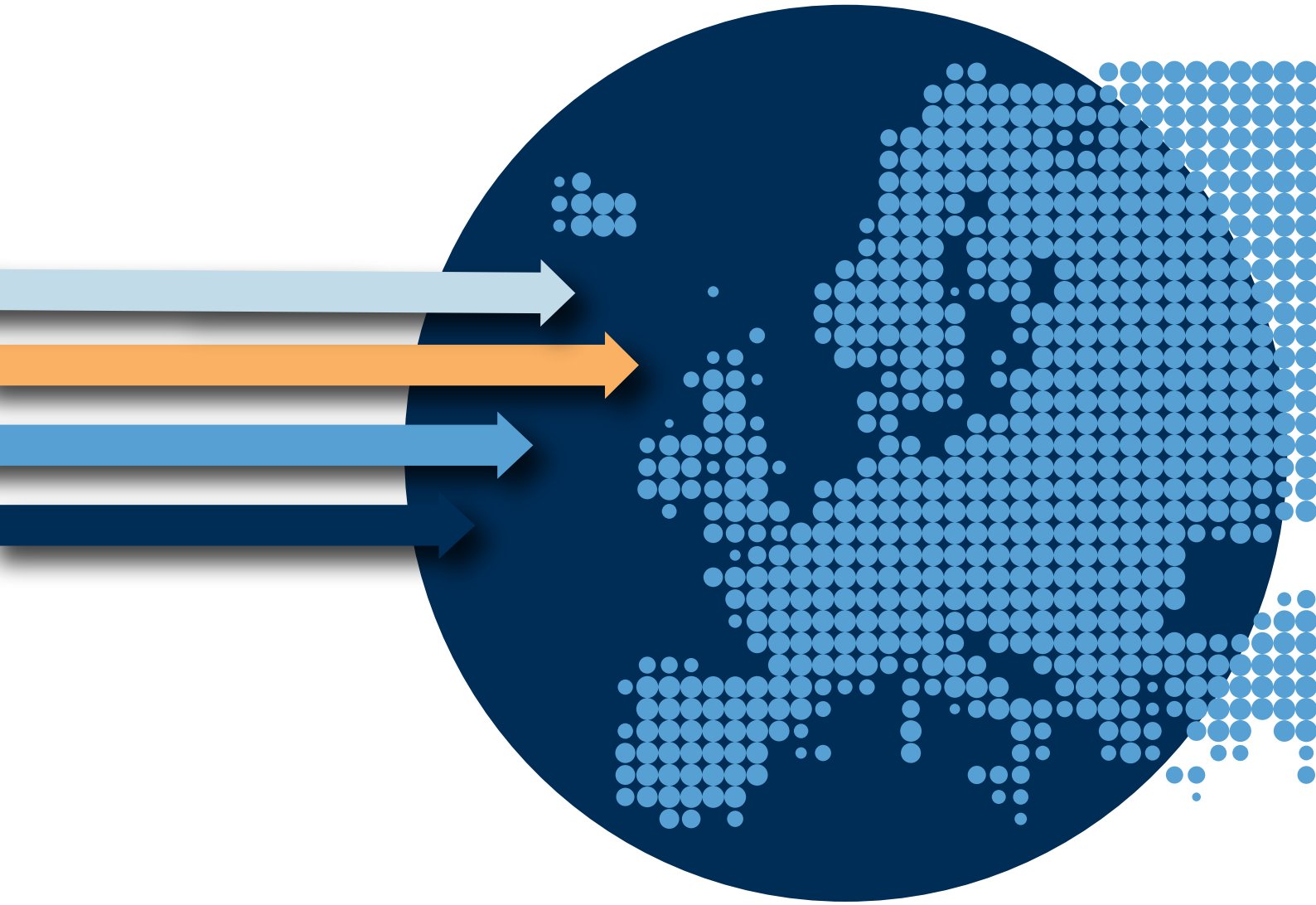
INNOVATIVE TREATMENTS FOR CANCER IN EUROPE

– VALUE, COST AND ACCESS



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INNOVATIVE TREATMENTS FOR CANCER IN EUROPE - VALUE, COST AND ACCESS

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Content

Foreword

This report is part of a long-term research project aimed at describing and analysing access to new cancer drugs. It focuses on a select group of countries, representing different levels of income and different health care systems, with different mechanisms for allocation of resources. We also look specifically at access patterns in a selected number of cancer diseases, where innovation and new drug introductions have been prominent; melanoma, Non-Small Cellular Lung Cancer (NSCLC), and multiple myeloma.

The report covers the period 2000-2013, which includes both a period of stable but slow growth in income as well as health care expenditures, followed by a period hit by economic crises. It is thus possible to look into and reveal how access is influenced by economic conditions.

While economic factors and affordability is important for access, it is not the only determinant of variations in access. However, there is no clear pattern in other determinants, indicating that countries are still searching for evidence-based approaches to adaption and use of new cancer drugs.

There is a pressure on regulatory authorities to find ways for early access to important cancer drugs, but even if FDA in the US has shorter time for approval, it is not regulatory delay, which is the main explanation for delayed access. More important factors are mechanisms for pricing and reimbursement, and particularly rigid hospital budgets. To overcome this, health care systems experiment with new payment mechanisms, which also can be useful for directing use to new cancer medicines, which provides most benefits for patients. We thus in this report also review this development in detail.

We are grateful to BMS for funding of the report and for helpful comments from Michael Lees. But we would like to state that it is the authors only who are responsible for the content and the conclusions.

Lund 16 March 2016

Bengt Jönsson, Ulf Persson and Nils Wilking

Abbreviations

CDF	Cancer Drugs Fund (UK)
CHMP	Committee for Medicinal Products for Human Use
CIRS	Centre for Innovation in Regulatory Science
CT	Computerized Tomographic Scanning
DALY	Disability-Adjusted Life Years
DRG	Diagnosis Related Groups
EC	European Commission
ECB	European Central Bank
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EUCAN	European Conservation Action Network
ERP	External Reference Pricing
FDA	Food and Drug Administration (USA)
LYG	Life Year Gained
MEA	Market Entry Agreements
MRI	Magnetic Resonance Imaging
NAS	New Active Substance
NCI	National Cancer Institute (USA)
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cellular Lung Cancer
PAS	Patient Access Schemes
PET	Positron Emission Tomography
PPT	Purchasing Power Parity

QALY	Quality Adjusted Life Year
SCLC	Small Cellular Lung Cancers
SMM	Smouldering Multiple Myeloma
TLV	The Dental and Pharmaceutical Benefits Agency (Sweden)
USD	US dollars
VBP	Value-Based Pricing
WHO	World Health Organization
WTP	Willingness To Pay

Executive Summary

Cancer is the second most common cause of death in the European Union (EU), after cardiovascular diseases, and approximately 2.7 million new cases are diagnosed each year. At the same time, drug development is moving faster than ever and a large proportion of drug development is allocated to cancer drugs. Among US biotech companies today, half are focusing on cancer and reports say that there are more than 800 new cancer agents in development (2015). While there is a great demand for new cancer drugs the increased utilization also present a challenge to the health care system. Drug development is costly and the price of innovative drugs can be high. The changing market puts high demands on budgets, policy makers and prescribing physicians.

This report explores the access to cancer drugs in a selection of countries across the EU. It focuses on how different countries address the challenge of balancing financial sustainability of the health care system and patients' access to modern cancer medicines, including issues of efficiency, affordability and equitable access between as well as within countries.

Pharmaceutical spending, relative to total health care expenditures and GDP per capita, has decreased since the millennium. Cost containment aimed at pharmaceutical spending in the EU in combination with an ageing population could be described as a "perfect storm" and may challenge the financial sustainability of both health care systems and the pharmaceutical industry in Europe. Cancer incidence increase by age and the share of people aged 65 years or older is expected to increase dramatically in the coming decades. Thus, cancer will put an increased pressure on health care systems and it's financing. This calls for a more efficient use of societal resources, while at the same time upholding dynamic efficiency in the pharmaceutical market.

New, innovative and more effective cancer drugs will be needed to face the demographic challenge and the increasing burden of cancer. Analysing different spending patterns in the European countries show that it is not always the highest spender, but the smartest spender, who achieves the best health outcomes. Although the forthcoming demographic change is likely to increase the cost of cancer, at least part of the cost increase can be dampened through investments in screening programs, shifts from inpatient to outpatient care and expired patents of widely-used cancer drugs. Hence, the cost of cancer may increase as a whole but improved treatment regimens and better preventive interventions can lower the cost per patient.

Parallel to the demographic changes is a rapid development in the medical management of cancer patients, from improvements in diagnostic techniques to advances in the medical treatment of cancer. Improved diagnostic methods and screening programs have facilitated early detection of tumours. Modern anti-tumour treatments target disease specific mechanisms, instead of all cells. Supportive drugs with a focus to improve patients' quality of life have ascended. Immune-oncology represents a promising new treatment approach for improvements in long term survival. In combination, the development of cancer treatment has led to improved cure rates as well as fewer and shorter hospitalizations.

Mapping market authorization and total sales gives an idea of market uptake of cancer drugs. Data show that total sales of oncology drugs in the included countries have increased substantially from €3 billion in 2003 to almost €11 billion in 2012. This is explained by a combination of increasing sales from established cancer medicines and the introduction of new ones. Sales of oncology drugs (when measured in Euros) have increased in all countries, but so has the between-country variation during the time period. Typically, sales have increased faster in countries with stronger public finances, part of which is likely explained by higher drug prices. Similar patterns were found when uptake of innovative cancer drugs was measured as sales over cases of mortality (used as a proxy of need for treatment) and the general finding was that richer countries adapt to new treatments faster than low income countries, although the results vary between drugs.

New individualised and targeted therapies and discoveries with few effective alternatives will require that decisions about market authorization and reimbursement are made under great uncertainty about risk-benefit and clinical value. This increases the uncertainty in decisions on pricing, reimbursement and use and presents new demands on risk sharing and evidence development, for example though instruments like adaptive licensing. Policies for management of uncertainty are thus becoming a new important policy area for cancer drugs. Some versions have already been tried but there is plenty of room for improvement, such as more detailed process plans and implementation programs that include pre-defined strategies for evidence collection following an initial approval.

A payment system for new cancer drugs should be designed with the additional objective of optimal use of the new drugs. Every new cancer drug face its own set of challenges and no one payment model will be superior in all cases. Designing a payment system requires attention to the fact that the value is not only uncertain but may also differ between users, e.g. for different types of cancer, line of treatment or subpopulations.

The aim is to ensure a fast and cost-effective access to safe and efficient cancer drugs. Common for all potential solutions is the need for collection of data on resource utilization and outcomes. Decisions must increasingly be based on objective and verifiable criteria, which require careful attention to what data should be collected, as well as how it should be analysed and interpreted. The development of payment systems based on prospective outcome data will thus be integrated with the scientific development of new cancer drugs. The payment system will be one of the factors determining access to new therapies and indirectly influence what type of therapies are developed in the future.

1 Introduction

1.1 Purpose and aim of the report

This report sets out to examine the access to cancer drugs in a selection of countries across the EU. The focus is how different countries are addressing the challenge of balancing financial sustainability of the health care system, and access for patients to modern cancer medicines. This includes issues of efficiency and affordability, as well as objectives for an equitable access between and within countries.

The report focuses on a selected number of cancer diseases where innovation is prominent, e.g. melanoma, Non-Small Cellular Lung Cancer (NSCLC), and multiple myeloma. The report includes a description of the situation as well as an analysis of the health care policies developed to make the necessary decisions at different levels in the health care system, including at the European level.

This chapter includes a description of the overall economic conditions and health care expenditures in the twelve countries studied (Austria, Belgium, Denmark, Finland, Germany, Hungary, the Netherlands, Norway, Poland, Sweden, Switzerland and the UK). It is followed by a description of the health burden of cancer in terms of incidence, prevalence and Disability-Adjusted Life Years (DALYs) lost due to cancer. Thereafter, estimates of the direct and indirect costs for cancer are presented and discussed. The chapter ends with a summary and conclusions.

1.2 Income levels and health care expenditures

Health care expenditures are in the long term closely related to the income level of different countries. In addition, due to the predominately public funding of health care, they are in the short and mid-term affected by the finances of the public sector. Hence, the 2008 financial crisis, which strongly affected the current accounts as well as the balance sheets with rising deficits and debt levels, had a significant impact on health care spending.

Figures 1.1 and 1.2 show the GDP per capita at market prices in the twelve countries studied for the period 2000-2013. The GDP per capita in Norway was twice as high as the EU average in 2000, but three times higher in 2013. Norway and Switzerland are to some extent outliers, and not members of the EU, but are included to illustrate how “rich countries”, with no public sector financial problems, have handled access to new cancer drugs in relation to other countries. Poland and Hungary have less than half of the GDP per capita than the EU average.

The other countries had rather similar GDP per capita in 2000 but it can be seen that for example Sweden has recovered better than UK, which was harder hit by the financial crises.

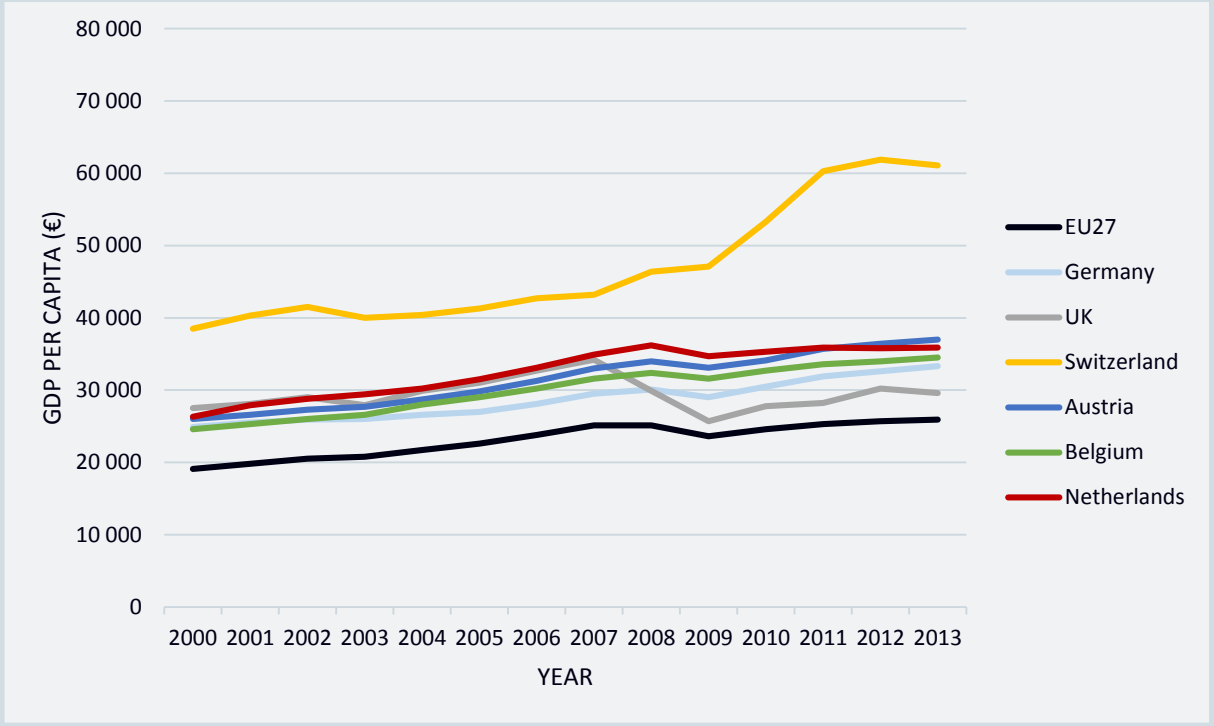

FIGURE 1.1. GDP PER CAPITA AT MARKET PRICES IN AUSTRIA, BELGIUM, EU27, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK, IN €, 2000-2013 [2].

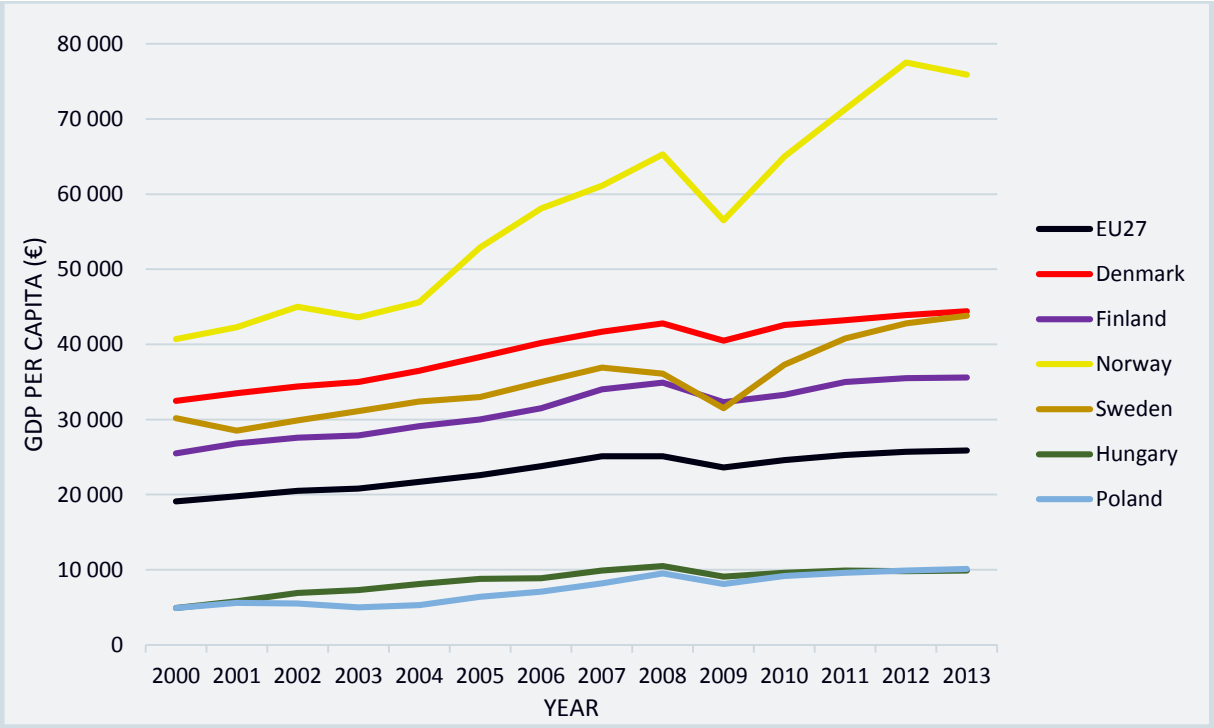

FIGURE 1.2. GDP PER CAPITA AT MARKET PRICES IN DENMARK, EU27, FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN, IN €, 2000-2013 [2].

Figures 1.3 and 1.4 show the GDP per capita in the different countries corrected for differences in purchasing power. Since health care is to a large extent produced by internal human resources, this is in a way a more correct comparison of differences in affordability between countries. You can also see that the differences are significantly reduced, from a span of €75 900 – 9 900 to €49 200 – 17 200. But Norway/Switzerland and Poland/Hungary are still significantly above and below, respectively, the other eight countries.

Yet, the un-adjusted differences in GDP per capita are important for the opportunities for a specific country to buy goods that are traded on international markets, where the strength of the currency determines what you can afford to pay. New cancer drugs, which are sold at European market prices, are thus relatively more expensive for countries with a lower GDP per capita at market price. The relative cost in relation to domestic resources, for example salaries for doctors and nurses, are also higher. We would thus expect that such economic factors, not related to the medical need or effectiveness of the drugs, would affect uptake and use. However, the magnitude of the effect may vary, and it is necessary to take into account that prices may vary between countries even for goods traded internationally.

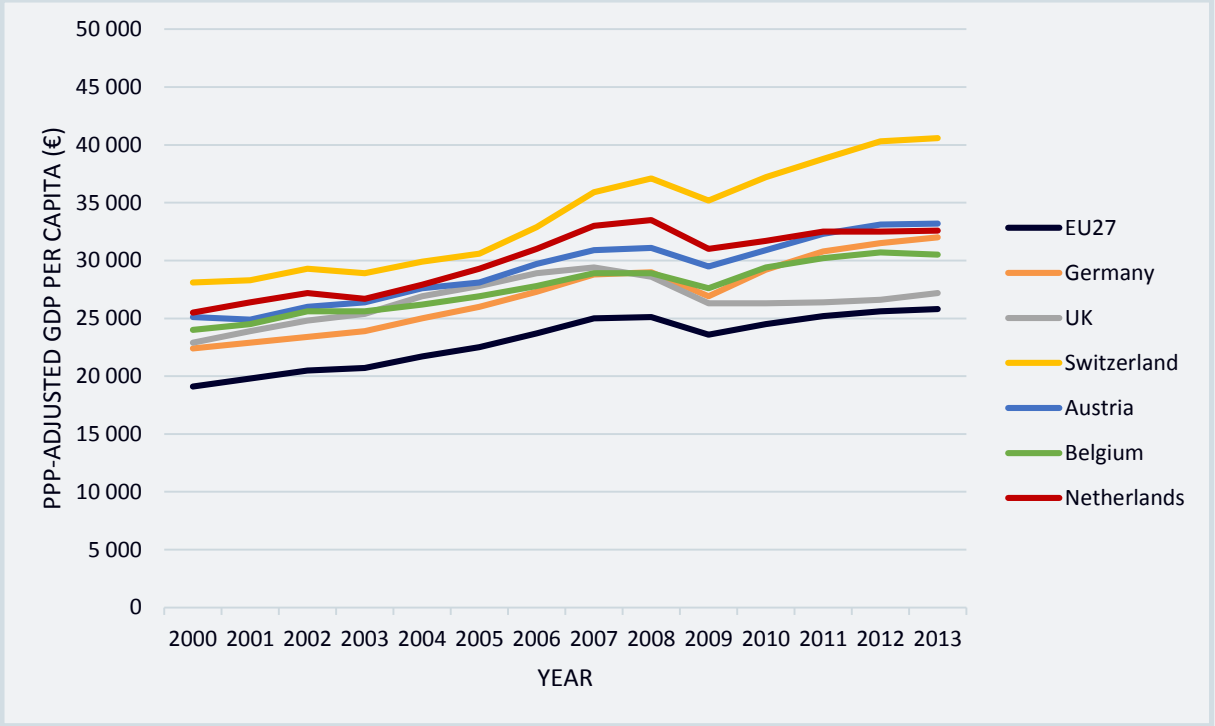

FIGURE 1.3. PPP-ADJUSTED GDP PER CAPITA AT MARKET PRICES 2000-2013 IN AUSTRIA, BELGIUM, EU27, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK, IN € [2].

