1-28	31%	
Blinatumomab cycle 3	15 mcg/m^2/day Day 1-28	10%	
Blinatumomab cycle 4 and 5	15 mcg/m^2/day Day 1-28	4%	
Abbreviations: mg, milligrams; mcg, microgram			

Appendix 5C - Clinical data sources

All three trials are non-randomized single-armed studies. However, the patient characteristics were considered similar across all three studies (see Table below). To derive OS and EFS estimates, the individual patient data (IPD) from each trial were combined directly without adjustment.

Table 1 - Patient characteristics for tisagenlecleucel studies

Characteristics	**ELIANA (DCO: 31/12/2017)**	**ENSIGN (DCO:06/10/2017)**	**B2101J (DCO: 31/01/2017)**	**Pooled**
Number of patients Infused	79	58	56	193
Age at diagnosis; mean (SD)	12.0 (5.38)	12.2 (5.3)	11.4 (4.9)	11.9 (5.2)
Proportion female	43.0 %	53.4%	44.6%	46.6%
Weight in kg, mean (SD)	41.9 (23.3)	43.1 (20.0)	39.9 (19.1)	41.7 (21.2)
Abbreviations: DCO, Data Cut-Off; SD, standard deviation				

The base case extrapolation is consistent with the updated B2101 and B2202 (data on file) and latest presentation of ELIANA data (April 2018).[20]

Appendix 5D - Notes on the employed societal perspective in this economic evaluation

There is no unanimous definition of what a 'societal perspective' in cost-effectiveness analysis should entail.[21] In this study we refer to all costs and benefits that are incurred or gained outside the health care sector as costs or benefits from a societal perspective. These include productivity losses of caregivers, travel and hotel costs for patients and caregivers, informal care costs, and future non-medical consumption.

Appendix 5E - The cost-effectiveness model

Since the aim was to estimate the cost-effectiveness of tisagenlecleucel on a patients' lifetime horizon, parametric survival models were established based on the OS and EFS for extrapolation beyond the observed data. For patients that survived five years after any treatment, OS was based on the literature of ALL long-term survivors. This choice was made to mitigate the uncertainties associated with the extrapolation of the survival data.

Vial sharing was not considered when estimating the drug cost in the base-case, but was explored in scenario analyses.

The PSM simulates the movement of a group of patients with the same characteristics over the period of a lifetime horizon. All patients start in the event-free survival (EFS) model states. EFS was defined as the time from the date of treatment initiation to the earliest date of death, relapse, or treatment failure. From EFS patients could either stay in EFS, move to the model state of progressive disease (PD) or die (i.e. move to the model state of death). The PD state included alive patients who relapsed or had a treatment failure. Once in PD, patient could either stay in that model state or die. Death is a so-called absorbing state from which no further transition is possible.

Although not modelled as a distinct model state, HSCT was considered in the model as it is an important clinical pathway for the treatment of r/r pALL. Efficacy benefits of subsequent HSCT were captured in the OS and EFS estimates of each treatment arm (both the intervention and comparator arms). Likewise, the cost and disutility of subsequent HSCT were added separately for each treatment arm.
The model was constructed and adapted in Microsoft Excel®. Some calculations for the survival analysis were performed in R and R Studio (e.g. the extrapolation of the survival curves).

Appendix 5F - Parametric survival extrapolation

Parametric survival modelling was used to fit both OS and EFS data and to project survival estimates in the CEA model. Specifically, the following survival distributions were considered: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised Gamma. Suitable parametric survival curves were chosen based on their goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) and a visual comparison of the survival distribution. The latter was validated by the clinical expert. In case extrapolated EFS would exceed OS, EFS was set equal to OS.

OS

Similar to other studies,[22–24] the observed OS data indicated a plateau phase of survival around the time point of five years. According to the clinical expert such a plateau phase is frequently observed in clinical practice and can be explained by that fact that in pediatric ALL, relapse and treatment-related deaths usually occur shortly after treatment initiation and plateau thereafter. However, the follow-up time of the trials used to populate OS were too short to identify the exact timing of the plateau phase. Therefore, the assumption of a plateau phase at three years and at five years were tested in two separate scenarios. After this period (three or five years), survival was assumed to be similar for all comparators and derived from long-term survival in ALL patients. The latter was modelled using the 2012 Dutch life table, with a mortality adjustment for five-year ALL survivors, using standardized-mortality rates (SMR) published in the literature.[25]

Based on both statistical (AIC/BIC values) and visual (expert opinion) fit, the log-normal distribution was chosen to extrapolate OS.

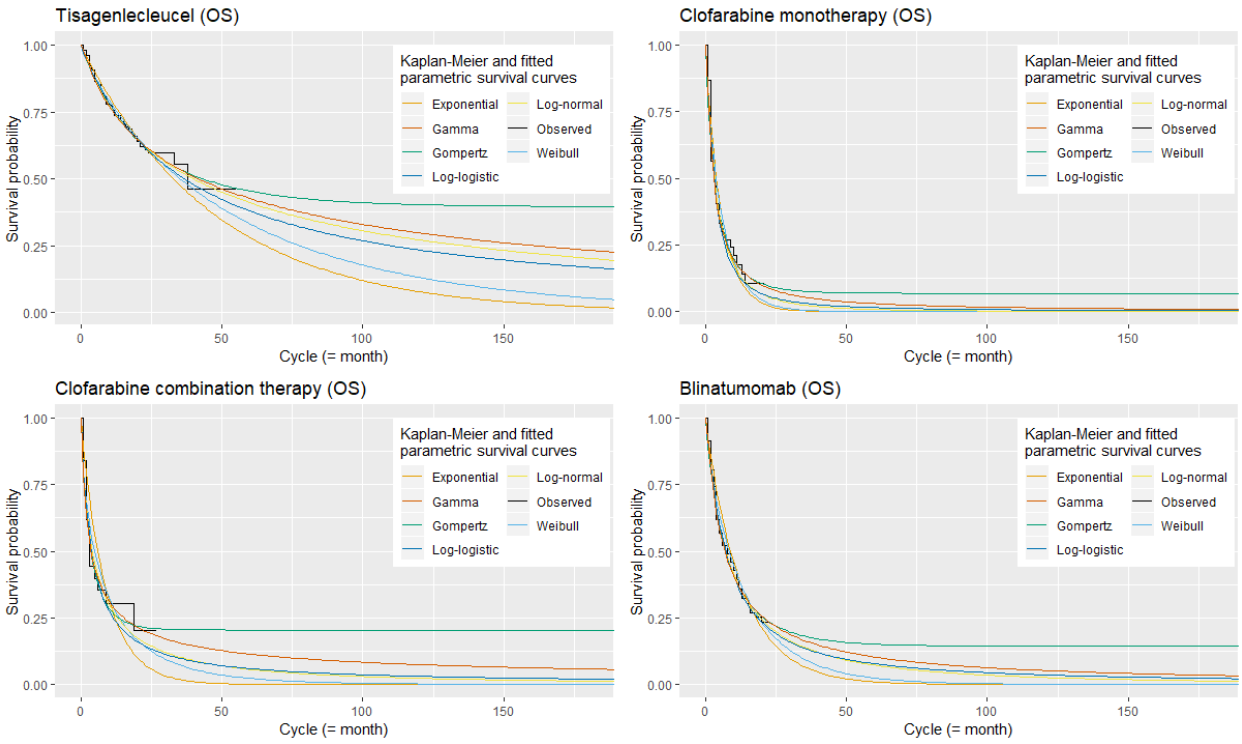


Figure 1 - Parametric survival extrapolation of observed survival data (OS)

Table 1 - Summary of goodness of fit statistics and ranks for OS urvival distributions

Distribution	**AIC[b]**	**AIC rank**	**BIC[b]**	**BIC rank**
Tisagenlecleucel				
Exponential	623.60	6	626.86	2
Weibull	624.00	8	630.53	5
Gompertz	621.30	2	627.82	3
Log-Normal	*619.81*	*1*	*626.34*	*1*
Log-Logistic	621.88	5	628.40	4
Gamma	621.68	3	631.46	6
Spline with single knot[a]	621.85	4	631.64	7
Spline with two knots[a]	623.83	7	636.88	8
Spline with three knots[a]	625.84	9	642.16	9
Spline with four knots[a]	627.84	10	647.41	10
Clofarabine monotherapy				
Exponential	261.42	9	256.29	1

Weibull	262.77	10	257.09	2
Gompertz	257.34	8	266.99	8
Log-Normal	*252.07*	*3*	*261.56*	*4*
Log-Logistic	252.87	4	263.53	6
Gamma	251.93	2	257.66	3
Spline with single knot[a]	251.32	1	261.83	5
Spline with two knots[a]	253.39	5	264.42	7
Spline with three knots[a]	253.87	6	269.14	9
Spline with four knots[a]	256.48	7	269.14	9
Clofarabine combination therapy				
Exponential	109.75	10	110.97	8
Weibull	106.95	9	109.39	7
Gompertz	102.92	2	105.36	1
Log-Normal	*103.04*	*3*	*105.47*	*2*
Log-Logistic	103.52	4	105.96	3
Gamma	103.78	5	107.44	5
Spline with single knot[a]	102.77	1	106.42	4
Spline with two knots[a]	104.04	6	108.92	6
Spline with three knots[a]	106.08	8	112.18	10
Spline with four knots[a]	104.29	7	111.60	9
Blinatumomab				
Exponential	343.79	7	346.04	5
Weibull	344.05	9	348.55	7
Gompertz	340.07	4	344.56	3
Log-Normal	*337.83*	*1*	*342.32*	*1*
Log-Logistic	339.31	3	343.81	2
Gamma	339.12	2	345.87	4
Spline with single knot[a]	340.09	5	346.84	6
Spline with two knots[a]	342.18	6	351.17	8
Spline with three knots[a]	343.79	7	355.03	9
Spline with four knots[a]	345.75	10	359.24	10
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion				

a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.
b. A smaller AIC or BIC value represents a better goodness of fit

EFS

Although the best statistical fit for EFS of tisagenlecleucel was achieved by the Weibull distribution (see eTable 3), the clinical expert found that this would not reflect clinical practice very well since the observed plateau phase was not reflected by this mode. Instead, the Gompertz distribution was the only parametric function, estimating a flat tail. Therefore, the Gompertz distribution was selected to extrapolate EFS in the base-case. For the comparator arms, EFS data was not available in the literature. Therefore, EFS curves for clofarabine monoetherapy, clofarabine combination therapy, and blinatumomab were derived from the available OS curves. We assumed that the cumulative hazard function for EFS would be proportional to cumulative hazard function for OS until the observed plateau phase was reached. This was justified because EFS is highly correlated with OS in cancer patients.[26] The magnitude of the hazard ratio between EFS and OS was based on data from a Dutch pALL study.[27]

To model the plateau phase for all comparators, no possibility of relapse was assumed after the start of the plateau. EFS was hence "flatten up" until it reached OS.

Table 2 - Summary of goodness of fit statistics and ranks for EFS survival distribution

Distribution	**AIC[b]**	**AIC rank**	**BIC[b]**	**BIC rank**
Tisagenlecleucel				
Exponential	264.20	8	266.57	8
Weibull	238.16	1	242.89	1
Gompertz	255.32	7	260.06	7
Log-Normal	240.20	6	244.94	3
Log-Logistic	239.31	3	244.05	2
Gamma	239.56	4	246.67	5
Spline with single knot[a, c]	238.59	2	245.70	4
Spline with two knots[a, c]	239.92	5	249.40	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion
a. Cubic spline models with one, two, three, and four knots expressed on the proportional hazard scale were fitted based on the method developed by Royston 2002.

b. A smaller AIC value represents a better goodness of fit.
c. Cubic spline models with three and four knots could not converge using observed EFS data based on the pooled trial data. No parametric functions were estimated for tisagenlecleucel using these models. The AIC weight calculation was based on the remaining functions.

Appendix 5G - Long-term ALL survival

To derive standard mortality rates (SMR), a literature review was conducted. The estimated SMR-adjusted survival rate was applied to all patients who remain alive at the start of the plateau phase (three or five years after treatment initiation). Four SMR publications for pALL long-term survivors were identified as the most relevant evidence (Table 3). Armstrong et al.[25] was used in the base-case, because it was the most recent study, based upon a very large patient group and specific to ALL survivors. SMR inputs from MacArthur et al., 2007[28] and Bhatia et al., 2005[29] were evaluated in the sensitivity analysis. The SMR rate publishes in Socie et al., 1999[30] were not included in the scenario-analysis since the study was outdated and the SMR were similar to Bhatia et al., 2005.[52] The estimated SMR-adjusted survival rate was applied to all patients who remain alive at the start of the plateau phase (three or five years after treatment initiation).

Table 3 - Standardized-mortality rates found in the literature

Publication	**Population**	**Sample Size**	**SMR Measure**
Base-case			
Armstrong et al., 2016[25]	All childhood cancer survivors diagnosed with cancer before age 21 (paediatric and adolescent) and alive at least 5 years after diagnosis	Overall sample size: 34,033; Sample size for ALL patients: 8,500	SMR for ALL 5-year survivors: 15.2
Scenario analysis			
MacArthur et al., 2007[28]	Individuals less than 20 years of age diagnosed with cancer who survived 5 years or more after diagnosis.	Overall sample size: 2,354; Sample size for ALL patients: 429	SMR for childhood cancer 5-year survivors: 9.05
Bhatia et al., 2005[29]	Paediatric, adolescent, and adult patients who survived two or more	Overall sample size: 854;	SMRs for ALL: 6-10 years from HSCT: 26.5;

	years after autologous HSCT for hematologic malignancies	Sample size for ALL patients: 59	11 or more years from HSCT: 4.2
Other publication (not included in scenario-analysis)			
Socie et al., 1999[30]	Paediatric, adolescent, and adult patients who received allogenic HSCT between 1980 to 1993 and were disease-free 2 years post procedure; 22% of patients were diagnosed with ALL, and among those, 45% received HSCT in CR1, 45% in CR2, and 10% not in remission	Overall sample size: 6,691; Sample size for ALL patients: 1,458	Relative mortality rate for ALL patients vs. general population: 5 years after HSCT: 25.9; 10 years after HSCT: 15.4
Abbreviations: ALL, acute lymphoblastic leukaemia; CR1, first complete remission; CR2, second complete remission; HSCT, haematopoietic stem cell transplant; SMR, standardised mortality ratio			

Appendix 5H - Cost calculations

Relevant willingness-to-pay threshold

To determine the relevant willingness-to-pay (WTP) threshold we used the iMTA Disease Burden Calculator (iDBC) tool.[31] Due to the high disease severity of pediatric r/r ALL, a WTP-threshold of up to 80,000 EUR per QALY gained is suggested for the evaluation of tisagenlecleucel.

Subsequent HSCT

The model assumed patients could receive subsequent HSCT after initial treatment. HSCT costs were considered in three parts: stem cell selection/harvesting, the cost of the transplantation procedure, and the cost of long-term follow-up (Table 5). All HSCT costs were based on the Dutch estimates in Blommestein et al.[32] As the HSCT costs depends upon the type of transplantation, the costs are weighted by the proportion of patients receiving each type of transplantation (20% allogeneic HSCT from a sibling donor, 40% allogeneic HSCT for a matched-unrelated donor and 40% allogeneic HSCT from umbilical cord blood). These proportions were based upon expert opinion.

Table 5 - Average HSCT costs in 2018 Euros

Component	**Cost**	**Source**

Total cost	***€217,590.02***	
HSCT harvesting cost	€66,581.35	Blommestein et al.[32]
HSCT procedure	€44,390.91	Blommestein et al.[32]
HSCT follow-up cost (up to 24 months post HSCT)	€106,617.76	Blommestein et al.[32]
Abbreviations: HSCT, haematopoietic stem cell transplantation		

Follow-up costs

Follow-up costs consisted of the costs of the outpatient visits and laboratory tests and procedures (e.g. full blood count, electrocardiogram, and bone marrow biopsy). The costs were assumed to vary by treatment, health state, and the time of follow-up.
For patients receiving clofarabine monotherapy, clofarabine combination therapy, and blinatumomab who remained in the EFS state, the frequency of follow-up was obtained from the UK Leukaemia and Lymphoma research guideline.[33] No specific Dutch figures were available for these follow-up visits. For patients receiving tisagenlecleucel who remained in the EFS state, the frequency of follow-up was derived from the ELIANA trial protocol.[16] The frequency of follow-up was assumed to be the same for PD state across all comparator arms, and was assumed to be the same as the EFS state of chemotherapies during year 1. Unit costs per provider visit and per test/procedure were informed by the Dutch EE guideline when available.[34] The NZa cost database served as an alternative source for the cost prices.

