Navigating reimbursement decision making of innovative medicines

Investigating the balance between patient access, pricing, risk mitigation and a sustainable healthcare system

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Colofon

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Navigating Reimbursement Decision Making of Innovative Medicines. Investigating the balance between patient access, pricing, risk mitigation and a sustainable healthcare system.

Het navigeren van vergoedingsbesluitvorming voor innovatieve geneesmiddelen. Het verkennen van het evenwicht tussen patiëntentoegang, prijstelling, risicobeperking en een duurzaam gezondheidzorgsysteem

Thesis

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Chapter 1

General introduction

Background

Life expectancy rising

In the past decade, life expectancy at birth has been rising in Organisation for Economic Co-operation and Development (OECD). The exception to this trend has been the years 2020 – 2021 which resulted from the global pandemic caused by the virus SARS-CoV-2 virus, commonly known as coronavirus (COVID-19). In the Netherlands, the average life expectancy for both men and women experienced a rise from 79.3 to 80.6 years between 2012 and 2019. The impact of the global pandemic temporarily reduced life expectancy in 2020 to 79.7 years but came back to almost pre-COVID levels, reaching 80.3 years in subsequent years [1]. Improvements in life expectancy are remarkable, however disease such as cancer are positively correlated with age [2,3]. Therefore, while cancer death rates have declined by 15% in OECD countries, the International Agency for Research on Cancer (IARC) anticipates a significant surge of 47% in cancer incidence between 2020 and 2040 [4]. Despite the progress in reducing cancer-related mortality, cancer has emerged as the leading cause of death in several countries, including the Netherlands, surpassing cardiovascular diseases. Current statistics indicate an incidence crude rate of 587.4 per 100,000 in Europe, with an estimated 3.4 million cases in one year [5].

Health spending in OECD countries has experienced an upward trajectory over the past decade. In the Netherlands, the per capita spending increased from $4,782 (US) in 2012 to $6,729 (US) in 2020. Although ranking 6th in health spending per capita, the percentage of healthcare spending as a share of GDP slightly decreased from 10.5% to 10.2% in the last decade, excluding the impact of the COVID-19 years [6].

Rising healthcare spending has often been attributed to an ageing population and the introduction of costly new technologies such as innovative cancer pharmaceuticals. However, in the Netherlands spending on pharmaceuticals as a percentage of healthcare spending has slightly decreased in the last decade (8.2% – 7.0%) and is ranked second lowest among OECD countries, –closely behind Denmark [7].

Investments in cancer research

The surge in cancer rates has prompted a substantial increase in investments in cancer drug research, projecting an estimated expenditure of approximately $307 billion (US) by 2026. This substantial investment is expected to target key areas, with 55% earmarked for breast, lung, prostate, and multiple myeloma research [8].

Between 2016 and 2020, public and philanthropic investments in cancer research globally were estimated at $24.5 billion, witnessing a year-on-year decline. Notably, 73.5% of these investments were directed towards pre-clinical research. In contrast, the pharmaceutical industry surpassed these figures by investing $114 billion across 33 OECD countries in

2018, with the 15 largest pharmaceutical companies reporting a combined investment of $133 billion in 2021 [9–11].

While increased investments have led to a plethora of new treatment options, concerns arise about the industry's efficiency, as reflected in the diminishing number of FDA-approved drugs per invested billion US dollars [12]. However, certain pharmaceutical companies have outperformed the Standard & Poor's 500 Index (S&P 500 index) in recent decades, suggesting the pharmaceutical sector's enduring appeal for investors [13].

Prices in hematology and oncology

The pricing of pharmaceuticals, particularly in hematology and oncology, has become a subject of active research and debate among stakeholders. The introduction of biologics in 1995 marked a turning point, with new drugs exceeding $100,000 per patient. Recent breakthroughs in blood cancer treatments, such as chimeric antigen receptor T-cell (CAR T-cell) therapies, have reached list prices of $373,000 (US) or €320,000, raising critical questions about accessibility and affordability [14].

Pharmaceuticals, particularly innovative ones, deviate from traditional goods, falling under the categories of "credence" or "experience" goods. A notable information asymmetry exists between producers and consumers, with quality assurance provided by government regulatory agencies. Additionally, the temporary monopoly created by patenting new pharmaceuticals offers companies an opportunity to recover research and development (R&D) costs. However, debates persist regarding the correlation between patents, innovation, and productivity [15,16].

Pricing methods

The temporary monopolistic conditions, constructed by patenting innovations, exclude innovative pharmaceutical products from traditional market economics. Therefore, competition is limited, and competitors on the supply side must await patent expiry to produce said pharmaceutical product. Consequently, value-based pricing is often applied for innovative pharmaceuticals, where pricing is related to the perceived value of the innovative medicines. Other pricing strategies i.e. volume-based, market-based or cost-based pricing are also utilized in specific cases. Cost-based pricing is commonly used by generic companies where competition is driven by efficient production and logistics. Competitive pricing can be a viable pricing strategy for products that have a direct competitor on or coming to market i.e. a so called 'me-too' pharmaceutical product.

Access issues

Unequal access to cancer drugs remains even when included on the World Health Organization (WHO) Essential Medicines List (EML) [17]. The income of a country plays a role in the access to oncology drugs with between 9-54% access for low-income and lower-middle-income countries, compared to 68-94% access in high-income countries [17]. Access

disparities for innovative cancer drugs also persists between high-income countries such as EU member states [18]. Although Marketing Authorization (MA) is similar for EU member states and centralized by the European Medicines Agency (EMA), access can vary due to differences in member state level reimbursement processes.

Considering access to care, it is important to realize that there is the right to health, i.e. a human right (article 25.1 of the Universal Declaration of Human Rights) as established by the United Nations (UN) [19]. The right to health encompasses the entitlement of access to essential medicines, thus making it the responsibility of states to procure access to medicines [20].

Moreover, the Treaty on the Functioning of the European Union (TFEU) mentions the following on health; "a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities" (art. 168(1) TFEU). However, the TFEU also mentions the responsibility of member States in the "management of health services and medical care and the allocation of the resources assigned to them" (art. 168(7) TFEU) [21]. However, in the White Paper titled: "Together for Health: A Strategic Approach for the EU 2008-2013" the European Commission (EC) identifies common health values, namely universality, access to good quality care, equity and solidarity [22]. When applying these core values to access to medicines, member States should insure adequate and equitable access to new therapies to their best ability.

Financial sustainability and health technology assessment (HTA)

Countries budgets are inelastic, since budgets are often fixed for a certain political determined period. Therefore, resources are scarce and need to be allocated efficiently, in the hope to maximize utility for all constituents. How to optimize the allocation of scarce resources in healthcare is the primary activities of Health Technology Assessment (HTA) research. According to the WHO definition HTA is: "a systematic and multidisciplinary process that aims to determine the value of a health technology and to inform guidance on how these technologies can be used in health systems around the world". Therefore, HTA is at the intersect between research and policy making and support decision makers with tangible evidence.

HTA falls under the responsibility of individual member states in the EU. A distinction can be made between member states that have independent review bodies that operate at arm's length of governments i.e. the Netherlands, France and Germany or bodies that are integrated within governments i.e. Italy, Greece or Spain (regional) [23]. Moreover, the type of model required by each agency/member state can differ. Both Austria and Germany required comparative clinical benefit assessment, while others i.e. Belgium and the Netherlands require clinical and cost-effectiveness models. Lastly, HTA agencies in EU member states can either provide binding (i.e. Germany and Sweden) or non-binding (i.e. the Netherlands, Belgium, and Austria) recommendations and funding decisions.

Strategies for reimbursement

Concerns exist about the sustainability of new healthcare interventions such as innovative cancer medicines, for healthcare systems. Since pricing of medicines is regarded as one of the most significant factors in determining accessibility, various approaches to pricing have been utilized in the past decades. Market entry agreements (MEA) exemplifies one of these approaches, and is widely used in EU member states for innovative cancer medicines, relying on the mitigation risks in either financial or effectiveness involved with the reimbursement [24]. However, the empirical evidence on the performance of MEAs remains scarce. Other, strategies for pricing –not yet utilized– include i.e. fair pricing models. These models introduce cost-based pricing methods to innovative medicines opposed to the commonly used value-based pricing. However, since these cost-based pricing models are not utilized by HTA agencies, the empirical evidence regarding the feasibility and desirability of these models remains to be studied.

Objectives

The overall aim of this thesis is to evaluate and describe current patient access to innovative cancer medicines, by looking at access disparities and current practice. Moreover, we study future challenges with the reimbursement of new technologies and possible strategies for mitigating risks involved with reimbursement. The thesis starts with an analysis of access to 12 innovative cancer medicines in 27 EU countries and the United Kingdom (UK). Thereafter, we evaluate the costs of innovative medicines in castration resistant prostate cancer (CRPC) and forecast future health expenditure attributable to CAR T-cell therapies. Then, we apply a cost-based pricing algorithm in different applications. The first application is cell and gene therapies in two rare diseases. The other is the application of the algorithm in case of indication expansion. Lastly, we evaluate a MEA made by the Dutch ministry of health from a value-based perspective.

The following research questions are addressed in this thesis:

1. Does patient access to innovative cancer medicines vary across EU member states?
2. What are the current costs and the impact of new innovative systemic therapies on the total costs in advanced prostate cancer?
3. How would the reimbursement of new CAR T-cell therapies impact healthcare expenditure in EU-5 countries and the Netherlands?
4. What would be the cost-based price for innovative gene and cell therapies?
5. How can cost-based pricing models be adapted to encompass the expansion of indications in innovative cancer medicines?
6. How do financial based MEAs perform in innovative cancer medicines subject to indication expansion?

Outline

This thesis is structured in four sections. Part A compromises two chapters namely: the current state of access to innovative cancer medicines in the EU and real-world costing of CRPC care in the Netherlands. Chapter 2 evaluates differences in regulatory times between the Food Drug Administration (FDA) and the EMA, therefore showing the difference in regulatory times between the United States (US) and the EU. Secondly the time-to-market defined as time to first access is evaluated across EU-27 and the UK. Lastly, we looked at the speed of uptake after reaching the market and the disparities between EU member states. Chapter 3 focuses on the real-world costs of treating CRPC patients in the Netherlands.

Part B (Chapter 4) focuses on a new cell therapy in hematology, namely CAR-T cell therapy and the possible economic consequences of reimbursing these new CAR T-cell therapies in EU-5 countries and the Netherlands. The analysis includes known CAR T-cell therapies and forecast future indications in the next decade and possible effect on health expenditure.

Part C compromises two chapters namely Chapter 5 and Chapter 6. Both chapters explore a cost-based pricing model for novel medicines. In Chapter 5 a cost-based pricing model is used to calculate prices for both a gene therapy and cell therapy product. Chapter 6 elaborates the previously used cost-based pricing algorithm to encompass pricing differentiation for products subject to indication broadening.

Part D (Chapter 7) focusses on the reimbursement of innovative cancer medicines subject to indication broadening, and in specific MEAs as a tool to mitigate risks for payers. As a case-study we researched a financial based agreement made in the Netherlands and reflect on their general desirability thru the lens of value-based pricing.

Part A.

Access disparities in Europe and real-world costs of cancer care.

Chapter 2.

Unequal Access to Newly registered Cancer Drugs leads to potential loss of life-years in Europe

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Carin A. Uyl-de Groot, Renaud Heine, Marieke Krol, Jaap Verweij. Cancers (2020)

Abstract

Many new cancer medicines have been developed that can improve patients' outcomes. However, access to these agents comes later in Europe than in the United States (US). The aim of this study is to assess the access in Europe to newly registered cancer drugs and to get more insight in the implications of these variations for patients.

A retrospective database study was conducted. Analyses involved 12 cancer drugs and 28 European countries in the period 2011–2018. Time to patient access, speed of drug uptake, and the potential loss of life years due to a delay in access have been studied.

Marketing approval for the cancer drugs came on average 242 days later in Europe than in the US, and actual patient access varied extensively across Europe. The average time to market in Europe was 403 days (range 17–1187 days). The delay in patient access of ipilimumab and abiraterone may have led to a potential loss of more than 30,000 life years.

It takes a long time for patients to get access to newly registered cancer drugs and there is great variation in access. The health outcomes can be substantially improved by faster processes.

Introduction

Cancer is a major cause of death and therefore a pressing international public health concern[25,26]. Cancer incidence is increasing in all European countries (EC). Sales of cancer drugs have more than doubled between 2005 and 2014 [27]. Because of the recent scientific advances, many new drugs have been developed that can improve overall survival (OS), prolong time to tumor progression (TTP), or decrease the chance of recurrence of cancer [28]. However, access to those drugs is not equal across Europe, as the time from a marketing approval to the actual availability and clinical use of new drugs varies greatly between European Union Member States [27,29,30]. Gann and colleagues observed delays in access to newly registered cancer drugs in some EC of over 4 years [31]. This is worrying as the access to treatment of a disease may affect patient survival, and lack of access conflicts with an individual's right to health [32]. This right was first laid down in the 1946 Constitution of the World Health Organization and in the 1948 Universal Declaration of Human Rights and ever since is an important cornerstone of many health policies [32].

Access to health care has been defined as "the timely use of services according to needs" [33,34]. Novel drugs are faced with long procedures before patients will have access, not only in the developmental phase, but also in the regulatory processes, after finalization of the pivotal trials. The United States (US) and the European Union (EU) each have their own agencies that provide market authorization for new medicines, respectively the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Market authorization is based on the evaluation of safety, efficacy, and quality of the product. Both agencies have special fast track procedures and accelerated approval programs. Moreover, for drugs with high potential patient value, FDA can provide a priority review, that has a maximal review time of 6 months [35]. The accelerated access procedure of EMA should maximally take 150 days, i.e., 5 months [36].

After market authorization, most EC have formal procedures that need to be followed before patients will have access to novel drugs. These procedures commonly include regulatory procedures, price regulations, and some form of health technology assessment to determine whether these drugs will be reimbursed by general means, for instance via a national health services system, or via health insurance schemes [30,37–40]. Given the increasing pressure on health care budgets, these national procedures are becoming increasingly complex. The procedures and the time they take differ substantially across countries.

Although it is in society's interest that new drugs, which are proven beneficial to patients, are equally accessible for people in need, it seems to be more and more difficult for EC to strike a balance between benefits and costs of novel cancer drugs [41,42]. As countries cope differently, resulting in variations in patient access, a deeper insight into the problem and its anticipated consequences is necessary.

The aim of this study is to assess variations in national patient access to several newly registered cancer drugs across Europe. Therefore, we compared the dates of submissions to FDA and EMA, the time to first uptake, and speed of uptake of these drugs and explored the impact of observed variations in access in terms of health outcomes.

Methods

This was a retrospective database study. Data were obtained from the following sources: pharmaceutical sales data was obtained from IQVIA's MIDAS® database [43]. Sales recorded in MIDAS can originate from both retail or hospital setting. The coverage differs by country and setting. Sales were expressed in standard units (SU)—defined as single tablet or vial—making it impossible to differentiate between dosages. We assumed the usage of varying dosages are similar across included countries. IQVIA's MIDAS® database did not encompass data on selected drugs for the Netherlands. Dutch data on first uptake were available for all drugs. However, sales data were obtained from manufactures (n = 8). We assumed sales data give a good approximation for the usage and access to selected drugs, as it is unlikely that influence of potential stocking of inventories is minimal.

We selected a variety of newly registered cancer drugs. The selection of the drugs was based on diversity in clinical evidence and diversity among indications. We limited our analysis to 12 "end of life medicines" for the indications breast cancer, gastric cancer, prostate cancer, and melanoma. The selected drugs are listed in Table 1. They were first registered between 2011 and 2017 and clinical evidence levels, as determined by the European Society Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) [44], differed. This scale considers outcomes such as (progression-free) survival and drug toxicity. It was hypothesized that the time to patient access may be shorter for drugs with high clinical benefit score (e.g., ESMO-MCBS score 4 or 5) than for drugs with a lower clinical benefit score (e.g., ESMO-MCBS score 2 or 3). Abiraterone, cabazitaxel, vemurafenib, enzalutamide, Palbociclib, and ribociclib had a priority review by FDA. Abiraterone, vemurafenib, and nivolumab underwent a fast track procedure at EMA.

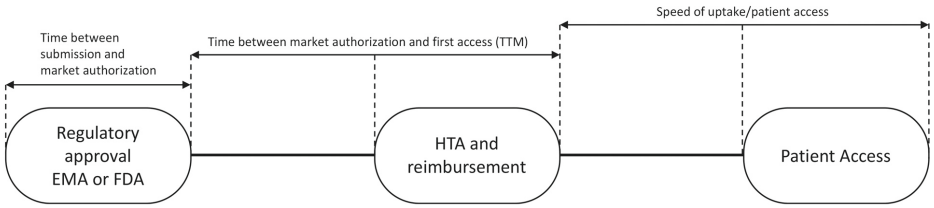
Table 1. Newly registered oncological drugs, first indications, clinical values, and duration of EMA and FDA procedures.

	First indication	Gain PFS, OS, TTP (median, months)	ESMO-MCBS*	Date of EMA submission	Date of EMA approval	Accelerated assessment (EMA)	Total time EMA (in days)	Date of FDA submission	Date of FDA approval	Priority review (FDA)	Total time FDA (in days)	Time between EMA and FDA approval (in days)
Abiraterone	Prostate cancer	3·9 months OS	4	17-Dec-10	5-Sep-2011	16-Dec-10	262	20-Dec-10	28-Apr-11	Yes	129	130
Cabazitaxel	Prostate cancer	2·4 months TTP	2	20-Apr-10	17-Mar-2011	n.a.	331	31-Mar-10	17-Jun-10	Yes	78	273
Dabrafenib	Melanoma	2·4 months PFS	4	24-Jul-12	26-Aug-2013	n.a.	398	30-Jul-12	29-May-13	No	303	89
Ipilimumab	Melanoma	3·7 months OS	4	05-May-10	12-Jul-2011	n.a.	433	10-Jun-10	15-Mar-11	No	278	119
Nivolumab	Melanoma	4·0 months PFS	4	02-Sep-14	19-Jun-2015	24-Jul-14	290	30-Jul-14	22-Dec-14	No	145	179
Vemurafenib	Melanoma	3·7 months PFS	4	04-May-11	17-Feb-2012	14-Apr-11	289	28-Apr-11	17-Aug-11	Yes	111	184
Pertuzumab	Breast cancer	6·1 months PFS	4	01-Dec-11	4-Mar-2013	n.a.	459	06-Dec-11	08-Jun-12	No	185	269
Enzalutamide	Prostate cancer	4·8 months OS	4	26-Jun-12	21-Jun-2013	n.a.	360	22-May-12	31-Aug-12	Yes	101	294
Pembrolizumab	Melanoma	1·3 months PFS	3	04-Jun-14	17-Jul-2015	n.a.	408	27-Feb-14	03-Sep-14	No	188	317
Ramucirumab	Gastric cancer	2·2 months OS	2	23-Aug-13	19-Dec-2014	n.a.	483	23-Aug-13	21-Apr-14	No	241	242
Palbociclib	Breast cancer	10·3 months PFS	3	30-Jul-15	9-Nov-2016	n.a.	468	30-Jun-14	03-Feb-15	Yes	218	645
Ribociclib	Breast cancer	PFS not reached	3	05-Sep-16	22-Aug-2017	n.a.	351	29-Aug-16	13-Mar-17	Yes	196	162
Average time (in days)								378		181	242	
Average time accelerated assessment/priority review (in days)								280		139	n.a.	
Average time in case no accelerated assessment/no priority review (in days)								410		223	n.a.	

General and indication-specific cancer data were used for determining the mortality rates per drug indication. Specific cancer mortality data were obtained from Eurostat for the years 2011–2015, mortality for the missing years 2016–2018 was based on extrapolations [45]. Analyses are performed on data from 2010–2018, for 28 European countries (Appendix A).

Subsequently, the time to patient access was determined for each drug. Time to patient access was defined as the sum of: (i) Time from regulatory submission to regulatory approval; (ii) time to first patient access, i.e., time to market (TTM); and (iii) speed of uptake of the drug (Figure 1).

Figure 1. Patient newly registered drug access pathway.



EMA: European Medicines Agency; FDA: USA Food and Drug Administration; HTA: health technology assessment; TTM: time to market.

The "time to market" for 28 European countries was calculated from the date of EMA registration of the drug to the dates of first sales in each country (Figure 1). These dates were defined as dates of first uptake and were obtained from IQVIA's MIDAS® database [43]. The speed of uptake was calculated by aggregating sales data (in standard units (SU) into the first 24 months of availability in a country and dividing by country-and indication-specific mortality, expressed by the number of cancer (specific) deaths as all drugs were registered for end of life settings. In the case of medicines with multiple indications, data were related to the overall cancer mortality in a country. As in general not all patients are in the appropriate medical condition to receive a new drug, we hypothesized that 80% of the eligible patients should have had access to the drugs.

Thereafter, time to first patient access in the 28 European countries was calculated. For the time of first patient access the date of EMA registration and first uptake in a country were calculated for each drug separately. As sales data are being reported on monthly basis, we assumed that the first uptake date would always be on the 1st of every month. Thereafter, these number of days were averaged for all 12 drugs.

Additionally, the speed of uptake in a country has been calculated by using the following formula:

$$Speed\ of\ uptake\ drug\ in\ country = \sum_{n=1}^{n=12} \left(\frac{sales\ volume\ drug\ after\ 1\ and\ 2\ years}{mortality\ drug\ indication\ in\ these\ years} \right)$$

n= type of drug, 12 drugs included in the analysis.

The sales volumes were calculated by summing up the sales volumes after exactly 1 and 2 years after the date of first uptake per drug per country. The outcomes were divided by the mortality that corresponded to the drug indication and the year. Thereof the average rank of all studied drugs per country has been derived.

To illustrate the impact of delay in patient access in European countries, we selected ipilimumab and abiraterone, as these drugs have a high clinical value (ESMO 4) and the trial results have shown an impact on the overall survival, namely an increase by 3.7 months and 3.9 months, respectively [46,47]. We calculated the loss in life years (LYs) due to a delayed access in their first year after market approval as for both drug indications new comparators were introduced later in time. We also estimated the loss in LYs due to a later introduction in Europe as compared to the US. For the number of patients in need for abiraterone and ipilimumab we used the dosing and the median number of cycles from the clinical trials [47,48]. The latter was related to the time to disease progression.

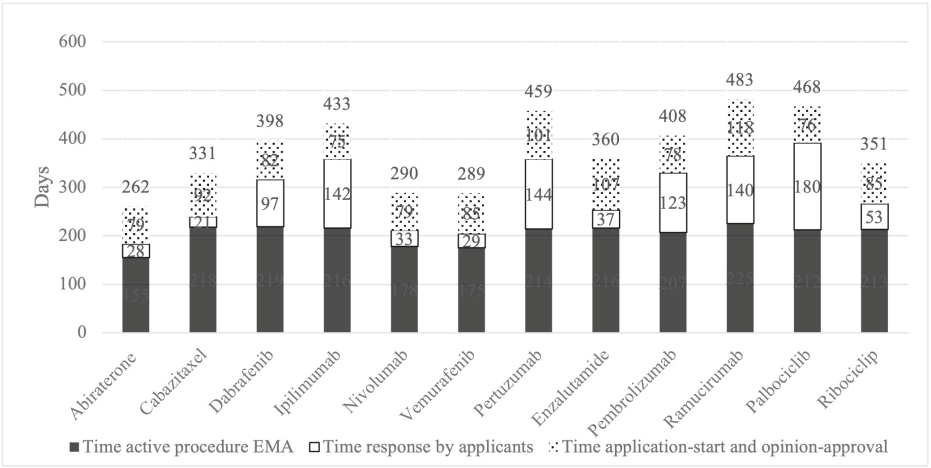
Further, the relation between FDA or EMA and between the ESMO-MCBS on the time to market and the speed of uptake has been studied by means of regression analyses (ANOVA). The ESMO-MCBS score was based on the results of the first publication. All statistical analyses were performed in SPSS Statistics version 25 for Windows (SPSS Inc. Chicago, IL, USA).

Results

Table 1 and Appendix A show the dates of the submission to, and approval by the EMA and FDA. The dates of submission to EMA and FDA were almost comparable, with the exception of palbociclib (395 days later in Europe). All drugs were first approved in the US. On average, the time to first registration was 181 days in the US (range 78–303 days) vs. 378 days in Europe (range 262–483 days), implying a difference in duration of the procedures of 197 days. Marketing approval for the cancer drugs came on average 242 days later in Europe than in the US. For the three drugs assessed in the accelerated trajectory of EMA, the average assessment period was 280 days. For drugs in the standard trajectory, this period was 410 days. The 6 drugs undergoing priority review by FDA, took an average time to market approval of 139 days, compared to 223 days for the drugs in the regular trajectory.

In Figure 2, the EMA trajectory is presented per studied drug. The actual EMA assessment time averaged 204 days and the time the applicants needed to answer queries averaged 86 days. The time between submission of the dossier and the start of the regulatory assessment procedure averaged 27 days, while the time between a positive opinion and approval averaged 61 days.

Figure 2. EMA trajectory of 12 newly registered oncological drugs (in days).

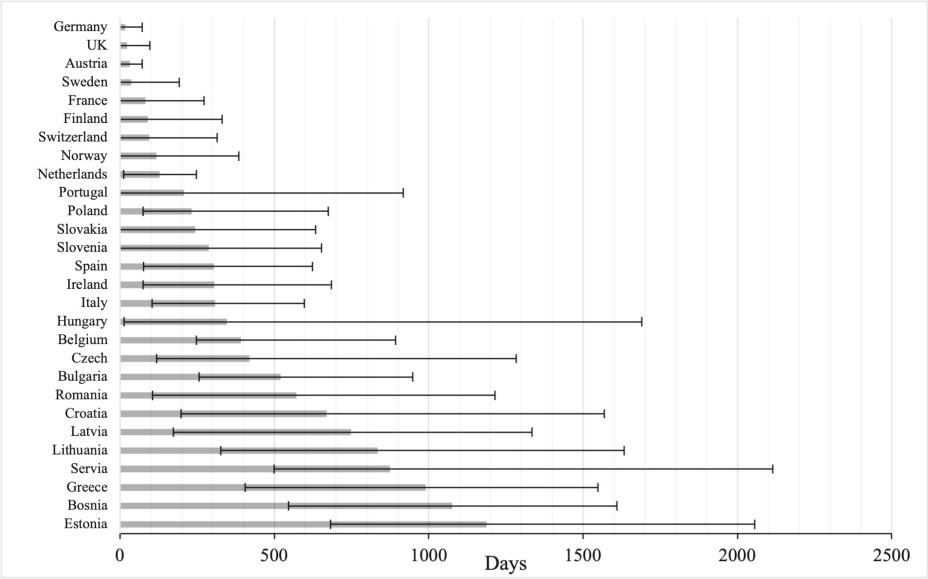


EMA: European Medicines Agency.

Further, there was no relation found in time between registration by FDA or EMA, and clinical value of the drugs as defined by clinical outcomes (OS, PFS, or TTP), or ESMO-MCBS score. For example, ipilimumab resulted in a gain of 3.7 months in OS and had an ESMO-MCBS score 4 and it took EMA 433 days to approve (FDA: 278 days). In contrast, for cabazitaxel, with 2.4 months increase in time to progression and ESMO-MCBS score 2 market authorization was given 331 days after submission of the EMA dossier (FDA priority review: 78 days).

Figure 3 and Appendix B present the average time from EMA registration to first uptake of the studied drugs across Europe. 2–8 Years after marketing approval, several countries still either had a very low uptake of drugs, or no uptake at all. Palbociclib had the fastest time to market from EMA registration until first uptake in the EC (average: 165 days), followed by nivolumab (average: 210 days), but 2 years after European market approval, these drugs were still not prescribed to patients in four and five countries, respectively. Note that, despite the relatively fast uptake of palbociclib, the time between US and EU market access was almost two years. For nivolumab this period was shorter, namely 179 days.

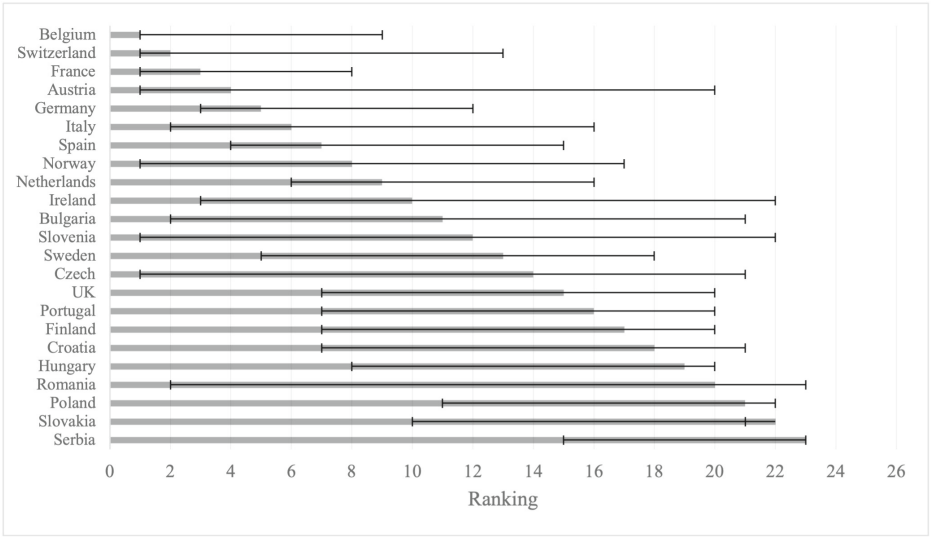
Figure 3. Time to first uptake for 12 newly registered oncological drugs across Europe (in days).



The average TTM in Europe amounted to 398 days (range 17–1187 days). In general, patients in Germany, the UK, and Austria had the most rapid potential access, with averages of 17, 22, and 31 days, respectively. Greece and many Eastern European countries were below the European average.

Figure 4 shows the speed of uptake of drugs 2 years after approval in a country. Belgium, Switzerland, France, and Austria had the highest uptake after two years. The UK and Sweden had relatively slow uptakes after 2 years.

Figure 4. Speed of drug uptake for 12 newly registered oncological drugs in first two years across Europe (average rank, range)



(Note: Too little access data for ranking: Lithuania, Greece, Bosnia, Estonia).

Concerning the time to first uptake in Eastern EC, Poland was fastest, followed by Slovakia and Slovenia. First patient access to the drugs in these countries was faster than, for instance, Spain, Ireland and Italy. Bulgaria, Romania, Croatia, and Latvia ranked low in time to first access, but both Bulgaria and Czech Republic thereafter had a rapid uptake.

A delay in patient access to new drugs may result in diminished patient benefits. We calculated that in Europe approximately 14,994 patients were eligible for treatment with ipilimumab in the first year after EMA approval (see Table 2 and Appendix C). Taking into account the sales per country in that first year approximately 11,184 melanoma patients were not treated with ipilimumab. Assuming an average gain in OS of 3.7 months (derived from Table 1), this may have resulted in a loss of 3448 life years. Applying the same calculation to prostate cancer patients eligible for abiraterone resulted in 55,853 non-treated patients, which would indicate a loss of 18,152 life years across Europe for abiraterone non-use. The delay in the EMA time to registration compared to the FDA time led to an extra estimated loss of 8639 life years for both drugs.

Table 2. Potential life years lost due to delay in access in abiraterone and ipilimumab across Europe.

	Abiraterone			Ipilimumab		
	Difference in track FDA -EMA	Delay in access after EMA registration	Total life years lost	Difference in track FDA -EMA	Delay in access after EMA registration	Total life years lost
Austria	115	204	318	50	31	81
Belgium	140	376	516	69	26	95
Bulgaria	89	249	338	40	13	53
Croatia	72	203	275	46	15	62
Czech Republic	157	440	597	114	38	152
Estonia	25	70	95	14	4	18
Finland	85	234	319	50	18	68
France	854	1803	2657	185	150	336
Germany	1126	2466	3592	394	219	613
Hungary	119	334	453	100	33	133
Ireland	84	234	318	44	17	61
Italy	602	1691	2293	433	143	576
Latvia	37	104	141	19	6	25
Lithuania	55	155	211	26	8	34
Netherlands	292	733	1025	194	72	266
Norway	117	273	390	94	31	125
Poland	507	1416	1923	385	127	512
Portugal	164	456	621	63	21	84
Romania	225	632	857	45	36	81
Serbia	102	287	389	68	22	90
Slovakia	92	256	349	58	19	77
Slovenia	41	113	155	32	11	42
Spain	580	1545	2126	240	79	318
Sweden	235	583	818	132	46	178
Switzerland	136	305	440	57	32	89
United Kingdom	1170	2988	4159	495	200	695
Total life years lost	7221	18152	25373	3448	1418	4867

Discussion

The results of our study show that, although the dates of submission to EMA and FDA did not differ for most drugs, on average newly registered cancer drugs entered the European market eight months later than the USA market. Moreover, time to patient access to the 12 newly registered cancer drugs included in the analyses differed strongly across Europe. Our analysis is the first showing the potential impact of a delay in access for patients. In the first year after EMA market authorization of ipilimumab and abiraterone almost 67,000 patients were unable to benefit from these drugs, resulting in an estimated loss of 21,600 life years. The longer EMA time to registration, as compared to the FDA time to registration, led to an extra estimated loss of 8693 life years.

Wilking and Jonsson previously studied patients' access to treatments in the five most common tumor types for the period 1999–2004 [29]. In that period Austria, Spain, and Switzerland were fastest in realizing patient access. As in our study the UK was quite slow in adoption of the cancer treatments. Another study compared the uptake and market share for direct acting antivirals in six European countries [49]. In Germany and France patients had early access and these countries were fast adopters of these drugs. Spain and Italy were late in first uptake, but they were fast adopters after first uptake. In the UK, patients had fast access, but the uptake was slow.

As all European countries cope differently with newly registered drugs, resulting in variation in patient access, a deeper understanding of the facilitators, barriers, and key actors involved in this process is necessary. According to Frost and Reich, access to an innovation depends of several factors, such as availability, affordability, and adoption of the intervention [50]. The availability of a newly registered drug in a country will be influenced by factors like time of market authorization, the duration of the reimbursement procedure and health technology assessment, the used pricing system (e.g., external reference pricing (ERP)) and the value of the drug. Affordability means that the drug is not too expensive. This is mainly influenced by the price, the gross domestic product (GDP) of a country, the health care expenditure of a country, the pharmaceutical spending of country, and the financing (co-payments or limits on number of patients treated). Adoption depends on the acceptance and amount of unmet need of the intervention as perceived by several actors, such as global organizations (FDA or EMA), governments, doctors, and individual patients. Further study of the facilitators, barriers, and key actors involved in the access of new drugs are highly recommended.

Recently, several methods have been developed in Europe and the US to deal with the assessment of the value and pricing of newly registered drugs, and their affordability in the health systems. Examples are the American Society for Clinical Oncology (ASCO) Value in Cancer Care Framework and the ESMO-MCBS [42,51]. These methods focus on the clinical benefit of the drugs and (partly) on value-based pricing, addressing cost or

cost-effectiveness of the new drug. In this study we have used the ESMO-MCBS to assess the clinical value of the studied drugs, but other instruments could be used as well. We expected that higher values of the ESMO-MCBS would result in a faster access. However, in our study a higher value, i.e., ESMO-MCBS 4–5, did not lead to a faster access of patients to these drugs.

Our study has a number of limitations. First, this study was based on data from several retrospective data sources. Each data source has several strong and weak points. IQVIA's MIDAS® database includes worldwide standardized sales data allowing unique cross-country comparisons over time. However, in some countries not all distribution channels (e.g., hospital/retail) are captured and the database does not include direct sales to clinics and private offices in all countries. Moreover, data coverage differs per country, which despite regular quality and validity checks, potentially impacts accuracy of data extrapolations.

Second, there may be differences in the quality of the registrations of cancer mortality in the EC. Some countries may have more reliable data than other countries. However, the methods to calculate the mortality rates are standardized.

Third, some drugs had registrations for the same indication or for a specific sub-indication (e.g., melanoma for patients with PDL-1 expression) and could be used as substitutes. Further, some drugs are used for multiple indications (e.g., nivolumab: lung cancer, melanoma). In case of multiple indications, we used overall cancer mortality rates of the countries to compare the uptake. As a result, we could not calculate the exact loss in life years as a result of the delay in access of patients to these treatments. Loss in palliative effect of the drugs (i.e., lost potential effects on quality of life rather than survival) is something we could also not assess.

Fourth, data about uptake of drugs should ideally be collected by using registry data, capturing data on patient and disease characteristics, and real-world use of the drugs (dosing and number of days/cycles). In the absence of such data in Europe, we used data from IQVIA MIDAS, Eurostat, and clinical trials [43,45–47]. Data on speed of uptake were based on sales data and on country specific cancer mortality rates as the drugs were end of life products. We estimated that 80% of the patients in real life were eligible for the drugs, as some patients would be too unfit and/or would have too many co-morbidities to enable treatment. For the number of patients in need for abiraterone and ipilimumab we used data from the clinical trials. It is possible that in clinical practice patients may receive fewer cycles, implying that more patients may have received these drugs. If so, this has resulted in a slight overestimation of loss of life years.

Fifth, the inclusion of drugs was based on a pragmatic approach. A different selection of drugs may have resulted in different time to access estimated. Moreover, this study was

focused on patient access to oncology drugs. Time to access and uptake may be different in other disease areas.

Finally, we selected two drugs to give an illustration of life years lost in Europe due to delays in patient access. The estimation of life years lost is based on a high-level calculation. It would be worthwhile to conduct a study including more drugs and more elaborate calculations.

Time to patient access in Europe is influenced by the complexity of national reimbursement processes. Most pharmaceutical companies first launch their product in Germany as it is the largest European market and reimbursement is automatic once EMA has approved drugs. A year of free pricing is allowed while price and reimbursement negotiations are ongoing [52]. Countries in which the reimbursement is dependent on the outcome of cost-effectiveness assessments (e.g., UK and The Netherlands) or in which lengthy negotiations with national and regional decision-makers have to take place (e.g., Spain and Italy) take a longer time to first access and have more limited uptake after two years. We assumed market access to be similar in all countries because of the centralized EMA procedure, however Norway and Switzerland have their own agencies, resulting in a 75-and 66-day delay, respectively [53,54]. Therefore, time to patient access in Norway and Switzerland has been slightly overestimated.

Several aspects can help shortening the time to patient access and increase uptake.

Specific early access programs can help facilitate early launches as exemplified in France, Sweden, and Italy [51]. Since the current processes of early access programs are generally complex, governments may be able to better facilitate these programs, for instance by allowing pharmaceutical companies to provide the medicines for free during the process of price negotiations and to reimburse the drugs according to the negotiated price once the negotiations have ended. The FDA assessment was on average substantially faster than the EMA assessment. This was during the whole study period (2010–2018). Therefore, improvements in the EMA procedure seem possible [55]. For instance, shortening the time from EMA submission to procedure start and the time from positive opinion to approval may accelerate the process by almost 3 months.

The coming decade, the number of patients with cancer is estimated to increase by 68% [56]. As stated before, patients have a right to health, i.e., the highest attainable standard of health as a fundamental right of every human being [32]. This makes it a legal obligation of countries to ensure timely access to acceptable and affordable health care of appropriate quality [56]. Fortunately, this issue will be addressed in the Pharmaceutical Strategy for Europe commissioned by the European Commission [57]. As many novel cancer drugs have entered the market and many others are upcoming, it is of utmost importance that all patients in need get access to the drugs with high clinical value as soon as possible.

Conclusions

This study shows that it takes a long time for European patients to get access to newly registered cancer drugs. Further, there is great inter-country variation of access to new cancer drugs. The delay in access may result in a potential loss of many life years. The health outcomes of European patients can substantially be improved by enabling faster and more general use of available new medicines

Chapter 3.

Real-world costs of castration-resistant prostate cancer in the Netherlands

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Abstract

Background: New treatment options that impact survival have become available for patients with castration-resistant prostate cancer (CRPC). Insight in the real-world costs of CRPC-treatment is lacking.

Design, setting and participants: The CAPRI-registry retrospectively included patients diagnosed with CRPC between 2010-2015 in the Netherlands. Patients treated with at least one life-prolonging drug were included in this analysis.

Outcome measurements and statistical analysis: Patient characteristics were analysed using descriptive statistics. Total healthcare costs (only costs occurring within the healthcare system) of CRPC-patients were calculated from start of first-line treatment until death, lost-to-follow-up, or study end (December 2017). Costs were stratified by treatment line and by type of treatment.

Results and limitations: A total of 1,937 patients were included in this analysis. Mean total costs were €67,174 per patient. On average, patients received 2.7 lines of systemic treatment. Costs of systemic treatment accounted for 59% of the total costs. Mean total/monthly costs stratified by treatment line were €28,705/€3,421 in line 1, €34,452/€5,083 in line 2 and, €31,751/€6,841 in line 3.

Conclusions: Real-world healthcare costs of CRPC are substantial, which is mainly driven by costs of systemic treatment. Therefore, it is important to assess the additional costs in relation to the additional benefits of new treatments compared to existing treatment options.

Patient summary: We analysed the healthcare costs of patients with castration-resistant prostate cancer (CRPC) in daily practice. The total costs of CRPC are mainly driven by costs of systemic treatment.

Introduction

Prostate cancer is the second most common type of cancer in men worldwide [58]. In the Netherlands, over 13,000 new cases of prostate cancer were diagnosed and almost 3,000 patients died in 2019 [59]. Treatment of metastatic prostate cancer is palliative. For these patients, treatment consists of androgen deprivation therapy (ADT) alone or in combination with chemotherapy, new androgen-receptor targeting agents or palliative radiotherapy [60,61]. Disease progression on ADT is called castration-resistant prostate cancer (CRPC).[4] Median overall survival (OS) of CRPC-patients with best supportive care without additional systemic life prolonging drugs is estimated to be 14 months [62].

From 2004 onwards, various treatments for CRPC with improved OS were introduced in the Netherlands (year introduced in the Netherlands in parentheses): docetaxel (2005), cabazitaxel (post-docetaxel: 2011), abiraterone (post-docetaxel: 2012, docetaxel naive: 2013), enzalutamide (post-docetaxel: 2013, docetaxel naive: 2015), radium-223 (2014), apalutamide (2019), and olaparib (2020) [25,63–72]. This has improved median OS to more than 30 months as was shown in a contemporary real-world cohort in the Netherlands[73].

It is expected that the incidence and prevalence of prostate cancer will increase due to an ageing population and life-prolonging treatments[60]. Furthermore, prostate cancer has impact on the economic burden: the total costs of prostate cancer in the Netherlands were almost 386 million Euros in 2017. This accounted for 0.44% of the total healthcare expenditures in the Netherlands. Almost 85% of the total costs of prostate cancer are related to hospital care [74]. Due to increased length of survival, expensive new treatments, increased treatment duration, earlier treatment and rising prostate cancer incidence, the economic burden will remain or increase. It is relevant to gain insight into the real-world healthcare costs of CRPC. Reimbursement decisions of new treatments are usually based on data from clinical trials, but patients in daily practice differ from patients in a trial setting and off-label use of treatments often occurs, which might result into higher costs [75–77]. Moreover, it is important to evaluate clinical value of treatments in the real-world and accompanying costs. The objective of this study is to provide insight into the real-world healthcare costs of patients with CRPC in the Netherlands.

Material and methods

Data source and patient population

Data were obtained from the Castration resistant prostate cancer registry: an observational study in the Netherlands (CAPRI) [76,76]. CAPRI is an observational multi-centre cohort study that contains data on patient characteristics, treatment, and outcomes of patients from 20 hospitals in the Netherlands. Patients newly diagnosed with castration-resistant prostate cancer (CRPC) were retrospectively included from January 1, 2010 till December 31, 2015. Patients were followed until death, lost-to-follow-up, or December 31, 2017 (N=3,616).

ADT in combination with chemotherapy for hormone-sensitive prostate cancer was only available at the end of the study period, therefore, these patients were excluded (N=16). It is estimated that 20% of all patients with CRPC in the Netherlands were included in the study population [75,76].

Patients who were treated with at least one of the following life-prolonging drugs (LPDs) were included in this study: docetaxel (DOC), cabazitaxel (CAB), abiraterone acetate plus prednisone (ABI+P), enzalutamide (ENZ), or radium-223 (Ra-223), while patients treated with another treatment (N=458) or who received no treatment (N=1,205) were excluded.

Cost analysis

Costing was performed according to the methodology of the Dutch costing manual [78].
A healthcare perspective was used: only costs occurring within the healthcare system were included. Cost components were determined by measuring patient level resource use and multiplying resource use with the unit cost (Table S1). Five main cost components were created.

1. treatment which encompasses systemic treatment (including radionuclides), surgery, radiotherapy, interventional radiology, bone health agents, growth factors, concomitant medication, and blood transfusion;
2. hospital visits which encompass outpatient visits, day care and emergency room stays (not all costs are necessarily CRPC-related);
3. hospital admissions including inpatient hospital stay and intensive care unit stay (not all costs are necessarily CRPC-related);
4. medical imaging including but not limited to bone scintigraphy, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, positron emission tomography-computed tomography (PET/CT) scan (not all costs are necessarily CRPC-related);
5. drug administration costs (only for intravenous treatments).

In the instance of missing resource use data, conditional mean imputation was performed (the condition being the next event for the patient) insuring internality of total cost of care.

Unit cost for outpatient visits, inpatient stay, emergency room (ER) visits and blood transfusions were obtained from the Dutch Manual for costing [78]. All costs were based on EUR 2018 unit cost data or adjusted for inflation with the Consumer Price Index (CPI) to the reference year 2018. Prices for systematic treatment or other pharmaceuticals related to the CRPC-treatment were procured from the Dutch National Healthcare Institute [79]. Other unit costs were acquired from the Dutch Healthcare Authority [80,81].

Data analysis

Patient and disease characteristics at the start of LPD treatment are summarised using descriptive statistics.

Costs were recorded until either death, lost-to-follow-up or the end of the study. Costs were stratified by line of treatment, from the beginning of systemic treatment until event (time to event), which could be either death, lost-to-follow-up or next treatment. Costs were also stratified by systemic treatment, which were divided into costs of systemic treatment and other costs (i.e., costs due to treatment (except systemic treatment), hospital visits, hospital admissions and medical imaging). A distinction was made between total costs and monthly costs (derived from the total cost divided by the time to event in months). Moreover, costs were classified in different categories: (drug) treatment, hospital visits, hospital admissions and medical imaging. Drug resource use accounted for full wastage. All aggregations of costs and descriptive statistics were performed in RStudio version 1.2.5019 [82].

Results

Patient and disease characteristics

Patient and disease characteristics at start life-prolonging drug 1 (LPD1) are shown in Table 1. In total, 1,937 patients were included in this study. Median age of the study population was 74 years (range: 46-99 years). Median PSA was 99 µg/L, median ALP 139 U/L, median LDH 231 U/L, and median haemoglobin 7.8 mmol/L. Most of the patients had a ECOG performance status of 1 (39%), had bone metastases (83%), and no known visceral metastases (42%).

Table 1. Patient characteristics

	All patients N = 1,937
Age, years	
Mean (SD)	*73 (8)*
Median (range)	*74 (46-99)*
Charlson Comorbidity Index, %	
6	*64*
7-8	*30*
9-10	*5*
>10	*1*
Gleason score, %	
7	*32*
8-10	*56*
Unknown	*13*
Opioid analgesic use	
Yes	*311 (16%)*
No	*732 (38%)*
Missing	*894 (46%)*
PSA (µ/L)	
Median (IQR)	*99 (41-239)*
Missing	*179 (9%)*

Table 1. Continued

	All patients N = 1,937
ALP (U/L)	
Median (IQR)	*139 (91-313)*
Missing	*270 (14%)*
LDH (U/L)	
Median (IQR)	*231 (192-308)*
Missing	*548 (28%)*
Hb (mmol/L)	
Median (IQR)	*7.8 (7-8.4)*
Missing	*297 (15%)*
ECOG performance status, n (%)	
0	*399 (21%)*
1	*760 (39%)*
2	*243 (13%)*
Missing	*535 (28%)*
Bone metastases, n (%)	
Yes	*1,605 (83%)*
No	*152 (8%)*
Missing	*180 (9%)*
Visceral metastases, n (%)	
Yes	*213 (11%)*
No	*820 (42%)*
Missing	*904 (47%)*

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; SD, standard deviation.

Total costs of all patients

Healthcare costs of CRPC-patients are presented in Table 2. The median follow-up period was 16.4 months (mean: 18.6 months). At the end of the follow-up period, 67% of all patients died, 14% was alive, 18% lost to follow-up, and 1% unknown. Mean total costs amounted to €67,174. Patients received on average 2.7 lines of systemic treatment. Costs of systemic treatment were €39,638, which accounted for 59% of the total costs. Other cost drivers were hospital admissions (13%; €9,018), drug administration (11%; €7,173), radiotherapy (6%; €4,293), hospital visits (6%; €4,213), and medical imaging (4%; €2,493).

Table 2. Costs of all patients

	All patients n = 1,937	
Follow-up period, months		
Mean (SD)		
Median (IQR)	18.6 (13.1)v16.4 (8.7-25.1)	
Deceased patients, %	67%	
Patients alive at cutoff date, %	14%	
	Mean resource use (SD)	*Mean costs (SD)*
Treatment		
Systemic treatment		*€39,638 (€35,070)*
Surgery	*2.70 (1.24)**	*€763 (€2,950)*
Radiotherapy	*0.10 (0.30)*	*€4,293 (€4,293)*
Interventional radiology	*0.37 (0.48)*	*€380 (€819)*
Bone resorption treatment	*0.29 (0.45)*	*€673 (€1,403)*
Growth factors	*0.31 (0.46)*	*€308 (€4,557)*
Concomitant medication	*0.04 (0.19)*	*€257 (€314)*
Blood transfusion	*0.78 (0.41)*	*€1,015 (€2,208)*
Drug administration	*0.32 (0.47)*	*€7,173 (€6,260)*
Hospital visits		
Outpatient visits	*23.85 (18.12)*	*€3,104 (€2,340)*
Daycare	*1.49 (4.21)*	*€736 (€2,083)*
Emergency room	*1.39 (1.88)*	*€373 (€507)*
Hospital admissions		
Inpatient hospital day	*14.81 (19.31)*	*€8,740 (€11,076)*
Intensive care unit day	*0.23 (2.47)*	*€278 (€3,044)*
Medical imaging		
Bone scan	*1.17 (1.67)*	*€291 (€413)*
CT scan	*1.64 (2.18)*	*€318 (€423)*
MRI scan	*0.56 (1.06)*	*€178 (€336)*
PET/CT scan	*1.22 (1.75)*	*€1,308 (€1,873)*
X-ray	*2.51 (3.36)*	*€300 (€401)*
Ultrasound	*0.53 (1.11)*	*€62 (€129)*
Other scan	*0.36 (1.09)*	*€36 (€109)*
Total costs		
Mean (SD)		*€67,174 (€45,409)*
Median (IQR)		*€58,143 (€32,262-€92,674)*

**Mean number of systemic treatment lines*
Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography-computed tomography; SD, standard deviation.

Costs per treatment line

Table 3 presents the mean total and monthly costs of LPD1, LPD2 and LPD3. All included patients (N=1,937) received an LPD1, 1,186 patients (61%) received an LPD2, and 572 patients (30%) received an LPD3. The proportion of complete cases (i.e., starting a next treatment or death) was 85% for LPD1, 84% for LPD2 and 82% for LPD3. Median time to event was 9.2 months for LPD1, 7.1 months for LPD2, and 6 months for LDP3). Mean total and monthly costs were the lowest for LPD1 (€28,705 and €3,421, respectively). Mean total costs were the highest for LPD2 (€34,452; monthly costs: €5,083), but mean monthly costs

were the highest for LPD3 (€6,841; total costs: €31,751). A total of 198 patients received further treatment line(s) after LPD3. Mean total costs of LPD4+ were €40,663.