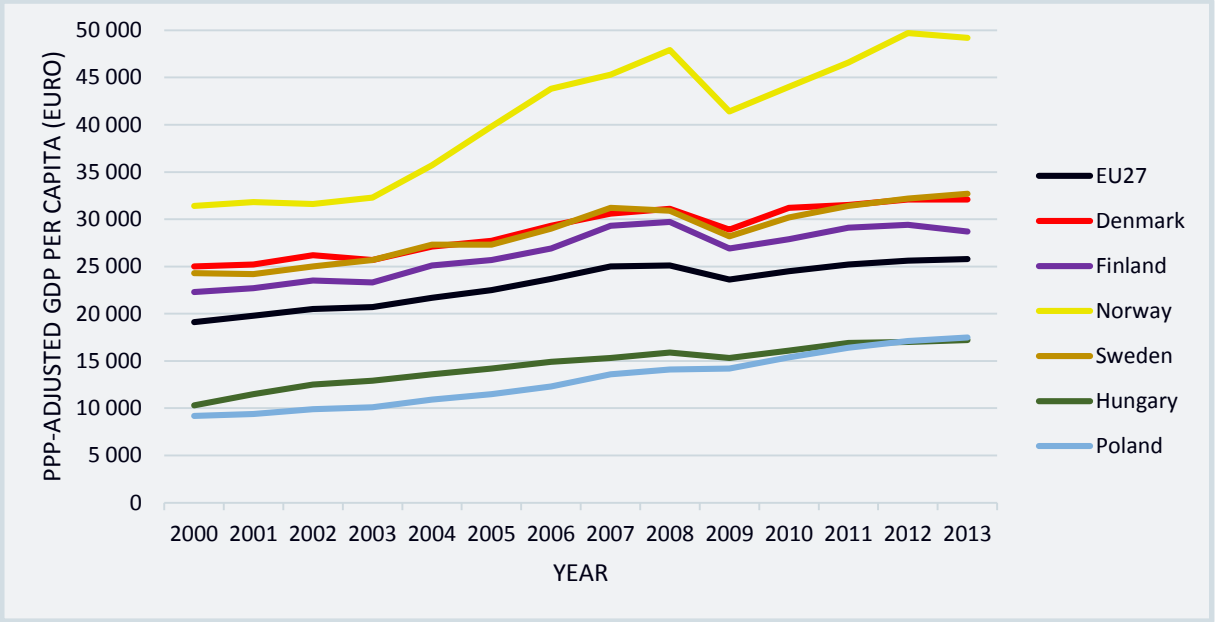

FIGURE 1.4. PPP-ADJUSTED GDP PER CAPITA AT MARKET PRICES 2000-2013 IN DENMARK, EU27, FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN, IN € [2].

Figures 1.5 and 1-6 show the share of GDP devoted to health care in the different countries. We can note that Poland and Hungary have lower shares of GDP devoted to health care. It is a general observation that the share of total resources devoted to health care increases with increasing GDP per capita. But we can observe that it is not Norway or Switzerland that have the highest share for health care expenditures; it is the Netherlands.

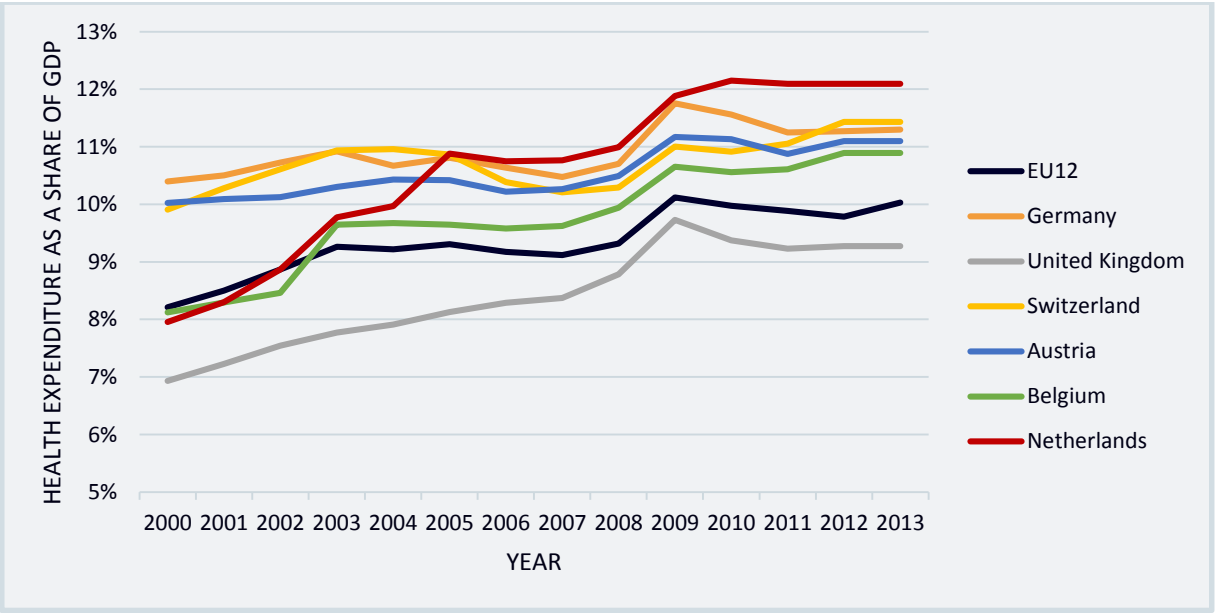

FIGURE 1.5. HEALTH EXPENDITURE AS SHARE OF GDP, 2000- 2013 (OR NEAREST YEAR) [2], IN AUSTRIA, BELGIUM, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK.

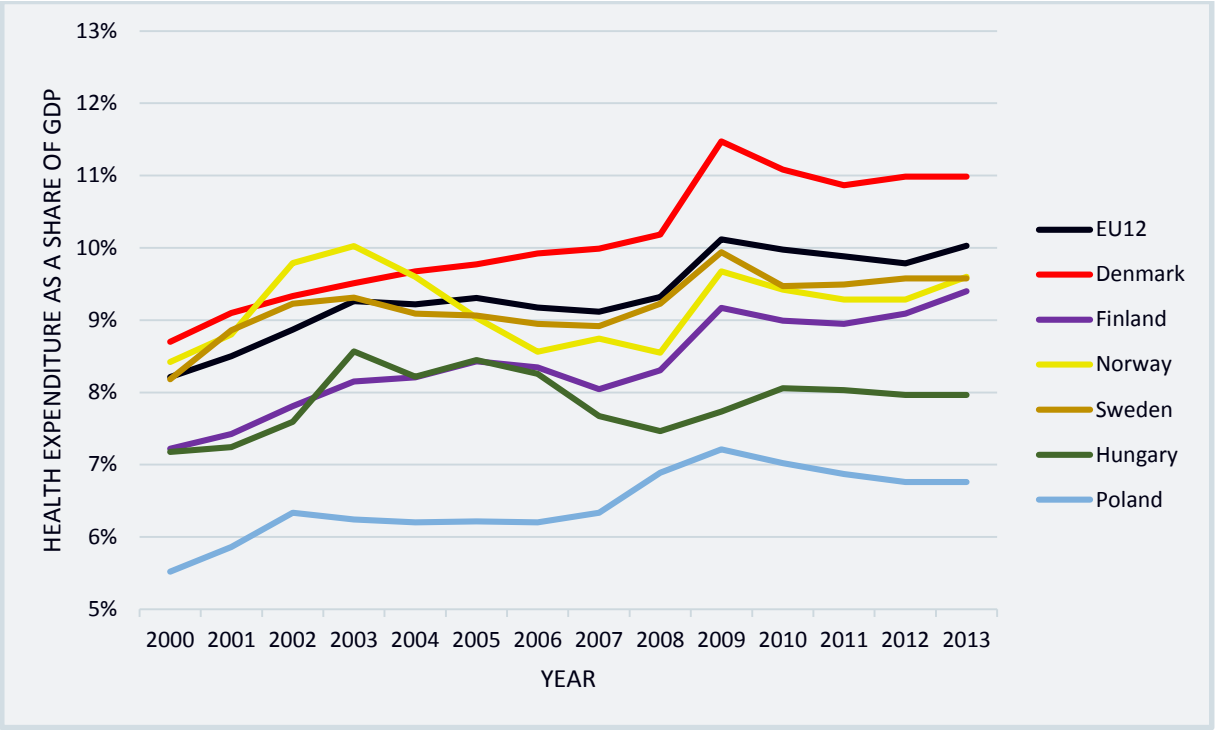

FIGURE 1.6. HEALTH EXPENDITURE AS SHARE OF GDP, 2000- 2013 (OR NEAREST YEAR) [2], IN DENMARK, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN.

In 2013, health expenditures as a share of GDP were between 7 and 12 percent in the twelve countries, compared to 5.5 to 10.5 percent in 2000. The Netherlands was among the countries with the largest increase, from 8 to 12 percent, while Sweden had a more modest increase from 8 to 9.5 percent during the period 2000-2013. Hungary and Poland are a bit behind the other countries, which will be the case for most income-related measures throughout this report.

Figures 1.7 and 1.8 show the health spending per capita in 2005 PPP-adjusted USD, which is the measure used for comparative reasons for data in the OECD statistics. Here, Poland and Hungary spend about PPP-adjusted USD 1,200 per capita on health care, i.e. nearly a third of the EU12 average of PPP-adjusted USD 3,500. Countries with lower prices seem to spend a smaller shares on health care, and we can see that even a PPP adjusted comparison shows a difference between the highest and lowest value that is more than four-fold.

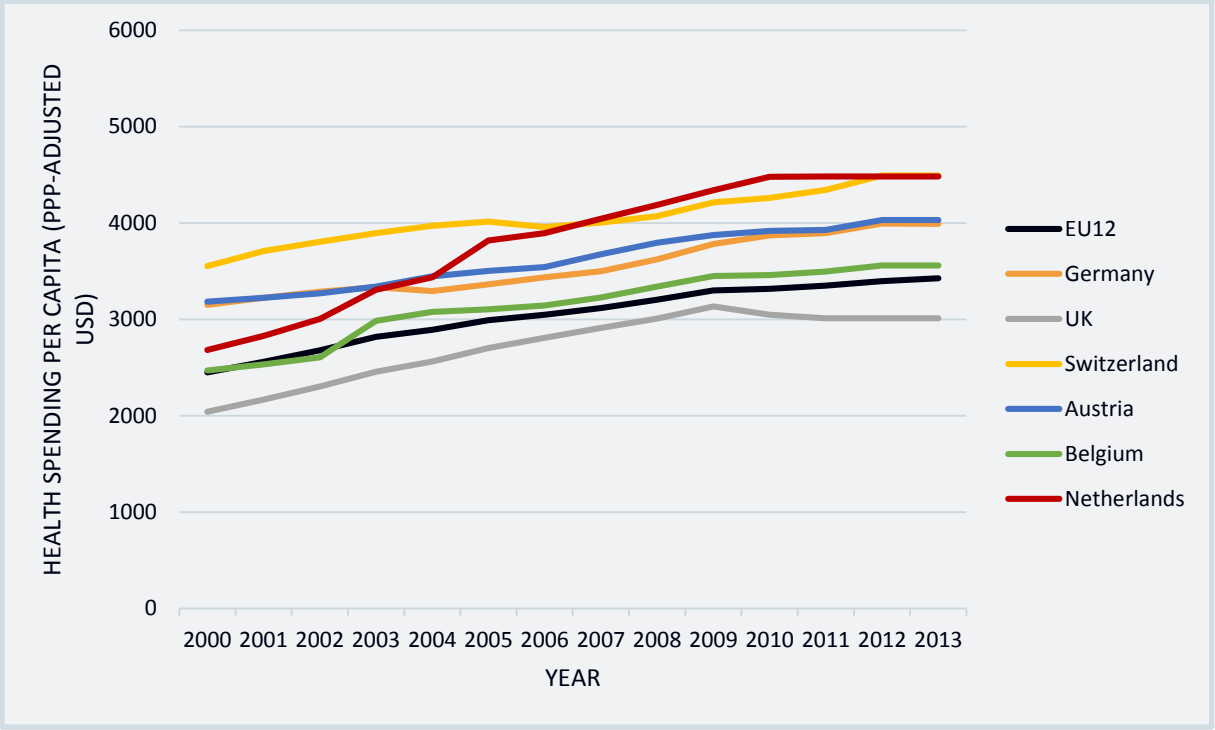

FIGURE 1.7. HEALTH SPENDING PER CAPITA 2000-2013 (OR NEAREST), PPP-ADJUSTED USD (2005 PRICES) [2] IN AUSTRIA, BELGIUM, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK.

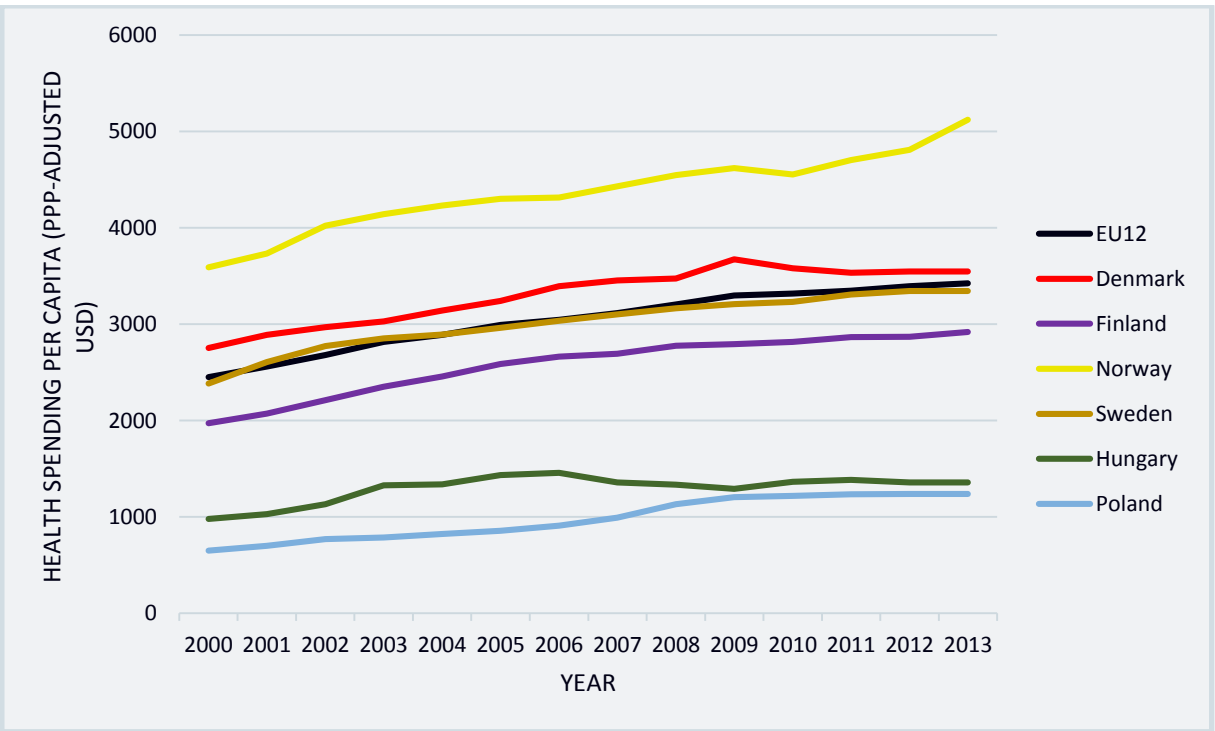

FIGURE 1.8. HEALTH SPENDING PER CAPITA 2000-2013 (OR NEAREST), PPP-ADJUSTED USD (2005 PRICES) [2] IN DENMARK, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN.

We now turn to the pharmaceutical expenditures in the different countries, shown in Figures 1.9 to 1.10. We can note that Hungary and Poland has the highest share of pharmaceuticals of total health care expenditures. Interestingly, the share is moving in different directions during the period; reduced in Poland and increased in Hungary. The explanation for this is partly the previously mentioned difference in the relative price of internationally priced pharmaceuticals and domestic salaries. The lowest share for pharmaceuticals is found in Norway and Denmark, around 6 percent. Switzerland too has a low share, which partly can be explained by its relatively high salaries. The average share in the twelve countries is 15 percent. This share has been rather stable during the period, but with a small decline since 2003.

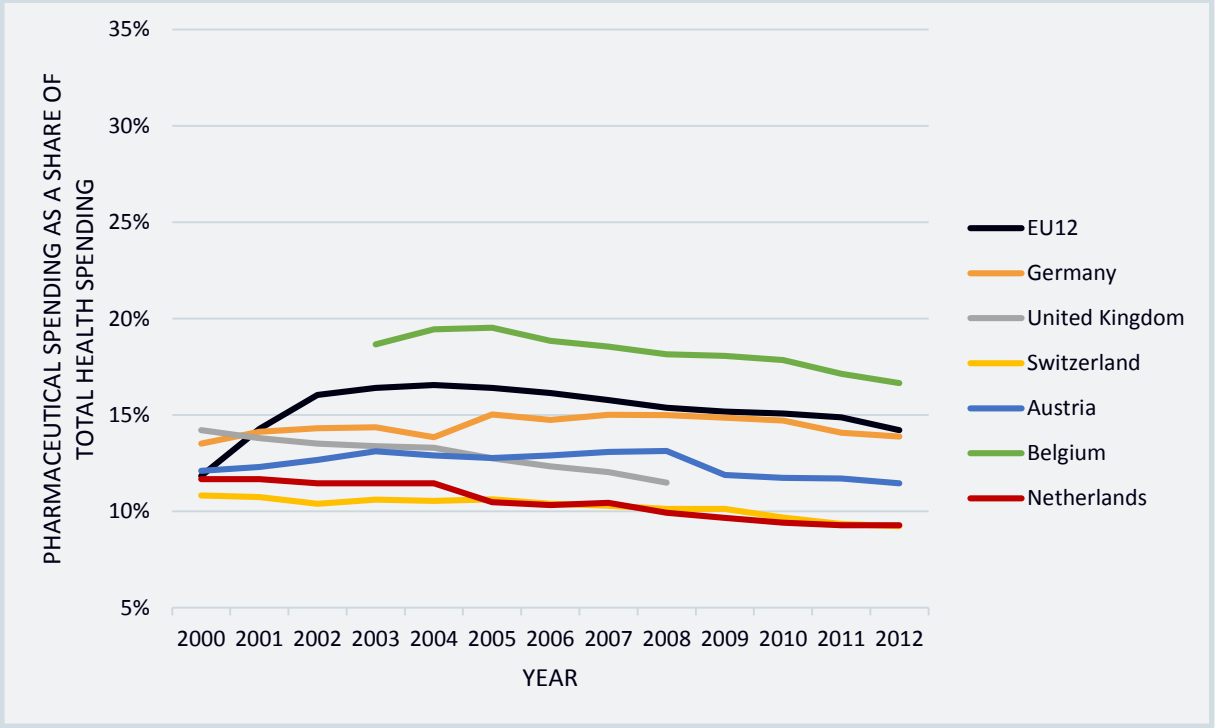

FIGURE 1.9. PHARMACEUTICAL SPENDING AS SHARE OF TOTAL HEALTH SPENDING, 2000-2012, IN AUSTRIA, BELGIUM, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK. DATA IS MISSING FOR THE UK FOLLOWING 2008 [2].