		Yearly frequency[a]				
Parameter	**Unit cost (2018)**	**Year 1**	**Year 2**	**Year 3-5**	**Years 5+**	**Source for Unit cost**
Tisagenlecleucel						
Consultant visit	€117.21	12	4	2	2	Dutch EE guideline[12]
Haematology panel	€6.83	16	4	2	0	NZa declaration code (2018): 070702 + 070718
Coagulation panel	€3.27	3	0	0	0	NZa declaration code (2018): 070737
Chemistry panel (including liver function test)	€3.57	16	4	2	0	Assumed to be equal to liver function test
Cerebrospinal fluid (CSF)	€24.65	1	0	0	0	NZa declaration code (2018): 074765
Serum test	€0.90	5	0	0	0	NZa declaration code (2010): 070516
B cell and T cell test	€23.23	8	2	2	0	NZa declaration code (2018): 70659
Electrocardiogram (ECG)	€132.18	1	0	0	0	Dutch EE guideline[12]
Bone marrow aspirate	€45.54	3	0	0	0	NZa declaration code (2010): 120095
Bone marrow biopsy	€45.54	3	0	0	0	NZa declaration code (2010): 120095
Echocardiogram	€139.49	0	0	0	0	NZa declaration code (2018): 39494
Liver function test	€3.57	0	0	0	0	NZa declaration code (2018): 074891 + 070489
Chemotherapy regimens						
Consultant visit	€117.21	6	4	2	2	Dutch EE guideline[12]
Haematology panel	€6.83	6	4	2	0	NZa declaration code (2018): 070702 + 070718
Coagulation panel	€3.27	0	0	0	0	NZa declaration code (2018): 070737
Chemistry panel (including liver function test)	€3.57	0	0	0	0	Assumed to be equal to liver function test
CSF	€24.65	1	0	0	0	NZa declaration code (2018): 074765

Serum test	€0.90	0	0	0	0	NZa declaration code (2010): 070516
B cell and T cell test	€23.23	0	0	0	0	NZa declaration code (2018): 70659
ECG	€132.18	0	0	0	0	Dutch EE guideline[12]
Bone marrow aspirate	€45.54	1	0	0	0	NZa declaration code (2010): 120095
Bone marrow biopsy	€45.54	0	0	0	0	NZa declaration code (2010): 120095
Echocardiogram	€139.49	1	0	0	0	NZa declaration code (2018): 39494
Liver function test	€3.57	6	0	0	0	NZa declaration code (2018): 074891 + 070489
Abbreviations: CSF, cerebrospinal fluid; ECG, electrocardiogram; a. Follow up frequencies for tisagenlecleucel were derived from ELIANA.[12] Follow up frequencies for chemotherapy regimens based on UK-specific Leukaemia and Lymphoma research guideline[55]						

Table 4 - Follow-up schedule and unit cost inputs for EFS patients

Parameter	Unit cost	Yearly frequency[a]	Source
Consultant visit	€117.21	6.00	Dutch EE guideline[12]
Haematology panel	€6.83	6.00	NZa declaration code (2018): 070702 + 070718
CSF	€24.65	1.00	NZa declaration code (2018): 074765
Bone marrow aspirate	€45.54	1.00	NZa declaration code (2010): 120095
Echocardiogram	€139.49	1.00	NZa declaration code (2018): 39494
Liver function test	€3.57	6.00	NZa declaration code (2018): 074891 + 070489
Abbreviations: CSF, cerebrospinal fluid; ECG, electrocardiogram; a. The test frequencies are assumed to be the same as first year follow-up frequency based on the UK-specific Leukaemia and Lymphoma Research guideline[55]			

Table 5 - Follow-up schedule and unit cost inputs for PD patients

Adverse event costs

Adverse event (AE) costs were calculated for tisagenlecleucel, clofarabine monotherapy, clofarabine combination therapy, and blinatumomab based on rates of AE and unit costs per AE. The AE rates inputs were obtained from the ELIANA trial data for tisagenlecleucel, Jeha et al. 2006 for clofarabine monotherapy, Hijiya et al. 2011 for clofarabine combination therapy, and von Stackelberg et al. 2016 for blinatumomab.[17–19] Only grades 3 or 4 AEs with greater than 5% rates in any of the arms were considered.

The AE costs were estimated based on the public available data from the Dutch Healthcare authority (opendisdata). This database holds information on so-called DBC products, which represent the average hospital reimbursements for a delivered diagnosis and treatment combination. The AE costs was estimated as the average price of all relevant DBC healthcare products in 2017, weighted by the number of patients who received each DBC healthcare products. It needs to be noted that the database only holds data on already closed healthcare trajectories. For this report, the most recent data was available on 1 September 2018, containing 75% of already closed trajectories in 2017. Costs for anaemia, thrombocytopenia, neutropenia, and febrile neutropenia were based on a retrospective costs analysis of haematological adverse events in chronic myeloid leukaemia patients in the Netherlands.[35]

Intravenous immunoglobulin (IVIG) was considered for the management of B-cell aplasia. Based on the ELIANA trial data, the model considered 73% of the patients that received tisagenlecleucel to also receive IVIG. The average time until B-cell recovery was assumed to be 11.4 months based on the a study by Maude et al.[36]

Grade 3 or 4 AEs > 5% for each comparator

Grade 3 or 4 AEs ≥ 5%	**Tisagenlecleucel**	**Clofarabine monotherapy**	**Clofarabine combination therapy**	**Blinatumomab**	**Unit Cost**	**Source for Unit Cost**
Source for AE rates	ELIANA[18]	Jeha et al. 2006[13]	Hijiya et al. 2011[16]	von Stackelberg et al. 2016[38]		
Acute renal failure	0.0%	0.0%	8.0%	0.0%	€309.20	OPENDIS data
Alanine aminotransferase increased	9.3%	0.0%	28.0%	15.7%	€0.00	Assumed to have no cost as this event category only describes a lab value abnormality, instead of a specific symptom or condition
Anaemia	12.0%	0.0%	64.0%	35.7%	€1,888.84	Bouwmans et al.
Anorexia	0.0%	19.7%	0.0%	0.0%	€1,550.05	OPENDIS data
Aspartate aminotransferase increased	14.7%	0.0%	40.0%	11.4%	€0.00	Assumed to have no cost as this event category only describes a lab value abnormality, instead of a specific symptom or condition
Bacteraemia	0.0%	13.1%	0.0%	0.0%	€3,181.21	OPENDIS data
Coagulopathy	0.0%	0.0%	12.0%	0.0%	€598.54	OPENDIS data
Cytokine-release syndrome	46.7%	0.0%	0.0%	5.7%	€13,373.01	The cytokine-release syndrome event cost is calculated as the sum of ICU admission cost together with

						tocilizumab drug and administration cost.
Decreased appetite	14.7%	0.0%	20.0%	0.0%	€598.45	OPENDIS data
Dermatitis	0.0%	12.0%	0.0%	0.0%	€1,062.22	OPENDIS data
Diarrhoea	1.3%	13.1%	0.0%	0.0%	€553.19	OPENDIS data
Enterococcal bacteraemia	0.0%	0.0%	12.0%	0.0%	€3,181.21	OPENDIS data
Epistaxis	0.0%	13.1%	0.0%	0.0%	€598.45	OPENDIS data
Febrile neutropenia	36.0%	49.2%	60.0%	17.1%	€2,957.93	Bouwmans et al.
Fibrinogen	0.0%	0.0%	0.0%	0.0%	€598.45	OPENDIS data
Gingival bleeding	0.0%	0.0%	12.0%	0.0%	€0.00	Assumed to have no cost as this event category only describes a lab value abnormality, instead of a specific symptom or condition
Hallucination	0.0%	13.1%	0.0%	0.0%	€633.53	OPENDIS data
Haemoglobin	0.0%	0.0%	0.0%	0.0%	€508.96	OPENDIS data
Hepatomegaly	0.0%	12.0%	0.0%	0.0%	€754.82	OPENDIS data
Hyperbilirubinemia	0.0%	0.0%	12.0%	0.0%	€0.00	Assumed to have no cost as this event category only describes a lab value abnormality, instead of a specific symptom or condition

Hypertension	0.0%	9.8%	0.0%	5.7%	€616.14	OPENDIS data
Hypokalaemia	14.7%	0.0%	36.0%	17.1%	€598.45	OPENDIS data
Hypophosphatemia	12.0%	0.0%	12.0%	0.0%	€598.45	OPENDIS data
Hypotension	20.0%	18.0%	24.0%	0.0%	€0.00	Assumed to have no cost as this event category only describes a lab value abnormality, instead of a specific symptom or condition
Increased lipase	0.0%	0.0%	20.0%	0.0%	€ 598.45	OPENDIS data
Leukocytes	0.0%	0.0%	0.0%	0.0%	€1,346.99	Assumed to be equal to the costs of neutropenia reported in Bouwmans et al.[35]
Leukopenia	0.0%	0.0%	16.0%	10.0%	€1,346.99	Assumed to be equal to the costs of neutropenia reported in Bouwmans et al.
Nausea	2.7%	16.4%	12.0%	0.0%	€598.45	OPENDIS data[56]
Neutropenia	0.0%	14.8%	52.0%	17.1%	€1,346.99	Bouwmans et al.
Neutrophil count decreased	26.7%	0.0%	0.0%	12.9%	€1,346.99	Assumed to be equal to the costs of neutropenia reported in Bouwmans et al.
Petechiae	0.0%	12.0%	0.0%	0.0%	€598.45	OPENDIS data
Platelet count decreased	18.7%	0.0%	0.0%	14.3%	€3,549.68	OPENDIS data

Platelets	0.0%	0.0%	0.0%	0.0%	€3,549.68	OPENDIS data
Pleural effusion	0.0%	9.8%	0.0%	0.0%	€704.95	OPENDIS data
Pneumonia	0.0%	9.8%	0.0%	0.0%	€2,336.92	OPENDIS data
Pulmonary edema	0.0%	0.0%	8.0%	0.0%	€1,081.76	OPENDIS data
Pyrexia	13.3%	14.8%	16.0%	14.3%	€1,352.59	OPENDIS data
Respiratory distress	0.0%	12.0%	0.0%	0.0%	€1,442.08	OPENDIS data
Sepsis	0.0%	13.1%	0.0%	0.0%	€3,138.01	OPENDIS data
Septic shock	0.0%	0.0%	12.0%	0.0%	€3,138.01	OPENDIS data
Staphylococcal infection	0.0%	9.8%	0.0%	0.0%	€1,292.57	OPENDIS data
Thrombocytopenia	0.0%	0.0%	64.0%	21.4%	€3,549.68	Bouwmans et al.[35]
Typhlitis	0.0%	0.0%	12.0%	0.0%	€1,307.39	OPENDIS data
White blood cell count decreased	18.7%	0.0%	0.0%	10.0%	€1,346.99	OPENDIS data
Hypocalcaemia	6.7%	0.0%	0.0%	0.0%	€598.45	OPENDIS data
Hypoxia	18.7%	0.0%	0.0%	0.0%	€754.68	OPENDIS data
Lymphocyte count decreased	20.0%	0.0%	0.0%	0.0%	€598.45	OPENDIS data
Blood bilirubin increased	13.2%	0.0%	0.0%	0.0%	€754.82	OPENDIS data

Encephalopathy	6.0%	0.0%	0.0%	0.0%	€2,963.30	OPENDIS data
Total AE Costs	**€9,834.70**	**€4,268.77**	**€8,084.51**	**€4,218.10**		
Abbreviations: AE, adverse event						

Patient and family costs

Patient and family costs consists of traveling costs (including parking), overnight stay at charity hotel and informal care costs. As treatment for r/r pALL is centralized in the Prinses Maxima Centrum, traveling costs were based on the average distance between the capitals of every Dutch province to the city of Utrecht. This average was weighted by the absolute population size of children aged 0 to 20 years per province.

Future medical costs

To avoid an underestimation of healthcare costs in life years gained, future medical costs were considered using the Practical Application to Include future Disease costs (PAID, version 3).[37,38]

Productivity losses

Costs for productivity losses were considered for parents of the paediatrics ALL patients. As no Dutch-specific data was available regarding these productivity losses, information from other European countries (UK and Sweden) was used. Hovén et al. 2013[39] assessed the work situation of parents at different points in time during and after the treatment for paediatric cancer. This study is used to identify the proportion of parents who experience productivity losses at time of second relapse. It was assumed that the second relapse occurred on average 3 months after the end of previous treatment which means that some parents already returned back to their work after an initial period of leave during the previous treatment phase. Eiser & Upton 2006[62] is used to identify the number of days parents took off (compassionate leave, unpaid leave and sick leave) to take care of their child. If the leave was longer than three months, it exceeded the friction cost period and therefore the total time taken off was set equal to the friction costing period in 2017 (101 days). Productivity losses were attributed to the first cycle for all patients and at time of death for patients who died at least 6 months after treatment initiation. It would have been more valid to incorporate these costs to patients with a relapse after 6 months, but it was not feasible to identify newly relapsed patients in the model structure. Since all relapsed patients will die shortly afterwards, and it is feasible to identify newly deaths, it was decided to incorporate productivity

losses at time of death. Productivity losses were only included for patients aged <18 years.

Potential productivity gains

To quantify the potential productivity gains of patients with long-term EFS we used published data on employment situations of long-term young adult survivors of childhood cancer in the Netherlands.[40] For patients in EFS that were older than 18 years of age, we assumed that 53% would be employed, earning a monthly income similar to the average standardized income in the Netherlands (€ 2,535).[40]

Appendix 5I - Disutilities in the model

Three studies were identified from the literature as possible input for the disutility of chemotherapy: Furlong et al. (2012)[41], Rae et al. (2014),[42] and Kwon et al. (2018).[43]Pot We considered the study of Kwon et al. (2018) most reliable as input for the chemotherapy-specific disutility since it was meta-regression based upon a systematic literature review. Furthermore, the disutilities were in line with the disutilities identified from Furlong et al. (2012) and Rae et al. (2014). Although the disutilities are similar for all therapies, the impact on the ICER is mainly determined by the varying duration. It needs to be noted that in probabilistic sensitivity analyses, both treatment-related disutilities together with their duration were varied per treatment regimen. In this way we accounted for the possibility of differing treatment-related disutilities per regimen.

It was assumed that tisagenlecleucel had similar disutility as chemotherapy. Since Kwon et al. (2018) did not report any estimate of duration associated with the reported disutilities, the disutility for chemotherapy and tisagenlecleucel was assumed to last for the duration of the treatment and the duration of hospitalisation, respectively. Both estimates are assumed to capture the utility decrements for all short-term AEs associated with the treatment, with the exception for the cytokine release syndrome (CRS).

Additional treatment disutilities associated with CRS were considered for patients with grades 3 or 4 CRS. The CRS rate for tisagenlecleucel was derived from the ELIANA trial data and the rate for blinatumomab was derived from von Stackelberg et al. 2016.[16,19] Simulated patients were assumed to have a utility of 0 (i.e. a disutility of 0.83 based on the utility of complete remission) for the duration of CRS. For the tisagenlecleucel arm, an additional treatment disutility was also considered for ICU stays not due to CRS by assuming that patients in the ICU would have a utility value of 0.

Patients receiving subsequent HSCT were assumed to have additional HSCT disutility. No paediatric-specific disutilities of an allogeneic HSCT could be found in the literature. Instead disutilities were derived from a systematic review of health state utilities in adult patients with acute myeloid leukaemia (Forsythe et al., 2018).[44]n Consequently, treatment disutility was 0.213 for the first 6 months after transplantation, 0.016 for HSCT recovery 6 to 12 months and 0.173 for patients with GvHD. From month 12 onwards no further HSCT related disutility was assumed with the exception of GvHD. We considered additional age-related decrements as the modelled population became older over the time horizon. These decrements were calculated based health utilities of healthy populations by different age groups using the EQ-5D index population norms and the Dutch time-trade-off value set.[45]e

Appendix 5J - Follow-up schedules

The unit prices for patient and family costs are provided in Table 1. The frequency of travel trips is dependent on the assumed yearly frequency of consultant visits (see Table 2).