Table 3. Costs per treatment line

	First-line treatment n = 1,937	**Second-line treatment n = 1,186**	**Third-line treatment n = 572**
Time to event, median (95%CI)	*9.2 (8.9-9.5)*	*7.1 (6.5-7.6)*	*6.0 (5.6-6.4)*
*Complete cases**	*85%*	*84%*	*82%*
Drugs, n (%)			
Abiraterone	*373 (19%)*	*453 (38%)*	*117 (20%)*
Enzalutamide	*407 (21%)*	*327 (28%)*	*118 (21%)*
Docetaxel	*1,131 (58%)*	*189 (16%)*	*60 (10%)*
Cabazitaxel	*NA*	*125 (11%)*	*198 (35%)*
Radium-223	*26 (1%)*	*92 (8%)*	*79 (14%)*
Treatment			
Systemic treatment	*€18,401*	*€22,062*	*€18,420*
	(€24,759)	*(€23,070)*	*(€15,078)*
Surgery	*€434*	*€319*	*€321*
	(€2,313)	*(€1,603)*	*(€1,651)*
Radiotherapy	*€1,212*	*€1,532*	*€1,468*
	(€2,887)	*(€3,327)*	*(€2,961)*
Interventional radiology	*€172*	*€205*	*€186*
	(€518)	*(€491)*	*(€418)*
Bone resorption treatment	*€279*	*€361*	*€386*
	(€976)	*(€997)*	*(€943)*
Growth factors	*€72*	*€262*	*€161*
Concomitant medication	*(€706)*	*(€4,720)*	*(€1,069)*
	€142	*€124*	*€91*
Blood transfusion	*(€185)*	*(€194)*	*(€136)*
	€343	*€491*	*€754*
	(€1,134)	*(€1,343)*	*(€1,535)*
Drug administration	*€4,045*	*€2,588*	*€3,694*
	(€3,852)	*(€3,320)*	*(€3,443)*
Hospital visits			
Outpatient visits	*€1,763*	*€1,419*	*€1,162*
	(€1,347)	*(€1,182)*	*(€1,028)*
Daycare	*€393*	*€310*	*€346*
	(€1,313)	*(€1,302)*	*(€1,148)*
Emergency room	*€200*	*€174*	*€159*
	(€342)	*(€336)*	*(€280)*
Hospital admissions			
Inpatient hospital day	*€4,408*	*€3,941*	*€4,218*
	(€8,559)	*(€6,196)*	*(€6,251)*
Intensive care unit day	*€217*	*€59*	*€43*
	(€2,952)	*(€849)*	*(€540)*

Table 3. Continued

	First-line treatment n = 1,937	Second-line treatment n = 1,186	Third-line treatment n = 572
Medical imaging			
Bone scan	*€161*	*€145*	*€103*
	(€256)	*(€229)*	*(€169)*
CT scan	*€173*	*€148*	*€139*
	(€263)	*(€233)*	*(€225)*
MRI scan	*€86*	*€90*	*€87*
	(€212)	*(€211)*	*(€200)*
PET/CT scan	*€680*	*€648*	*€589*
	(€1,184)	*(€1,142)*	*(€1,011)*
X-ray	*€162*	*€144*	*€122*
	(€288)	*(€238)*	*(€206)*
Ultra sound	*€33*	*€34*	*€22*
	(€86)	*(€92)*	*(€61)*
Other	*€18*	*€16*	*€19*
	(€62)	*(€63)*	*(€72)*
Systemic treatment	*€18,401*	*€22,062*	*€18,420*
	(€24,759)	*(€23,070)*	*(€15,078)*
Other costs	*€10,304*	*€12,390*	*€13,331*
	(€11,975)	*(€11,754)*	*(€10,452)*
Total costs			
Mean (SD)	*€28,705*	*€34,452*	*€31,751*
	(€28,682)	*(€26,740)*	*(€19,840)*
Median (IQR)	*€17,785*	*€27,170*	*€28,657*
	(€10,876-€35,234)	*(€16,712-€44,119)*	*(€17,783-€40,830)*
Costs per month			
Mean (SD)	*€3,421*	*€5,083*	*€6,841*
	(€4,766)	*(€3,660)*	*(€9,258)*
Median (IQR)	*€2,702*	*€4,224*	*€5,447*
	(€1,383-€4,024)	*(€3,262-€5,881)*	*(€3,757-€7,733)*

**Patient died during treatment line or received a next treatment line*
Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography-computed tomography; SD, standard deviation.

Costs per treatment

Mean total and monthly costs per treatment are shown in Figure 1 and proportion of systemic treatment per line are presented in Figure 2. ENZ had the highest mean total costs (€43,945; SD: €33,542), followed by CAB (€38,545; SD: €19,982), ABI (€38,375; SD: €31,449), and Ra-223 (€37,572; SD €17,855). Mean monthly costs were the highest for CAB (€8,199; SD: €4,809), followed by Ra-223 (€6,491; SD: €3,329), ENZ (€4,996; SD: €4,180), and ABI (€4,344; SD: €2,282). DOC had the lowest mean total and monthly costs (€17,438; SD: €12,799; €2,186; SD: €2,289, respectively). For all treatments, costs of systemic treatment accounted for the largest part of the total costs (58-76%), except for DOC (31%).

Figure 1. Mean total and monthly costs per treatment

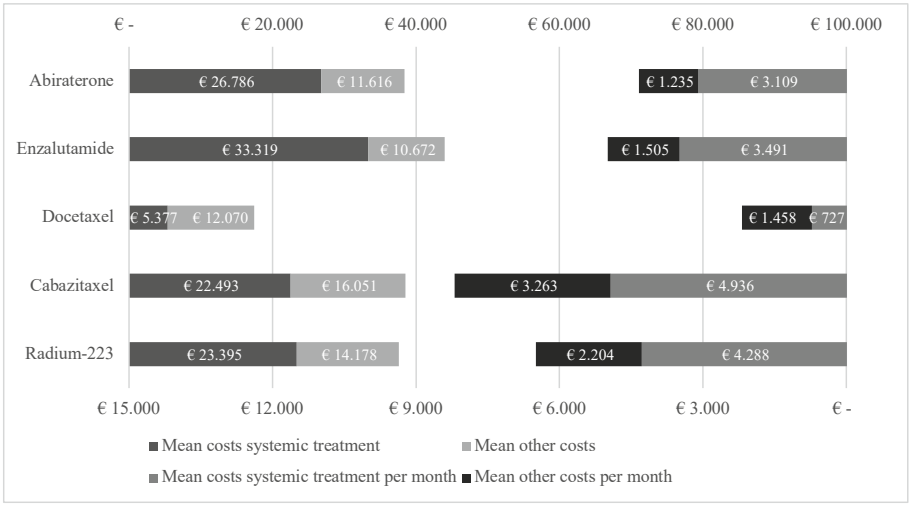
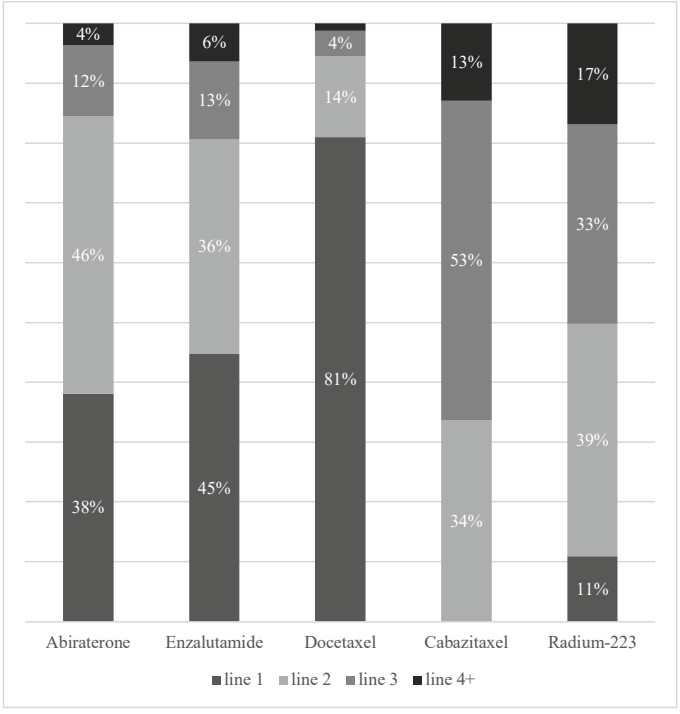


Figure 2. Systemic treatment per line (%)



Discussion

This study aimed to estimate the real-world costs of patients with CRPC in the Netherlands. Mean total treatment costs were €67,174 per patient. Total costs were mainly driven by the costs of systemic drugs (59%; €39,638). Monthly costs increased with each subsequent treatment line (LPD1: €3,421, LPD2: €5,083, LPD3: €6,841). The low monthly costs of LPD1 are driven by use of DOC in LPD1 (58%), which is relatively inexpensive compared to the other systemic treatments. Moreover, the share of systemic treatment costs is lower for LPD3 compared to LPD1 and LPD2. This is explained by the fact that more supportive care is given for LPD3. ENZ had the highest total costs of all treatments, which might be explained by a longer time on treatment and survival compared to the other LPDs. CAB had the highest costs per month (€8,199). These costs are mainly driven by supportive care costs (e.g., day care costs). Moreover, CAB is only given in line 2 or higher and costs increase in subsequent treatment lines, which could explain the high monthly costs of CAB.

Systemic treatment costs are the main driver of the total costs. The only exception is DOC since DOC was the only systemic drug out of patent at time of the study. However, it is likely that the actual costs incurred for systemic therapy were lower, as a result of hospitals purchasing these pharmaceuticals from the manufacturers with confidential discounts [83]. Hospitals could also have incurred lower costs for systemic treatment due to parallel import of these pharmaceuticals [84]. It is expected that the total treatment costs will decrease: CAB is out of patent per April 2021 and ABI will follow in September 2022. Therefore, generics are expected to reach the market leading to a price reduction. In contrary, the use of LPDs earlier in the course of disease (non-metastatic CRPC or hormone sensitive prostate cancer (HSPC)) [85,86] and new LPDs such as Olaparib, Darolutamide and Lutetium-177-PSMA-617 will likely increase diagnostic costs for molecular assays and total drug costs [70,87,88]. Moreover, in this study, drug wastage and no vial-sharing were assumed. However, costs will be lower when no drug wastage and vial-sharing occurs in daily practice. Current drug costs might differ as well, as costs of this study were based on EUR 2018 unit costs.

The results of this study were comparable to the results of a German study that studied the treatment-related healthcare costs of metastasised CRPC (mCRPC) [89]. Kreis et al. reported monthly healthcare costs of €7,631 for CAB, €2,392 for DOC, €5,226 for ABI, and €5,079 for ENZ. Monthly costs were comparable to our results, but there are small differences compared to our study. Differences could be due to differences in healthcare systems, unit costs, or treatment patterns. Since unit prices were not reported, a more detailed comparison of the studies was not possible. Another study reported healthcare costs per patient per year ranging from $27,549 (€22,708; estimated monthly cost: €1,892) for non-metastasised CRPC (nmCRPC) to $182,156 for mCRPC (€150,104; estimated monthly cost: €12,509). In the study by Wu et al., 85% of the mCRPC-patients was initially treated with an oral treatment (ABI+P or ENZ) compared to 40% in our study, which may explain

the differences in costs [90]. Unit prices were also not reported in this study, therefore, a more detailed comparison was not possible. The total costs per CRPC-patient were higher compared to the costs of non-small cell lung cancer (€28,468), but lower compared to the costs of metastatic cutaneous melanoma (€105,078) in the Netherlands [91,92].

This study has several limitations. First, all costs from CRPC-diagnosis until death, end of follow-up or last known date were measured, most of these costs are related to CRPC. As measured supportive care costs might also be related to other diseases than CRPC, reported costs may be overestimated. Second, 14% of all patients is still alive at the end of follow-up. These patients may use healthcare after follow-up, which will increase the total costs. Third, patients were included in the CAPRI-registry between 2010 and 2015. However, until 2013, only DOC was available as LPD1. Therefore, ENZ, ABI+P or Ra-223 as LPD1 is underrepresented in this analysis. The results should thus be regarded against the backdrop of the time period in which data were collected and may not be representative for the clinical practice nowadays. For further research, it is recommended to update this study to obtain faster insight into the real-world costs of CRPC. Up-to-date information is expected from the recently started CAPRI 3.0.

This study estimated the healthcare costs of CRPC in a real-world setting. Such data is of importance if one wants to estimate the cost-effectiveness of new treatments to inform healthcare decision-making. Costing data based on the real-world are preferable in cost-effectiveness models, as they reflect the clinical practice. In this study, the costs of CRPC management or treatments were not compared to its effectiveness (cost-effectiveness analysis). As a result, this study could not provide information on how expenditures could be decreased or how resource use could be allocated in a more cost-effective way.

Conclusions

In this study, we studied the real-world healthcare costs of CRPC in the Netherlands. We concluded that the real-world healthcare costs of CRPC were considerably high, namely €67,174 on average. These costs are mainly driven by the costs of systemic treatments. To keep healthcare affordable, it is of utmost importance to weigh the clinical value of new treatments against their costs.

Part B.

Economic ramifications of new therapies in hematology

Chapter 4.

Health Economic Aspects of Chimeric Antigen Receptor T-Cell Therapies for Hematological Cancers: Present and Future

Renaud Heine, Frederick W. Thielen, Marc Koopmanschap, Marie José Kersten, Hermann Einsele, Ulrich Jaeger, Pieter Sonneveld, Jorge Sierra, Carin Smand, Carin A. Uyl-de Groot. HemaSphere (2021).

Abstract

Since 2018, two chimeric antigen receptor (CAR) T-cell therapies received approval from the European Medicine Agency, with list prices around 320,000 EUR per treatment. These high prices raise concerns for patient access and the sustainability of health care systems. We aimed to estimate the costs and budget impact associated with CAR T-cell therapies for current and future indications in hematological cancers from 2019 – 2029.

We focused on the former EU-5 and the Netherlands. We conducted a review of list prices, health technology assessment reports, budget impact analysis dossiers, and published cost-effectiveness analyses. We forecasted the ten-year health expenditures on CAR T-cells for several hematological cancers in selected EU countries.

Nine cost-effectiveness studies were identified and list prices for CAR T-cell therapies ranged between 307,200 EUR and 350,000 EUR. Estimated additional costs for pre- and post-treatment were 50,359 EUR per patient, while the incremental costs of CAR T-cell therapy (when compared to care as usual) ranged between 276,086 EUR and 328,727 EUR. We estimated market entry of CAR T-cell therapies for chronic mantle cell lymphoma (MCL), follicular lymphoma (FL), lymphocytic leukemia (CLL), multiple myeloma (MM), and acute myeloid leukemia (AML) in 2021, 2022, 2022, 2022, and 2025, respectively. Cumulative expenditure estimates for existing and future indications from 2019 – 2029 were on average 28.5 billion EUR, 32.8 billion EUR, and 28.9 billion EUR when considering CAR T-cell therapy costs only, CAR T-cell therapy costs including pre- and post-treatment, and incremental CAR T-cell therapy costs, respectively.

CAR T-cell therapies seem to be promising treatment options for hematological cancers but the financial burden on health care systems in the former EU-5 and the Netherlands will contribute to a substantial rise in health care expenditure in the field of hematology.

Introduction

It took almost 40 years from the time chimeric antigen receptor (CAR) T-cell therapy was first described in the 1980s to the approval of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2017 and 2018, respectively.[93] Thus far, the EMA approved tisagenlecleucel for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that are refractory, in relapse post-transplant or in second or later relapse as well as for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Axicabtagene ciloleucel is currently approved by the EMA for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. Both therapies are autologous treatments and second-generation CAR Ts.

After novel drugs receive central approval by the EMA, each European member state handles its own approval and reimbursement procedure. With list prices of approximately 289,550 EUR (373,000 USD) in the US and 320,000 EUR in Europe, CAR T-cell therapies belong to the most expensive cancer treatments at the moment. This has consequently raised concerns regarding patient access to these therapies and the financial sustainability of health care systems in general. CAR T-cell therapies are expected to bring substantial health benefits, but also exposes healthcare systems to very large expenditures. Simultaneously, an increase in trial activity heralds an expansion of CAR T-cell therapies to many more indications in the near future, of which hematological cancers currently play the most significant role.[94] Therefore, these therapies may have a considerable incremental budget impact on healthcare expenditures, especially in the field of hematology-oncology. Moreover, the costs associated with these therapies are not limited to acquisition costs alone. Other costs that will have a substantial impact on healthcare expenditures are hospitalization, intensive care unit (ICU) stays, as well as other costs related to the treatment of adverse events and laboratory work. Furthermore, patients who live longer will also incur future medical costs unrelated to their condition for which they received CAR T-cell therapy. Conversely, longer survival may also lead to a return to productive work of survivors in remission.

In addition, substitution effects may reduce the financial impact of CAR T-cells such as avoiding the current standard of care treatment and a potential reduction in the numbers of autologous and/or allogeneic stem cell transplantation following treatment.

Overall, the application of CAR T-cell therapies may result in higher overall healthcare spending and opportunity costs –money can only be spent once– leading to a change in the allocation of the available healthcare budget. Without any formal assessment with regards to the financial aspects of these therapies, their costs remain intangible and

vague. Even though economic evaluations and budget impact analyses can shed light on the economic burden of new therapies in general, such assessments are not formally required in most countries (in Europe and elsewhere) for drug reimbursement decision making and therefore such data are scarce.

The European Hematology Association (EHA) is concerned about the sustainability of the pricing of new oncological treatments, and in particular of CAR T-cell therapy, possibly exposing health systems to very large expenditures. Therefore, the EHA has commissioned the Institute for Medical Technology Assessment (iMTA) to forecast future health expenditures, based on the adoption of CAR T-cell therapies in hematological cancers.

This study aimed to estimate the costs and budget impact associated with CAR T-cell therapies for current and future indications in hematological cancers in Europe from 2019 to 2029. The results of this study can be used by health care decision-makers in their budgetary planning as they elucidate the future economic burden of CAR T-cell therapies in several European countries.

Materials and Methods

We followed a four-stepped approach and focused on six European member states: the former EU-5 (i.e. Germany, Spain, France, United Kingdom, and Italy) and the Netherlands. First, we conducted a review of list prices, health technology assessment (HTA) reports, budget impact analysis (BIA) dossiers, and published cost-effectiveness analyses (CEA). Second, we identified potential future indications and estimated the eligible patient population for both registered and selected upcoming indications. Third, we validated our findings with international clinical experts in the field of hematology-oncology. Finally, based on the gathered information in the previous steps, we predicted the ten-year health expenditures on CAR T-cells for several hematological cancers in the selected EU member states. The forecast entails different cost calculations namely: i) costs of CAR T-cell therapies only; ii) costs of CAR T-cell therapies and costs of care, as well as iii) incremental costs associated with the substitution of former therapies by CAR T-cell therapies.

Review of list prices and cost-effectiveness publications

We retrieved list prices for tisagenlecleucel and axicabtagene ciloleucel from HTA/BIA reports published by national reimbursement authorities. In addition, we searched for published CEA studies to complement potential missing or unpublished data. These publications were searched through EMBASE on 09-05-2019 with an update search on 20-04-2020 (see Appendix 1 for the full search strategy). Only economic evaluations for hematological diseases were included.

Identification of future indications and estimation of the eligible patient population

To identify future indications for CAR T-cells, we searched clinictrials.gov for all registered studies on CAR T-cell therapies (search term: "chimeric antigen receptor") for hematological cancers on 03-05-2019. This search included early phase 1, phase 1, phase 2, phase 3, and phase 4 trials. All studies were ranked according to the indication studied (most to least often studied indication). Through a semi-structured interview, several clinical experts were asked to validate this ranking and to (re)arrange it according to the sequence of expected market entry.

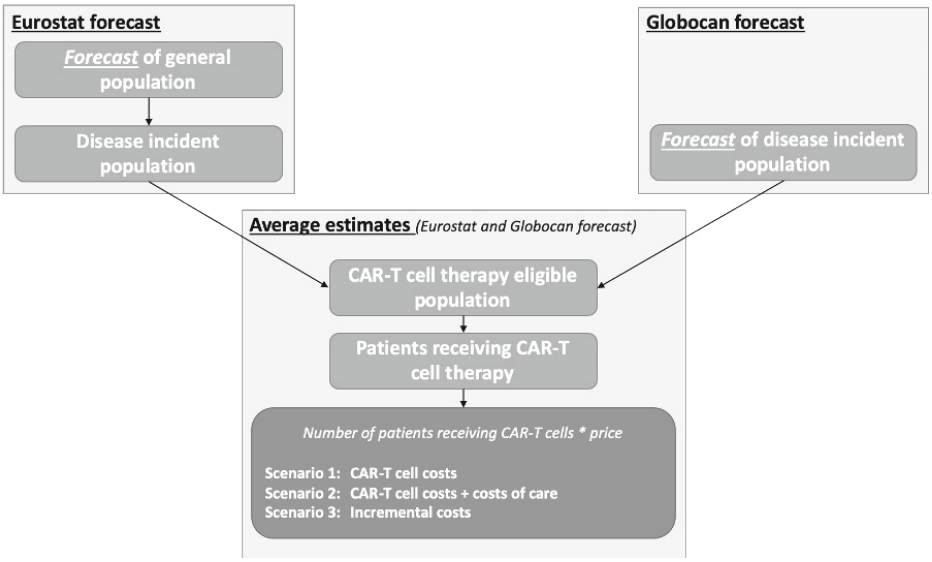
To estimate the eligible patient population for CAR T-cells, we focused on the two indications for which CAR T-cells already have market authorization (pALL and DLBCL) and the top five potential future indications identified by the clinical experts. The eligible patient population was calculated based on previous population forecasts by using two data sources, namely Eurostat and Globocan.[7]

In the Eurostat forecast, several assumptions were made on the future development for fertility, mortality, and net migration to predict the population of European member states to the year 2080 (based on the population in 2016).[95] We assumed a linear trend between the 2016 and 2080 Eurostat data and calculated the yearly population per country of interest. For our purpose, we defined the *disease incident population* by estimating the yearly crude incidence rate (IR) per 100,000 for each disease and country of interest. For pALL and DLBCL, the yearly disease IRs were taken from HTA/BIA reports. For future indications, or in the absence of published data from HTA/BIA reports, we used data from the European Cancer Information System (ECIS).[96] Subsequently, the crude IRs were applied to projected population data by Eurostat.[95]

The online database GLOBOCAN offers information on projected IRs of different cancer types for the time between 2018 and 2040 for several countries.[97] To derive the number of patients for each cancer subtype of interest, we applied proportions based on the literature.[98–101]

Both forecast approaches are depicted in Figure 1.

Figure 1: Flowchart of forecast approaches



The proportion of *patients eligible for CAR T-cell therapy* per country was calculated based on HTA/BIA reports. Most publications stated the yearly number of incident cases and the total number of patients eligible for CAR T-cell therapy. From these numbers, we calculated the proportion of eligible patients and applied this rate to all incident cases to derive the total yearly number of eligible patients for CAR T-cells per disease and country. The CAR T-cell therapy eligible patient population for all future indications was based on expert opinion.

Validation with clinical experts

Clinical experts in the field of hematology-oncology were asked to validate our intermediate findings via semi-structured interviews. Respondents were asked about their experience with CAR T-cell therapies, possible future hematological indications, resource use during pre-treatment, treatment, and post-treatment with CAR T-cell therapies in their own country, and the plausibility for CAR T-cell therapies to be manufactured within specialized hospitals (point-of-care manufacturing).

Expenditure estimation of CAR T-cell therapies for current and selected future indications

Expenditures were estimated for three scenarios. In *Scenario 1*, the CAR T-cell therapy eligible patient population was multiplied with the average list price for the currently approved CAR T-cell therapies in the former EU-5 and the Netherlands. For all new indications, the costs for CAR T-cell therapies were assumed to be similar to the average list price.

For *Scenario 2*, we added costs for pre-treatment, concomitant medication, adverse events (AEs), and hospitalization (including follow-up) to the price of CAR T-cell therapy.

Information on resource use (i.e. medication dosage and the number of hospital days etc.) were taken from available HTA/BIA reports or based on expert opinion. Prices for medication, hospitalization (including ICU admission), and AEs were based on costs reported in HTA/BIA reports or the literature.[102–108] In case country-specific prices could not be found, the average of available prices was used. Finally, clinical experts were asked to validate these data.

For *Scenario 3*, we calculated the incremental costs of CAR T-cell therapy, i.e. the costs of *Scenario 2* minus the costs of care as usual. These incremental costs were derived from the published CEAs identified for this study. Thereafter, we multiplied the eligible patient population with incremental costs of CAR T-cell therapy. Average incremental costs observed in DLBCL were used to estimate incremental costs for future indications.

For all scenarios and indications, we assumed a market penetration rate of 45% in the first year after registration and 90% thereafter.[109]

Results

Results of list prices and cost-effectiveness publications

HTA reports and BIA dossiers were found for Germany,[110–112] France,[113–115] the UK[116–118] the Netherlands[119–121] and Spain. Only in German publications, list prices were stated for all indications. In France, all prices were marked as confidential, and in the UK, prices were stated for all indications treated with tisagenlecleucel. The UK price for axicabtagene ciloleucel was marked confidential, i.e. it was concealed in the report. Dutch prices were available for axicabtagene ciloleucel and tisagenlecleucel.

For Italy and Spain, HTA/BIA reports were not publicly available. List prices for these countries were retrieved from documents of the Italian Medicines Agency (AIFA),[122,123] and the Spanish Ministry of Health.[124,125] Table 1 presents an overview of all list prices.

Table 1: Overview of list prices

Country	**List price (excl. VAT)**			
	Axicabtagene ciloleucel (Yescarta®)		**Tisagenlecleucel (Kymriah®)**	
	DLBCL		pALL	DLBCL
France		350,000 EUR	320,000 EUR	320,000 EUR
Germany		327,000 EUR	320,000 EUR	320,000 EUR
Italy		327,000 EUR	300,000 EUR	300,000 EUR
The Netherlands		327,000 EUR	320,000 EUR	320,000 EUR
Spain		327,000 EUR	320,000 EUR	320,000 EUR
UK		300,000 GBP	282,000 GBP	282,000 GBP

The initial literature search detected nine cost-effectiveness analyses,[126–129,129–133] and the search for grey literature found three HTA reports[134–136] and one report from an ERG (Evidence Review Group) for a NICE STA.[129] Two publications were added following the update search.[130,137] The publication by Walton et al. (2019)[25] presented results from the ICER HTA report and is therefore included in the following summary, instead of the HTA report. Most studies focused on pALL patients, while three publications[132,133,138] studied relapsed/refractory (r/r) DLBCL as indication. The ICER report[134] presented results for both r/r pALL and r/r DLBCL.

The results are summarized in Table 2.

Table 2: Overview of cost-effectiveness analysis publications

Author, year	Indication, treatment	Base-case settings	Scenario analysis	Total costs	Total effects in QALYs	ICER: CAR T-cell versus
Lin et al.[139], 2018	pALL , Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	Yes, 5-year relapse-free survival rates (i.e. 40% - 0%)	[2017 USD] Clo-M: 314,000 Clo-C: 374,000 Blina: 282,000 CAR T-cell: 599,000	Clo-M: 3.12 Clo-C: 3.52 Blina: 3.57 CAR T-cell: 8.74	[USD/QALY] Best-case scenario (40% 5-year relapse-free survival rate): Clo-M: 61,315, Clo-C: 43,103, Blina: 50,712
Whittington et al.[127], 2018	pALL, Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	Yes, other discount rates, different survival curve fitting, future health care cost (included / not included	[2017 USD] Clo-M: 337,256 CAR T-cell: 666,754	Clo-M: 2.10 CAR T-cell: 9.28	[USD/QALY] Base-case scenario: 46,000
Sarkar et al.[128], 2018	pALL, Tisagenlecleucel	Perspective: health care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	No	[2017 USD] Clo-C: 440,600 CAR T-cell: 968,800	Clo-C: 8.58 CAR T-cell: 16.76	[USD/QALY] Payer perspective: 64,600
Walton et al.[129], 2019	pALL, Tisagenlecleucel	Perspective: NA Horizon: lifetime Discount rate (costs/ effects): 3.5%/3.5%	No	[2017 GBP] Salvage chemo: NA Blina: NA CAR T-cell: NA	Salvage chemo: NA Blin: NA CAR T-cell: NA	[GBP/QALY] Deterministic: Salvage chemo 45,397, Blina: 27,732
Furzer et al. ,2020[130]	pALL, Tisagenlecleucel	Perspective: Public insurer Horizon: 60 years Discount rate (costs/ effects): 1.5%/1.5%	Yes, long-term cure rates varying between 10% and 40%	[2018 USD] Comparator (combination of chemo and HSCT): 86,597 CAR T-cell: 442,098	Comparator: 5.05 CAR T-cell: 14.90	[USD/QALY] Optimistic scenario: 53,933
Thielen et al. ,2020[137]	pALL, Tisagenlecleucel	Perspective: Societal Horizon: lifetime Discount rate (costs/ effects): 4%/1.5%	Yes, different perspectives, shorter plateau phase, different time horizons, alternative standardized mortality rate input, vial sharing assumed, longer duration of IVIG administration, different parametric extrapolation models resulting in different cure rates	[2018 EUR] Clo-M: 160,803 Clo-C: 193,920 BlinaL 267,259 CAR T-cell: 552,679	Clo-M: 0.74 Clo-C: 1.70 Blina: 2.25 CAR T-cell: 11.26	[EUR/QALY] Base-case Clo-M: 36,378 EUR/QALY Clo-C: 31,052 EUR/QALY Blina: 31,682 EUR/QALY

Table 2: Continued

Author, year	Indication, treatment	Base-case settings	Scenario analysis	Total costs	Total effects in QALYs	ICER: CAR T-cell versus
Roth et al.[132], 2018	DLBCL, Axicabtagene ciloleucel	Perspective: health care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	Yes, patients in long term remission experience 10% or 20% lower survival compared to age-matched US general population	[2018 USD] R-DHAP: 172,737 CAR T-cell: 552,921	R-DHAP: 1.13 CAR T-cell: 7.67	[USD/QALY] Base-case scenario: 58,146
Lin et al.[138], 2019	DLBCL, Tisagenlecleucel and Axicabtagene ciloleucel	Perspective: health care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	Yes, PFS at 5 years: Axicabtagene: 40% to 20% and Tisagenlecleucel: 35% to 15%	[2018 USD] Combination: R-DHAP, R-GDP, R-GEMOX, R-ICE, SCT: 169,000 Axicabtagene ciloleucel: 651,000 Tisagenlecleucel: 529,000	Combination: R-DHAP, R-GDP, R-GEMOX, R-ICE, SCT: 1.78 Axicabtagene ciloleucel: 5.50 Tisagenlecleucel: 3.92	[USD/QALY] Axicabtagene ciloleucel versus combination (40% 5-year progression-free survival): 129,570, Tisagenlecleucel versus combination (35% 5-years progression-free survival): 168,224
Whittington et al.[133], 2019	DLBCL, Axicabtagene ciloleucel	Perspective: public payer care Horizon: lifetime Discount rate (costs/ effects): 3%/3%	Yes, different extrapolation of OS and PFS curves, different perspectives, different time horizons	[Year not clear USD] R-DHAP: 151,200 CAR T-cell: 554,700	R-DHAP: 3.37 CAR T-cell: 9.19	[USD/QALY] Public payer perspective, standard parametric: 230,900

dentification of future CAR T-cell indications

The search on clinicaltrials.gov resulted in a total of 246 studies, of which most were attributed to non-Hodgkin's lymphoma (N = 97), followed by ALL (N = 84), multiple myeloma (MM) (N = 38), chronic lymphocytic leukemia (CLL) (N = 22), acute myeloid leukemia (AML) (N = 19), and others (N = 35). Several studies addressed multiple indications and targets. The three most studied target antigens were CD19 (N = 161), followed by BCMA (N = 19) and CD22 (N = 20).

The clinical experts expected that mantle cell lymphoma (MCL), follicular lymphoma (FL), MM, CLL, and AML, would be the first indications for which CAR T-cell therapy would become available in the near future. Based on phases of the clinical trials and clinical expert opinion, we estimated market entry of CAR T-cell therapies for MCL in 2021. For the indications of MM, CLL, and FL market entry was estimated for the year 2022. Finally, it was expected that CART T-cell therapies for AML would be available in 2025.

Estimation of the eligible patient population

Reported yearly IRs varied not only across but also within countries. Although targeting the same indication, HTA/BIA reports for DLBCL stated different yearly incidences for the same indication and hence different numbers of eligible patients within the same country. For our analysis, we used country averages for pALL and DLBCL in case more than one estimate was available. IRs for MCL, FL, AML, MM, and CLL were taken from ECIS (see Appendix VII).

The proportion of eligible patients for CAR T-cell therapies were available for pALL in Germany, France, and the Netherlands and varied between 6% (FR) and 11% (DE). For DLBCL the proportions were known for Germany, France, the UK, and the Netherlands, varying between 12% (FR) and 22% (UK). Missing data for these indications (i.e. pALL and DLBCL) in all other countries were imputed with the mean proportion from countries with available data (see for details Appendix VII).

To estimate the number of patients for the different cancer sub-types from Globocan, we used US figures, since European data were not available. As proportions were not available from one single source, data for pALL were based on the Surveillance, Epidemiology, and End Results Program (SEER) of the US National Cancer Institute.[140] Most recent data for ALL and CLL were taken from the 2019 facts and figures sheet published by the American Cancer Society,[98] and DLBCL estimates were based on Li et al.[141] Proportions of MCL and FL patients from non-Hodgkin lymphoma were taken from Sandoval-Sus et al.[100] (2017) and Cerhan et al.[99], respectively.

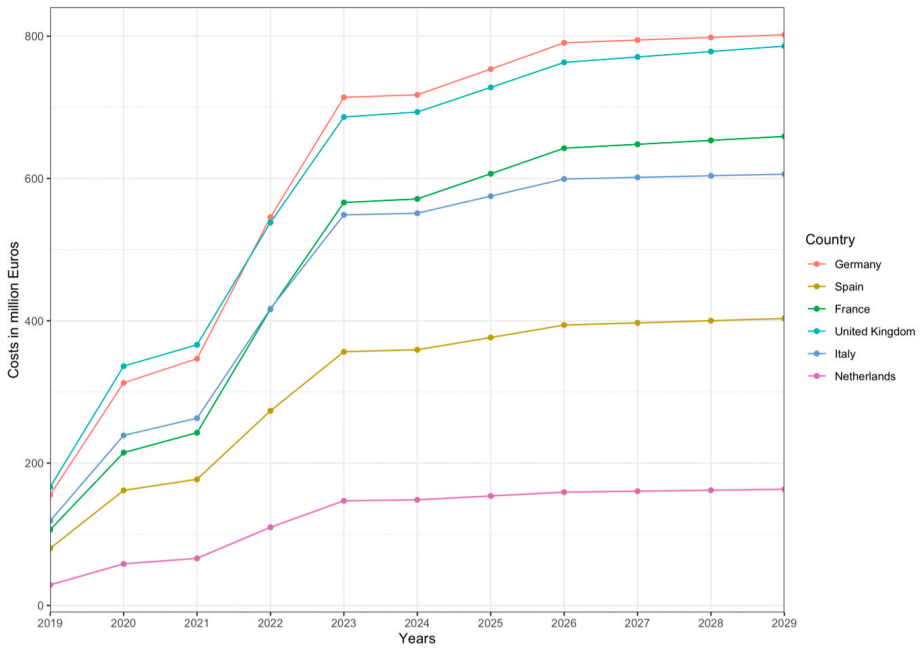
For the period 2019-2029, we estimated a total average of 103,750 patients being eligible for CAR T-cell therapies, ranging from 95,954 patients (Eurostat forecast) to 111,545 patients (Globocan forecast) for the indications pALL, DLBCL, MCL, FL, AML, CLL, and MM.

Expenditure estimation of CAR T-cell therapies for current and selected future indications per scenario

Scenario 1 estimation based on list prices

Multiplying costs for CAR T-cell therapies with the number of eligible patients in the former EU-5 and NL resulted in average cumulative expenditures varying between 1.4 billion EUR for the Netherlands to 6.7 billion EUR for Germany. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019 to 2029 were on average 0.8 billion EUR, 13.5 billion EUR, 2.3. billion EUR, 6.4 billion EUR, 1.2 billion EUR, 0.9 billion EUR, and 3.5 billion EUR, respectively (total average: 28.5 billion EUR). Figure 2 depicts the yearly average forecasted expenditure per country for scenario 1 across all indications.

Figure 2: Total average costs per country in scenario 1 (all indications)



Scenario 2 Total CAR T-cell therapy costs, including pre- and post- costs

Resource use and prices for the cost items considered for scenario *2* could partly be retrieved from sources for the Netherlands, the UK, Germany, and France (see Table 4 for an overview of the average resource use and cost prices). The additional costs for CAR T-cell therapy amounted to 50,359 EUR for each patient receiving CAR T-cell therapy, with a substantial amount necessary for lymphodepletion and administering CAR T-cells, namely 26,615 EUR. In Table 5, these costs are shown. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019

to 2029 were on average 0.9 billion EUR, 15.7 billion EUR, 2.5 billion EUR, 7.4 billion EUR, 1.4 billion EUR, 1.1 billion EUR, and 4 billion EUR, respectively (total average: 32.8 billion EUR).

Table 3: Cost components and resource use of pre- and post- CAR T-cell therapy

Item	Type	Value in EUR
Leukapheresis and cryopreservation	Costs	4,947
CAR T-cell administration + Lymphodepletion	Costs	15,033
ICU stay (per day)	Costs	1,444
Hospital stay at hematology/oncology ward (per day)	Costs	628
Intravenous immunoglobulin IVIG (per dose)	Costs	2,032
Tocilizumab (per event)	Costs	1,483
Treatment of febrile neutropenia (per event)	Costs	4,953
Treatment of anemia (average costs per event, incl. transfusion)	Costs	2,961
Treatment of thrombocytopenia (per event)	Costs	2,417
Oncologist/hematologist (per visit)	Costs	145
Neurologist (per visit)	Costs	103
MRI scan (per scan)	Costs	214
PET-CT scan (per scan)	Costs	1,110
Percentage of patients receiving tocilizumab	Resource use	60%*
Percentage of patients receiving IVIG	Resource use	24%
Assumed average number of days in hospital (including pre- and post-treatment)	Resource use	14
Assumed average number of ICU days (including pre- and post-treatment)	Resource use	2
Percentage of patient admitted to ICU	Resource use	20%*
Probability of patients with cytokine release syndrome (CRS) ≥3	Resource use	18%
Probability of patients with febrile neutropenia (FN)	Resource use	23%
Probability of patients with neurological events ≥3	Resource use	20%
Probability of patients with anemia	Resource use	27%
Probability of patients with thrombocytopenia	Resource use	19%
Duration of follow up (in years)	Resource use	15*

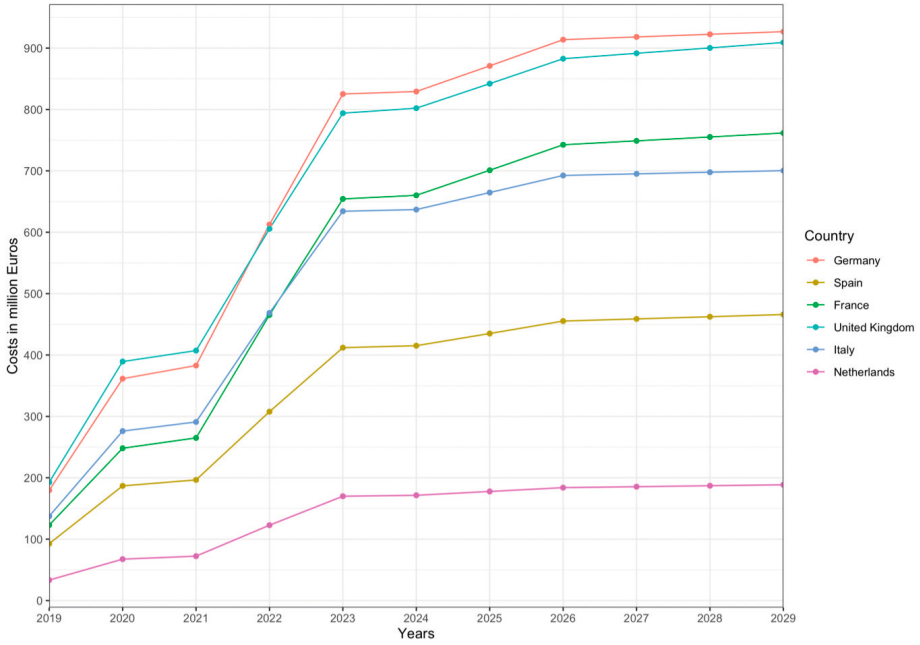
* = based on clinical experts

Table 4: Average total costs pre- and post- CAR T-cell administration in former EU-5 and NL

Item	Value in EUR
Average cost of care pre- CAR T-cell administration	7.147
Average cost lymphodepletion and administering CAR-T	26.615
Average cost of care managing AE's	10.524
Average cost of follow up	6.074
Total cost of pre and post- CAR-T care	**50.359**

Multiplying the total costs of pre- and post- CAR T-cell care with the number of eligible patients per indication and country resulted in total cumulative expenditures between 7.7 billion EUR (DE) and 1.6 billion EUR (NL). Figure 3 depicts average forecasted costs (all indications) per country for scenario 2.

Figure 3: Total average costs per country in scenario 2 (all indications)



Scenario 3 Incremental costs of introducing CAR T-cell therapy

Of all CEA studies reviewed, the total average incremental costs of CAR T-cell therapies when compared to care as usual were 276,086 EUR and 328,727 EUR for patients with pALL and DLBCL, respectively. Cumulative expenditure estimates in our base-case for pALL, DLBCL, MCL, FL, AML, CLL, and MM for all included countries from 2019 to 2029 were on average 0.7 billion EUR, 13.8 billion EUR, 2.3 billion EUR, 6.5 billion EUR, 1.2 billion EUR, 0.9 billion EUR, and 3.5 billion EUR, respectively (total average: 28.9 billion EUR).

Figure 4: Expenditure forecast per scenario (all countries and indications)

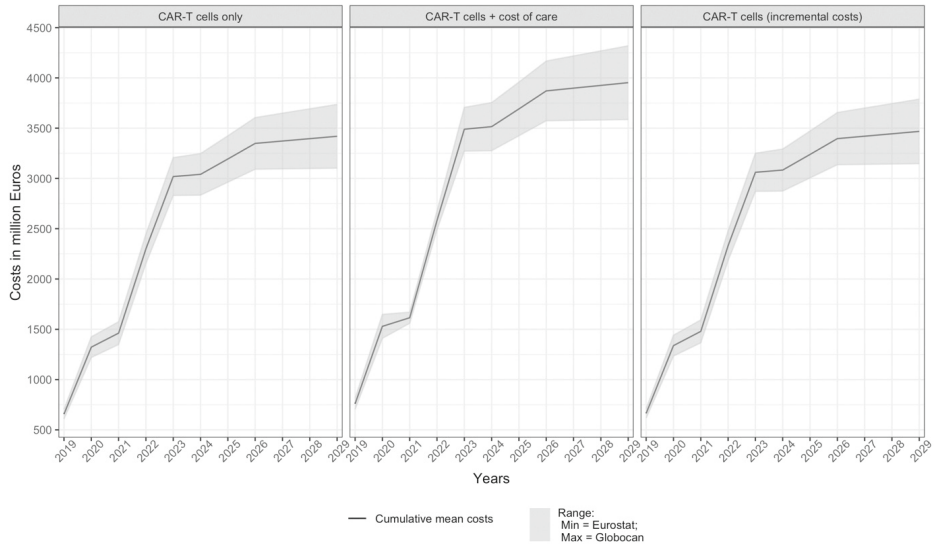


Figure 4 depicts the average expenditure across all countries and indications of all three scenarios. The upper and lower bounds are the estimates based on the Globocan and Eurostat approach, respectively.

Discussion

In our analysis, we estimated future expenditures associated with CAR T-cell therapies for a set of hematological indications in six European member states between 2019 and 2029. The average cumulative costs in all six countries for all included indications were estimated at 28.5 billion EUR (scenario 1) with a steady increase in yearly average costs across the time range studied. Average yearly costs increased in a step-wise manner which can be explained by the assumed drug penetration rate and predicted new indication launches. For the year 2019, we assumed penetration rates of 45% for current CAR T-cell therapies for DLBCL and pALL. This penetration rate peaks in 2020 (90%) and remains stable thereafter. For the year 2021 we assumed new product launches for MCL and in the year 2022 new launches for FL, MM, and CLL. Even with an initial penetration rate of 45% for the first year of the product launch, this is a major cost driver that more than doubled the yearly average costs. Finally, the product launch for AML was estimated for the year 2025 and is responsible for another stepwise increase in predicted yearly cumulative costs.

It seems obvious that new product launches have a considerable impact on any expenditure. Therefore, the methodology for estimating the expenditure of these launches is crucial. However, there is no reliable way of knowing at what time exactly new CAR T-cell therapies will be available for treatment. For product launches of future indications, we used data on

available clinical trials on clinicaltrials.gov and estimated their future availability based on the time between the trial start date and the published date of the respective HTA reports for tisagenlecleucel and axicabtagene ciloleucel. In case several trials were currently running, we selected studies from the biggest sponsor in terms of market capitalization. However, this approach neglects the possibility of failing trials that would not lead to market access of a drug, the possibility of smaller companies to be the first to receive market access for their drug, or the possibility of postponing market access due to internal decisions. Therefore, we validated our findings with clinical experts who suggested CAR T-cell therapy launches in the years 2021 and 2022 for MCL and FL, respectively.

The eligible patient population for CAR T-cell therapies in the different EU member states was based on the population projection by Eurostat[95] with fixed incidence rates, and the incidence projection from Globocan, over the period 2019 to 2029. Both strategies were used to congregate an average patient population. The factual eligible patient population could deviate from our projection due to unforeseen events and assumptions. Our assumptions and results were validated by clinical experts, but forecasts are sensitive to changes in outcomes and business strategies. Besides, future clinical pathways may also change, accommodating for new treatments that are currently in the pipeline. Advancements in other immunotherapies and targeted therapies could affect future uptake of CAR T-cell therapies as well. Currently, available CAR T-cell therapies (i.e. tisagenlecleucel and axicabtagene ciloleucel) are being investigated for the second-line treatment of patients with DLBCL (NCT03570892, NCT03391466) which will make those therapies available to an even larger patient population. Moreover, lisocabtagene maraleucel is also being investigated in a second-line setting for patients with B-cell non-Hodgkin lymphomas (NCT03575351). If CAR T-cell therapies are utilized in second-line settings, this would considerably increase the eligible patient population.

Besides the uncertainties regarding the number of patients eligible for CAR T-cell therapies, the price of the therapy itself is associated with a high degree of uncertainty. For our analysis, we used list prices whenever available. However, actual prices for CAR T-cell therapies are mostly subject to confidential negotiations. Hence, the actual price per country is unknown. For our analysis, the price of CAR T-cell therapies for future indications was assumed to be 323,500 EUR per treatment, based on an average of the known list prices for DLBCL patients. This estimation could be inaccurate, due to existing and future competing treatment options. Moreover, clinical experts already reported a new and lower price for tisagenlecleucel in Germany of 275,000 EUR per treatment. Such a price reduction could be the result of the two CAR T-cell therapies (i.e. tisagenlecleucel and axicabtagene ciloleucel) currently competing for DLBCL. The expected approval of lisocabtagene maraleucel[142] (Celgene) could drive up competition even more. To allow competition with the two existing CAR T-cell therapies, could lead to an even further reduction in prices. Per contra, Celgene might price lisocabtagene maraleucel higher than its competitor considering the possibility of being best-in-class.[143] Yet another scenario that could affect prices of

CAR T-cell therapies is the point-of-care production within hospitals, leaving health care payers with only the manufacturing costs. Specialized hospitals in several countries are exploring the possibility to make their own CAR T-cell treatments in the future. We have asked clinical experts whether they think it would be an option for lowering the price and improving the access to CAR T-cells for patients. In Germany and the Netherlands, the probability was estimated above 50% and the cost of own production was estimated to be 50,000 EUR – 70,000 EUR per CAR T-cell treatment. This means that one treatment may cost approximately 80,000 EUR (including pre- and post-care costs) instead of 375,000 EUR. In the literature, the manufacturing costs have been estimated at 65,000 USD.[144] Moreover, companies such as Cellectis or Servier are currently working on the development of allogeneic CAR T-cell therapies (NCT03190278, NCT02808442). These off-the-shelf CAR T-cell therapies could be manufactured in batches instead of on-demand, resulting in economies of scale, and possibly lower cost for health care payers. Lastly, the possibility of *in vivo* reprogramming of T cells, to e.g. be active against CD19 positive cells, could potentially reduce treatment costs by circumventing *ex vivo* manufacturing of T cells.[145]

While the price for CAR T-cell therapies may be subject to changes, the cost of care associated with CAR T-cell therapy could also decrease over time. This may be due to possible reductions in side-effects or different adverse event profiles with future CAR T-cell therapies. Likewise, our forecasted incremental costs may differ. Our estimates are based on relatively scarce cost-effectiveness data on both tisagenlecleucel and axicabtagene ciloleucel. For future indications, we assumed an average of the known costs. However, according to clinical experts, the incremental costs associated with CAR T-cell therapies for MM could be much lower when compared to DLBCL for instance. This may be caused by the chronic nature of MM and its current high costs for the standard of care, which could be redundant after CAR T-cell therapies.

Other cell and gene therapies that have regenerative or curative potential are currently being developed for various indications.[146] The limited duration of clinical trials, is coincidentally accompanied by uncertainty in long-term effects. Moreover, the possibility to cure patients with a single administration presents a new challenge for pricing and reimbursement of these therapies.[147] Current pricing of gene therapies ought to reflect expected long-term effects and its curative potential. For instance, Novartis has priced Zolgensma, a gene therapy medication used to treat spinal muscular atrophy in children less than 2 years old, at approximately 1.887 million EUR (2.125 million USD), which makes it the most expensive drug currently available.[148] Spark Therapeutics Inc's Luxturna gene therapy for patients with inherited retinal disease, was priced at approximately 754,817 EUR (850,000 USD) for both eyes. One aspect these cell and gene therapies share is their high prices which are often justified by significant treatment effects. However, long-term efficacy results are not yet available, and some patients may need subsequent CAR T-cell therapies or allogeneic stem cell transplantation. In addition, some patients might need additional (other) gene therapies in the future. It remains unclear who should bear

the financial risk stemming from the uncertainty in the clinical value. Consequently, reimbursement decision-makers in many EU member states seem to be reluctant in applying "standard" reimbursement criteria to CAR T-cell therapies.

Several EU member states and the UK adopted various pricing and reimbursement schemes. While France and the UK opted for coverage with evidence development schemes, both Italy and Spain negotiated outcomes-based staged payment agreements. Outcomes-based rebates were negotiated in Germany, and in Austria, different cost-sharing agreements are in place, varying between provinces. In the Netherlands tisagenlecleucel for pALL, patients is reimbursed through standard criteria, since its estimated budget impact was found to be relatively low (approximately 10 children per year were estimated to be eligible). Axicabtagene ciloleucel for DLBCL patients on the other hand was placed in the so-called 'lock' for 421 days, before being reimbursed. The different reimbursement schemes for the former EU-5 are analyzed and discussed in depth elsewhere.[149]

At the 2020 EHA/EBMT CAR T-cell congress in Sitges, manufacturers signaled a willingness to further cooperate with payers reaching reimbursement agreements. Presented options were discounts of list prices, price-volume agreements, outcome-based agreements based on patient-level outcomes, value-based agreements based on additional clinical evidence, or a price by indication. Despite this, CAR T-cell therapies are still not affordable for many countries.

We limited our study to the former EU-5 and the Netherlands, all of which are already reimbursing CAR T-cell therapies. However, difficulties regarding reimbursement are even greater in Eastern Europe, resulting in many patients currently lacking access to these promising treatments.

The future market of CAR T-cell therapies has been studied previously, although not with a specific focus on hematology-oncology.

The decision resources group (DRG) for instance published a report on CAR T-cell therapies in the pipeline and a forecast snapshot. Without revealing the employed methodology, the DRG estimated the CAR T-cell therapy market at approximately 1.5 billion EUR (1.7 billion USD) by 2026 for the hematological malignancies. It is not clear whether these figures ought to reflect the US, European, or a global market. Our estimation exceeds the DRG figures by far but since the methodological approaches cannot be compared, it remains open which forecasted aspects differ.

Another study estimated 114,737 cumulative treated patients in the US between the years 2019 and 2029 for all hematological cancers.[109] This is relatively close to our estimate considering a fundamentally different methodological approach and the inclusion of different cancer types. In terms of costs, Quinn et al.[150] mention a range between 11.1

billion EUR (12.5 billion USD) and 88.8 billion EUR (100 billion USD) for all hematological cancers. Our estimates fall within this range. However, it needs to be noted that although the US population is comparable to the studied population in terms of size (US population is roughly 96% of the former EU-5 + NL), costs for CAR T-cell therapies are generally higher in the US.

Finally, we conclude that, although current and future CAR T-cell therapies seem promising in hematological cancers, with the current price-setting the financial burden on health care systems in former EU-5 and the Netherlands is considerable. Some European countries are struggling with associated costs of pre- and post- care for CAR T-cell therapies as these costs are reimbursed insufficiently. Further, the pricing of CAR T-cell therapies is high and it can be expected that new and commercial CAR T-cell therapies will be in a similar price range. Combined with the expected expansion of indications, the financial burden on health care systems will increase substantially with direct effects on patient access to these new treatment options. Specialized hospitals could produce CAR T-cell treatments themselves in the future at lower costs, which could drive procurement costs down. Stimulating this development may contribute to better patient access but future research and development from manufacturers must be guaranteed.

Part C.

Cost-based pricing models

Chapter 5.

Towards sustainability and affordability of expensive cell and gene therapies? Applying a cost-based pricing model to estimate prices for Libmeldy and Zolgensma

FW Thielen, RJSD Heine, S van den Berg, RMT ten Ham, CA Uyl-de Groot. Cytotherapy (2022).

Abstract

Drug prices are regarded as one of the most influential factors in determining accessibility and affordability to novel therapies. Cell- and gene-therapies (CGTs) such as OTL-200 (brand name: Libmeldy) and AVXS-101 (brand name: Zolgensma) with (expected) list prices of 3.0 million EUR and 1.9 million EUR per treatment, respectively spark a global debate on the affordability of such therapies. The aim of this study was to use a recently published cost-based pricing model to calculate prices for CGTs, with OTL-200 and AVXS-101 as case study examples.