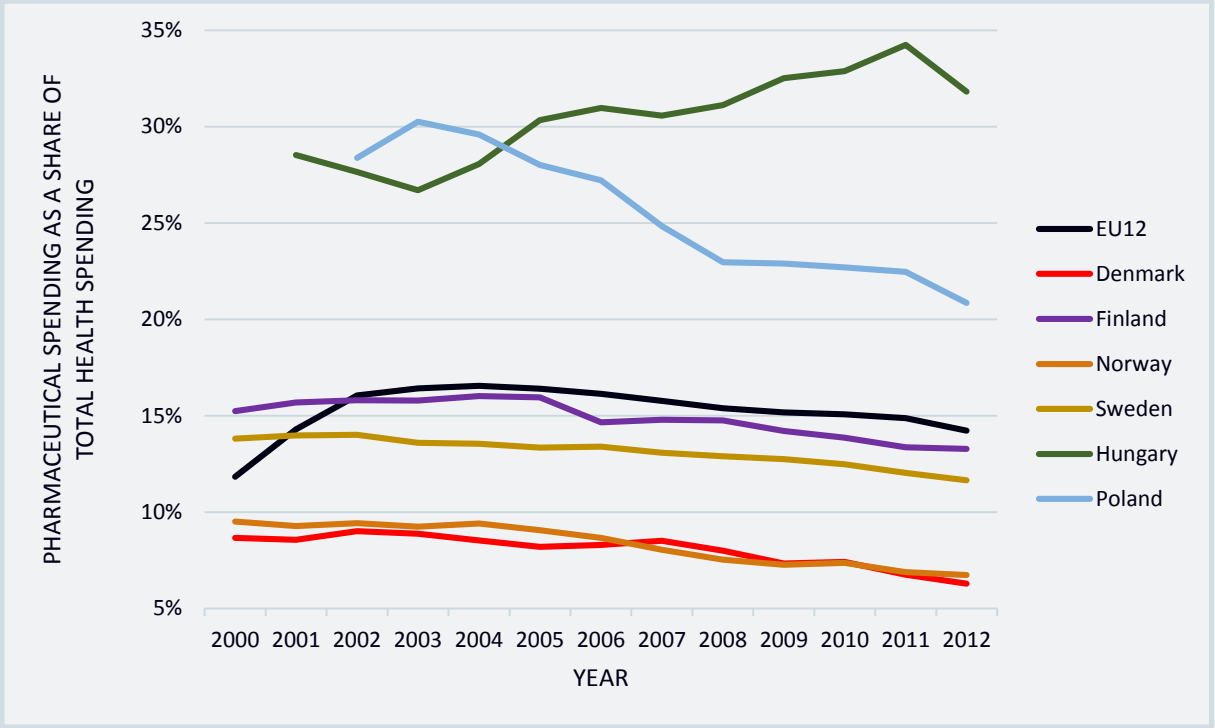

FIGURE 1.10. PHARMACEUTICAL SPENDING AS SHARE OF TOTAL HEALTH SPENDING, 2000-2012 [2], IN DENMARK, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN.

If we look at the PPP-adjusted pharmaceutical spending per capita, Figures 1.11 to 1.12, Poland and Hungary are at the bottom, and Belgium at the top. The steady increase in per capita spending in Germany over the period is also noticeable.

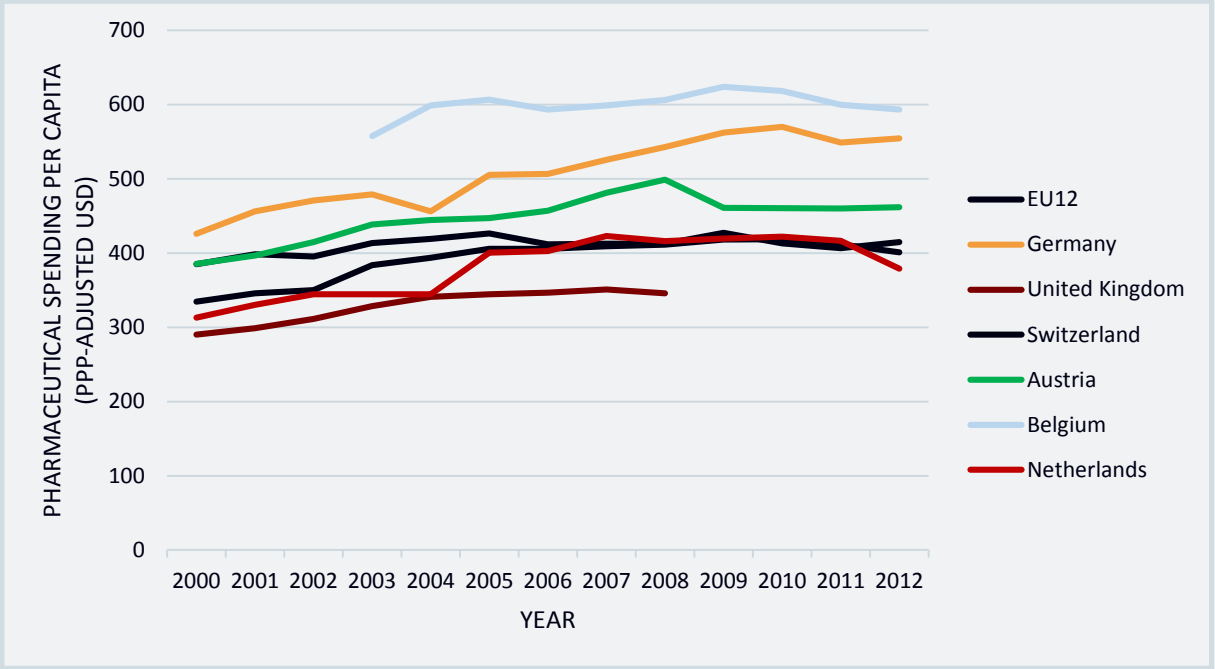

FIGURE 1.11. PHARMACEUTICAL SPENDING PER CAPITA 2000-2012, PPP-ADJUSTED USD (2005-PRICES) [3], FOR EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK. DATA IS MISSING FOR THE UK FOLLOWING 2008.

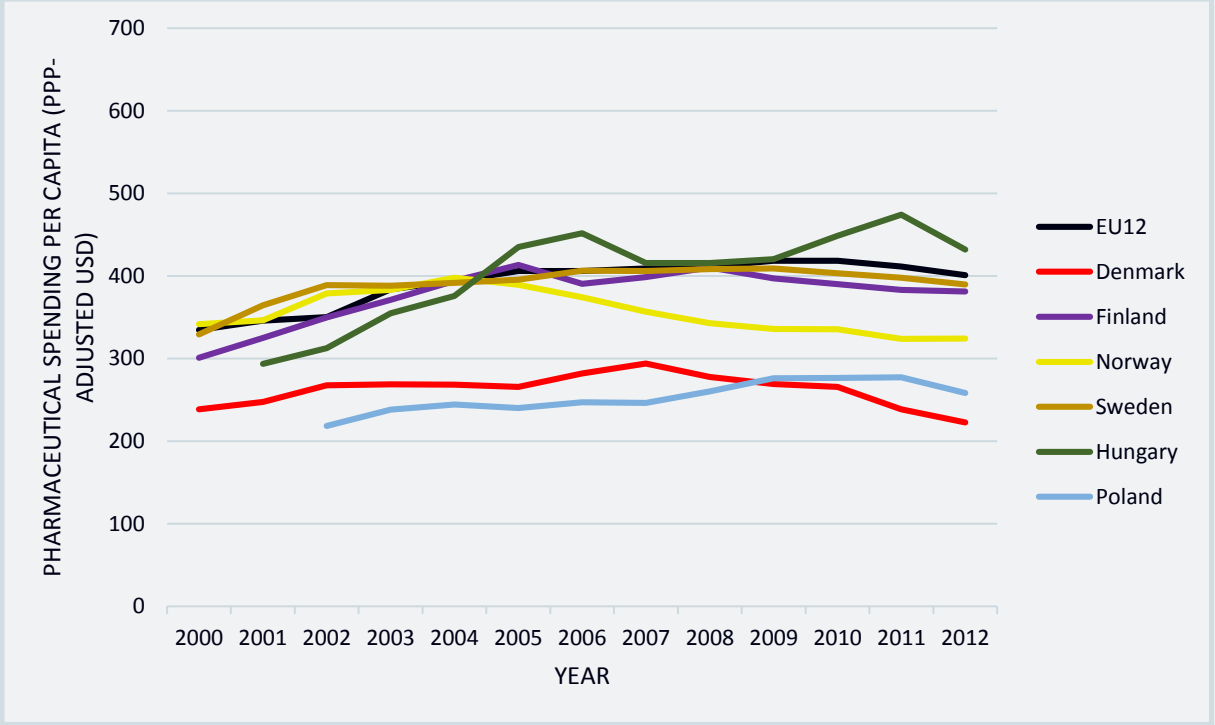

FIGURE 1.12. PHARMACEUTICAL SPENDING PER CAPITA 2000-2012, PPP-ADJUSTED USD (2005-PRICES) [4], IN DENMARK, EU12 (REFERRING TO THE AVERAGE VALUE OF THE TWELVE EUROPEAN COUNTRIES INCLUDED), FINLAND, HUNGARY, NORWAY, POLAND AND SWEDEN.

Pharmaceutical spending has in most cases decreased somewhat following 2008, but the stagnation and drop in pharmaceutical spending started before the financial crisis of 2008. Although the financial crisis of 2008 is believed to have had an impact on the decreasing pharmaceutical spending, other factors such as patent expirations for, e.g. blockbuster cancer drugs, as well as an increase in the use of generic drugs may have contributed to the effect.

The perspective and conclusions about spending levels on pharmaceuticals may thus depend on the data presented. While there is a relation between GDP per capita, health care spending and pharmaceutical spending, there are several factors that influence the variation over time, some economic and some related to specific policy decisions. While pharmaceuticals only account for 1 to 2 percent of GDP, and cancer medicines only account for a minor part of this, there are a number of other factors that define access to specific cancer medicines. However, it is important to have the economic factors in mind when interpreting policies and national decisions. In times when economic growth is slow, or even negative, it is particularly difficult for new treatment opportunities to get a budget, since many new alternatives compete for the available resources. And budgets have a tendency to be rigid and difficult to change, and explicit disinvestment proposals are often met with strong opposition. The period 2000-2013 is thus an important and interesting period to study, as it followed the 1990s, with a strong growth in pharmaceutical spending.

It is also important to remember that resources are needed not only for pharmaceuticals, but also for increasing capacity for diagnosis and patient follow-up, to make sure that the potential improvements in outcome from new drugs are realized in clinical practice.

1.3 Cancer burden in the EU

The health burden of cancer can be measured in several ways, and different measures can be useful for different purposes. Incidence may be of special interest for preventive programs, prevalence for chronic diseases, premature mortality can be seen as a measure of unmet medical need, and improvements in survival can be of interest in studies of therapeutic progress over time. Disability-Adjusted Life Years (DALY) is a measure that combines the impact of survival with disability and is the closest to what economists view as a measure of disease burden.

In this section we will take a closer look on cancer incidence, mortality, prevalence, survival and other measures of the burden of cancer in the countries studied, and for the specific cancers. The link between burden of the disease and the resources used is important for the understanding variations in access.

1.3.1 Incidence and mortality

In 2012, the estimated number of newly diagnosed cases of cancer[1] was 2.7 million in the EU28 [3]. Out of the 5.0 million people that died in the EU28 in 2012 [5], some 1.3 million died from cancer [6], and similar numbers are expected for 2013 [3]. This makes cancer the second most common cause of death in the European Union, after cardiovascular diseases[2] [7].

A comprehensive study conducted in Europe by Ferlay and colleagues in 2013 [7] presents the latest estimation of cancer incidence and mortality. Even though the data collection methodology has changed slightly since the authors' 2007 publication, and caution thus should be taken when interpreting the time trend, these estimates were built by the same authors and some tendencies seem to be consistent with findings of the literature on the epidemiological evolution of the different cancers.

The 2.7 million new cancer cases diagnosed in 2012 were about 10 percent more than 6 years earlier when comparing absolute numbers, while the number of deaths remains practically unchanged given the changing demographics, indicating that the European all-cancers mortality rate is slowly starting to recede.

Figures 1.13 to 1.16 shows the 2012 crude incidence rate, i.e. the number of newly diagnosed cancer cases per 100,000 inhabitants, in a selected number of countries and cancers (all cancers, lung cancer, multiple myeloma and melanoma). In these figures, and all figures following this section, EU12 refer to the average value of the twelve countries in focus in this report (Austria, Belgium, Denmark, Finland, Germany, Hungary, the Netherlands, Norway, Poland, Sweden, Switzerland and the UK). EU27 refer to the EU average prior to the inclusion of Croatia as a member state.

[1] Cancer refers here to ICD-10 code C00-96/C44, i.e. all cancer types but non-melanoma skin cancer.
[2] Cancer refers here to malignant neoplasms (ICD-10 code C00-C97). Cardiovascular diseases refer to diseases of the circulatory system (I00-I99).

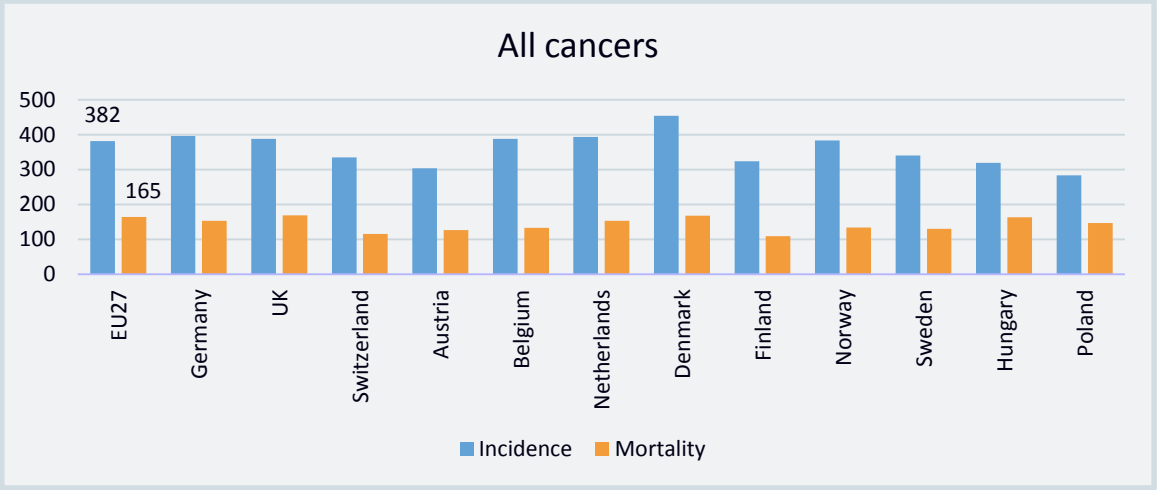

FIGURE 1.13. INCIDENCE AND MORTALITY OF ALL CANCERS BUT NON-SKIN MELANOMA FOR OUR EU12 COUNTRIES AND FOR EU27, PER 100,000 INHABITANTS, IN 2012 [7].

Crude incidence and mortality rates, i.e. not corrected for differences in population age and sex, are relevant for comparing the burden of disease and available resources. As is seen in Figure 1.14 to 1.16 below, there is no clear pattern of availability of resources and the burden of disease.

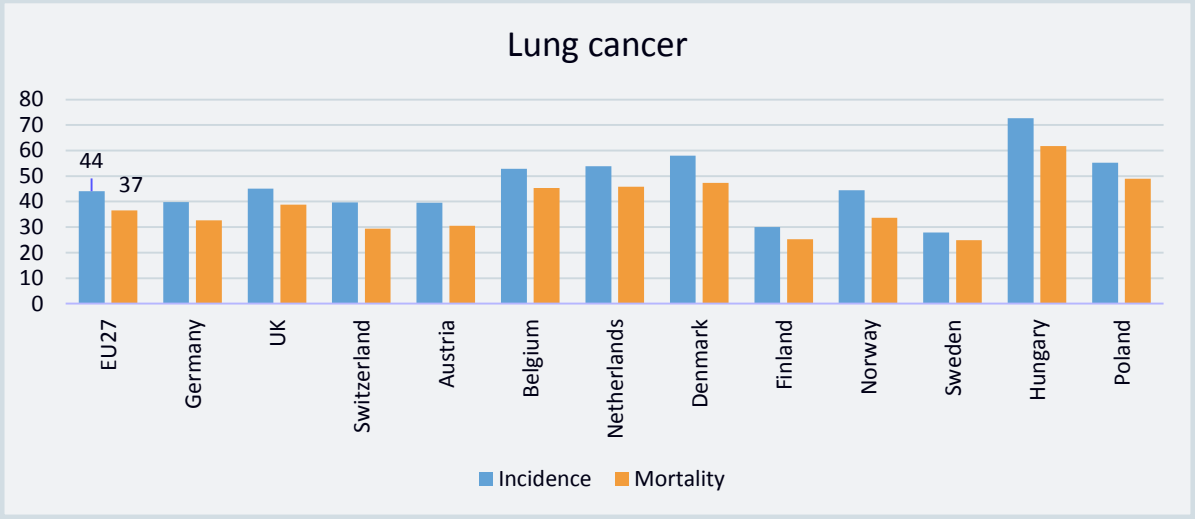

FIGURE 1.14. INCIDENCE AND MORTALITY OF LUNG CANCER FOR OUR EU12 COUNTRIES AND FOR EU27, PER 100,000 INHABITANTS, IN 2012 [7].

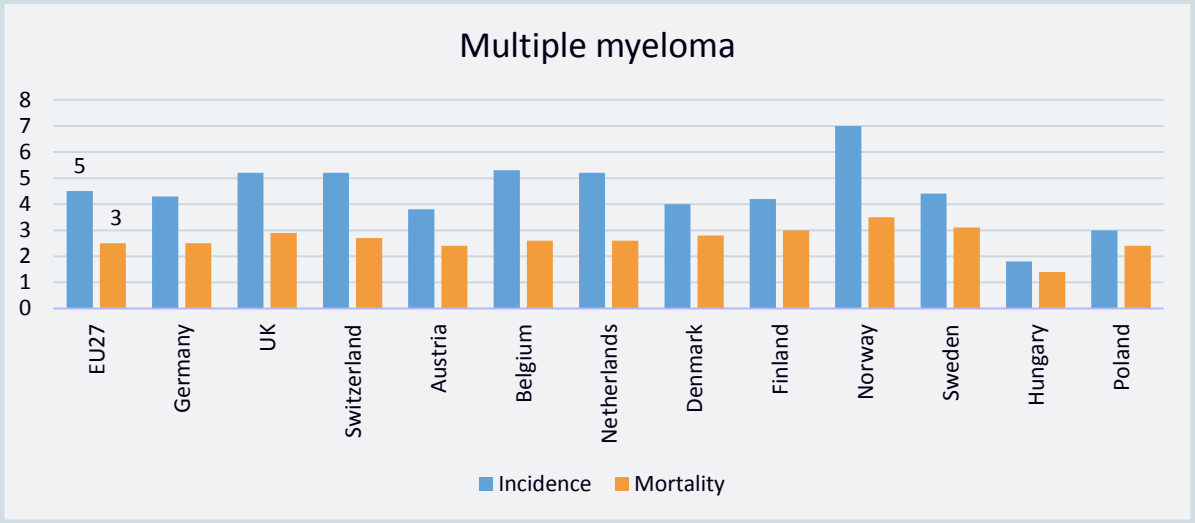

FIGURE 1.15. INCIDENCE AND MORTALITY OF MULTIPLE MYELOMA FOR OUR EU12 COUNTRIES AND FOR EU27, PER 100,000 INHABITANTS, IN 2012 [7].

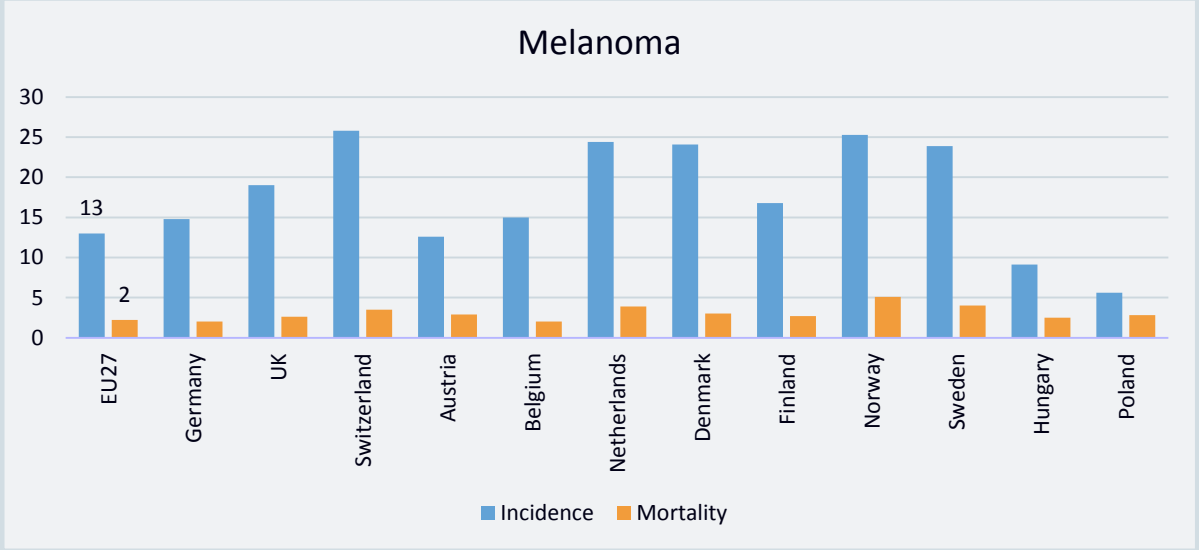

FIGURE 1.16. INCIDENCE AND MORTALITY OF MELANOMA FOR OUR EU12 COUNTRIES AND FOR EU27, PER 100,000 INHABITANTS, IN 2012 [7].