Table 2 - Follow-up frequencies of consultant visits

Time	**Yearly frequency of assumed consultant visits**	
	Tisagenlecleucel	**Chemptherapy regimens**
Year 1	12	6
Year 2	4	4
Years 3-5	2	2
Year 5+	2	1

Appendix 5K - Scenario analyses

#	Scenario	Scenario assumption	Incremental costs per QALY gained		
			Clofarabine monotherapy (+/- allo-SCT)	**Clofarabine combination (+/- allo-SCT)**	**Blinatumomab (+/- allo-SCT)**
BASE-CASE RESULTS (societal perspective including future non-medical consumption)			€ 36,378	€ 37,531	€ 31,682
1	Plateau phase	After 3 years	€ 31,798	€ 33,641	€ 29,219
2	Short time horizon I	20 year time horizon	€ 64,749	€ 67,190	€ 57,509
3	Short time horizon II	40 year time horizon	€ 40,727	€ 42,042	€ 35,548
4	Alternative SMR input	Bhatia et al.[52]	€ 31,951	€ 32,888	€ 27,805
5		MacArthur et al.[51]	€ 34,115	€ 35,152	€ 29,698
6	Vial sharing	Consider vial sharing	€ 37,552	€ 38,107	€ 39,026
7	IVIG cost duration assumption	Consider IVIG cost for the entire duration of EFS among those without subsequent HSCT	€ 49,969	€ 52,847	€ 47,932
8	OS for all arms	Exponential	€ 46,563	€ 44,166	€ 37,121
9		Weibull	€ 41,579	€ 41,476	€ 34,059
10		log-logistic	€ 38,965	€ 40,195	€ 34,140
11		Gamma	€ 36,742	€ 40,770	€ 32,561
12		Gompertz	€ 37,282	€ 47,147	€ 33,816
13		Spline with single knot	€ 37,194	€ 44,932	€ 31,598
14		Spline with two knots	€ 36,988	€ 46,728	€ 31,299
15	EFS for tisagenlecleucel	Exponential (approx. 8%	€ 41,870	€ 44,008	€ 37,642

		cured after 5 years)			
16		Weibull (approx. 32% cured after 5 years)	€ 37,276	€ 38,575	€ 32,636
17		log-logistic (approx. 38% cured after 5 years)	€ 36,585	€ 37,771	€ 31,901
18		log-normal (approx. 40% cured after 5 years)	€ 36,364	€ 37,515	€ 31,666
19		Gamma (approx. 30% cured after 5 years)	€ 37,558	€ 38,904	€ 32,937
20		Spline with single knot (approx. 29% cured after 5 years)	€ 37,766	€ 39,146	€ 33,159
21		Spline with two knots (approx. 35% cured after 5 years)	€ 36,893	€ 38,128	€ 32,228
22	Clinical trial data	Use of observed data during trial period	€ 36,491	€ 37,826	€ 31,813
Abbreviations: OS, overall survival; HR, Hazard Ratio; MAIC, Matched-adjusted indirect comparison; IVIQ, intraveneous immunoglobin; EFS, Event-free survival; HSCT, hematopoietic stem cell transplantation					

Appendix 5L - Comparing results to other cost-effectiveness studies

		This study	NICE mock[a] appraisal	Lin et al.[b]	Sarkar et al.[c]	Whittington et al.[d]	CADTH report
Incremental costs							
	Clo-M	EUR 391,879	EUR 559,520 (GBP 503,256)	EUR 248,492 (USD 285,000)	NA	EUR 287,289 (USD 329,498)	EUR 296,795 (CAD 464,323)
	Clo-C	EUR 358,759	NA	EUR 196,178 (USD 225,000)	460,538 (USD 528,200)	NA	EUR 239,556 (CAD 374,774)
	Blina	EUR 285,420	NA	EUR 276,392 (USD 317,000)	NA	NA	EUR 275,117 (CAD 402,248)
Incremental effects							
LYs							
	Clo-M	13.27	11.95	13.00	NA	7.91	13.22
	Clo-C	11.55	NA	12.05	Not stated	NA	9.85
	Blina	10.84	NA	12.05	NA	NA	10.77
QALYs							
	Clo-M	10.77	10.07	5.62	NA	7.18	11.32
	Clo-C	9.56	NA	5.22	8.18	NA	8.61
	Blina	9.01	NA	5.17	NA	NA	9.36
ICER / QALY							
	Clo-M	EUR 32,378	EUR 55,583 (GBP 49,994)	EUR 53,461 (USD 61,315)	NA	EUR 39,995 (USD 45,871)	EUR 32,788 (CAD 51,295)
	Clo-C	EUR 37,531	NA	EUR 37,582 (USD 43,103)	EUR 56,325 (USD 64,600)	NA	EUR 34,768 (CAD 54,393)
	Blina	EUR 31,682	NA	EUR 44,216 (USD 50,712)	NA	NA	EUR 34,356 (CAD 53,749)

Abbreviations: CAD, Canadian Dollar, EUR, Euro; ICER, incremental cost-effectiveness ratio; LY, life years; NA, not applicable; QALY, quality-adjusted life year; USD, US dollar

a. Based on the curative intent scenario

b. Based the scenario '40% 5-year relapse-free survival rate'

c. Based on the base case scenario

d. Whittington et al. report the same results as in the ICER report

Appendices for Chapter 6

Title of Chapter in dissertation: Cost-effectiveness of lenalidomide plus rituximab versus rituximab monotherapy in patients with previously treated follicular lymphoma. A societal view.

Appendix 6A – Methods

Target population and subgroups

The characteristics of the standard patient cohort (base-case patients) were based on individual patient data (IPD) from the AUGMENT study.[46] The AUGMENT publication includes a group of patients with marginal zone lymphoma (MZL, N = 63). In AUGMENT, patients were randomized by stratification for disease histology (FL versus MZL), amongst other strata.[46] Therefore, AUGMENT IPD can be analyzed for FL patients only, without breaking trial randomization. To be consistent with the latest approval for marketing authorization of lenalidomide, we analyzed all patients diagnosed with FL (N = 295).[47] The standard FL patient cohort had a mean age of 61 years (standard deviation [SD]: 11 years), a mean body surface area of 1.85 (SD: 0.24) and 52% were female. Approximately 53% had received one systemic anti-lymphoma regimen prior to R-LEN or R-mono, while the remainder had received two or more prior regimens.

Setting and location

This analysis is performed preliminary for a Dutch setting.

Study perspective

Perspectives considered are: healthcare, societal, and societal plus future non-medical costs. The latter two are further described in the methods section of the paper. The healthcare perspective is defined below.

Healthcare perspective

The healthcare perspective in this study comprises health sector costs (i.e. drug acquisition, drug administration), adverse events (AEs), follow-up care (e.g. subsequent

treatment and routine check-ups) and future medical cost (i.e. medical costs related and unrelated to the modelled disease).

Comparators

Treatment schedules of R-mono and R-LEN were based on the AUGMENT treatment schedules.[46]

Rituximab monotherapy (R-mono)

Rituximab 375 mg/m2 subcutaneously (very first dose intravenously) on days 1, 8, 15, and 22 in cycle 1 and on day 1 of every subsequent 28-day cycle until cycle 5

Rituximab plus lenalidomide (R-LEN)

The dosing schedule of rituximab in R-LEN is similar to the schedule of R-mono. According to the AUGMENT trial protocol, both dosing and dose adjustments of lenalidomide are dependent on the patients' creatinine clearance level. Patients with a creatinine clearance of 60 mL/min (1.0 mL/sec) received oral lenalidomide at a dose of **20 mg**. Patients with moderate renal insufficiency and a creatinine clearance level of 30mL/min but < 60 mL/min (0.5 mL/sec but <1.0 mL/sec) received a starting dose of **10 mg**. In case patients stayed free of drug-related Grade 3 or 4 toxicities for at least 2 cycles, the dose could be increased to **15 mg** at the discretion of the treating physician. When toxicities occurred or persisted, dose adjustments were possible, depending on the starting dose. In this case **5 mg** or **2.5 mg** doses were allowed. For the model base case, the proportion of doses were derived from the AUGMENT trial data. Per cycle, the proportion of all allowed dosages (i.e. 2.5 - 10 mg) was calculated based on the number of patients that received the drug during the respective cycle.

Time horizon

Lifetime horizon (defined in methods section of the study).

Discount rate

To adjust for the effect of differential timing (i.e. some costs and consequences occurring later in time than others), both costs and effects were discounted according to the Dutch EE guideline at 4% and 1.5%, respectively.[48]

Choice of health outcomes

Considered health outcomes were life years (LYs) and quality adjusted life years (QALYs).

Measurement of effectiveness

Probabilities for the model state membership

Probabilities for the model state membership were determined based on partitioned survival analyses for overall survival (OS) and progression-free survival (PFS) as explained by Latimer (2013).[49] Progression-free-survival (PFS) and overall survival (OS) of R-LEN and R-mono were extrapolated based on AUGMENT data of FL patients (independent review committee [IRC] dataset submitted to the EMA).

Internal validity of the parametric functions was assessed through visual inspection and statistical goodness-of-fit criteria (i.e. Akaike's Information Criterion, and the Bayesian Information Criterion).[50] External and clinical validity was confirmed by several clinical experts in the field of hematology-oncology. Since long-term survival extrapolation can exceed general population mortality, we adjusted for this by modelling background survival using Dutch life tables. In addition, we implemented a finite treatment effect for R-LEN on both OS and PFS extrapolations five years after treatment start. Consequently, the hazard ratio of the two parametric survival curves was kept constant as of this time point.

Visual inspection of the log-cumulative hazards plots suggested that proportional hazards cannot be assumed for either PFS or OS. Hence, the treatment arms (i.e. R-LEN and R-mono) were extrapolated separately.

Empirical PFS and its extrapolation of are depicted in Figure 1and Figure 2.

Corresponding AIC and BIC values are summarized in Table 3 and Table 4.

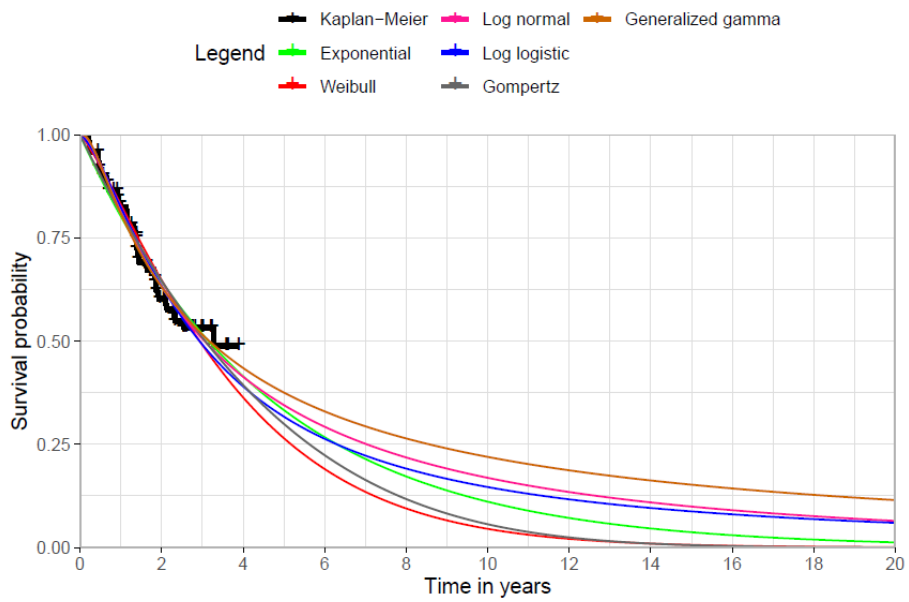


Figure 1 - Empirical and extrapolated PFS: R-LEN

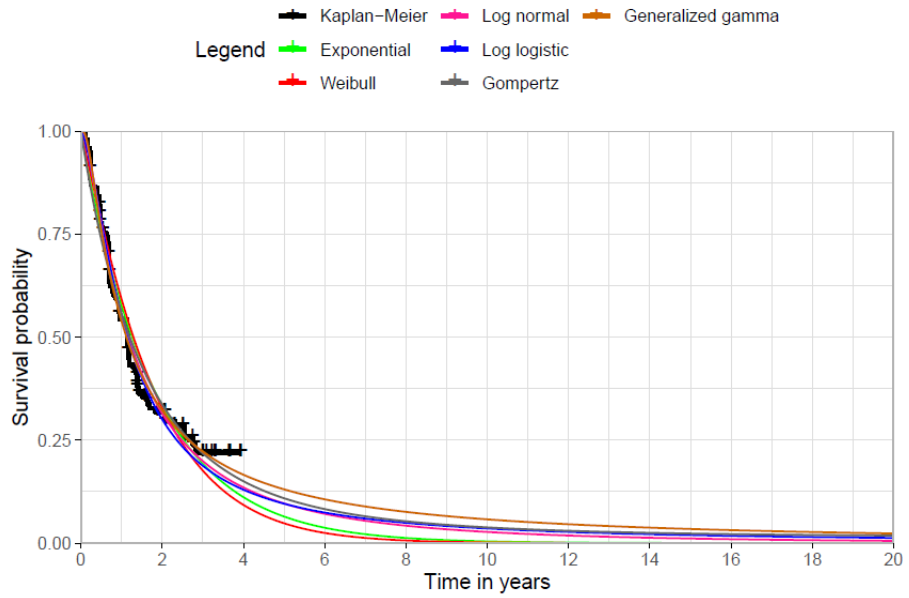


Figure 2 - Empirical and extrapolated PFS: R-mono

Table 3 - AIC, BIC and estimated median survival of R-LEN PFS, based on AUGMENT IPD

Type	Median survival (years)	AIC	AIC rank	BIC	BIC rank
Observed	3.3	NA	NA	NA	NA
Exponential	3.2	944.49	5	947.48	3
Weibull	2.9	943.81	4	949.80	5
Log normal	3.1	939.19	1	945.17	1
Log logistic	2.9	941.10	3	947.08	2
Gompertz	3.1	946.33	6	952.31	6

Generalized gamma	3.2	940.79	2	949.76	4
AIC = Akaike's information criterion, BIC = Bayesian Information Criterion, NA = Not applicable					

Table 4 - AIC, BIC and estimated median survival of R-mono PFS, based on AUGMENT IPD

Type	**Median survival (years)**	**AIC**	**AIC rank**	**BIC**	**BIC rank**
Observed	1.2	NA	NA	NA	NA
Exponential	1.3	1517.31	4	1520.31	4
Weibull	1.3	1518.19	6	1524.18	6
Log normal	1.2	1502.77	2	1508.76	1
Log logistic	1.2	1505.14	3	1511.13	2
Gompertz	1.2	1517.96	5	1523.95	5
Generalized gamma	1.1	1502.76	1	1511.75	3
AIC = Akaike's information criterion, BIC = Bayesian Information Criterion, NA = Not applicable					

Empirical OS and its extrapolation of are depicted in Figure 1and Figure 2. Corresponding AIC and BIC values are summarized in Table 3 and Table 4.