Using the pricing model proposed by Uyl-de Groot and Löwenberg, we estimated a price for both therapies. We searched the literature and online public sources to estimate (a) research and development (R&D) expenses adjusted for risk of failure and cost of capital, (b) the eligible patient population, and (c) costs of drug manufacturing to calculate a base-case price for OTL-200 and AVXS-101. All model input parameters were varied in a stepwise, deterministic sensitivity analysis and scenario analyses to assess their impact on the calculated prices.

Prices for OTL-200 and AVXS-101 were estimated at 1,048,138 EUR and 380,444 EUR per treatment, respectively. In deterministic sensitivity analyses, varying R&D estimates had the highest impact on the price for OTL-200, while for AVXS-101 changes in the profit margin changed the calculated price substantially. Highest prices in scenario analyses were achieved when assuming the lowest number of patients for OTL-200 and highest R&D expenses for AVXS-101. The lowest R&D expenses scenario resulted in lowest prices for either therapy.

Our results show that, using the proposed model, prices for both OTL-200 and AVXS-101 lie substantially below the currently (proposed) list prices for both therapies. Nevertheless, the uncertainty of the used model input parameters is considerable, which translates in a wide range of estimated prices. This is mainly because of a lack of transparency from pharmaceutical companies regarding R&D expenses and the costs of drug manufacturing. Simultaneously, the disease indications for both therapies remain heavily understudied in terms of their epidemiological profile. Despite the considerable variation in the estimated prices, our results may support the public debate on value-based and cost-based pricing models, and on “fair” drug prices in general.

Material and methods

Pricing model

The cost-based pricing model described by Uyl-de Groot and Löwenberg was used to estimate the prices of two CGTs using *OTL-200* and *AVXS-101* as case studies.[56] The model combines the costs of research and development (C_{rd}), the number of patients that can benefit from the new drug during the time in years left of patent protection (N_p), the costs to manufacture the drug (C_{man}), and a profit margin (M_p) to calculate a price for the novel therapy (C_{tx}, see Equation 1).

$$C_{tx} = \left(\frac{C_{rd}}{N_P} + C_{man}\right) * (1 + M_p) \qquad \text{(Equation 1)}$$

To adhere to the original model methodology, the perspective of this study is set to the "more developed regions" as defined by the *United Nations* (UN) *Department of Economic and Social Affairs* (i.e., Europe, Northern America, Australia/New Zealand, and Japan).[151]

Input parameters for the pricing model were extracted from the literature and public online sources. All prices and costs are stated in 2020 EUR and were inflated with the Dutch *consumer price index* (CPI) using the R package *cbsodataR*,[152] when necessary. For eventual currency conversions (i.e. in case costs or prices were stated in a currency other than EUR) the R package *priceR* was used to retrieve (historical) exchange rates.[153]

In the following sections, we briefly describe the general methodology used to estimate the model inputs, outline the key assumptions, and state values for the model base-case analysis (see also Table 1). More information on all input parameters can be found in the Appendices.

Estimating costs for research and development (Crd)

For this analysis, we sought to estimate expenses for research and development (R&D) for *OTL-200* and *AVXS-101* as precisely as possible. To this end, we followed an approach similar to recently conducted study by Wouters et al.[154] (2020), which received the highest "suitability score" (81 out of a maximum of 96) in the review by Schlander et al.[155] (2021). The suitability score framework was designed by the authors of the review to assess how comprehensively the included studies identified and incorporated appropriate factors to estimate R&D expenses. This framework includes 16 factors, classified into three domains, with a high suitability score indicating that studies considered and addressed a wider range of factor. Detailed information in this framework can be found in the Appendix of the original publication.[155]

In a first step, we reviewed publicly available financial reports from all companies involved in the R&D process of the case studies. Such reports mainly included filings of financial statements that public companies are required to submit to the US *Security and exchange commission* (SEC). Publicly traded firms submit either quarterly of annual filings to the

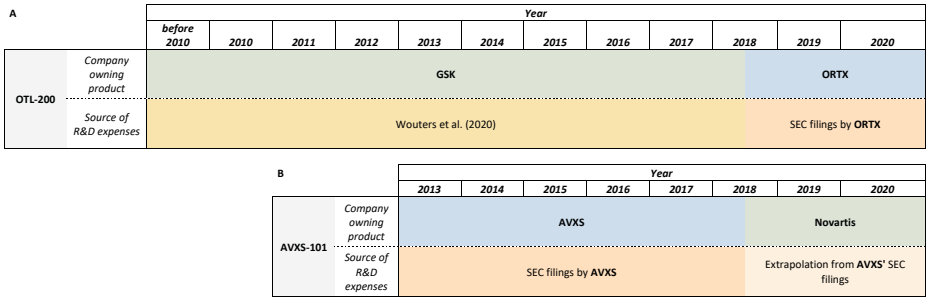
SEC (Forms 10-Q and 10-K, respectively). From these filings, information on R&D expenses were extracted, starting from the year a particular product was first mentioned in the SEC filings or company reports. We refer to all costs taken from the SEC filings and other not already adjusted costs as "out-of-pocket". Furthermore, we distinguished between several stages of pharmaceutical drug development that both therapies underwent until their first marketing approval, namely (a) pre-clinical phase, (b) Phase I clinical, and (c) Phase II clinical. Similar to previous studies, we considered phase I/II studies as Phase II.[154,156] In case R&D expenses for these stages could not be deduced or approximated from the SEC filings, we used lump sum estimates per stage as estimated by Wouters et al.[154] (2020).

R&D efforts for *OTL-200* and *AVXS-101* were done by different companies. *OTL-200* was initially researched by *GlaxoSmithKline* (GSK) and transferred to *Orchard therapeutics plc.* (ORTX) through an asset purchase in the third quarter of 2018.[157] *AVXS-101* was first development by *AveXis* (AVXS) and added to the product portfolio of *Novartis International AG* (Novartis) in the second quarter of 2018, after a company acquisition.[158]

While bigger companies usually do not report R&D expenses stratified by therapeutic area or even on product level, smaller manufacturers often do so. Indeed, both ORTX and AVXS reported expenditures on R&D in their filings to the SEC. These expenditures included costs for (a) any type of overhead, (b) employees (i.e. salary, benefits, stock-based compensations), (c) consultations (i.e. fees, stock-based compensations), (d) material (i.e. acquisition, developing, manufacturing), (e) studies (i.e. pre-clinical studies, clinical studies), (f) licenses (up-front payments), and (g) any type of regulatory approval.[157(p10),159] Following these definitions, we assumed that all relevant R&D expenses for the therapies of two case studies were included.

An overview of the sources used to estimate R&D expenses for both case studies is depicted in Figure 1.

Figure 1 - Overview of sources used to estimate R&D expenses for OTL-200 (A) and AVXS-101 (B)



AVXS = AveXis; GSK = GlaxoSmithKline; ORTX = Orchard therapeutics plc.; R&D = research and development; SEC = US Security and exchange commission

Second, we accounted for so-called "abandoned" drugs or "failed projects".[154,160] Similar to Wouters et al.[154] (2020), we used development phase-specific success rates published by Wong et al.[156] (2019) to correct for this (see Table 1). Third, we considered a real cost of capital rate of 10.5% as done in previous studies.[154,161]

Since lump sums reported by Wouters et al. (2020) already included a success rate adjustment and cost of capital for pre-clinical stages, we adjusted R&D lump sums for Phase 1 and Phase 2 accordingly.

R&D costs for OTL-200

Estimated R&D expenses for OTL-200 were based on costs made by GSK and ORTX. Since GSK only reported global figures on R&D expenses in all their SEC filings, we assumed lump sum costs for both the pre-clinical phase and Phase II for GSK (see Table 1).[154] Expenses for Phase I were not considered because both safety and efficacy of OTL-200 (formally known as GSK-2696274), were assessed in a Phase I/II clinical study (NCT 01560182). Lump sum costs for Phase II were corrected with a cost of capital for the time between the start of clinical trial in April 2010 and the transferral of rights from GSK to ORTX in the third quarter of 2018 (i.e. 8.3 years).[162] This resulted in total assumed R&D expenses of 488.93 million EUR when capitalized and risk adjusted (sum of pre-clinical and Phase II, out-of-pocket expenditures were 298.22 million EUR), incurred by GSK.[154]

Although OTL-200 was already in its registrational phase, we considered further R&D expenses made by ORTX, assuming that R&D efforts continued until first marketing approval was issued. For these expenses, we relied on ORTX's SEC filings. In the annual SEC filings (i.e. 10-K form), ORTX reported R&D expenses for therapeutic areas (i.e. neurometabolic disorder, primary immune deficiencies, blood disorders, as well as other research and preclinical programmes under development) for the years 2018 to 2020. For this analysis, we used reported R&D expenses for the therapeutic area of neurometabolic disorders starting from the last quarter in 2018 (i.e. after ORTX had acquired OTL-200 form GSK) until its first marketing approval by the *European Medicines Agency* (EMA).[163] Consequently, we assumed total capitalized and risk adjusted R&D expenses for ORTX of 51.28 million EUR (16.29 million EUR out-of-pocket). A detailed calculation can be found in Appendix A.

Combining all capitalised and risk adjusted R&D expenses of GSK and ORTX resulted in a total of 540.2 million EUR for OTL-200 (314.51 million EUR out-of-pocket).

R&D costs for AVXS-101

Assumed R&D expenses for AVXS-101 were based on costs made by AVXS and Novartis. In the 2015 annual filing (10-K) to the SEC, AVXS stated that it did not begin R&D activities of AVXS-101 until the year 2013.[159] Furthermore, all 10-K filings for the years 2015 to 2018 stated that substantially all of the company's R&D expenses "have been associated with

AVXS-101".[159] Based on this statement, we assumed that all reported R&D expenses by AVXS could be attributed to AVXS-101. AVXS defined R&D expenses similar to ORTX, and a total of 2.87 billion EUR when capitalised and risk adjusted (out-of-pocket expenditure where 0.41 billion EUR) could be attributed to this therapy.[159] An overview of all R&D expenses reported by AVXS can be found in the Appendix B.

To estimate the remaining R&D expenses for AVXS-101 between AVXS' last SEC filing and the first marketing approval of the product in the US (May 2019), we estimated average monthly R&D expenses based on the last available SEC filing (AVXS 2018 10-Q form, see Appendix B).[158] This was done because Novartis acquired AVXS and detailed R&D expenses by product or therapeutic area could no longer be retrieved. In addition, lump sum estimates for a registrational phase were not available from Wouters et al. (2020).[154] In total, we added capitalized and risk adjusted R&D expenses of 323.42 million EUR (266.84 million EUR out-of-pocket) for the period between March 2018 and May 2019 to the total R&D expenses, reported by AVXS. This led to a total estimate of R&D expenses of 3.19 billion EUR for AVXS-101 when capitalized and risk adjusted (678.77 million EUR out-of-pocket).

Number of eligible patients during patent protection (nP)

The number of eligible patients during the remaining patent protection of both products was calculated using incidence and prevalence rates from the literature for MLD (OLT-200) and SMA (AVXS-101). Prevalence rates were multiplied with the population estimation from the *2019 UN Revision of World Population Prospects*.[164] These data were taken from the R package wpp2019.[165] Incidence rates (or more precisely: "birth prevalence rates" in these cases), were multiplied with the estimated number of newborns in the UN more developed regions. These data were based on yearly interpolated births from the year 2020 onwards (time of marketing approval for OTL-200 and AVXS-101).[166]

Estimating the duration of remaining patent protection

In contrast to Uyl-de Groot & Löwenberg we extended the definition of the "number of patent years after registration" to also include all applicable intellectual property protection (IPP) such as patent protection, or regulatory protection (RP) such as data protection, or market exclusivity (whichever comes last).[160]

For OTL-200, we could only find information on RP with regard to the granted orphan market exclusivity period ending on 18 December 2030.[167] Reliable figures on further IPP coverage could not be found. For AVXS-101, we retrieved pertinent data from the 2020 SEC filings by Novartis (see Appendix C), stating that the latest regular data protection would be somewhere in 2031.[168] We assumed that both OTL-200 and AVXS-101 would be covered by IPP or RP for at least 10 years.

Estimating incidence of patients with MLD

In line with current marketing approval of OTL-200 in the EU,[169] we only considered an MLD *incident* population with an average incidence rate of 1.6 per 100,000 new-borns, based on the study of Van Rappard et al. (2015).[170] Furthermore, we restricted the patient population, eligible for OTL-200, to one third because previous studies with comparable therapies in this indication demonstrated that only a fraction of diagnosed patients are eligible for therapy.[171] This choice was validated with clinical experts (see Acknowledgements).

Consequently, we estimated a total of 683 MLD patients eligible for OTL-200 over a period of 10 years. More details can be found in the Appendix D.

Estimating incidence and prevalence of patients with SMA

Marketing approval for AVXS-101 differs between the US, Japan, and the EU. While in the US and Japan AVXS-101 was approved for patients with SMA below the age of two years, the EMA did not indicate any age restrictions. Nevertheless, it is mentioned that "[...] there is limited experience in patients 2 years of age and older [...]".[172] Based on this statement and for this analysis, we assumed that patients above the age of two years, would not receive AVXS-101 in Europe.

Assuming a general age restriction of two years, we considered Type I and II SMA patients to be eligible for AVXS-101. This categorisation was based on the literature, and more detail can be found in the Appendix D.[173,174]

While in theory, the age of onset for SMA Type IIIa could be before two years of age, we did not include these patients in our analysis, because a recent study suggested that the minimum age of onset for this type might in fact be later.[175]

For our analysis, we relied on SMA type specific prevalence and incidence rates as summarised in a recent systematic literature review.[176] Consequently, we assumed average prevalence rates of 0.17 per 100,000, and 1.78 per 100,000, for SMA Type I and II, respectively. Average assumed incidence rates were 5.77 per 100,000 new-borns, and 5.89 per 100,000 new-borns, for SMA Type I and II, respectively. These data were used to calculate the total number of patients.

However, due to the explicit age restrictions in the US and Japan, and the assumed similar age restriction in the EU we only included SMA Type II patients below the age of two years. Since no information on the age distribution of SMA Type II patients were available, we approximated this distribution by calculating the proportion of individuals under the age of two years in the general population of the UN "more developed region", which was 3%.[164]

To be consistent with the current marketing approval in the US and Japan, we considered SMA Type I and Type II for these regions and did not stratify by SMN2 copy involvement. For Europe,

we considered all SMA Type I patients and all SMA Type II patients with up to three copies of the SMN2 gene, according to the EMA approval. Information on the distribution of SMN2 copies were taken from the literature.[177] For all other countries fulfilling the more developed region criteria, we assumed eligible patients similar to the definition of the US and Japan.

The total eligible patient population for AVXS-101 for the base-case analysis were 13,607 patients over a period of 10 years.

Costs of drug manufacturing (cM)

Manufacturing costs specific to OTL-200 or AVXS-101 were not available from the SEC filings or the literature. Therefore, we assumed those costs to be similar to the production costs of an adeno-associated virus (AAV) mediated Factor IX gene therapy. Costs for the latter were estimated through a micro-costing (ingredient list) approach, for a recently published cost-effectiveness analysis.[178] Hence, we assumed 63,477 EUR for the production costs of OTL-200 and AVXS-101 per therapy for one patient.

Since manufacturing cost estimates were derived from an academic facility, our model considers an additional 30% margin for sales and marketing costs in addition to the production costs, as suggested by Uyl-de Groot and Löwenberg (2018).[160]

Profit margin (mP)

Uyl-de Groot and Löwenberg (2018) suggested that a reasonable profit margin would ideally be linked to the level of clinical benefit.[160] To this end, they suggested profit margins of 20%, 30%, and 40% for marginal, moderate, and high levels of clinical benefit, respectively. However, such a benefit cannot yet fully be determined for either therapy because clinical (long-term) evidence for these treatments is lacking. Therefore, we used an arbitrary profit margin of 20% for the base-case analysis. The impact of a wider range of profit margins (i.e., between 10% and 60%) on the calculated price was examined in the deterministic sensitivity analyses.

Table 1 - Base case values from the literature to estimate model input parameters

Type	Description	Value in use	Reference
Development phase-specific success rate	Pre-clinical to approval	13.8%	Same assumption as Wouters et al. (2020)[154]
	Phase I to approval	13.8%	Wong et al. (2019)[156]
	Phase II to approval	35.1%	Wong et al. (2019)[156]
	Phase III to approval	59.0%	Wong et al. (2019)[156]
	Submission for marketing authorisation to approval	83.2%	Wong et al. (2019)[156]
Global lump sum costs for R&D phases (all capitalized and risk adjusted)	Pre-clinical[a]	209,439,080 EUR	Wouters et al. (2020)[154]
	Phase I[b]	337,615,565 EUR	Wouters et al. (2020)[154]
	Phase II[c]	252,929,385 EUR	Wouters et al. (2020)[154]
MLD	Average incidence rate	1.6 per 100,000 newborns	Van Rappard et al. (2015)[170]
SMA	Percentage of SMA patients with up to three SMN2 gene copies (used to calculate patients in Europe)	94.66 %	Calucho et al. (2018)[177]
	1 copy of SMN2 gene	0.34%	Calucho et al. (2018)[177]
	2 copies of SMN2 gene	16.55%	Calucho et al. (2018)[177]
	Average incidence rate: SMA Type I	5.77 per 100,000 newborns	Verhaart et al. (2017)[176]
	Average incidence rate: SMA Type II	5.89 per 100,000 newborns	Verhaart et al. (2017)[176]
	Average prevalence rate: SMA Type I	0.17 per 100,000	Verhaart et al. (2017)[176]
	Average prevalence rate: SMA Type II	1.78 per 100,000	Verhaart et al. (2017)[176]
Patent duration	Remaining regulatory or intellectual protection: AVXS-101	10 Years	Novartis SEC form: '2020 20-F'[168]
	Remaining regulatory or intellectual protection: OTL-200	10 Years	Assumption
Profit margin	Profit margin	20 %	Uyl-de Groot & Löwenberg (2018)[160]

[a] Already capitalized and risk adjusted in original source, hence no out-of-pocket could be stated
[b] Out-of-pocket: 45,690,948 EUR
[c] Out-of-pocket: 88,778,214 EUR

An overview of base case values for the cost-based pricing model per therapy can be found in Table 2.

Table 2 – Base-case and scenario input values for OTL-200 and AVXS-101

	OTL-200	AVXS-101
R&D expenses (C_{rd}) in EUR		
Base-case	540,204,057	3,191,067,181
Scenario 1[a]	227,778,464	1,624,092,896
Scenario 2[a]	2,207,848,401	3,959,441,065
Eligible number of patients during patent protection (N_p)		
Base-case	683	13,607
Scenario 3[b]	597	7,077
Scenario 4[c]	768	23,626
Cost of drug manufacturing (C_{man}) in EUR[d]		
Base-case	63,477	63,477
Scenario 5[e]	23,033	23,033
Scenario 6[f]	84,333	84,333
Profit margin (M_p) in %		
Base-case	20	20
Scenario 7	0	0
Scenario 8[g]	76.5	76.5

[a] Estimated from a truncated normal distribution assuming the base-case R&D estimate per drug as the mean; standard deviation and upper/lower bounds are based on Schlander et al. (2021)[155] (see Appendix G)
[b] Based on minimum reported incidence and prevalence rates (see Appendix D)
[c] Based on maximum reported incidence and prevalence rates (see Appendix D)
[d] This does not include a 30% margin for sales and marketing, which is added in the model calculations
[e] Based on the minimum reported value in ten Ham et al. (2020)[179]
[f] Based on maximum reported value (53,683 EUR) in ten Ham et al. (2020) and adding the absolute difference between lowest and highest reported values (i.e. 30,650 EUR) because ten Ham et al. argued that the maximum value was likely to be an underestimation of the real costs
[g] Based on maximum reported value in Ledley et al. (2020)[180]
R&D = Research and development; C_{man} = Cost of drug manufacturing; C_{rd} = Cost of research and development; M_p = Profit margin N_p = Number of patients

Deterministic sensitivity and scenario analyses

To test the impact of the different model input parameters and assumptions on the price calculations, we varied parameters in deterministic and scenario analyses.

In the deterministic sensitivity analysis, we re-calculated the price for OTL-200 and AVXS-101 by stepwise increasing and decreasing all model input parameters (i.e. C_{rd}, N_p, C_{man}, and M_p) by five steps between the minimum value from the scenario analysis (see below) and the base-case value, and five steps between the base-case value and the maximum value in from the scenario analysis. The value for each step was calculated by dividing the difference between the minimum (or maximum) value and the base-case value by five.

In scenario analyses, we varied model input parameters for which upper and lower bound estimates could be informed by the literature. For this, we used the base-case estimates

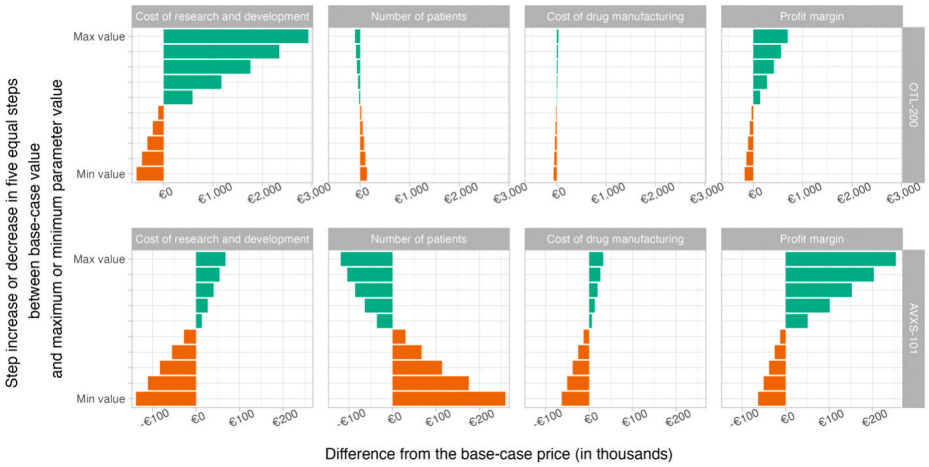
as reference points and varied each input parameter step by step, while keeping all other parameters similar to the base-case (see Table 2). In this way, we were able to show a range of realistic cost-based prices for both products. In the absence of reliable R&D expenses for cell and gene therapies specifically, we used minimum (i.e., 146 million EUR; 161 million USD) and maximum (i.e., 4.11 billion EUR; 4.54 billion USD) estimates reported in a review by Schlander et al.[155] However, using these ranges directly would inflate the margins disproportionally. This is because the review included costly phase III trials, many different therapeutic classes, and a large variation of drug sample inclusion periods, among other factors. And since both OTL-200 and AVXS-101 were approved based on Phase II trials with less than 25 participants,[169,181–183] employing the 4.11 billion EUR estimate for R&D expenses of both products would be too high. Therefore, we chose to determine both minimum and maximum R&D estimates for each therapy based on the 0.05 and 0.95 percentile of a truncated normal distribution. The distribution's mean was the base-case R&D estimate of the respective therapy, while values for standard deviation and upper/lower bounds were based on the total range reported by Schlander and colleagues. Hence, by varying only the mean, we received different R&D estimates for each drug, reflecting the relative uncertainty around the base-case estimates (see Appendix G for more information). The number of eligible patients for OTL-200 and AVXS-101 were based on minimum and maximum incidence and prevalence rates found in the literature (see Appendix D). Lower estimates for drug manufacturing costs were approximated with a study by ten Ham et al. (2020) on cell manufacturing costs.[179] Since higher bound estimates for drug manufacturing costs were reported to be underestimations, we added the absolute difference between lower and higher reported estimates to the highest estimate. This resulted in maximum costs for drug manufacturing of 84,333 EUR. Finally, we assumed no profit margin (i.e. 0%) for the lowest possible estimate and 76.5% as highest value, based on Ledley et al. (2020).[180]

Results

With the input values presented in Table 2, the model proposed by Uyl-de Groot & Löwenberg (2018) (Equation 1) results in an estimated base-case price of 1,048,138 EUR, and 380,444 EUR per treatment and patient, for OTL-200 and AVXS-101 respectively.

The results of the deterministic sensitivity analysis are summarised in Figure 2.

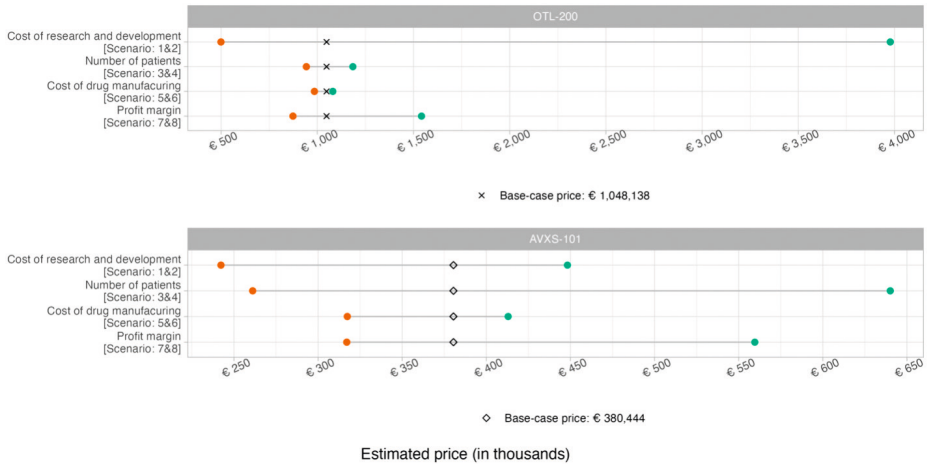
Figure 2 - Results of the deterministic sensitivity analysis



The deterministic sensitivity analysis showed that the variation of the model input parameters had different effects on the calculated total price of either case study. For instance, assuming higher R&D expenses for OTL-200, resulted in a substantial increase of the calculated price, while increasing assumed R&D expenses for AVXS-101 had a relatively smaller effect on the price. In addition, it can be seen that R&D expenses have the most impact on the price calculated for OTL-200, while for AVX-101 increasing the assumed profit margin causes the highest price increase, followed by assuming less eligible patients. All input parameters and the results of the deterministic sensitivity analysis can be found in Appendix E.

The results of the different scenario analyses (see Figure 3 and Appendix F) show that the highest price for both OTL-200 (i.e. 3,978,114 EUR) and AVXS-101 (i.e. 640,112 EUR) were achieved when assuming the highest R&D expenses for OTL-200 and assuming the lowest number of patients for AVXS-101. Furthermore, the lowest price for OTL-200 (i.e. 499,221 EUR) and AVXS-101 (i.e. 242,253 EUR) resulted from assuming the lowest R&D expenses.

Figure 3 - Results of the scenario analyses



Considering both deterministic sensitivity and scenario analyses, the price range for OTL-200 was between 499,221 EUR and 3,978,114 EUR, with a base-case point estimate of 1,048,138 EUR. In comparison, the price range for AVXS-101 was narrower with prices between 242,253 EUR and 640,112 EUR, and a base-case point estimate of 380,444 EUR.

When only out-of-pocket R&D expenses were considered, the estimated drug prices were 651,596 EUR and 158,885 EUR for OTL-200 and AVXS-101, respectively.

Discussion

In this study, we meticulously estimated all necessary input parameters to calculate drug prices for OTL-200 and AVXS-101 using the pricing model suggested by Uyl-de Groot & Löwenberg (2018). All model input parameters were based on publicly available evidence and R&D expenses were adjusted based on current methodological approaches. The calculated prices for OTL-200 and AVXS-101 were 1,048,138 EUR and 380,444 EUR per treatment, respectively. Lowest and highest prices in deterministic sensitivity and scenario analyses ranged between 499,221 EUR to 3,978,114 EUR per patient and treatment for OTL-200 and 242,253 EUR to 640,112 EUR for AVXS-101. Our deterministic sensitivity analyses demonstrated that a variation of the input parameters (i.e., increase or decrease) had distinct effects on the price outcome. Similarly, when assuming both minimum and maximum values of input parameters in scenario analyses, the estimated prices changed considerably. Nevertheless, most calculated prices in this study were substantially lower than the currently (proposed) list prices for either therapy (list price for OTL-200: between 2.5 and 3.0 million EUR; AVXS: approximately 1.9 million EUR).

Cost of research and development (Crd)

In recent years, several cost-based pricing models such as the one from the *International Association of Mutual Benefit Societies* (AIM),[184] the "discounted cash flow" model,[185,186] or "rate of return pricing"[187] have been suggested to estimate prices for novel drugs. Model input parameters across these models vary, but all include at least R&D expenses. This demonstrates the relative importance of this input parameter to all models. While most of these cost-based pricing models use lump sum estimations, we sought to estimate each model input parameter, and particularly R&D expenses, as precisely as possible for two reasons. First, because the original published model by Uyl-de Groot and Löwenberg (2018) also used actual costs rather than lump sums for their example calculations. Second, the two selected case studies (i.e., OTL-200 and AVXS-101) were partly developed at smaller companies that reported their R&D expenses rather detailed in their pertinent SEC filings.

The deterministic sensitivity analysis showed that the assumed R&D expenses can have a tremendous impact on the calculated price, especially when the number of eligible patients is low. This exhibits the relative importance of knowing the true value of the R&D expenses when using the pricing model. Since both ORTX and AVXS (partly) reported R&D expenses (for OTL-200 and AVXS-101, respectively) in their SEC filings, we believe that we indeed could approximate the total expenses precisely.

Our estimated R&D expense estimations for OTL-200 (i.e., 540 million EUR) and AVXS-101 (i.e., 3.19 billion EUR) fall within the range of expenses reported in the literature. In a recent systematic review of the literature, Schlander et al. (2021) reported that R&D expense estimates ranged between approximately 146 million EUR (161 million USD) to 4.11 billion EUR (4.54 billion USD).[154,155,188] Even the most extreme values explored in our deterministic sensitivity analysis are covered by this range. Nevertheless, all assumed R&D expenses of the base-case, remain at a the low- to mid-range of the reported spectrum in the literature. This may be due to diverging definitions of R&D expenses in the literature and those used by ORTX and AVXS for the SEC filings. For the latter two for instance, it seems that costs for abandoned drugs were not included. In our analysis, R&D estimates for OTL-200 included a success rate adjustment of costs of capital for the pre-clinical phase at GSK. This is because the used lump sum estimates for this development period, estimated by Wouters et al. (2020), already included these items.[154] While there is no reliable way to precisely estimate additional costs for abandoned drugs,[155] we believe that such costs are not applicable to AVXS-101. This is mainly because AVXS was founded in the same year it started researching AVXS-101 (i.e. 2013) and had devoted all of its R&D expenses to this therapy at least until 2018.[159]

Accounting for cost of capital and applying a success rate adjustment to the R&D expenses found in the SEC filings or the literate increased the original expenses substantially. While this has an equally large influence on the calculated cost-based price, it is reasonable to include this adjustment because manufacturers and investors also account for those in

their day-to-day business and investment decisions. Estimating a cost-based price without such parameters would not yield a realistic result that can be used for policy purposes in a competitive market. For instance, a report from 2019 calculated that industry-wide, 53% of spending on R&D is lost in cost of capital, 40% on out-of-pocket failure costs and only 7% on out-of-pocket success costs.[189] Without risk and cost of capital adjustments, prices for OTL-200 and AVXS-101 would nearly be half the currently estimated prices (i.e., 651,596 EUR and 158,885 EUR, respectively).

It needs to be noted that all assumed R&D expenses in this study neglect other indirect public (financial) contributions towards the development of OTL-200 and AVXS-101. This choice was made because the proposed pricing model does not define how to account for these contributions and because estimating those will add additional uncertainty to the numbers employed in this analysis. Other studies have found that such public investments may significantly impact the total assumed R&D expenses and even exceed the manufacturer's investment by a factor of 1.5-5.1.[190] To estimate the total value of public investments for the orphan drug bedaquiline, Gotham et al.[190] (2020) for instance considered orphan drug tax credits (ODTC), priority review vouchers (PRVs), drug donation programmes and publicly funded clinical trials.

Under the US Orphan Drug Act, manufacturers may be eligible for an ODTC for up to 25% (or 50% before the year 2017) of qualified clinical testing expenses. Claiming the ODTC tax credit affects the company's eligibility for (parts of) the regular R&D tax credits and hence the incremental gain of using an ODTC will be lower than 25%. In addition, the impact of ODTCs on lowering costs for developing new treatments for rare diseases seems to be affected by the type of company claiming the ODTC. Especially newer, pre-market developers without prior drug approval will not be able to use ODTCs until they have tax liability that could be reduced by the credit, which can take more than 12 years.[191] However, since ODTCs are transferrable, pre-market companies owning ODTCs may be more attractive for potential mergers and acquisitions with established companies.[191,192] Gotham et al.[190] (2020) estimated total ODTC (using a 50% rate) value of 22 million USD to 36 million USD for a duration of seven years and across fifteen trials. Hypothetically deducting these costs from our estimated R&D expenses would be covered by the range calculated in scenario 1.

On the contrary, if the value of PRVs would need to be deducted from the total R&D expenses could affect the results more significantly. Depending on several factors (e.g., approval acceleration in months and fifth-year sales of the therapy), values of PRVs were estimated to range between 28 million USD to 691 million USD.[193] However, accounting for such PRVs remains a methodological choice associated with quite some uncertainty. First, companies may use acquired PRVs on different, future FDA submissions. Second, PRVs can be sold at any time to other companies. Hence, redeeming or selling PRVs would theoretically decrease R&D expenses which would lead to a lower price. As of 2021, ORTX

did not possess a PRV for OTL-200, although one may granted upon future FDA approval.[194] For AVXS-101, the FDA did issue a PRV to AVXS in 2019, but it is unclear how this was or will be used.[195]

Finally, regarding drug donation programmes and publicly funded trials, we could neither find information on those for OTL-200, nor for AVXS-101.

For the development phase-specific success rate factors we relied on previously published aggregate data. Generally, these success rates increase with advanced clinical phases, and phase III trials are conducted before marketing approval. Consequently, the latest conducted phase (i.e., mostly phase III) also presents with the most favourable success rate of more than 50%. However, in the case of OTL-200 and AVXS-101, the latest conducted phases before marketing approval were phase II studies (and not phase III studies). If, from the start of drug development, it could have been anticipated that a phase II study is sufficient for marketing approval, using a success rate of 35.1% for both case studies might be an underestimation of the true success rate. With an increasing success rate, the R&D expenses for this phase would decrease, which would in turn lead to a decrease in the estimated price for the therapy.

Earlier research suggested that development costs for orphan drugs can differ from development costs for non-orphan drugs.[196] This could warrant an adjustment of the assumed global lump sum costs of clinical studies here. However, this was not done because the average cost estimates used in this study were based on a sample that already contained a large proportion of orphan drugs.[154]

Number of eligible patients during patent duration

The total number of eligible patients in the model is related to the remaining duration of IPP or RP. With a longer lasting IPP or RP, more patients become eligible.

Prices for OTL-200 and AVXS-101 were calculated for the study year 2021, which impacted the estimated time remaining with IPP or RP. The deterministic sensitivity analysis showed that an increase in the number of eligible patients had a substantial impact on the calculated price, particularly when the patient population is rather small (as for MLD). The magnitude of this effect was different for both therapies. For instance, increasing the patient population eligible for OTL-200 by 200% resulted in a price decrease of 46%, while for AVXS-101 the same increase of patients resulted in a price decrease of 4%.

Making a clear distinction between patents and other protection such as orphan drug designation as well as data and market exclusivity might become of particular importance for CGTs. This is because many therapies rely on the same fundamental technologies (i.e., vector or lentiviral technology) and licensing such patent becomes increasingly common. While underlying patents of such technologies seem to be heavily under attack from several

parties using the European Patent Office's opposition procedure, legally challenging an orphan drug designation is much more complicated.[197]

Generally, information on IPP or RP duration are difficult to retrieve. And even databases such as "DrugPatentWatch" did not include information on the therapies studied here.[198] Simultaneously, original patent holders seem to be reluctant to share information on which patents are licensed for particular products or therapies.[199]

For the model calculations, the number of eligible patients was also determined by the epidemiological data used in this study. While epidemiological studies on disease incidence and prevalence generally provide a reliable overview, data for indications targeted by CGTs are scarce. Many indications for CGTs are complex and not yet fully understood. For instance, most epidemiological studies on SMA types are considered outdated as they typically relied on clinical rather than genetic disease diagnosis.[176]

Incidence and prevalence rates based on genetic screening would most likely reveal an underestimation of total assumed eligible cases for our analysis. Consequently, an increase in the patient population would lead to decrease in the estimated price of AVXS-101 based on the pricing model. In some European countries such as the Netherlands, SMA carrier screening as part of a newborn screening are currently planned but not yet implemented.[200] Once newborns will routinely be tested, patients can be diagnosed and treated earlier. This would increase the total eligible patient population for many genetic conditions.

For this analysis, we did not consider factors such as market penetration rates and the possibility that novel, more effective drugs for the same indication might be launched before the IPP or RP expires. Such scenarios would impact the number of eligible patients but are not part of the original pricing model. Including assumptions on market penetration such as 45% in the first and 90% in the second year,[150,201] may increase the calculated prices through lowering estimates of the patient population. CGTs will most likely never reach 100% coverage due to reasons such as the availability of non-CGTs products, individual preferences of using or prescribing novel therapies, or payer-imposed access restrictions.[150] Currently, the price model does not correct for this. If and when novel, more effective therapies will enter the market prior to the IPP or RP expiration cannot be known reliably. Since the aim of this study was to apply the model by Uyl-de Groot and Löwenberg using currently available evidence, we based our estimates on the number of eligible patients on the literature. We did not speculate on scenarios that would limit or extend this number based on an arbitrary time before or after patent expiration. Hence, the pricing model cannot precisely account for such scenarios.

Cost of drug manufacturing (Cm)

Compared to more conventional medicinal products, such as small molecules and biologics, the manufacturing of CGTs is a complicated process with distinct challenges.[202] This complexity can be attributed to their specific characteristics. For instance, batches are often personalized for individual patients, manufacturing processes are often manual, and starting materials are scarce as well as costly.[203–206] In addition, upfront investment and risk associated with designing and maintaining *good manufacturing practice* (GMP) facilities for the production of CGTs are significant.[207] Although biomedical researchers and developers acknowledge the importance of cost and economic consequences of strategic decisions in manufacturing development, little information is available on the cost of CGT manufacturing itself. This, in part can be explained by political sensitivity of publicly disclosing such information. Few studies are available which share lump-sum cost of parts of manufacturing development of very heterogenic CGTs. In needs to be noted that these studies were conducted in public settings such as academia or hospitals.[179,208] It is likely that the actual manufacturing cost of the two case studies differ substantially. For instance, manufacturing costs may decrease over time due to technological advancements. In addition, manufacturers with an extensive CGT portfolio, may already have GMP facilities at their disposal which can be upscaled, or further decentralised.[209,210] To assess the impact of change in manufacturing costs, we varied the model input parameters to account for a wide range (i.e., - 50% to + 200%). The sensitivity analysis showed that a further decrease in manufacturing costs might lead to a substantial decrease in the estimated drug price and vice versa.

Profit margin (Mp)

Setting a profit margin for the base case analysis was a highly debated item throughout this research. Following the example calculations of Uyl-de Groot and Löwenberg (2018), we used the arbitrary profit margin of 20%. We want to highlight that this choice does not reflect any judgement about an acceptable or even "fair" profit margin for the pharmaceutical industry. The selected margin rather reflects the lower spectrum of the actual profit made in this industry. Recently, Ledley et al. (2020) studied the profitability of 35 large pharmaceutical companies compared to other large public companies between the years 2000 and 2018.[180] Gross profit and EBITDA (earnings before interest, taxes, depreciation, and amortization) margins as a percentage of revenue were 76.5% and 29.4%, respectively.[180]

Final remarks and conclusion

This study adds to the existing body of literature on cost-based pricing models by showing how the needed model input parameters could be estimated, and what their impact is on the calculated price. In addition, the input parameters used and stated here, may facilitate the calculation of cost-based prices for OTL-200 and AVXS-101 with other models to compare their results.

Furthermore, our analysis showed that evidence for most of the model input parameters are scarce and associated with considerable uncertainty. Since variation of each parameter can impact the calculated price substantially, research efforts should focus on eliciting their true values when using this model. While the number of eligible patients can be revealed through epidemiological studies, evidence on R&D expenses and manufacturing costs heavily depend on the information provided by the pharmaceutical industry. There seems to be movement in this debate and the World Health Organization (WHO) has recently pushed for clearer drug pricing.[211,212] But although the demand for more transparency in setting drug prices and disclosing R&D expenses is growing, it might take years before reliable figures are available.[213–215]

With the current uncertainty in most model input parameters, the estimated prices varied considerably. Using the here presented base-case estimates as benchmarks for OTL-200 or AVXS-101 should therefore only been done with great caution. Also, a setback of cost-based pricing models with the use of case-specific input parameters for R&D costs is that it does not reward efficiency during the R&D process. In this study, this applies more to AVXS-101 than to OTL-200 because for the latter, most R&D costs were estimated using lump sum assumptions from literature. Nevertheless, the results may support the (public) debate on value-based and cost-based pricing models, and on "fair" drug prices in general.

Chapter 6.

Applying a cost-based pricing model for innovative cancer treatments subject to indication expansion: a case study for pembrolizumab and daratumumab

RJSD Heine, FW Thielen, RHJ Mathijssen, RWF van Leeuwen, MG Franken CA Uyl-de Groot. PLOS One (2024).

Abstract

Expanding the indication of already approved immuno-oncology drugs presents treatment opportunities for patients but also strains healthcare systems. Cost-based pricing models are discussed as a possibility for cost containment. This study focuses on two drugs, pembrolizumab (Keytruda) and daratumumab (Darzalex), to explore the potential effect of indication broadening on the estimated price when using the cost-based pricing (CBP) model proposed by Uyl-de Groot and Löwenberg (2018).

The model was used to calculate cumulative yearly prices, cumulative prices per indication, and non-cumulative indication-based prices using inputs such as research and development (R&D) costs, manufacturing costs, eligible patient population, and a profit margin. A deterministic stepwise analysis and scenario analysis were conducted to examine how sensitive the estimated price is to the different input assumptions.

The yearly cumulative cost-based prices (CBPs) ranged from €52 to €885 for pembrolizumab per vial and €823 to €31,941 for daratumumab per vial. Prices were higher in initial years or indications due to smaller patient populations, decreased over time or after additional indications. Sensitivity analysis showed that the number of eligible patients had the most significant impact on the estimated price. In the scenario analysis the profit margin contributed most to a higher CBPs for both drugs. Lower estimates resulted from assumed lower R&D costs.

The estimated CBPs are consistently lower than Dutch list prices for pembrolizumab (€2,861), mainly resulting from larger patient populations in registered indications. However, daratumumab's list prices fall within the range of modeled CBPs depending on the year or indication (€4,766). Both CBPs decrease over time or with additional indications. The number of eligible patients and initial R&D costs have the most significant influence on the CBPs. These findings contribute to the ongoing discussions on pharmaceutical pricing, especially concerning cancer drugs with expanding indications.

Introduction

The International Agency for Research on Cancer (IARC) reported an estimated 19.3 million new cases of cancer in 2020 [4], forecasting a 47% surge in its incidence between 2020 and 2040 [216]. In several countries cancer has become the leading cause of death, surpassing cardiovascular diseases [5]. Rising cancer rates are paralleled by an increase in cancer drug development, especially in immuno-oncology (IO) [217].

The new therapies that made it to the market have, however, driven up the spending on drugs both in the European Union (EU) and the United States (US) [219,220]. In the EU-28, the estimated gross sales of oncology drugs grew from €18.0 billion in 2012 to €30.2 billion in 2017, an annual growth rate of 11% [220]. During the same period, however, the sales volume of oncology drugs only rose by 2% per year. The increment in spending was, therefore, primarily driven by the introduction of new high-priced therapies [220]. A study in the US estimated that if all eligible patients would have access to all new drugs or drug indications that were approved in 2018, the extra spending would be $39.5 billion, representing an increase over 75% compared to 2017 expenditures [221].

DeMartino et al. (2021) identified 46 new oncology drug approvals in 2018 of which 29 (63%) were approvals of the same drug for new indications. Therefore, the expansion of indications for existing oncology drugs now surpasses the number of approvals for new oncology drugs. Pembrolizumab (Keytruda®) and Daratumumab (Darzalex®) are two examples of antineoplastic agents with high drug costs [56,222]. Pembrolizumab, a programmed death receptor (PD-1) inhibitor, was firstly approved in September 2014 for unresectable or metastatic melanoma by the Food and Drug Administration (FDA) [223] and in July 2015 by EMA [224]. Since its initial approval, pembrolizumab has been granted 37 new FDA approvals across various indications. [224] Daratumumab (Darzalex®) received approval from the FDA in November 2015 and in May 2016 from the EMA [225], for patients with multiple myeloma (MM). Daratumumab has been granted 9 new indications by the FDA since first approval.

Moreover, both pembrolizumab and daratumumab rank in the top five for increased drug spending between 2017 and 2018 in the Netherlands: based on list prices, spending rose 123.8% for pembrolizumab and 171.4% for daratumumab [226].

In response to soaring drug prices, Uyl-de Groot and Löwenberg (2018) proposed a cost-based pricing model [56]. Although their model considers expenditures related to research and development (R&D), costs for drug manufacturing, sales and marketing, the potential patient population within the remaining patent period, and a profit margin, it does, however, not take broadening expanding of indications into account. The model by Uyl-de Groot and Löwenberg (2018) was previously used to calculate prices for Cell and Gene therapies (CGTs) [222], but it was not, however, yet used for (expensive) anticancer drugs with

expanding indications. Other measures such as minimum effectiveness criteria, managed entry agreements (MEAs), multi criteria decision analyses (MCDA) and differential/tiered pricing including indication-based pricing are being utilized to address rising spending [24]. However, in this study we focus on another measure namely, transparent pricing models.

Cost-based models can contribute to the future development of sustainable pricing models and the debate on "fair" drug pricing. Therefore, we advanced the model of Uyl-de Groot and Löwenberg (2018) [56] by incorporating the element of broadening of indications. Daratumumab and pembrolizumab represent both histology-agnostic and histology specific, drugs that are subject to indication broadening. We modelled a range of cost-based prices for both pembrolizumab and daratumumab and compared these with known list prices.

Materials and methods

Pricing model

The original model of Uyl-de Groot and Löwenberg (2018) [56] incorporates research and development costs (C_{rd}), manufacturing and marketing costs (C_{man}), the eligible patient population over the remaining patent time (N_p), and a profit margin (M_p) and [56] estimates a cost-based price (CBP) per treatment ($C_{tx,}$ see equation 1).

$$C_{tx} = \left(\frac{C_{rd}}{N_p} + C_{man} \right) * (1 + M_p) \qquad \text{Equation 1}$$

Our algorithm (see equation 2) advances the model of Uyl-de Groot and Löwenberg (2018) [56] by including expanding indications. The CBP is calculated for each time interval in years ($C_{tx(i)}$) by summing the initial cost of research and development (C_{rd}) and the number of new indications (N_{ind}) multiplied by the cost of research and development for a new indication (C_{ex}). The total R&D costs are divided by the sum of eligible patients over the remaining patent time (N_p). Costs for manufacturing are derived from the weighted dose (D_{ind}) multiplied by the cost of manufacturing per gram (C_{man}). Lastly, the profit margin (M_p) and sales & marketing margin (M_{sm}) are applied. For this study, we also adjusted the algorithm to calculate an estimated CBP per vial facilitating a direct comparison with current prices.

$$C_{tx(i)} = \left(\frac{\sum_{i=t1}^{n} C_{rd} + (N_{ind} * C_{ex})}{\sum_{i=t1}^{n} N_p} + \sum_{i=t1}^{n} D_{ind}\, C_{man} \right) * \left(1 + M_p + M_{sm}\right) \quad \text{(Equation 2)}$$

We used the population *"more developed regions"* as defined by the *United Nations* (UN-MDR), which includes Europe, North America, Australia/New Zealand, and Japan [227].

Costs for research and development (Crd) and cost for a new indication (Cex)

Estimating initial and new indication R&D costs was not feasible due to a lack of stratified reporting of these expenses by type of product or indication from the pharmaceutical companies Janssen Pharmaceutica and Merck. Therefore, we used the mean estimation

for antineoplastic and immunomodulating agents from Wouters et al. (2020) [228] as a base-case namely €4937.4 million (95% CI, €3446.4 million – €6641.9 million) (see Table 1). This accounts for the costs of failed trials, cost of capital (10.5%) and all clinical phases of the drug development.

Literature on R&D costs for broadening indications is also lacking. However, some studies published costs associated with repurposing of existing drugs. Although these costs might differ from seeking a new indication, repurposing costs were considered the closest approximation to the incurred investment needed for broadening indications. Nosengo (2016) [229] estimated the costs associated with the repurposing of a new drug to be €347 million due to the possibility to skip phase I trials and the lower risk of serious side effects.

The eligible patient population during the remaining patent period

Incidence rates from the International Agency for Research on Cancer (IARC) [4] were used to discern the eligible patient population for both pembrolizumab and daratumumab in all relevant indications across selected countries (UN-MDR). This was achieved by multiplying non-country-specific incidence rates with the estimated population from the 2022 *UN Revision of World Population Prospects* [227], retrieved from the R package wpp2022 [230].

Eligible patient populations

The obtained patient populations were adjusted to account for cancer subtype, stage, treatment line, symptomatic disease (only in case of daratumumab), and market share. We also accounted for patients not treated (assumed to be 25% for pembrolizumab and 0% or 5% for daratumumab), patients participating in clinical trials (assumed to be 10%) and percentage of eligible patients, informed through clinical opinion [231]. Lastly, market share (MS) was defined as the existence of a competitor in the market (no competitor for daratumumab and two competitors for pembrolizumab (i.e., nivolumab (Opdivo®) monotherapy and nivolumab plus ipilimumab (Yervoy®) combination therapy for certain indications. The MS for pembrolizumab was, therefore, restricted to 50% in case one competitor was approved and 33% if both competitors were approved.

Patent expiry prediction

Patent expiry was predicted for pembrolizumab and daratumumab in 2028 and 2025, respectively [232]. The selected patent expiry year is conservative for pembrolizumab as the patent for the United States (US) is predicted to expire in 2036. Moreover, Janssen Pharmaceutica has developed a subcutaneous injection formulation that will likely remain under patent protection until 2035 [233]. This should, however, not hamper the introduction of generics, and probably only plays a role in MS retention.

A key deviation from the original model by Uyl-de Groot and Löwenberg (2018) [56] is the time-dependency to enable the inclusion of broadening indications. (i.e., the remaining patent years are dependent on the time within the model).

Cost of pharmaceutical manufacturing

Manufacturing costs for both drugs were not found in the literature. However, the production and advances made with regard to bioprocessing in the production of monoclonal antibodies (mAbs) have been studied and in some instances costs associated with their production have been reported [234–236]. Despite the variance in production cost estimates (€34 - €174) the mean estimated cost per gram of a mAbs ranged between €55 and- €68 we used €55 per gram for the base-case. In our model, cost of manufacturing are used in conjunction with the dose per gram of mAbs (Appendix V & VI).

Adjusting for inflation and currency change

All prices and costs were expressed in 2022 Euro (EUR). When necessary, prices and cost were adjusted for inflation and currency exchange rates, following the methodology of Turner et al. (2019) [237]. We assumed all cost inputs to be non-tradable resources.

Profit margin

The model proposed by Uyl-de Groot and Löwenberg (2018) recommended a variable profit margin linked to the clinical benefit [56], ranging from 20% for marginal benefits to 40% for high-level of benefits. However, using different profit margins based on clinical benefit for each indication expansion would overcomplicate the calculations. Therefore, we assumed a 20% profit margin for the base-case and varied the profit margin in sensitivity analyses.

Current value-based prices

An 1,800 mg daratumumab subcutaneous solution is listed for €8,735 in the US [238] and €4,766 in the Netherlands [239]. The list price for pembrolizumab varies across countries ranging from €5,350 in the US [240], €3,078 in the United Kingdom (UK) [241], and €2,861 in the Netherlands [242] for a 4ml vial containing 25mg/ml.

Sensitivity analysis

To address uncertainty in model input parameters, we performed a stepwise deterministic one-way sensitivity analysis (DSA), varying cost inputs, profit margin and the number of eligible patients. Prices for both drugs were recalculated with increments of 10%, ranging from -30% to +30%.