There are great differences in the incidence and mortality for the three specific cancer types. For multiple myeloma Hungary and Poland have both lower incidence and mortality compared to the other countries included while the opposite is true for lung cancer. Norway has a high incidence of multiple myeloma, while both incidence and mortality is low in Hungary. Both incidence and mortality for melanoma is low in Germany and UK. A breakdown on incidence and mortality by age group is presented below, which may further illuminate the sources of the variation.

TABLE 1.1. CANCER INCIDENCE FOR OUR EU12 COUNTRIES FOR SELECTED CANCERS BY AGE GROUP, PER 100,000 INHABITANTS, IN 2012 [7].

Lung Cancer	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
EU12	0.0	1.0	8.4	26.8	58.7	104.7	157.3	209.6	251.2	240.0
Germany	0.0	0.9	9.4	26.8	58.0	95.1	131.4	169.5	201.3	196.2
UK	0.0	1.0	5.2	16.4	37.2	74.8	132.0	202.2	270.5	333.3
Switzerland	0.0	0.9	4.3	19.9	46.9	89.5	138.9	185.0	220.3	203.1
Austria	0.0	0.9	8.7	25.0	54.7	98.4	144.4	175.8	191.6	179.5
Belgium	0.1	1.4	12.7	35.9	73.8	125.2	182.5	239.6	278.1	231.2
Netherlands	0.0	1.5	13.0	33.8	68.9	117.7	176.2	244.1	305.1	260.9
Denmark	0.0	0.9	6.4	26.3	60.1	112.5	182.0	267.4	353.6	352.9
Finland	0.0	0.6	2.1	10.0	25.6	55.6	96.1	140.4	176.9	200.9
Norway	0.0	1.1	4.0	16.6	40.5	85.4	143.5	213.7	270.7	268.3
Sweden	0.0	0.9	3.2	10.0	25.8	55.9	94.8	140.0	175.6	147.8
Hungary	0.0	1.7	26.0	69.2	139.3	211.6	267.2	286.8	284.4	242.7
Poland	0.0	0.6	5.8	31.8	74.0	135.2	198.0	251.0	286.7	262.8
Multiple Myeloma	**0-14**	**15-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75+**
EU12	0.0	0.2	1.1	2.4	4.7	8.2	12.7	18.4	25.2	30.6
Germany	0.0	0.2	1.0	2.2	4.4	7.7	12.4	18.4	25.1	29.7
UK	0.0	0.2	1.3	2.6	5.1	8.8	14.1	20.7	28.5	39.6
Switzerland	0.0	0.2	1.1	3.1	6.1	9.4	13.3	20.1	28.5	37.0
Austria	0.0	0.2	1.1	2.1	3.9	6.8	10.6	15.1	20.9	27.5
Belgium	0.0	0.2	1.2	3.0	5.8	10.2	16.1	23.0	29.8	33.4
Netherlands	0.0	0.1	1.1	2.7	5.6	9.8	15.5	22.6	30.2	34.1
Denmark	0.0	0.1	1.0	2.2	4.2	7.6	11.3	16.9	23.0	25.5
Finland	0.0	0.1	0.6	1.6	4.0	7.2	11.9	16.6	23.1	34.3
Norway	0.0	0.2	1.9	4.3	7.7	12.9	19.4	27.6	38.9	49.3
Sweden	0.0	0.2	1.1	2.3	4.4	7.8	12.9	18.8	26.4	28.6
Hungary	0.0	-	-	1.0	2.2	3.9	5.8	7.9	10.5	11.7
Poland	0.0	0.1	0.7	1.7	3.5	6.2	9.4	13.1	16.9	16.4
Melanoma	**0-14**	**15-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75+**
EU12	0.2	9.1	18.9	22.5	27.3	32.9	40.1	47.6	54.2	63.6
Germany	0.1	7.3	13.5	16.1	21.3	27.6	35.2	42.7	48.4	54.4
UK	0.1	9.2	20.7	24.4	28.8	34.3	40.8	48.6	56.7	70.6
Switzerland	0.6	14.8	26.9	31.0	37.1	44.9	55.9	67.2	76.1	87.3
Austria	0.2	7.6	13.5	15.5	18.1	21.6	25.9	30.5	35.5	43.8
Belgium	0.2	9.9	19.5	21.5	23.5	26.1	29.6	32.8	35.8	41.0
Netherlands	0.6	13.8	29.5	34.8	40.6	46.4	52.5	57.9	61.6	63.9
Denmark	0.2	15.7	27.5	30.4	35.8	41.7	49.4	57.3	63.6	71.6
Finland	0.1	6.2	15.3	19.6	25.0	31.3	39.9	49.3	57.8	71.4
Norway	0.1	8.3	22.5	29.3	38.1	48.1	62.0	76.7	90.0	109.4
Sweden	0.1	9.4	24.6	30.3	36.7	45.2	55.3	66.7	77.5	92.8
Hungary	0.2	5.0	8.9	10.5	13.0	16.3	20.5	24.8	27.7	31.5
Poland	0.1	1.4	4.4	6.6	9.1	11.8	14.6	17.0	19.4	24.9

TABLE 1.2. CANCER MORTALITY FOR OUR EU12 COUNTRIES FOR SELECTED CANCERS BY AGE GROUP, PER 100,000 INHABITANTS, IN 2012 [7].

Lung Cancer	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
EU12	0.0	0.5	5.5	18.5	41.8	77.6	121.5	170.2	218.3	246.0
Germany	0.0	0.5	4.6	17.6	38.2	69.2	106.0	141.8	177.5	195.9
UK	0.0	0.5	3.2	10.9	28.7	59.6	107.8	168.9	235.5	321.6
Switzerland	0.0	0.5	5.4	17.1	34.8	59.4	91.5	130.4	166.8	171.0
Austria	0.0	0.3	2.9	15.1	35.1	68.1	106.5	136.2	159.8	175.3
Belgium	0.0	0.8	8.4	24.5	52.2	89.4	134.1	190.3	250.6	297.4
Netherlands	0.0	0.5	6.9	21.3	46.6	84.8	132.5	193.3	271.8	320.4
Denmark	0.0	0.5	7.4	20.7	41.3	81.9	131.8	205.6	284.9	351.1
Finland	0.0	0.3	2.4	6.2	19.2	42.2	76.3	115.6	153.8	189.1
Norway	0.0	0.3	1.9	8.9	25.5	56.2	101.1	155.8	215.8	246.3
Sweden	0.0	0.3	1.7	4.6	17.1	38.8	74.1	118.4	163.5	187.0
Hungary	0.0	1.0	17.8	51.9	103.7	169.3	222.9	254.2	267.5	246.7
Poland	0.0	0.3	3.4	23.0	58.9	111.7	173.0	231.7	272.3	249.9
Multiple Myeloma	**0-14**	**15-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75+**
EU12	0.0	0.0	0.3	0.6	1.3	3.2	5.9	10.0	15.7	28.8
Germany	0.0	0.0	0.2	0.6	1.2	2.8	5.2	9.1	15.1	26.5
UK	0.0	0.1	0.3	0.7	1.5	3.3	6.0	10.2	16.3	31.9
Switzerland	0.0	0.0	0.2	0.8	1.4	3.3	6.0	10.5	16.5	28.7
Austria	0.0	0.0	0.2	0.4	1.2	2.6	5.2	8.5	13.6	27.5
Belgium	0.1	0.0	0.3	0.6	1.3	2.7	5.0	9.1	15.7	30.7
Netherlands	0.0	0.0	0.2	0.6	1.3	2.9	5.4	9.2	14.6	29.3
Denmark	0.0	0.0	0.2	0.7	1.3	3.5	6.6	11.5	17.6	29.0
Finland	0.0	0.0	0.3	0.5	1.6	3.7	6.7	10.7	16.9	33.8
Norway	0.0	0.0	0.3	0.3	1.2	4.1	7.8	12.8	19.7	41.7
Sweden	0.0	0.0	0.5	0.8	0.8	2.8	6.8	12.4	19.0	35.4
Hungary	0.0	0.0	-	0.5	1.1	2.2	3.9	5.8	8.3	11.7
Poland	0.0	0.0	0.4	0.8	2.0	3.9	6.5	10.3	15.5	19.1
Melanoma	**0-14**	**15-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75+**
EU12	0.0	0.5	2.0	2.7	3.8	5.3	7.4	10.2	13.1	20.5
Germany	0.0	0.3	1.2	1.8	2.5	3.4	4.7	6.3	8.2	14.4
UK	0.0	0.5	1.6	2.3	3.1	4.3	6.1	8.4	11.0	17.0
Switzerland	0.0	0.5	1.7	2.7	4.1	6.4	9.0	12.5	15.2	23.8
Austria	0.0	0.4	1.7	2.6	3.6	4.9	6.7	9.1	12.0	21.0
Belgium	0.0	0.5	1.4	1.9	2.4	3.4	4.7	6.6	8.1	11.0
Netherlands	0.0	0.9	3.1	4.0	5.3	7.1	9.7	12.7	14.9	21.4
Denmark	0.0	0.6	2.2	2.9	3.7	4.7	6.9	9.3	12.1	20.3
Finland	0.0	0.4	1.5	1.9	3.2	4.5	6.2	8.8	12.4	20.5
Norway	0.0	0.8	3.2	4.3	6.1	8.8	12.3	17.6	22.8	33.8
Sweden	0.0	0.5	2.3	3.2	4.5	6.4	9.7	13.9	18.8	28.8
Hungary	0.0	0.6	1.8	2.3	3.0	4.1	6.1	8.3	10.3	16.2
Poland	0.0	0.5	1.9	2.8	3.9	5.3	6.8	8.7	10.9	17.7

Figure 1.17 shows the relationship between GDP per capita and all-cancer mortality for the 12 countries included in the report. There is a slight tendency of a negative relation, but the correlation is very weak.

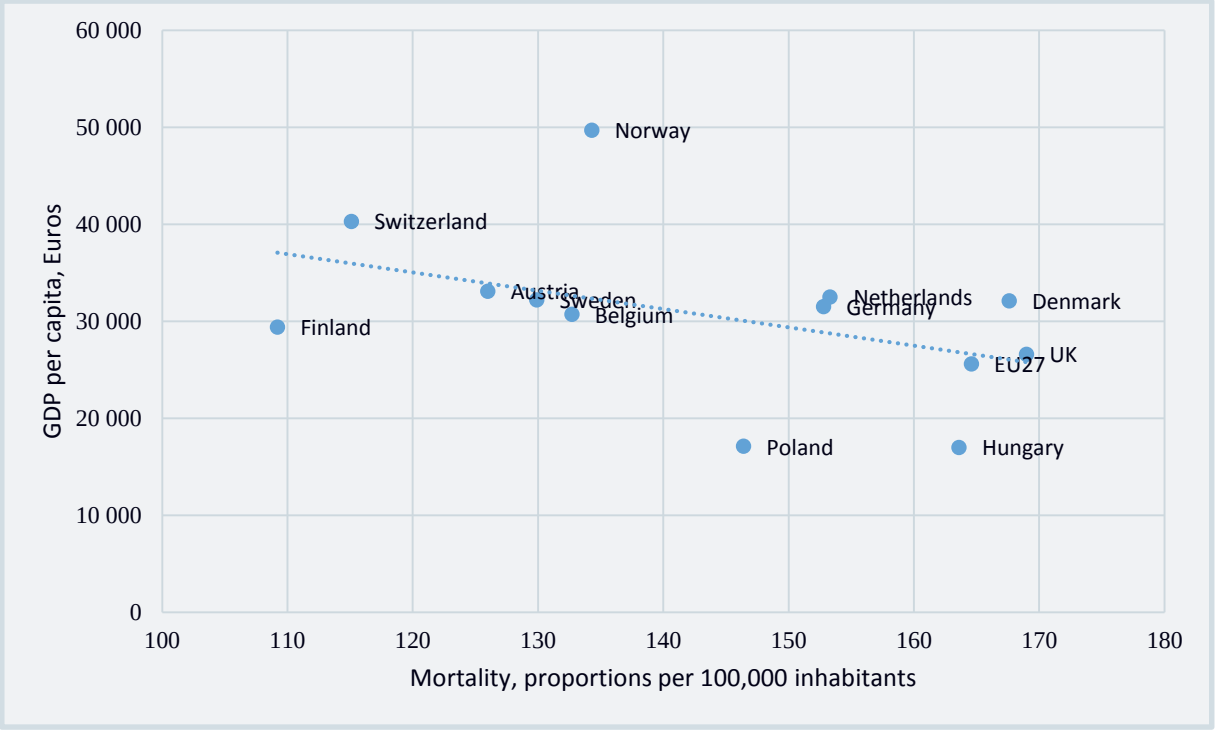

FIGURE 1.17. SCATTER PLOT OF 2012 GDP PER CAPITA AND MORTALITY FOR OUR EU12 COUNTRIES [7].

1.3.2 Prevalence

"Cancer prevalence is the number or proportion of the population living with cancer in a given time point or during a specified time period. Data on cancer prevalence are usually provided in the form of 1-year, 3-year and/or 5-year prevalence and describe the number of patients diagnosed with cancer and still alive one/three/five year(s) after the diagnosis in the given population. For instance, 5-year prevalence in 2012 includes all cancer cases diagnosed within the 5 previous years and still alive in 2012." [7]

In the EU27 with its 500 million inhabitants in 2012, the 1-year, 3-year, and 5-year overall cancer prevalence was around 440, 1,126, and 1,670 per 100,000 inhabitants respectively [7]. Large variations are, however, seen between the European countries. Belgium was the country among the 12 selected for this report with the highest 5-year prevalence – 2,143 cases per 100,000 – and Poland had the lowest 5-year prevalence – 1,072 cases per 100,000. Prevalence does not only vary between countries but also between cancers. Prevalence of lung cancer, as well as incidence and mortality, is higher in Eastern Europe, here represented by Hungary and Poland.

In Figures 1.18 to 1.21 the 2012 5-year prevalence per 100,000 inhabitants is seen for all cancers and for the different cancers.

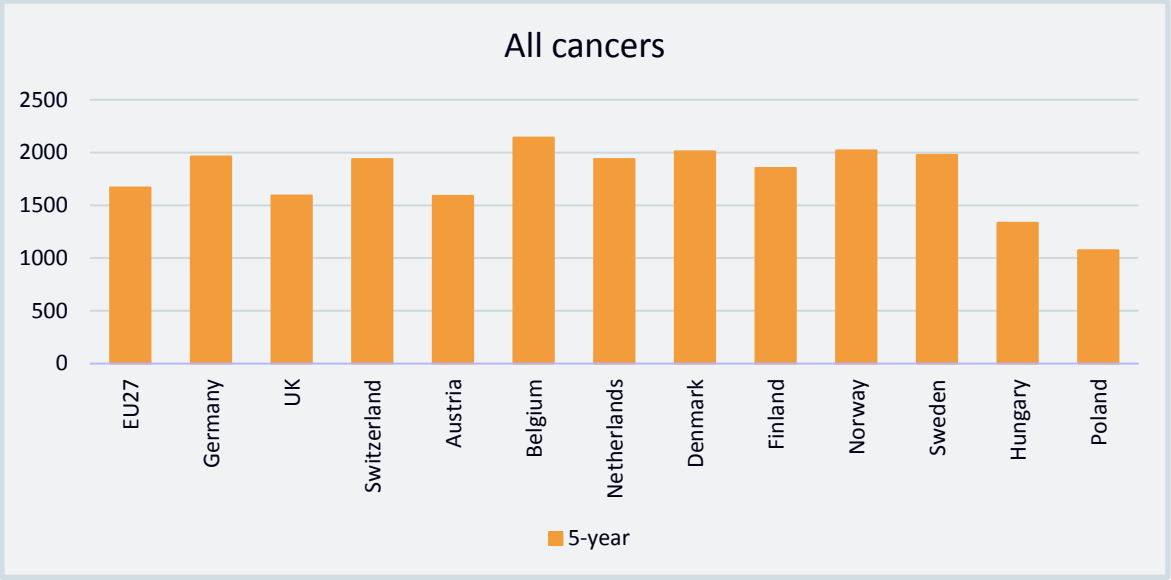

FIGURE 1.18. ESTIMATED PREVALENCE OF ALL CANCERS BUT NON-SKIN MELANOMA (C00-C97/C44), PER 100,000 INHABITANTS, FOR OUR EU12 COUNTRIES AND FOR EU27 IN 2012 [7].

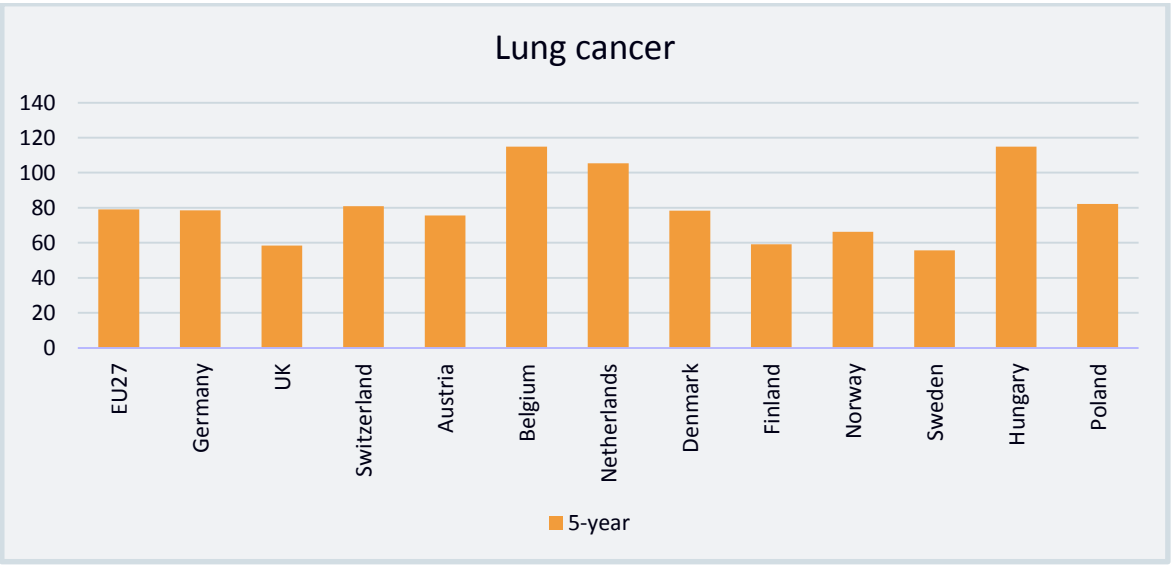

FIGURE 1.19. ESTIMATED PREVALENCE OF LUNG CANCER (C33-C34), PER 100,000 INHABITANTS, FOR OUR EU12 COUNTRIES AND FOR EU27 IN 2012 [7].

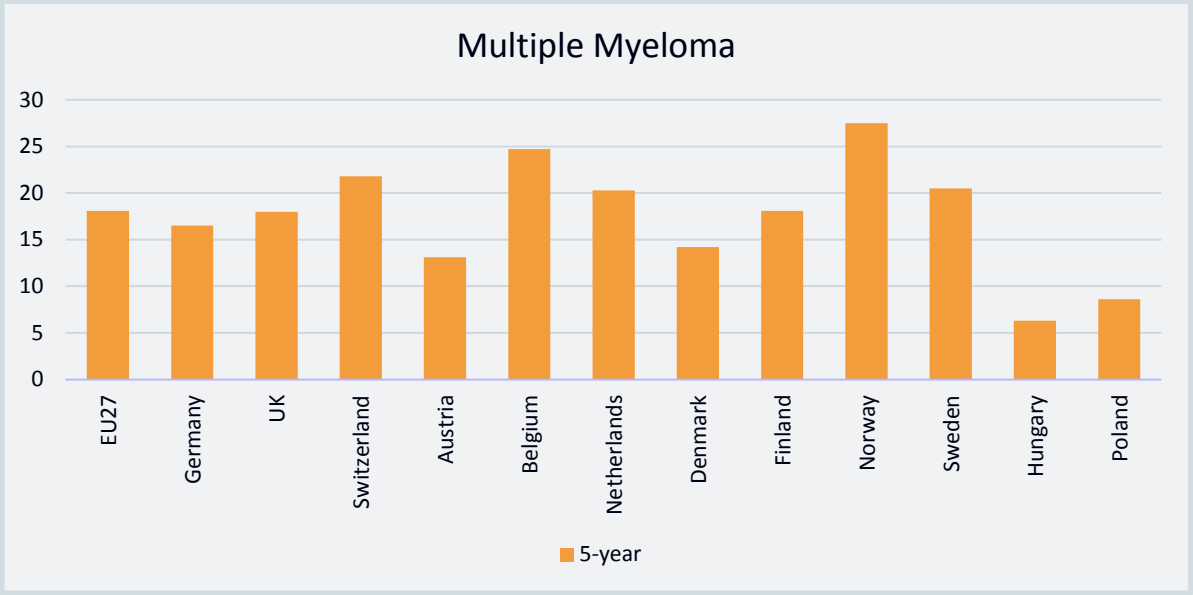

FIGURE 1.20. ESTIMATED PREVALENCE OF MULTIPLE MYELOMA (C88 + C90), PER 100,000 INHABITANTS, FOR OUR EU12 COUNTRIES AND FOR EU27 IN 2012 [7].