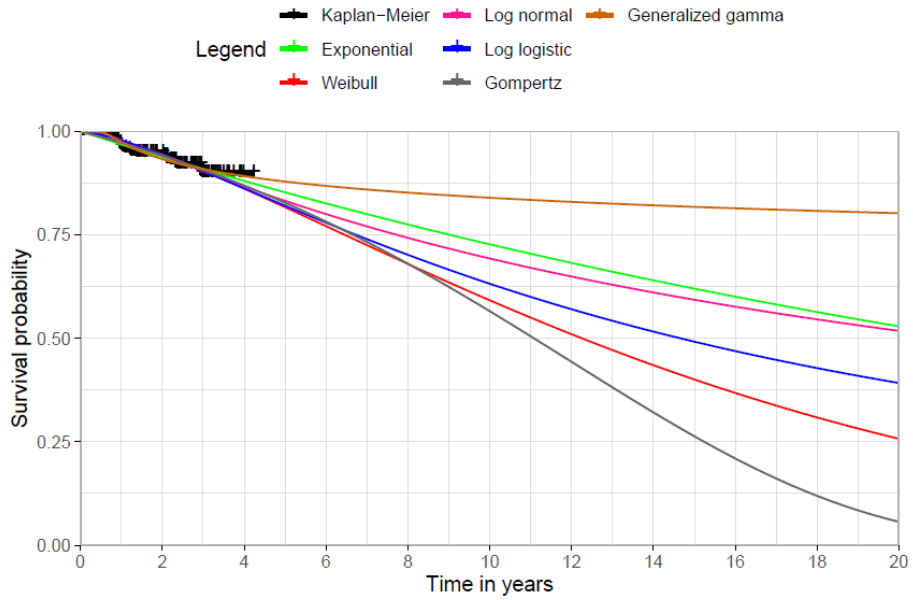


Figure 3 - Empirical and extrapolated OS: R-LEN

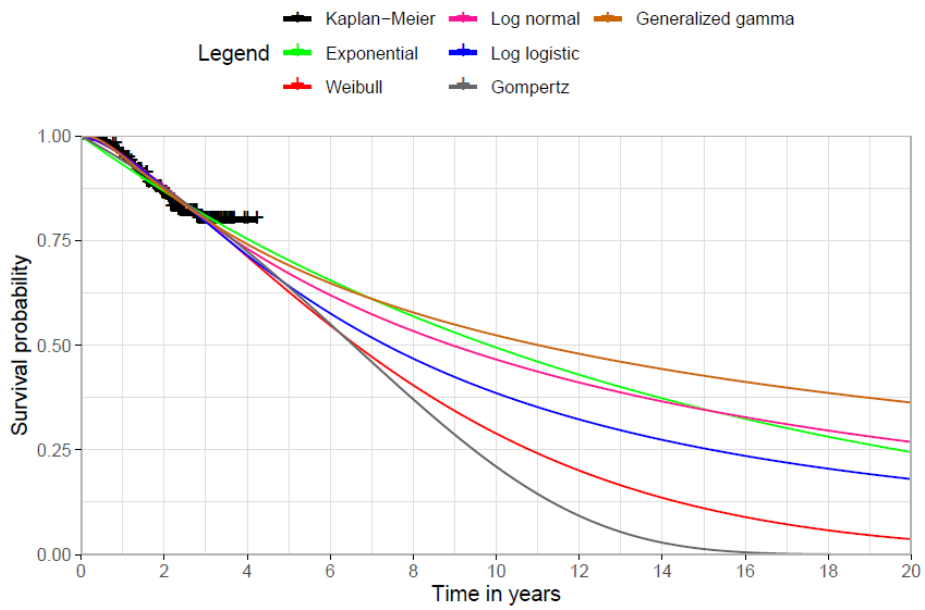


Figure 4 - Empirical and extrapolated OS: R-mono

Table 5 - AIC, BIC and estimated median survival of R-LEN OS, based on AUGMENT IPD

Type	Median survival (years)	AIC	AIC rank	BIC	BIC rank
Observed	Not reached	NA	NA	NA	NA
Exponential	21.8	229.63	3	232.62	1
Weibull	12.3	230.48	5	236.46	4
Log normal	24.4	229.30	2	235.28	2
Log logistic	14.7	230.34	4	236.32	3
Gompertz	11.1	231.45	6	237.44	5
Generalized gamma	Not reached	228.48	1	237.45	6
AIC = Akaike's information criterion, BIC = Bayesian Information Criterion, NA = Not applicable					

Table 6 - AIC, BIC and estimated median survival of R-mono OS, based on AUGMENT IPD

Type	Median survival (years)	AIC	AIC rank	BIC	BIC rank
Observed	Not reached	NA	NA	NA	NA
Exponential	9.8	460.59	5	463.59	1
Weibull	6.6	459.56	4	465.56	4
Log normal	8.9	457.63	1	463.62	2
Log logistic	7.4	458.89	2	464.88	3
Gompertz	6.6	461.95	6	467.94	5
Generalized gamma	11	459.42	3	468.41	6
AIC = Akaike's information criterion, BIC = Bayesian Information Criterion, NA = Not applicable					

General population mortality

The economic model considered general population mortality (i.e. background mortality) to ensure that none of the extrapolated OS curves can exceed general population mortality. Background survival was modelled using the 2016 Dutch life table from the human mortality database (HMD). Latest available data for the Netherlands were from 2019 and covered the years 1850 through 2016 (the latter is the latest year with complete data). HMD for females and male were combined to calculate the pooled estimate. This was based on the observed female to male ratio (female = 52%) in AUGMENT. The reported HMD rates were converted to probabilities.[51]

Measurement and valuation of preference based outcomes

To calculate health state utility values for the model, the subsequent analyses were based on IPD from AUGMENT. The observed utilities were valued with the Dutch value set.[52]

Health-state utilities for the economic model were estimated following the pertinent ISPOR Good Research Practices Task Force Report.[53] Consequently, the HRQoL data were:

1. Analyzed based on the needs of the economic analysis, meaning utilities were analyzed with the aim to determine average population utilities for the model health states;
2. transformed with a simple linear transformation ($X = 1 - U$) to use common methods for analyzing right-skewed data (in this case a generalized estimating equation [GEE]);
3. modelled to explicitly include prognostic factors (to potentially increase the generalizability of results).

The appropriate GEE model was selected in a two-stepped fashion. First, GEE random effects models (i.e. assuming an "independent" working correlation structure)[54] were fitted with the R package geepack (version 1.2.1)[55] to a "training" dataset containing a random sample of 80% of the HRQoL evaluable population in AUGMENT. The best three performing models, were selected based on the "quasi-likelihood under the independence model criterion" (QIC).[56] Each of these three models were updated with the following working correlation structures: "autoregressive" (also known as

multiplicative or *time series*),[54] "exchangeable", and "unstructured". Per model, the best working correlation structure was chosen based on its QIC. Model QICs and their ranks (based on the QIC) were calculated using the R package MuMIn (version 1.43.15). Second, the best fitting three models were used to predict the utilities of the remaining 20% of the HRQoL evaluable population in AUGMENT. To compare the model fits, the root mean squared error (RMSE) was calculated. Finally, the model with the lowest RMSE was chosen to estimate utilities for the model, based on the entire HRQoL evaluable population in AUGMENT.

The predicted mean (also referred to a marginal mean), including confidence intervals from the final GEE model was estimated using the R package emmeans (version 1.4.3.1). The scope of the GEE model was based on all possible combinations of the independent variables which resulted in a total of 129 models. The intercept-only model was chosen to calculate the estimated marginal utility mean as it was the simplest model and showed both the lowest QIC and RMSE. The estimated marginal mean was 0.856 (SE: 0.009) when back-transferred from utility decrements to utilities. This value was used for the model base case.

For a scenario analysis, we used other utilities from a commonly cited source in cost-effectiveness analysis in the field of FL.[57] According to this study, the utility value for PFS and PD were 0.805 and 0.736, respectively.

Estimating resources and costs

Treatment costs

Drug prices were taken from the Dutch drug database (G-standaard) via the Z-index (version April 2020).[58] All administration costs were based on a micro-costing study of intravenous and subcutaneous (s.c.) administration of rituximab in the Netherlands.[59] According to clinical expert opinion, s.c. administration of rituximab is considered for R-mono therapy or when the combination drug can be given orally (p.o.). Therefore, rituximab in R-LEN and R-mono was assumed the be administered s.c. in the base-case. Drug prices for lenalidomide and rituximab are mentioned in the study. All other costs are reported in the table below.

Table 7 - Drug prices (other than rituximab and lenalidomide)

Treatment	administration	contents	unit	price incl. VAT
Cyclophosphamide	i.v.	500	mg	€ 8.87
	i.v.	750	mg	€ 42.76
	i.v.	1000	mg	€ 14.02
	i.v.	2000	mg	€ 38.58
Vincristine	i.v.	1	mg	€ 11.09
	i.v.	2	mg	€ 22.18
Prednisone	p.o.	2.5	mg	€ 0.37
	p.o.	5	mg	€ 0.05
	p.o.	20	mg	€ 0.65
	p.o.	30	mg	€ 0.64
Doxorubicin	i.v.	10	mg	€ 10.89
	i.v.	20	mg	€ 21.80
	i.v.	50	mg	€ 54.53
	i.v.	100	mg	€ 109.07
	i.v.	200	mg	€ 218.15
Obinutuzumab	i.v.	1000	mg	€ 3,892.41
Bendamustine	i.v.	25	mg	€ 51.19
	i.v.	100	mg	€ 220.62
Idelalisib	p.o.	100	mg	€ 65.68
	p.o.	150	mg	€ 65.68

Follow-up

According to the HOVON Clinical Practice Guideline (CPG) 2020, after two years of follow-up, the frequency of most resource use decreases (e.g. visits decrease from 3-monthly to 6-monthly visits).[60] Since the guideline does not distinguish between follow-up in progression and progression free, the model assumes that for patients in PD, the resource use frequency will not decrease. The follow-up schedule for patients in PFS and PD is summarized in Table 8.

Table 8- Follow-up schedule based on HOVON 2020

Type	Details	PFS		PD
		Year 1-2	After years 2	All years

Medical history; physical examination	Presence of B-symptoms; lymphadenopathy, hepatosplenomegaly	3-monthly	6-monthly	3-monthly
Laboratory	Hb, WBC, platelets, LDH, creatinine	3-monthly	6-monthly	3-monthly
	TSH	yearly	yearly	yearly
Imaging	Abdominal ultrasound[a]	6-monthly	yearly	6-monthly
	CT	NA	NA	Newly progressed[b]
[a]Abdominal ultrasound is optional and assumed for all patients in the model to keep estimates conservative; [b]CT imaging is only recommended in case of suspecting a progression; NA = not applicable				

According to HOVON CPG 2020, CT imaging is recommended only in case of suspecting progression. In the model, all newly progressed patients are assumed to receive a CT scan. It was assumed that follow-up visits requiring a medical history and physical examination are done at the outpatient clinic of a haemato-oncology hospital department.

Subsequent treatment

For all newly progressed patients in the model, subsequent treatment was assumed as a one-time cost. According to clinical experts, possible treatment options after R-LEN and R-mono include R + cyclophosphamide + vincristine + prednisolone (R-CVP), R + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP), R + bendamustine (R-benda), Idelalisib, and obinutuzumab plus bendamustine (O-benda). The treatment schedule was taken from the HOVON CPG 2020.[60] In short, R-benda and O-benda were assumed for six treatment cycles. Since idelalisib is recommended until disease progression, 11 months until progression were assumed based on Gopal et al. (2014).[61]

The distribution of subsequent treatments was based on expert opinion are summarized in Table 9.

Table 9: Distribution of subsequent treatment lines

Treatment type	Distribution after R-LEN	Distribution after R-mono

R-CVP	21%	21%
R-CHOP	21%	21%
R-benda	21%	21%
Idelalisib	16%	16%
O-benda	21%	21%

Adverse events

The frequency and types of AEs (i.e. grade 3-4 AEs with more than 5% occurrence in AUGMENT) included in the model base case analysis are summarized in Table 10.

Table 10: Considered AEs from AUGMENT

Adverse event	**N (proportions)**	
	R-LEN	**R-mono**
Neutropenia	74 (0.5)	18 (0.12)
Leukopenia	10 (0.07)	3 (0.02)
Anemia	7 (0.05)	1 (0.01)

Disutilities for neutropenia and anemia were taken from Nafees et al. (2008),[62] and Swinburn et al. (2010),[63] respectively. Values for leukopenia could not be found and were assumed equal to neutropenia, similar to the assumption of its costs. An overview of the considered disutility values is presented in Table 11.

Table 11: AE disutility values

Adverse event	**Disutility**	**Standard error**	**Source**
Leukopenia	0.090	0.015	Assumed same as Neutropenia
Neutropenia	0.090	0.015	Nafees et al. (2008)[62]
Anemia	0.119	0.023	Swinburn et al. (2010)[63]

AE frequencies were valued with prices for anaemia (€ 1,595) and neutropenia (€ 1,171) based on a retrospective costs analysis of hematological adverse events in chronic myeloid leukemia patients in the Netherlands.[35] Since no costs for leukopenia could be found in the literature, these costs were assumed to be equal to the costs of neutropenia.

Resource use and costs considered for the societal perspective

Travel

For the average distance of simulated patients to the hospital and all prices regarding their travel, we referred to the Dutch costing manual.[34]

Productivity losses

Since the actual retirement age in the Netherlands (66 years) was later than the age of the standard patient population, we considered productivity losses following the friction cost method.[64,65] Dutch data on the friction period (15.3 weeks), the percentage of the working population (68% aged 55-65 years) and the average number of working hours (32 hours/week, pooled for men and women) were retrieved from the latest available data of Statistics Netherlands.[66] We assumed that 50% of patients returned to work after front-line therapy,[67] meaning that we attributed productivity losses to 34% (68% of 50%) of the simulated patients.

Informal care

Informal care resource use (i.e. hours of care per week) was estimated using the AUGMENT IPD on patients' health-related quality of life (HRQoL) and the iCARE tool (version 1.0).[68,69] This resource use was valued with prices from the Dutch costing manual.[34]

Currency, price date, and conversion

All costs in this study are expressed in 2019 Euros and prices of earlier years were indexed to 2019 with the pertinent consumer price index.[66]

Choice of model

A three-state partitioned survival model was used and is explained in the study. The model simulation was performed in Microsoft Excel, while AUGMENT IPD were analyzed in R Studio for R.

Cost-effectiveness model

The simulation extends over the entire patient life (i.e. lifetime horizon) and assumes a four-weekly cycle length. Several input parameters were used to estimate the relative effectiveness and costs of R-LEN when compared to R-mono. These included different

cost items, toxicity, quality of life, disease progression and survival of the simulated cohort.

Assumptions

Several assumptions were made for the model base-case which were validated with the clinical experts.

Rituximab

The use of biosimilars of rituximab is allowed as per HOVON2020 guideline.[60] Some medical experts stated that rituximab biosimilars are widely used in clinical practice as their price is substantially lower when compared to the branded product. However, the list prices (according to the z-index) of these biosimilars are similar to the reference drug as discounts are given at the hospital level and are confidential. Therefore, this analysis does not distinguish between reference or biosimilar drugs for rituximab. Furthermore, rituximab can be given subcutaneously (s.c.) at physician's discretion, as long as the first dose is given intravenously (i.v.). The economic model accounted for the latter. According to the clinical experts, rituximab is however usually given i.v. due to lower prices of rituximab biosimilars (i.v.) when compared to the rituximab (s.c.). Since the list prices of rituximab and its biosimilars were equal, the mentioned price difference does not apply to the model. Following the clinicians' opinion, rituximab s.c. applications are considered for rituximab monotherapy and when all combination drugs can be substituted either s.c. or orally (p.o.). For R-LEN and R-mono, the proportion of patients receiving rituximab s.c. was therefore assumed to be 100% in the model case, with the exception of the very first administration being i.v..

Lenalidomide

According to the AUGMENT trial protocol,[46] both dosing and dose adjustments of lenalidomide are dependent on the patients' creatinine clearance level. Patients with a creatinine clearance of 60 mL/min (1.0 mL/sec) received oral lenalidomide at a dose of 20 mg. Patients with moderate renal insufficiency and a creatinine clearance level of 30mL/min but < 60 mL/min (0.5 mL/sec but <1.0 mL/sec) received a starting dose of 10 mg. In case patients stayed free of drug-related Grade 3 or 4 toxicities for at least 2

cycles, the dose could be increased to 15 mg at the discretion of the treating physician. When toxicities occurred or persisted, dose adjustments were possible, depending on the starting dose. In this case 5 mg or 2.5 mg doses were allowed. For the model base case, the proportion of doses were derived from the AUGMENT trial data. Per cycle, the proportion of all allowed dosages (i.e. 2.5 - 10 mg) were calculated based on the number of patients that received the drug during the respective cycle. The total number of patients that received lenalidomide throughout the twelve cycles in AUGMENT are listed in Table 12.

Table 12: Number and proportion of patients receiving lenalidomide per treatment cycle in AUGMENT

Cycle	Patients receiving lenalidomide (N)	Lenalidomide dosing				
		2.5 mg	5 mg	10 mg	15 mg	20 mg
1	175	0 %	0 %	13.7 %	0 %	86.3 %
2	169	0 %	1.8 %	13.0 %	5.9 %	79.3 %
3	166	0 %	3.0 %	9.6 %	12.7 %	74.7 %
4	158	0 %	3.2 %	12.0 %	16.5 %	68.4 %
5	158	0.6 %	4.4 %	13.3 %	20.9 %	60.8 %
6	155	1.3 %	5.8 %	12.9 %	21.9 %	58.1 %
7	147	2 %	7.5 %	12.9 %	19.7 %	57.8 %
8	140	1.4 %	7.9 %	13.6 %	20.7 %	56.4 %
9	136	0.7 %	6.6 %	16.2 %	19.9 %	56.6 %
10	130	2.3 %	6.2 %	18.5 %	19.2 %	53.8 %
11	127	2.4 %	7.1 %	18.1 %	18.9 %	53.5 %
12	125	2.4 %	6.4 %	20.0 %	17.6 %	53.6 %
mg = milligram						

In a scenario analysis we assumed that all patient would receive the full starting dose (20 mg) throughout the treatment period to the influence of this assumption on the ICER (see scenario results).