Table 1. Input parameters for the base-case analysis

Category.	Description	Value	References
Cost	R&D costs associated with the development of antineoplastic and immunomodulating agents, capitalized and risk adjusted. Unadjusted for inflation and currency change.	€4937.4 million	Wouters et al. (2020) [228]
	Cost of manufacturing per gram of mAbs	€55	Ou Yang et al. (2019) [235]
	R&D costs associated with each new indication.	€347 million	Nosengo (2016) [229]
Incidence rate per 100,000	Multiple myeloma	7.6	IARC [4]
	Melanoma	21.7	IARC [4]
	Lung Cancer	69.5	IARC [4]
	Head and neck cancer	21.8	IARC [4]
	Hodgkin Lymphoma	2.5	IARC [4]
	Bladder cancer	26.3	IARC [4]
	Gastric and Oesophagus cancer	32.1	IARC [4]
	Cervical cancer	13.3	IARC [4]
	Non-Hodgkin Lymphoma	19.2	IARC [4]
	Liver cancer	14.4	IARC [4]
	Non melanoma skin cancer	80.3	IARC [4]
	Kidney cancer	19.3	IARC [4]
	Oesophagus cancers	8.0	IARC [4]
	Corpus uteri cancer	33.7	IARC [4]
	Colorectum cancer	68.1	IARC [4]
	Breast cancer	142.0	IARC [4]
Patent expiry (year)	Daratumumab	2025	Busse & Lüftner (2019) [232]
	Pembrolizumab	2028	Busse & Lüftner (2019) [232]
Profit margin (in %)	Profit margin	20%	Uyl-de Groot & Löwenberg (2018) [56]

mAbs: monoclonal antibodies

We further conducted scenario analysis for inputs where lower and upper bounds were available in the literature, keeping all other inputs constant (see Table 2). The applications of different scenarios provided a range of CBPs around the base-case. This is valuable considering the lack of exact inputs and dependence on surrogate inputs to populate the model. Costs of initial R&D were retrieved from Wouters et al. (2020) [228] which reported a lower bound of €3,446.4 million and an upper bound of €6,641.9 million for antineoplastic and immunomodulating agents. Moreover, a scenario was modelled with R&D costs that were not capitalized, as the inclusion of cost of capital and the rate at which it should be applied are still under debate [243]. For costs associated with each new indication, we created a scenario following the guidelines set out by AIM, namely 10% of initial R&D costs (€4,937.4

million) [244]. A lower bound of €33 and an upper bound of €174 informed by Kelly (2009) [236] was used for manufacturing costs. Two scenarios modelled the profit margin: a profit margin of 0% and a profit margin of 76.5% (i.e., corresponding to the highest estimate found in Ledley et al. (2020) [245]. One scenario modelled a less conservative remaining patent period, namely 2035 for daratumumab and 2036 for pembrolizumab. Lastly, one scenario modelled implementing indication-based price (IBP) as certain countries within the EU have implemented IBP [246]. The indication-based cost-based price (IBCBP) was calculated for each new indication, the price reflects non-cumulative R&D costs and patient population.

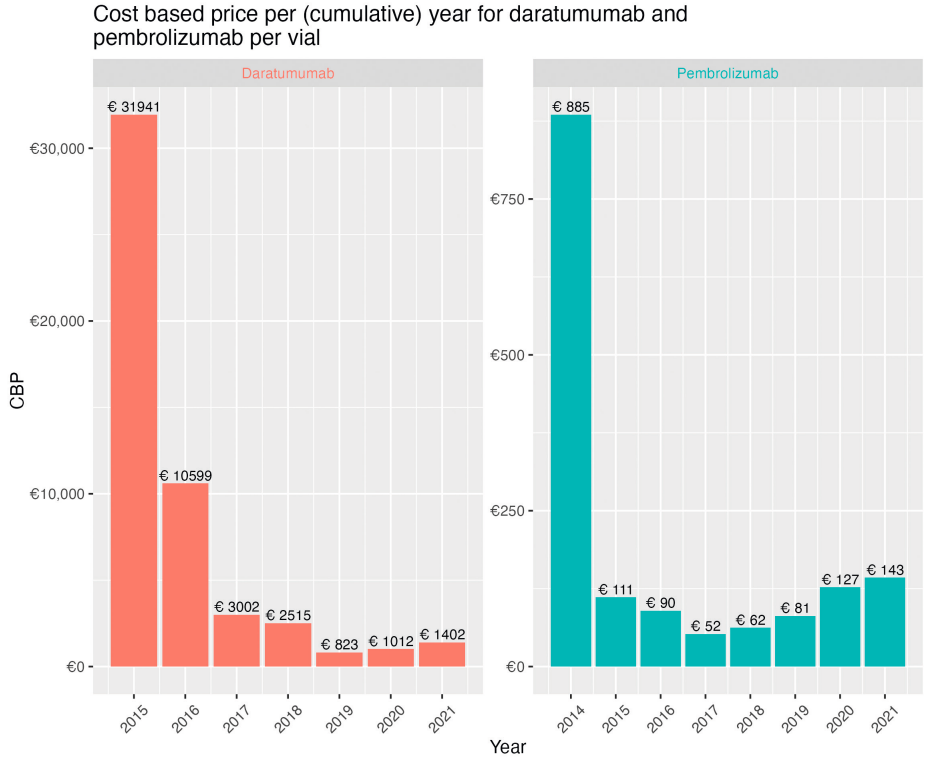
Table 2. Inputs utilized in base-case and scenario analysis for daratumumab and pembrolizumab, both unadjusted and adjusted for PPP and inflation.

Input	Unadjusted input	Adjusted for 1st year daratumumab (2015)	Adjusted for 1st year pembrolizumab (2014)
Costs associated with R&D			
Base-case	$4,461,200,000 [228]	€3,795,249,282	€3,165,890,999
Scenario 1 Cost R&D (CI)	$3,114,000,000 [228]	€2,649,154,098	€2,209,850,393
Scenario 2 Cost R&D (CI)	$6,001,300,000 [228]	€5,105,449,097	€4,258,823,109
Scenario 3 Cost R&D (uncapitalized)	$1,032,000,000 [228]	€877,947,023	€732,358,897
Cost associated with each new indication			
Base-case	$300,000,000 [229]	€267,020,244	€222,740,834
Scenario 4 based on AIM method	$446,120,000 [244]	€379,524,928	€316,589,100
Cost of product manufacturing (per gram)			
Base-case	$51 [235]	€42.61	€35.55
Scenario 5 cost manufacturing (low)	$26 [236]	€25.89	€21.59
Scenario 6 cost manufacturing (high)	$134 [236]	€133.43	€111.30
Profit margin in %			
Base-case	20 [56]	20	20
Scenario 7 profit margin 0%	0	0	0
Scenario 8 highest profit margin	76.5 [245]	76.5	76.5
Patent period			
Scenario 9 patent period	2035 & 2036[233]	2035	2036
Type of cost-based price model			
Scenario 10 indication-based pricing (IBP)	IBP	IBP	IBP

Results

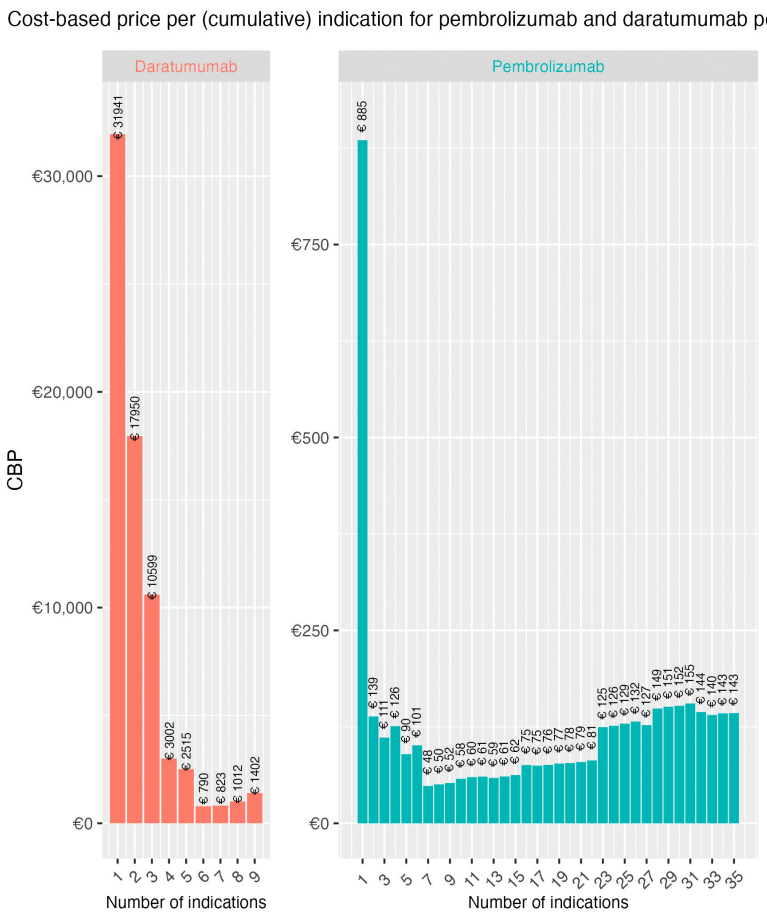
Figure 1 shows the CBP per year for both drugs. The introduction year (i.e., the first year a drug accesses the market), both cost-based prices are considerably higher due to the initial R&D costs and the relatively small initial patient populations, namely €885 for pembrolizumab and €31,941 for daratumumab. In the years thereafter, the CBPs decreased considerably; the minimum of prices amounted to €52 (pembrolizumab) and to €823 (daratumumab). The CBPs initially decreased considerably but slowly increased after four to five years, partly due to the diminishing patent period (i.e., in case the remaining patent period becomes smaller the time remaining to recoup subsequent investments decreases).

Figure 1. CBP per cumulative year for daratumumab and pembrolizumab per vial.



The CBP algorithm was modified to enable indication-specific cumulative results, meaning that instead of being time-dependent in years (t) the algorithm is dependent on the number of indications (i). The algorithm sums R&D costs and eligible patients per new indication instead of per calendar year. Figure 2 depicts the estimated prices for each drug and cumulative indication. As – the first year after market access for both drugs only compromised one indication CBPs are identical.

Figure 2. CBP per cumulative indication for daratumumab and pembrolizumab per vial.



The sharp decrease in price in the first few indications is consistent with large initial R&D costs and a small patient population in the first indications. The CBP per indication increases over time due to the shrinking remaining patent period and subsequent investments made in new indications. Obtained CBPs for pembrolizumab are in all cumulative indications lower than the actual list price in the United States (€5,350) and the Netherlands (€2,861). The difference ranges between -€1,976 – -€2,809 and -€4,465 – -€5,298 per vial for the Netherlands and United States, respectively (see appendix IX). CBPs of daratumumab fall both above and below the list prices in both the United States (€8,735) and the Netherlands (€4,766). The difference ranges between €23,2206 – €-7,945 and €27,175 – €-3,976 for the United States and the Netherlands, respectively (see appendix IX).

Stepwise sensitivity analysis

Input parameters are most sensitive in the first years/indications and become less sensitive over time. The number of eligible patients was the most sensitive input, yielding a range between €662 – €45,581 per vial and €42 – €1,262 across years for both daratumumab and pembrolizumab, respectively. The larger variation in CBPs for daratumumab results from the small patient population in the first indication, namely MM patients that received at least three prior treatments. Varying the initial costs associated with R&D resulted in prices ranging between €676 – €41,489 for daratumumab and between €43 – €1,149 for pembrolizumab. The remaining two input parameters were to a smaller extent sensitive, ranging between €790 – €33,219 and €50 – €921 for daratumumab and pembrolizumab, respectively varying the profit margin and between €790 – €33,219 and €50 – €921 for manufacturing costs. Further results obtained within the stepwise DSA can be found in Appendix VII & VIII.

Similarly to the DSA, the scenarios explored resulted in larger impacts in the earlier years/indications. The 8th scenario, exploring a profit margin of 76.5%, resulted in the highest CBP for both daratumumab and pembrolizumab (i.e., €43,972 and €1219, respectively). The lowest estimates resulted from the 3th scenario, implementing uncapitalized costs of R&D, namely €445 for daratumumab and €30 for pembrolizumab. Results from the scenario analysis can be found in Figure 3 and Figure 4.

Figure 3. Scenario analysis for daratumumab using a cumulative cost-based price per year per vial.

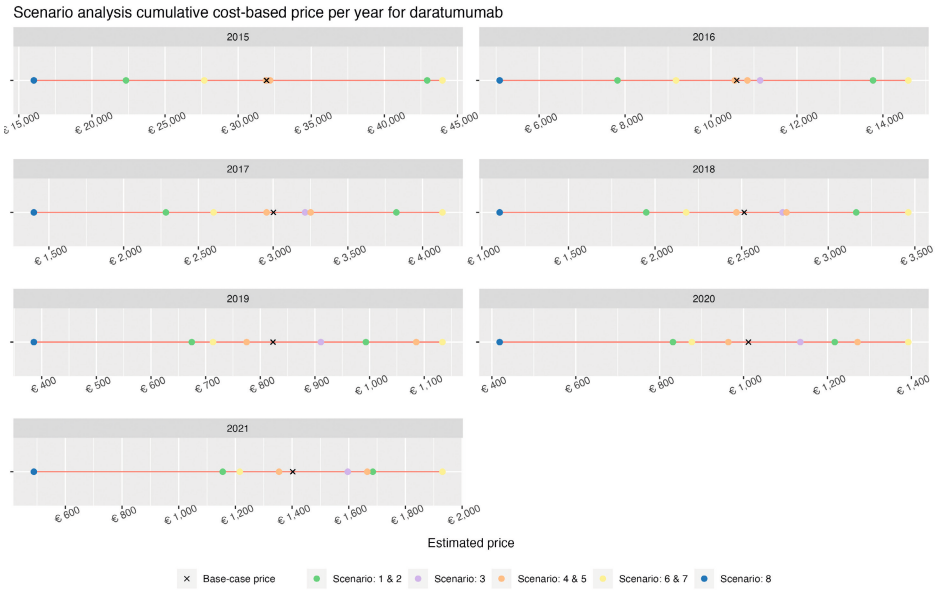
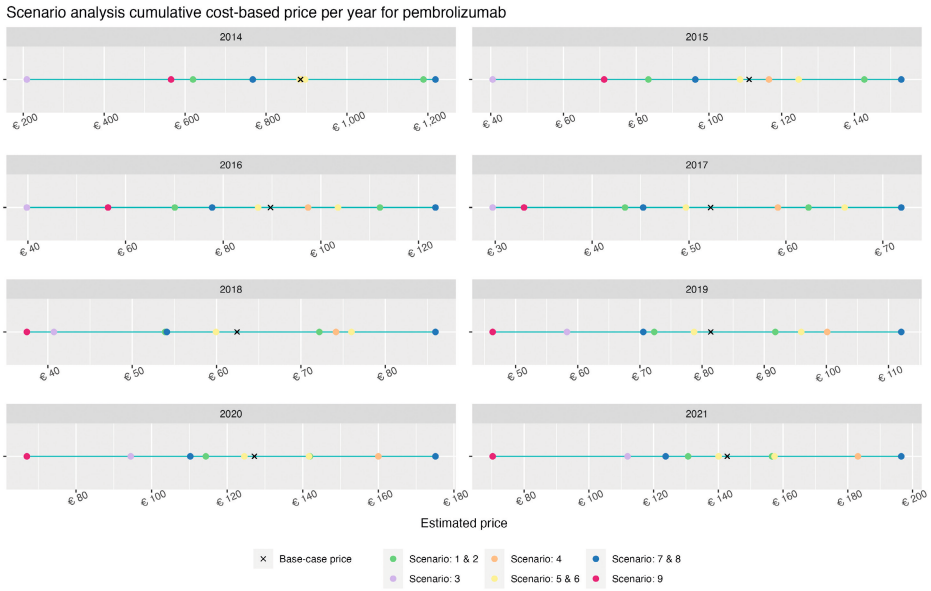
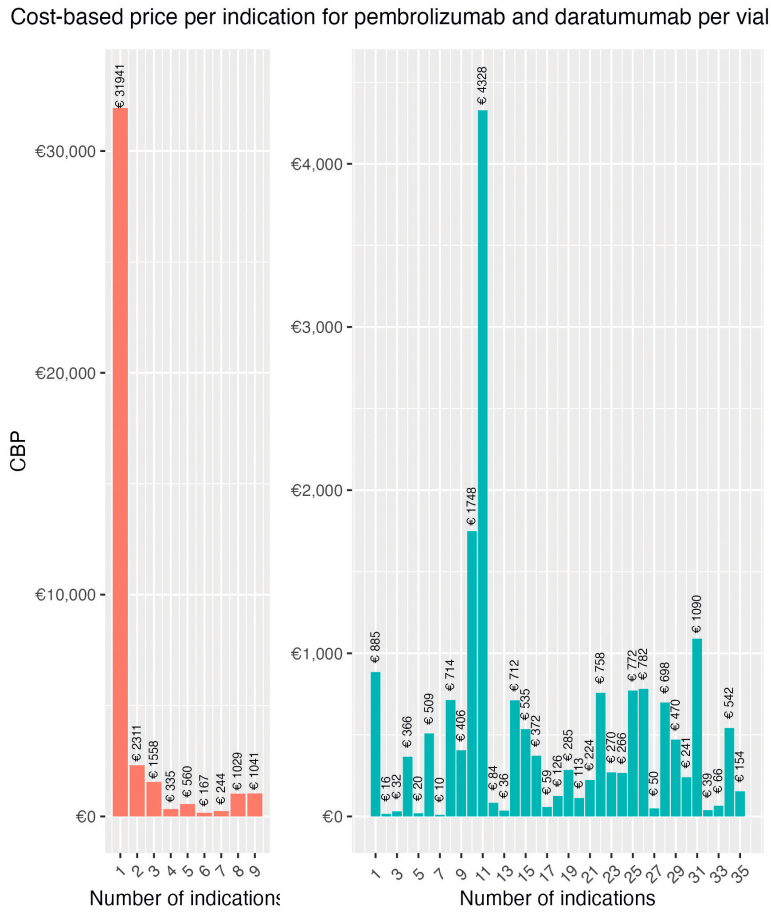


Figure 4. Scenario analysis for pembrolizumab using a cumulative cost-based price per year per vial.



Instead of cumulative CPBs, the 10th scenario explored indication-based pricing (IBP) (see Figure 5). IBP only considers the R&D spending made for a specific indication; therefore the first indication captures all initial R&D and later indications only the extra R&D spending. IBPs present higher variability due to the non-cumulative nature of the algorithm. IBCBPs ranged from €167 to €31,941 for daratumumab, showcasing considerably lower prices. Similarly, IBCBPs for pembrolizumab reached considerable lows, namely €16 per vial for NSCLC (2nd indication). Low CBPs are attributable to larger patient populations and relatively small extra R&D costs. The highest CBP for pembrolizumab was calculated for the 11th indication (refractory primary mediastinal large B-cell lymphoma), namely €4,328.

Figure 5. Implementation of indication-based pricing (10th scenario) for daratumumab and pembrolizumab.



Discussion

In this study, we investigated the application of a CBP model in pembrolizumab and daratumumab, two expensive oncology drugs with indication broadening. Obtained CBPs vary greatly over time or indications ranging between €823 – €31,941 and €52 – €885 for daratumumab and pembrolizumab, respectively. Modelled CBPs are foremost sensitive to the number of eligible patients and initial R&D costs.

Both daratumumab and pembrolizumab received EMA and FDA approval. Moreover, both drugs are approved in Australia by the Therapeutics Goods Administration (TGA) [247,248] and in Japan by the Pharmaceutical and Medicinal Devices Agency (PMDA) [249]. However, list prices differ across countries. List prices for daratumumab fall within our estimated

CBPs depending on the year. In contrast, list prices for pembrolizumab were between 66.8% and 98.4% higher in the Netherlands than our estimated CBPs, mainly resulting from a large number of indications and, consequently, a high number of modelled eligible patients.

The approval for pembrolizumab took 188 days at the FDA and 408 days for the EMA[250]. After approval, patients did not always have access due to pricing and reimbursement (P&R) negotiations. In July 2017, the Netherlands reimbursed pembrolizumab for NSCLC and all upcoming indications, making a confidential price managed entry agreement (MEA) with Merck [251]. A report from the OECD (2019) found that 9 out of 14 of their members implemented MEAs for pembrolizumab [252]. In September 2018, a confidential price agreement was also enacted for daratumumab in the Netherlands [253]. Other countries i.e., Italy also have a MEA for daratumumab [254]. Since current P&R negotiations in the EU are predominantly grounded in value-based theory, where relative (cost-)effectiveness is assessed based on country specific criteria, differences amongst countries can lead to diverging decisions and ultimately disparate patient access.

Strengths

The selection of daratumumab and pembrolizumab exemplifies the broadening of indications in histology-agnostic (i.e., pembrolizumab) and histology-specific (i.e., daratumumab) cancer treatments. The eligible patient population for each product was based on new incident cases. Although this potentially could have led to an underestimation of eligible patients due to the omission of prevalent cases, this is a conservative approach which would otherwise result in a lower CBP. The costs associated with initial R&D take into account the costs of failed trials, cost of capital (10.5%) and all clinical phases of the drug development, therefore, giving a realistic aggregate estimate of costs associated with the development of a drug. Moreover, the utilized estimates are specific for antineoplastic and immunomodulating agents, which is arguably more accurate than more general estimations.

To our knowledge, CBP models are not yet utilized for P&R negotiations. However, the use of CBP models in costly treatment P&R negotiations could facilitate curtailing excess profits. Moreover, the *"model's flexibility"* enables payers to estimate a CBP for each year and/or indication, needing minimal extra inputs. If cost-based pricing facilitates lower list prices, price-sensitive prescribers might be less reluctant to prescribe these pharmaceuticals, resulting in broader patient access. Moreover, in countries where healthcare is publicly financed, lower drug prices could result in lower healthcare spending or create room for investments in other parts of the healthcare system.

Limitations

The quality of the results obtained from the CBP models are dependent on the accurateness of inputs, therefore each model input needs scrutinizing.

First the costs associated with manufacturing of both pharmaceutical products are based on prices per gram of mAbs produced. These costs might, however, vary depending on the production process which was explored in the 5th and 6th scenarios. Moreover, the packaging and distribution of each product were omitted and therefore is likely to underestimate the actual costs. This is especially true for pembrolizumab since lower doses of active pharmaceutical ingredient (API) are packed per vial in comparison to daratumumab.

Secondly, initial R&D costs were extracted from Wouters et al. (2020) [228]. Although the distinction was made for antineoplastic and immunomodulating agents, the exact spending on R&D for each product could not be estimated. The use of one lumpsum has several drawbacks namely, both daratumumab and pembrolizumab received accelerated approval, reaching the market before phase III clinical trial results [255,256]. Moreover, daratumumab received orphan designation [257] and pembrolizumab received orphan designation for some indications [258] making both drugs eligible for tax credits. Government funded research or subsidies received are also not accounted for. Furthermore, double counting of additional R&D costs is possible since initial R&D costs were not dissected per indication, and therefore could potentially include R&D spending on additional indications, as acknowledged by Wouters et al. (2020) [228]. The R&D costs reported by Wouters et al. (2020) [228] range in the upper bound of estimates available in the literature [243]. Transparency on R&D costs per individual product is generally lacking in large pharmaceutical companies. The European Parliament adopted a resolution in November 2021 [259] that refers to the 72nd World Health Assembly (WHA) resolution that took place in May 2019, where the importance of transparency of markets for medicines is stressed. Moreover, the 72nd WHA resolution mentions the request to: "analyse the availability of data on inputs throughout the value chain, including data on clinical trials and price information". If implemented, this could lead to greater transparency in R&D spending in the future. Improving transparency on R&D costs would increase the accuracy of the model estimates and contribute to a fair dialogue on pharmaceutical pricing.

Thirdly, more research is needed to accurately estimate the R&D costs associated with the broadening of indications. We used the price of repurposing a pharmaceutical product as a surrogate [229], however, this likely overestimates the cost of R&D since the development takes place within the same pharmaceutical company and likely in parallel resulting in better optimized processes. Per contra, the cost of failure in the indication broadening was not accounted for, since failure probabilities might not be similar to the failure rates in drug repurposing. However, the failure rate in drug repurposing is low (45%) compared to innovative drugs [260]. Non-profit repurposing has been successful in the past with smaller investments (i.e., Sanofi's fexinidazole only required $55 million) [261]. Others estimated the cost of repurposing at ≥60% of the *de novo* drug discovery costs [262]. The International Association of Mutual Benefit Societies (AIM) developed a CBP algorithm that only uses 10% of the original costs of R&D for any subsequent indication.

In the CBP models the remaining patent period is fixed to the first indication. However, different indications can have divergent patent expiry times or market exclusivity expiry dates.

Another limitation of our model is the assumptions that revenue diminish to zero after patent expiration date. This results in a simplification of reality, it is possible –like in the case with adalimumab– that the originator keeps part of the market after patent expiration [263]. However, predicting the decay in revenue would have introduced more uncertainties in the models.

Lastly the population eligible is based on the MDR, these also include countries that may get delayed access or no access at all, i.e., Eastern European countries [250], this might lead to an overestimation of the eligible patient population especially in early years or indications. However, if there is any uptake outside MDR countries, the patient population might be underestimated, leading to an overestimation in CBPs.

It should be noted that our CBP algorithm estimates an ex-factory price excluding any value-added tax (VAT) or margins for wholesalers and thus not incorporates costs charged in a pharmacy. The price a pharmaceutical company charges is referred to as the ex-factory price.

If cost-based pricing would be implemented as a standalone evaluation system for P&R negotiations, this could discourage pharmaceutical companies to operate efficiently –since payers would pay for all R&D/operating costs– and could thus hinder the development of advanced new treatments. If cost-based pricing would be implemented as an additional requirement to Health Technology Assessment (HTA) procedures, a drawback could be possible delays in patient access, due to longer P&R negotiations, which could stifle innovation in the long-term, since investing in pharmaceutical sector becomes less attractive.

Moreover, cost-based pricing models do not integrate effectiveness and thus cannot inform policy makers which treatment choice would be preferable. Therefore cost-based pricing models might be complementary to value-based economic evaluation but cannot substitute currently used processes.

Future possible improvements

The utilized CBP model currently lacks the ability to implement differential pricing amongst selected countries, namely MDR as defined by the UN. Differential pricing is entrenched in economic theory and commonly refers to *"positive price discrimination",* where the price is varied across markets to accommodate for price-sensitive countries while maximizing profits [264]. A possibility to achieve a differential CBP could be to weigh the price based on the gross domestic product (GDP) per capita. However, implementation of differential pricing in CBP models must be studied further.

Secondly, the profit margin applied in the CBP model was fixed at 20 percent. A variable profit margin dependent on clinical benefit could be envisaged in the future. The profit margin for pharmaceuticals for cancers could, for example, be made dependent on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [265].

Implications for payers

The difference between list prices and calculated CBPs can vary greatly depending on the type of model and moment in time or the indication. However, the calculated CBP prices per year or cumulative indication for pembrolizumab always remained lower than United States and Dutch list prices (see appendix IX). This implies that if payers would – complementary to value-based pricing– introduce the need for CBP analysis, prices would negatively be affected. In the case of daratumumab the implications are rather different, namely due to small patient numbers in the first indications, CBP per cumulative indication surpass the United States and the Netherlands list prices considerably. We notice, however, a sharp decline over indications (and time) due to rising eligibility. Importantly prices must be renegotiated over time or with the introduction of new indications. In this instance, the use of CBP by payers could result in higher prices at first and drop in later indications.

Recommendations

The implementation of a CBP model can be structured in various ways. we recommend making CBP models –if indication-based pricing is not applicable– dependent on a time interval (possibly 1 or 2 years), this enables price stability and reduces the need for continuous updates. The identification of broadening indications for pharmaceutical products should be considered for initial P&R negotiations and possible managed MEAs should be tailored accordingly. Precautions should be taken especially when implementing confidential price agreements with long lifespans or be flexible to allow periodic price adjustments.

Conclusion

The implementation of a CBP model for pharmaceutical products which are subject to indication broadening i.e., pembrolizumab and daratumumab, shows the possibility for price reductions over time and/or indications. In countries that have IBPs i.e., France and Switzerland the IBCBP version of the algorithm could be utilized, aiding stakeholders in pricing of subsequent indications. In conclusion the use of CBP models can foster the dialogue on *fair pricing* for pharmaceutical products and can be remodelled to accommodate for indication broadening.

Part D.

Strategies to mitigate risks in reimbursement

Chapter 7

Market entry agreements for innovative pharmaceuticals subject to indication broadening: a case study for pembrolizumab in the Netherlands

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Abstract

Managed entry agreements (MEAs) and especially financial based agreements are commonly used in European countries for innovative cancer pharmaceuticals. These agreements facilitate access to innovative treatments while mitigating financial risks for payers. This study focuses on the confidential price agreement made by the Dutch government for the reimbursement of pembrolizumab, the implications of broadening indications on cost-effectiveness, and the viability or desirability of said agreement.

We selected five indications where pembrolizumab was deemed effective and developed portioned survival models for each indication. Survival and progression-free survival data from the published trials were utilized to recreate individual patient data and we extrapolated --using parametric models-- to a time horizon of 30 years. Inputs for both quality of life and costs were derived from available literature and were indexed.

The incremental cost-effectiveness ratios (ICERs) ranged between €35,313 and €322, 349 per quality-adjusted life-year (QALY) depending on the indication. Only one indication fell under the €80,000 (or €100,000) cost-effectiveness threshold. When applying the average reported discount on intramural pharmaceuticals in the Netherlands, ICERs ranged between €20,881 and €252,934 per QALY gained, and the €80,000 (or €100,000) threshold was met in three indications out of five.

Our results show that pembrolizumab could be cost-effective in some indications, depending on the confidential price agreement established. However, the possibility of reimbursing not cost-effective care when the price is anchored in one indication remains possible. Indication-based pricing (IBP) could help align value and price for innovative pharmaceuticals that are subject to indication broadening.

Introduction

Innovative cancer pharmaceuticals deliver added value for patients and the life expectancy of cancer patients has improved over the years[266,267]. However, new anticancer pharmaceuticals have seriously contributed to the rise in spending on pharmaceuticals in both the European Union (EU) and the United States (US) [220]. By 2023, it is estimated that the global pharmaceutical market will exceed $1.5 trillion and 50% of the expenditure will go towards specialty pharmaceuticals, which includes oncology pharmaceuticals [268]. The rising expenditure in oncology is not solemnly attributable to new pharmaceuticals, but also to the expansion of indications of existing oncology pharmaceuticals. A recent study found that in 2018 63% of new approvals were for new indications of existing oncology pharmaceuticals, thus surpassing the number of approvals for new oncology pharmaceuticals [221].

Although the growth rate in pharmaceutical expenditure is lower in the EU, namely 1-4% in the EU compared to 4-7% in the US, concerns about the sustainability of healthcare systems persist. Godman et al. (2021) identified various possible approaches to enhance sustainability of healthcare systems, such as minimum effectiveness levels for new cancer pharmaceuticals, multicriteria decision analyses (MCDAs), differential pricing, fair pricing models, amortization models, de-linkage models, and managed entry agreements (MEA) [24]. Some of these approaches are not yet utilized in practice by payers i.e., fair pricing models, others like MEA are broadly used in EU countries.

MEAs are arrangements between pharmaceutical companies and healthcare payers, allowing innovative pharmaceuticals with considerable uncertainty in either financial impact and/or performance to reach patients [252]. Two main categories exist, namely financial based agreements and performance-based agreements [269]. Financial based agreements mostly aim at managing the uncertainty around budget impact of a new pharmaceutical or technology and include confidential discounts or rebates, utilization caps, and price volume agreements [270]. For pharmaceutical companies confidential discounts are essential since they do not impact external reference pricing (ERP). ERP utilizes list prices not transactional prices, therefore higher prices can be retained by pharmaceutical companies if discounts remain confidential [270]. In countries that require cost-effectiveness analyses (CEA) to be performed i.e., the Netherlands, confidential discounts can reduce the incremental cost-effectiveness ratio (ICER) or uncertainty around the ICER [270]. Performance-based agreements aim at reducing uncertainty surrounding the effectiveness of a new pharmaceutical or technology, including i.e., performance guarantee and coverage with evidence development (CED) [270].

Pembrolizumab (Keytruda®) is a programmed death receptor (PD-1) inhibitor, that was approved in September 2014 for unresectable or metastatic melanoma by the Food and Drug Administration (FDA) and later in July 2015 by the European Medicine Agency

(EMA) [224,255]. Until 2022, pembrolizumab has received 37 new approvals across different indications by the FDA, inclusive of an approval regardless of tumour type [271]. The EMA has approved pembrolizumab for 24 indications as of December 2023 [272]. Pembrolizumab is subject to financial based agreements in various EU countries, including Belgium, Italy, Lithuania, Portugal, Sweden, and the Netherlands [252].

The Netherlands only reimbursed pembrolizumab as of 1 July 2017 after having put a reimbursement decision on hold (known as "the lock") since 2016 due to concerns about budget impact. The "lock" is triggered by an expected >€40 million budget impact for all indications or >€50k per patient year and >€10 million budget impact for one indication [273]. The National Health Care Institute (Zorginstituut Nederland, ZIN) advised (non-binding) the minister to wait with reimbursement until a price agreement was made (being the period in "the lock"), which should improve the cost-effectiveness and reduce the impact on the healthcare budget [251]. The confidential discounted price was negotiated for non-small-cell cancer (NSCLC), Hodgkin lymphoma and future proven to be effective indications [251].

However, in 2022, pembrolizumab was the third best-selling pharmaceutical agent after COVID-19 vaccines and adalimumab (Humira®), generating $20.9 billion [274]. It ranked first in inpatient pharmaceutical spending in the Netherlands, according to 2019 data, estimating a spending of €210 million based on list prices [275]. Furthermore, pembrolizumab ranked in the top five for increased pharmaceutical spending in the Netherlands between 2017 and 2018, based on known list prices, as its spending rose by 123.8% [226].

The financial based MEA for pembrolizumab in the Netherlands has insured access to patients while mitigating uncertainty around the budget impact. The Netherlands use a price anchored in the initial indication for follow-on indications. Since CEAs were no longer required for future indications, the cost-effectiveness of pembrolizumab in new indications is certainly not guaranteed. If pembrolizumab is effective but not cost-effective in new indications, this could lead to crowding out of other healthcare interventions and general net loss of health care in the Dutch population. The MEA for pembrolizumab in the Netherlands had a limited time span of 3 years, and the Dutch Ministry of Health could try to prolong or renegotiate after it its expiration date. With this case study we explore the cost-effectiveness of pembrolizumab in five indications, in an attempt to evaluate the MEA made for the Netherlands.

Methods

To evaluate the MEA for pembrolizumab in the Netherlands, we looked at the cost-effectiveness of pembrolizumab in 5 different indications. Indications were randomly chosen, with the sole criterion being demonstrated clinical benefit in the corresponding clinical trial. Moreover, a scenario analysis was run to evaluate at what price pembrolizumab would be cost-effective.

Partitioned survival models (PSM) were constructed for the indications found in Keynote-006, Keynote-010, Keynote-024, Keynote-048 and Keynote-426, namely advanced melanoma, previously treated PD-L1-positive advanced NSCLC, PD-L1-positive NSCLC, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) and advanced renal-cell carcinoma (RCC), respectively [255,276–279]. Each PSM model is comprised of three health states, namely progression free survival (PFS), overall survival (OS) and death. Moreover, all models have a healthcare perspective.

Both OS and PFS were extracted from the trials or the updated (5 year) trial results with the juicr package (version 0.1) in RStudio® [82,280]. Thereafter, pseudo-individual patient data (IPD) was reconstructed from published Kaplan-Meier survival curves, using the algorithm developed by Guyot et al. (2012) [281]. The pseudo-IPD was utilized to fit parametric models (exponential, Weibull, gamma, lognormal, loglogistic or Gompertz) and extrapolate these to a life-time horizon (30 years), making use of the Darthpack package R [282]. Chosen parametric curves for each trial can be found in Table 1. and have been validated by a clinical expert. As some indications reach a plateau phase, we corrected for background mortality using converging hazards approach and the Dutch lifetables provided by the R package HMDHFplus (version 2.0.1). Moreover, because health-state utilities were not always reported, we converted OS to accommodate for time-to-death (TTD) utilities [283,284]. Comparators were limited to the direct comparators in the previously mentioned trials, and no subgroup analysis were performed.

Table 1. Chosen parametric curves.

TRIAL	STATE	PHARMACEUTICAL	MODEL	AIC
KEYNOTE-006 ADVANCED MELANOMA	OS	Pembrolizumab	Gompertz	2938.052
		Ipilimumab	Gompertz	1452.445
	PFS	Pembrolizumab	Log-normal	3138.446
		Ipilimumab	Log-logistic	1301.662
KEYNOTE-010 PREVIOUSLY TREATED PD-L1-POSITIVE ADVANCED NSCLC	OS	Pembrolizumab	Log-normal	4745.578
		Docetaxel	Log-logistic	2182.874
	PFS	Pembrolizumab	Log-normal	3989.409
		Docetaxel	Log-normal	1786.810
KEYNOTE-024 PD-L1-POSITIVE NSCLC	OS	Pembrolizumab	Log-normal	663.332
		Five platinum-based chemotherapy**	Log-normal	593.512
	PFS	Pembrolizumab	Log-normal	543.701
		Five platinum-based chemotherapy**	Log-normal	677.976
KEYNOTE-048 R/M HNSCC	OS	Pembrolizumab	Log-normal	305.082
		Cetuximab, carboplatin/ cisplatin & 5-fluorouracil	Log-logistic	1706.148
	PFS	Pembrolizumab	Log-logistic	1551.797
		Cetuximab, carboplatin/ cisplatin + 5-fluorouracil	Log-logistic	1650.860
KEYNOTE-426 ADVANCED RCC	OS	Pembrolizumab + axitinib	Gamma	1502.129
		Sunitinib	Weibull*	1804.719
	PFS	Pembrolizumab + axitinib	Log-normal	2161.479
		Sunitinib	Log-normal	2062.702

Overall survival (OS), progression-free survival (PFS), programmed death-ligand 1 (PD-L1), non-small cell lung cancer (NSCLC), recurrent or metastatic (R/M), head and neck squamous cell carcinoma (HNSCC), renal-cell carcinoma.
*based on clinical experts opinion.
**carboplatin plus pemetrexed, cisplatin plus peme- trexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel.

Health-state (HS) utilities or time-to-death utilities were retrieved from either patient reported outcomes studies linked to the corresponding trials or relevant literature and can be found in Table 2. Utilities ranged between 0.85 and 0.396, with sharp decreases in utilities observed in the last days of life.

Table 2. Utility inputs.

TRIAL	TIME-TO-DEATH DAYS OR HEALTH STATE	UTILITIES	REFERENCES
KEYNOTE-006	> 360	0.85	Wang et al. [285]
	270-360	0.78	
	180-270	0.74	
	90-180	0.75	
	30-90	0.69	
	< 30	0.48	
	PFS ipilimumab	0.83	
	PFS pembrolizumab	0.86	
	Post progression	0.78	
KEYNOTE-010	> 360	0.807	Huang et al. [286]
	180-360	0.728	
	90-180	0.688	
	30-90	0.602	
	< 30	0.396	
	PFS	0.761	
	OS	0.687	
KEYNOTE-024	> 360	0.805	Huang et al. [287]
	180-360	0.726	
	30-180	0.632	
	< 30	0.537	
	PFS	0.71	Chouaid et al. [288]
	Post progression	0.67	
KEYNOTE-048	PFS	0.82065	Borse et al. [289]
	Post progression	0.77848	
KEYNOTE-426	> 360	0.824	Bensimon et al. [290]
	180 -360	0.769	
	90-180	0.750	
	30-90	0.594	
	< 30	0.462	
	PFS pembrolizumab + axitinib	0.760	Xander et al. [291]
	PFS sunitinib	0.720	
	Post progression	0.660	

Overall survival (OS), progression-free survival (PFS).

Costs were extracted from available literature, namely Dutch HTA reports, CEA and real-world costing studies. Both costs and outcomes were discounted per required Dutch guidelines, namely 4% for costs and 1.5% outcomes. Costs occurring within the healthcare setting were included, namely treatment costs, healthcare resource use costs, adverse

events costs and end of life costs. Aggregated main cost inputs for each model can be found in Appendix IV.

The MEA for pembrolizumab in the Netherlands is confidential, and; the agreed upon financial discount has not been made public. However, the Dutch government does publish the average discount achieved in all financial based agreements for intramural pharmaceuticals. And the last know average discount was 33.6% in 2020 [273]. We created a scenario utilizing the average discount rate to test the cost-effectiveness across different indications.

Results

The ICERs obtained ranged between €35,313 and €322,349. The highest incremental effects, namely 2.38 QALY, were found in the PD-L1 positive NSCLC indication. Highest incremental costs were found in the advanced melanoma model and are mainly the result of incremental treatment costs (see Appendix V). Each ICER for all modelled indications and stratification by time-to-death utility or health-state utility can be found in Table 3.

Table 3. Deterministic ICERs

TRIAL AND INDICATION	TYPE UTILITY	ICER	INCREMENTAL COSTS	INCREMENTAL QALYS
KEYNOTE-006 MELANOMA	TTD	€154,025	€237,402	1.54
KEYNOTE-006 MELANOMA	HS	€176,709	€237,402	1.34
KEYNOTE-010 ADVANCED NSCLC	TTD	€173,449	€159,218	0.92
KEYNOTE-010 ADVANCED NSCLC	HS	€196,758	€159,218	0.81
KEYNOTE-024 NSCLC	TTD	€35,313	€83,907	2.38
KEYNOTE-024 NSCLC	HS	€45,576	€83,907	1.84
KEYNOTE-048 R/M HNSCC	HS	€126,330	€84,977	0.67
KEYNOTE-426 ADVANCED RCC	TTD	€322,349	€223,766	0.69
KEYNOTE-426 ADVANCED RCC	HS	€312,793	€223,766	0.72

Non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), renal-cell carcinoma (RCC), recurrent or metastatic (R/M), time-to-death (TTD), health state (HS).

The use of time-to-death utilities instead of health-state utilities resulted in ICERs that were between 13% and 30% lower in all indications but one (i.e. advanced RCC). The incremental QALYs using health-state-based utilities in RCC are higher due to the higher utility value assigned to the PFS state in patients modelled in the pembrolizumab arm. Time-to-death utilities could not be found for HNSCC and therefore the related health-state utilities were used, however combined with time-to-death disutilities. The time-to-death disutilities were applied based on OS and were similar between pembrolizumab and comparator.

The highest Dutch cost-effectiveness threshold of €80,000 per QALY gained was only met in one indication, namely first-line use of pembrolizumab in metastatic PD-L1-positive NSCLC patients (KEYNOTE-024). All other indications did not meet the €80,000 per QALY threshold.

Both KEYNOTE-010 and KEYNOTE-024 trials have studied the efficacy of pembrolizumab in NSCLC patients. However, the latter study focuses on first-line treatment compared to advanced and previously treated patients in the KEYNOTE-010. This (largely) explains the incremental cost difference between both patient populations, since most patients in first-line treatment received a second line of treatment after progression.

ICERs are often sensitive to the price of new therapies, especially if costs are relatively high compared to other inputs. Since the actual price agreed upon for pembrolizumab in the Netherlands is not known, we utilized a fixed 33.6% discount in scenario analyses for each modelled indication [273]. The ICERs in the aforementioned scenario ranged between €20,881 and €252,934 per QALY gained. In three out five studied indications, the deterministic ICERs were below the €80,000 per QALY threshold. All computed ICERs stratified by time-to-death utility or health-state utility can be found in **Table 4**.

Table 4. ICERs across studied indications with a 33.6% price reduction of pembrolizumab price.

TRIAL AND INDICATION	TYPE UTILITY	ICER	INCREMENTAL COSTS	INCREMENTAL QALYS
KEYNOTE-006 MELANOMA	TTD	€50,747	€78,218	1.54
KEYNOTE-006 MELANOMA	HS	€58,221	€78,218	1.34
KEYNOTE-010 ADVANCED NSCLC	TTD	€112,323	€103,108	0.92
KEYNOTE-010 ADVANCED NSCLC	HS	€127,418	€103,108	0.81
KEYNOTE-024 NSCLC	TTD	€20,881	€49,615	2.38
KEYNOTE-024 NSCLC	HS	€26,949	€49,615	1.84
KEYNOTE-048 R/M HNSCC	HS	€75,468	€50,764	0.67
KEYNOTE-426 ADVANCED RCC	TTD	€260,662	€160,539	0.69
KEYNOTE-426 ADVANCED RCC	HS	€252,934	€160,539	0.72

Non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), renal-cell carcinoma (RCC), recurrent or metastatic (R/M), time-to-death (TTD), health state (HS).

To reach the €80,000 threshold for the remaining indications, namely advanced previously treated advanced NSCLC (KEYNOTE-010) and advanced RCC (KEYNOTE-426), the price reduction needed for pembrolizumab would be 52% and 100%, respectively. This implies that if the pembrolizumab price would be free, it would still not meet Dutch cost-effectiveness thresholds for advance RCC due to added healthcare costs and limited incremental QALYs.

Discussion

Considering a willingness to pay (WTP) of €80,000, pembrolizumab is not cost-effective at the list price in the Netherlands for four out of five indications, with ICERs ranging between €35,313 and €322,349 per QALY gained.

The relatively low ICER in previously untreated advanced NSCLC is partly caused by the fact that 53% of the control arm received pembrolizumab after progression. This was also the case in the KEYNOTE-024 trial and is applied in our model, resulting in negative incremental costs in the progression health state (see Appendix V).

These ICERs obtained substantiate the need for MEAs to mitigate financial uncertainty and in this case budget impact. Applying the average discount for intramural pharmaceuticals achieved by the Dutch Ministry of Health depicts a different situation where 3 additional indications were deemed cost-effective.

The ICERs modelled are mostly in line with other published cost-effectiveness studies, however some are diverging. The advance melanoma model based on KEYNOTE-006 has a somewhat higher ICER namely €154,025 per QALY. Wang et al. (2017) computed an ICER of $81,091 per QALY with a 20-year time horizon. Moreover, other parametric models were utilized, resulting in smaller incremental costs [285]. Our modelled ICER for advanced and previously treated NSCLC (KEYNOTE-010) of €173,449 per QALY is very close to the ICER reported by Huang et al. (2017) namely $168,619 per QALY [286]. The cost-effectiveness literature based on the results from KEYNOTE-024 (first-line NSCLC) has been reviewed by Qiao et al. (2021) and found ICERs ranging between $49,000 and $103,000 per QALY gained. Our estimates are slightly below this range, namely €35,313 to €45,576 per QALY, depending on the method utilized to incorporate utilities [292]. The modelled ICER for HNSCC was €126,330 per QALY gained, which is slightly higher compared to Massetti et al. (2020) who estimated €80,736 per QALY gained [293]. Lastly, the modelled ICERs for the RCC indication (KEYNOTE-426) were the highest, namely €322,349 or €312,793 depending on the method used to incorporate utilities. Bensimon et al. (2020) reported ICERs ranging between $70,037 per QALY to $174,995 per QALY, and are mostly the result of different extrapolation inputs, resulting in very different incremental QALYs namely 2.73 vs 0.69 – 0.72 in our model. Another cost-effectiveness study for the Netherlands by Xander et al. (2023) reported an ICER of €368,396 per QALY gained, which is very similar to our modelled ICERs.

Strengths

Our study encompasses various indications within cancer. The models are not overcomplicated and make use of commonly used methodology in cost-effectiveness studies. Moreover, all models are similar in their structure and include three health states. The utilized costing inputs are based on previously submitted dossiers and costing studies,

specific for the Dutch healthcare system. Utility inputs were used from trial-reported quality of life studies or other cost-effectiveness studies. Moreover, if available (n=4), both health-state and time-to-death utilities were incorporated, inadvertently showing the effect of using each type in our models. We corrected for background mortality and discounted our results based on Dutch guidelines. Lastly, the extrapolation of OS, PFS and choice of the parametric model was validated by an oncologist.

Limitations

We did not perform any probabilistic sensitivity analyses for each cost-effectiveness model, since this fell out of the scope of this study. Moreover, we did not have access to IPD from each trial, creating the need for pseudo-IPD creation. The cost-effectiveness models have a healthcare perspective, even though the Dutch authority requires a societal perspective for HTA purposes. These mentioned limitations are the result of careful considerations, and deliberation on the level of evidence needed to evaluate the MEA between the Dutch Ministry of Health and pharmaceutical company for pembrolizumab.

MEAs can effectively reduce prices in the case of financial based agreements and provide access to innovative pharmaceuticals to patients. However, the negotiation time needed for MEAs can also hamper access if early access programs are not available for patients.

Contrariwise, the use of financial based agreements could potentially result in crowding out of other effective care if the drug is not cost-effective in a particular indication. Our results showed that, without discount, four out of five indications selected would not meet cost-effectiveness thresholds and, even after factoring in a discount, the possibility (n=2) remains that pembrolizumab is not cost-effective in a particular indication.

Therefore, it is in the interest of payers to correctly assess the risks involved in making a MEA and mitigate these risks. Payers can mitigate risks accompanying MEAs by i.e., having limited timespan for the agreement in place, making sure re-evaluation is done periodically. Another possible approach would be indication-based pricing (IBP). Within IBP three distinct modus operandi exist namely, prices are either different for each indication, a single weighted average list price is determined across indications or a single list price is set, corresponding to the highest value indication with different net prices per indication [294].

Several EU countries have implemented a form of IBP, however the Netherlands has not. Currently; the price for follow-on indications is anchored to the price of the initial indication. Other types of MEAs have been implemented in the past in the Netherlands. Between 2006 and 2012 the possibility for quick but conditional access to “expensive” hospital drugs was possible under conditional financing (CF). The CF required 4-year coverage with evidence development (CED). Although the policy made quick access possible to patients, the implementation of CEDs remained challenging in both procedural and methodological aspects [295].

Our case-study results showed that with the average discount (33.6%) some ICERs fall well below the €80,000 threshold. Therefore, it could be argued that the use of pembrolizumab in not cost-effective indications might not be as problematic when viewed as grouped spending. Moreover, if future indications have tremendous outcomes for patients, e.g., the combination therapy enfortumab-vedotin with pembrolizumab in previously untreated locally advanced metastatic urothelial carcinoma, the discounted price anchored in the first indication might be favoured by payers [296]. Lastly, the Netherlands spent 7% (in 2022) of their healthcare spending on pharmaceuticals. This is considerably lower than neighbouring countries, i.e., Belgium spent 11% on pharmaceuticals (in 2021) and Germany spent 14% (in 2021) [7]. Therefore, the current reimbursement system and MEAs in the Netherlands might be deemed sufficient.

Conclusion

Our results showed that, without discount, four out of five indications selected for pembrolizumab would not meet cost-effectiveness thresholds. Therefore, demonstrating the potential risks for both payers and pharmaceutical companies when engaging in MEAs, especially in financial based agreements for products subject to indication expansion. Moreover, our study shows the possibility of reimbursing not cost-effective care when the price is anchored in one indication. IBP could help align value and price for innovative pharmaceuticals.

Chapter 8

General discussion

Background:

The increase in both life expectancy and cancer rates has led to a rise in health spending in the Organisation for Economic Co-operation and Development (OECD) countries over the last few decades [1,6,297]. In combination with increased prices for new technologies, these factors potentially form a threat to the financial sustainability of healthcare systems. In the European Union (EU) the member states are responsible for managing health services and the distribution of resources[21]. Member states have responded to these challenges by developing policies that require (pharmaceutical) companies to demonstrate clinical benefit or/and cost-effectiveness after marketing authorization, before new technologies are reimbursed. These policies are commonly referred to as the fourth hurdle, with safety, efficacy and quality (first three hurdles) not being sufficient anymore for reimbursement [298]. In some instances, new technologies, such as new cancer drugs and cell and gene therapies, are expected to deliver great value to patients, but bare considerable costs due to their high prices [299]. Certain countries have implemented managed entry agreements (MEAs) to manage the financial risk and uncertainty associated with the long-term effectiveness of these therapies. However, the impact of implementing such arrangements is yet to be fully understood [300]. Novel approaches to pricing of innovative cancer pharmaceuticals have theoretically been explored, however not utilized in practice. Quantitative studies that clarify the processes in the current policy environment can aid in comprehending reimbursement processes and have the potential to be valuable to policy makers, ultimately influencing patient access and quality of the healthcare.

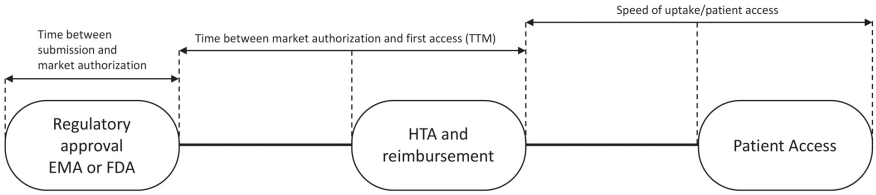
This thesis focusses on patient access, pricing, costs and current policies impacting reimbursement of innovative cancer pharmaceuticals. Part A examines the current state of access to innovative cancer medicines in the EU, the differences in regulatory and market access times, and the real-world costs of treating castration-resistant prostate cancer (CRPC) patients with new cancer pharmaceuticals in the Netherlands. Part B focuses on a new cell therapy in hematology, namely chimeric antigen receptor (CAR) T-cell therapy, and the possible economic consequences of reimbursing these new therapies in 6 European countries based on current and future indications. Part C delves into a cost-based pricing model applicable to novel medicines, including gene therapy and cell therapy. It also examines how this model can accommodate pricing variations for products affected by indication broadening, such as pembrolizumab and daratumumab. Part D reflects on the use of managed entry agreements (MEAs) as a tool to mitigate risks for payers when reimbursing innovative cancer medicines subject to indication broadening, using a case-study of a financial-based agreement for pembrolizumab in the Netherlands.

Does patient access to innovative cancer medicines vary across EU member states?