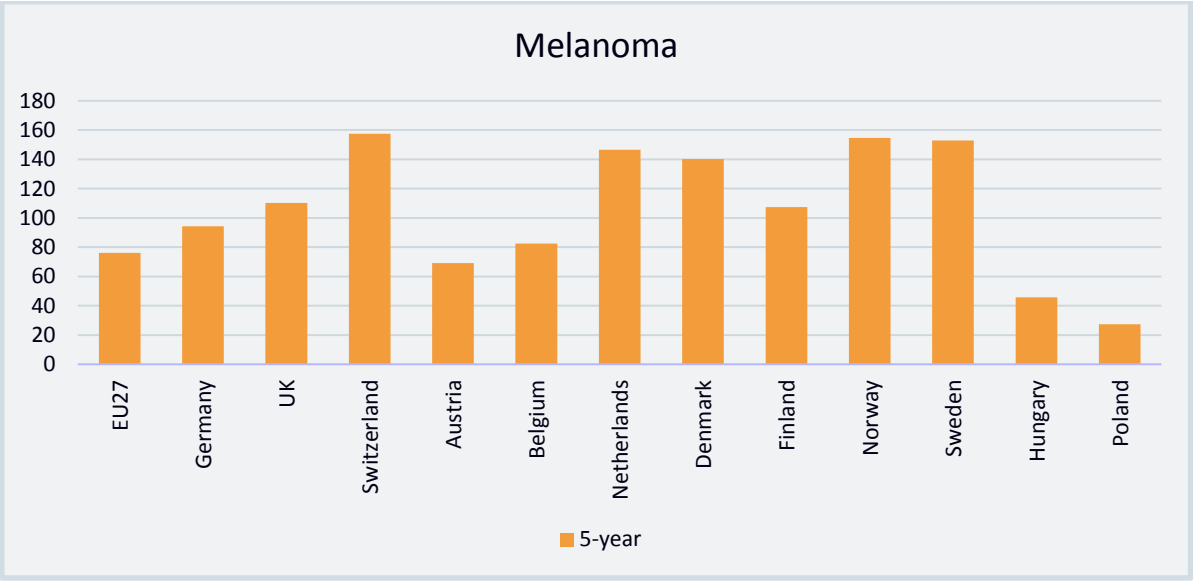

FIGURE 1.21. ESTIMATED PREVALENCE OF MELANOMA (C43), PER 100,000 INHABITANTS, FOR OUR EU12 COUNTRIES AND FOR EU27 IN 2012 [7].

Prevalence is determined by the survival, which is related to age. The burden related to prevalence differs depending on whether the cancer is cured or if there is a need for continued treatment.

As in the case for incidence, prevalence of lung cancer is relatively high in Hungary and Poland while it is lower for the rarer cancer multiple myeloma. Life styles and penetration and use of diagnostic techniques may to a large extent explain this relationship.

1.3.3 Survival

Figures 1.22 to 1.25 show the 1-, 3-, and 5-year relative survival for the EU12, except for Hungary for which data is lacking. Data was collected from the European Cancer Registry (EUROCARE-5) for patients diagnosed in 2000-2007.

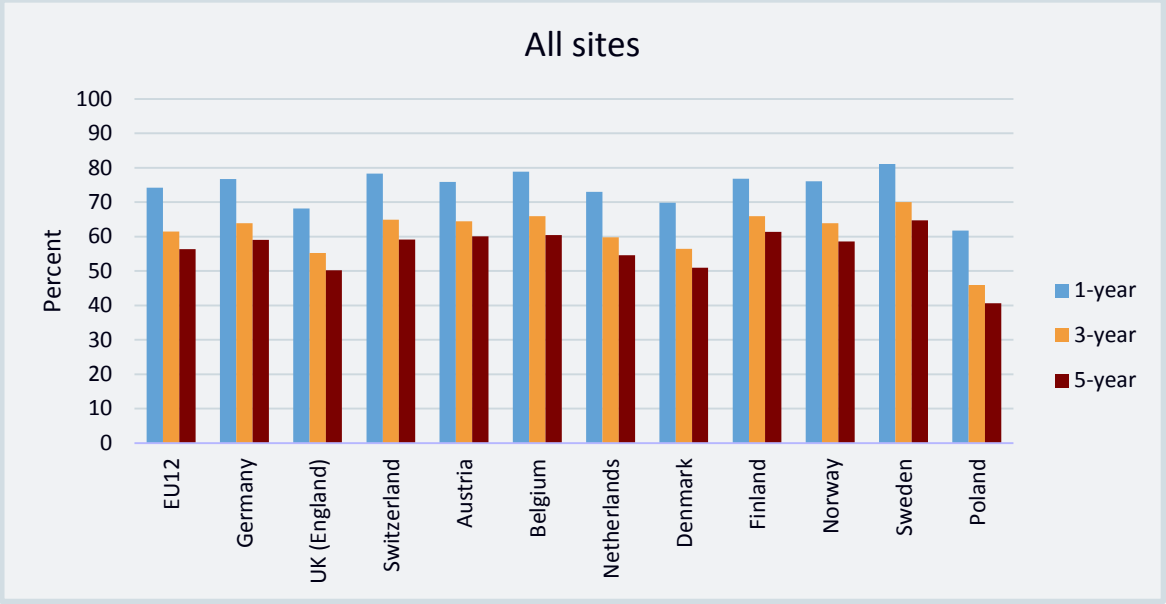

FIGURE 1.22. AGE-ADJUSTED RELATIVE SURVIVAL FOR ALL CANCERS PATIENTS IN BOTH SEXES, FOR OUR EU12 COUNTRIES AND FOR EU27, CASES DIAGNOSED 2000-2007 [7].

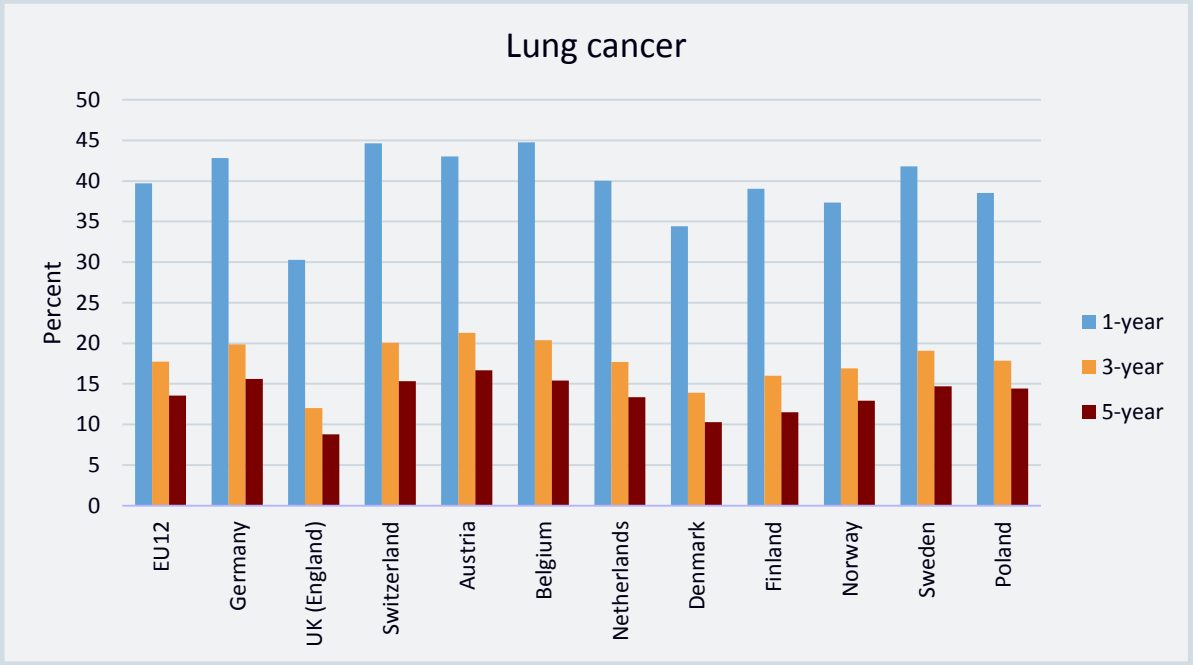

FIGURE 1.23. AGE-ADJUSTED RELATIVE SURVIVAL FOR LUNG CANCER PATIENTS IN BOTH SEXES, FOR OUR EU12 COUNTRIES AND FOR EU27, CASES DIAGNOSED 2000-2007 [7].

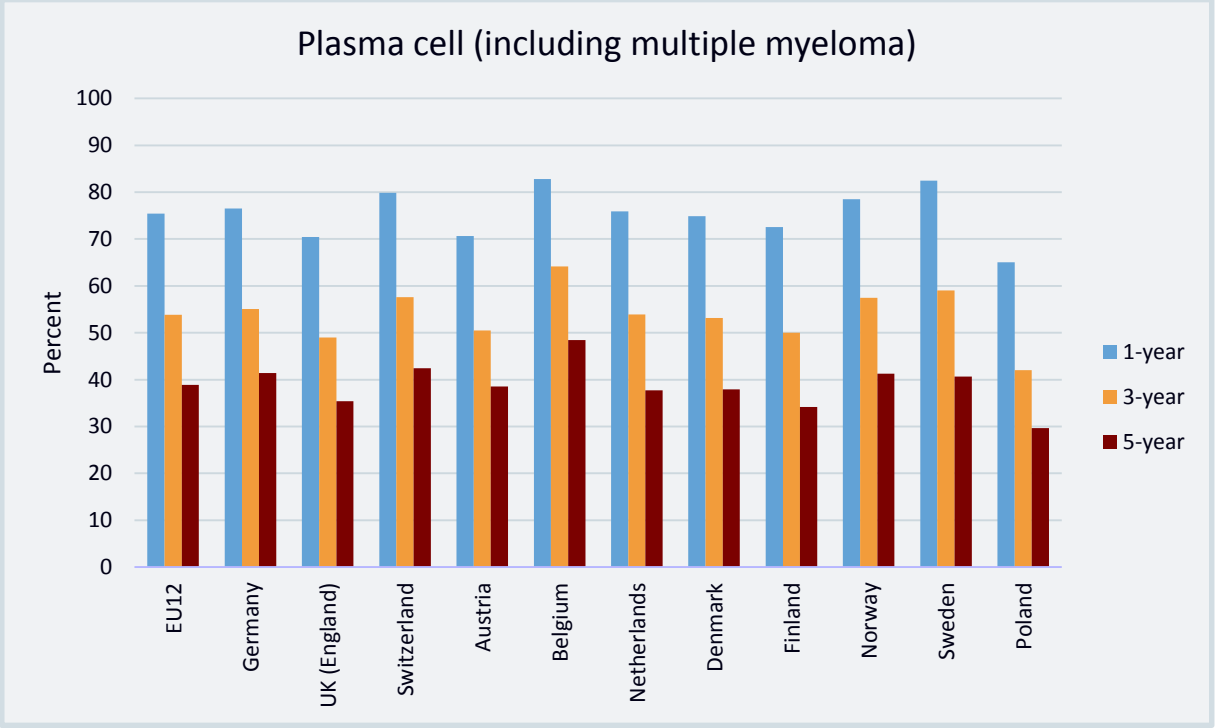

FIGURE 1.24. AGE-ADJUSTED RELATIVE SURVIVAL FOR MYELOMA PATIENTS IN BOTH SEXES, FOR OUR EU12 COUNTRIES AND FOR EU27, CASES DIAGNOSED 2000-2007 [8].

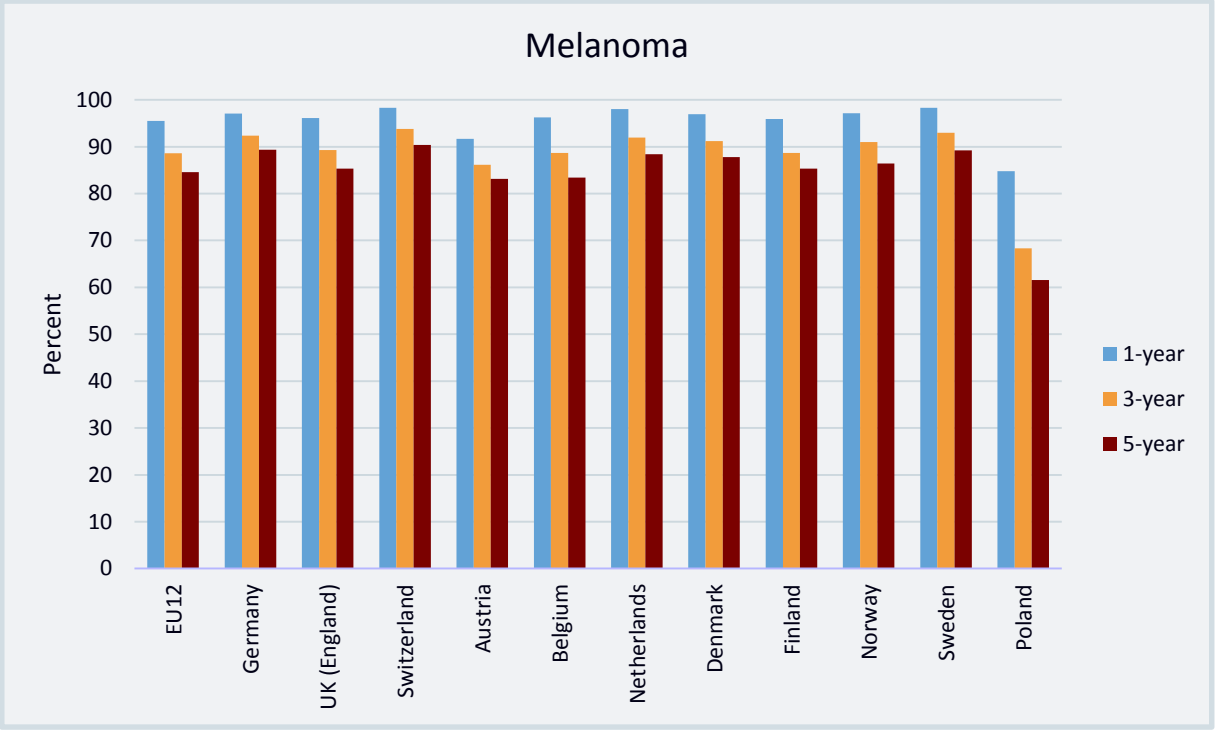

FIGURE 1.25. AGE-ADJUSTED RELATIVE SURVIVAL FOR MELANOMA PATIENTS IN BOTH SEXES, FOR OUR EU12 COUNTRIES AND FOR EU27, CASES DIAGNOSED 2000-2007 [8].

1.3.4 DALYs lost

The most commonly used measure of the burden of disease is the loss of Disability-Adjusted Life Years (DALYs). DALYs is a term developed by the World Health Organization (WHO) and the World Bank to measure the number of years of life lost due to premature mortality and disability combined.

In the twelve countries of this study the total DALYs lost amounts to 80,002,199 in 2012. The largest cause of DALYS lost are due to cardiovascular disease (20.5 percent) followed by malignant neoplasms (cancer; 19.3 percent), mental and behavioural diseases (14.5 percent), and injuries (8.7 percent). Table 1.3 show the amount of DALYs lost for all causes (i.e. all diseases, accidents etc.) and for cancer.

TABLE 1.3. DISABILITY-ADJUSTED LIFE YEARS LOST DUE TO DISEASE IN 2012, FOR OUR EU12 COUNTRIES, IN THOUSANDS [9]

Country	All Causes	Cancer (all types)	Share (Cancer/ All Causes)
EU12 (total)	80 002.2	15 460.8	19.3%
Germany	25 519.4	5 017.4	19.7%
UK	17 856.3	3 417.5	19.1%
Switzerland	2 038.9	363.6	17.8%
Austria	2 464.7	457.0	18.5%
Belgium	3 259.2	639.3	19.6%
Netherlands	4 474.7	1 041.8	23.3%
Denmark	1 665.2	373.5	22.4%
Finland	1 585.2	254.9	16.1%
Norway	1 337.5	237.9	17.8%
Sweden	2 614.4	464.3	17.8%
Hungary	4 131.2	833.0	20.2%
Poland	13 055.4	2 360.8	18.1%

Lung cancer is the cancer type causing the most DALYs losses due to its relative high prevalence and mortality. Lung cancer cause 2,832,800 out of the 15,461,000 DALYs lost by cancer, which corresponds to a fraction of 17.2 percent in Sweden to 28.5 percent in Hungary. This is seen in Table 1.4. The two countries with the highest lung cancer share of total cancer DALYs lost – Hungary and Poland - are also the countries with the highest mortality rates.

TABLE 1.4. SHARE OF DALYS LOST FOR ALL CANCERS ATTRIBUTABLE TO THE CANCERS HIGHLIGHTED IN THIS REPORT, FOR OUR EU12 COUNTRIES [10]

Country	Lung Cancer	Melanoma	Lymphoma, Multiple Myeloma
EU12	22.7%	2.3%	4.5%
Germany	21.1%	2.0%	4.7%
UK	22.3%	2.4%	5.0%
Switzerland	20.2%	2.8%	4.9%
Austria	20.4%	2.8%	5.1%
Belgium	25.5%	2.3%	4.4%
Netherlands	25.1%	2.8%	4.4%
Denmark	23.9%	2.6%	3.8%
Finland	18.7%	2.4%	6.3%
Norway	20.9%	4.0%	4.9%
Sweden	17.2%	3.3%	5.3%
Hungary	28.5%	1.7%	2.7%
Poland	25.2%	2.0%	3.3%

1.3.5 Economic burden

The clinical burden of cancer also leads to a heavy burden on society in a number of ways. Apart from the human suffering of people receiving the diagnosis and their relatives, there is also an economic burden in terms of costs of treatment and losses of production when people are unable to work. The patients and their relatives also face an economic burden by reduced income and costs related to formal and informal care and adjustments to disability.

The economic burden of cancer is composed of direct costs and indirect costs. Among the direct costs are public and private expenditures on outpatient care, inpatient care, medications, screening programs, primary prevention measures, etc. The indirect costs comprise of costs due to productivity loss and informal care costs.

Comparative studies on the economic burden of cancer are still rare. Jönsson and Wilking (2009) estimated the direct cost of cancer in 2007 using best available data at that time [11]. The estimates for the study countries are shown in the table below. Data on the share of cancer-related expenditures were obtained from national sources or other country-specific publications (see Appendix of the reference for the applied methodology). Table 1.5 illustrates that the share of cancer-related direct costs on total health care expenditures ranges from 5 percent in Poland to 7.3 percent in Sweden. Data for Germany show that this share increased from 5.2 percent in 2002 to 5.8 percent in 2004, but that it then stabilized on 6.2 percent in 2006 and 6.1 percent in 2008 [12].

TABLE 1.5. EXPENDITURES ON HEALTH AND ESTIMATED DIRECT COSTS FOR CANCER IN 2007, FOR OUR EU12 COUNTRIES. SOURCE: JÖNSSON AND WILKING (2009)

	Health expenditure share of GDP	Health expenditure in M€ PPS	Health expenditures per capita in € PPS	Cancer share of health expenditures	Direct costs of cancer per capita in € PPS
Austria	10.2	26 780	3 227	6.4% [a]	207
Belgium	9.6	29 863	2 821	6.4% [a]	181
Bulgaria	7.7	5 608	730	4.0%	29
Czech Republic	7.1	14 820	1 441	5.0%	72
Denmark	9.4	15 635	2 872	6.4% [a]	185
Estonia	5.0	1 200	894	3-5%	36
Finland	7.5	11 488	2 117	4.4%	95
France	11.2	196 469	3 099	6.6%	205
Germany	10.7	247 058	3 001	7.2%	216
Greece	10.1	27 392	2 452	6.4% [a]	158
Hungary	7.8	12 348	1 227	5.0%	61
Iceland	9.4	936	3 042	6.4% [a]	195
Ireland	8.2	12 922	2 996	6.4% [a]	193
Italy	8.9	132 778	2 245	6.4% [a]	144
Latvia	6.4	2 094	918	3-5%	37
Lithuania	5.9	2 980	880	3-5%	35
Luxembourg	7.7	2 535	5 324	6.4% [a]	342
Netherlands	9.2	49 553	3 029	5.0%	170
Norway	9.1	19 563	4 179	6.4% [a]	269
Poland	6.2	31 537	827	5.0%	41
Portugal	10.2	20 073	1 894	6.4% [a]	122
Rumania	5.5	11 936	553	3-5%	22
Slovakia	7.1	6 516	1 208	3-5%	48
Slovenia	8.5	3 776	1 878	3-5%	75
Spain	8.2	97 582	2 194	6.4% [a]	141
Sweden	9.2	26 333	2 890	7.2%	207
Switzerland	11.4	29 727	3 959	6.4% [a]	254
United Kingdom	8.2	143 223	2 356	5.6%	13
Europe		1 182 725	2 336	6.3%	148

[a] The cancer share of the health expenditure for countries with no data available is estimated at the cancer share of the total health expenditures in Czech republic, Finland, France, Germany, Hungary, the Netherlands, Poland, Swede and the United Kingdom.
Original data source: Health Expenditures: Eurostat (2007): Per capita health expenditures on health share WHO (2005). Table 1-7. Expenditures on health and estimated direct costs of cancer 2007

A lack of data on the use of cancer care resources and their prices are a major limitation for the preparation of such studies [9]. As a solution, the OECD has suggested the implementation of disease-specific health accounts [13]. This would not only facilitate international comparisons, but most importantly provide (national) policy makers with clear evidence on the amount of resources being spent on different diseases and on how spending evolves over time.