Analytical methods

LYs were estimated based on the extrapolated survival considering general population mortality and the assumed treatment effect (see model transition probabilities). To derive QALYs, we valued these LYs with HRQoL utilities collected in AUGMENT through the EQ-5D-3L questionnaire.[70]

Deterministic sensitivity analysis (DSA)

For the DSA, we changed relevant model input parameters to values representing upper and lower bounds. These bounds were assumed to be in the upper or lower 25th percentile of a pre-specified distribution. While costs were assumed to follow a gamma distribution (i.e. they were non-negative and right-skewed), proportions and utilities were assumed to follow a beta distribution to ensure that values stayed within the bounds of 0 and 1.

Probabilistic sensitivity analysis (PSA)

The PSA was conducted with a Monte-Carlo simulation of 1,000 iterations. In each iteration, the model inputs were randomly drawn from the pre-specified distributions (gamma, beta, or normal). The efficacy inputs were modelled using parametric estimated of bootstrapped samples of the original IPD for PFS and OS estimations in the base-case. Whenever available, the standard error (SE) of the selected distributions was obtained directly from the same data source that informed the mean value. In the absence of this data, the SE was assumed to be 10% of its mean values.

Scenario analyses

The conducted scenario analyses are summarized in the table below.

Table 13 - Scenario analyses

Scenario Number	**Scenario name**	**Scenario description**
1	Utilities: Wild et al.	Utility values based on Wild et al. (PF: 0.805; PD: 0.736)
2	Utilities: AE disutilities	Assuming utility decrements for adverse events. Neutropenia: 0.090[62] Leukopenia: same as neutropenia Anaemia: 0.119[63]
3	Utilities: no age-adjustment	No age-adjusted utility decrements
4	Drug administration: all R i.v.	Intravenous drug administration for rituximab assumed for all treatment regimens containing rituximab
5	Drug administration: all R s.c.	Subcutaneous drug administration for rituximab assumed for all treatment regimens containing rituximab

6	Drug administration: assume no vial sharing	No vial sharing is assumed.
7	Lenalidomide not based on AUGMENT (20mg dosing)	All patients in R-LEN are assumed to receive 20mg of lenalidomide (maximum dose) during the entire treatment duration.
8	Treatment effect duration: 3 years	Treatment effect waning assumed after three years post treatment.
9	Treatment effect duration: 7 years	Treatment effect waning assumed after seven years post treatment.
10	Treatment effect duration: 10 years	Treatment effect waning assumed after ten years post treatment.
11	Treatment effect duration: infinite	No treatment effect waning assumed post treatment (i.e. distribution of patients in each model state entirely based on parametric extrapolation).
12	PFS distribution R-LEN & R-mono (AUGMENT): Exponential	Alternative parametric distribution selected to model PFS.
13	PFS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	Alternative parametric distribution selected to model PFS.
14	PFS distribution R-LEN & R-mono (AUGMENT): Gompertz	Alternative parametric distribution selected to model PFS.
15	PFS distribution R-LEN & R-mono (AUGMENT): Log-logistic	Alternative parametric distribution selected to model PFS.
16	PFS distribution R-LEN & R-mono (AUGMENT): Log-normal	Alternative parametric distribution selected to model PFS.
17	OS distribution R-LEN & R-mono (AUGMENT): Exponential	Alternative parametric distribution selected to model OS.
18	OS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	Alternative parametric distribution selected to model OS.
19	OS distribution R-LEN & R-mono (AUGMENT): Gompertz	Alternative parametric distribution selected to model OS.
20	OS distribution R-LEN & R-mono (AUGMENT): Log-logistic	Alternative parametric distribution selected to model OS.
21	OS distribution R-LEN & R-mono (AUGMENT): Weibull	Alternative parametric distribution selected to model OS.
22	Drug price: lenalidomide -10%	Price discount of 10% for lenalidomide.
23	Drug price: lenalidomide -20%	Price discount of 20% for lenalidomide.
24	Drug price: lenalidomide -30%	Price discount of 30% for lenalidomide.
25	Drug price: lenalidomide -40%	Price discount of 40% for lenalidomide.
26	Drug price: lenalidomide -50%	Price discount of 50% for lenalidomide.

27	Average starting age: 62 years	Average cohort starting age set to 62 years
28	Average starting age: 64 years	Average cohort starting age set to 64 years
29	Average starting age: 66 years	Average cohort starting age set to 66 years
30	Average starting age: 68 years	Average cohort starting age set to 68 years
31	Average starting age: 70 years	Average cohort starting age set to 70 years
32	Average starting age: 72 years	Average cohort starting age set to 72 years

Appendix 6B – Results

Burden of disease

We used the iMTA Disease Burden Calculator (iDBC) tool to determine the pertinent willingness-to-pay threshold. Input variables for the mean population age (61 years) and percentage of males in the population (48%) were based on AUGMENT IPD. Relevant parameters for the standard of care (SoC) such as the remaining life expectancy and QALYs were based on the model estimates for R-mono. Uncertainty around the estimates are calculated by the tool, using model PSA estimates (1,000 iterations) of the undiscounted QALYs of R-mono. The results of the iDBC indicate two possible WTP thresholds for this analysis. A threshold of € 20,000 or € 50,000 per QALY gained are applicable with a probability of 48.4% and 51.6%, respectively (see Table 14).

Table 14: iDBC results

Items	**R-mono**	
	Deterministic results	**Probabilistic results; mean (95% CI)**
Model-estimated remaining QALY (undiscounted average of 1,000 simulations)	10.93	10.93 (10.53 - 11.32)
QALYS without diseases (corrected for age and gender; iDBC calculated)	18.74	18.38 (17.35 – 19.30)
Absolute QALY loss (absolute shortfall, iDBC calculated)	7.81	7.45 (8.77 – 6.03)
Proportional shortfall (iDBC calculated)	0.42	0.41 (0.38 – 0.43)
Applicable threshold (iDBC calculated)	€ 80,000: 0%	

	€ 50,000: 51.6% € 20,000: 48.4%

Discounted results

Healthcare perspective

Total costs from a healthcare perspective were 165,547 EUR for R-LEN and 102,223 EUR for R-mono.

Total incremental costs of R-LEN from a healthcare perspective were 63,324 EUR, and 50,848 EUR when future medical costs were not considered. The ICER was 37,951 EUR/QALY gained from a healthcare perspective (30,659 EUR/QALY when excluding future medical costs).

Full societal perspective (including future non-medical costs)

With a societal perspective including future non-medical costs, costs for R-LEN and R-mono increased to 299,943 EUR and 217,687 EUR, respectively.

Undiscounted results

Table 15 - Undiscounted costs and effects

		Costs in EUR										Effects	
Perspective		*Drug acquisition*	*Drug administration*	*Adverse events*	*Subsequent treatment*	*Follow-up*	*Informal care*	*Productivity losses*	*Future medical (unrelated diseases)*	*Future non-medical*	*Total costs*	*Life years (PFS; PD)*	*QALYs (PFS; PD)*
Societal	R-LEN	58,445	1,111	745	22,774	12,829	41,358	6,169	138,409	NA	**281,841**	15.1 (3.4; 0)	12.5 (2.9; 9.7)
	R-mono	7,015	696	177	22,774	11,087	34,721	6,165	114,885	NA	**197,521**	12.6 (1.8; 10.9)	10.5 (1.5; 9.1)
	Increments	51,430	415	568	0	1,742	6,636	4	23,524	NA	**84,320**	2.4 (1.6; 0.8)	2 (1.4; 0.6)
Healthcare	R-LEN	58,445	970	745	22,564	12,487	NA	NA	138,409	NA	**233,620**	15.1 (3.4; 0)	12.5 (2.9; 9.7)
	R-mono	7,015	595	177	22,564	10,799	NA	NA	114,885	NA	**156,035**	12.6 (1.8; 10.9)	10.5 (1.5; 9.1)
	Increments	51,430	374	568	0	1,688	NA	NA	23,524	NA	**77,585**	2.4 (1.6; 0.8)	2 (1.4; 0.6)
Societal incl. future non-medical consumption costs	R-LEN	58,445	1,111	745	22,774	12,829	41,358	6,169	138,409	145,501	**427,341**	15.1 (3.4; 0)	12.5 (2.9; 9.7)
	R-mono	7,015	696	177	22,774	11,087	34,721	6,165	114,885	122,284	**319,805**	12.6 (1.8; 10.9)	10.5 (1.5; 9.1)
	Increments	51,430	415	568	0	1,742	6,636	4	23,524	23,216	**107,536**	2.4 (1.6; 0.8)	2 (1.4; 0.6)

Table 16 - Undiscounted ICERs

	Perspective		
	Societal	***Healthcare***	***Societal incl. future non-medical consumption costs***
Incremental costs (EUR) per LY gained	34,888	32,101	44,494

Incremental costs (EUR) per QALY gained	42,076	38,715	53,662

Probabilistic sensitivity analysis

Healthcare perspective

Assuming a WTP-threshold of 50,000 EUR/QALY gained, the probability of R-LEN being cost-effective was 82% from a healthcare perspective.

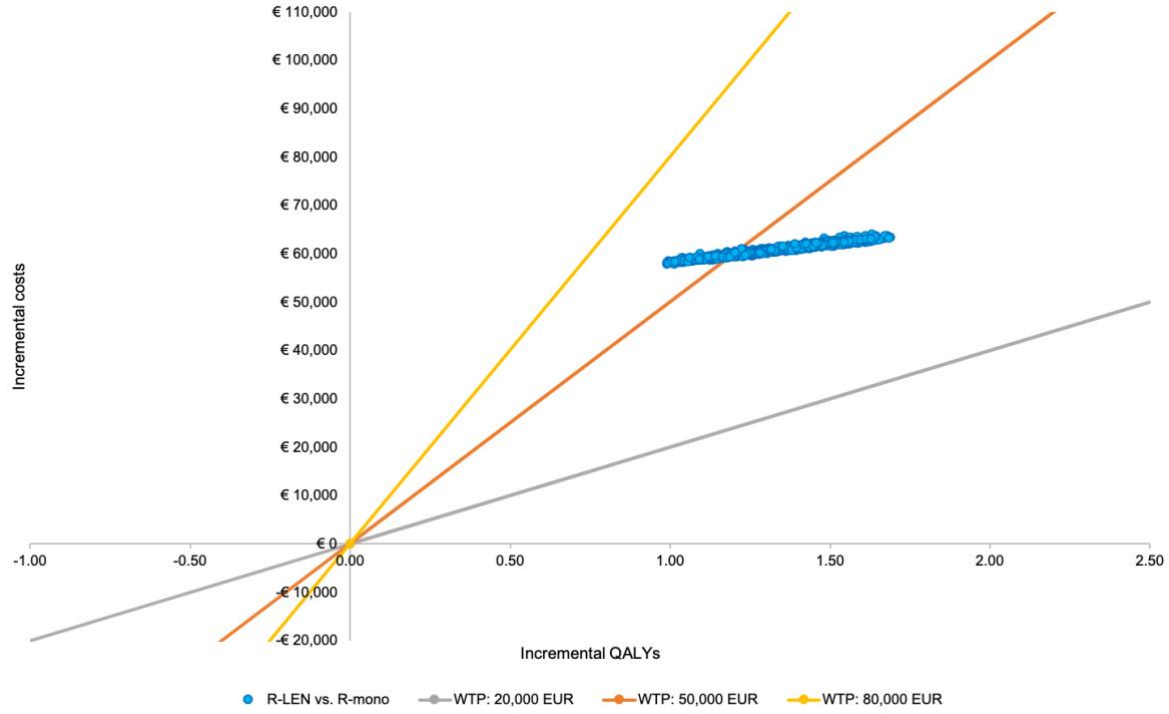


Figure 5 - CE plane (health care perspective)

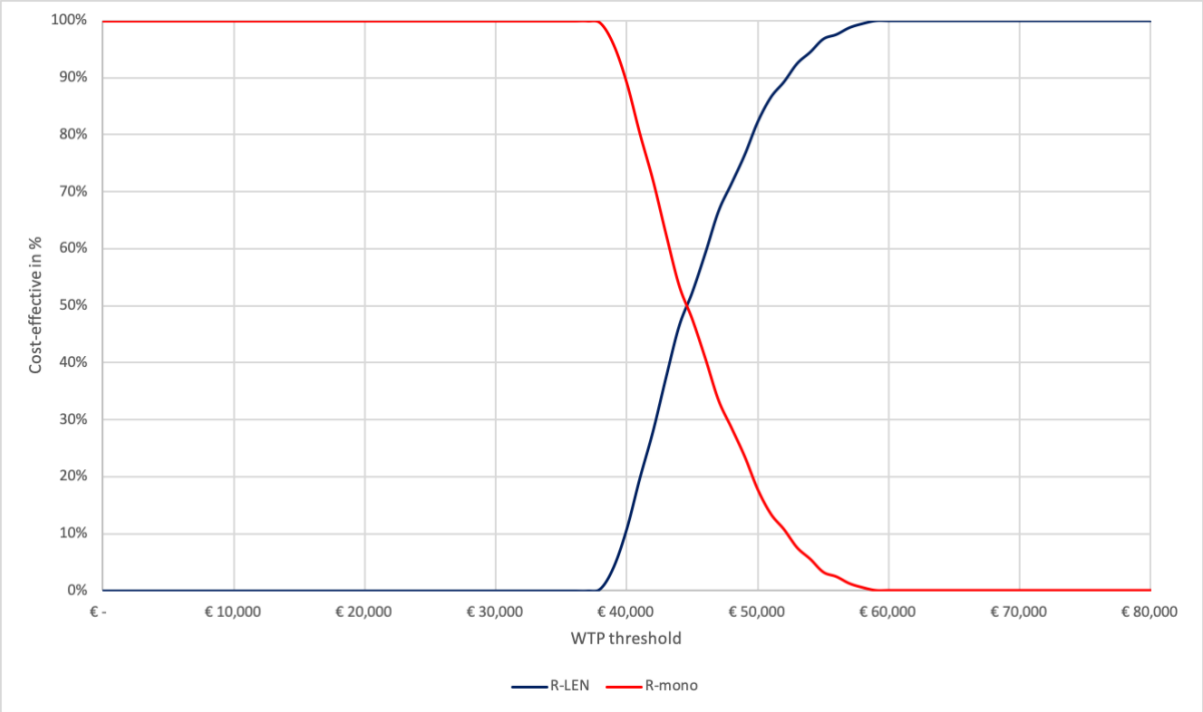


Figure 6 - CEAC (health care perspective)

Societal perspective considering future non-medical consumption costs

Assuming a WTP-threshold of 50,000 EUR/QALY gained, the probability of R-LEN being cost-effective was 3% from a full societal perspective

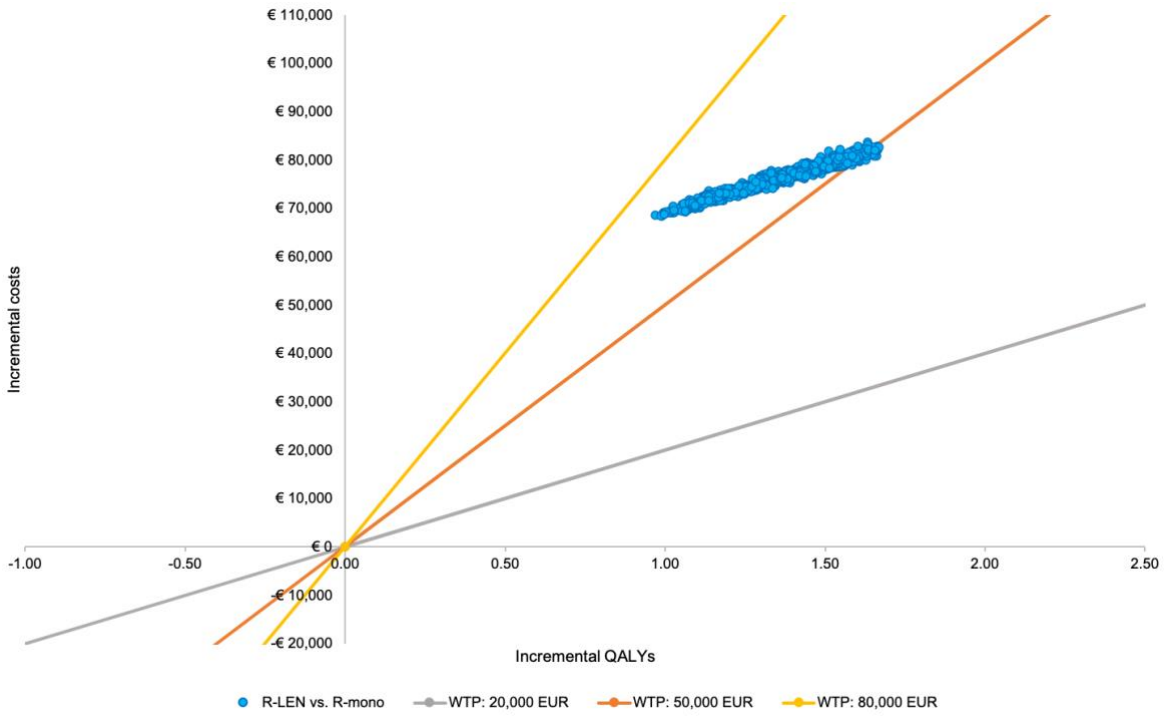


Figure 7 - CE plane societal perspective plus future non-medical consumption costs