In Chapter 2 we explored access to 12 innovative end of life cancer medicines in the EU. The analysis is based on retrospective data in both retail and hospital setting covering different cancers and medicines with varying European Society Medical Oncology-Magnitude of

Clinical Benefit Scale (ESMO-MCBS) scores. Patient access was assessed for each medicine and split in: (i) time from regulatory submission to regulatory approval; (ii) time to first patient access, i.e., time to market (TTM); and (iii) speed of uptake of the drug (see Figure 1).

Figure 1. Patient access pathway.



The average time needed for regulatory approval was 181 days (range 78–303 days) in the US (FDA) vs. 378 days (range 262-483 days) in EU (EMA). The average time-to market (TTM) in Europe amounted to 398 days (range 17-1187). Countries with low TTM i.e. Germany the UK and Austria averaged 17, 22 and 31 days, respectively. The Netherlands TTM is lower than the EU average in our analysis, namely 128 days, however still much higher than neighboring country Germany. The countries with the longest TTM were mostly Eastern European countries and Greece. The TTM in Belgium was relatively high compared with neighboring countries, namely 392 days. However, when raking countries based on their speed of uptake Belgium came first followed by Switzerland, France Austria and Germany. The Netherlands ranked 9th and is therefore outperformed by all direct neighbors. Delayed access to new effective medicines may result in diminished patient benefits.

European cancer patients have delayed access to innovative cancer medicines compared to the US (8 months), partly due to longer assessment time at the EMA. There are significant disparities in the timing of access to innovative cancer medicines for patients residing in different member states across Europe. Moreover, fast reimbursement did not always lead to fast adoption. For example, the Netherlands and the UK had relatively low TTM, but are ranked relatively low based on speed of uptake. Contrarily Belgium, Italy and Spain had delayed first access, however they were fast adopters after first uptake.

European countries cope differently with the introduction of innovative cancer medicines, resulting in varying patient access. Frost and Reich describe availability, affordability and adoption as factors influencing access to innovation [50]. The availability in a country is influenced by factors such as market authorization time, reimbursement procedure duration, health technology assessment, pricing system (e.g., external reference pricing), and drug added value. The affordability depends on the pricing of the innovative treatment and the willingness to pay (WTP) or ability to pay of member states or patients if co-payments are required. The adoption of innovative cancer medicines is dependent on the perceived unmet need by relevant stakeholder namely, governments, doctors and patients.

Changes in the regulatory environment, such as the Pharmaceutical Strategy for Europe commissioned by the European Commission (EC) and the Joint Clinical Assessment (JCA), are expected to improve patient access in the EU [301]. The pharmaceutical strategy will deliver shorter active review times, possibly shortening the approval period, resulting in faster patient access.

What are the current cost of prostate cancer care and the impact of new innovative systemic therapies on the total costs?

In the second chapter of Part A, we delve into the real-world costs associated with castration resistant prostate cancer (CRPC) and the impact of new systemic therapies on total costs. The study was based on retrospective data from the CAPRI-registry. Patients included in the analysis (n=1,937) had to receive at least one life-prolonging drug (LPD) and be diagnosed between 2010 – 2015. The average total healthcare costs per patient were €67,174, with on average €39,638 (59% of total costs) allocated specifically for systemic treatment. The second and third highest cost components were €9,018 for hospital admissions (13%) and €7,173 for drug administration (11%).

Splitting costs per line of systemic therapy brings insight into the development of costs over treatment period. The mean total costs per line of treatment do not follow a linear trend, namely €28,705 for the first-line, €34,452 for the second-line and €31,751 for the third-line. If a fourth or more lines of treatment with an LPD were given the average total costs amounted to €40,663. The median time on each line of systemic treatment decreased from 9.2 months (8.9–9.5 95%CI) in the first line to 7.1 months (6.5–7.6 95%CI) in the second-line and lastly 6.0 months (5.6–6.4 95%CI) in the third-line. Therefore, the mean cost per month in each line increased from €3,421 in the first-line to €5,083 in the second-line, and lastly €6,841 in the third-line of LPD treatment. The mean first-line systemic treatment costs are the lowest, driven by the number of patients receiving docetaxel in the first-line (58%).

Enzalutamide had the highest mean total costs (€43,945; SD: €33,542), followed by cabazitaxel (€38,545; SD: €19,982), abiraterone (€38,375; SD: €31,449), and radium-223 (€37,572; SD: €17,855). Mean monthly costs were highest for cabazitaxel (€8,199; SD: €4,809), followed by Radium-223 (€6,491; SD: €3,329), enzalutamide (€4,996; SD: €4,180), and abiraterone (€4,344; SD: €2,282). Docetaxel had the lowest mean total and monthly costs (total cost €17,438; SD: €12,799; monthly costs €2,186; SD: €2,289, respectively).

The real-world costs of patients with CRPC is mainly driven by costs associated with systemic treatment. The exception is docetaxel, which is also the only systemic treatment not under patent at the time of data cut-off. The monthly treatment costs increase with each subsequent systemic treatment administered. However, the actual costs incurred for systemic therapy were probably lower than reported, as hospitals may have purchased these pharmaceuticals from manufacturers at confidential discounts [83]. Additionally, hospitals could have incurred lower costs for systemic treatment due to parallel import

of these pharmaceuticals [84]. Treatment cost for both cabazitaxel and abiraterone have probably dropped since the data cut-off due to patent expiry and generics entering the market [302,303]. Enzalutamide will still be under patent protection till 2026 in Europe after which prices will likely also decrease [304]. Per contra new systemic therapies or combinations such as olaparib and abiraterone could maintain or increase CRPC treatment costs [305].

How would the reimbursement of new advanced therapies impact healthcare expenditure in the EU?

In blood cancers new promising advances have been made, such as CAR T-cell therapy. However, the list prices for these new therapies amount to approximately €320,000, being only the costs of the administering the CAR T-cells. As with therapies like stem cell transplantations the pre- and post-treatment healthcare costs were also considerable, i.e., around €50,000 per patient receiving CAR T-cell therapy. To forecast the 10-year health expenditure associated with reimbursement of CAR T-cell therapies for hematological cancers in the selected EU countries, the future indications are estimated. Based on clinical trials in the pipeline and clinical expert opinion, the estimated market entry of CAR T-cell therapies for chronic mantle cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, multiple myeloma, and acute myeloid leukemia is expected to occur between 2021- and 2025. Existing CAR T-cell therapies and expected future therapies were utilized in combination with incidence rates and predicted population size. We forecasted three scenarios, namely the increase in costs due to CAR T-cell therapies only, the cost of both CAR T-cell therapy and additional health care, and lastly the incremental costs associated with the substitution of previous therapies by CAR T-cell therapies. In the first scenario cumulative expenditure on CAR T-cell therapy ranged from €1.4 billion for the Netherlands to €6.7 billion for Germany. Total costs for all selected countries per indication ranged between €0.8 billion and €13.7 billion, respectively for pediatric acute lymphoblastic leukemia (pALL) and diffuse large B-cell lyphoma (DLBCL). Moreover, the forecasted expenditure for all years and indications reached €28.6 billion. In the second scenario the addition of healthcare resource use resulted in cumulative expenditure ranging between €0.9 for pALL and €15.8 billion for DLBCL. The total average expenditure was estimated at €32.9 billion. The third scenario yielded expenditure estimates between €0.7 billion (pALL) and €13.8 billion, with a total average of €28.9 billion.

The study showed that the expenditure on CAR T-cell therapies will largely increase in studied countries. Nevertheless, prices for CAR T-cell therapy might decline due to price negotiations with payers and competition from other manufacturers entering the market i.e. Celgene has entered the market for DLBCL with their lisocabtagene CAR T-cell therapy [306]. Moreover, some hospitals are considering the possibility of making CAR T-cell therapies in-house, aiming at reducing the price below €100,000 per patient [307]. In Spain a group of academics cells their CAR T-cell product for less than a third of the list price (€89,000) which implies the possibility to reduce the expenditure considerably [308]. Lastly, the price of CAR T-cell therapies is partly reflecting the complicated manufacturing process, requiring

the cells from the patients. Off-the-shelf CAR T-cell therapies are currently being developed, as these could be manufactured in batches economies of scale would drive the price down. Since these products are not yet on the market, the price remains unknown. However, the expectation is that prices should be lower and thus lower the expenditure.

Our analysis indicates that innovative treatments, such as CAR T-cell therapy for hematological cancers, can considerably impact health expenditure, and put significant finical burden on healthcare systems in the EU-5 and the Netherlands. Moreover, expenditure on CAR T-cell therapy is likely to increase dependent on the success of clinical trials in upcoming indications. Hence, payers should exercise caution regarding the financial burden of innovative treatments, which could potentially impact patient access to these new therapies.

What would be the cost-based price for innovative gene and cell therapies?

Prices of innovative therapies are closely correlated with accessibility and affordability. Therefore, we explore cost-based pricing in chapter 5 for new cell and gene therapies, such as OTL-200 (brand name: Libmeldy) and AVXS-101 (brand name: Zolgensma). Both therapies have sparked a debate on pricing, due to their price, namely €3.0 million and €1.9 million per treatment, respectively.

We used the pricing algorithm proposed by Uyl-de Groot and Löwenberg to estimate prices for both OTL-200 and AVXS-101 [56]. The estimated cost-based prices in the base-case were €1,048,138 and €380,444 per treatment and patient, for OTL-200 and AVXS-101, respectively. These estimated prices are sensitive to the inputs utilized in the algorithm. Therefore, we explored sensitivity of inputs with a deterministic sensitivity analysis. Both OTL-200 and AVXS-101 reached lowest prices in the scenario with the low R&D costs namely €499,221 and €242,253 respectively. Hence, the price range for OTL-200 compared to the base case is larger than for AVXS-101.

Most calculated prices remained below the currently reported list prices of €2.5 – €3.0 million for OTL-200 and approximately €1.9 million for AVXS-101. The cost-based prices calculated for both innovative therapies are highly sensitive to the inputs used in the algorithm, therefore it is important to estimate these as meticulously as possible. With the current availability and uncertainty in model inputs, the estimated prices varied considerably. Hence, calculated prices in the base-case should be used with caution. Moreover, the general use of cost-based pricing models should be scrutinized as it does not reward efficiency, as would be expected in a capitalist free-market economy. Nevertheless, cost-based prices can spark (public) debate on "fair" drug prices and the desirability of different pricing models contrasting commonly used value-based pricing models.

How can cost-based pricing models be adapted to encompass the expansion of indications in innovative cancer medicines?

The broadening of indications in existing oncology medicines has recently surpassed the number of approvals for new medicines [221]. The clinical benefit in new indications may vary compared to the initial indication. Following a value-based pricing rationale, varying clinical benefit would warrant different prices. In Part C we explored cost-based pricing models and build on existing methodology (Uyl-de Groot & Löwenberg) to encompass the broadening of indications in cancer medicines. The algorithm was adjusted to calculate (i) cost-based price per cumulative year (ii) cost-based price per cumulative indication (iii) cost-based and indication-based price, per vial. As a case study daratumumab and pembrolizumab were selected. The cost-based price per cumulative year ranged between €885 and €52 for pembrolizumab and between €31,941 and €823 for daratumumab. The first year resulted in the highest price due to the high cost of R&D and the limited eligible patient population in the first indications approved. The cumulative indication-based prices for pembrolizumab and daratumumab ranged between €885 – €48 and €31,941 – €790 respectively. The prices per cumulative indication start high and decrease sharply after the first few indications. After reaching a low, prices slowly increase again because of extra R&D costs and diminished remaining patent period to recoup these investments. All obtained prices were below list prices for pembrolizumab, namely €5,350 in the United States and €2,861 in the Netherlands. In the case of daratumumab cost-based prices ranged both above and below list prices (United States €8,735, Netherlands €4,766) with differences ranging between €23,2206 – €-7,945 and €27,175 – €-3,976 for the United States and the Netherlands, respectively. The stepwise sensitivity analysis showed that for both medicines the number of eligible patients was the most sensitive input, especially for daratumumab since the first indication had a small eligible patient population. In the scenario analysis we implemented indication-based cost-based pricing (IBCBP) resulting in prices from €167 to €31,941 for daratumumab, for pembrolizumab prices dropped considerably, namely €16 per vial for NSCLC (2nd indication). Low CBPs are attributable to larger patient populations and relatively small extra R&D costs. IBCBP can also result in higher CBPs i.e., pembrolizumab's 11th indication (refractory primary mediastinal large B-cell lymphoma) had a CBP of €4,328.

Cost-based pricing models are not yet utilized for pricing and reimbursement (P&R) negotiations. However, the use of cost-based pricing models in costly treatment P&R negotiations could facilitate curtailing excess profits. Furthermore, if cost-based pricing leads to lower list prices, price-sensitive prescribers may be more willing to prescribe these medicines, which could result in increased patient access. However, if cost-based pricing would be implemented as a standalone evaluation system for P&R negotiations, this could discourage pharmaceutical companies to operate efficiently –since payers would pay for all R&D/operating costs– and could thus hinder the development of advanced new treatments [309].

The implementation of cost-based pricing as an additional requirement to Health Technology Assessment (HTA) procedures could possibly cause delays in patient access, due to longer P&R negotiations, which could stifle innovation in the long-term, since investing in pharmaceutical sector becomes less attractive. However, the implementation of a cost-based pricing for pharmaceutical products which are subject to indication broadening i.e., pembrolizumab and daratumumab, shows the possibility for price reductions over time and/or indications.

How do financial based MEAs perform in innovative cancer medicines subject to indication expansion?

Various possible approaches exist to enhance sustainability of healthcare systems, MEAs are one of the approaches used by payers to mitigate risks, while guarantee access to patients. Financial based agreements can be enacted in various ways, however most commonly confidential price agreements are utilized. The Netherlands made a financial based agreement for the first two indication and all upcoming indications of pembrolizumab in 2017. However, since pembrolizumab has been subjected to indication broadening, how this agreement performs in terms of cost-effectiveness remains unknown. To evaluate the confidential price agreement made five indications were selected and portioned survival models (PSM) were constructed. The incremental cost-effectiveness ratios (ICERs) ranged between €35,313 and €322,349 per QALY gained dependent on the indication and the methodology used for the inclusion of utility (time-to-death vs. health-state utility). In only one out of five indication pembrolizumab was cost-effective (at €80,000 threshold) namely first-line use of pembrolizumab in metastatic PD-L1-positive non-small cell lung cancer (NSCLC) patients (KEYNOTE-024).

Since the financial agreement made is confidential, the achieved discount is unknown. Therefore, we implemented the average discount achieved by Dutch Ministry of Health (VWS) for intramural medicines, namely 33.6% as a scenario analysis. The ICERs in the scenario ranged between €20,881 and €252,934 per QALY gained. Moreover, in three out five studied indications, the deterministic ICERs were below the €80,000 per QALY threshold. The advanced non-small cell lung cancer (NSCLC) and advanced renal-cell carcinoma (RCC) indication remained above the cost-effectiveness threshold with ICERs of €112,323 and €252,934 respectively.

Considering a willingness to pay (WTP) of €80,000, pembrolizumab is not cost-effective at the list price in the Netherlands for four out of five indications. However, when applying the average discount for intramural pharmaceuticals achieved by VWS, results depict a different situation, where 3 additional indications were deemed cost-effective. Therefore, demonstrating the potential risks for both payers and pharmaceutical companies when engaging in MEAs, especially in financial based agreements for products subject to indication expansion. Our results show the possibility of reimbursing not cost-effective care when the price is anchored in one indication. However, in some indication the ICERs

were considerably lower than commonly used thresholds, indicating payers might reach a balance with non-cost-effective indications. Indication-based pricing (IBP) could help align value and price for innovative pharmaceuticals.

Suggestions to improve access to innovative cancer pharmaceuticals

Regulatory approval in the EU can be obtained centrally namely at the EMA. The process considers the first three hurdles namely, safety, efficacy and quality. It is of great importance to guarantee patient safety and access to effective care. However, innovative medicines that are under review for longer periods of time may result in longer waiting periods for patients to gain access to them. Hence, it is crucial to strike a balance between quality assessment and efficiency and speed of the said assessment. Our results have shown that the counterpart in the US, the FDA, has considerably shorter regulatory approval times. The EU could therefore strive to match the speed of the FDA at least if granting priority review. The assessment time is 210 and 150 active days for standard and accelerated assessment, respectively. After the assessment the European Commission (EC) gets a maximum of 67 days for the authorization. The reformed, yet to be implemented, pharmaceutical legislation aims at a modern but simplified regulatory framework with faster authorizations, namely 180 days for the EMA and 46 days for the EC [310]. If the shorter timeline is met by the EMA and the European commission, patients could benefit from earlier access. Although there might be more room for improvement since the FDA has shorter assessment time according to our results.

Smaller countries within the EU have previously collaborated when it comes to pricing and reimbursement of new treatments, i.e., the Beneluxa initiative which has been active since 2015 [311]. At the start the initiative comprised the Netherlands and Belgium, however Luxembourg, Austria and Ireland joint later. By working together these member states have an advantage when negotiating pricing of "expensive" innovative therapies. Collaborating on P&R seems sensible for these small member states, and seems to positively impact patient access i.e., the Beneluxa initiative managed successful pricing negotiation for atidarsagene autotemcel (brandname Libmeldy) treating the rare disease Metachromatic Leukodystrophy (MLD) [312].

However, when collaborating on pricing, differential pricing becomes impossible. Therefore, the countries engaging in negotiations should be homogenous in their willingness/ability to pay. Other examples of cross-country collaboration on pricing seems to reflect this i.e., the Valletta Declaration (Croatia, Cyprus, Greece, Italy, Malta, Portugal, Romania, Slovenia and Spain) or the Fair and Affordable Pricing (FaAP) (Croatia, Czechia, Hungary, Lithuania, Poland, Slovakia and Latvia) [313].

The reimbursement of an innovative therapy is inherently subject to a certain level of uncertainty. The costs and effects may exhibit variation across different indications for the same product. Additionally, in instances where a cure is postulated, it does not invariably

lead to a sustained remission or cure, until the data has reached a state of maturity. Therefore, making the process of pricing and reimbursement cyclic could help ensure value for patients, while maintaining a healthy equilibrium between costs incurred and value for patients. These notions are not novel and have been proposed in the past [314]. The Netherlands has implemented a more cyclic decision-making process with the repetitive use of MEAs for "highly priced" oncological medicines in recent years. These, for the most part, financial based agreements have a limited timespan which allows the government to renegotiate after said agreement is out of date.

Additionally, as we have shown in this thesis, from a cost-based pricing perspective products with many new indications might benefit from shorter agreements periods or even the use of indication-based pricing. We have also shown the potential for pricing indications differently from a value-based perspective, namely by continuing to assess cost-effectiveness after the first indication. Other countries already utilize a form of indication-based pricing, namely Estonia and Latvia have differential indication-based pricing at the point of sale, Belgium, France and Italy use differential prices per indication by implementing ex-post rebates. In Germany a single price is used however weighted per indication, which could therefore still be considered as a form of indication-based pricing [315].

Different policies exist to contain the rising expenditure on pharmaceuticals. The Netherlands already implemented generic substitution by having doctors prescribe the molecule name instead of the brand name in 1995 [316]. Although the Netherlands is in the top three countries in Europe with the highest share of generics in the pharmaceutical market, in both volume and value, the UK and Germany still have higher generic substitution [10]. This indicates that there is still room for improvement when it comes to generic substitution in the Netherlands.

Other strategies have been proposed to enhance the sustainability of healthcare systems that were not applied in this thesis. Firstly, the minimum effectiveness criteria could be adjusted, only reimbursing a higher price if a certain standard in clinical benefit has been met. In the Netherlands the Dutch Oncology Society (NVMO) has recently adjusted its PASKWIL (palliative, adjuvant, specific side effects, quality of life, impact of treatment and level of evidence) framework, raising the required benefit from 12-week to 16 weeks with a hazard-ratio (HR) of <0.7 if the overall survival in the control arm is >12 months [317]. The drawbacks associated with these measures are: first the difficulties in obtaining complete data and not surrogate endpoints, second the perceived value for the patient might differ from the criteria set, and lastly innovation often fallows smaller incremental steps therefore not awarding merits to smaller gains could impact the willingness to innovate and invest in R&D of different stakeholders.

Another strategy to consider is multicriteria decision analyses (MCDA). The use of a broader perspective in the assessment of a new technology could help decisionmakers in methodically incorporating other aspects in the decision-making process.

Other previously proposed strategies could require a more radical change in the way innovation is brought to the market. These include 'push' (providing grants for research projects) and 'pull' (reward agreed upon research accomplishments) models or even 'pooling' initiatives were R&D is open source and stakeholder work together towards a certain goal. De-linkage models have also been proposed, disconnecting profitability from sales volume entirely. However, these models could disincentives private stakeholders to invest in R&D and only function were the market fails i.e., for the development of novel antibiotics.

HTA is the fourth hurdle manufactures face in bringing innovative medicines to patients. In this thesis the delay and access and possible consequences for patients have been addressed. All stakeholders agree on the importance of broad and equitable patient access, however, differ in the approach needed to achieve this goal. The speed at which patients gain access is partly the result of deliberate policies, that try to ensure sustainability within the healthcare system. Germany has different policies when it comes to innovative medicines, granting access to patient directly after marketing authorization by the EMA. However, Germany spends 13.9% of healthcare spending on pharmaceuticals, which is considerably higher than the Netherlands (8%) [7]. Between 2006 and 2012 the Netherlands provided the possibility for quick but conditional access to "expensive" hospital drugs. The conditional financing (CF) required 4-year coverage with evidence development (CED). Although the policy made quick access possible to patients, the implementation of CEDs remained challenging in both procedural and methodological aspects [295]. Policies aimed at ensuring the sustainability of healthcare systems must continually adapt to effectively address the dynamic and evolving innovation landscape.

New complex therapies i.e., cell and gene therapies might require new models to enable reimbursement. If prices are deemed too high, considering uncertainties around their effectiveness, payers might propose payment if performances target are met. Recently this strategy has been adopted for the reimbursement of atidarsagene autotemcel treating the rare disease MLD, namely, payment is conditional on positive response after administration of the therapy [312,318].

Inevitably, choices in policy making will affect both patient access and the healthcare expenditure.

Challenges for future research

This thesis contributed to the scientific evidence base on patient access, costs in reimbursing new innovative therapies, the application of cost-based pricing for orphan drugs and immune-oncological medicines subject to indication broadening and lastly the performance of managed entry agreements in the Netherlands. However, important challenges and possible research opportunities remain.

Quick and affordable patient access to innovative medicines remains an issue in many countries, the Netherlands is no exception. We have shown that access disparities can be caused by various policies, some at supranational level but also at member state level. We focused mainly on policies that shape the fourth hurdle, namely HTA and pricing and reimbursement policies. These policies aim at decerning valuable innovative treatments, and the equilibrium needed between promoting innovation and the sustainability of healthcare systems. Future research endeavors could center on constructing a comprehensive framework or modular components that harmonize both affordability and sustainability, with the aim to promote equitable access while concurrently bolstering competitiveness and investment attractiveness [319]. More research is especially needed in the pricing of innovative treatments, since this component has been recognized as a bottleneck for patient access [320,321]. Moreover, future research could investigate the effect of joint pricing and reimbursement practice around the EU member states.

In the last chapter of this thesis, we investigated the performance or managed entry agreements in the Netherlands. However, the selected case study represents merely one instance among the myriad of managed entry agreements. Consequently, future research endeavors could delve into alternative agreements i.e., performance-based agreements or other types of finical based agreements. Additionally, investigating agreements with varying lifespans and assessing the impact of cyclic reevaluation on these agreements would be valuable areas of exploration.

In 2021 the European Parliament (EP) passed regulation 2021/2282 (amending directive 2011/24/EU) resulting in the upcoming introduction of the Joint Clinical Assessment (JCA) which aims to harmonize the clinical assessment across member states and country specific HTA bodies [322]. The JCA –which is projected to start in 2025– is intended to streamline processes with a single submission of data to evaluate relative effectiveness and safety. This could result in opportunities for both member states and pharmaceutical companies to efficiently bring their innovations to the EU market. After the introduction of the JCA, the introduced policies and effect on patient access should be investigated.

Disparities in patient access amongst EU member states should be reduced, but other parts of the world have in some cases no access at all, due to their economic and political situation. The World health Organization (WHO) has shown initiative by organizing the 'Fair pricing forum' and following the resolution adopted by the World Health Assembly

in 2019 namely WHA72.8 stating the need for: "Improving the transparency of markets for medicines, vaccines, and other health products" [323,324]. However, transparency is not yet achieved within the pharmaceutical market. Hence, further exploration is needed to gain better insights into the processes involved in bringing medicines to the market and the requisite investments. These data have the potential to stimulate discussions regarding pharmaceutical pricing and can serve as valuable inputs for refining cost-based pricing models, thereby enhancing their accuracy. Nevertheless, it falls upon policy makers and payers to employ the aforementioned information to attain appropriate pricing for innovative medicines.

Summary

Introduction

In the past decade, life expectancy at birth has been rising, simultaneously health spending has experienced an upward trajectory over the past decade and has been attributed to an ageing population and the introduction of costly new technologies i.e., innovative cancer pharmaceuticals. However, in the Netherlands spending on pharmaceuticals as a percentage of healthcare spending has slightly decreased in the last decade. Nevertheless, there remains a need to allocate resources efficiently within the healthcare sector which is the primary activity of Health Technology Assessment (HTA) research. The pricing and reimbursement decision making varies across countries within the EU and can ultimately impact patient access to novel technologies.

The overall aim of this thesis is to evaluate and describe current patient access to innovative medicines and future challenges with the reimbursement of new technologies and possible strategies for mitigating risks involved with reimbursement. This thesis is structured in four sections. Part A compromises two chapters evaluating patient access and the effect on costs related to novel systematic treatment options. Part B focuses on a new cell therapy in hematology, and the possible economic consequences of reimbursing these new therapies. Part C investigates cost-based pricing models for innovative medicines in rare diseases and those affected by indication broadening. Part D explores the reimbursement of innovative cancer medicines subject to indication broadening, and in specific managed entry agreements as a tool to mitigate risks for payers.

Part A: Access and costs of innovative cancer medicines

Part A compromises two chapters namely: the current state of access to innovative cancer medicines in the EU and real-world costing of CRPC care in the Netherlands. In the first chapter we explored delayed patient access with the focus on three areas namely: regulatory approval times, time-to-market and speed of uptake after first uptake. Retrospective sales data was utilized as a proxy for patient access, as it is unlikely countries would stockpile these innovative medicines. The average time needed for regulatory approval was 181 days (range 78–303 days) in the US (FDA) vs. 378 days (range 262-483 days) in EU (EMA). The average difference in days between FDA and EMA regulatory approval was 242 days. The time-to market (TTM) was defined as the number of days between EMA approval and first uptake in a member state. The average TTM in Europe amounted to 398 days (range 17-1187). Countries with low TTM i.e. Germany the UK and Austria averaged 17, 22 and 31 days, respectively. The Netherlands TTM is lower than the EU average in our analysis, namely 128 days, however still much higher than neighboring country Germany. The countries with the longest TTM were mostly Eastern European countries and Greece. The TTM in Belgium was relatively high compared with neighboring countries, namely 392 days. However, when raking countries based on their speed of uptake Belgium came first followed by Switzerland, France Austria and Germany. The Netherlands ranked 9th and is

therefore outperformed by all direct neighbors. Delayed access to new effective medicines may result in diminished patient benefits. As an example, the delayed access to ipilimumab and abiraterone in the first year after marketing approval resulted in a potential loss of life years of 3,448 and 18,152 years respectively.

In the second chapter we explored the real-world costs of treating castration resistant prostate cancer (CRPC) patients in the Netherlands. Retrospective individual patient data (IPD) from the Dutch CAPRI-registry was utilized. Patients included in the analysis (n=1,937) had to receive at least one life-prolonging drug (LPD) and be diagnosed between 2010 – 2015. A total of 1,937 patients were included in the study. Mean total costs were €67,174. On average, patients received 2.7 lines of systemic treatment. Costs of systemic treatment accounted for 59% of the total costs. Mean total costs stratified by treatment line were the highest for second-line treatment: €34,452, but third-line treatment accounted for the highest mean costs per month: €6,841. Mean total costs per treatment were the highest for enzalutamide (€43,030) and cabazitaxel accounted for the highest monthly costs per treatment (€7,732). The real-world costs of patients with CRPC is mainly driven by costs associated with systemic treatment. The monthly treatment costs increase with each subsequent systemic treatment administered. Therefore, it is of importance to assess the additional costs versus the additional benefits of new treatments.

Part B: Economic ramifications of new therapies in hematology

Since 2018, 2 chimeric antigen receptor (CAR) T-cell therapies received approval from the European Medicine Agency, with list prices around €320,000 per treatment. We aimed to estimate the costs and budget impact associated with CAR T-cell therapies for current and future indications in hematological cancers from 2019 to 2029. We focused on the former France, Germany, Spain, Italy and the United Kingdom (EU-5) and the Netherlands. We conducted a review of list prices, health technology assessment reports, budget impact analysis dossiers, and published cost-effectiveness analyses. We forecasted the 10-year health expenditures on CAR T-cells for several hematological cancers in selected European Union countries. Nine cost-effectiveness studies were identified and list prices for CAR T-cell therapies ranged between €307,200 and €350,000. Estimated additional costs for pre- and post-treatment were €50,359 per patient, whereas the incremental costs of CAR T-cell therapy (when compared with care as usual) ranged between €276,086 and €328,727. We estimated market entry of CAR T-cell therapies for chronic mantle cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, multiple myeloma, and acute myeloid leukemia in 2021, 2022, 2022, 2022, and 2025, respectively. Cumulative expenditure estimates for existing and future indications from 2019 to 2029 were on average €28.5 billion, €32.8 billion, and €28.9 billion when considering CAR T-cell therapy costs only, CAR T-cell therapy costs including pre- and post-treatment, and incremental CAR T-cell therapy costs, respectively. CAR T-cell therapies seem to be promising treatment options for hematological cancers but the financial burden on healthcare systems in the former

EU-5 and the Netherlands will contribute to a substantial rise in healthcare expenditure in the field of hematology.

Part C: Cost-based pricing models

Drug prices are regarded as one of the most influential factors in determining accessibility and affordability to novel therapies. Part C consist of two chapters, exploring cost-based pricing in both treatments for rare diseases and imuno-oncological treatments subject to indication broadening. The aim of the first study was to use a recently published cost-based pricing model –proposed by Uyl-de Groot and Löwenberg– to calculate prices for cell and gene therapies, with OTL-200 and AVXS-101 as case study examples. The inputs needed were (i) research and development (R&D) expenses adjusted for risk of failure and cost of capital, (ii) the eligible patient population and (iii) costs of drug manufacturing to calculate a base-case price for OTL-200 and AVXS-101. All model input parameters were varied in a stepwise, deterministic sensitivity analysis and scenario analyses to assess their impact on the calculated prices. Prices for OTL-200 and AVXS-101 were estimated at €1,048,138 and €380,444 per treatment, respectively. In deterministic sensitivity analyses, varying R&D estimates had the greatest impact on the price for OTL-200, whereas for AVXS-101, changes in the profit margin changed the calculated price substantially. Highest prices in scenario analyses were achieved when assuming the lowest number of patients for OTL-200 and highest R&D expenses for AVXS-101. The lowest R&D expenses scenario resulted in lowest prices for either therapy.

Our results show that, using the proposed model, prices for both OTL-200 and AVXS-101 lie substantially below the currently (proposed) list prices for both therapies. Nevertheless, the uncertainty of the used model input parameters is considerable, which translates in a wide range of estimated prices. This is mainly because of a lack of transparency from pharmaceutical companies regarding R&D expenses and the costs of drug manufacturing. Simultaneously, the disease indications for both therapies remain heavily understudied in terms of their epidemiological profile. Despite the considerable variation in the estimated prices, our results may support the public debate on value-based and cost-based pricing models, and on “fair” drug prices in general.

As aforementioned the second chapter within Part C explored the use of a cost-based pricing algorithm for imuno-oncological treatments subject to indication broadening. Chapter 6 takes pembrolizumab (Keytruda) and daratumumab (Darzalex) as case study, to explore the potential effect of indication broadening on the estimated price when using the cost-based pricing (CBP) model proposed by Uyl-de Groot and Löwenberg. The model was adapted to calculate cumulative yearly prices, cumulative prices per indication, and non-cumulative indication-based prices using inputs such as research and development (R&D) costs, manufacturing costs, eligible patient population, and a profit margin. Sensitivy of inputs was examined with a deterministic stepwise analysis and scenario analysis. The yearly cumulative cost-based prices ranged between €52 to €885 for pembrolizumab per

vial (25mg/ml containing 4ml) and €823 to €31,941 for daratumumab per vial (120mg/ml containing 15ml). Prices were higher in initial years or indications due to smaller patient populations, decreased over time or after additional indications. Determinstic stepwise sensitivity analysis showed that the number of eligible patients had the most significant impact on the estimated price. In the scenario analysis the profit margin was changed to 76.5% wich resulted in the highrst cost-based prices for both drugs. Lowest estimates in the scenario analysis resulted from impolementing uncapitalized R&D costs. Our results show that estimated cost-based prices are consistently lower than Dutch list prices for pembrolizumab (€2,861), mainly resulting from larger patient populations in registered indications. However, daratumumab's list prices fall within the range of modeled CBPs depending on the year or indication (€4,766). Both calculated cost-based prices decrease over time or with additional indications. The number of eligible patients and initial R&D costs have the most significant influence on the obtained prices. Therefore, underlying the importance of transparancy needed to correctly estimate inputs utilized in the algorithm. These findings contribute to the ongoing discussions on pharmaceutical pricing of innovative cancer medicines, specifically if indications are expending.

Part D: Strategies to mitigate risks in reimbursement

Part D consist of the last chapter namely addressing market entry agreements (MEAs) for innovative pharmaceuticals subject to indication broadening, and the general discussion of this thesis. MEAs and especially financial based agreements are commonly used in European countries for innovative cancer pharmaceuticals and facilitate access to innovative treatments while mitigating financial risks for payers. This chapter focuses on the confidential price agreement made by the Dutch government for the reimbursement of pembrolizumab, the implications of broadening indications on cost-effectiveness, and the viability or desirability of said agreement. To tests this hypothesis we selected five indications where pembrolizumab was deemed effective and developed portioned survival models for each indication. Survival and progression-free survival data from the published trials were utilized to recreate individual patient data and extrapolated –using parametric models– to a time-horizon of 30 years. If necessary overall survival was corrected for background mortality. Inputs for both quality of life and costs were derived from available literature and were indexed. The incremental cost-effectiveness ratios (ICERs) ranged between €35,313 and €322, 349 per quality-adjusted life-year (QALY) depending on the indication. The highest incremental effects, namely 2.38 QALY, and lowest ICERs were found in the PD-L1 positive non-small cell lung cancer (NSCLC) indication. At list price only one indication fell under the €80,000 cost-effectiveness threshold. When applying the average reported discount on intramural pharmaceuticals in the Netherlands (33.6%), ICERs ranged between €20,881 and €252,934 per QALY gained, and the €80,000 threshold was met in three indications out of five, namely melanoma, NSCLC and head and neck squamous cell carcinoma. In both advanced NSCLC and advanced renal-cell carcinoma (RCC) indications remained above previously mentioned threshold, namely with ICERs of €112,323 and €252,934 respectively. In conclusion, pembrolizumab is cost-effective in one

of the selected indications at list price, other indications selected could be cost-effective depending on the confidential price agreement established. However, the possibility of reimbursing not cost-effective care when the price is anchored in one indication remains possible also assuming the average discount achieved in intramural medicines. Indication-based pricing (IBP) could help align value and price for innovative pharmaceuticals that are subject to indication broadening.

Nederlandse samenvatting

Introductie

In het afgelopen decennium is de levensverwachting bij de geboorte gestegen, terwijl de uitgaven voor gezondheidszorg in dezelfde periode een opwaartse trend hebben doorgemaakt. Dit wordt toegeschreven aan een vergrijzende bevolking en de introductie van kostbare nieuwe technologieën, zoals innovatieve kanker geneesmiddelen. In Nederland zijn de uitgaven aan farmaceutische producten als percentage van de totale gezondheidsuitgaven echter licht gedaald in het afgelopen decennium. Desondanks blijft er behoefte aan efficiënte allocatie van middelen binnen de gezondheidssector, wat de belangrijkste activiteit is van Health Technology Assessment (HTA) onderzoek. De besluitvorming over prijsstelling en vergoeding varieert tussen landen binnen de Europese Unie (EU) en kan uiteindelijk invloed hebben op de toegang van patiënten tot nieuwe geneesmiddelen.

Het overkoepelende doel van dit proefschrift is het evalueren en beschrijven van de huidige toegang van patiënten tot innovatieve geneesmiddelen en toekomstige uitdagingen bij de vergoeding van nieuwe technologieën, evenals mogelijke strategieën om financiële risico's bij vergoeding te beperken. Het proefschrift is opgebouwd uit vier delen. Deel A omvat twee hoofdstukken waarin de toegang van patiënten en de effecten op de kosten van nieuwe systematische behandelingsopties worden geëvalueerd. Deel B richt zich op een nieuwe celtherapie in de hematologie en de mogelijke economische gevolgen van vergoeding van deze nieuwe therapieën. Deel C onderzoekt op kosten gebaseerde prijsmodellen voor innovatieve geneesmiddelen bij zeldzame ziekten en bij indicatieverbreding. Deel D verkent de vergoeding van innovatieve kankergeneesmiddelen bij indicatieverbreding, en specifieke overeenkomsten voor pakketbeheer als instrument om risico's voor betalers te beperken.

Deel A: Toegang en kosten tot innovatieve kanker geneesmiddelen

Deel A omvat twee hoofdstukken, namelijk: de huidige stand van zaken met betrekking tot de toegang tot innovatieve kankergeneesmiddelen in de EU en de werkelijke kosten van de zorg voor patiënten met castratieresistente prostaatkanker (CRPC) in Nederland. In het eerste hoofdstuk hebben we vertraagde toegang voor patiënten onderzocht, met de focus op drie gebieden: goedkeuringstijden bij marktautorisatie, de tijd tussen autorisatie en eerste gebruik (time-to-market) en snelheid van adoptie na goedkeuring. Retrospectieve verkoopgegevens werden gebruikt als een proxy voor patiënttoegang, omdat het onwaarschijnlijk is dat landen deze innovatieve geneesmiddelen zouden opslaan. De gemiddelde tijd die nodig was voor marktautorisatie door de Food and drug Agency (FDA) was 181 dagen (bereik 78–303 dagen) in de Verenigde Staten (VS) versus 378 dagen (bereik 262-483 dagen) in de EU door de Europeaan Medicines Agenecy (EMA). Het gemiddelde verschil in dagen tussen FDA- en EMA-autorisatie was 242 dagen. De time-to-market (TTM) werd gedefinieerd als het aantal dagen tussen EMA-goedkeuring en eerste gebruik in een lidstaat. De gemiddelde TTM in Europa bedroeg 398 dagen (bereik

17-1187). Landen met een lage TTM, zoals Duitsland, het Verenigd Koninkrijk en Oostenrijk, hadden respectievelijk gemiddeld 17, 22 en 31 dagen. De TTM in Nederland is lager dan het EU-gemiddelde in onze analyse, namelijk 128 dagen, maar nog steeds veel hoger dan het buurland Duitsland. De landen met de langste TTM waren voornamelijk Oost-Europese landen en Griekenland. De TTM in België was relatief hoog in vergelijking met buurlanden, namelijk 392 dagen. Toch kwam België als eerste uit de bus bij het rangschikken van landen op basis van hun snelheid van adoptie, gevolgd door Zwitserland, Frankrijk, Oostenrijk en Duitsland. Nederland stond op de 9e plaats en wordt dus overtroffen door alle directe buurlanden. Vertraagde toegang tot nieuwe effectieve geneesmiddelen kan leiden tot verminderde patiënten uitkomsten. Als voorbeeld resulteerde de vertraagde toegang tot ipilimumab en abirateron in het eerste jaar na goedkeuring voor een potentieel verlies van levensjaren van respectievelijk 3,448 en 18,152 jaren.

In het tweede hoofdstuk hebben we de werkelijke kosten van de behandeling van patiënten met castratieresistente prostaatkanker (CRPC) in Nederland onderzocht. We gebruikten retrospectieve individuele patiëntgegevens (IPD) uit het Nederlandse CAPRI-register. Patiënten die in de analyse waren opgenomen (n=1.937) moesten ten minste één levensverlengend geneesmiddel (LPD) ontvangen en werden gediagnosticeerd tussen 2010 en 2015. In totaal werden 1.937 patiënten in de studie opgenomen. De gemiddelde totale kosten bedroegen €67.174. Gemiddeld ontvingen patiënten 2.7 lijnen systemische behandeling. De kosten van systemische behandeling vertegenwoordigden 59% van de totale kosten. De gemiddelde totale kosten per behandellijn waren het hoogst voor tweedelijnsbehandeling: €34.452, maar derdelijns behandeling zorgde voor de hoogste gemiddelde kosten per maand: €6.841. De gemiddelde totale kosten per behandeling waren het hoogst voor enzalutamide (€43.030) en cabazitaxel zorgde voor de hoogste maandelijkse kosten per behandeling (€7.732). De werkelijke kosten van patiënten met CRPC worden voornamelijk bepaald door de kosten van systemische behandeling. De maandelijkse behandelingskosten nemen toe bij elke opeenvolgende systemische behandeling die wordt toegediend. Het is daarom belangrijk om de extra kosten af te wegen tegen de extra voordelen van nieuwe behandelingen.

Deel B: Economische gevolgen van nieuwe therapieën in de hematologie

Sinds 2018 hebben twee chimere antigeenreceptor (CAR) T-celtherapieën goedkeuring gekregen van het EMA, met lijstprijzen van ongeveer €320.000 per behandeling. We hebben geprobeerd de kosten en de budgetimpact te schatten van CAR T-celtherapieën voor huidige en toekomstige indicaties bij hematologische kankers van 2019 tot 2029. We hebben ons gericht op Frankrijk, Duitsland, Spanje, Italië en het Verenigd Koninkrijk (EU-5) en Nederland. We hebben een overzicht gemaakt van lijstprijzen, beoordelingsrapporten, dossiers voor budget impactanalyse en gepubliceerde kosteneffectiviteitsanalyses. We hebben de uitgaven voor CAR T-cellen voor verschillende hematologische kankers in geselecteerde Europese landen voor de komende 10 jaar voorspeld. Er werden negen kosteneffectiviteitsstudies geïdentificeerd en de lijstprijzen voor CAR T-celtherapieën varieerden tussen €307.200

en €350.000. Geschatte extra kosten voor pre- en postbehandeling bedroegen €50.359 per patiënt, terwijl de incrementele kosten van CAR T-celtherapie (vergeleken met de gebruikelijke zorg) varieerden tussen €276.086 en €328.727. We schatten dat nieuwe indicaties voor CAR T-celtherapieën in 2021, 2022, 2022, 2022 en 2025 op de markt zullen komen voor chronische mantelcellymfoom, folliculair lymfoom, chronische lymfatische leukemie, multipel myeloom en acute myeloide leukemie, respectievelijk. De cumulatieve uitgavenschattingen voor bestaande en toekomstige indicaties van 2019 tot 2029 bedroegen gemiddeld €28,5 miljard, €32,8 miljard en €28,9 miljard, rekening houdend met alleen de kosten van CAR T-celtherapie, de kosten van CAR T-celtherapie inclusief pre- en postbehandeling, en de incrementele kosten van CAR T-celtherapie, respectievelijk. CAR T-celtherapieën lijken veelbelovende behandelopties voor hematologische kankers, maar de financiële last voor gezondheidssystemen in de voormalige EU-5 en Nederland zal bijdragen aan een aanzienlijke stijging van de uitgaven in de hematologie.

Deel C: Kosten gebaseerde prijsmodellen

De prijzen van geneesmiddelen worden beschouwd als een van de meest invloedrijke factoren bij het bepalen van de toegankelijkheid en betaalbaarheid van nieuwe therapieën. Deel C bestaat uit twee hoofdstukken die kosten gebaseerde prijsmodellen onderzoeken voor zowel behandelingen van zeldzame ziekten als immuno-oncologische behandelingen die onderhevig zijn aan indicatieverbreding. Het doel van de eerste studie was om een recent voorgesteld op kosten gebaseerde prijsmodel (Uyl-de Groot en Löwenberg) te gebruiken, om prijzen te berekenen voor cel- en gentherapieën, met OTL-200 (Libmeldy) en AVXS-101 (Zolgensma) als casestudyvoorbeelden. De benodigde invoergegevens waren (i) onderzoek- en ontwikkelingskosten (R&D) aangepast voor het risico van mislukking en de kapitaalkosten, (ii) de in aanmerking komende patiëntenpopulatie en (iii) de kosten van geneesmiddelenproductie om een op kosten gebaseerde prijs te berekenen voor OTL-200 en AVXS-101. Alle benodigde parameters werden stapsgewijs gevarieerd in een deterministische gevoeligheidsanalyse en scenarioanalyses om hun impact op de berekende prijzen te beoordelen. De prijzen voor OTL-200 en AVXS-101 werden geschat op respectievelijk €1.048.138 en €380.444 per behandeling. In deterministische gevoeligheidsanalyses hadden variaties in R&D-schattingen de grootste invloed op de prijs voor OTL-200, terwijl voor AVXS-101 veranderingen in de winstmarge de berekende prijs aanzienlijk veranderden. De hoogste prijzen in scenarioanalyses werden behaald bij de veronderstelling van het laagste aantal patiënten voor OTL-200 en de hoogste R&D-kosten voor AVXS-101. Het scenario met de laagste R&D-kosten resulteerde in de laagste prijzen voor beide therapieën.

Onze resultaten tonen aan dat, met behulp van het voorgestelde model, de prijzen voor zowel OTL-200 als AVXS-101 aanzienlijk lager liggen dan de momenteel (voorgestelde) lijstprijzen voor beide therapieën. Desondanks is de onzekerheid van de gebruikte parameters aanzienlijk, wat zich vertaalt in een breed scala van geschatte prijzen. Dit komt voornamelijk door een gebrek aan transparantie van farmaceutische bedrijven met

betrekking tot R&D-kosten en de kosten van geneesmiddelenproductie. Tegelijkertijd blijven de ziekte-indicaties voor beide therapieën zwaar onderzocht in termen van hun epidemiologisch profiel. Ondanks de aanzienlijke variatie in de geschatte prijzen kunnen onze resultaten het publieke debat ondersteunen over waarde- en prijsmodellen voor prijsstelling van geneesmiddelen, en over "eerlijke" geneesmiddelenprijzen in het algemeen.

Het tweede hoofdstuk binnen Deel C onderzocht het gebruik van een kosten gebaseerde prijsmodel voor prijsstelling van immuno-oncologische behandelingen die onderhevig zijn aan indicatieverbreding. Hoofdstuk 6 neemt pembrolizumab (Keytruda) en daratumumab (Darzalex) als casestudy om het potentiële effect van indicatieverbreding op de geschatte prijs te onderzoeken bij gebruik van het kosten gebaseerde prijsmodel (CBP) voorgesteld door Uyl-de Groot en Löwenberg. Het model werd aangepast om cumulatieve jaarlijkse prijzen, cumulatieve prijzen per indicatie en niet-cumulatieve indicatie-gebaseerde prijzen te berekenen met behulp van parameters neamelijk, onderzoek- en ontwikkelingskosten (R&D), productiekosten, in aanmerking komende patiëntenpopulatie en een winstmarge. De gevoeligheid van de parameters werd onderzocht met een deterministische stapsgewijze analyse en scenarioanalyse. De jaarlijkse cumulatieve kosten op basis van prijsstelling varieerden tussen €52 en €885 voor pembrolizumab per flacon (25 mg/ml, 4 ml) en €823 tot €31.941 voor daratumumab per flacon (120 mg/ml, 15 ml). De prijzen waren hoger in de beginjaren of indicaties vanwege kleinere patiëntenpopulaties, maar namen af na verloop van tijd of na toevoeging van nieuwe indicaties. De deterministische stapsgewijze gevoeligheidsanalyse toonde aan dat het aantal in aanmerking komende patiënten de grootste invloed had op de geschatte kosten gebaseerde prijs. In de scenarioanalyse werd de winstmarge gewijzigd naar 76,5%, wat resulteerde in de hoogste prijs voor beide geneesmiddelen. De laagste schattingen in de scenarioanalyse werden verwezenlijkt door niet gekapitaliseerde R&D-kosten te implementeren. Onze resultaten tonen aan dat geschatte op kosten gebaseerde prijs consequent lager zijn dan de Nederlandse lijstprijzen voor pembrolizumab (€2.861), voornamelijk als gevolg van grotere patiëntenpopulaties in geregistreerde indicaties. De lijstprijzen van daratumumab (€4.766) vallen echter binnen het bereik van gemodelleerde prijzen, afhankelijk van het jaar of de indicatie. Beide op kosten gebaseerde prijzen nemen af na verloop van tijd of bij toevoeging van extra indicaties. Het aantal in aanmerking komende patiënten en de initiële R&D-kosten hebben de meest significante invloed op de verkregen prijzen. Dit benadrukt het belang van transparantie bij het correct schatten van de gebruikte parameters in het algoritme. Deze bevindingen dragen bij aan de lopende discussies over de farmaceutische prijsstelling van innovatieve kankergeneesmiddelen, met name als het gaat om indicatie-uitbreiding.

Deel D: Strategieën om financiële risico's bij vergoeding te beperken

Deel D bestaat uit het laatste hoofdstuk, waarin wordt ingegaan op markttoetredingsovereenkomsten (MEAs) voor innovatieve geneesmiddelen die onderhevig zijn aan indicatieverbreding, en de algemene discussie van dit proefschrift. MEAs, en met name financiële arrangementen, worden veel gebruikt in Europese landen

voor innovatieve kankermedicijnen en vergemakkelijken de toegang tot innovatieve behandelingen terwijl financiële risico's voor betalers worden beperkt. Dit hoofdstuk richt zich op de vertrouwelijke prijsafspraak die de Nederlandse overheid –specifiek het ministerie voor volksgezondheid welzijn en sport (VWS)– heeft gemaakt voor de vergoeding van pembrolizumab, de implicaties van indicatieverbreding op kosteneffectiviteit, en de levensvatbaarheid of wenselijkheid van deze overeenkomst. Om deze hypothese te testen, hebben we vijf indicaties geselecteerd waarbij pembrolizumab als effectief werd beschouwd en afzonderlijke kosteneffectiviteit modellen ontwikkeld voor elke indicatie. Overlevings- en progressievrije overlevingsgegevens uit gepubliceerde onderzoeken werden gebruikt om individuele patiëntgegevens te reconstrueren en geëxtrapoleerd –met behulp van parametrische modellen– naar een tijdsbestek van 30 jaar. Indien nodig werd de algehele overleving gecorrigeerd voor achtergrondsterfte. Invoergegevens voor zowel kwaliteit van leven als kosten werden afgeleid uit beschikbare literatuur en geïndexeerd. De incrementele kosten-effectiviteitsratio's (ICERs) varieerden tussen €35.313 en €322.349 per kwaliteitsaangepast levensjaar (QALY), afhankelijk van de indicatie. De hoogste incrementele effecten, namelijk 2,38 QALY, en de laagste ICERs werden gevonden bij de PD-L1-positieve niet-kleincellige longkanker (NSCLC) indicatie. Bij de lijstprijzen voldeed slechts één indicatie aan de kosteneffectiviteitsdrempel van €80.000. Bij toepassing van de gemiddelde gerapporteerde korting op intramurale geneesmiddelen in Nederland (33,6%) varieerden de ICERs tussen €20.881 en €252.934 per gewonnen QALY, en de drempel van €80.000 werd gehaald bij drie van de vijf indicaties, namelijk melanoom, NSCLC en plaveiselcelcarcinoom van het hoofd en de nek. In zowel gevorderd NSCLC als gevorderd niercelcarcinoom (RCC) bleven de ICERs boven de eerdergenoemde drempel, namelijk met ICERs van respectievelijk €112.323 en €252.934. Concluderend is pembrolizumab kosteneffectief bij één van de geselecteerde indicaties tegen de lijstprijzen, terwijl andere geselecteerde indicaties kosteneffectief kunnen zijn, afhankelijk van de vertrouwelijke prijsafspraak. De mogelijkheid om niet-kosteneffectieve zorg te vergoeden wanneer de prijs is verankerd in één indicatie blijft echter mogelijk, zelfs als we uitgaan van de gemiddelde korting die wordt bereikt bij intramurale geneesmiddelen. Indicatie-gebaseerde prijsstelling (IBP) kan helpen om waarde en prijs in lijn te brengen voor innovatieve geneesmiddelen die onderhevig zijn aan indicatieverbreding.