1.3.5.1 Direct costs

Direct costs comprise a wide range of different cost categories that have a direct impact on the public health care budget and costs covered by the patient. Direct costs include public and private expenditures on outpatient care, inpatient care including curative and palliative care, medications, screening programs, primary prevention measures, and public grants for cancer research.

Table 1.6 shows the estimated cancer-related direct costs on total health care expenditures in a recent comprehensive study on the cost of cancer in 2009 in Europe [13]. Data on total health care expenditures were obtained from Eurostat.

TABLE 1.6. HEALTH CARE EXPENDITURES (DIRECT COSTS) ON CANCER PER CAPITA IN€, BY COUNTRY (NOT ADJUSTED FOR PPP), FOR AUSTRIA, BELGIUM, DENMARK, EU27, FINLAND, GERMANY, HUNGARY, THE NETHERLANDS, POLAND, SWEDEN AND THE UK IN 2009 [13].

Country	Primary	Outpatient	A&E	Inpatient	Drugs	Total	Share of total health care expenditure
EU27	6	11	1	57	27 (26%)	102	4%
Germany	9	21	0,4	119	33 (18%)	182	5%
UK	2	17	1	47	17 (24%)	85	3%
Austria	4	6	3	90	41 (28%)	144	
Belgium	3	6	1	51	32 (34%)	94	4%
Netherlands	10	15	1	82	22 (17%)	130	3%
Denmark	1	10	2	54	37 (36%)	104	3%
Finland	4	27	4	86	29 (19%)	151	2%
Sweden	5	26	4	44	25 (24%)	105	5%
Hungary	3	2	1	12	22 (56%)	39	
Poland	3	10	0,4	16	7 (19%)	37	3%

A&E – cancer related Accidents and Emergency care

The share of health care expenditures devoted to cancer presented in Table 1.6 varies between 3 and 5 percent. This is far lower than in the study by Jönsson and Wilking referred to above. There are several reasons for this, but the main is probably an underestimation of resources used in primary and outpatient care, where diagnosis related data are lacking. There is also an underestimate of drugs used for patients with cancer not included in the ATC groups L1 and L2.

The study for the EU27 countries also estimated the composition of health care costs for cancer in 2009 [13]. Here, health care cost were split into five categories; primary care, outpatient care, emergency care, hospital inpatient care, and drugs. Thus the study does not include all relevant direct costs and leaves out spending on health promotion and prevention activities, spending on screening programs and publicly funded cancer research. According to the EU27 study, costs for inpatient care account for more than half and drugs for more than a quarter of all health care costs,

respectively, see Figure 1.26. The figure also illustrates that the share of the different cost categories vary considerably between cancer types. For colorectal and lung cancer, expenditures on inpatient care account for more than two thirds of all health care costs and expenditures on outpatient care exceed those for drugs. By contrast, drug costs are the main cost category for prostate cancer. However, the estimates on drug expenditures for specific cancer types should be regarded with caution since their proportions are only based on real data from Germany and the Netherlands in this study.

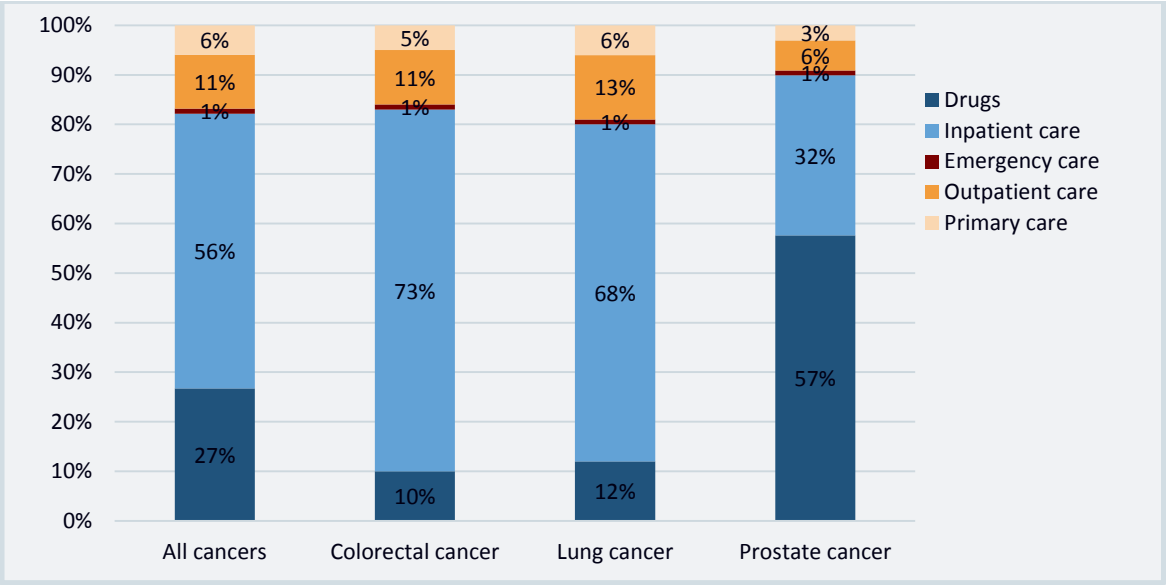

FIGURE 1.26 COMPOSITION OF HEALTH CARE EXPENDITURES BY CANCER TYPE IN THE EU27, 2009 [13].

The same study also showed that the composition of health care expenditures on cancer differs significantly across countries (as seen in Table 1.6). In Europe, about a quarter of expenditures on cancer are allocated to drugs. There are differences between countries, with Hungary on top with over 50 percent of costs for cancer attributed to drugs, reflecting the country's generally high share for drugs in health care expenditures. Germany, Netherlands, Finland and Poland have the lowest shares, below 20 percent. Hospital inpatient care accounts for almost two thirds of the expenditures in Germany. The share of expenditures on outpatient care is comparatively small in in most countries, but quite significant in Poland with 27 percent and in Sweden with 25 percent. The figures should be interpreted with care, since accounting systems are not perfectly aligned.

1.3.5.2 Indirect costs

To assess the economic burden of cancer from a societal perspective, indirect costs have to be added to direct costs. Indirect costs mainly stem from four areas. The first one is productivity loss

due to earnings foregone due to premature death (i.e. mortality) of people of working age. The second one is productivity loss attributable to the morbidity of cancer patients that leads to lost working days due to sick leave. Early retirement due to patient morbidity forms the third area. Finally, informal care for cancer patients gives rise to indirect costs as relatives/friends forgo earnings to provide unpaid care.

As Table 1.7 indicates, the share of indirect costs on total costs has been estimated as 60 percent for all cancers in the EU27 [13], but differs greatly between cancer types, in the same way as we have seen for direct costs as in Figure 1.26. For lung cancer, the share of indirect costs is 77 percent, whereas for prostate cancer indirect costs account for 36 percent of total costs. This pattern is partly attributable to the low survival rates in lung cancer patients and their comparatively young average age, since both of these factors impact the size of productivity losses due to mortality. In contrast, many prostate cancer patients are already retired and thus the productivity losses due to mortality are small. At the same time the higher survival rates in prostate cancer patients may also cause the treatment to last longer, which drives up direct costs.

TABLE 1.7. DIRECT AND INDIRECT COSTS OF CANCER BY COUNTRY IN THE EU27 AND IN EACH OF THE TWELVE COUNTRIES IN FOCUS IN THIS REPORT, IN BILLION € IN 2009 [13].

Country	Total costs	Direct costs	Indirect costs
EU27 Total	126.21	40%	60%
Germany	35.13	42%	58%
UK	14.44	36%	64%
Switzerland	N/A	N/A	N/A
Austria	2.64	46%	54%
Belgium	3.21	31%	69%
Netherlands	6.35	34%	66%
Denmark	2.24	26%	74%
Finland	1.51	57%	47%
Norway	N/A	N/A	N/A
Sweden	2.77	35%	65%
Hungary	0.98	40%	60%
Poland	3.64	38%	62%

In Table 1.8 the composition of the indirect costs is presented by country. Mortality and morbidity represents the productivity losses due to cancer-related mortality and morbidity.

TABLE 1.8 INDIRECT COSTS, IN €, FOR CANCER CARE IN THE EU27 AND IN EACH OF THE TWELVE COUNTRIES IN FOCUS IN THIS REPORT.

Country	Mortality	Morbidity	Informal care costs	Total indirect costs
EU27 Total	42 565	9431	23 216	75 212
Germany	11607	2213	6414	20 234
UK	6186	682	2334	9 202
Switzerland	N/A	N/A	N/A	N/A
Austria	750	136	550	1 436
Belgium	1047	604	553	2 204
Netherlands	2519	706	983	4 208
Denmark	1010	380	277	1 667
Finland	467	77	166	710
Norway	N/A	N/A	N/A	N/A
Sweden	923	478	397	1 798
Hungary	416	48	122	586
Poland	1306	386	550	2 242

Table 1.9 show the direct, indirect and total costs for lung cancer, by country, in 2009 [13]. An observation from Table 1.9 is that lung cancer accounts for around 15 percent of the total costs of cancer, reflecting the high share of indirect costs of lung cancer due to the comparatively high mortality of lung cancer patients.

TABLE 1.9. DIRECT AND INDIRECT COSTS OF LUNG CANCER BY COUNTRY IN THE EU27 AND IN EACH OF THE TWELVE COUNTRIES IN FOCUS IN THIS REPORT, IN BILLION €, 2009 [14].

Country	Total costs	% cost of all cancers	Direct costs	Indirect costs
EU27 Total	18.78	15%	23%	77%
Germany	5.09	14%	26%	74%
UK	2.18	15%	21%	79%
Switzerland	N/A	N/A	N/A	N/A
Austria	0.389	15%	28%	72%
Belgium	0.55	17%	16%	84%
Netherlands	1.10	17%	19%	81%
Denmark	0.39	17%	13%	87%
Finland	0.17	11%	36%	64%
Norway	N/A	N/A	N/A	N/A
Sweden	0.32	11%	24%	76%
Hungary	0.20	20%	19%	82%
Poland	0.72	20%	27%	73%

Figure 1.27 depicts the composition of indirect costs for each cancer type. For prostate cancer, informal care is the main driver of indirect costs with 63 percent, whereas for lung cancer productivity loss due to mortality is the main driver of indirect costs with 68 percent. For colorectal

cancer, informal care costs and productivity loss due to mortality are both important drivers of indirect costs. As explained before, many prostate cancer patients are already retired and thus the productivity losses are small, but their comparatively good survival prospects cause high costs for informal care. The opposite is true for lung cancer patients, which are younger and have comparatively poor survival prospects.

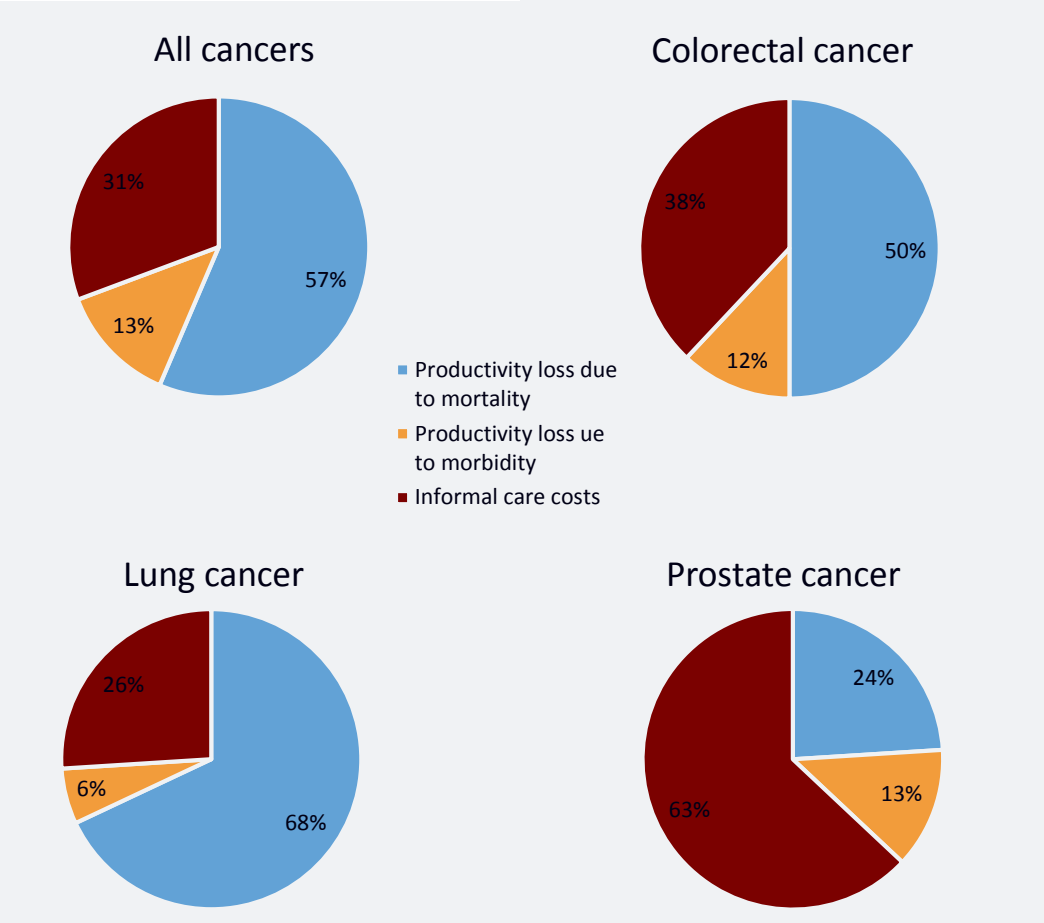

FIGURE 1.27 COMPOSITION OF INDIRECT COSTS BY CANCER TYPE IN THE EU27, 2009 [15].

As pointed out before, a recent study estimated the direct costs to account for around 40 percent of the economic burden of cancer in the EU27, and the indirect costs for the remaining 60 percent (see Table1.6). The investigated countries do not deviate too far from this aggregate. In a study of Sweden (which also excludes informal care costs) for the year 2004, the share of direct costs was 53 percent and of indirect costs 47 percent [1].

1.3.5.3 Development of costs for cancer over time

Lack of data prevents a comprehensive analysis of the development of cost of cancer over time. For some cancer types, cost of inpatient care has been reduced due to a shift to ambulatory care. But it is impossible to have a clear picture of the magnitude of the shifts in costs.

Indirect costs have been reduced due to improved treatments with fewer side effects and improved survival. However, the exact savings cannot be calculated for all countries and all cancer types.

The best documented cost category is that of cancer drugs, which showed a rapid increase in the years after 2000 but has levelled off in the last few years. This is shown for Sweden in Figure 1.28. A more detailed description of the development of expenditures for cancer drugs is presented in chapter 3.

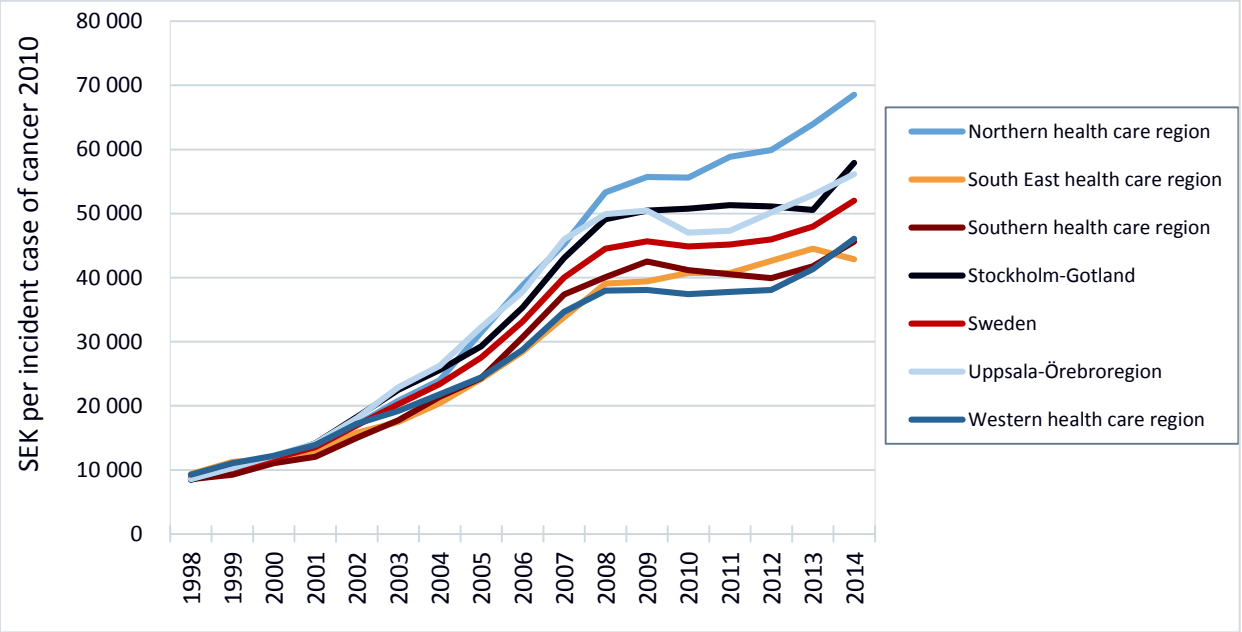

FIGURE 1. 28 EXPENDITURES FOR CANCER DRUGS IN SWEDEN 2000-2012 EXPRESSED AS SEK/INCIDENT CANCER CASE FOR THE SIX HEALTH CARE REGIONS IN SWEDEN, INCLUDING THE NATIONAL AVERAGE. SALES DATA WAS COLLECTED FROM APOTEKET (ATC CODE 4; ALL MOLECULES).

1.4 Chapter summary

GDP per capita and health care spending, measured both as share of GDP per capita and as PPP-adjusted health spending per capita, have increased between the years 2000-2012. Health spending as share of GDP per capita increased in all countries in 2008-2009 while GDP per capita decreased between the same years. This may be due to health care being less affected by market fluctuations in the short term. Instead, a financial crisis may lead to a stagnation or decrease of health spending in the long term. The rise in health spending as share of GDP in 2008-2009 is most plausibly

explained by a decreasing GDP per capita, making health spending a greater share of GDP per capita ceteris paribus. This is supported by health spending as share of GDP per capita stabilizing the years following 2009 while GDP per capita has been increasing in most cases.

If PPP-adjusted GDP per capita and health spending per capita have been increasing 2000-2013 so should pharmaceutical spending per capita, all else equal. Instead, pharmaceutical spending per capita has remained fairly stable or even decreased in some cases in 2000-2012. This is also seen by pharmaceutical spending as share of total health spending which has been decreasing in most countries following the first few years of the 21st century.

As seen in Figures 1.9 to 1.11 the pharmaceutical spending per capita in the EU12 has remained quite stable since the years before the 2008 financial crisis, Germany being the exception, increasing their spending per capita from USD505 in 2005 to USD555 in 2012. Seen as share of total health spending, pharmaceutical spending has decreased, implying that pharmaceutical spending is now a lesser share of health spending than it was in the year 2000. No dramatic effects are seen following the financial crisis but pharmaceutical spending is decreasing or constant while the cost of developing pharmaceuticals has increased the last couple of decades.

The stagnation of, or drop in, pharmaceutical spending is to be contrasted by high and rising costs of oncology drug development, reported (in 2007) to be in excess of USD 1 billion [2,3]. The cost containment policies aimed at pharmaceutical spending in the EU in combination with ageing populations have been mentioned as a “perfect storm” and may challenge the financial sustainability of health care systems and the pharmaceutical industry in Europe.

Cancer incidence is increasing by age. The share of people aged 65 years or over of the total population is expected to increase dramatically in the coming decades and will in some cases almost double in share. This means that, ceteris paribus, both cancer incidence and prevalence will increase; the total use of cancer drugs will increase; in- and out-of-hospital treatments and stays will increase; cancer will put an increased pressure on health care systems and its financing; the cancer share of mortality and disability will increase. The expected demographic change calls for a more efficient use of society’s resources, while at the same time upholding dynamic efficiency in the pharmaceutical market. New, innovative and more effective cancer drugs will be needed to face the demographic challenge and to keep cancer patients out of hospitals.

This section has shown that the share of cancer-related direct costs on total health expenditures ranges from 5 percent in Poland to 7.3 percent in Sweden. Purchasing power adjusted per-capita

spending on cancer is more than three times higher in Sweden, Germany and France than in Poland and the differences between countries are even greater when considering unadjusted per-capita spending on cancer. Furthermore, indirect costs account for around 60 percent of total costs in all countries, yet this share differs greatly between cancer types. Overall, productivity loss due to morbidity and premature death is of the same magnitude as the total direct health care expenditures.

From these observations two important findings can be deducted. Firstly, the largest part of the economic burden of cancer (i.e. indirect costs) accrues to areas that lie outside the direct scope of the health care system. Nonetheless, this fact should not overshadow the importance of a comprehensive cancer management system. Appropriate care has an immediate impact on indirect costs by preventing premature death, reducing morbidity and cutting early retirement. The second finding stresses this as well. Despite fairly similar levels of spending in France, Germany and Sweden, these countries differ in their achieved outcomes as measured by survival rates. This highlights the importance for health policy to set the right priorities in cancer care and that a sole focus on spending is too narrow.