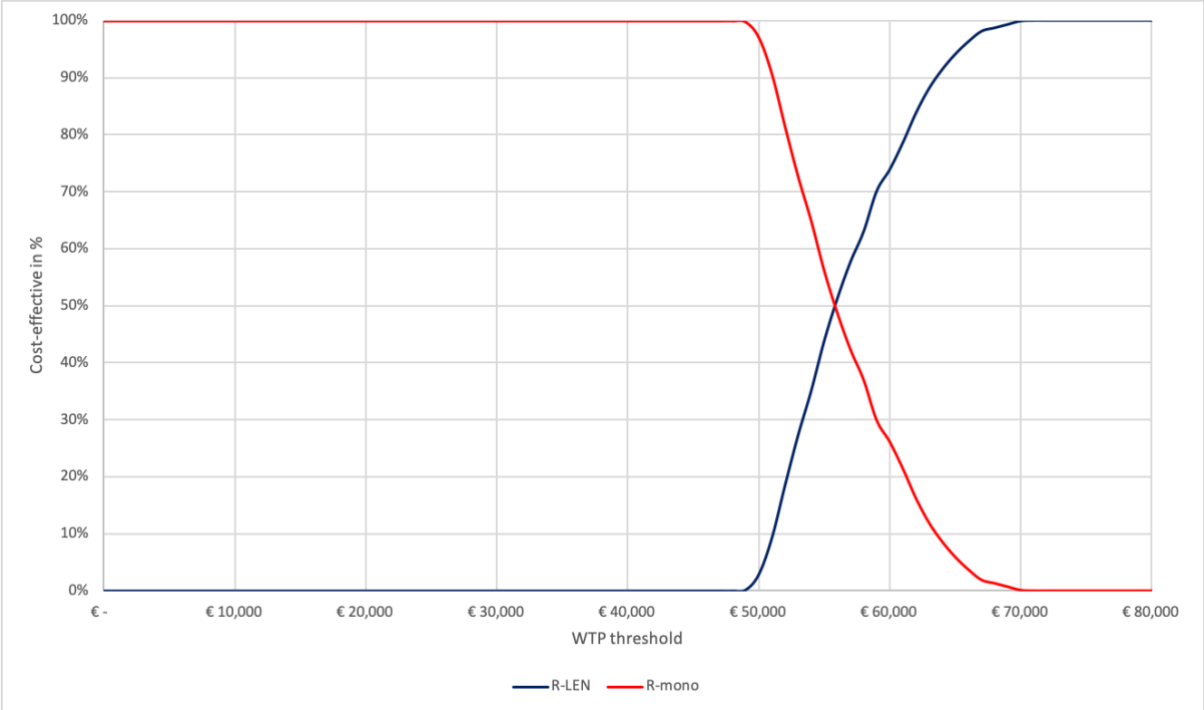


Figure 8 - CEAC (societal perspective plus future non-medical consumption costs)

Scenario analyses

Health care perspective

Table 17 - Results of the scenario analysis (health care perspective)

Number	Name	Incremental costs	Incremental Lys	Incremental QALYs	ICER/LY	ICER/QALY	% difference to base case	Cost-effective at 20,000 EUR/QALY	Cost-effective at 50,000 EUR/QALY	Cost-effective at 80,000 EUR/QALY
	Base case	*€ 63,324*	*2.01*	*1.67*	*€ 31,567*	*€ 37,951*	*0%*	No	Yes	Yes
1	Utilities: Wild et al.	€ 63,324	2.01	1.54	€ 31,567	€ 41,045	8%	No	Yes	Yes
2	Utilities: AE disutilities	€ 63,324	2.01	1.63	€ 31,567	€ 38,964	3%	No	Yes	Yes
3	Utilities: no age-adjustment	€ 63,324	2.01	1.71	€ 31,567	€ 36,963	-3%	No	Yes	Yes
4	Drug administration: all R i.v.	€ 64,222	2.01	1.67	€ 32,014	€ 38,489	1%	No	Yes	Yes
5	Drug administration: all R s.c.	€ 63,431	2.01	1.67	€ 31,620	€ 38,014	0%	No	Yes	Yes
6	Drug administration: assume no vial sharing	€ 63,618	2.01	1.67	€ 31,713	€ 38,127	0%	No	Yes	Yes
7	Lenalidomide not based on AUGMENT (20mg dosing)	€ 73,149	2.01	1.67	€ 36,464	€ 43,839	13%	No	Yes	Yes
8	Treatment effect duration: 3 years	€ 58,222	1.21	1.01	€ 48,263	€ 57,894	34%	No	No	Yes
9	Treatment effect duration: 7 years	€ 67,720	2.64	2.19	€ 25,612	€ 30,855	-23%	No	Yes	Yes
10	Treatment effect duration: 10 years	€ 73,129	3.37	2.79	€ 21,714	€ 26,240	-45%	No	Yes	Yes
11	Treatment effect duration: infinite	€ 82,053	4.39	3.61	€ 18,685	€ 22,739	-67%	No	Yes	Yes
12	PFS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 61,873	2.01	1.67	€ 30,843	€ 37,081	-2%	No	Yes	Yes
13	PFS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 62,132	2.01	1.67	€ 30,972	€ 37,236	-2%	No	Yes	Yes
14	PFS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 61,729	2.01	1.67	€ 30,772	€ 36,995	-3%	No	Yes	Yes
15	PFS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 62,509	2.01	1.67	€ 31,161	€ 37,462	-1%	No	Yes	Yes
16	PFS distribution R-LEN & R-mono (AUGMENT): Log-normal	€ 62,732	2.01	1.67	€ 31,272	€ 37,596	-1%	No	Yes	Yes
17	OS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 61,918	1.83	1.53	€ 33,766	€ 40,512	6%	No	Yes	Yes
18	OS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 67,455	2.55	2.12	€ 26,436	€ 31,884	-19%	No	Yes	Yes
19	OS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 55,708	1.07	0.91	€ 52,018	€ 61,155	38%	No	No	Yes
20	OS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 62,163	1.89	1.58	€ 32,893	€ 39,412	4%	No	Yes	Yes
21	OS distribution R-LEN & R-mono (AUGMENT): Weibull	€ 57,579	1.35	1.15	€ 42,498	€ 50,283	25%	No	No	Yes
22	Drug price: lenalidomide -10%	€ 58,303	2.01	1.67	€ 29,064	€ 34,941	-9%	No	Yes	Yes
23	Drug price: lenalidomide -20%	€ 53,282	2.01	1.67	€ 26,561	€ 31,932	-19%	No	Yes	Yes
24	Drug price: lenalidomide -30%	€ 48,261	2.01	1.67	€ 24,058	€ 28,923	-31%	No	Yes	Yes
25	Drug price: lenalidomide -40%	€ 43,240	2.01	1.67	€ 21,555	€ 25,914	-46%	No	Yes	Yes
26	Drug price: lenalidomide -50%	€ 38,219	2.01	1.67	€ 19,052	€ 22,905	-66%	No	Yes	Yes

Societal perspective

Table 18 - Results of the scenario analysis (societal perspective)

Number	Name	Incremental costs	Incremental Lys	Incremental QALYs	ICER/LY	ICER/QALY	% difference to base case	Cost-effective at 20,000 EUR/QALY	Cost-effective at 50,000 EUR/QALY	Cost-effective at 80,000 EUR/QALY
	Base case	*€ 67,566*	*2.01*	*1.67*	*€ 33,681*	*€ 40,493*	*0%*	No	Yes	Yes
1	Utilities: Wild et al.	€ 67,566	2.01	1.54	€ 33,681	€ 43,794	8%	No	Yes	Yes
2	Utilities: AE disutilities	€ 67,566	2.01	1.63	€ 33,681	€ 41,574	3%	No	Yes	Yes
3	Utilities: no age-adjustment	€ 67,566	2.01	1.71	€ 33,681	€ 39,440	-3%	No	Yes	Yes
4	Drug administration: all R i.v.	€ 68,669	2.01	1.67	€ 34,231	€ 41,154	2%	No	Yes	Yes
5	Drug administration: all R s.c.	€ 67,701	2.01	1.67	€ 33,749	€ 40,574	0%	No	Yes	Yes
6	Drug administration: assume no vial sharing	€ 67,860	2.01	1.67	€ 33,828	€ 40,669	0%	No	Yes	Yes
7	Lenalidomide not based on AUGMENT (20mg dosing)	€ 77,391	2.01	1.67	€ 38,579	€ 46,381	13%	No	Yes	Yes
8	Treatment effect duration: 3 years	€ 60,838	1.21	1.01	€ 50,432	€ 60,496	33%	No	No	Yes
9	Treatment effect duration: 7 years	€ 73,206	2.64	2.19	€ 27,686	€ 33,354	-21%	No	Yes	Yes
10	Treatment effect duration: 10 years	€ 79,960	3.37	2.79	€ 23,742	€ 28,691	-41%	No	Yes	Yes
11	Treatment effect duration: infinite	€ 90,623	4.39	3.61	€ 20,636	€ 25,114	-61%	No	Yes	Yes
12	PFS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 66,112	2.01	1.67	€ 32,957	€ 39,621	-2%	No	Yes	Yes
13	PFS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 66,365	2.01	1.67	€ 33,082	€ 39,773	-2%	No	Yes	Yes
14	PFS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 65,967	2.01	1.67	€ 32,884	€ 39,534	-2%	No	Yes	Yes
15	PFS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 66,745	2.01	1.67	€ 33,272	€ 40,001	-1%	No	Yes	Yes
16	PFS distribution R-LEN & R-mono (AUGMENT): Log-normal	€ 66,969	2.01	1.67	€ 33,384	€ 40,135	-1%	No	Yes	Yes
17	OS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 65,880	1.83	1.53	€ 35,927	€ 43,104	6%	No	Yes	Yes
18	OS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 72,731	2.55	2.12	€ 28,503	€ 34,378	-18%	No	Yes	Yes
19	OS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 58,324	1.07	0.91	€ 54,459	€ 64,026	37%	No	No	Yes
20	OS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 66,246	1.89	1.58	€ 35,053	€ 42,001	4%	No	Yes	Yes
21	OS distribution R-LEN & R-mono (AUGMENT): Weibull	€ 60,736	1.35	1.15	€ 44,828	€ 53,040	24%	No	No	Yes
22	Drug price: lenalidomide -10%	€ 62,545	2.01	1.67	€ 31,178	€ 37,484	-8%	No	Yes	Yes
23	Drug price: lenalidomide -20%	€ 57,524	2.01	1.67	€ 28,676	€ 34,475	-17%	No	Yes	Yes
24	Drug price: lenalidomide -30%	€ 52,503	2.01	1.67	€ 26,173	€ 31,465	-29%	No	Yes	Yes
25	Drug price: lenalidomide -40%	€ 47,482	2.01	1.67	€ 23,670	€ 28,456	-42%	No	Yes	Yes
26	Drug price: lenalidomide -50%	€ 42,461	2.01	1.67	€ 21,167	€ 25,447	-59%	No	Yes	Yes

Societal perspective plus future non-medical consumption costs

Table 19 - Results of the scenario analysis (societal perspective plus future non-medical consumption costs)

Number	Name	Incremental costs	Incremental Lys	Incremental QALYs	ICER/LY	ICER/QALY	% difference to base case	Cost-effective at 20,000 EUR/QALY	Cost-effective at 50,000 EUR/QALY	Cost-effective at 80,000 EUR/QALY
	Base case	*€ 82,256*	*2.01*	*1.67*	*€ 41,004*	*€ 49,296*	*0%*	No	Yes	Yes
1	Utilities: Wild et al.	€ 82,256	2.01	1.54	€ 41,004	€ 53,316	8%	No	No	Yes
2	Utilities: AE disutilities	€ 82,256	2.01	1.63	€ 41,004	€ 50,613	3%	No	No	Yes
3	Utilities: no age-adjustment	€ 82,256	2.01	1.71	€ 41,004	€ 48,014	-3%	No	Yes	Yes
4	Drug administration: all R i.v.	€ 83,358	2.01	1.67	€ 41,554	€ 49,957	1%	No	Yes	Yes
5	Drug administration: all R s.c.	€ 82,390	2.01	1.67	€ 41,071	€ 49,377	0%	No	Yes	Yes
6	Drug administration: assume no vial sharing	€ 82,550	2.01	1.67	€ 41,151	€ 49,472	0%	No	Yes	Yes
7	Lenalidomide not based on AUGMENT (20mg dosing)	€ 92,080	2.01	1.67	€ 45,902	€ 55,184	11%	No	No	Yes
8	Treatment effect duration: 3 years	€ 69,871	1.21	1.01	€ 57,919	€ 69,478	29%	No	No	Yes
9	Treatment effect duration: 7 years	€ 92,201	2.64	2.19	€ 34,870	€ 42,009	-17%	No	Yes	Yes
10	Treatment effect duration: 10 years	€ 103,580	3.37	2.79	€ 30,756	€ 37,167	-33%	No	Yes	Yes
11	Treatment effect duration: infinite	€ 120,183	4.39	3.61	€ 27,368	€ 33,306	-48%	No	Yes	Yes
12	PFS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 80,801	2.01	1.67	€ 40,279	€ 48,425	-2%	No	Yes	Yes
13	PFS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 81,054	2.01	1.67	€ 40,405	€ 48,576	-1%	No	Yes	Yes
14	PFS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 80,656	2.01	1.67	€ 40,207	€ 48,338	-2%	No	Yes	Yes
15	PFS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 81,434	2.01	1.67	€ 40,595	€ 48,804	-1%	No	Yes	Yes
16	PFS distribution R-LEN & R-mono (AUGMENT): Log-normal	€ 81,658	2.01	1.67	€ 40,706	€ 48,938	-1%	No	Yes	Yes
17	OS distribution R-LEN & R-mono (AUGMENT): Exponential	€ 79,499	1.83	1.53	€ 43,354	€ 52,015	5%	No	No	Yes
18	OS distribution R-LEN & R-mono (AUGMENT): Generalized gamma	€ 90,990	2.55	2.12	€ 35,659	€ 43,008	-15%	No	Yes	Yes
19	OS distribution R-LEN & R-mono (AUGMENT): Gompertz	€ 67,365	1.07	0.91	€ 62,902	€ 73,952	33%	No	No	Yes
20	OS distribution R-LEN & R-mono (AUGMENT): Log-logistic	€ 80,385	1.89	1.58	€ 42,535	€ 50,965	3%	No	No	Yes
21	OS distribution R-LEN & R-mono (AUGMENT): Weibull	€ 71,702	1.35	1.15	€ 52,922	€ 62,616	21%	No	No	Yes
22	Drug price: lenalidomide -10%	€ 77,235	2.01	1.67	€ 38,501	€ 46,287	-7%	No	Yes	Yes
23	Drug price: lenalidomide -20%	€ 72,214	2.01	1.67	€ 35,998	€ 43,278	-14%	No	Yes	Yes
24	Drug price: lenalidomide -30%	€ 67,192	2.01	1.67	€ 33,495	€ 40,269	-22%	No	Yes	Yes
25	Drug price: lenalidomide -40%	€ 62,171	2.01	1.67	€ 30,992	€ 37,260	-32%	No	Yes	Yes
26	Drug price: lenalidomide -50%	€ 57,150	2.01	1.67	€ 28,489	€ 34,251	-44%	No	Yes	Yes

Appendix 6C – Comparison of results

NICE appraisal

To convert GBP to EUR, we used the average rate of 1.1399 for the years 2019 (i.e. 1 January 2019 to 31 December 2019) published by the European Central Bank.[71]

Zhang et al. (2020)

To convert USD to EUR, we used the average rate of 0.8476 for the years 2018 (i.e. 1 January 2018 to 31 December 2018) published by the European Central Bank.[72]

Appendix 6D – Completed CHEERS checklist

Item No	Section/item	Reported in
Title and Abstract		
1	Title	Study
2	Abstract	Study
Introduction		
3	Background and objectives	Study
Methods		
4	Target population and subgroups	Study and Appendix 1
5	Setting and location	Study

6	Study perspective	Study
7	Comparators	Study and Appendix 1
8	Timehorizon	Study and Appendix 1
9	Discount rate	Appendix 1
10	Choice of health outcomes	Study and Appendix 1
11	Measurement of effectiveness	Appendix 1
12	Measurement and valuation of preferences	Appendix 1
13	Estimating resources and costs	Study and Appendix 1
14	Currency, price date, and conversion	Study and Appendix 1
15	Choice of model	Study and Appendix 1
16	Assumptions	Study and Appendix 1
17	Analytical methods	Study and Appendix 1
Results		
18	Study parameters	Study and Appendix 2
19	Incremental costs and outcomes	Study and Appendix 2
20	Characterizing uncertainty	Study and Appendix 2
21	Characterizing heterogeneity	Study and Appendix 2
Discussion		
22	Study findings, limitations, generalizability, and current knowledge	Study
Other		
23	Source of funding	Study
24	Conflict of interest	Study

Appendices for Chapter 7

Title of Chapter in dissertation: Obinutuzumab in combination with chemotherapy for the first-line treatment of patients with advanced follicular lymphoma. An evidence review group evaluation of the NICE single technology appraisal.