PhD portfolio

	Year	ECTS
Courses		
HTA modelling in R	2021	1.4
Elements of Pharmaceutical/Biotech Pricing	2022	0.4
Symposia & congresses		
European Fair Pricing Network conference	2020	1.0
MultiJuse 2	2020	1.0
HollandBio event toegankelijkheid	2020	1.0
ISPOR Europe 2022	2022	1.0
IHRSC event Rotterdam	2023	1.0
PPRI conference	2024	1.0
Teaching activities		
Health Technology Assessment (Master)	2019-2020	0.4
Health Technology Assessment (Master)	2020-2021	0.8
Interprofesioneel onderwijs EMC	2020-2021	0.4
Pharmaceutical Pricing and Market Access (Master)	2020-2021	0.4
Advanced Health Economic Modelling (Master)	2021-2022	0.4
Pharmaceutical Pricing and Market Access (Master)	2021-2022	0.4
Health Technology Assessment (Master)	2021-2022	0.8
Interprofesioneel onderwijs EMC	2021-2022	0.8
Advanced Health Economic Modelling (Master)	2022-2023	0.8
Pharmaceutical Pricing and Market Access (Master)	2022-2023	0.4
Supervision		
Master thesis (1 students)	2019-2020	1.5
Master thesis (2 students)	2020-2021	3.0
Master thesis (3 students)	2021-2022	4.5
Lecturing		
Kwaliteit van Zorg (GW104)	2022-2023	0.8
Presentation		
CBP model presentation	2022-2023	0.8
Total		25.6

List of publications

INCLUDED IN THIS DISSERTATION

Unequal Access to Newly registered Cancer Drugs leads to potential loss of life-years in Europe
Carin A. Uyl-de Groot, Renaud Heine, Marieke Krol, Jaap Verweij. Cancers (2020) 12(8), 2313

Health Economic Aspects of Chimeric Antigen Receptor T-Cell Therapies for Hematological Cancers: Present and Future
Renaud Heine, Frederick W. Thielen, Marc Koopmanschap, Marie José Kersten, Hermann Einsele, Ulrich Jaeger, Pieter Sonneveld, Jorge Sierra, Carin Smand, Carin A. Uyl-de Groot. HemaSphere (2021)5(2):p e524

Towards sustainability and affordability of expensive cell and gene therapies? Applying a cost-based pricing model to estimate prices for Libmeldy and Zolgensma
FW Thielen, RJSD Heine, S van den Berg, RMT ten Ham, CA Uyl-de Groot. Cytotherapy (2022) VOLUME 24, ISSUE 12, P1245-1258

Applying a cost-based pricing model for innovative cancer treatments subject to indication expansion: a case study for pembrolizumab and daratumumab
RJSD Heine, FW Thielen, RHJ Mathijssen, RWF van Leeuwen, MG Franken CA Uyl-de Groot. PLOS ONE (2024) 19(2):e0293264

Market entry agreements for innovative pharmaceuticals subject to indication broadening: a case study for pembrolizumab in the Netherlands
Renaud J.S.D. Heine, MSc, Ron H.J. Mathijssen, PhD, Floor A.J. Verbeek, MSc, Chantal Van Gils, PhD, Carin A. Uyl-de Groot, PhD. Value Health. (2024)

NOT INCLUDED IN THIS DISSERTATION

Variation in the utilization of medical devices across Germany, Italy, and the Netherlands: A multilevel approach
Stefan Rabbe, Meilin Möllenkamp, Benedetta Pongiglione, Hedwig Blommestein, Pim Wetzelaer, Renaud Heine, Jonas Schreyögg, Health Economics (2022) ;31(S1):135-156

Variation in revascularisation use and outcomes of patients in hospital with acute myocardial infarction across six high income countries: cross sectional cohort study
Peter Cram, Laura A Hatfield, Pieter Bakx, Amitava Banerjee, Christina Fu, Michal Gordon, Renaud Heine, Nicole Huang, Dennis Ko, Lisa M Lix, Victor Novack, Laura Pasea, Feng Qiu, Therese A Stukel, Carin Uyl de Groot, Lin Yan, Bruce Landon, BMJ. (2022) 377:e069164

Variation in care for patients presenting with hip fracture in six high-income countries: A cross-sectional cohort study
Nitzan Burrack, Laura A. Hatfield, Pieter Bakx, Amitava Banerjee, Yu-Chin Chen, Christina Fu, Carlos Godoy Junior, Michal Gordon, Renaud Heine, Nicole Huang, Dennis T. Ko, Lisa M. Lix, Victor Novack, Laura Pasea, Feng Qiu, Therese A. Stukel, Carin Uyl-de Groot, Bheeshma Ravi, Saeed Al-Azazi, Gabe Weinreb, Peter Cram, Bruce E. Landon,
Journal of the American Geriatrics Society (2023) 71:3780–3791

Differences in Treatment Patterns and Outcomes of Acute Myocardial Infarction for Low- and High-Income Patients in 6 Countries
Bruce E. Landon, Laura A. Hatfield, Pieter Bakx, Amitava Banerjee, Yu-Chin Chen, Christina Fu, Michal Gordon, Renaud Heine, Nicole Huang, Dennis T. Ko, Lisa M. Lix, Victor Novack, Laura Pasea, Feng Qiu, Therese A. Stukel, Carin Uyl-de Groot, Lin Yan, Gabe Weinreb, Peter Cram, JAMA (2023) Volume:329, Issue:13, Page(s):1088-1097

Sex-Based Disparities in Acute Myocardial Infarction Treatment Patterns and Outcomes in Older Adults Hospitalized Across 6 High-Income Countries: An Analysis from the International Health Systems Research Collaborative
Lu H, Hatfield LA, Al-Azazi S, Bakx P, Banerjee A, Burrack N, Chen YC, Fu C, Gordon M, Heine R, Huang N, Ko DT, Lix LM, Novack V, Pasea L, Qiu F, Stukel TA, Uyl-de Groot C, Weinreb G, Landon BE, Cram P. Circ Cardiovasc Qual Outcomes (2024)

List of abbreviations

ABI	Abiraterone
ADT	Androgen deprivation therapy
AE	Adverse event
AIFA	Italian Medicines Agency
AIM	Association of Mutual Benefit Societies
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ASCO	American Society for Clinical Oncology
AVV	Adeno-associated virus
AVXS	AveXis
BIA	Budget impact analysis
CAB	Cabazitaxel
CAPRI	Castration resistant prostate cancer registry
CAR	Chimeric antigen receptor
CBP	Cost-based pricing
CEA	Cost-effectiveness analysis
CED	Coverage with evidence development
CGTs	Cell- and gene-therapies
CLL	Lymphocytic leukemia
COVID-19	Corona virus disease of 2019
CPI	Consumer price index
CRPC	Castration resistant prostate cancer
CT	Computed tomography
DLBCL	Diffuse large B-cell lymphoma
DOC	Docetaxel
DRG	Decision resources group
DSA	Deterministic sensitivity analysis
EBITDA	Earnings before interest, taxes, depreciation, and amortization
EC	European Commission
ECIS	European Cancer Information System
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
EMA	European Medicines Agency
EML	Essential Medicines List
ENZ	Enzalutamide
EP	European Parliament
ER	Emergency room

ERG	Evidence Review Group
ERP	External reference pricing
ESMO-MCBS	European Society Medical Oncology-Magnitude of Clinical Benefit Scale
EU	European Union
FaAP	Fair and Affordable Pricing
FDA	Food and Drug Administration
FL	Follicular lymphoma
GDP	Gross domestic product
GMP	Good manufacturing practice
GSK	GlaxoSmithKline
HNSCC	Head and neck squamous cell carcinoma
HS	Health-state
HSPC	Hormone sensitive prostate cancer
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
IBCBP	Indication-based cost-based price
IBP	Indication-based pricing
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive care unit
iMTA	Institute for Medical Technology Assessment
IO	Immunu-oncology
IPD	Individual patient data
IPP	Intellectual property protection
IR	Incidence rate
JCA	Joint Clinical Assessment
LDH	Lactase dehydrogenase
LPD	Life-prolonging drug
LY	Life year
MA	Market Authorization
MCDA	Multi criteria decision analyse
MCL	Mantle cell lymphoma
MCRPC	Metastatic castration resistant prostate cancer
MEA	Market entry agreement
MLD	Metachromatic leukodystrophy
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MS	Market share
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NVMO	Dutch Oncology Society
ODTC	Orphan drug tax credits
OECD	Organisation for Economic Co-operation and Development

ORTX	Orchard therapeutics plc
OS	Overall survival
P&R	Pricing and reimbursement
PD-L1	Programmed death-ligand 1
PET/CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal large B-cell lymphoma
PMDA	Pharmaceutical and Medicinal Devices Agency
PRV	Priority review voucher
PSM	Partitioned survival models
QALY	Quality-adjusted life year
R&D	Research and Development
Ra-223	Radium-223
RCC	Renal cell carcinoma
RP	Regulatory protection
S&P 500	Standard & Poor's 500
SARS-CoV-2	Severe acute respiratory syndrome 2
SD	Standard deviation
SEC	Security and exchange commission
SMA	Spinal muscular atrophy
SMN2	Survival of motor neuron 2
STA	Single technology appraisal
SU	Standard units
TFEU	Treaty on the Functioning of the European Union
TGA	Therapeutics Goods Administration
TTD	Time-to-death
TTM	Time-to market
TTP	Time to tumor progression
UK	United Kingdom
UN	United Nation
UN-MDR	United Nations More Developed Regions
US	United States
USD	United States Dollar
VAT	Value-added tax
WHA	World Health Assembly
WHO	World Health Organization
WTP	Willingness to pay

About the author

Renaud Jean Simon David Heine was born on July 24, 1992, in Liège. From a young age, he attended a Dutch school in Maastricht. During high school, his interest in healthcare blossomed following a brief internship at the cardiology ward of the academic hospital in Maastricht. In 2012, he embarked on a bachelor's degree in European Public Health at Maastricht University. Upon graduation, he secured a traineeship at a Public Affairs firm in Brussels, where he primarily focused on antimicrobial resistance.

After gaining insight into European policymaking, he pursued further academic training at Erasmus University in Rotterdam in 2016. Over the next few years, he completed both a master's in Health Economics, Policy and Law, and a master's in Healthcare Management. Subsequently, he worked as a junior researcher at the Erasmus School of Health Policy and Management, which paved the way for his PhD journey in 2020. His research centered on patient access, pharmaceutical pricing, and health technology assessment. Additionally, he contributed to various projects, particularly in Health Systems comparison research with European and international partners.

At the conclusion of his three years as a PhD candidate, he relocated to Munich to finalize his PhD thesis. In 2024, he joined the management team of Lauterbacher Mühle, a cardiac rehabilitation clinic in southern Germany.

Appendices

Appendices Chapter 2

Appendix I Time from drug submission to drug approval by EMA (A) and FDA (B)

A Drug	Date of EMA submission	Start procedure	Rapporteur's first Assessment Report	List of question to the applicant	Answers from the applicant	Outstanding issues	Response to outstanding issues	CHMP positive opinion	Approval	Accelerated assessment (EMA)	Total EMA (in days)
Abiraterone	17-Dec-2010	19-Jan-2011	11-Apr-2011	20-May-2011	17-Jun-2011	n.a.	n.a.	21-Jul-2011	5-Sep-2011	16-Dec-2010	262
Cabazitaxel	20-Apr-2010	26-May-2010	12-Aug-2010	24-Sep-2010	15-Oct-2010	n.a.	n.a.	20-Jan-2011	17-Mar-2011	n.a.	331
Dabrafenib	24-Jul-2012	15-Aug-2012	5-Nov-2012	14-Dec-2012	21-Feb-2013	25-Apr-2013	23-May-2013	27-Jun-2013	26-Aug-2013	n.a.	398
Ipilimumab	5-May-2010	26-May-2010	15-Aug-2010	24-Sep-2010	12-Jan-2011	17-Mar-2011	18-Apr-2011	19-May-2011	12-Jul-2011	n.a.	433
Nivolumab	2-Sep-2014	24-Sep-2014	15-Dec-2014	22-Jan-2015	20-Feb-2015	26-Mar-2015	30-Mar-2015	23-Apr-2015	19-Jun-2015	24-Jul-2014	290
Vemurafenib	4-May-2011	25-May-2011	12-Aug-2011	22-Sep-2011	14-Oct-2011	17-Nov-2011	24-Nov-2011	15-Dec-2011	17-Feb-2012	14-Apr-2011	289
Pertuzumab	1-Dec-2011	21-Dec-2011	14-Mar-2012	20-Apr-2012	17-Aug-2012	18-Oct-2012	12-Nov-2012	13-Dec-2012	4-Mar-2013	n.a.	459
Enzalutamide	26-Jun-2012	15-Aug-2012	2-Nov-2012	14-Dec-2012	16-Jan-2013	21-Mar-2013	25-Mar-2013	25-Apr-2013	21-Jun-2013	n.a.	360
Pembrolizumab	4-Jun-2014	25-Jun-2014	12-Sep-2014	24-Oct-2014	20-Feb-2015	23-Apr-2015	27-Apr-2015	21-May-2015	17-Jul-2015	n.a.	408
Ramucirumab	23-Aug-2013	25-Sep-2013	12-Dec-2013	23-Jan-2014	24-Apr-2014	26-Jun-2014	14-Aug-2014	25-Sep-2014	19-Dec-2014	n.a.	483
Palbociclib	30-Jul-2015	20-Aug-2015	9-Nov-2015	17-Dec-2015	22-Apr-2016	23-Jun-2016	15-Aug-2016	15-Sep-2016	9-Nov-2016	n.a.	468
Ribociclib	5-Sep-2016	29-Sep-2016	20-Dec-2016	26-Jan-2017	17-Feb-2017	21-Apr-2017	22-May-2017	22-Jun-2017	22-Aug-2017	n.a.	351
Average time from submission to approval EMA											378
Average time accelerated assessment EMA											280
Average time no accelerated assessment EMA											410

EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use

B	Date of FDA submission	Date of FDA approval	Priority review (FDA)	Total time FDA (in days)
Abiraterone	20-Dec-2010	28-Apr-2011	Yes	129
Cabazitaxel	31-Mar-2010	17-Jun-2010	Yes	78
Dabrafenib	30-Jul-2012	29-May-2013	No	303
Ipilimumab	10-Jun-2010	15-Mar-2011	No	278
Nivolumab	30-Jul-2014	22-Dec-2014	No	145
Vemurafenib	28-Apr-2011	17-Aug-2011	Yes	111
Pertuzumab	6-Dec-2011	8-Jun-2012	No	185
Enzalutamide	22-May-2012	31-Aug-2012	Yes	101
Pembrolizumab	27-Feb-2014	3-Sep-2014	No	188
Ramucirumab	23-Aug-2013	21-Apr-2014	No	241
Palbociclib	30-Jun-2014	3-Feb-2015	Yes	218
Ribociclib	29-Aug-2016	13-Mar-2017	Yes	196
Average time from submission to approval FDA				181
Average time priority review FDA				139
Average time no priority review FDA				223

FDA: USA Food and Drug Association

Appendix II Time from EMA registration until first uptake per drug per country (in days, 2011–2018)

	Country	Abirate-rone	Cabazi-taxel	Dabra-fenib	Ipili-mumab	Nivolu-mab	Vemura-fenib	Pertuzu-mab	Enzalu-tamide	Pembroli-mumab	Ramuci-mumab	Palboci-clib	Riboci-clib	Average	No Access*
1	Germany	26	0	36	0	12	13	28	0	72	11	0	10	17	0
2	UK	0	15	97	19	12	13	0	0	41	0	0	71	22	0
3	Austria	0	0	67	50	12	13	58	0	72	11	22	71	31	0
4	Sweden	0	0	36	19	12	13	0	26	41	192	0	101	37	0
5	France	0	168	67	0	0	258	272	0	103	39	0		82	1
6	Finland	331	0	67	172	12	13	0	87	72	70	173		91	1
7	Switzerland	26	15	159	80	165	0	0	87	103	314	84	101	95	0
8	Norway	57	0	128	385	74	135	211	26	133	100	0	163	118	0
9	Netherlands**	176	247	53	197	20	135	140	12	116	40	234	163	128	0
10	Portugal	0	0	918	232	43	470	303	57	0	376	84	0	207	0
11	Poland	149	76	674	203	74	166	119	149	407	405	143	222	232	0
12	Slovakia	149	76	67	538	470	0	303	634	72	253	112		243	1
13	Slovenia	270	381	371	172	652	258	423	299	0	436	0	191	288	0
14	Spain	118	76	279	446	196	623	454	452	225	314	357	101	303	0
15	Ireland	149	685	371	172	74	378	89	391	377	131	538		305	1
16	Italy	543	229	432	597	104	470	150	177	194	253	143	405	308	0
17	Hungary	362	1690	340	446	43	13	119	299	256	131	84	375	347	0
18	Belgium	300	350	248	293	256	378	454	422	377	892	387	343	392	0
19	Czech	392		1283		621	409	454	118	225	131	143		420	3
20	Bulgaria	788	838	949		562	288	393	483	256	376	265		520	2
21	Romania	757	1203	674	111	378	105	242	1214	742		296		572	2
22	Croatia	1426	1568	736		348	197	454	695	346	862	387	343	669	1
23	Latvia	1334					1200			285		173		748	8
24	Lithuania	1061	1384	797	1633		500	819		591	405	326		835	3
25	Servia	969	2115	1283			684	576	969	499				1014	5
26	Greece						1018		1548				405	990	9
27	Bosnia			1558			743	546	1610	925				1076	7
28	Estonia	1122	2056	889		682								1187	8
	Average	404	549	484	288	210	315	264	390	251	261	165	192	403	1.9

* Number of countries with no access; ** Data missing for cabazitaxel, enzalutamide, palbociclib, dabrafenib; EMA: European Medicines Agency.

Appendix III Calculation of number of lost life years ipilimumab (A) and abiraterone (B)

A	Number of melanoma deaths in 2012*	Number of patients need ipilimumab (80%)	Perc. patients not treated 1 year after EMA approval	Number of patients not treated	Number of lost life years after EMA approval	Number of lost life years between FDA -EMA approval**	Total number of lost life years due to delay
Austria	385	308	53%	163	50	31	81
Belgium	315	252	89%	225	69	26	95
Bulgaria	161	129	100%	129	40	13	53
Croatia	188	150	100%	150	46	15	62
Czech Republic	463	370	100%	370	114	38	152
Estonia	55	44	100%	44	14	4	18
Finland	222	178	92%	164	50	18	68
France	1853	1482	41%	601	185	150	336
Germany	2705	2164	59%	1278	394	219	613
Hungary	407	325	100%	325	100	33	133
Ireland	216	173	83%	143	44	17	61
Italy	1757	1406	100%	1406	433	143	576
Latvia	77	61	100%	61	19	6	25
Lithuania	104	83	100%	83	26	8	34
Netherlands	887	710	89%	629	194	72	266
Norway	383	306	100%	306	94	31	125
Poland	1564	1251	100%	1248	385	127	512
Portugal	259	207	98%	204	63	21	84
Romania	443	354	41%	146	45	36	81
Serbia	276	221	100%	221	68	22	90
Slovakia	236	189	100%	189	58	19	77
Slovenia	130	104	99%	103	32	11	42

Appendix III Continued

A	Number of melanoma deaths in 2012*	Number of patients need ipilimumab (80%)	Perc. patients not treated 1 year after EMA approval	Number of patients not treated	Number of lost life years after EMA approval	Number of lost life years between FDA -EMA approval**	Total number of lost life years due to delay
Spain	971	777	100%	777	240	79	318
Sweden	569	455	94%	429	132	46	178
Switzerland	399	319	58%	184	57	32	89
United Kingdom	2466	1973	81%	1606	495	200	695
Total/Average	17492	13993	88%	11184	3448	1418	4867

* Source: reference 19; ** Time between FDA and EMA approval of ipilimumab: 120 days; Perc: percentage; EMA: European Medicines Agency; FDA: USA Food and Drug Association.

B	Number of prostate cancer deaths in 2012*	Number of patients need abiraterone (80%)	Perc. patients not treated 1 year after EMA approval	Number of patients not treated	Number of lost life years after EMA approval	Number of lost life years between FDA-EMA approval**	Total number of lost life years due to delay
Austria	1238	990	63%	626	204	115	318
Belgium	1513	1210	96%	1157	376	140	516
Bulgaria	959	767	100%	767	249	89	338
Croatia	780	624	100%	624	203	72	275
Czech Republic	1693	1354	100%	1354	440	157	597
Estonia	268	215	100%	215	70	25	95
Finland	914	731	99%	721	234	85	319
France	9217	7374	75%	5549	1803	854	2657
Germany	12158	9726	78%	7588	2466	1126	3592
Hungary	1285	1028	100%	1028	334	119	453
Ireland	903	723	100%	721	234	84	318
Italy	6502	5202	100%	5202	1691	602	2293

Appendix III Continued

B	Number of prostate cancer deaths in 2012*	Number of patients need abiraterone (80%)	Perc. patients not treated 1 year after EMA approval	Number of patients not treated	Number of lost life years after EMA approval	Number of lost life years between FDA-EMA approval**	Total number of lost life years due to delay
Latvia	400	320	100%	320	104	37	141
Lithuania	598	478	100%	478	155	55	211
Netherlands	3154	2523	89%	2254	733	292	1025
Norway	1263	1010	83%	839	273	117	390
Poland	5475	4380	99%	4358	1416	507	1923
Portugal	1776	1421	99%	1404	456	164	621
Romania	2432	1945	100%	1945	632	225	857
Serbia	1104	883	100%	883	287	102	389
Slovakia	997	798	99%	789	256	92	349
Slovenia	445	356	98%	349	113	41	155
Spain	6266	5012	95%	4755	1545	580	2126
Sweden	2532	2026	89%	1795	583	235	818
Switzerland	1465	1172	80%	938	305	136	440
United Kingdom	12639	10111	91%	9195	2988	1170	4159
Total/Average	77975	62380	94%	55853	18152	7221	25373

* Source: reference 19; ** Time between FDA and EMA approval of abiraterone: 130 days; Perc: percentage; EMA: European Medicines Agency; FDA: USA Food and Drug Association.

Appendices Chapter 4

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 I Reference trial to estimate market entry of future indications

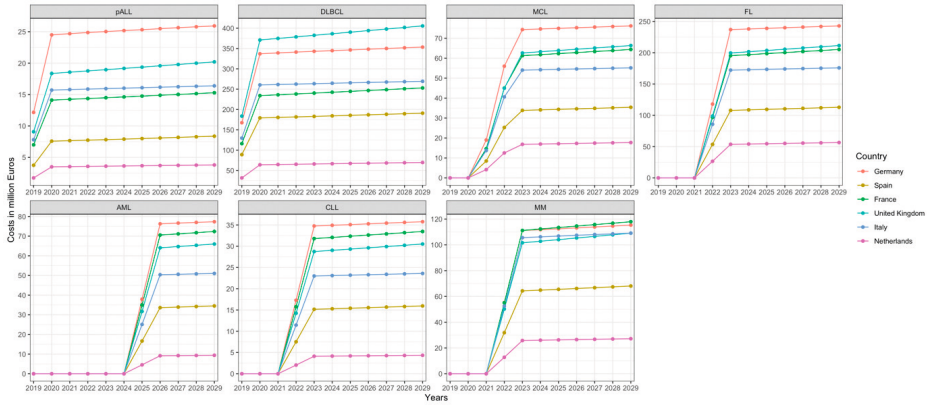
The chosen reference trials to estimate the time of market entry for future CAR T-cell therapy indications are summarized in the table below.

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 II Eligible patient population

Eligible patient population obtained by averaging both Eurostat and Globocan.

Appendix III Forecasted expenditure per indication and country 2019 – 2029



Appendix IV 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 VI 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[140]
	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)[141]
	Mantle cell lymphoma	0.08	Cerhan et al. (2020)[99]
	Follicular lymphoma	0.26	Sandoval-Sus et al.(2017)[100]

Appendix VII 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

Appendix chapter 5.

Estimation of R&D expenses for OTL-200 by Orchard therapeutics plc

An overview of the reported R&D expenses for neurometabolic disorders is presented in Table 3.

Table 3 - Reported expenses for OTL-200 by Orchard therapeutics plc.

Year	Expenses in USD	Expenses in 2020 EUR (converted and indexed)	Source
2018	87,243,000	76,838,072	10-K form 2019
2019	39,042,000	35,317,578	10-K form 2019
2020	17,714,000	15,939,205	10-K form 2020

EUR = Euro (currency); NA = not applicable; R&D = Research and development; USD = United States Dollars

The *2019 10-K* report mentioned a total of nine products in the research pipeline, of which four (25%) targeted neurometabolic disorders.[325] In the *2020 10-K* form, this share rose to six out of twelve (17%) products.[326] These proportions were used to estimate the R&D expenses share of OTL-200 of all neurometabolic disorders. In the absence of information for the years 2017-2019, we assumed the proportion for these years as for the year 2019 (i.e., 25%).

Table 4 summarises the assumed R&D expenses for OTL-200 in the group of neurometabolic disorders.

Table 4 - Estimated R&D expenses for OTL-200 based on SEC filing and share on ORTX's neurometabolic disorder portfolio

Year	Expenses in EUR	Assumed share of OTL-200	Risk rate adjustment	Cost of capital	Expenses adjusted for share, time, risk, and cost of capital
2018[a]	19,209,518	0.25	35.1%	10.5%	15,118,602
2019	35,317,578	0.25	35.1%	10.5%	27,796,242
2020	15,939,205	0.17	35.1%	10.5%	83,63,163

EUR = Euro (currency)

[a] Here we consider only costs for the last quarter (i.e., three months) of the total R&D expenses made in 2018 because ORTX acquired OTL-200 in that time.

Appendix B

Estimation of R&D expenses for AVXS-101 by AveXis

Between 2013 and 2018, AveXis reported total research and development expenses of 2,867,649,241 EUR (including currency conversion, and adjustment for the consumer price index, success rate and cost of capital) in their SEC filings (see Table 5). These costs were used as input for the base-case analysis.

Table 5 – Research and development expenses for AVXS-101 by AveXis

Year	Stated expenses in USD	Expenses in 2020 EUR (corrected for succes rate and including cost of capital)	Clinical phase	Remark	Source
2013	362,609	2,388,304	Pre-clinical		10-K form 2015
2014	13,550,422	168,273,624	Pre-clinical, Phase I	Phase I started in April 2014	10-K form 2015
2015	27,493,460	213,224,709	Phase I		10-K form 2015
2016	58,891,667	456,597,399	Phase I		10-K form 2016
2017	150,391,000	1,513,385,481	Phase I, Phase II	Phase II started in September 2017	10-k form 2017
2018	199,709,000	513,779,724	Phase II		10-Q form ended March 31, 2018

Reported R&D expenses in AveXis' SEC filings were only available until March 31, 2018 because the company entered into an *Agreement and Plan of Merger* with Novartis (see also Section 3.1.2).[158] In addition, reported expenses for the first months of 2018 were rather high and had increased by 179,400,000 USD (approx. 158,004,083 EUR) when compared to the same three months in 2017. This increase was primarily due to 135,200,000 USD (approx. 119,075,541 EUR) of expenses recognised pursuant to licences and agreements with REGENXBIO SMA and Généthon.[158] In addition, R&D expenses increased due to increased spending at the manufacturing facility on materials and supplies, salary and personnel (resulting from increased headcount), process and development (primarily

laboratory testing), non-cash stock-based compensation expenses, fixed asset depreciation, payment made to support third party research, rent expense, utilities, and clinical trials.

For this analysis, R&D expenses were considered up to and including the first of marketing approval of AVXS-101in the US by the FDA in May 2019. Therefore, we extrapolated R&D expenses between the last AveXis SEC filing (i.e. Q-10 in 2018) until May 2019. To this end, we estimated monthly R&D expenses based on the latest available SEC filing of AveXis (i.e. Q-10 in 2018).158 This was necessary because after the merger (with Novartis AG), Novartis AG did not report R&D figures for AVXS-101separately. Monthly R&D expenses were calculated by subtracting the expenses recognised pursuant to the REGENXBIO SMA License and the Généthon agreement described above (i.e. a total of 135,200,000 USD) from the total R&D expenses for the first quarter in 2018 (i.e. 199,709,000 USD) and dividing this by three months. Monthly R&D expenses were hence estimated to be 21,503,000 USD (19,061,008 EUR). Adjusted with a success rate of 83.2% (because AVXS-101 was already in its registrational phase and a yearly cost of capital rate of 10.5%, monthly R&D expenses for this period were 23,101,281 EUR. Multiplied by 14 months, a total of 323,417,940 EUR for the time between March 2018 and May 2019 were added.

Appendix C

Number of patent years left for OTL-200

No reliable figures on IPP could be retrieved for OTL-200. In their SEC filings, ORTX mentioned that they "do not own any patents or patent applications that cover Libmeldy".[194] Eventual IPP rights seem to be covered by license agreements with GSK. The European Union Register of medicinal products for human use states that the orphan market exclusivity for OTL-200 will expire on 18 December 2030.[167]

Number of patent years left for AVXS-101

The number of patent years left for AVXS-101was extracted from the 2020 20-F form to the SEC by Novartis AG. The reported patents can be fully owned, co-owned, or exclusively in-licensed by Novartis AG and relate to at least one dosage strength of AVXS-101, the method of treatment, or its use as it is currently approved and marketed.

The reported data on intellectual property or regulatory protection for AVXS-101 are summarised in Table 6.

Table 6 - Current intellectual property or regulatory protection for AVXS-101 (by Novartis AG)

Type of protection	Year of expiration	Country/region
Patent on vector	2024	US
Patent on vector	2024	US
Patent on vector	2026	US
Patent on method of treatment	2028	US
Patent on method of treatment	2028	US
ODE for SMA	2026	US
RDP	2031	US
Patent on vector	2024	EU
Patent on vector	2028	EU
Patent on method of use	2028	EU
Patent on method of use	2028	EU
ODE for SMA	2030	EU
RDP	2030	EU

EU = European Union; ODE = Orphan drug exclusivity; RDP = Regular data protection; SMA = Spinal muscular atrophy; US = United States

For the base case analysis, we assumed the maximum time for the patent expiration (i.e., the year 2031).

Appendix D

Estimating incidence and prevalence rates

Metachromatic leukodystrophy (MLD)

MLD *incidence* rates (or birth prevalence rates) were reported to be between 1.4 - 1.8 per 100,000.[170,327] For the base-case analysis we assumed an average incidence rate of 1.6 per 100,000. The assumed incident eligible cases over a period of 10 years are summarised in Table 7.

Table 7 - Total assumed eligible incident population for OTL-200

Region	Total eligible patients based on mean	Total eligible patients based on min	Total eligible patients based on max
Europe	378.31	331.02	425.60
Other (more developed)	304.34	266.30	342.39
Total	682.66	597.33	767.99

Spinal muscular atrophy (SMA)

Childhood SMA is categorised into three clinical groups (i.e. Type I to Type III SMA), based on the age of onset and clinical course.[173,174] While SMA can be classified according to these groups, it should be noted that the disorder demonstrates a continuous range of severity.[328]

For this analysis we relied on SMA type specific incidence and prevalence rates summarised in a recent systematic literature review by Verhaart *et al.* (2017).[176]

Current marketing approval for AVXS-101 also involves some stratification of the survival motor neuron (SMN) gene. This is because SMA is caused by homozygous disruption of the SMN gene by deletion, conversion or mutation.[329] The SMN gene is present in multiple copies in the human genome: one SMN1 and several SMN2. In more than 98% of patients with SMA, SMN1 is homozygously disrupted by deletion, rearrangement, or mutation, while at least one copy of SMN2 is typically retained.[330,331]

Of those patients, we assumed that all SMA Type I and Type II patients would be eligible for AVXS-101in the US and Japan. For the region of Europe, we used the definition of the EMA approval in which all SMA Type I patients would be eligible and those SMA Type II patients with up to three copies of the SMN2 gene. The proportion of the latter was based in information provided in Calucho *et al.* (2018) and was 94.66%.[177]

Type I SMA

Included prevalent patients

Since life expectancy of patients with SMA Type I is usually below the age of two years, we used the total prevalent population with SMA Type I to calculate the eligible patient population for the first year of the analysis. The total SMA Type I *prevalent* cases for the first year of the analysis that are considered eligible for AVS-101, are summarised in Table 8. This estimate considers that 98% of SMA cases present with a disrupted SMN1 gene and would therefore be eligible for therapy.[330,331]

Table 8 - Total prevalent SMA Type I cases in the UN 'more developed' region based in mean, min, and max prevalence rates (PR)

SMA	Based on mean PR	Based on min PR	Based on max PR
Type I	2,172	1,249	3,494

Included incident patients

The total SMA Type I *incident* cases were based on all incident cases as from the first year of the analysis until patent expiration of AVS-101. The base-case assumes a patent expiration after 10 years. Based in this, the number of eligible SMA Type I patients are summarised in Table 9. This estimation accounts for 98% of patients presenting with a disrupted SMN1 gene and includes only patients with up to three copies of the SMN2 gene for the region of Europe.

Table 9 - Estimated SMA Type I patients eligible for AVXS-101in 10 years

Region	SMA Type	Based on mean IR	Based on min IR	Based on max IR
Europe	I	4,013	2,503	6,812
Other (more developed)	I	3,229	2,013	5,480

Total included SMA Type I prevalent and incidence patients were thus 9,414 patients, based on the mean reported prevalence and incidence rates over a ten-year period. Based on the minimum and maximum reported prevalence and incidence rates, this were 5,765 and 15,786 patients, respectively over a ten-year period.

Type II SMA

Included prevalent patients

Eligible *prevalent* patients for AVXS-101with SMA Type II were estimated by calculating the SMA Type II prevalent population (taking into account that 98% of the cases present with a disrupted SMN1 gene and only considering those patients with up to three SMN2 copies for the region of Europe) and considering only those 3% that were thought to be below the age of two years. These estimates are presented in Table 10.

Table 10 - Total eligible SMA Type II cases in 10 years, under the age of two years in the UN 'more developed' region based on mean, min, and max prevalence rates (PR)

Region	Based on mean PR	Based on min PR	Based on max PR
Europe	370	119	761
Other (more developed)	275	88	566

Included incident patients

The total eligible *incident* SMA Type II population was based on all incident cases as from the first year of the analysis until patent expiration of AVS-101 (i.e. 10 years). The assumed cases are presented in Table 11.

Table 11 - Estimated SMA Type II patients eligible for AVXS-101

Region	Based on mean IR	Based on min IR	Based on max IR
Europe	1,900	592	3,487
Other (more developed)	1,648	514	3,024

Total included SMA Type I prevalent and incidence patients were thus 4,193 patients, based on the mean reported prevalence and incidence rates over a ten-year period. Based on the minimum and maximum reported prevalence and incidence rates, this were 1,313 and 7,838 patients, respectively over a ten-year period.

In conclusion, the total eligible patient population for AVXS-101for the base-case analysis was 13,607 patients (9,414 for Type I and 4,193 for Type II), based on the mean reported incidence and prevalence rates.

Appendix E

Results of the deterministic sensitivity analysis

Table 12 - Results of the deterministic sensitivity analysis

Therapy	Model input parameter changed	Value in use	Price in EUR	Absolute difference from base-case price in EUR
OTL-200	Cost of research and development	227,778,464	499,221	-548,917
		290,263,583	609,004	-439,134
		352,748,701	718,788	-329,350
		415,233,820	828,571	-219,567
		477,718,938	938,355	-109,783
		873,732,926	1,634,133	585,995
		1,207,261,795	2,220,128	1,171,990
		1,540,790,663	2,806,123	1,757,985
		1,874,319,532	3,392,118	2,343,980
		2,207,848,401	3,978,114	2,929,976
	Number of patients	597	1,184,861	136,723
		614	1,154,454	106,316
		631	1,125,703	77,565
		649	1,098,477	50,339
		666	1,072,657	24,519
		700	1,025,088	-23,050
		717	1,003,131	-45,007
		734	982,192	-65,946
		751	962,200	-85,938
		768	943,093	-105,045
	Cost of drug manufacturing	23,033	985,045	-63,093
		31,122	997,664	-50,474
		39,211	1,010,283	-37,855
		47,299	1,022,901	-25,237
		55,388	1,035,520	-12,618
		67,648	1,054,645	6,507
		71,819	1,061,152	13,014
		75,991	1,067,659	19,521
		80,162	1,074,166	26,028
		84,333	1,080,673	32,535
	Profit margin	0%	873,448	-174,690
		4%	908,386	-139,752
		8%	943,324	-104,814

Table 12 Continued

Therapy	Model input parameter changed	Value in use	Price in EUR	Absolute difference from base-case price in EUR
		12%	978,262	-69,876
		16%	1,013,200	-34,938
		36%	1,187,890	139,752
		52%	1,327,642	279,504
		68%	1,467,393	419,255
		84%	1,607,145	559,007
		100%	1,746,897	698,759
AVXS-101	Cost of research and development	1,624,092,896	242,253	-138,191
		1,937,487,753	269,891	-110,553
		2,250,882,610	297,529	-82,915
		2,564,277,467	325,167	-55,277
		2,877,672,324	352,806	-27,638
		3,344,741,958	393,997	13,553
		3,498,416,734	407,549	27,105
		3,652,091,511	421,102	40,658
		3,805,766,288	434,654	54,210
		3,959,441,065	448,207	67,763
	Number of patients	7,077	640,112	259,668
		8,383	555,815	175,371
		9,689	494,244	113,800
		10,995	447,299	66,855
		12,301	410,322	29,878
		15,611	344,318	-36,126
		17,615	316,412	-64,032
		19,618	294,216	-86,228
		21,622	276,125	-104,319
		23,626	261,103	-119,341
	Cost of drug manufacturing	23,033	317,351	-63,093
		31,122	329,970	-50,474
		39,211	342,588	-37,856
		47,299	355,207	-25,237
		55,388	367,825	-12,619
		67,648	386,951	6,507
		71,819	393,458	13,014
		75,991	399,965	19,521
		80,162	406,472	26,028
		84,333	412,979	32,535

Table 12 Continued

Therapy	Model input parameter changed	Value in use	Price in EUR	Absolute difference from base-case price in EUR
	Profit margin	0%	317,037	-63,407
		4%	329,718	-50,726
		8%	342,400	-38,044
		12%	355,081	-25,363
		16%	367,763	-12,681
		36%	431,170	50,726
		52%	481,896	101,452
		68%	532,622	152,178
		84%	583,348	202,904
		100%	634,073	253,629

Appendix F

Results of the scenario analyses

Table 13 - Results of the scenario analyses for OTL-200 and AVXS-101

Scenario number	Price for OTL-200 in 2020 EUR	Price for AVXS-101 in 2020 EUR
1	499,221	242,253
2	3,978,114	448,207
3	1,184,861	640,112
4	943,093	261,103
5	985,045	317,351
6	1,080,673	840,781
7	873,448	317,037
8	1,541,636	559,570

Appendix G

For both therapies we had estimated R&D expenses for the base-case analysis. For the deterministic sensitivity and scenario analyses, we sought to increase and decrease these base-case estimates to cover a reasonable range of possible R&D values for each therapy separately. To this end, we based the minimum and maximum R&D values of each therapy on the 0.05 and 0.95 percentiles of a truncated normal distribution, respectively.[332]

Due to its symmetrical properties, the normal distribution was suitable because the probability of occurrence of values below and above the assumed mean (in this case the

base-case R&D estimates) was sought to be similar.[332] In addition, truncation allowed limiting R&D expenses to positive values.[332]

The truncated normal distribution was parametrized as follows. For the mean, we used the base-case R&D estimate of each therapy (i.e., different estimate per therapy).

The standard deviation (SD) was assumed to be equal to the SD of the R&D expense range reported by Schlander et al. (i.e., 146 million EUR to 4.11 billion EUR). Since Schlander et al. did not report the SDs for the 45 included unique estimates, we used the improved "range rule of thumb", suggested by Ramírez and Cox.[333]

Lower and upper truncation bounds were based on minimum (i.e., 146 million EUR; 161 million USD) and maximum (i.e., 4.11 billion EUR; 4.54 billion USD) R&D values reported in a recent review.[155]

Consequently, the SD and lower/upper bounds (informed by the literature) were kept constant, while the mean of the truncated normal distribution was depending on the therapy.

These calculations were done using R version 4.2.1 and the R package truncnorm (Version 1.08).

Appendix Chapter 6

Appendix I. All indications approved until 2022 for Pembrolizumab

Indication	Year	Indication description	FDA Date	Trial FDA
1	2014	Advanced or unresectable melanoma who are no longer responding to other drugs.	04/09/2014	KEYNOTE-001
2	2015	Advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1.	02/10/2015	KEYNOTE-001
3	2015	First-line treatment of patients with unresectable or metastatic melanoma.	18/12/2015	Phase 3 trial, KEYNOTE-006
4	2016	Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.	05/08/2016	KEYNOTE-012
5	2016	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] of 50 percent or more), with no EGFR or ALK genomic tumor aberrations.	24/10/2016	phase 3 KEYNOTE-024
6	2017	Adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy.	14/03/2017	KEYNOTE-087
7	2017	Combination with Pemetrexed and Carboplatin, a commonly used chemotherapy regimen, for the first-line treatment of metastatic non-squamous NSCLC, irrespective of PD-L1 expression.	10/05/2017	KEYNOTE-021, Cohort G1
8	2017	Advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy.	18/05/2017	KEYNOTE-052
9	2017	Previously Treated Patients with Recurrent Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer Whose Tumors Express PD-L1.	22/09/2017	KEYNOTE-059
10	2018	Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1.	12/06/2018	KEYNOTE-158 Cohort E
11	2018	Adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after two or more prior lines of therapy.	13/06/2018	KEYNOTE-170
12	2018	Combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.	20/08/2018	Phase 3 KEYNOTE-189
13	2018	Combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC).	30/10/2018	Phase 3 KEYNOTE-407
14	2018	Hepatocellular carcinoma (HCC) previously treated with sorafenib.	09/11/2018	KEYNOTE-224

Appendix I. Continued

Indication	Year	Indication description	FDA Date	Trial FDA
15	2018	Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).	19/12/2018	Phase 2 CITN-09/ KEYNOTE-017
16	2019	Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.	19/02/2019	Phase 3 EORTC1325/ KEYNOTE-054
17	2019	Monotherapy for the first-line treatment of patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1.	11/04/2019	Phase 3 KEYNOTE-042
18	2019	Combination with Inlyta (axitinib), a tyrosine kinase inhibitor, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).	22/04/2019	Phase 3 KEYNOTE-426
19	2019	First-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).	11/06/2019	KEYNOTE-048
20	2019	Monotherapy for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.	18/06/2019	KEYNOTE-158 (cohort G) and KEYNOTE-028 (cohort C1)
21	2019	Monotherapy for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1.	31/07/2019	KEYNOTE-181
22	2019	Combination with Lenvima for advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), patients with disease progression and not candidate for curative surgery or radiation.	17/09/2019	Phase 2 KEYNOTE-146/ Study 111
23	2020	Monotherapy for Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.	08/01/2020	KEYNOTE-057
24*	2020	Additional recommended dosage of 400 mg every six weeks (Q6W) for Keytruda, Merck's anti-PD-1 therapy, across all adult indications, including monotherapy and combination therapy.	28/04/2020	na
25*	2020	Monotherapy for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors.	17/06/2020	KEYNOTE-158
26	2020	Monotherapy for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.	24/06/2020	Phase 2 KEYNOTE-629 trial

Appendix I. Continued

Indication	Year	Indication description	FDA Date	Trial FDA
27	2020	Monotherapy for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.	29/06/2020	KEYNOTE-177
28	2020	Monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).	15/10/2020	Phase 3 KEYNOTE-204
29	2020	Combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10).	13/11/2020	Phase 3 KEYNOTE-355 trial
30	2021	Locally advanced or metastatic esophageal or gastroesophageal junction (GEJ), carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with platinum- and fluoropyrimidine-based chemotherapy.	23/03/2021	Phase 3 KEYNOTE-590
31	2021	Combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.	05/05/2021	Phase 3 KEYNOTE-811 trial
32	2021	Monotherapy for the treatment of patients with locally advanced cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.	06/07/2021	Phase 2 KEYNOTE-629 trial
33	2021	Combination with Lenvima, for advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), with disease progression and not candidate for curative surgery or radiation.	22/07/2021	Phase 3 KEYNOTE-775/ Study 309 trial
34	2021	High-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery.	27/07/2021	Phase 3 KEYNOTE-522 trial
35	2021	Combination with Lenvima, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).	11/08/2021	Phase 3 CLEAR (Study 307)/KEYNOTE-581 trial
36	2021	Combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1).	13/10/2021	Phase 3 KEYNOTE-826
37	2021	Adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.	18/11/2021	Phase 3 KEYNOTE-564 trial

*Indication not included in the CBP model.

Appendix II. All indications approved until 2022 for Daratumumab

Indication	Year	Indication description	Date FDA	Trial FDA
1	2015	Patients with multiple myeloma who have received at least three prior treatments.	16/11/2015	SIRIUS study & GEN501 study
2	2016	Patients with multiple myeloma who have received at least two prior treatments.	20/05/2016**	GEN501 & MMY2002 & MMY1002 & MMY1001 & GEN503
3	2016	Multiple myeloma patients combined with either lenalidomide/bortezomib + dexamethasone, one prior treatment.	21/11/2016	Phase 3 POLLUX & Phase 3 CASTOR
4	2017	Daratumumab + Pomalidomide and Dexamethasone for patients with multiple myeloma who have received at least two prior therapies (including lenalidomide and a proteasome inhibitor).	16/06/2017	Phase I (MMY1001, EQUULEUS)
5	2018	Daratumumab + Bortezomib + Melphalan + Prednisone, newly diagnosed multiple myeloma patient's ineligible for transplant.	07/05/2018	Phase 3 ALCYONE
6*	2019	Split-dosing regimen for Ddaratumumab, option to split the first infusion over two consecutive days.	12/02/2019	Phase 1b EQUULEUS
7	2019	Daratumumab + lenalidomide + dexamethasone, newly diagnosed transplant ineligible	27/06/2019	Phase 3 MAIA
8	2019	Daratumumab + Bortezomib + Thalidomide + Dexamethasone (VTd) for newly diagnosed patients with multiple myeloma who are eligible for ASCT.	26/09/2019	Phase 3 CASSIOPEIA
9*	2020	Subcutaneous formulation Daratumumab.	01/05/2020	Phase 3 COLUMBA
10	2020	Daratumumab + Carfilzomib + Dexamethasone R/R multiple myeloma patients who received three previous lines of therapy.	20/08/2020	Phase 3 CANDOR trial
11	2021	Daratumumab + Pomalidomide + Dexamethasone for adult patients with multiple myeloma who received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory.	20/05/2021**	Phase 3 APOLLO

*Indication not included in the CBP model.
**Date from EMA approval.

Appendix III. Inputs utilized to calculate the patient population for Pembrolizumab

Indication	Incidence crude rate per 100,000	Subtype cancer %	Stage	Percent treated	Patients not in clinical trial %	% PD-L1 expression	Percent expected	MS 2014	MS 2015	MS 2016	MS 2017	MS 2018	MS 2019	MS 2020	MS 2021
1	21.7	1.00	0.23	0.75	0.90	1.00	0.21	0.50	0.33	0.33	0.33	0.33	0.33	0.33	0.33
2	69.5	0.84	0.81	0.75	0.90	0.55	1.00	0.00	0.50	0.50	0.50	0.50	0.50	0.50	0.50
3	21.7	1.00	0.23	0.75	0.90	1.00	1.00	0.00	0.33	0.33	0.33	0.33	0.33	0.33	0.33
4	20.76	1.00	0.37	0.75	0.90	1.00	0.08	0.00	0.00	0.50	0.50	0.50	0.50	0.50	0.50
5	69.5	0.84	0.81	0.75	0.90	0.55	1.00	0.00	0.00	0.50	0.50	0.50	0.50	0.50	0.50
6	2.5	1.00	1.00	0.75	0.90	1.00	0.09	0.00	0.00	0.00	1.00	1.00	1.00	0.50	0.50
7	69.5	0.84	0.81	0.75	0.90	1.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	0.50	0.50
8	26.3	1.00	0.15	0.75	0.90	0.50	1.00	0.00	0.00	0.00	0.50	0.50	0.50	0.50	0.50
9	32.1	1.00	0.29	0.67	0.90	1.00	0.15	0.00	0.00	0.00	1.00	1.00	1.00	1.00	0.50
10	13.3	1.00	1.00	0.75	0.90	1.00	0.03	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
11	19.2	0.03	0.15	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
12	69.5	0.84	0.28	0.60	0.90	1.00	0.18	0.00	0.00	0.00	0.00	1.00	1.00	0.50	0.50
13	69.5	0.84	0.21	0.60	0.90	1.00	0.70	0.00	0.00	0.00	0.00	1.00	1.00	0.50	0.50
14	14.4	0.75	0.09	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.50	0.50	0.33	0.33
15	80.3	1.00	0.00	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
16	21.7	1.00	0.10	0.75	0.90	1.00	0.57	0.00	0.00	0.00	0.00	0.00	0.50	0.50	0.50
17	69.5	0.84	0.81	0.75	0.90	0.55	0.40	0.00	0.00	0.00	0.00	0.00	0.50	0.50	0.50
18	19.3	0.77	0.42	0.75	0.90	1.00	0.50	0.00	0.00	0.00	0.00	0.00	0.33	0.33	0.33
19	20.76	1.00	0.49	0.50	0.90	1.00	0.44	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00
20	69.5	0.16	0.67	0.75	0.90	1.00	0.54	0.00	0.00	0.00	0.00	0.00	1.00	0.50	0.50
21	8	1.00	1.00	0.75	0.90	0.50	1.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.50
22	33.7	1.00	0.01	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00

Appendix III. Continued

Indication	Incidence crude rate per 100,000	Subtype cancer %	Stage	Percent treated	Patients not in clinical trial %	% PD-L1 expression	Percent expected	MS 2014	MS 2015	MS 2016	MS 2017	MS 2018	MS 2019	MS 2020	MS 2021
23	26.3	1.00	0.29	0.75	0.90	0.50	0.50	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00
24*	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
25*	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
26	80.3	0.22	0.04	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00
27	68.1	1.00	0.15	0.75	0.90	1.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.33	0.33
28	2.5	0.95	1.00	0.75	0.90	1.00	0.09	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00
29	142	0.12	0.30	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00
30	8	1.00	1.00	0.75	0.90	1.00	0.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50
31	8	1.00	0.25	0.75	0.90	0.50	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50
32	80.3	0.22	0.05	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
33	33.7	1.00	0.01	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
34	142	0.12	0.60	0.75	0.90	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
35	19.3	0.90	0.36	0.75	0.90	1.00	0.56	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50
36	13.3	1.00	1.00	0.75	0.90	1.00	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
37	19.3	0.90	0.36	0.75	0.90	1.00	0.46	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50

* Indication not included in the CBP model.

Appendix IV. Inputs utilized to calculate the patient population for daratumumab.

Indication	Incidence crude rate per 100,000	Subtype cancer	Symptomatic	Percent treated	Patients not in clinical trial	Percent Line treatment	Percent expected	MS 2015	MS 2016	MS 2017	MS 2018	MS 2019	MS 2020	MS 2021
1	7.6	1.00	0.90	1.00	0.90	0.15	0.13	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	7.6	1.00	0.90	1.00	0.90	0.38	0.07	0.00	1.00	1.00	1.00	1.00	1.00	1.00
3	7.6	1.00	0.90	1.00	0.90	0.61	0.02	0.00	1.00	1.00	1.00	1.00	1.00	1.00
4	7.6	1.00	0.90	1.00	0.90	0.61	0.45	0.00	0.00	1.00	1.00	1.00	1.00	1.00
5	7.6	1.00	0.90	1.00	0.90	1.00	0.07	0.00	0.00	0.00	1.00	1.00	1.00	1.00
6*	na	na	na	na	na	na	na	na	na	na	na	na	na	na
7	7.6	1.00	0.90	1.00	0.90	1.00	0.43	0.00	0.00	0.00	0.00	1.00	1.00	1.00
8	7.6	1.00	0.90	0.95	0.90	1.00	0.48	0.00	0.00	0.00	0.00	1.00	1.00	1.00
9*	na	na	na	na	na	na	na	na	na	na	na	na	na	na
10	7.6	1.00	0.90	1.00	0.90	0.15	0.48	0.00	0.00	0.00	0.00	0.00	1.00	1.00
11	7.6	1.00	0.90	1.00	0.90	0.38	0.48	0.00	0.00	0.00	0.00	0.00	0.00	1.00

Appendix V. Inputs to calculate dosage pembrolizumab

Indication	Median PFS (months)	Confidence interval	Fixed mg dose	Mg per kg	Days between doses	Total dose mg
1	5.5	3.4 - 6.9	0	10	14	8968
2	10.3	6.7 - na	200	0	21	2986
3	5.5	3.4 - 6.9	0	10	14	8968
4	2.1	1.9 - 2.1	0	10	14	3424
5	7.9	na	200	0	21	2290
6	13.6	11.1 - 16.7	200	0	21	3942
7	8.8	7.6 - 9.2	200	0	21	2551
8	2.2	na	200	0	21	638
9	3.0	na	200	0	21	870

Appendix V. Continued

Indication	Median PFS (months)	Confidence interval	Fixed mg dose	Mg per kg	Days between doses	Total dose mg
10	2.1	na	200	0	21	609
11	4.3	2.8 - 13.8	200	0	21	1246
12	9.0	8.1 - 9.9	200	0	21	2609
13	8.0	6.3 - 8.4	200	0	21	2319
14	4.9	3.5 -6.7	200	0	21	1420
15	16.8	4.6 - 43.4	0	2	21	3652
16	8.5	5.7 - 15.2	200	0	21	2464
17	7.1	na	200	0	21	2058
18	15.7	13.6 - 20.2	200	0	21	4551
19	2.3	na	200	0	21	667
20	4.5	4.3 - 5.4	200	0	21	1304
21	2.2	2.1 - 3.2	200	0	21	638
22	7.4	5.3 - 8.7	200	0	21	2145
23	4.2	3.4 - 9.1	200	0	21	1217
24*	na	na	na	na	na	na
25*	na	na	na	na	na	na
26	12.0	na	200	0	21	3478
27	16.5	na	200	0	21	4783
28	13.2	na	200	0	21	3826
29	9.7	na	200	0	21	2812
30	6.3	6.2 - 6.9	200	0	21	1826
31	10.6	na	200	0	21	3073

Appendix V. Continued

Indication	Median PFS (months)	Confidence interval	Fixed mg dose	Mg per kg	Days between doses	Total dose mg
32	12.0	na	200	0	21	3478
33	6.6	na	200	0	21	1913
34	7.5	na	200	0	21	2174
35	23.9	20.8 - 27.7	200	0	21	6928
36	10.4	9.1 - 12.1	200	0	21	3015
37	11.8	na	200	0	21	3412

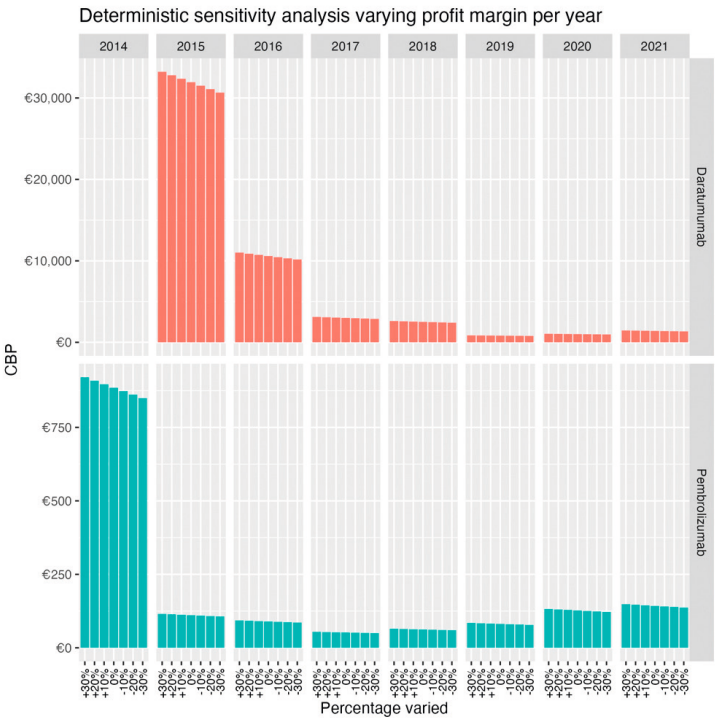
* Indication not included in the CBP model.