To provide a forward-looking statement on the development of the economic burden is difficult. Demographic change is still the driving force behind an increasing number of new cancer cases. More diagnoses (incidence) mean more patients to be taken care of by the health care system, which has implications both for direct and indirect costs.

Direct costs are likely to increase, because of the sheer greater number of patients to be treated, but also because screening programs are steadily being extended (e.g. for colorectal cancer) and primary prevention measures (e.g. human papilloma virus (HPV) vaccination to prevent cervical cancer) being implemented and enforced. The latter two measures are, however, expected to decrease the cost for care in the long-term. Drugs as the cost-driver behind increasing direct costs for cancer care are a debated issue. New targeted cancer therapies allow a greater share of patients to be treated but often come at a high price which has dramatically increased drug costs in the last decade. Yet, the increase has levelled off in recent years and might be further moderated in the coming years as some widely-used cancer drugs come off patent (see Chapter 3). If the shift from intravenous to oral delivery methods of drugs continues, hospital inpatient care costs could be expected to decrease, as more patients can be treatment at home.

Indirect costs may also increase simply because of the continuing rise in cancer patients. A productivity loss due to morbidity might therefore increase as a whole, but not necessarily at the

individual level if cancer care becomes more effective. The latter could possibly even contribute to a reduction in early retirement and general sick leave. Informal care costs are likely to increase because patients live longer with the disease and therefore need care for a longer period of time. Nonetheless, productivity loss due to mortality might decrease as survival rates continue to increase. Finally, if increased primary prevention efforts succeed in shifting cancer cases away from younger people and/or more deadly cancer types (e.g. lung cancer), a reduction in indirect costs could be expected.

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2 Medical Review

This chapter includes a summary of current and historic cancer epidemiology. It describes cancer prevalence and incidence, both for all cancers and for selected cancer diagnoses. The chapter also presents a brief review of some of the more significant developments seen in the management of cancer patients, from improvements in diagnostic techniques to advances in the medical treatment of cancer.

2.1 Cancer epidemiology and development of cancer drug usage

An estimated 14 million new cancer cases and 8.2 million cancer deaths occurred worldwide in 2012, with 57% of new cancer cases and 64% of the cancer deaths occurring in the less developed regions. The most commonly diagnosed cancers worldwide are lung (1.8 million; 16.7%), breast (1.67 million; 11.9%) and colorectal cancers (1.36 million; 9.7%). The most common causes of cancer death are lung (1.82 million; 22%), stomach (723,000; 8.8%) and liver cancer (746,000; 9%) [1].

In Europe, cancers of the female breast (464,000), colorectal (447,000), prostate (417,000) and lung (410,000), represented half of the overall cancer incidence in 2012. The most common causes of death from cancer were cancers of the lung (353,000), colorectal (215,000), breast (131,000) and stomach (107,000) [2,3]. This makes cancer the second most common cause of death after cardiovascular diseases [4,5].

Agents inhibiting cancer growth (chemotherapy) were first discovered in the 1940s with the alkylating agents and antimetabolites- two groups of agents still in use [6,7]. During the 1950-1970ies, further classes of cell toxic agents were discovered and it became clear that chemotherapy could actually cure some haematological malignancies. The introduction of platinum compounds was a major breakthrough, as it resulted in high cure rates in metastatic testicular cancer, a previously untreatable solid tumour form. These results confirmed that chemotherapy could potentially cure cancer and provided a rationale for introducing chemotherapy, in combination with surgery and radiotherapy. The potential value of adjuvant chemotherapy after surgery was first demonstrated in 1974 in osteosarcomas [8]. Gradually, chemotherapy has been introduced in various tumour forms, as palliative treatment to relieve symptoms and increase the quality of life in late stages of the disease, or in conjunction with surgery and/or radiotherapy, in order to increase cure rates, or as first line therapy with curative intent. Cancer treatment has become multimodal,

requiring multidisciplinary teams in order to achieve optimal results. As for chemotherapy, there has been a trend towards using combinations of agents with different mechanisms of action in order to achieve maximal effect. Major obstacles for maximal effect using conventional chemotherapeutic agents have been the side effects and the development of drug resistance by tumours.

As cancer patients now live longer. There has been an increased demand for supportive care and development of a wide range of drugs, aimed at improving quality of life and reducing chemotherapy side effects. The development of potent antiemetic agents, hematopoietic growth factors and broad spectrum antibiotics has enabled intensified treatment schedules, resulting in increased efficacy. This has also led to a shift in cancer care from mainly in-hospital treatments in the 1980s to a continuously increasing proportion of outpatient treatments.

Until the 1980ies, drug discovery in oncology was dominated by academia and publicly sponsored institutions like the National Cancer Institute (NCI) in the US. The last decades has seen a dramatic change in drug discovery and advances in biological research, enabling the identification of more specific targets of intervention and efforts are now concentrated on finding agents that act on these targets. The improved techniques in molecular medicine and increased investments in the oncology area, have led to a transformation from publicly funded programs in the 1970ies and 1980ies, to a major international industrial effort increasing the impetus of drug discovery and drug development in oncology. Of the biotech companies in the US today, half are focussing on cancer. According to a recent review, there are more than 800 new cancer agents in development [9].

2.2 Advances in diagnostic techniques

Radiology has come to play a key role in oncology, not only as a diagnostic tool but also as a method of evaluating efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980ies and 1990ies; Computerized Tomographic Scanning (CT) and Magnetic Resonance Imaging (MRI) have greatly improved the diagnostic accuracy. Other methods, such as ultrasound and bone scintigraphy are also useful. Currently, Positron Emission Tomography (PET) in combination with CT (PET/CT) is introduced in clinical practice with the advantage of being more sensitive in differentiating between viable and non-viable tumour tissue. The development of improved radiological techniques, with the ability to accurately separate responders from non-responders after only a brief treatment time, or perhaps even before onset of treatment (tracers, probes etc.) will be pivotal in decreasing the number of patients receiving treatment with no benefit.

Advances in molecular medicine, e.g. gene- and protein profiling techniques, have contributed to increased understanding of cell and cancer biology and has also provided more accurate classification of various tumour forms. By analysing the gene expression of a wide range of tumours, it has been possible to identify genes that provide tumour-specific characteristics. In some cases it is also possible to predict if an individual tumour will respond to certain treatments [10]. Pharmacogenomics has become an important field in cancer research and drug development. Soon, pharmacogenomics together with analyses of tumours, determining potential response to treatment (chemo sensitivity tests), will be available on a larger scale in the clinical setting.

Less than 2% of human diseases are caused by one gene (monogenic), the rest are caused by multiple genes in combination, or by changes in the proteins they encode. The deciphering of the entire human proteome is underway and will undoubtedly shed new light on disease mechanisms and possible targets of intervention. Already, the individual protein patterns of different tumour types are being mapped and has demonstrated that patients with a specific type of cancer have certain protein patterns present in their blood [11].

2.2.1 The basis for recent advances in the medical treatment of cancer – understanding biology of tumour cells and the microenvironment

Progress in molecular medicine has led to increased understanding of how cancer evolves and how cancer cells are characterised by defects in DNA repair mechanisms, leading to an accumulation of genetic defects, fuelling tumour development, also increasing the risk of – for instance – acquired drug resistance.

The development of invasive cancer is a process with many steps, with an accumulation of genetic changes occurring over a long time period (5-20 years) [12]. Intense research during the last century has increased knowledge about the human cell and its molecular mechanisms, and medical oncology entered a new phase in the 21st century focussing on finding drugs targeting different molecular markers. Furthermore, increased knowledge of cancer biology has reduced use of highly cell-toxic treatments and increased use of agents, targeting pathways in the cell.

The main areas of targeted drugs used in clinical practice today:

- Targeting of the cell cycle and apoptosis, DNA replication/transcription and repair
- Inhibition of hormones, growth factors and cell signalling pathways
- Inhibition of angiogenesis
- Biotherapy
- Immuno-oncology

Most chemotherapeutic agents act by inhibiting DNA replication. Often the actual mechanism of action were not known until long after the introduction of the agent in the clinical setting. Actually, the mechanisms of action of some older chemotherapeutic agents still remain unclear. In 1984, it was shown that anthracyclines, one of the most effective class of compounds in conventional chemotherapy at the time, worked by affecting topoisomerase activity [13]. This discovery started the work towards finding other agents with similar mechanisms of action. In the 1990ies, the topoisomerase inhibitors irinotecan and topotecan were introduced with significant clinical impact in – for instance – colon cancer. During the 1990ies the knowledge of the role of microtubules in cell division, proliferation and chemotaxis made way for several new agents; taxans (paclitaxel and docetaxel), and vinca alkaloids (vinblastine, vincristine, and vinorelbine), derived from plant toxins. Since their introduction in the 1990ies, these agents have increased the survival in cancer and impressive responses are seen in a wide variety of cancers. There are also several new agents in clinical trials with similar anti-tumour mechanisms.

New antimetabolite agents have been introduced during the last decade; gemcitabine with efficacy in pancreatic and lung cancer [10], and pemetrexed with efficacy in non-small cell lung cancer [10]. Capecitabine is a drug in an oral formulation, similar to 5-FU, with a wide range of indications, enabling many patients to take the treatment at home.

2.2.2 Targeting hormones, growth factors & cell signalling pathways

Intracellular signal transduction pathways are activated by e.g. proteins, amino acids and lipids. The binding to matched receptors activates various enzyme systems, ultimately resulting in changes in protein synthesis, cellular behaviour or growth [14].

The introduction of endocrine drugs was the first treatments focused on a well-defined molecular target. Interfering with the production of hormones or blocking their action has become cornerstones in the treatment of both breast- and prostate cancer. Tamoxifen, which acts by blocking oestrogen stimulation, was the first hormonal drug to be widely used in breast cancer. Since its introduction in the 1970ies, tamoxifen has proved valuable in the treatment of metastatic breast cancer, as well as for adjuvant treatment after surgery, decreasing the risk of relapse of 50%. The efficacy and relatively low toxicity of tamoxifen has led to the development of a large number of new classes of hormonal agents for the treatment of hormone sensitive breast cancer.

In breast cancer, a number of aromatase inhibitors used in post-menopausal women (e.g. anastrozole, letrozole and exemestane) have been introduced in the last decades and together with other agents with similar mechanisms of action (e.g. fulvestrant, megestrol) they provide valuable

therapeutic options in metastatic breast cancer. In prostate cancer, anti-androgens (e.g. flutamide, bicalutamide and nilutamide) have been developed as an alternative to testicular ablation. Additionally, gonadotrophin releasing hormone analogues (e.g. goserelin, leuprolide), that block the production of testosterone are used to achieve chemical castration. The latest development in prostate cancer includes drugs that block the intra-tumoural synthesis of androgens in patients with hormone refractory disease. These drugs, abiraterone and enzalutamid, were initially approved in patients progressing on first line chemotherapy (docetaxel) but are now approved pre-chemotherapy in patients developing hormone refractory disease.

Growth factors play an important role in stimulating cell growth during cell development and are essential in cell populations where constant proliferation and tissue renewal is required (e.g. skin, bone marrow and intestine). Growth factors stimulate cell growth by binding to cell surface receptors, starting a cascade of activity of specific enzymes in the cell. Many cancers overexpress growth factor receptors and/or have mutations in the related gene that lead to defects in the signal transduction, resulting in rapid growth as well as invasion of normal tissue [15].

Most research efforts have focused on families of growth factors that are known to be over expressed in various tumour types, such as the Epidermal Growth Factor Receptor (EGFR), including Human Epidermal Growth Factor Receptor (HER2), Vascular Endothelial Growth Factor (VEGF) receptor, Platelet-Derived Growth Factor (PDGF) receptor and Insulin-like Growth Factor (IGF-1) receptor. The tumour status of for instance BRAF, KRAS, EGFR and HER2 can be determined through a diagnostic test, thereby making testing of patients an important step in eligibility for treatment. The proportion of positive patients is the following: BRAF 50% in metastatic melanoma, EGFR 10-35% (depending on ethnicity) in lung cancer, wKRAS 50% in colorectal cancer, and HER2 15% in breast cancer.

There are two main groups of agents that have demonstrated efficacy in interfering with growth factor signalling; monoclonal antibodies, and small molecular drugs blocking the tyrosine kinases, the first step in most signal transductions. Cetuximab, a monoclonal antibody developed against EGFR, has demonstrated efficacy in metastatic colorectal cancer by increasing time to disease progression [16]. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients with advanced head and neck tumours [17]. Erlotinib [18] has demonstrated efficacy and increased survival as monotherapy in non-small-cell lung cancer (NSCLC), and gefitinib [19] has demonstrated efficacy in a subset of patients with the same disease. The latest drug to be approved in colorectal cancer is panitumumab. This is also a monoclonal antibody developed against the EGFR, although the effect is only seen in a subpopulation of patients with a non-mutated version

of the oncogene KRAS, wKRAS (also cetuximab) [20,21]. Treatment with the monoclonal antibody trastuzumab directed against HER2 has led to marked prolonged survival in metastatic breast cancer. Adjuvant treatment with trastuzumab results in an approximately 50% reduction in recurrence in patients with HER2-positive disease [22]. The combination of dual HER2 blockade with trastuzumab and pertuzumab has been shown to be superior to trastuzumab alone in the metastatic setting and has now become standard of care [24,25]. The trastuzumab – emtansine, T-DM1 (monoclonal antibody linked with a strong cytotoxic agent) combination is used for the treatment of metastatic breast cancer. Lapatinib, a small molecule interaction with both the HER2 and EGFR (HER1) is also in clinical use.

Chronic myeloid leukaemia (CML) was the first malignant disease, for which a characteristic genetic abnormality, the Philadelphia chromosome was described. In the 1980ies, the genetic alteration was identified as the BCR-ABL fusion gene and the protein it encodes was established as the cause of the initial phase of CML. Imatinib, an agent inhibiting BCR-ABL activity results in complete responses in 80% of patients [26]. Unfortunately, resistance to imatinib occurs, but the mechanisms of resistance have been clarified and an agent that restores sensitivity to imatinib in 14 of the 15 resistance mechanisms described has already been developed [28]. Imatinib also inhibits another cell enzyme, C-KIT, which is mutated in 95% of patients with gastrointestinal stromal tumours. Treatment with imatinib results in long-lasting tumour regression [29,30] and has been an enormous step forward, since the disease does not respond to conventional chemotherapy. For patients that had become resistant to imatinib there are new therapeutic options including dasatinib and nilotinib . These drugs are now also approved as first line treatment.

The agents that inhibit growth factors and their signal transduction pathways represent a new class of anti-tumour agents and their place in the clinical setting continues to evolve. In some cases like gastrointestinal stromal tumours and renal cancer, for which there are no active chemotherapy alternatives, they are first-line options. In other tumour forms it remains to be seen if these agents will replace conventional chemotherapy as first-line treatment. Data support the concept of combining these agents with radiotherapy and chemotherapy and combining agents inhibiting different pathways (e.g. bevacizumab [targeting VEGF] in combination with erlotinib [targeting EGFR] in both renal and non-small-cell lung cancer) [31]. However, the additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies does need to be determined. Although, in breast cancer the use of dual HER2 blockade with trastuzumab and pertuzumab is now standard of care in the metastatic setting.

Another key challenge with these agents, as with conventional chemotherapy, is to predict responders. The clinical trials and initial introduction of gefitinib (outside the EU) illustrate the complexity of clinical trials in different patient populations, the value of post-marketing surveillance, and also the potential of today's biological research. The first studies of gefitinib indicated high response rates in the Japanese population that subsequently were not consistently seen in other patient populations. Further analysis indicated that certain subgroups (non-smokers, female patients with tumours of particular histological characteristics) were more likely to respond to treatment [33]. Genetic analysis identified mutations in the EGFR correlating to response to gefitinib [7].

TABLE 2.1. TARGETED DRUGS FOR USE IN ONCOLOGY

Generic name	Trade name	Drug class	Target
Aldesleukin	Proleukin	Cytokine	IL2
Romidepsin	Istodax	HDAC inhibition	HDAC
Sipuleucel-T	Provenge	Immunostim	Immune system
Vorinostat	Zolinza	HDAC inhibition	HDAC
Alemtuzumab	Campath	Antibody	CD52
Bevacizumab	Avastin	Antibody	VEGF
Brentuximab vedotin	Adcetris	Antibody	CD30
Cetuximab	Erbitux	Antibody	EGFR
Denosumab	Xgeva	Antibody	RANKL
Ibritumomab tiuxetan	Zevalin	Antibody	CD20
Ipilimumab	Yervoy	Antibody	CTLA-4
Obinutuzumab	Gazyva	Antibody	CD20
Ofatumumab	Arzerra, HuMax-CD20	Antibody	CD20
Panitumumab	Vectibix	Antibody	EGFR
Pembrolizumab	Keytruda	Antibody	PD-1
Pertuzumab	Perjeta	Antibody	HER2
Ramucirumab	Cyramza	Antibody	VEGFR2
Rituximab	Rituxan, Mabthera	Antibody	CD20
Tositumomab	Bexxar	Antibody	CD20
Trastuzumab	Herceptin	Antibody	HER2
Ziv-aflibercept	Zaltrap	Antibody	PIGF, VEGFA/
Imatinib	Glivec	small molecular drug	bcr-abl, ckit
Sorafenib	Nexavar	small molecular drug	VEGFR, PDGFR
Afatinib	Gilotrif	Small molecule	EGFR (HER1), HER2
Axitinib	Inlyta	Small molecule	KIT, PDGFRβ, VEGFR1/2/3
Belinostat	Beleodaq	Small molecule	HDAC
Bortezomid	Velcade	Small molecule	Proteasome
Bosutinib	Bosulif	Small molecule	ABL
Cabozantinib	Cometriq	Small molecule	FLT3, KIT, MET, RET, VEGFR2
Carfilzomib	Kyprolis	Small molecule	Proteasome
Ceritinib	Zykadia	Small molecule	ALK
Crizotinib	Xalkori	Small molecule	ALK, MET
Dabrafenib	Tafinlar	Small molecule	BRAF
Dasatinib	Sprycel	Small molecule	ABL
Erlotinib	Tarceva	Small molecule	EGFR (HER1)
Everolimus		Small molecule	mTOR
Gefitinib	Iressa	Small molecule	EGFR (HER1)
Ibrutinib	Imbruvica	Small molecule	BTK
Idelalisib	Zydelig	Small molecule	PI3K
Lapatinib	Tykerb, Tyverb	Small molecule	HER2, EGFR (HER1)
Nilotinib	Tasigna	Small molecule	ABL
Ponatinib	Iclusig	Small molecule	ABL, FGFR1-3, FLT3, VEGFR2
Regorafenib	Stivarga	Small molecule	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3
Sunitinib	Sutent	Small molecule	VEGFR, PDGFR
Temsirolimus	Torisel	Small molecule	mTOR
Trametinib	Mekinist	Small molecule	MEK
Vandetanib	Caprelsa	Small molecule	EGFR (HER1), RET, VEGFR2
Vemurafenib	Zelboraf	Small molecule	BRAF
Vismodegib	Erivedge	Small molecule	PTCH
Pazopanib		Small molecule drug	VEGFR, PDGFR

2.2.3 Inhibiting angiogenesis

The development of new blood vessels, angiogenesis, is an important normal physiological function, especially during pregnancy, growth, inflammation and wound healing. The regulation of angiogenesis is complex, with stimulating and inhibiting factors that, under normal conditions, are kept in balance. It has long been recognised that some tumours are highly vascularised. However, it was not until the 1970s that Judah Folkman hypothesised that tumours need angiogenesis for their continued growth [6]. We now know that tumours will not grow beyond 1-2 mm [34] without blood vessels of their own. In addition, autopsies have shown that many elderly have small, early-stage cancers (such as of the thyroid gland, breast and prostate) [35-37]. The point at which the tumour starts producing pro-angiogenic factors (angiogenic switch) is believed to be one of the most important steps in transforming these '*dormant*' tumours into rapidly growing tumours with metastatic potential .

Several growth factors are involved in angiogenesis but VEGF has been identified as the most important in many tumour forms. Both monoclonal antibodies targeting VEGF and tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed. Bevacizumab, a monoclonal antibody against VEGF, has increased survival in patients with metastatic colon and lung cancer . Preliminary data indicated an effect in breast cancer, and the drug was approved both in the US and in EU for the use in metastatic breast cancer. The US approval has been withdrawn based on poor later results [40].

In renal cancer, not responding to conventional chemotherapy, bevacizumab has extended the period of stable disease [41,42]. Recent studies has also shown efficacy of bevacizumab in ovarian and cervical carcinoma . Bevacizumab represents an important breakthrough in cancer therapy as it is the first agent in this new class of drugs showing efficacy in a range of tumours. Two agents, sorafenib and sunitinib malate, inhibiting tyrosine kinase targeting the VEGF receptor pathway are also approved and have demonstrated efficacy in a variety of tumour forms [43]. Furthermore, continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has an effect on tumour angiogenesis [45].

As with other new classes of drugs, the final place for anti-angiogenesis treatment in the management of cancer remains to be determined. The ability to predict responders to this type of treatments is an interesting question. Initial studies, using anti-angiogenesis treatment combined with conventional chemotherapy have led to varied results, mostly indicating an additive value of such combination.