Appendix 7A - ERG Adjustment to the CS Base Case

Number	Item	CS base case	ERG adjustment	Reason
Fixing errors				
1	Correction of PFS mortality rate for obin-chemo+obin	Pooled monthly death probability for treatment specific death probability in PFS: 0.113%	New value: 0.096%	Wrong referencing
2	Correction of adverse event costs for anaemia	Management of anaemia: £2,117	New value: £3,021	Wrong referencing
3	Correction of AE frequency calculations when AE-related disutilities were incorporated in the cost effectiveness analysis	Wrong cell referencing in Excel file	Correction of cell referencing	Wrong cell referencing in Excel file
4	Correction of the implementation of "no vial sharing" costs for obinutuzumab drug acquisition costs	100% vial sharing was assumed even when "no vial sharing" was selected.	This error was corrected.	Wrong implementation
5	Correction of errors in the sensitivity analysis	Several errors for upper and lower values used for	These errors were corrected	Wrong calculation of values

		administration cost items.		
Fixing violation				
1.a	Increasing the age at baseline	Average age of cohort: 57.9 years	Average age of cohort: 62.6 years	The age set by ERG was expected to better reflect the UK population
1.b	Adjusting of the patient distribution per chemotherapy arm	Distribution based on a questionnaire-based UK sample: 29% bendamustine 13% CHOP 36% CVP	New distribution: 68% bendamustine 31% CVP 1% CHOP	The new distribution was chosen to be in line with the GALLIUM trial, which was considered to better reflect the UK population than the market research questionnaire used in the CS
1.c	Adjusting the proportion of females in the model	The proportion of females used was 50.6%	A proportion of 53.2% females was used	The value stated in the CS was believed by the ERG to be a reporting error and was therefore corrected.
2	Choosing different PFS and post progression survival (PPS) (early PD only) mortality rates for the treatment arms	Same mortality rates for the treatment arms were chosen	Different mortality rates for the treatment arms were chosen	The ERG argued that, in case a treatment effect is sought, different mortality rates per treatment arm should be used (regardless of their statistical significance) to better reflect results of the GALLIUM study.
3	Applying utility decrements with age	No utility decrements with an increasing in age were considered	A decline in utilities was considered for an increase in age	The ERG considered utility decrements since the GALLIUM study was not powered to detect any difference in utilities for different age groups.
Matters of judgement				
1	Choosing different PFS data and	INV-PFS data was used and an exponential	IRC-PFS data and a Weibull distribution for	The ERG believed that, since the GALLIUM trial was an open-label trial,

	parametric survival distribution	distribution was chosen for PFS data extrapolation	PFS data extrapolation were chosen for the base case	the independent review committee instead of the investigator assessed results should be used.
2	AE disutilities	No AE disutilities were applied	AE disutilities were applied	The ERG applied AE disutilities as an indirect way to reflect differences in utilities between the two treatment arms.
3	Vial sharing	Vial sharing was assumed	No vial sharing was assumed	The ERG considered the assumption of "no vial sharing" more plausible, incurring the full costs of each vial opened.
4	AE costs and disutilities	An arbitrary threshold of 2% to the SAEs were applied to each SAE grade separately to indicate the most relevant SAEs.	The same SAE threshold (2%) was chosen, but once an SAE was included, all grades (≥ 3) were considered as well.	The ERG found it more plausible to include all (higher) grade once one SAE was included based on the 2% threshold, than assuming that for instance grade 3 of an SAE might be considered, while grades 4 and 5 of the same SAE type might not.
AE = adverse event, CS = company submission, ERG = evidence review group, INV = investigator, IRC = independent review committee, PD = progressive disease, PFS = progression-free survival, PPS = post progression survival, SAE = severe adverse event				

Appendix 7B - Alternative ERG Scenarios

Scenario number	*Scenario description*
1a	*Treatment effect duration: 5 years*
1b	*PFS Gompertz distribution*
1c	*INV-PFS data*
1d	*Pooled mortality*
2a	*No AE disutilities*
2b	*No utility decrement with age*
2c	*GALLIUM utilities for PFS and PD*

2d	*Wild et al utilities for PFS and PD*
2e	*Bec et al. utilities for PDS and PD*
2f	*GADOLIN utilities for PFS and PD*
2g	*GALLIUM utilities for PFS and mapping FACT-Lym for PD*
2h	*GALLIUM utilities for PFS and GADOLIN for PD*
2i	*GALLIUM utilities for PFS and Bec et al. for PD*
2j	*Different utilities for early and late PD*
3a	*demographic characteristics in the GALLIUM trial*
4a	*chemotherapy distribution UK market research*
4b	*chemotherapy distribution in the GALLIUM trial – all patients*
4c	*chemotherapy distribution 100% bendamustine*
4d	*chemotherapy distribution 100% CHOP*
4e	*chemotherapy distribution 100% CVP*
4f	*vial sharing*

Appendices for Chapter 8

Title of Chapter in dissertation: Health Economic Aspects of Chimeric Antigen Receptor T-Cell Therapies for Haematological Cancers. Present and Future.

Appendix 8A - Search strategy in EMBASE

('chimeric antigen receptor t-cell'/exp OR 'car t-cell' OR 'car t-lymphocyte' OR 'car engineered t-cell' OR 'car engineered t-lymphocyte' OR 'car modified t-cell' OR 'car modified t-lymphocyte' OR 'chimeric antigen receptor t-cell' OR 'chimeric antigen receptor t-lymphocyte') AND ('cost effectiveness analysis'/exp OR 'cost effectiveness' OR 'cost effectiveness analysis' OR 'cost effectiveness ratio' OR 'cost efficiency analysis')

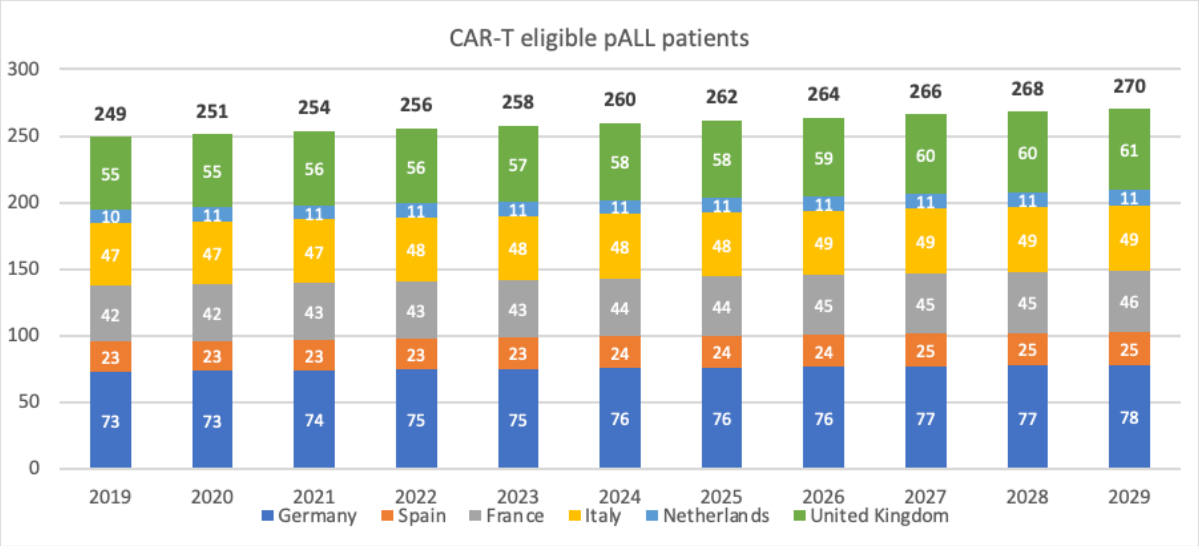
Appendix 8B - Reference trial to estimate market entry of future indications

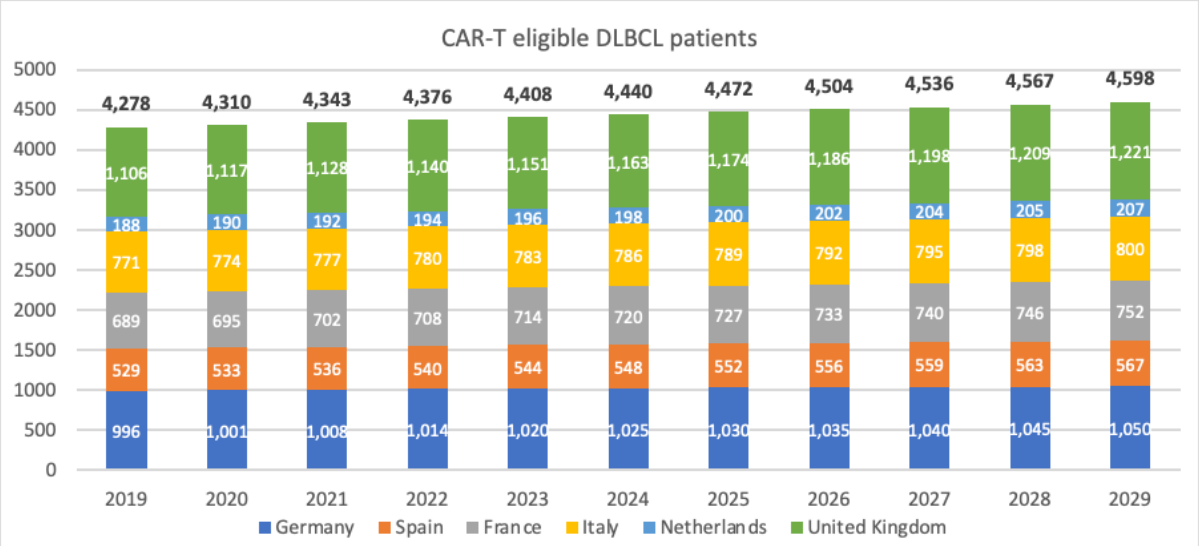
The chosen reference trials to estimate the time of market entry for future CAR T-cell therapy indications are summarized in the table below.

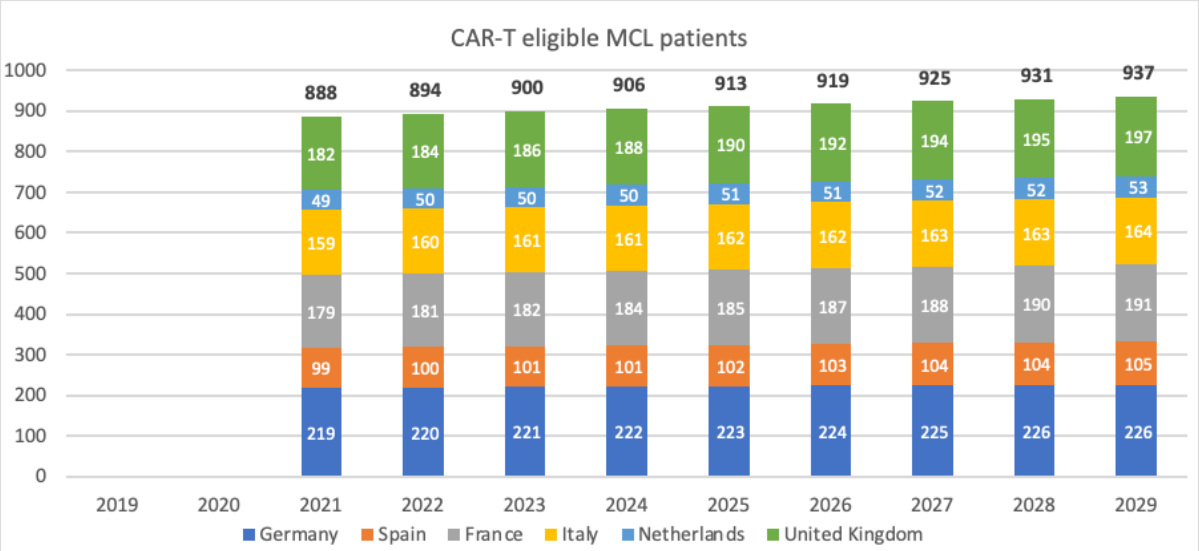
Trial name	**Drug name**	**Indication**	**Target**	**Phase**	**Funding body**	**Sponsor**	**Study start date (dd/mm/yyyy)**
NCT03904069	AMG 553	AML	FLT3	I	Industry	Amgen	15/05/2019
NCT03331198	JCAR017	CLL	CD19	I/II	Industry	Celgene	26/12/2017
NCT03331198	Bb2121	MM	BCMA	II	Industry	Celgene	13/12/2018

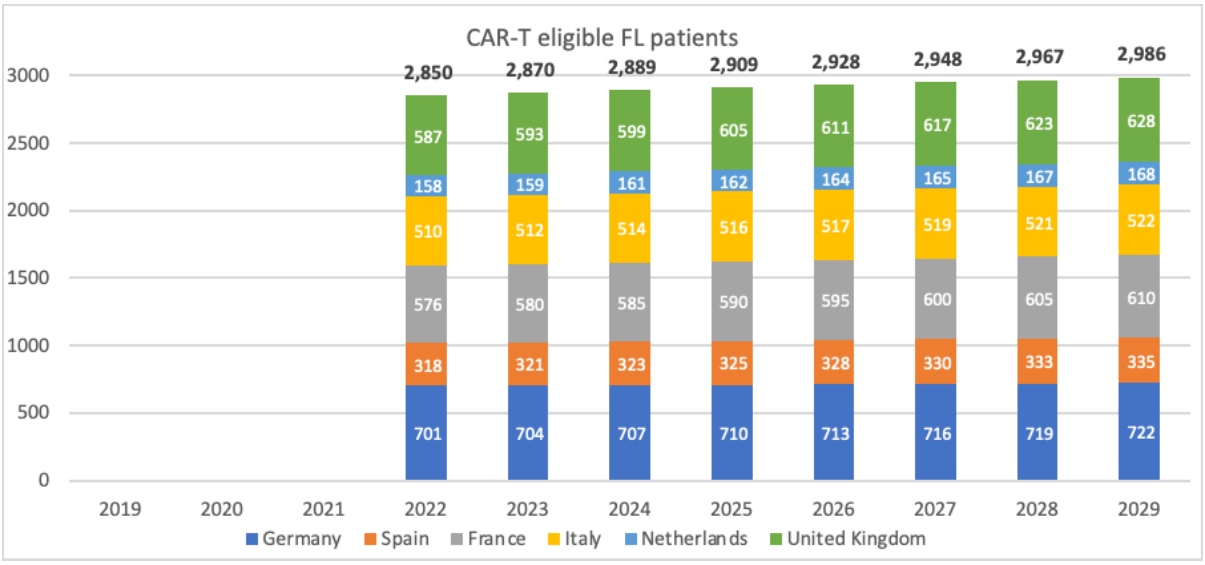
Appendix 8C - Eligible patient population

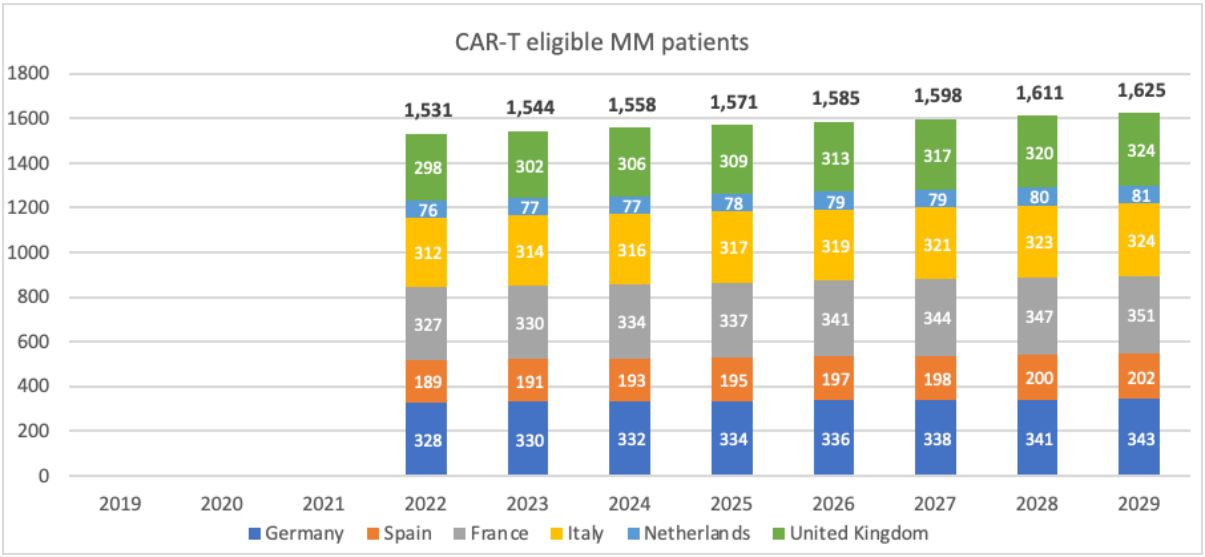
Eligible patient population obtained by averaging both Eurostat and Globocan.