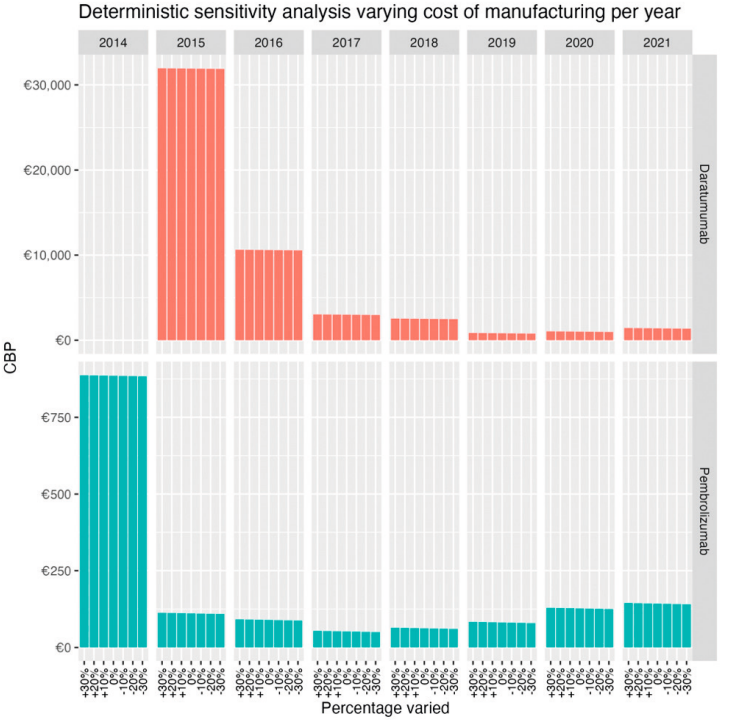
Appendix VI. Inputs to calculate dosage daratumumab

Indication	Median PFS	Confidence interval	Mg per kg	Last dose schedule	Dose schedule I	Dose schedule II	Dose schedule III	Total dose mg
1	4.0	2.8 - 5.6	16	7	na	na	na	20871
2	3.7	2.76 - 4.63	16	7	na	na	na	19045
3	44.5	34.1 - na	16	28	7	14	28	66208
4	8.8	4.6 - 15.4	16	28	7	14	28	19640
5	36.4	32.1 - 45.9	16	28	7	21	28	42084
6*	na	na	na	na	na	na	na	na
7	60.0	54.8 - na	16	28	7	14	28	86235
8	24.0	na	16	56	7	14	56	30053
9*	na	na	na	na	na	na	na	na
10	28.6	22.7 - na	16	28	7	14	28	30123
11	16.9	na	16	28	7	14	28	14861

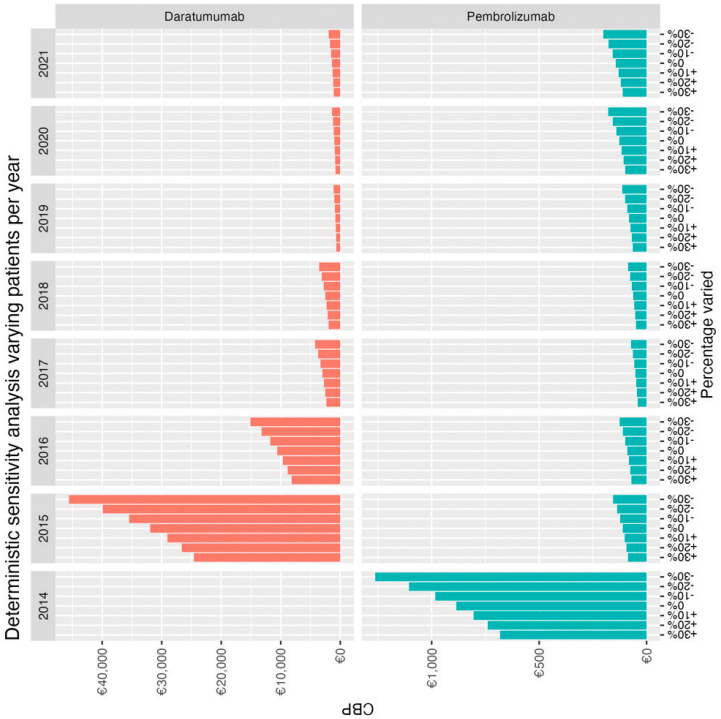
* Indication not included in the CBP model.

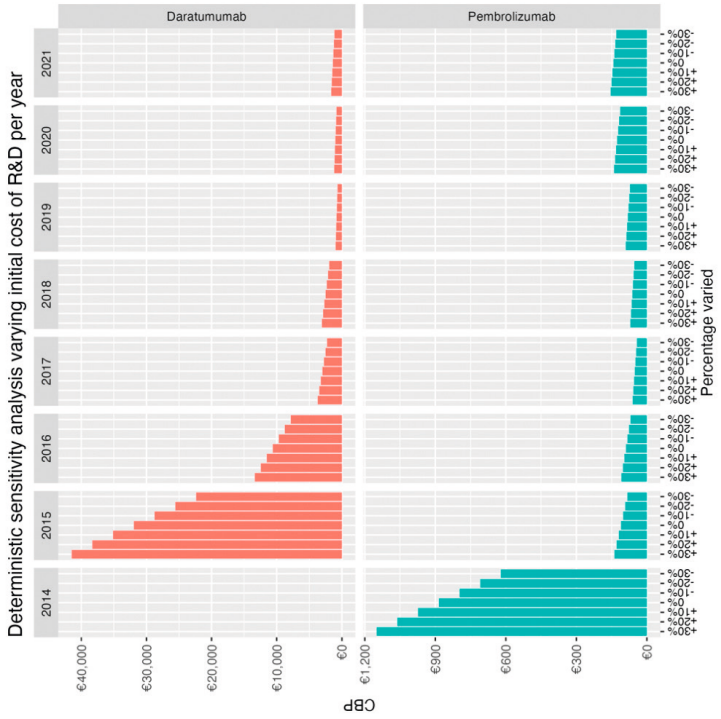
Appendix VII. DSA analysis varying the profit margin and costs associated with manufacturing



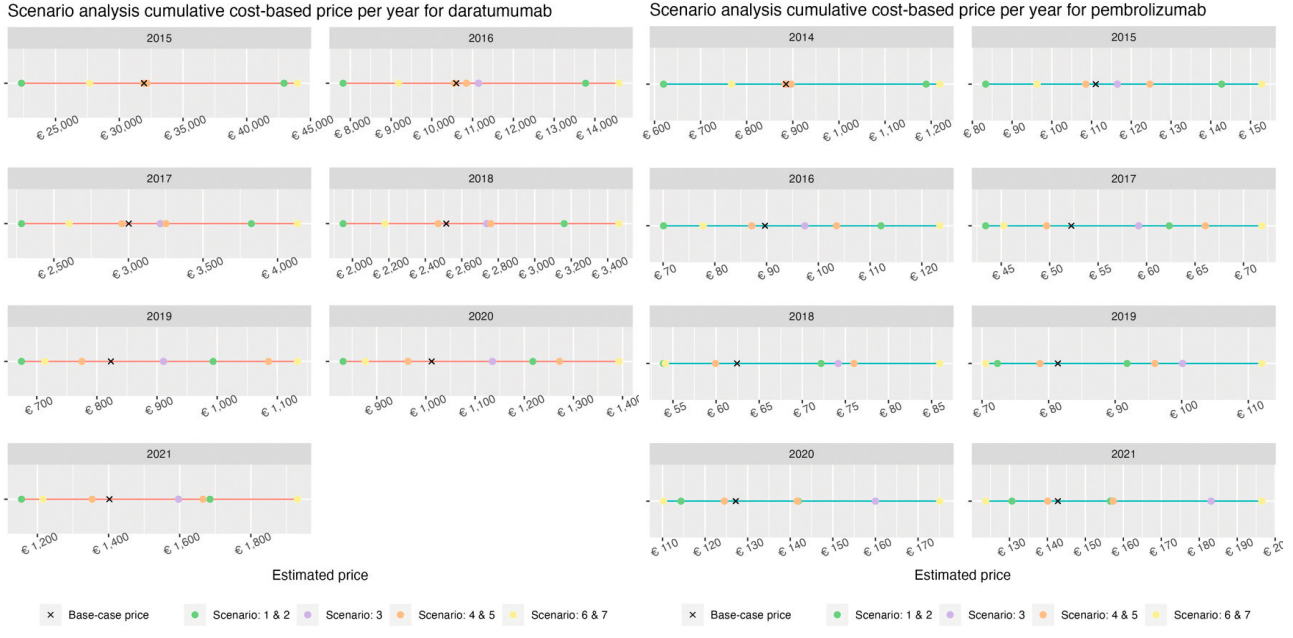


Appendix VIII. DSA analysis varying number of eligible patients and the initial cost of R&D

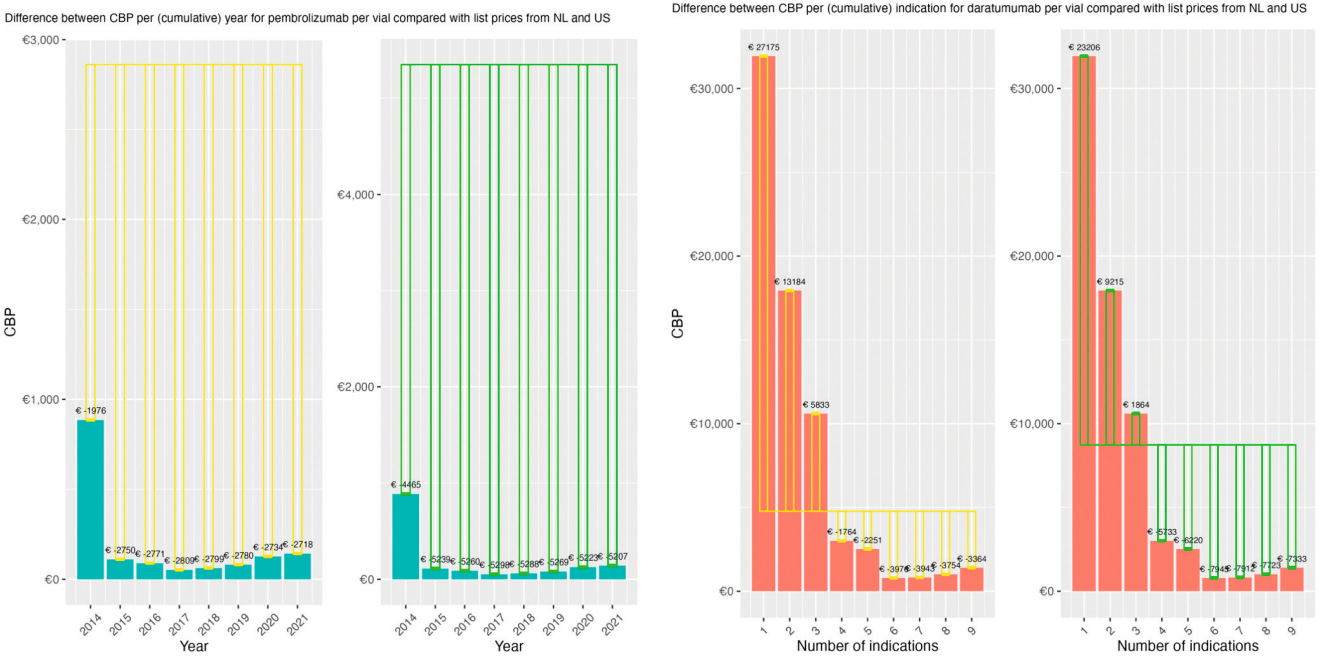




Appendix IX. Scenario analysis for daratumumab & pembrolizumab using a cumulative cost-based price per year per vial.



Appendix X. Difference between CBP for both daratumumab and pembrolizumab with US and Dutch list prices.



Chapter 7 Supplementary material

Appendix I. AIC and BIC values for extrapolation of OS and PFS in all included studies.

Trial	Type	Drug	Model	AIC	BIC
KEYNOTE-006	OS	Ipilimumab	Exponential	1526.727	1530.355
			Weibull (AFT)	1504.100	1511.355
			Gamma	1513.068	1520.323
			log-Normal	1464.556	1471.811
			log-Logistic	1474.482	1481.738
			Gompertz	1452.445	1459.700
		Pembrolizumab	Exponential	3021.700	3026.021
			Weibull (AFT)	3000.724	3009.366
			Gamma	3009.594	3018.236
			log-Normal	2945.656	2954.297
			log-Logistic	2965.605	2974.247
			Gompertz	2938.052	2946.694
	PFS	Ipilimumab	Exponential	1395.423	1399.051
			Weibull (AFT)	1387.969	1395.224
			Gamma	1396.271	1403.526
			log-Normal	1306.403	1313.658
			log-Logistic	1301.662	1308.917
			Gompertz	1337.054	1344.309
		Pembrolizumab	Exponential	3306.424	3310.745
			Weibull (AFT)	3239.470	3248.112
			Gamma	3264.289	3272.931
			log-Normal	3138.446	3147.087
			log-Logistic	3161.823	3170.465
			Gompertz	3146.297	3154.939
KEYNOTE-010	OS	Docetaxel	Exponential	2236.506	2240.344
			Weibull (AFT)	2237.114	2244.790
			Gamma	2238.338	2246.014
			log-Normal	2185.472	2193.147
			log-Logistic	2182.874	2190.549
			Gompertz	2214.311	2221.986
		Pembrolizumab	Exponential	4839.595	4844.132
			Weibull (AFT)	4810.893	4819.966
			Gamma	4825.499	4834.573
			log-Normal	4745.578	4754.651
			log-Logistic	4745.628	4754.701
			Gompertz	4760.376	4769.450

Appendix I. Continued

Trial	Type	Drug	Model	AIC	BIC
	PFS	Docetaxel	Exponential	1848.180	1852.018
			Weibull (AFT)	1850.153	1857.829
			Gamma	1847.849	1855.525
			log-Normal	1786.810	1794.486
			log-Logistic	1795.738	1803.413
			Gompertz	1836.244	1843.919
		Pembrolizumab	Exponential	4369.181	4373.718
			Weibull (AFT)	4198.386	4207.459
			Gamma	4269.062	4278.135
			log-Normal	3989.409	3998.482
			log-Logistic	3991.962	4001.036
			Gompertz	4044.159	4053.233
KEYNOTE-24	OS	Five platinum based chemotherapy*	Exponential	599.568	602.585
			Weibull (AFT)	601.241	607.275
			Gamma	601.521	607.556
			log-Normal	593.512	599.546
			log-Logistic	596.317	602.352
			Gompertz	597.991	604.025
		Pembrolizumab	Exponential	669.169	672.206
			Weibull (AFT)	668.774	674.848
			Gamma	669.519	675.593
			log-Normal	663.332	669.406
			log-Logistic	665.274	671.348
			Gompertz	663.465	669.539
	PFS	Five platinum based chemotherapy*	Exponential	695.728	698.745
			Weibull (AFT)	682.244	688.278
			Gamma	679.794	685.828
			log-Normal	677.976	684.011
			log-Logistic	681.364	687.398
			Gompertz	690.498	696.533
		Pembrolizumab	Exponential	554.127	557.164
			Weibull (AFT)	554.940	561.014
			Gamma	555.669	561.743
			log-Normal	543.701	549.775
			log-Logistic	549.002	555.076
			Gompertz	549.213	555.287
KEYNOTE-048	OS	Cetuximab, carboplatin/ cisplatin & 5-fluorouracil	Exponential	1729.609	1733.151

Appendix I. Continued

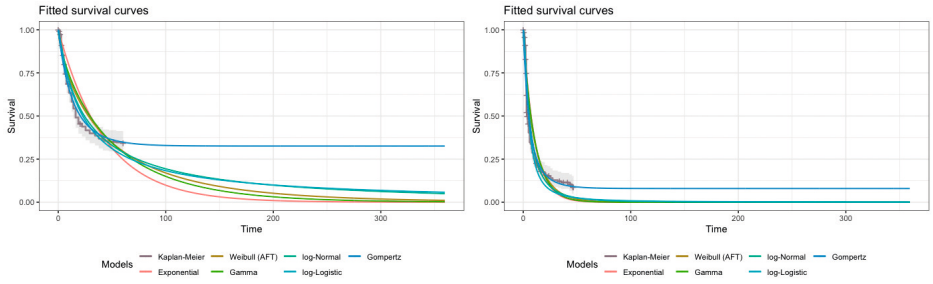
Trial	Type	Drug	Model	AIC	BIC
			Weibull (AFT)	1723.120	1730.202
			Gamma	1718.289	1725.371
			log-Normal	1719.794	1726.877
			log-Logistic	1706.148	1713.230
			Gompertz	1731.550	1738.633
		Pembrolizumab	Exponential	1680.622	1684.171
			Weibull (AFT)	1680.010	1687.108
			Gamma	1681.890	1688.988
			log-Normal	1658.715	1665.813
			log-Logistic	1662.206	1669.304
			Gompertz	1669.194	1676.292
	PFS	Cetuximab, carboplatin/ cisplatin & 5-fluorouracil	Exponential	1697.662	1701.203
			Weibull (AFT)	1687.410	1694.493
			Gamma	1677.963	1685.046
			log-Normal	1665.580	1672.663
			log-Logistic	1650.860	1657.943
			Gompertz	1699.639	1706.722
		Pembrolizumab	Exponential	1597.573	1601.122
			Weibull (AFT)	1594.600	1601.698
			Gamma	1598.697	1605.795
			log-Normal	1552.583	1559.681
			log-Logistic	1551.797	1558.895
			Gompertz	1564.027	1571.125
KEYNOTE-426	OS	Sunitinib	Exponential	1803.525	1807.586
			Weibull (AFT)	1804.719	1812.841
			Gamma	1804.348	1812.471
			log-Normal	1799.346	1807.469
			log-Logistic	1802.728	1810.851
			Gompertz	1805.509	1813.632
		Pembrolizumab + Axitinib	Exponential	1508.835	1512.903
			Weibull (AFT)	1502.154	1510.291
			Gamma	1502.129	1510.266
			log-Normal	1508.852	1516.989
			log-Logistic	1502.207	1510.344
			Gompertz	1504.709	1512.846
	PFS	Sunitinib	Exponential	2099.447	2103.509
			Weibull (AFT)	2099.621	2107.744

Appendix I. Continued

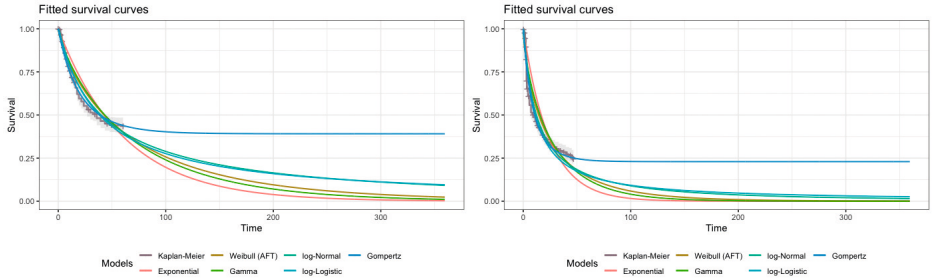
Trial	Type	Drug	Model	AIC	BIC
			Gamma	2096.623	2104.746
			log-Normal	2062.702	2070.824
			log-Logistic	2077.358	2085.481
			Gompertz	2100.380	2108.503
		Pembrolizumab + Axitinib	Exponential	2189.895	2193.963
			Weibull (AFT)	2190.616	2198.753
			Gamma	2188.622	2196.759
			log-Normal	2161.479	2169.616
			log-Logistic	2174.298	2182.435
			Gompertz	2190.797	2198.934

*carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin + gemcitabine, cisplatin plus gemcitabine, or carboplatin + paclitaxel.

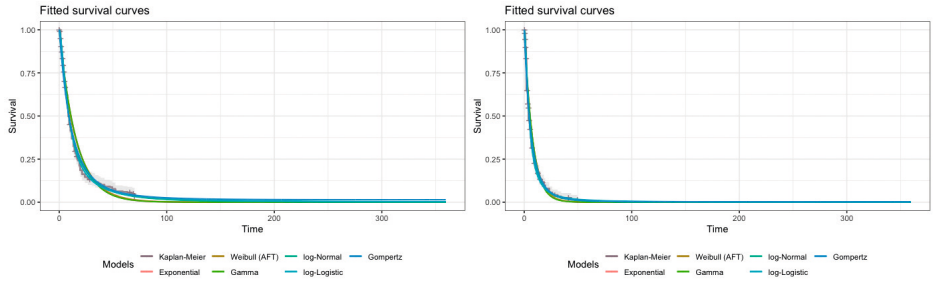
Appendix II. Graphs depicting fitting of parametric models.



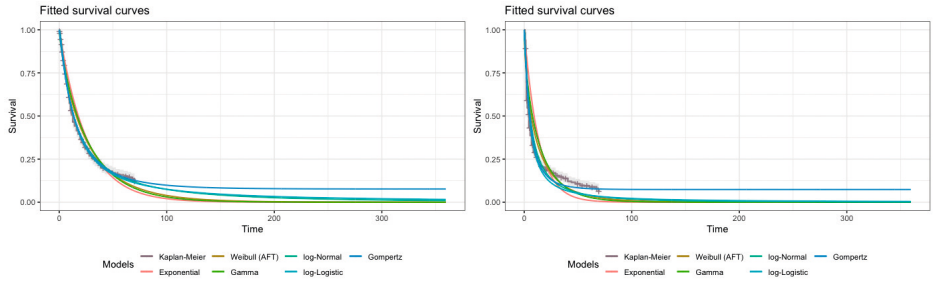
KEYNOTE-006 ipilimumab PFS and OS.



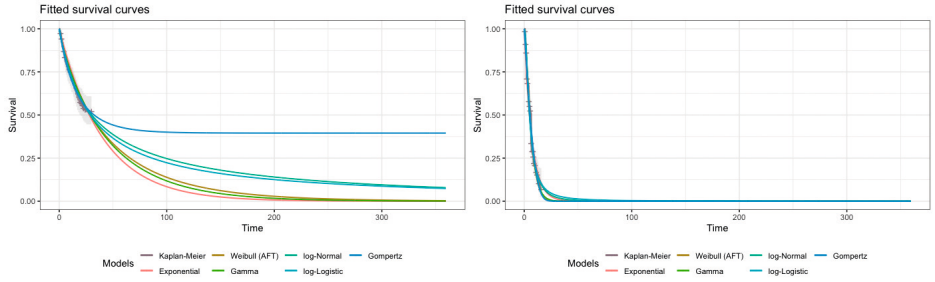
KEYNOTE-006 pembrolizumab PFS and OS.



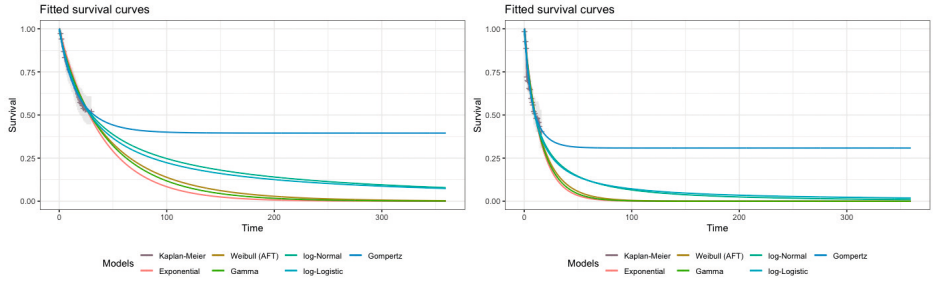
KEYNOTE-010 docetaxel PFS and OS.



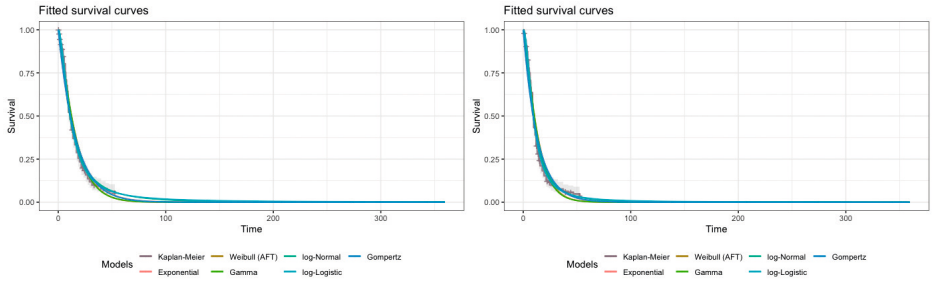
KEYNOTE-010 pembrolizumab PFS and OS.



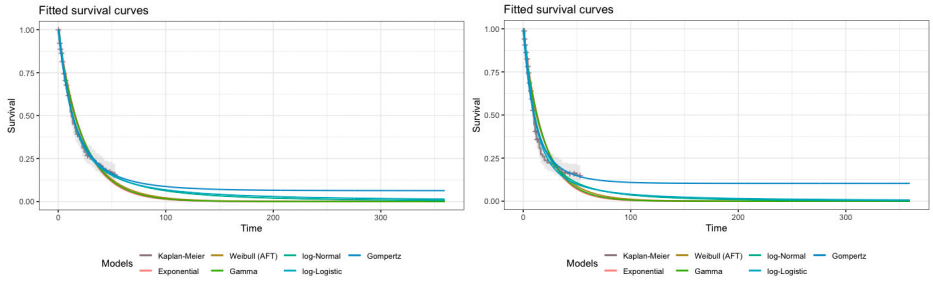
KEYNOTE-024 chemo PFS and OS.



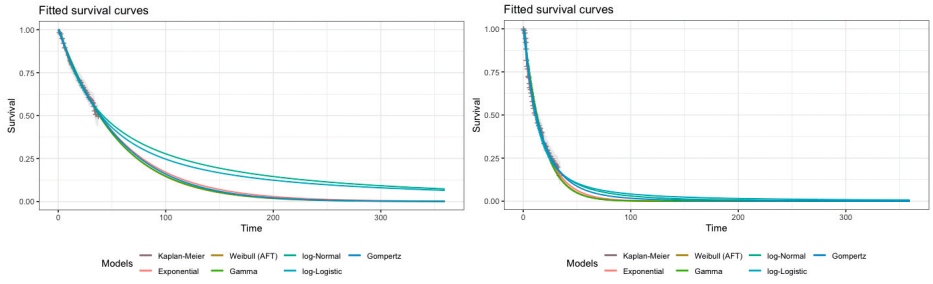
KEYNOTE-024 pembrolizumab PFS and OS.



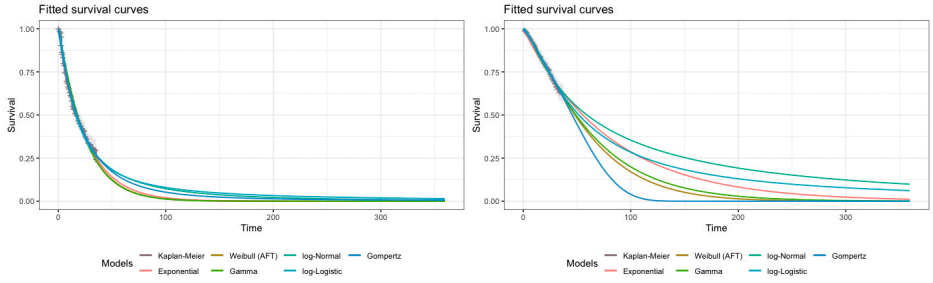
KEYNOTE-048 chemo PFS and OS.



KEYNOTE-048 pembrolizumab PFS and OS.

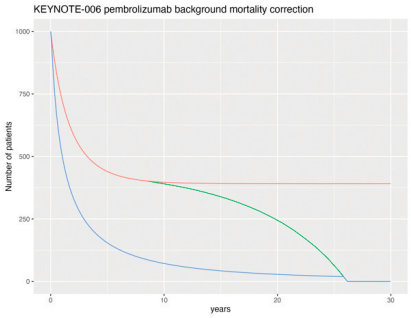


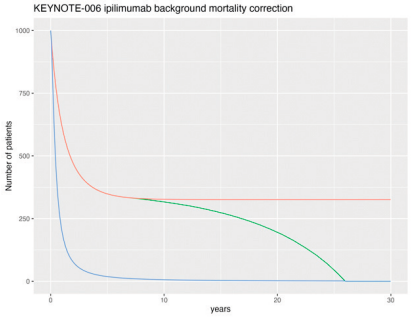
KEYNOTE-426 sunitinib PFS and OS.



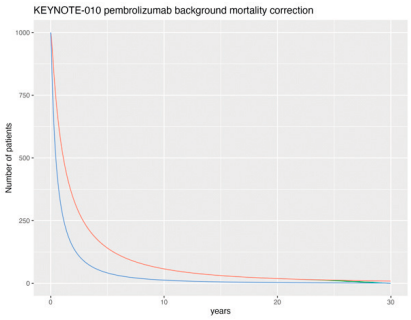
KEYNOTE-426 pembrolizumab + axitinib PFS and OS.

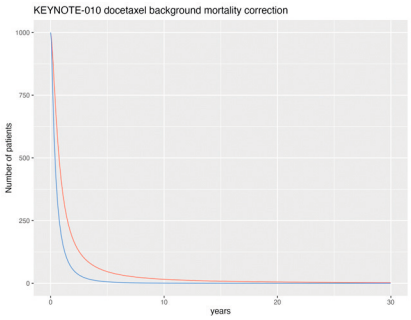
Appendix III. Background mortality correction.



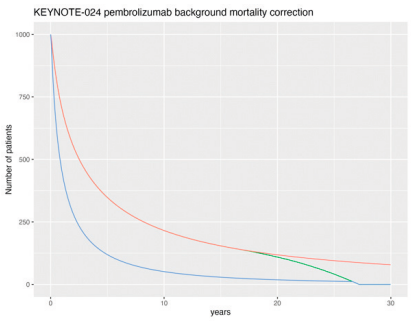


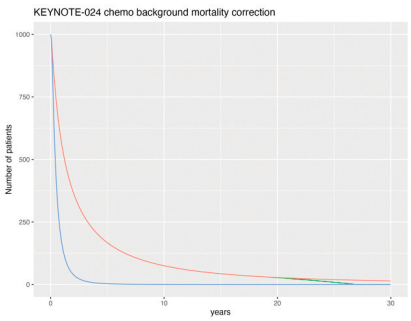
KEYNOTE-006



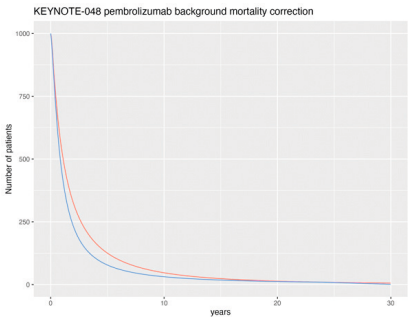


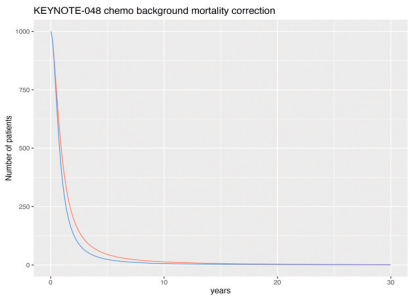
KEYNOTE-010



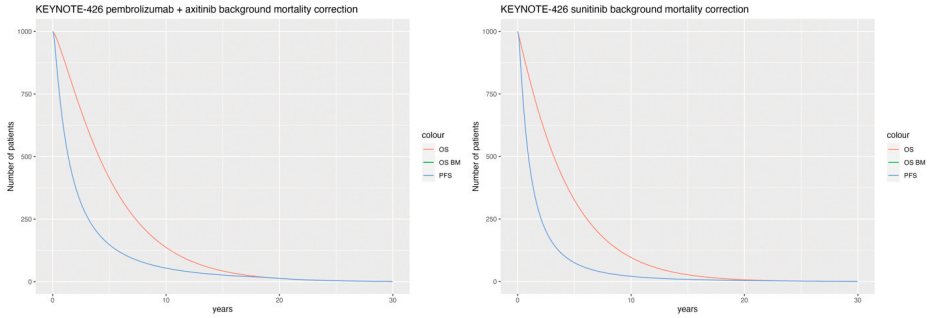


KEYNOTE-024





KEYNOTE-048



KEYNOTE-426

Appendix IV. Main aggregated cost inputs for each model.

Trial	Cost item description	Cost per cycle	Main reference
KEYNOTE-006	Treatment pembrolizumab	€ 24,314.76	medicijnkosten.nl [334]
	Treatment ipilimumab	€ 17,813.25	medicijnkosten.nl [335]
	Healthcare costs PFS pembrolizumab	€ 554.73	Leeneman et al. (2020) [92]
	Healthcare costs PFS ipilimumab	€ 727.66	Leeneman et al. (2020) [92]
	Healthcare costs PD pembrolizumab*	€ 2,414.93	Pakketadvies [251]
	Healthcare costs PD ipilimumab*	€ 4,386.60	Pakketadvies [251]
	End of life costs	€ 1,505.40	Pakketadvies [251]
KEYNOTE-010	Treatment pembrolizumab	€ 13,095.36	medicijnkosten.nl [334]
	Treatment docetaxel	€ 914.01	medicijnkosten.nl [336]
	Healthcare costs PFS pembrolizumab	€ 181.67	Pakketadvies [251]
	Healthcare costs PFS docetaxel	€ 181.67	Pakketadvies [251]
	Healthcare costs PD pembrolizumab*	€ 2,414.93	Pakketadvies [251]
	Healthcare costs PD chemo*	€ 4,386.60	Pakketadvies [251]
	Adverse event costs pembrolizumab	€ 237.38	Pakketadvies [251]
	verse event costs docetaxel	€ 836.87	Pakketadvies [251]
	End of life costs	€ 1,505.40	Pakketadvies [251]
KEYNOTE-024	Treatment pembrolizumab	€ 5,943.96	medicijnkosten.nl [334]
	Treatment Chemo's	€ 2,397.20	medicijnkosten.nl [337]
	Healthcare costs PFS pembrolizumab	€ 181.67	Pakketadvies [251]
	Healthcare costs PFS chemo	€ 181.67	Pakketadvies [251]
	Treatment costs PD pembrolizumab*	€ 5,166.20	Medicijnkosten.nl [338]
	Treatment costs PD chemo*	€ 22,672.47	medicijnkosten.nl [334]
	Healthcare costs PD pembrolizumab*	€ 2,414.93	Pakketadvies [251]
	Healthcare costs PD chemo*	€ 4,386.60	Pakketadvies [251]
	End of life costs	€ 1,505.40	Pakketadvies [251]

Appendix IV. Continued

Trial	Cost item description	Cost per cycle	Main reference
KEYNOTE-048	Treatment pembrolizumab	€ 5,943.96	medicijnkosten.nl [334]
	Treatment Chemo's	€ 1,615.10	medicijnkosten.nl [339]
	Healthcare costs PFS pembrolizumab	€ 4,131.29	Van der linden et al. (2016) [340]
	Healthcare costs PFS chemo	€ 3,305.03	Van der linden et al. (2016) [340]
	Healthcare costs PD pembrolizumab*	€ 2,414.93	Pakketadvies [251]
	Healthcare costs PD chemo*	€ 4,386.60	Pakketadvies [251]
	End of life costs	€ 1,505.40	Pakketadvies [251]
KEYNOTE-426	Treatment pembrolizumab + Axitinib	€ 6,167.66	medicijnkosten.nl [334]
	Treatment Sunitinib	€ 2,392.53	medicijnkosten.nl [341]
	Healthcare costs PFS pembrolizumab	€ 1,587.23	Xander et al. (2023) [291]
	Healthcare costs PFS chemo	€ 1,278.25	Xander et al. (2023) [291]
	Treatment costs PD pembrolizumab*	€ 24,829.95	Xander et al. (2023) [291]
	Treatment costs PD chemo*	€ 37,173.94	Xander et al. (2023) [291]
	Healthcare costs PD pembrolizumab*	€ 1,656.59	Xander et al. (2023) [291]
	Healthcare costs PD chemo*	€ 655.55	Xander et al. (2023) [291]
	End of life costs	€ 14,568.61	Xander et al. (2023) [291]

Progression-free survival (PFS), progressed disease (PD).
*One-off costs

Appendix V. Decomposed ICERs.

Trial / indication	Variable	Pembrolizumab	Comparator	Increment
KEYNOTE-006	Total costs	€499,168.93	€261,766.43	€237,402.49
	Cost treatment PFS	€473,764.56	€247,605.26	€226,159.30
	Cost healthcare PFS	€23,219.89	€10,114.45	€13105.44
	Cost healthcare PD	€1,066.48	€2,857.76	-€1791.29
	Cost end of life	€1,118.00	€1,188.96	-€70.96
	Utility QALYs TTD	8.93	7.39	1.54
	Utility QALYs HS	6.51	5.16	1.34
KEYNOTE-010	Total costs	€176,000.36	€16,781.91	€159,218.45
	Cost treatment PFS	€169,887.72	€10,353.39	€159,534.33
	Cost healthcare PFS	€3,403.32	€2,057.80	€1345.52
	Cost healthcare PD	€1,102.37	€2,107.70	-€1,005.33
	Cost end of life	€1,369.58	€1,426.15	-€56.58
	Cost adverse events	€237.38	€836.87	-€599.49
	Utility QALYs TTD	1.97	1.05	0.92
	Utility QALYs HS	1.84	1.03	0.81
KEYNOTE-024	Total costs	€121,926.61	€38,019.51	€83,907.10
	Cost treatment PFS	€106,035.82	€13,470.61	€92,565.21
	Cost healthcare PFS	€6,329.00	€2,019.11	€4309.89
	Cost healthcare PD	€5,916.55	€21,352.75	-€15,436.20
	Cost end of life	1229.58	1505.09	-275.51
	Utility QALYs TTD	4.63	2.26	2.38
	Utility QALYs HS	3.78	1.94	1.84
KEYNOTE-028	Total costs	€207,070.88	€122,093.91	€84,976.97
	Cost treatment PFS	€105,789.49	€34,288.41	€71,501.08
	Cost healthcare PFS	€97,078.22	€83,248.98	€13,829.24
	Cost healthcare PD	€409.81	€721.64	-€311.83
	Cost end of life	€1,377.71	€1,419.23	-€41.52
	Utility QALYs HS	1.88	1.21	0.67
KEYNOTE-426	Total costs	€373,180.73	€149,414.44	€223,766.29
	Cost treatment PFS	€256,025.16	€46,455.69	€209,569.47
	Cost healthcare PFS	€66,866.30	€37,229.48	€29,636.82
	Cost healthcare PD	€17,318.98	€25,347.31	-€8,028.33
	Cost treatment PD	€14,090.63	€25,658.82	-€11,568.19
	Cost end of life	€13,302.94	€13,764.72	-€461.78
	Cost adverse events	€636.73	€958.42	-€321.69
	Utility QALYs TTD	4.00	3.31	0.69
	Utility QALYs HS	3.58	2.86	0.72

Progression-free survival (PFS), progressed disease (PD), Quality adjusted life-years (QALYs), time-to-death (TTD), health state (HS).

References

1. Health status - Life expectancy at birth - OECD Data. theOECD. Accessed November 20, 2023. http://data.oecd.org/healthstat/life-expectancy-at-birth.htm
2. Gu X, Zheng R, Xia C, et al. Interactions between life expectancy and the incidence and mortality rates of cancer in China: a population-based cluster analysis. *Cancer Commun*. 2018;38(1):1-15. doi:10.1186/s40880-018-0308-x
3. Tanskanen T, Seppä KJM, Virtanen A, Malila NK, Pitkäniemi JM. Cancer Incidence and Mortality in the Oldest Old: A Nationwide Study in Finland. *Am J Epidemiol*. 2021;190(5):836-842. doi:10.1093/aje/kwaa236
4. Cancer today. Accessed January 18, 2022. http://gco.iarc.fr/today/home
5. Netherlands S. 3 in 10 deaths caused by cancer. Statistics Netherlands. Accessed January 18, 2022. https://www.cbs.nl/en-gb/news/2019/27/3-in-10-deaths-caused-by-cancer
6. Health resources - Health spending - OECD Data. theOECD. Accessed November 20, 2023. http://data.oecd.org/healthres/health-spending.htm
7. Health resources - Pharmaceutical spending - OECD Data. theOECD. Accessed November 2, 2023. http://data.oecd.org/healthres/pharmaceutical-spending.htm
8. Sullivan R. The gross imbalances of cancer research must be addressed. *Nature*. 2023;621(7977):S15-S15. doi:10.1038/d41586-023-02609-2
9. McIntosh SA, Alam F, Adams L, et al. Global funding for cancer research between 2016 and 2020: a content analysis of public and philanthropic investments. *Lancet Oncol*. 2023;24(6):636-645. doi:10.1016/S1470-2045(23)00182-1
10. OECD. *Health at a Glance 2021: OECD Indicators*. Organisation for Economic Co-operation and Development; 2021. Accessed December 29, 2023. https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2021_ae3016b9-en
11. Aitken M. The Resilience of R&D: Pharma Posted Record Output in 2021. *Pharm Exec*. 2022;42(3). Accessed December 29, 2023. https://www.pharmexec.com/view/the-resilience-of-r-d-pharma-posted-record-output-in-2021
12. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov*. 2012;11(3):191-200. doi:10.1038/nrd3681
13. Lo AW. Can Financial Economics Cure Cancer? *Atl Econ J*. 2021;49(1):3-21. doi:10.1007/s11293-021-09704-7
14. Heine R, Thielen FW, Koopmanschap M, et al. Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future. *HemaSphere*. 2021;5(2):e524. doi:10.1097/HS9.0000000000000524
15. Scott Morton F, Kyle M. Chapter Twelve - Markets for Pharmaceutical Products11The authors thank Tom McGuire for editorial advice and improvements and participants at the Handbook conference for helpful suggestions. In: Pauly MV, Mcguire TG, Barros PP, eds. *Handbook of Health Economics*. Vol 2. Handbook of Health Economics. Elsevier; 2011:763-823. doi:10.1016/B978-0-444-53592-4.00012-8
16. Boldrin M, Levine DK. The Case against Patents. *J Econ Perspect*. 2013;27(1):3-22. doi:10.1257/jep.27.1.3
17. Fundytus A, Sengar M, Lombe D, et al. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. *Lancet Oncol*. 2021;22(10):1367-1377. doi:10.1016/S1470-2045(21)00463-0
18. Post C, Van Laarhoven HWM, Hollak C. Time to access to novel anticancer drugs in Europe, a case study in seven European countries. *J Clin Oncol*. 2022;40(16_suppl):1586-1586. doi:10.1200/JCO.2022.40.16_suppl.1586
19. Human rights. Accessed December 12, 2023. https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health

20. Bayefsky AF. Office of the United Nations High Commissioner for Human Rights. In: Bayefsky A, ed. *The UN Human Rights Treaty System in the 21 Century*. Brill | Nijhoff; 2000:451-458. doi:10.1163/9789004502758_044
21. *Consolidated Version of the Treaty on the Functioning of the European Union*. Vol 326.; 2012. Accessed December 21, 2023. http://data.europa.eu/eli/treaty/tfeu_2012/oj/eng
22. COM(2007)630 - White paper - Together for Health: A Strategic Approach for the EU 2008-2013 - EU monitor. Accessed December 21, 2023. https://www.eumonitor.eu/9353000/1/j9vvik-7m1c3gyxp/vikqhlwzkwyx
23. Fontrier AM, Visintin E, Kanavos P. Similarities and Differences in Health Technology Assessment Systems and Implications for Coverage Decisions: Evidence from 32 Countries. *PharmacoEconomics Open*. 2021;6(3):315-328. doi:10.1007/s41669-021-00311-5
24. Godman B, Hill A, Simoens S, et al. Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(4):527-540. doi:10.1080/14737167.2021.1884546
25. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1151-1210. doi:10.1016/S0140-6736(17)32152-9
26. Vogler S, Vitry A, Babar ZUD. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. *Lancet Oncol*. 2016;17(1):39-47. doi:10.1016/S1470-2045(15)00449-0
27. Jönsson B, Hofmarcher T, Lindgren P, Wilking N. *Comparator Report on Patient Access to Cancer Medicines in Europe Revisited*.; 2016.
28. Heymach J, Krilov L, Alberg A, et al. Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol*. 2018;36(10):1020-1044. doi:10.1200/JCO.2017.77.0446
29. Wilking N, Jönsson B. A pan-European comparison regarding patient access to cancer drugs. Published online 2005.
30. Costa-Font J, McGuire A, Varol N. Regulation effects on the adoption of new medicines. *Empir Econ*. 2015;49(3):1101-1121. doi:10.1007/s00181-014-0903-x
31. Gann CN, Morsli N, Kaiser R. Industry corner: perspectives and controversies - The challenges of patient access to new medicines. *Ann Oncol*. 2017;28(3):658-663. doi:10.1093/annonc/mdw569
32. World Health Organization. Constitution of the world health organization. Published online 1995.
33. Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Hafizur Rahman M. Poverty and Access to Health Care in Developing Countries. *Ann N Y Acad Sci*. 2008;1136(1):161-171. doi:10.1196/annals.1425.011
34. Campbell SM, Roland MO, Buetow SA. Defining quality of care. *Soc Sci Med*. 2000;51(11):1611-1625. doi:10.1016/S0277-9536(00)00057-5
35. Commissioner O of the. Priority Review. *FDA*. Published online March 11, 2018. Accessed April 4, 2024. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review
36. Accelerated assessment | European Medicines Agency. Accessed April 4, 2024. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/accelerated-assessment
37. Kashoki M, Hanaizi Z, Yordanova S, et al. A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why. *Clin Pharmacol Ther*. 2020;107(1):195-202. doi:10.1002/cpt.1565
38. Danzon PM, Epstein AJ. Effects of Regulation on Drug Launch and Pricing in Interdependent Markets. Published online May 2008. doi:10.3386/w14041
39. Lanjouw JO. Patents, Price Controls, and Access to New Drugs: How Policy Affects Global Market Entry. Published online May 2005. doi:10.3386/w11321
40. Martinalbo J, Bowen D, Camarero J, et al. Early market access of cancer drugs in the EU. *Ann Oncol*. 2016;27(1):96-105. doi:10.1093/annonc/mdv506
41. Uyl-de Groot CA, de Vries EGE, Verweij J, Sullivan R. Dispelling the myths around cancer care delivery: It's not all about costs. *J Cancer Policy*. 2014;2(1):22-29. doi:10.1016/j.jcpo.2014.01.001

42. Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. *Ann Oncol*. 2016;27(8):1423-1443. doi:10.1093/annonc/mdw213
43. MIDAS®. Accessed April 4, 2024. https://www.iqvia.com/solutions/commercialization/brand-strategy-and-management/market-measurement/midas
44. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol*. 2015;26(8):1547-1573. doi:10.1093/annonc/mdv249
45. Database - Eurostat. Accessed April 4, 2024. https://ec.europa.eu/eurostat/web/health/database
46. ESMO. ESMO-MCBS Scorecards. Accessed April 4, 2024. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards
47. Hodi FS, O'day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
48. de Bono Johann S., Logothetis Christopher J., Molina Arturo, et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. *N Engl J Med*. 2011;364(21):1995-2005. doi:10.1056/NEJMoa1014618
49. R&D, Competition and Diffusion of Innovation in the EU: The Case of Hepatitis C - OHE. OHE - Leading intellectual authority on global health economics. Published January 7, 2018. Accessed April 4, 2024. https://www.ohe.org/publications/rd-competition-and-diffusion-innovation-eu-case-hepatitis-c/
50. Frost LJ, Reich MR. Creating Access To Health Technologies In Poor Countries. *Health Aff (Millwood)*. 2009;28(4):962-973. doi:10.1377/hlthaff.28.4.962
51. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. *J Clin Oncol*. 2016;34(24):2925-2934.
52. First Biopharma Product Launch in Europe: How to Succeed. Published September 4, 2018. Accessed April 4, 2024. https://www.lek.com/insights/ei/first-biopharma-product-launch-europe-what-it-takes-succeed
53. Swissmedic 2019 © Copyright. Authorised human medicines with new active substances. Accessed April 4, 2024. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines.html
54. Legemiddelsøk. Legemiddelsøk. Accessed April 4, 2024. https://www.legemiddelsok.no:443/?searchquery=&f=Han;MtI;Vir;ATC;Var;Mar;Mid;Avr;gen;par;&pane=0
55. Roberts SA, Allen JD, Sigal EV. Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe. *Health Aff (Millwood)*. 2011;30(7):1375-1381. doi:10.1377/hlthaff.2011.0231
56. Uyl-de Groot CA, Löwenberg B. Sustainability and affordability of cancer drugs: a novel pricing model. *Nat Rev Clin Oncol*. 2018;15(7):405-406. doi:10.1038/s41571-018-0027-x
57. European Commission - Have your say. European Commission - Have your say. Published July 8, 2020. Accessed March 11, 2024. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceuticals-safe-and-affordable-medicines-new-EU-strategy-_en
58. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492
59. NKR Cijfers. Accessed April 8, 2024. https://iknl.nl/nkr-cijfers
60. Richtlijnen. Accessed April 8, 2024. https://iknl.nl/nkr/evaluatie-met-nkr-data/richtlijnen?pagina=/richtlijn/item/pagina.php&richtlijn_id=980
61. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. 2021;79(2):243-262. doi:10.1016/j.eururo.2020.09.042

62. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract*. 2011;65(11):1180-1192. doi:10.1111/j.1742-1241.2011.02799.x
63. Tannock Ian F., de Wit Ronald, Berry William R., et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *N Engl J Med*. 2004;351(15):1502-1512. doi:10.1056/NEJMoa040720
64. Bono JS de, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *The Lancet*. 2010;376(9747):1147-1154. doi:10.1016/S0140-6736(10)61389-X
65. Scher Howard I., Fizazi Karim, Saad Fred, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197. doi:10.1056/NEJMoa1207506
66. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992. doi:10.1016/S1470-2045(12)70379-0
67. Parker C., Nilsson S., Heinrich D., et al. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *N Engl J Med*. 2013;369(3):213-223. doi:10.1056/NEJMoa1213755
68. Beer Tomasz M., Armstrong Andrew J., Rathkopf Dana E., et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. *N Engl J Med*. 2014;371(5):424-433. doi:10.1056/NEJMoa1405095
69. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160. doi:10.1016/S1470-2045(14)71205-7
70. de Bono Johann, Mateo Joaquin, Fizazi Karim, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020;382(22):2091-2102. doi:10.1056/NEJMoa1911440
71. Smith Matthew R., Saad Fred, Chowdhury Simon, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*. 2018;378(15):1408-1418. doi:10.1056/NEJMoa1715546
72. BOM Archieven. NVMO. Accessed April 9, 2024. https://www.nvmo.org/bom-type/bom/
73. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. The effects of new life-prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population. *Prostate Cancer Prostatic Dis*. 2021;24(3):871-879. doi:10.1038/s41391-021-00344-1
74. Prostaatkanker | Volksgezondheid en Zorg. Accessed April 9, 2024. https://www.vzinfo.nl/prostaatkanker#bronverantwoording
75. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry. *Eur Urol Focus*. 2018;4(5):694-701. doi:10.1016/j.euf.2016.09.008
76. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. Second-Line Cabazitaxel Treatment in Castration-Resistant Prostate Cancer Clinical Trials Compared to Standard of Care in CAPRI: Observational Study in the Netherlands. *Clin Genitourin Cancer*. 2019;17(5):e946-e956. doi:10.1016/j.clgc.2019.05.018
77. Mullins CD, Montgomery R, Tunis S. Uncertainty in assessing value of oncology treatments. *The Oncologist*. 2010;15 Suppl 1:58-64. doi:10.1634/theoncologist.2010-S1-58
78. Kanters TA, Bouwmans CAM, Linden N van der, Tan SS, Roijen LH van. Update of the Dutch manual for costing studies in health care. *PLOS ONE*. 2017;12(11):e0187477. doi:10.1371/journal.pone.0187477
79. Nederland Z. Medicijnkosten.nl. Accessed April 9, 2024. https://www.medicijnkosten.nl/
80. DIS open data. Accessed April 9, 2024. https://www.opendisdata.nl/
81. NZa zorgproductapplicatie. Accessed April 9, 2024. https://zorgproducten.nza.nl/
82. RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

83. Monitor geneesmiddelen in de medisch specialistische zorg januari 2019 - Nederlandse Zorgautoriteit. Accessed January 18, 2024. https://puc.overheid.nl/nza/doc/PUC_264248_22/1/
84. Iravani F, Mamani H, Nategh E. External Reference Pricing and Parallel Imports of Pharmaceuticals: A Policy Comparison. *Prod Oper Manag*. 2020;29(12):2716-2735. doi:10.1111/poms.13246
85. Abirateron en prednison toegevoegd aan androgeendeprivatietherapie bij hormoongevoelig prostaatcarcinoom. NVMO. Accessed April 9, 2024. https://medischeoncologie.nl/artikelen/2018/april/editie-2/abirateron-en-prednison-toegevoegd-aan-androgeendeprivatietherapie-bij-hormoongevoelig-prostaatcarcinoom
86. Sweeney Christopher J., Chen Yu-Hui, Carducci Michael, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*. 2015;373(8):737-746. doi:10.1056/NEJMoa1503747
87. Fizazi Karim, Shore Neal, Tammela Teuvo L., et al. Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide. *N Engl J Med*. 2020;383(11):1040-1049. doi:10.1056/NEJMoa2001342
88. Sartor Oliver, de Bono Johann, Chi Kim N., et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2021;385(12):1091-1103. doi:10.1056/NEJMoa2107322
89. Kreis K, Horenkamp-Sonntag D, Schneider U, Zeidler J, Glaeske G, Weissbach L. Treatment-Related Healthcare Costs of Metastatic Castration-Resistant Prostate Cancer in Germany: A Claims Data Study. *PharmacoEconomics - Open*. 2021;5(2):299-310. doi:10.1007/s41669-020-00219-6
90. Wu B, Li SS, Song J, Pericone CD, Behl AS, Dawson NA. Total cost of care for castration-resistant prostate cancer in a commercially insured population and a medicare supplemental insured population. *J Med Econ*. 2020;23(1):54-63. doi:10.1080/13696998.2019.1678171
91. van der Linden N, Bongers ML, Coupé VMH, et al. Costs of non-small cell lung cancer in the Netherlands. *Lung Cancer Amst Neth*. 2016;91:79-88. doi:10.1016/j.lungcan.2015.10.015
92. Leeneman B, Uyl-de Groot CA, Aarts MJB, et al. Healthcare Costs of Metastatic Cutaneous Melanoma in the Era of Immunotherapeutic and Targeted Drugs. *Cancers*. 2020;12(4):1003. doi:10.3390/cancers12041003
93. Jürgens B, Clarke NS. Evolution of CAR T-cell immunotherapy in terms of patenting activity. *Nat Biotechnol*. 2019;37(4):370-375. doi:10.1038/s41587-019-0083-5
94. Charrot S, Hallam S. CAR-T Cells: Future Perspectives. *HemaSphere*. 2019;3(2):e188. doi:10.1097/hs9.0000000000000188
95. eurostat. People in the EU - population projections. [Internet].
96. European Commission. European Cancer Information System. Estimates of cancer incidence and mortality in 2018, for all countries. [Internet].
97. GCO, IARC. Globocan. Cancer tomorrow. Accessed December 3, 2019. http://gco.iarc.fr/tomorrow/home
98. American Cancer Society. *Cancer Facts & Figures 2019*. American Cancer Society; 2019:76.
99. Cerhan JR. Epidemiology of Follicular Lymphoma. *Hematol Oncol Clin North Am*. 2020;34(4):631-646. doi:10.1016/j.hoc.2020.02.001
100. Sandoval-Sus JD, Sotomayor EM, Shah BD. Mantle Cell Lymphoma: Contemporary Diagnostic and Treatment Perspectives in the Age of Personalized Medicine. *Hematol Oncol Stem Cell Ther*. 2017;10(3):99-115. doi:10.1016/j.hemonc.2017.02.003
101. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. *Pathology (Phila)*. 2018;50(1):74-87. doi:https://doi.org/10.1016/j.pathol.2017.09.006
102. Bouwmans C, Janssen J, Huijgens P, Uyl-de Groot C. Costs of haematological adverse events in chronic myeloid leukaemia patients: a retrospective cost analysis of the treatment of anaemia, neutropenia and thrombocytopenia in patients with chronic myeloid leukaemia. *J Med Econ*. 2009;12(2):164-169. doi:10.3111/13696990903149479
103. Hakkaart-van Roijen L, van der Linden N, Bouwamans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Bijlage 1.