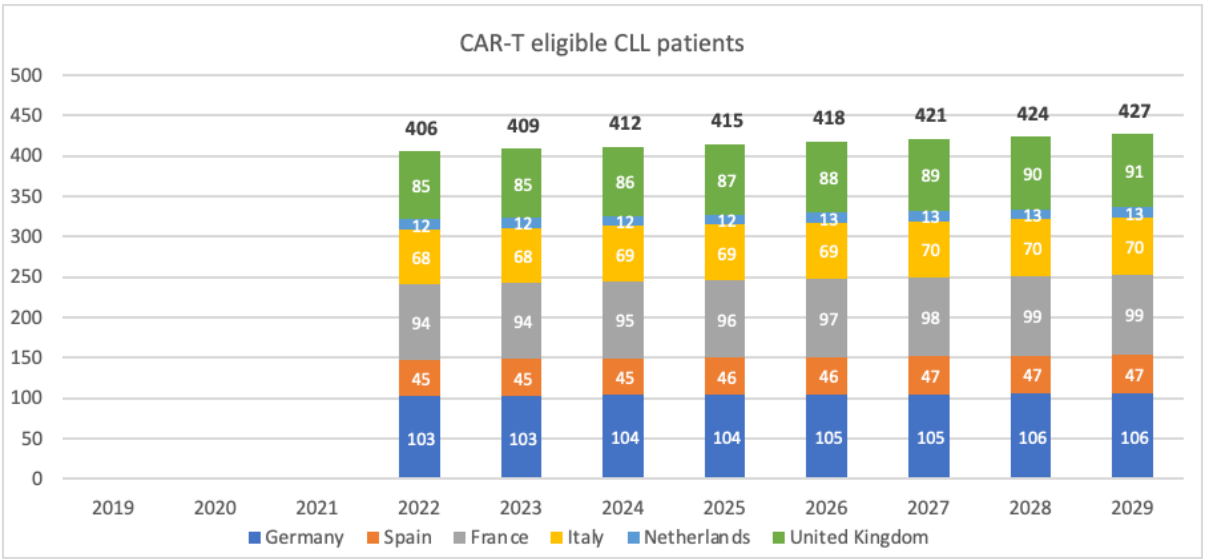

CAR-T eligible pALL patients
300
250
200
150
100
50
0
249 251 254 256 258 260 262 264 266 268 270
55 55 56 56 57 58 58 59 60 60 61
10 11 11 11 11 11 11 11 11 11 11
47 47 47 48 48 48 48 49 49 49 49
42 42 43 43 43 44 44 45 45 45 46
23 23 23 23 23 24 24 24 25 25 25
73 73 74 75 75 76 76 76 77 77 78
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom

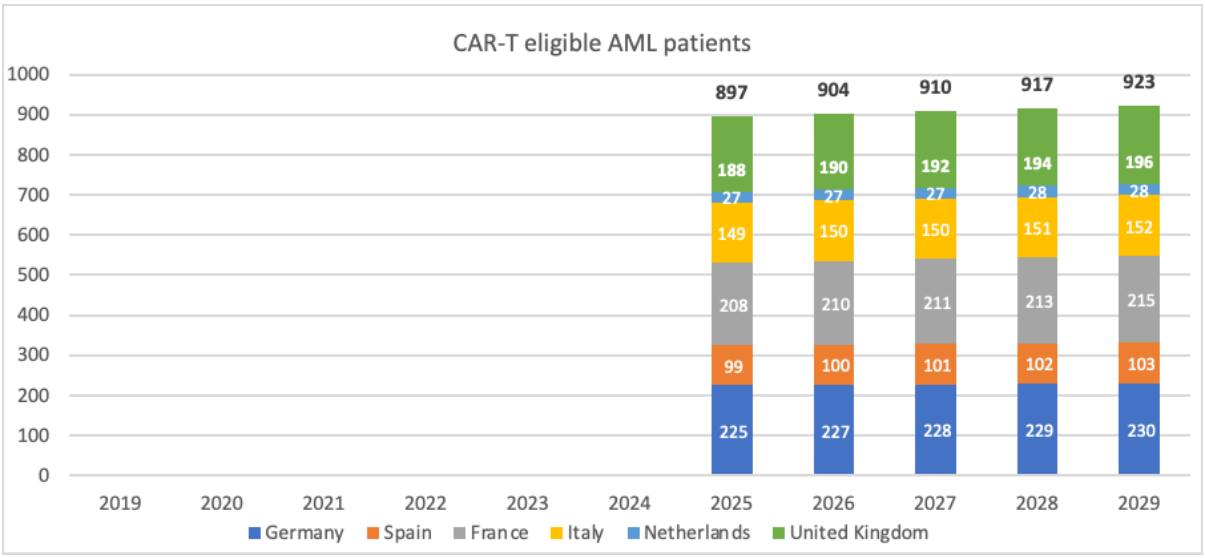

CAR-T eligible DLBCL patients
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
4,278 4,310 4,343 4,376 4,408 4,440 4,472 4,504 4,536 4,567 4,598
1,106 1,117 1,128 1,140 1,151 1,163 1,174 1,186 1,198 1,209 1,221
188 190 192 194 196 198 200 202 204 205 207
771 774 777 780 783 786 789 792 795 798 800
689 695 702 708 714 720 727 733 740 746 752
529 533 536 540 544 548 552 556 559 563 567
996 1,001 1,008 1,014 1,020 1,025 1,030 1,035 1,040 1,045 1,050
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom


CAR-T eligible MCL patients
1000
900
800
700
600
500
400
300
200
100
0
888 894 900 906 913 919 925 931 937
182 184 186 188 190 192 194 195 197
49 50 50 50 51 51 52 52 53
159 160 161 161 162 162 163 163 164
179 181 182 184 185 187 188 190 191
99 100 101 101 102 103 104 104 105
219 220 221 222 223 224 225 226 226
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom

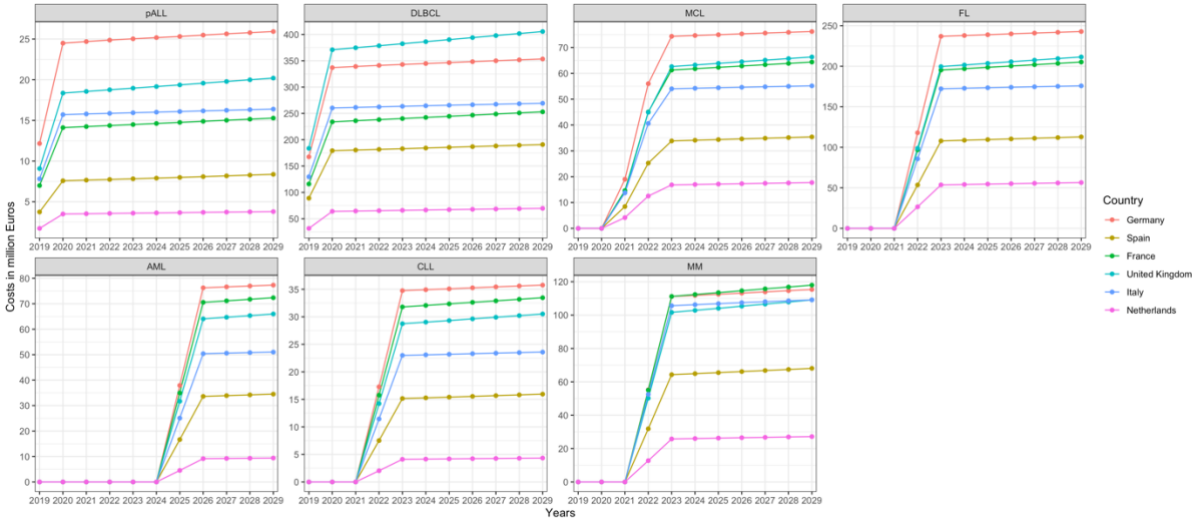

CAR-T eligible FL patients
3000
2500
2000
1500
1000
500
0
2,850
2,870
2,889
2,909
2,928
2,948
2,967
2,986
587 593 599 605 611 617 623 628
158 159 161 162 164 165 167 168
510 512 514 516 517 519 521 522
576 580 585 590 595 600 605 610
318 321 323 325 328 330 333 335
701 704 707 710 713 716 719 722
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom


CAR-T eligible MM patients
1800
1600
1400
1200
1000
800
600
400
200
0
1,531
1,544
1,558
1,571
1,585
1,598
1,611
1,625
298 302 306 309 313 317 320 324
76 77 77 78 79 79 80 81
312 314 316 317 319 321 323 324
327 330 334 337 341 344 347 351
189 191 193 195 197 198 200 202
328 330 332 334 336 338 341 343
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom


CAR-T eligible CLL patients
500
450
400
350
300
250
200
150
100
50
0
406
409
412
415
418
421
424
427
85 85 86 87 88 89 90 91
12 12 12 12 13 13 13 13
68 68 69 69 69 70 70 70
94 94 95 96 97 98 99 99
45 45 45 46 46 47 47 47
103 103 104 104 105 105 106 106
2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029
Germany Spain France Italy Netherlands United Kingdom



Appendix 8D - Forecasted expenditure per indication and country 2019 – 2029



Appendix 8E - Incidence rates (for Eurostat forecast) and proportion of eligible patients for CAR T-cell therapy

Indication	**IR per 100,000**						**Proportion eligible for CAR T-cell therapy**					
	DE	ES	FR	UK	IT	NL	DE	ES	FR	UK	IT	NL
pALL	2.2	1.0[a]	3.3	2.7	2.7[a]	2.0	0.11	0.09[b]	0.06	0.09[b]	0.09[b]	0.10
DLBCL	5.6	7.3[a]	6.3	6.7	7.5[a]	7.1	0.19	0.17[c]	0.15	0.22	0.17[c]	0.15
MCL	1.8	1.4	1.7	1.6	1.8	1.9	0.17[d]	0.17[d]	0.17[d]	0.17[d]	0.17[d]	0.17[d]
FL	5.9	4.6	5.5	5.3	5.8	6.1	0.15[d]	0.15[d]	0.15[d]	0.15[d]	0.15[d]	0.15[d]

AML	6.1	4.7	6.8	6.1	5.6	3.4	0.05[d]	0.05[d]	0.05[d]	0.05[d]	0.05[d]	0.05[d]
CLL	6.9	8.7	9.5	7.0	10.2	10.1	0.02[d]	0.02[d]	0.02[d]	0.02[d]	0.02[d]	0.02[d]
MM	6.1	4.7	6.8	6.1	5.6	3.4	0.11[d]	0.11[d]	0.11[d]	0.11[d]	0.11[d]	0.11[d]

[a]Incidence rate based on ECIS data

[b]Imputed with available data (average) from countries with available data (based on pALL)

[c]Imputed with available data (average) from countries with available data (based on DLBCL)

[d]Based on expert opinion (average)

Appendix 8F - Proportions of cancer sub-types for the Globocan forecast

Cancer type in GLOBOCAN	**Cancer sub-type of interest**	**Proportion used**	**Source**
Leukemia	Pediatric acute lymphoblastic leukemia	0.09	SEER[73]
	Acute myeloid leukemia	0.32	American Cancer Society
	Chronic lymphocytic leukemia	0.37	American Cancer Society
Multiple myeloma	Multiple myeloma	NA	
Non-Hodgkin lymphoma	Diffuse large B-cell lymphomas	0.35	Li et al. (2018)[74]
	Mantle cell lymphoma	0.08	Cerhan et al. (2020)[75]
	Follicular lymphoma	0.26	Sandoval-Sus et al.(2017)[76]

Appendix 8G - Proportion eligible for CAR T-cell therapy

Disease	Country	Incidence per year	Incidence rate per 100,000	Eligible for CAR-T	Proportion eligible for CAR-T	Source
pALL	DE	531	2.2	56	0.11	HTA report (IQWiG)
	ES	116	1.0	#N/A	0.09	ECIS data base
	FR	648	3.3	38	0.06	HTA report (HAS)
	GB	520	2.7	#N/A	0.09	HTA report, committee papers (NICE)
	IT	375	2.7	#N/A	0.09	ECIS data base
	NL	98	2.0	10	0.10	HTA report (ZiN)
DLBCL	DE	5102	6.2	1088	0.21	HTA report axicel (IQWiG)
	DE	4102	5.1	659	0.16	HTA report tisagenlecleucel
	ES	3375	7.3	#N/A	0.17	Galceran et al.
	FR	4096	6.1	715	0.17	HTA report axicel (HAS)
	FR	4376	6.5	511	0.12	HTA report tisagenlecleucel (HAS)
	GB	4442	6.7	972	0.22	HTA report axicel (NICE)
	GB	#N/A	#N/A	#N/A	#N/A	HTA report tisagenlecleucel (NICE)
	IT	4568	7.5	#N/A	0.17	Epidemiologia & Prevenzione
	NL	1200	7.1	175	0.15	HTA report axicel (ZiN)
	NL	1100	7.0	#N/A	0.15	HTA report tisagenlecleucel (ZiN)
AML	DE	4353	5.3		0.05	
	ES	1868	4.0		0.05	
	FR	3862	5.9		0.05	
	GB	3528	5.3		0.05	
	IT	2858	4.8		0.05	
	NL	505	2.9		0.05	
MM	DE	1185	6.9		0.11	
	ES	7131	8.7		0.11	
	FR	6205	9.5		0.11	
	GB	3261	7		0.11	
	IT	6034	10.2		0.11	
	NL	6757	10.1		0.11	
CLL	DE	5033	6.1		0.02	
	ES	2160	4.7		0.02	
	FR	4465	6.8		0.02	
	GB	4079	6.1		0.02	
	IT	3304	5.6		0.02	
	NL	583	3.4		0.02	
FL	DE	4730	5.9		0.17	
	ES	2092	4.6		0.17	
	FR	3684	5.5		0.17	
	GB	2832	5.3		0.17	
	IT	3578	5.8		0.17	
	NL	1047	6.1		0.17	
MCL	DE	1484	1.8		0.17	
	ES	656	1.4		0.17	
	FR	1156	1.7		0.17	
	GB	888	1.6		0.17	
	IT	1123	1.8		0.17	
	NL	328	1.9		0.17	

Legend
Estimated
Based on source
To be filled
Filled with other estimates

References

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