104. Weycker D, Danel A, Marciniak A, Bendall K, Lipsitz M, Pettengell R. Economic costs of chemotherapy-induced febrile neutropenia among patients with non-Hodgkin's lymphoma in European and Australian clinical practice. *BMC Cancer*. 2012;12(1):362. doi:10.1186/1471-2407-12-362
105. Bock JO, Brettschneider C, Seidl H, et al. Ermittlung standardisierter Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. *Gesundheitswesen*. 2014;77(01):53-61. doi:10.1055/s-0034-1374621
106. Högy B, Keinecke HO, Borte M. Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. *Eur J Health Econ*. 2005;6(1):24-29. doi:10.1007/s10198-004-0250-5
107. Lefrant JY, Garrigues B, Pribil C, et al. The daily cost of ICU patients: A micro-costing study in 23 French Intensive Care Units. *Anaesth Crit Care Pain Med*. 2015;34(3):151-157. doi:10.1016/j.accpm.2014.09.004
108. Tan S, Martin J, Pezzi A, et al. Microcosting study of ICU costs in three European countries. *Crit Care*. 2008;12(2):P526. doi:10.1186/cc6747
109. Quinn C, Young C, Thomas J, Trusheim M. Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System. *Value Health*. 22(6):621-626. doi:10.1016/j.jval.2019.03.014
110. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Tisagenlecleucel (Akute Lymphatische B-ZellLeukämie). Bewertung Gemäß § 35a Abs. 1 Satz 11 SGB V. Nr. 689*.; 2018.
111. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Tisagenlecleucel (Diffuses Großzelliges B-ZellLymphom). Bewertung Gemäß § 35a Abs. 1 Satz 11 SGB V. Nr. 689*.; 2018.
112. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Axicabtagen-Ciloleucel (Primär Mediastinales Großzelliges B-Zell-Lymphom) – Bewertung Gemäß § 35a Abs. 1 Satz 11 SGB V. Nr. 716*.; 2019.
113. Haute Autorité de santé. Kymriah® (Tisagenlecleucel) Lymphome diffus à grandes cellules B [Internet].
114. Haute Autorité de santé. Kymriah® (Tisagenlecleucel) Leucémie aigue lymphoblastique [Internet].
115. Haute Autorité de santé. YESCARTA® (axicabtagene ciloleucel) Lymphomes diffus à grandes cellules B (LDGCB) et lymphome médiastinal primitif à grandes cellules B (LMPGCB) réfractaire ou en rechute, après au moins deux lignes de traitement systémique. [Internet].
116. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. Committee papers. [Internet].
117. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Appraisal consultation committee papers. [Internet].
118. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. [Internet].
119. ZiN. *Pakketadvies Axicabtagene Ciloleucel (Yescarta®)*. Zorginstituut Nederland; 2019.
120. ZiN. *Pakketadvies Tisagenlecleucel (Kymriah®) [DLBCL]*.; 2019.
121. ZiN. *Pakketadvies Tisagenlecleucel (Kymriah®) [pALL]*.; 2019.
122. AIFA. AIFA approva la rimborsabilità della prima terapia CAR-T. Accessed December 3, 2019. https://www.aifa.gov.it/-/aifa-approva-la-rimborsabilita-della-prima-terapia-car-t
123. AIFA. *Regime Di Rimborsabilita' e Prezzo Del Medicinale per Uso Umano «Yescarta».* Agenzia Italiana del Farmaco; 2019. Accessed December 3, 2019. https://www.aifa.gov.it/documents/20142/961234/Determina_DG-1643-2019_Yescarta.pdf/26464c52-5e7b-e97d-74d5-f66f69039fa0
124. Secretaria general de sanidad y consumo. Nota Informativa de la Reunión de la Comisión Interministerial de Precios de los Medicamentos. Sesión 187 de 30 de Noviembre de 2018. Published 2018. https://www.mscbs.gob.es/profesionales/farmacia/pdf/NOTA_INFORMATIVA_DE_LA_CIPM_187_web.pdf

125. Secretaria general de sanidad y consumo. Nota Informativa de la Reunión de la Comisión Interministerial de Precios de los Medicamentos. Sesión 189 de 18 de Marzo de 2019. Published 2019. https://www.mscbs.gob.es/profesionales/farmacia/pdf/NOTA_INFORMATIVA_DE_LA_CIPM_189_web.pdf
126. Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *J Clin Oncol*. 2018;36(32):3192-3202. doi:10.1200/JCO.2018.79.0642
127. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. *JAMA Pediatr*. 2018;172(12):1161-1168. doi:10.1001/jamapediatrics.2018.2530
128. Sarkar R, Gloude NJ, Murphy JD. Cost-effectiveness of chimeric antigen receptor T-cell therapy in pediatric relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol*. 2018;36(15). doi:10.1200/JCO.2018.36.15-suppl.6610
129. Walton M, Sharif S, Simmonds M, Claxton L, Hodgson R. Tisagenlecleucel for the Treatment of Relapsed or Refractory B-cell Acute Lymphoblastic Leukaemia in People Aged up to 25 Years: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics*. Published online April 13, 2019. doi:10.1007/s40273-019-00799-0
130. Furzer J, Gupta S, Nathan PC, et al. Cost-effectiveness of Tisagenlecleucel vs Standard Care in High-risk Relapsed Pediatric Acute Lymphoblastic Leukemia in Canada. *JAMA Oncol*. 2020;6(3):393-401. doi:10.1001/jamaoncol.2019.5909
131. Thielen FW, Dongen-Leunis A van, Arons AMM, Ladestein JR, Hoogerbrugge PM, Uyl-de Groot CA. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *Eur J Haematol*. 2020;105(2):203-215. doi:10.1111/ejh.13427
132. Roth JA, Sullivan SD, Lin VW, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *J Med Econ*. 2018;21(12):1238-1245. doi:10.1080/13696998.2018.1529674
133. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. *JAMA Netw Open*. 2019;2(2):e190035-e190035. doi:10.1001/jamanetworkopen.2019.0035
134. Institute for Clinical and Economic Review. *Chimeric Antigen Receptor T-Cell Therapy for BCell Cancers: Effectiveness and Value. Final Evidence Report.*; 2018.
135. CADTH. *Tisagenlecleucel for Acute Lymphoblastic Leukemia: Economic Review Report*. Canadian Agency for Drugs and Technologies in Health (CADTH); 2019:61.
136. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess*. 2017;21(7):1-204. doi:10.3310/hta21070
137. Thielen FW, Dongen-Leunis A van, Arons AMM, Ladestein JR, Hoogerbrugge PM, Groot CU de. Cost-Effectiveness of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-cell acute Lymphoblastic Leukemia. *Eur J Haematol*. n/a(n/a). doi:10.1111/ejh.13427
138. Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. *J Clin Oncol*. 2019;37(24):2105-2119. doi:10.1200/JCO.18.02079
139. Lin J, Lerman B, Barnes J, et al. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2018;36:JCO.2018.79.064. doi:10.1200/JCO.2018.79.0642
140. SEER. Acute Lymphocytic Leukemia - Cancer Stat Facts. SEER. Published 2019. Accessed December 3, 2019. https://seer.cancer.gov/statfacts/html/alyl.html
141. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. *Pathology (Phila)*. 2018;50(1):74-87. doi:10.1016/j.pathol.2017.09.006

142. Jeremy S. Abramson, Leo I. Gordon, Maria Lia Palomba, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *J Clin Oncol*. 2018;36(15_suppl):7505-7505. doi:10.1200/JCO.2018.36.15_suppl.7505
143. Makita S, Imaizumi K, Kurosawa S, Tobinai K. Chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma: opportunities and challenges. *Drugs Context*. 2019;8:212567-212567. doi:10.7573/dic.212567
144. Meghan Luchi KC. *Placing Your CAR-T Bets*. The Boston Consulting Group; 2018:7.
145. Pfeiffer A, Thalheimer FB, Hartmann S, et al. In vivo generation of human CD19-CAR T cells results in B-cell depletion and signs of cytokine release syndrome. *EMBO Mol Med*. 2018;10(11). doi:10.15252/emmm.201809158
146. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell*. 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012
147. Orkin SH, Reilly P. Paying for future success in gene therapy. *Science*. 2016;352(6289):1059-1061. doi:10.1126/science.aaf4770
148. AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families. Novartis. Accessed March 2, 2020. https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families
149. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *J Mark Access Health Policy*. 2020;8(1). doi:10.1080/20016689.2020.1715536
150. Quinn C, Young C, Thomas J, Trusheim M. Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System. *Value Health*. 22(6):621-626. doi:10.1016/j.jval.2019.03.014
151. United Nations, Department of Economics and Social Affairs. Definition of Regions. Accessed February 16, 2021. https://population.un.org/wpp/DefinitionOfRegions/
152. de Jonge E. *cbsodataR: Statistics Netherlands (CBS) Open Data API Client*.; 2020. https://github.com/edwindj/cbsodataR
153. Condylios S. *priceR: Economics and Pricing Tools*.; 2021. https://github.com/stevecondylios/priceR
154. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 2020;323(9):844-853. doi:10.1001/jama.2020.1166
155. Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. *PharmacoEconomics*. 2021;39(11):1243-1269. doi:10.1007/s40273-021-01065-y
156. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;20(2):273-286.
157. Orchard Therapeutics. 2019 10-K form. Published 2020. Accessed April 30, 2021. https://www.sec.gov/Archives/edgar/data/0001748907/000156459020007353/ortx-10k_20191231.htm
158. AveXis Inc. 2018 10-Q form. Published 2019. Accessed January 29, 2021. https://www.sec.gov/Archives/edgar/data/0001652923/000155837018004054/avxs-20180331x10q.htm
159. AveXis Inc. 2015 10-K form. Published 2016. Accessed January 27, 2021. https://www.sec.gov/Archives/edgar/data/0001652923/000104746916011350/a2227870z10-k.htm
160. Uyl-de Groot CA, Löwenberg B. Sustainability and affordability of cancer drugs: a novel pricing model. *Nat Rev Clin Oncol*. 2018;15(7):405-406. doi:10.1038/s41571-018-0027-x
161. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi:10.1016/j.jhealeco.2016.01.012
162. European Medicines Agency. EMA/584450/2020. CHMP assessment report. Libmeldy. Published 2020. Accessed October 12, 2021. https://www.ema.europa.eu/en/documents/assessment-report/libmeldy-epar-public-assessment-report_en.pdf

163. Orchard Therapeutics. Pipeline. Orchard Therapeutics. Published 2021. Accessed November 16, 2021. https://www.orchard-tx.com/approach/pipeline/
164. United Nations, Department of Economics and Social Affairs. World Population Prospects - Population Division - United Nations. Accessed February 19, 2021. https://population.un.org/wpp/
165. Division UNP. *Wpp2019: World Population Prospects 2019*.; 2020. http://population.un.org/wpp
166. Our World in Data. Number of births and deaths per year. Number of births and deaths per year, More Developed Regions. Published 2021. Accessed February 22, 2021. https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100
167. European Commission. Union Register of medicinal products for human use. Product information. Libmeldy. Union Register of medicinal products. Published 2020. Accessed November 17, 2021. https://ec.europa.eu/health/documents/community-register/html/h1493.htm
168. Novartis AG. 2020 20-F form. Published 2021. Accessed January 29, 2021. https://www.sec.gov/Archives/edgar/data/0001114448/000137036821000006/a21012620f.htm
169. European Medicines Agency. Libmeldy. European Medicines Agency. Published October 13, 2020. Accessed June 11, 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy
170. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. *Best Pract Res Clin Endocrinol Metab*. 2015;29(2):261-273. doi:10.1016/j.beem.2014.10.001
171. van Rappard DF, Boelens JJ, van Egmond ME, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience. *Blood*. 2016;127(24):3098-3101. doi:10.1182/blood-2016-03-708479
172. European Medicines Agency. Libmeldy. European Public Assessment Report. Annex I - Summary of product characteristics. Published 2020. Accessed June 18, 2021. https://www.ema.europa.eu/en/documents/product-information/libmeldy-epar-product-information_en.pdf
173. Munsat T. International SMA consortium meeting. *Neuromuscal Discord*. 1992;2:423-428.
174. Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy: clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol*. 1995;52(5):518-523.
175. Coratti G, Messina S, Lucibello S, et al. Clinical Variability in Spinal Muscular Atrophy Type III. *Ann Neurol*. 2020;88(6):1109-1117. doi:https://doi.org/10.1002/ana.25900
176. Verhaart IEC, Robertson A, Leary R, et al. A multi-source approach to determine SMA incidence and research ready population. *J Neurol*. 2017;264(7):1465-1473. doi:10.1007/s00415-017-8549-1
177. Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord*. 2018;28(3):208-215. doi:10.1016/j.nmd.2018.01.003
178. Bolous NS, Chen Y, Wang H, et al. The Cost-effectiveness of Gene Therapy for Severe Hemophilia B: A Microsimulation Study from the United States Perspective. *Blood*. Published online April 28, 2021. doi:10.1182/blood.2021010864
179. Ham RMT ten, Hövels AM, Hoekman J, et al. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. *Cytotherapy*. 2020;22(7):388-397. doi:10.1016/j.jcyt.2020.03.432
180. Ledley FD, McCoy SS, Vaughan G, Cleary EG. Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies. *JAMA*. 2020;323(9):834. doi:10.1001/jama.2020.0442
181. European Medicines Agency. Zolgensma. European Medicines Agency. Published March 24, 2020. Accessed March 26, 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma
182. Novartis AG. AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA). Novartis. Published 2019. Accessed August 9, 2022. https://www.novartis.com/news/media-releases/avexis-receives-fda-approval-zolgensma-first-and-only-gene-therapy-pediatric-patients-spinal-muscular-atrophy-sma

183. Novartis AG. Novartis receives approval from Japanese Ministry of Health, Labour and Welfare for Zolgensma® the only gene therapy for patients with spinal muscular atrophy (SMA). Novartis. Published 2020. Accessed March 26, 2021. https://www.novartis.com/news/media-releases/novartis-receives-approval-from-japanese-ministry-health-labour-and-welfare-zolgensma-only-gene-therapy-patients-spinal-muscular-atrophy-sma
184. International Association of Mutual Benefit Societies. *A European Drug Pricing Model for Fair and Transparent Prices*.; 2020. Accessed May 3, 2021. https://www.aim-mutual.org/wp-content/uploads/2019/12/AIMfairpricingModel.pdf
185. Nuijten MJC, Vis J. Economic comments on proposal for a novel cancer drug pricing model. *Nat Rev Clin Oncol*. 2018;15(9):587-587. doi:10.1038/s41571-018-0083-2
186. Nuijten M, Capri S. Pricing of orphan drugs in oncology and rare diseases. *J Mark Access Health Policy*. 2020;8(1):1838191. doi:10.1080/20016689.2020.1838191
187. Berdud M, Drummond M, Towse A. Establishing a reasonable price for an orphan drug. *Cost Eff Resour Alloc*. 2020;18(1):31. doi:10.1186/s12962-020-00223-x
188. DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. Research and development costs for new drugs by therapeutic category. A study of the US pharmaceutical industry. *PharmacoEconomics*. 1995;7(2):152-169. doi:10.2165/00019053-199507020-00007
189. Gupta Strategists. The cost of opportunity. A study on pharmaceutical R&D costs. Accessed June 15, 2022. https://gupta-strategists.nl/storage/files/The-cost-of-opportunity-Gupta-Strategists.pdf
190. Gotham D, McKenna L, Frick M, Lessem E. Public investments in the clinical development of bedaquiline. *PLOS ONE*. 2020;15(9):e0239118. doi:10.1371/journal.pone.0239118
191. Biotechnology Innovation Organization. Impact of the Orphan Drug Tax Credit on treatments for rare diseases. [Report] Prepared for the Biotechnology Industry Organization and the National Organization for Rare Disorders. Published 2015. Accessed May 3, 2022. https://www.bio.org/sites/default/files/legacy/bioorg/docs/EY%20BIO%20Orphan%20Drug%20Tax%20Credit%20Report%202015%2006%2016.pdf
192. Allen EJ. *The Information Content of the Deferred Tax Valuation Allowance: Evidence from Venture Capital Backed IPO Firms*. Social Science Research Network; 2012. doi:10.2139/ssrn.2161340
193. Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff Proj Hope*. 2016;35(5):776-783. doi:10.1377/hlthaff.2015.1314
194. Orchard Therapeutics. 2020 10-K form. Published 2021. Accessed April 30, 2021. https://www.sec.gov/Archives/edgar/data/0001748907/000156459021010035/ortx-10k_20201231.htm
195. Issuance of Priority Review Voucher; Rare Pediatric Disease Product. Federal Register. Published June 24, 2019. Accessed May 3, 2022. https://www.federalregister.gov/documents/2019/06/24/2019-13356/issuance-of-priority-review-voucher-rare-pediatric-disease-product
196. Jayasundara K, Hollis A, Krahn M, Mamdani M, Hoch JS, Grootendorst P. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet J Rare Dis*. 2019;14(1):12. doi:10.1186/s13023-018-0990-4
197. Hollywood J, Denney F. The rise of patent wars in Europe's gene therapy space. Published 2019. Accessed July 30, 2021. https://www.cms-lawnow.com/ealerts/2019/12/the-rise-of-patent-wars-in-europes-gene-therapy-space?cc_lang=en
198. Friedman Y. DrugPatentWatch. Deep knowledge on small-molecule drugs and the global patents covering them. Published 2021. Accessed July 30, 2021. //www.DrugPatentWatch.com/about.php
199. Boman L. UPenn, Nationwide Children's Hospital refuse to disclose which patents they licensed to Novartis for Zolgensma. Knowledge Ecology International. Published 2019. Accessed July 30, 2021. https://www.keionline.org/31019
200. Gezondheidsraad. *Neonatale Screening Op Spinale Spieratrofie [Newborn Screening of Spinal Muscular Atrophy]. Nr.2019/15*.; 2019. file:///Users/frederick/Downloads/neonatale-screening-op-spinale-spieratrofie.pdf
201. Heine R, Thielen FW, Koopmanschap M, et al. Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future. *HemaSphere*. 2021;5(2):e524. doi:10.1097/HS9.0000000000000524

202. Iancu EM, Kandalaft LE. Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting. *Curr Opin Biotechnol*. 2020;65:233-241. doi:10.1016/j.copbio.2020.05.005
203. ten Ham RMT, Nievaart JC, Hoekman J, et al. Estimation of manufacturing development costs of cell-based therapies: a feasibility study. *Cytotherapy*. Published online February 13, 2021. doi:10.1016/j.jcyt.2020.12.014
204. Rivière I, Roy K. Perspectives on Manufacturing of High-Quality Cell Therapies. *Mol Ther J Am Soc Gene Ther*. 2017;25(5):1067-1068. doi:10.1016/j.ymthe.2017.04.010
205. Campbell A, Brieva T, Raviv L, et al. Concise Review: Process Development Considerations for Cell Therapy. *Stem Cells Transl Med*. 2015;4(10):1155-1163. doi:10.5966/sctm.2014-0294
206. Moutsatsou P, Ochs J, Schmitt RH, Hewitt CJ, Hanga MP. Automation in cell and gene therapy manufacturing: from past to future. *Biotechnol Lett*. 2019;41(11):1245-1253. doi:10.1007/s10529-019-02732-z
207. Digiusto DL, Melsop K, Srivastava R, Tran CAT. Proceedings of the first academic symposium on developing, qualifying and operating a cell and gene therapy manufacturing facility. *Cytotherapy*. 2018;20(12):1486-1494. doi:10.1016/j.jcyt.2018.07.008
208. Abou-El-Enein M, Römhild A, Kaiser D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs. *Cytotherapy*. 2013;15(3):362-383. doi:10.1016/j.jcyt.2012.09.006
209. Ran T, Eichmüller SB, Schmidt P, Schlander M. Cost of decentralized CAR T-cell production in an academic nonprofit setting. *Int J Cancer*. 2020;147(12):3438-3445. doi:https://doi.org/10.1002/ijc.33156
210. Harrison RP, Zylberberg E, Ellison S, Levine BL. Chimeric antigen receptor–T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. *Cytotherapy*. 2019;21(2):224-233. doi:10.1016/j.jcyt.2019.01.003
211. WHO agrees watered-down resolution on transparency in drug costs. *Reuters*. https://www.reuters.com/article/us-health-pricing-idUSKCN1SY0W4. Published May 28, 2019. Accessed May 4, 2022.
212. At WHO Forum on Medicines, countries and civil society push for greater transparency and fairer prices. Accessed May 4, 2022. https://www.who.int/news/item/13-04-2019-at-who-forum-on-medicines-countries-and-civil-society-push-for-greater-transparency-and-fairer-prices
213. Chit A, Parker J, Halperin SA, Papadimitropoulos M, Krahn M, Grootendorst P. Toward more specific and transparent research and development costs: the case of seasonal influenza vaccines. *Vaccine*. 2014;32(26):3336-3340. doi:10.1016/j.vaccine.2013.06.055
214. Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol*. 2017;14(6):381-390. doi:10.1038/nrclinonc.2017.31
215. Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. *JAMA*. 2016;316(8):858-871. doi:10.1001/jama.2016.11237
216. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
217. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol*. 2018;29(1):84-91. doi:10.1093/annonc/mdx755
218. Yu JXA, Upadhaya S, Hubbard-Lucey V. Immuno-oncology drug development forges on despite COVID-19. *Nat Rev Drug Discov*. 2020;19. doi:10.1038/d41573-020-00166-1
219. Scalo JF, Rascati KL. Trends and issues in oncology costs. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14(1):35-44. doi:10.1586/14737167.2014.864561
220. Greiner W, Patel K, Crossman-Barnes CJ, Rye-Andersen TV, Hvid C, Vandebrouck T. High-Expenditure Disease in the EU-28: Does Drug Spend Correspond to Clinical and Economic Burden in Oncology, Autoimmune Disease and Diabetes? *PharmacoEconomics - Open*. 2021;5(3):385-396. doi:10.1007/s41669-020-00253-4
221. DeMartino PC, Miljković MD, Prasad V. Potential Cost Implications for All US Food and Drug Administration Oncology Drug Approvals in 2018. *JAMA Intern Med*. 2021;181(2):162-167. doi:10.1001/jamainternmed.2020.5921

222. Thielen FW, Heine RJSD, Berg S van den, Ham RMTT, Groot CAU de. Towards sustainability and affordability of expensive cell and gene therapies? Applying a cost-based pricing model to estimate prices for Libmeldy and Zolgensma. *Cytotherapy*. 2022;24(12):1245-1258. doi:10.1016/j.jcyt.2022.09.002
223. First Approval of PD-1 Inhibitor: Pembrolizumab in Unresectable or Metastatic Melanoma - The ASCO Post. Accessed January 20, 2022. https://ascopost.com/issues/october-15-2014/first-approval-of-pd-1-inhibitor-pembrolizumab-in-unresectable-or-metastatic-melanoma/
224. EMA. Keytruda. European Medicines Agency. Published September 17, 2018. Accessed May 26, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda
225. EMA. Darzalex. European Medicines Agency. Published September 17, 2018. Accessed May 26, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex
226. Feiten en cijfers over dure geneesmiddelen | Vektis.nl. Vektis. Accessed January 19, 2023. https://www.vektis.nl/intelligence/publicaties/factsheet-dure-geneesmiddelen
227. World Population Prospects - Population Division - United Nations. Accessed August 3, 2022. https://population.un.org/wpp/DefinitionOfRegions/
228. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA*. 2020;323(9):844-853. doi:10.1001/jama.2020.1166
229. Nosengo N. Can you teach old drugs new tricks? *Nature*. 2016;534(7607):314-316. doi:10.1038/534314a
230. Division UNP. wpp2019: World Population Prospects 2019. Published online January 31, 2020. Accessed August 4, 2022. https://CRAN.R-project.org/package=wpp2019
231. Nederland Z. Horizonscan geneesmiddelen. Accessed August 5, 2022. https://www.horizonscangeneesmiddelen.nl/zoeken?search-field=pembrolizumab
232. Busse A, Lüftner D. What Does the Pipeline Promise about Upcoming Biosimilar Antibodies in Oncology? *Breast Care*. 2019;14(1):10-16. doi:10.1159/000496834
233. Kansteiner F. J&J's next-gen Darzalex sparks drug delivery royalties battle. Fierce Pharma. Published September 24, 2020. Accessed August 4, 2022. https://www.fiercepharma.com/pharma/genmab-takes-j-j-to-arbitration-court-over-subq-darzalex-royalties
234. Klutz S, Holtmann L, Lobedann M, Schembecker G. Cost evaluation of antibody production processes in different operation modes. *Chem Eng Sci*. 2016;141:63-74. doi:10.1016/j.ces.2015.10.029
235. Comparison between Batch and Continuous Monoclonal Antibody Production and Economic Analysis | Industrial & Engineering Chemistry Research. Accessed August 15, 2022. https://pubs.acs.org/doi/pdf/10.1021/acs.iecr.8b04717
236. Kelley B. Industrialization of mAb production technology: The bioprocessing industry at a crossroads. *mAbs*. 2009;1:443-452. doi:10.4161/mabs.1.5.9448
237. Turner HC, Lauer JA, Tran BX, Teerawattananon Y, Jit M. Adjusting for Inflation and Currency Changes Within Health Economic Studies. *Value Health*. 2019;22(9):1026-1032. doi:10.1016/j.jval.2019.03.021
238. Darzalex Faspro Prices, Coupons, Copay & Patient Assistance. Drugs.com. Accessed November 29, 2022. https://www.drugs.com/price-guide/darzalex-faspro
239. Nederland Z. daratumumab. Accessed November 30, 2022. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/d/daratumumab
240. Keytruda Prices, Coupons, Copay & Patient Assistance. Drugs.com. Accessed December 1, 2022. https://www.drugs.com/price-guide/keytruda
241. NICE fails to recommend pembrolizumab in final draft guidance. European Pharmaceutical Review. Accessed December 5, 2022. https://www.europeanpharmaceuticalreview.com/news/115242/nice-fails-to-recommend-pembrolizumab-in-final-draft-guidance/
242. Nederland Z. KEYTRUDA INFVLST CONC 25MG/ML FLACON 4ML | Medicijnkosten.nl. Accessed December 1, 2022. https://www.medicijnkosten.nl/medicijn?artikel=KEYTRUDA+INFVLST+CONC+25MG%2FML+FLACON+4ML&id=85bf8970309cc9bde819cec562ee13dc

243. Rennane S, Baker L, Mulcahy A. Estimating the Cost of Industry Investment in Drug Research and Development: A Review of Methods and Results. *Inq J Health Care Organ Provis Financ*. 2021;58:00469580211059731. doi:10.1177/00469580211059731
244. AIM OFFERS A TOOL TO CALCULATE FAIR AND TRANSPARENT EUROPEAN PRICES FOR ACCESSIBLE PHARMACEUTICAL INNOVATIONS. https://www.aim-mutual.org/wp-content/uploads/2021/06/AIMs-fair-pricing-model-Accompanying-paper-to-the-fair-pricing-calculator_June2021.pdf
245. Ledley FD, McCoy SS, Vaughan G, Cleary EG. Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies. *JAMA*. 2020;323(9):834-843. doi:10.1001/jama.2020.0442
246. Value-based pricing of drugs with multiple indications or in combinations — lessons from Europe | Nature Reviews Clinical Oncology. Accessed January 24, 2023. https://www.nature.com/articles/s41571-021-00561-6
247. Administration (TGA) TG. DARZALEX daratumumab 100 mg/5 mL concentrated solution for infusion vial (281842). Therapeutic Goods Administration (TGA). Published May 26, 2022. Accessed November 29, 2022. https://www.tga.gov.au/resources/artg/281842
248. Administration (TGA) TG. KEYTRUDA pembrolizumab (rch) 100mg/4 mL concentrated injection vial (263932). Therapeutic Goods Administration (TGA). Published May 26, 2022. Accessed November 29, 2022. https://www.tga.gov.au/resources/artg/263932
249. Review Reports: Drugs | Pharmaceuticals and Medical Devices Agency. Accessed November 29, 2022. https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html#select11
250. Uyl-de Groot CA, Heine R, Krol M, Verweij J. Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe. *Cancers*. 2020;12(8):2313. doi:10.3390/cancers12082313
251. Ministerie van Volksgezondheid W en S. Pakketadvies sluisgeneesmiddel pembrolizumab (Keytruda®) bij de behandeling van niet-kleincellig longkanker - Advies - Zorginstituut Nederland. Published December 14, 2016. Accessed December 5, 2022. https://www.zorginstituutnederland.nl/publicaties/adviezen/2016/12/14/pakketadvies-pembrolizumab-keytruda
252. *Performance-Based Managed Entry Agreements for New Medicines in OECD Countries and EU Member States: How They Work and Possible Improvements Going Forward*. Vol 115.; 2019. doi:10.1787/6e5e4c0f-en
253. Ministerie van Volksgezondheid W en S. Pakketadvies sluisgeneesmiddel daratumumab (Darzalex®) bij multipel myeloom (ziekte van Kahler) - Advies - Zorginstituut Nederland. Published November 28, 2017. Accessed December 5, 2022. https://www.zorginstituutnederland.nl/publicaties/adviezen/2017/11/28/pakketadvies-daratumumab-darzalex-bij-multipel-myeloom
254. Procedura di applicazione Managed Entry Agreement - DARZALEX. Accessed June 12, 2023. https://www.aifa.gov.it/en/-/procedura-di-applicazione-managed-entry-agreement-darzalex-21-03-2018-
255. Raedler LA. Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable or Metastatic Melanoma. *Am Health Drug Benefits*. 2015;8(Spec Feature):96-100.
256. Bhatnagar V, Gormley NJ, Luo L, et al. FDA Approval Summary: Daratumumab for Treatment of Multiple Myeloma After One Prior Therapy. *The Oncologist*. 2017;22(11):1347-1353. doi:10.1634/theoncologist.2017-0229
257. Search Orphan Drug Designations and Approvals. Accessed August 28, 2023. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=397113
258. Search Orphan Drug Designations and Approvals. Accessed August 28, 2023. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=481715
259. Texts adopted - A Pharmaceutical Strategy for Europe - Wednesday, 24 November 2021. Accessed December 7, 2022. https://www.europarl.europa.eu/doceo/document/TA-9-2021-0470_EN.html
260. Rudrapal M, Khairnar SJ, Jadhav AG, Rudrapal M, Khairnar SJ, Jadhav AG. Drug Repurposing (DR): An Emerging Approach in Drug Discovery. In: *Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications*. IntechOpen; 2020. doi:10.5772/intechopen.93193

261. Mullard A. Low-cost non-profit drug repurposing. *Nat Rev Drug Discov*. 2019;18(1):7-7. doi:10.1038/nrd.2018.228
262. Badria FA. *Drug Repurposing: Hypothesis, Molecular Aspects and Therapeutic Applications*. BoD – Books on Demand; 2020.
263. Moorkens E, Godman B, Huys I, et al. The Expiry of Humira® Market Exclusivity and the Entry of Adalimumab Biosimilars in Europe: An Overview of Pricing and National Policy Measures. *Front Pharmacol*. 2021;11. Accessed August 25, 2023. https://www.frontiersin.org/articles/10.3389/fphar.2020.591134
264. Danzon PM. Differential Pricing of Pharmaceuticals: Theory, Evidence and Emerging Issues. *PharmacoEconomics*. 2018;36(12):1395-1405. doi:10.1007/s40273-018-0696-4
265. ESMO. About the ESMO-MCBS. Accessed December 8, 2022. https://www.esmo.org/guidelines/esmo-mcbs/about-the-esmo-mcbs
266. Howard DH, Chernew ME, Abdelgawad T, Smith GL, Sollano J, Grabowski DC. New Anticancer Drugs Associated With Large Increases In Costs And Life Expectancy. *Health Aff (Millwood)*. 2016;35(9):1581-1587. doi:10.1377/hlthaff.2016.0286
267. Chen AJ, Hu X, Conti RM, Jena AB, Goldman DP. Trends in the Price per Median and Mean Life-Year Gained Among Newly Approved Cancer Therapies 1995 to 2017. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. 2019;22(12):1387-1395. doi:10.1016/j.jval.2019.08.005
268. The Global Use of Medicine in 2019 and Outlook to 2023. Accessed September 20, 2023. https://www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023
269. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future. *Front Pharmacol*. 2017;8:171. doi:10.3389/fphar.2017.00171
270. Dabbous M, Chachoua L, Caban A, Toumi M. Managed Entry Agreements: Policy Analysis From the European Perspective. *Value Health*. 2020;23(4):425-433. doi:10.1016/j.jval.2019.12.008
271. FDA Approves Second Biomarker-Based Indication for Merck's Keytruda (pembrolizumab), Regardless of Tumor Type. Drugs.com. Accessed September 29, 2023. https://www.drugs.com/newdrugs/fda-approves-second-biomarker-based-indication-merck-s-keytruda-pembrolizumab-regardless-tumor-type-5268.html
272. Keytruda | European Medicines Agency. Accessed December 5, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda#ema-inpage-item-overview
273. Ministerie van Volksgezondheid W en S. Onderzoeksrapport Equalis over effecten van de sluis voor dure geneesmiddelen - Rapport - Zorginstituut Nederland. Published August 16, 2023. Accessed March 22, 2024. https://www.zorginstituutnederland.nl/publicaties/rapport/2023/08/16/onderzoeksrapport-equalis-over-effecten-van-de-sluis-voor-dure-geneesmiddelen
274. Buntz B. 50 best-selling pharmaceuticals of 2022: Market leaders and trends. Drug Discovery and Development. Published April 18, 2023. Accessed October 18, 2023. https://www.drugdiscoverytrends.com/50-of-2022s-best-selling-pharmaceuticals/
275. Zaken M van A. Monitor Medisch Specialistische Zorg 2022 - Rapport - Rijksoverheid.nl. Published June 8, 2022. Accessed October 18, 2023. https://www.rijksoverheid.nl/documenten/rapporten/2022/06/08/monitor-medisch-specialistische-zorg-2022
276. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*. 2016;387(10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
277. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *N Engl J Med*. 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774
278. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet*. 2019;394(10212):1915-1928. doi:10.1016/S0140-6736(19)32591-7

279. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714
280. Lajeunesse MJ. juicr: Automated and Manual Extraction of Numerical Data from Scientific Images. Published online April 30, 2021. Accessed October 3, 2023. https://cran.r-project.org/web/packages/juicr/index.html
281. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9. doi:10.1186/1471-2288-12-9
282. Alarid-Escudero F, Krijkamp E, Pechlivanoglou P, et al. A need for change! A coding framework for improving transparency in decision modeling. *PharmacoEconomics*. 2019;37(11):1329-1339. doi:10.1007/s40273-019-00837-x
283. Netherlands S. Life tables. Statistics Netherlands. Accessed November 13, 2023. https://www.cbs.nl/en-gb/our-services/methods/statistical-methods/output/life-tables
284. Versteegh M, Helm I van der, Mokri H, Oerlemans S, Blommestein H, Baal P van. Estimating Quality of Life Decrements in Oncology Using Time to Death. *Value Health*. 2022;25(10):1673-1677. doi:10.1016/j.jval.2022.06.002
285. Wang J, Chmielowski B, Pellissier J, Xu R, Stevinson K, Liu FX. Cost-Effectiveness of Pembrolizumab Versus Ipilimumab in Ipilimumab-Naïve Patients with Advanced Melanoma in the United States. *J Manag Care Spec Pharm*. 2017;23(2):184-194. doi:10.18553/jmcp.2017.23.2.184
286. Huang M, Lou Y, Pellissier J, et al. Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States. *J Med Econ*. 2017;20(2):140-150. doi:10.1080/13696998.2016.1230123
287. Huang M, Lou Y, Pellissier J, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. *Pharmacoeconomics*. 2017;35(8):831-844. doi:10.1007/s40273-017-0527-z
288. Chouaid C, Agulnik J, Goker E, et al. Health-Related Quality of Life and Utility in Patients with Advanced Non–Small-Cell Lung Cancer: A Prospective Cross-Sectional Patient Survey in a Real-World Setting. *J Thorac Oncol*. 2013;8(8):997-1003. doi:10.1097/JTO.0b013e318299243b
289. Borse RH, Ramakrishnan K, Gandhi J, Dhankhar P, Chirovsky D. Cost-effectiveness of pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma in the United States. *J Med Econ*. 2022;25(1):954-965. doi:10.1080/13696998.2022.2095826
290. Bensimon AG, Zhong Y, Swami U, et al. Cost-effectiveness of pembrolizumab with axitinib as first-line treatment for advanced renal cell carcinoma. *Curr Med Res Opin*. 2020;36(9):1507-1517. doi:10.1080/03007995.2020.1799771
291. Xander NSH, Fiets WE, Uyl-de Groot CA. Cost-effectiveness and budget impact of pembrolizumab+axitinib versus sunitinib in patients with advanced clear-cell renal cell carcinoma in the Netherlands. *Front Oncol*. 2023;13. Accessed October 18, 2023. https://www.frontiersin.org/articles/10.3389/fonc.2023.1205700
292. Qiao N, Insinga R, de Lima Lopes Junior G, Cook J, Sénécal M. A Review of Cost-Effectiveness Studies of Pembrolizumab Regimens for the Treatment of Advanced Non-small Cell Lung Cancer. *PharmacoEconomics Open*. 2021;5(3):365-383. doi:10.1007/s41669-020-00255-2
293. Massetti M, Even C, Geoffrois L, et al. PCN81 Cost-Effectiveness Analysis of Pembrolizumab for the Treatment of Recurrent or Metastatic Head and Neck Squamous CELL Carcinoma in Patients Whose Tumor Expressed Programmed Death-Ligand 1 at Combined Positive Score ≥1 in France. *Value Health*. 2020;23:S436. doi:10.1016/j.jval.2020.08.218
294. Preckler V, Espín J. The Role of Indication-Based Pricing in Future Pricing and Reimbursement Policies: A Systematic Review. *Value Health*. 2022;25(4):666-675. doi:10.1016/j.jval.2021.11.1376
295. Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: The Dutch reality check. *Health Policy*. 2019;123(3):267-274. doi:10.1016/j.healthpol.2018.09.016

296. Powles TB, Valderrama BP, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). *Ann Oncol*. 2023;34:S1340. doi:10.1016/j.annonc.2023.10.106
297. Health status - Deaths from cancer - OECD Data. theOECD. Accessed November 20, 2023. http://data.oecd.org/healthstat/deaths-from-cancer.htm
298. Paul JE, Trueman P. 'Fourth hurdle reviews', NICE, and database applications. *Pharmacoepidemiol Drug Saf*. 2001;10(5):429-438. doi:10.1002/pds.600
299. The gene-therapy revolution risks stalling if we don't talk about drug pricing. Accessed March 11, 2024. https://www.nature.com/articles/d41586-023-01389-z
300. Gamba S, Pertile P, Vogler S. The impact of managed entry agreements on pharmaceutical prices. *Health Econ*. 2020;29(S1):47-62. doi:10.1002/hec.4112
301. A pharmaceutical strategy for Europe - European Commission. Published March 11, 2024. Accessed March 11, 2024. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en
302. Abiraterone Mylan | European Medicines Agency. Accessed January 18, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/abiraterone-mylan
303. Cabazitaxel Accord | European Medicines Agency. Accessed January 18, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/cabazitaxel-accord
304. Form 10-K. Accessed January 18, 2024. https://www.sec.gov/Archives/edgar/data/1011835/000119312515062576/d850483d10k.htm
305. Lynparza | European Medicines Agency. Accessed January 18, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza
306. Breyanzi | European Medicines Agency. Accessed January 22, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi
307. A Big Step forward for cancer immunotherapy. Accessed January 22, 2024. https://www.amsterdamumc.org/en/research/institutes/cancer-center-amsterdam/news/a-big-step-forward-for-cancer-immunotherapy-.htm
308. Cliff ERS, Kelkar AH, Russler-Germain DA, et al. High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions. *Am Soc Clin Oncol Educ Book*. 2023;(43):e397912. doi:10.1200/EDBK_397912
309. Hollis A. Sustainable Financing of Innovative Therapies: A Review of Approaches. *PharmacoEconomics*. 2016;34(10):971-980. doi:10.1007/s40273-016-0416-x
310. Q&A: Revision of the Pharmaceutical legislation. European Commission - European Commission. Accessed January 31, 2024. https://ec.europa.eu/commission/presscorner/detail/en/qanda_23_1844
311. Beneluxa initiative | BeNeLuxA. Accessed February 2, 2024. https://beneluxa.org/collaboration
312. Beneluxa Initiative announces successful conclusion of Libmeldy price negotiations, directly benefiting patients in three countries | BeNeLuxA. Accessed February 2, 2024. https://beneluxa.org/news1
313. Vogler S. Annex 2. Examples of cross-country collaboration on pricing and reimbursement. In: *Payer Policies to Support Innovation and Access to Medicines in the WHO European Region [Internet]*. World Health Organization; 2022. Accessed February 2, 2024. https://www.ncbi.nlm.nih.gov/books/NBK587869/
314. Franken M. Decision Making in Drug Reimbursement.
315. Addressing challenges in access to oncology medicines - OECD. Accessed February 5, 2024. https://www.oecd.org/health/health-systems/addressing-challenges-in-access-to-oncology-medicines.htm
316. Steenhoek A, Koopmanschap M, Piepenbrink JF. [40 years of medicines policy in the Netherlands: from financial constraints to medicines shortages?]. *Ned Tijdschr Geneeskd*. 2020;164:D4568.
317. Over de adviezen. NVMO. Accessed February 9, 2024. https://www.nvmo.org/over-de-adviezen/

318. Ministerie van Volksgezondheid W en S. Kamerbrief over vergoeding Libmeldy per 19 januari 2024 - Kamerstuk - Rijksoverheid.nl. Published January 24, 2024. Accessed March 6, 2024. https://www.rijksoverheid.nl/documenten/kamerstukken/2024/01/24/kamerbrief-over-vergoeding-libmeldy-per-19-januari-2024
319. About ASCERTAIN. ASCERTAIN. Accessed February 12, 2024. https://www.access2meds.eu/about-ascertain/
320. Barrios C, de Lima Lopes G, Yusof MM, Rubagumya F, Rutkowski P, Sengar M. Barriers in access to oncology drugs — a global crisis. *Nat Rev Clin Oncol*. 2023;20(1):7-15. doi:10.1038/s41571-022-00700-7
321. Leighl NB, Nirmalakumar S, Ezeife DA, Gyawali B. An Arm and a Leg: The Rising Cost of Cancer Drugs and Impact on Access. *Am Soc Clin Oncol Educ Book*. 2021;(41):e1-e12. doi:10.1200/EDBK_100028
322. *Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on Health Technology Assessment and Amending Directive 2011/24/EU (Text with EEA Relevance)*. Vol 458.; 2021. Accessed January 3, 2024. http://data.europa.eu/eli/reg/2021/2282/oj/eng
323. WHO. Accessed February 12, 2024. https://whofairpricingforum.com/
324. WHA72.8 - Improving the transparency of markets for medicines, vaccines, and other health products. Accessed February 12, 2024. https://www.who.int/publications/m/item/wha72.8
325. Orchard Therapeutics. Orchard Therapeutics Corporate Presentation August 2020. Published 2020. Accessed January 14, 2021. https://ir.orchard-tx.com/static-files/a8aefd1a-836b-41d9-baab-ee60f0710647
326. Orchard Therapeutics. Our Story. Orchard Therapeutics. Published 2021. Accessed May 4, 2021. https://www.orchard-tx.com/about/our-story/
327. Poorthuis BJHM, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. *Hum Genet*. 1999;105(1):151-156. doi:10.1007/s004399900075
328. Prior TW, Nagan N, Sugarman EA, Batish SD, Braastad C. Technical standards and guidelines for spinal muscular atrophy testing. *Genet Med*. 2011;13(7):686-694.
329. Lunn MR, Wang CH. Spinal muscular atrophy. *The Lancet*. 2008;371(9630):2120-2133. doi:10.1016/S0140-6736(08)60921-6
330. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80(1):155-165.
331. Hahnen E, Forkert R, Marke C, et al. Molecular analysis of candidate genes on chromosome 5q13 in autosomal recessive spinal muscular atrophy: evidence of homozygous deletions of the SMN gene in unaffected individuals. *Hum Mol Genet*. 1995;4(10):1927-1933.
332. Paprocka I, Kempa WM, Ćwikła G. Predictive Maintenance Scheduling with Failure Rate Described by Truncated Normal Distribution. *Sensors*. 2020;20(23):6787. doi:10.3390/s20236787
333. Ramirez A, Cox C. Improving on the Range Rule of Thumb. *Rose-Hulman Undergrad Math J*. 2012;13(2):15. https://scholar.rose-hulman.edu/rhumj/vol13/iss2/1
334. Nederland Z. KEYTRUDA INFUSIEPOEDER FLACON 50MG | Medicijnkosten.nl. Accessed November 14, 2023. https://www.medicijnkosten.nl/medicijn?artikel=KEYTRUDA+INFUSIEPOEDER+-FLACON+50MG&id=54aeb7397a0bba0f05a81f7db8341ded
335. Nederland Z. YERVOY INFVLST CONC 5MG/ML FLACON 10ML | Medicijnkosten.nl. Accessed November 14, 2023. https://www.medicijnkosten.nl/medicijn?artikel=YERVOY+INFVLST+CONC+5MG%2FML+FLACON+10ML&id=14d88456e772cfb5842e1782041e6a73
336. Nederland Z. DOCETAXEL SEACROSS INFVLST CONC 20MG/ML FL 1ML | Medicijnkosten.nl. Accessed November 14, 2023. https://www.medicijnkosten.nl/medicijn?artikel=DOCETAXEL+-SEACROSS+INFVLST+CONC+20MG%2FML+FL+1ML&id=0005039ddc31f468040f-7b972055506c
337. Nederland Z. CARBOPLATINE ACCORD INFVLST CONC 10MG/ML FL 5ML | Medicijnkosten.nl. Accessed November 14, 2023. https://www.medicijnkosten.nl/medicijn?artikel=CARBOPLATINE+ACCORD+INFVLST+CONC+10MG%2FML+FL++5ML&id=7afb66dd7d243c81152fc8ae01a1d13d

338. Nederland Z. VEGZELMA INFVLST CONC 25MG/ML FLACON 4ML | Medicijnkosten.nl. Accessed November 15, 2023. https://www.medicijnkosten.nl/medicijn?artikel=VEGZELMA+INFVLST+CONC+25MG%2FML+FLACON+4ML&id=a908b8006da22979ced068306bce9027
339. Nederland Z. ERBITUX INFVLST 5MG/ML FLACON 20ML | Medicijnkosten.nl. Accessed November 15, 2023. https://www.medicijnkosten.nl/medicijn?artikel=ERBITUX+INFVLST+5MG%2FML+FLACON++20ML&id=d3f606d1ea98a6d6749a1153ed01141e
340. van der Linden N, Buter J, Pescott CP, et al. Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck in the Netherlands. *Eur Arch Otorhinolaryngol*. 2016;273(2):455-464. doi:10.1007/s00405-015-3495-y
341. Nederland Z. SUNITINIB ACCORD CAPSULE 50MG | Medicijnkosten.nl. Accessed November 15, 2023. https://www.medicijnkosten.nl/medicijn?artikel=SUNITINIB+ACCORD+CAPSULE+50MG&id=85c15c023b4c7d1a9d282e0cc4c63839