In the 1970s, the hybridoma technique [46,47] enabled mass production of antibodies with a single binding site. The first clinical trials were conducted using murine antibodies (from mice) targeting tumour cell surface structures (antigens). Unfortunately, the results did not meet the expectations, largely because of low target specificity of the antibodies. The development of antibodies with major parts of the molecule of human origin and only the binding fraction being murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of antibodies makes them attractive therapeutic options.

TABLE 2.2. MONOCLONAL ANTIBODIES APPROVED FOR USE IN ONCOLOGY

Generic name/Tradename	Indication
Alemtuzumab/Campath/MabCampath	Chronic lymphocytic leukaemia
Bevacizumab/Avastin	Colorectal cancer
Brentuximab vedotin / Adcetris	Hodgkin lymphoma Anaplastic large cell lymphoma
Cetuximab/Erbitux	Colorectal cancer
Denosumab / Xgeva	Giant cell tumour of the bone Bone event prevention in cancer
Gemtuzumab /Mylotarg	Acute myeloid leukaemia
Ibritumomab tiuxetan/Zevalin	Non-Hodgkin's lymphoma
Ipilimumab / Yervoy	Malignant Melanoma
Obinutuzumab / Gazyva	Chronic lymphocytic leukaemia
Ofatumumab / Arzerra	Chronic lymphocytic leukaemia
Panitumumab / Vectibix	Colorectal cancer (KRAS wild type)
Panitumumab/Vectibix	Colorectal cancer
Pembrolizumab / Keytruda	Malignant Melanoma
Pertuzumab / Perjeta	Breast Cancer
Ramucirumab / Cyramza	Gastric cancer or Gastroesophageal junction (GEJ) adenocarcinoma
Rituximab/MabThera	NHL
Tositumomab/Bexxar	Non-Hodgkin's lymphoma
Trastuzumab/Herceptin	Breast cancer
Trastuzumab-emtasine	Breast cancer

2.2.4 Immuno-oncology

The stimulation of human immune system responses has long been thought a promising approach of cancer therapy, although until recently, immunotherapeutic drugs had provided very limited clinical effect. In April 2010, sipuleucel-T became the first therapeutic vaccine to be approved by the US Food and Drug Administration (FDA) for the treatment of patients with prostate cancer. Subsequently, in 2011, ipilimumab, a fully human monoclonal antibody which blocks cytotoxic T-lymphocyte-associated antigen-4, became the first agent approved in the EU for the treatment of adult patients with unresectable or metastatic melanoma. The success of these agents has further motivated others to undertake research in immuno-oncology. Increased understanding of the fundamentals of immunology has identified many ways in which the immune system can be augmented to treat cancer, including priming/boosting of the immune system, T-cell modulation,

reducing immunosuppression in the tumour microenvironment and enhancing adaptive immunity. An additional benefit of using an immuno-oncology approach to treatment is that these agents target the immune system and not the cancer, and therefore have the potential of adaptable and durable cancer control across a variety of tumour types. In 2015 a new class of drugs that block PD-1 (Programmed cell death protein 1) were approved for cancer treatment. The PD-1 and PD1-ligand (L) inhibitors, activate the immune system to attack tumors. PD1 drugs were approved in the EU in 2015 for the use in melanoma and for lung cancer (NSCLC adenocarcinoma). The dual inhibitory effect of PD-1 promotes apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes and reducing apoptosis in regulatory T cells (suppressor T cells). The PD-1 inhibitors presently approved are pembrolizumab and nivolomab. In 2016 PD1 drugs have received further approval in lung and renal cancer. Several new indications are expected for both these PD1 as well as PD1-L drugs; alone or in combination, over the next 2-3 years.

Over the last 5 years a number of new studies have shown the increasing role of immune-oncology. The 2015 ASCO meeting was dominated by the data presented on immune-oncology, especially in malignant melanoma and lung cancer, but several other tumour types are presently in the focus of ongoing pivotal trials [48].

2.2.5 Advances in supportive drug treatment

Supportive drugs enable intensified treatment schedules and improved quality of life for patients suffering adverse symptoms of cancer or the treatment. Patients with metastatic disease, treated with chemotherapy, often develop fatigue, low levels of red blood cells (anaemia), decreased white blood cell counts (neutropenia) and nausea.

The fatigue of cancer patients is often multifactorial: it may be related to side effects of treatment or psychological stress. Many tumours also secrete substances (cytokines) that may cause fatigue. However, fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but drugs currently in use (e.g. epoetin alpha, epoetin beta, erythropoetin) increase the production of red blood cells reducing the need of blood transfusions. In addition, chemotherapy is often associated with bone marrow depression which lead to anaemia, neutropenia and thrombocytopenia which may delay consecutive doses of treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad spectrum antibiotics and platelet transfusion techniques has decreased morbidity and mortality and has also enabled intensified treatment schedules, increasing cure rates.

There are also several agents that prevent nausea (e.g. ondansetron, granisetron). Bisphosphonates (e.g. pamidronat, zoledronic acid), and RANKL (denosumab), reduce the risk of skeletal events (fractures) as well as providing relief from the pain caused by skeletal metastases.

2.2.6 Advances towards curing cancer

Although cancer is a common disease, affecting roughly every third person during their lifetime, approximately 50-60% of patients diagnosed with cancer will either be 'cured' or will die from other causes. Progress in medical treatment of cancer has been made in almost every area. In most tumours, stepwise and relatively modest improvements have over time resulted in impressive increases in the proportion of patients considered cured. For instance, the overall breast cancer mortality in the USA and UK has been reduced by 25% from the 1980ies to the year 2000 . This progress is to some extent the result of screening programs, enabling earlier detection of the disease, but it is also a true reduction in mortality due to improvements in adjuvant treatment. Anthracycline based poly-chemotherapy reduces the annual breast cancer death rate by about 38% for women younger than 50 years and by about 20% for those in the age of 50-69 years. Additional use of 5 years tamoxifen treatment in oestrogen receptor positive (HER2-positive) disease results in a reduction of the annual breast cancer death rate by 31%. There is now a discussion about prolonging this treatment to 10 years. Improved chemotherapeutic regimens have increased survival further and recently, adjuvant treatment with the monoclonal antibody trastuzumab in patients with HER2-positive disease has shown a 50% decreased relapse risk and a 33% reduced mortality risk [49,50]. Considerable progress has also been made in other major tumour groups. In colon cancer (CRC) adjuvant chemotherapy have reduced mortality with 20-30% [35] and chemotherapy in the metastatic setting has four-folded average survival, from 5 to 20 months [52]. In other diseases like aggressive Non-Hodgkin's Lymphoma (NHL), the combination of CHOP (Cyclophosphamide/ Hydroxydaunorubicin/Oncovin/Prednisone or Prednisolone) and rituximab results in a five year survival rate of 58% in patients over 60 years of age [53-55] and a 2-year overall survival of 95% in patients under 61 years of age . In recent publications by Gondos, Brenner and Pulte significant improvements in the outcome of NHL, CML and multiple myeloma (MM) have been described based on the SEER (the Surveillance, Epidemiology, and End Results) database in the US.

These publications represent epidemiological support for the value of innovative drugs in oncology and haematology. Similar support for treatment effects at a population level has been reported by von Plessen and co-workers. They reported a significant improvement in the outcome for patients

with advanced non-small-cell lung cancer (NSCLC) in Norway, linked to the introduction of palliative chemotherapy [58].

In other areas of oncology, such as testicular cancer and Hodgkin's disease, the changes in cure rates have been sudden and dramatic. With the introduction of the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone) in 1967, cure rates of over 50% were obtained in patients with advanced Hodgkin's disease [59]. This was a milestone in medical oncology, proving the ability of cure even in advanced stages of the disease. Since then, even higher cure rates (90%) have been obtained using new combinations of chemotherapy [60]. In testicular cancer, the prognosis has turned from one of the worst to one of the best among the oncological diagnoses. The introduction of cisplatin in the 1970ies was an immediate breakthrough in the treatment of testicular cancer [61]. The addition of chemotherapy agents to surgery and local radiotherapy has further increased curative rates in patients with metastatic testicular cancer disease to approximately 90 to 95%. However, it is important to note that breast cancer is a much more common disease; the number of patients cured of breast cancer far exceeds number of patients cured of testicular cancer and Hodgkin's disease.

2.2.7 Advances towards the prevention of cancer

Epidemiological research has shown that cancer risk is associated with various external and lifestyle factors such as smoking, alcohol consumption, obesity, exercise habits and exposure to certain viruses. For example, it has been known for more than 50 years that smoking increases the risk of developing many cancers, especially lung cancer. Very little has been done in order to change smoking habits, which has resulted in the global epidemic of lung cancer we see. The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials with tamoxifen in women with an increased genetic risk of breast cancer who were found to benefit from treatment with tamoxifen (50% risk reduction) [62]. In the USA, the FDA has approved the use of tamoxifen as a preventive agent in high-risk patients. Recently, raloxifene (an agent similar to tamoxifen) has proved as efficient as tamoxifen as a preventive agent and with less side effects [63]. Several breast cancer prevention studies with aromatase inhibitors have also been performed [64]. Other agents that have indicated effect as preventive agents are non-steroidal anti-inflammatory drugs in colon cancer [65], finasteride in prostate cancer [66] and recently statins in breast cancer [3,67]. The first vaccines against human papilloma virus (HPV) – the cause of the vast majority of cervical cancers –was introduced in 2005.

The fact that there are agents that can be used for prevention of cancer is in itself an important milestone in oncology. The area of cancer prevention is complex and involves political as well as medical measures. From a medical perspective, the main challenge is finding preventive agents/measures that are non-toxic and well tolerated. As costs for cancer treatments continue to increase, the value of preventive measures will become more interesting.

2.2.8 Specific tumour types addressed in this report

2.2.8.1 Malignant melanoma

Although melanoma accounts for only 4% of all skin cancers, it causes the greatest number of skin cancer-related deaths worldwide. In 2012, there were 82,100 new cases of cutaneous melanoma and 15,700 deaths in Europe and an estimated 81,240 new cases and 12,190 deaths in the United States [68]. Despite prevention campaigns aimed at reducing the excessive sun exposure, the incidence of melanoma is increasing at a faster rate than most other cancers, particularly in young Caucasian women. Early detection and excision of superficial cutaneous melanoma is the best means of reducing mortality. However, once a patient develops metastatic disease the prognosis is dismal. In a recent meta-analysis of phase II trials, 1- and 2-year overall survival rates in patients with metastatic melanoma were approximately 25% and 10%, respectively, and median survival time was 6.2 months [70]. Before 2011, treatment options for patients with metastatic melanoma were limited to chemotherapy and InterLeukin-2 (IL-2). Although chemotherapy with dacarbazine is the best established treatment, it has never shown to improve survival over supportive care [69].

Treatment with IL-2 is restricted to treatment centres with intensive care facilities and specialists in cardiopulmonary or intensive care medicine for the management of side-effects[70,71]. Metastatic melanoma has therefore been a focus for the development of novel approaches . Studies of melanoma have played a central role in understanding the immune response to cancer. Investigations have largely been facilitated by the relative accessibility of melanoma lesions and the fact that melanoma is one of the easiest cancers to adapt to tissue culture [71].. Furthermore, a number of clinical observations relating to the activity of the immune system in melanoma provide strong evidence that the immune system can naturally react to and destroy or control melanoma .

Targeted treatment of malignant melanoma

During the last 5 years, as pointed out previously in this chapter, several agents have been shown to significantly improve survival in patients with metastatic melanoma. Vemurafenib and dabrafenib, inhibitors of mutated BRAF protein kinase, has been shown to be highly active in

patients with BRAF muted metastatic melanoma. BRAF mutations are found in approximately 50% of patients with metastatic melanoma. In these patients, BRAF inhibitors will induce tumour responses in a high percentage of patients (50-80%). Responses may sometime be short lived, but some patients have had long lasting responses. Combined BRAF inhibition and MEK inhibition has been shown to be of additional value in some studies .

However, immune-oncology represents a new and major step forward in the treatment of patients with metastatic melanoma, both for BRAF mutated and non-mutated patients. Ipilimumab and now the Programmed cell Death Protein 1 (PD-1) inhibitors (e.g. nivolumab and pembrolizumab) alone or in combination, has established immune-oncology as front line therapy for patients with metastatic melanoma. How to schedule and make best use of both BRAF/MEK inhibitors as well as CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 inhibitors, still remains to be established. This will of course be evaluated in prospective clinical studies, but studies of "real world patients" i.e. clinical effectiveness, will be extremely important. The establishment of databases for collection of clinical "real life" data are under way and will be a major source of information in the future [78]

2.2.8.2 Multiple myeloma

Multiple myeloma (MM) accounts for 1% of all cancers and approximately 10% of all haematological malignancies. The incidence in Europe is 4.5–6.0 per 100,000 inhabitants and year with a median age at diagnosis between 65 and 70. The mortality in MM is 4.1 per 100,000 inhabitants and year. MM evolve from an asymptomatic pre-malignant stage termed Monoclonal Gammopathy of Undetermined Significance (MGUS). MGUS progresses to MM at a rate of 1% per year. In some patients, an intermediate asymptomatic but more advanced pre-malignant stage termed Smouldering (or indolent) Multiple Myeloma (SMM) can be recognised. SMM progresses to MM at a rate of 10% per year over the first 5 years following diagnosis [80].

Treatment of myeloma

Immediate treatment is not recommended at the present time for patients with SMM. Treatment should be initiated in all patients with active MM fulfilling the CRAB (Calcium, renal, anaemia and bone) criteria, (hypercalcaemia >11.0 mg/dl), creatinine >2.0 mg/ml, anaemia (Hb <10 g/dl), active bone lesions), and in symptomatic patients (non-transplant setting). Oral combinations of Melphalan and Prednisone (MP) are considered standard care in Europe. The two following options are recommended based on data from randomised phase III trials [I, A]: Melphalan/Prednisone/ Thalidomide (MPT) [81], or Bortezomib/Melphalan/Prednisone (BMP) [82]; both MPT and BMP are

approved in this setting by the European Medicines Agency (EMA). Cyclophosphamide/ Thalidomide/Dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates but does not show clear survival advantage over MP [83,84]. Lenalidomide combined with low-dose dexamethasone also yields important response and survival rates. For patients in good clinical condition (e.g. fit patients; < 65-70 years of age), induction followed by high-dose therapy with Autologous Stem Cell Transplantation (ASCT) is the standard treatment [II, B] [85]. Response rates to induction therapy have significantly increased over time. Bortezomib-dexamethasone is superior to the classical VAD regimen (Vincristine, Adriamycin and high-dose Dexamethasone) [II, B] [87-89], and has become the backbone of induction therapy before ASCT. The addition of a third agent to bortezomib-dexamethasone, e.g. thalidomide (VTD), doxorubicin (DVD or PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher response rates in phase II trials and have become standards of care in many countries. Three prospective studies have already shown that VTD is superior to TD or bortezomib-dexamethasone . Based on response rates, depth of response and PFS as surrogate markers for outcome, three-drug combinations including at least bortezomib and dexamethasone are currently the standard treatment before ASCT. Melphalan (200 mg/m2 i.v.) is the standard preparative regimen before ASCT [II, B] [92]. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM [III, B]. The benefit of tandem ASCT was observed in patients that were not reaching very good partial response after the first ASCT [93]. There are ongoing trials running both in Europe and US comparing prospectively single versus tandem ASCT. There is still not enough evidence that consolidation therapy should be systematically applied.

2.2.8.3 Non-small cell lung cancer

Deaths from lung cancer exceeds any other type of malignancy worldwide [94,95], it has been the most important cause of cancer death in males since the 1960ies, and has actually equalled breast cancer in mortality in women since the 1990ies. To date, smoking cessation is the most important method to reduce the death toll. In countries with effective tobacco control measures, the incidence of new lung cancer is declining in males and is reaching a plateau for females [94]. In the European Union in 2013, lung cancer mortality fell in men (−6%) compared with 2009 while cancer death rates in women are increasing (+7%) approaching the levels of men [96]. Non-Small Cellular Lung Cancers (NSCLC) account for 85% to 90% of lung cancers, while Small Cellular Lung Cancers (SCLC) has been decreasing in many countries over the last two decades [97] [96]. Smoking is the main cause of lung cancer, responsible for more than 80% of cases. The observed variations in lung cancer rates across countries largely reflect smoking habits. There are several other known risk

factors including exposure to asbestos, arsenic, radon, and non-tobacco-related polycyclic aromatic hydrocarbons, and interesting hypotheses about indoor air pollution (e.g. coal-fuelled stoves and cooking fumes) suspected to contribute to the relatively high burden of non-smoking-related lung cancer in women in some countries, especially in Asia. Prevalence of lung cancer in females without a history of tobacco smoking is estimated to represent 19% compared with 9% of male lung carcinoma in the US [98]. Women are over-represented among younger patients, raising the question of gender-specific differences in the susceptibility to lung carcinogens [99]. In recent times, an increase in the proportion of NSCLC patients who are never-smokers has been observed, especially in Asian countries [100,101]. These new epidemiological data have resulted in '*non-smoking-associated lung cancer'* being considered a distinct disease entity, where specific molecular and genetic tumour characteristics are being recognized.

Treatment of lung cancer

Surgery remains the preferred treatment option in early stage NSCLC (stage I and II). It has been shown that the addition of postoperative chemotherapy will result in a significant survival improvement.

Targeted therapy of lung cancer

In recent years, various molecular targeted therapies have been developed for the treatment of advanced lung cancer. Gefitinib is a drug which targets the tyrosine kinase domain of EGFR, often expressed in NSCLC. It does not improve survival, although Asian, non-smoking females appear to have benefit from gefitinib [102].

Erlotinib, another EGFR tyrosine kinase inhibitor, increased survival in NSCLC [101] and was approved by the FDA in 2004 for second-line treatment [104]. Erlotinib is most effective in patients with specific mutations in EGFR, and in females, Asians, non-smokers, and patients with bronchioloalveolar carcinoma [105].

The angiogenesis inhibitor bevacizumab (in combination with paclitaxel and carboplatin), improves the survival of patients with advanced NSCLC [106-112]. However, there are severe side effects with lung bleeding, particularly in patients with squamous cell carcinoma.

Crizotinib shows benefit in a subset of NSCLC tumours, characterized by the EML4-ALK fusion oncogene. EML4-ALK is found in some relatively young, never or light smokers with adenocarcinoma. Nivolumab, a human IgG4 anti-PD-1 monoclonal antibody first approved for metastatic melanoma, has recently also been approved for the treatment of NSCLC.

Advances in cytotoxic drugs, pharmacogenetics show promise, and a number of targeted agents are at the early stages of clinical research, such as cyclo-oxygenase-2 inhibitors the apoptosis promoter exisulind, proteasome inhibitors, bexarotene, the EGFR inhibitor cetuximab, the tyrosine kinase inhibitor sorafenib and vaccines. Future areas of research include ras proto-oncogene inhibition, phosphoinositide 3-kinase inhibition, histone deacetylase inhibition, and tumour suppressor gene replacement.

2.3 Conclusions

Medical oncology has entered an exciting phase of treatments designed to target disease-specific mechanisms. In some tumour forms these agents will replace the generally cytotoxic agents as first line treatment, whereas in other tumour forms their final place in the therapeutic arsenal is still unclear. The number of new agents with antitumor effects has accelerated during the last 10 years and, judging from the number of ongoing trials and pipelines of pharmaceutical companies, there is every reason to believe that this trend will continue in years to come. Intense research in molecular medicine and tumour biology will also lead to the identification of an increasing number of potential targets of intervention. However, this is only realised once these drugs are adopted into routine clinical practice and reach the patients who may benefit.

2.4 Chapter summary

- Cancer treatment today is characterized by multimodal therapy approaches; surgery, radiotherapy and an increasing number of anti-tumour drugs. Optimal treatment of cancer patients requires multidisciplinary teams; surgeons, radiotherapists, medical oncologists, diagnostic radiologists, pathologists, specialized nurses and psychosocial support.
- Most anti-tumour drugs are introduced in patients with late stage or metastatic disease. In many cases, efficacy in late stage disease translates to increased cure rates when the drug is introduced in the adjuvant setting in conjunction with surgery or with a curative intent as first-line treatment.
- Traditional anti-tumour drugs have been cell toxic (effect on all cells, not only cancer cells), with often severe side effects. The progress in molecular medicine has enabled the development of new agents that target more disease specific mechanisms with a different toxicity profile.
- Improved diagnostic methods and screening programs have facilitated early detection of tumours, improving cure rates.
- The development of new anti-tumour agents has led to the introduction of an increasing number of compounds with a focus on improving the quality of life for patients – supportive drugs.
- The decreased toxicity of new agents, a trend towards oral agents, and the use of supportive drugs have enabled patients to spend fewer days in hospital and led to an increased number of day-care treatments.
- It is already possible to predict if a patient is likely to respond to treatments by different molecular markers. Gene/protein expression analyses of tumours are likely to improve accuracy in the treatment offered to individual patients in the near future.

- The use of new diagnostic tools, including functional imaging, to evaluate therapy effects is increasing.
- The latest development in oncology includes activating the body's own immune system in the treatment of cancer. Immuno-oncology has rapidly become standard of care in metastatic malignant melanoma and progress is also ongoing in a number of other tumour types. At present, immune-oncology represents the most promising new treatment.

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3 Market Uptake of Selected Oncology Drugs

Chapter 3 deals with the market uptake of selected oncology drugs, by mapping their market authorization and total sales in the 12 countries selected. The numbers presented focus on the selected diseases whose medical progress have been described in Chapter 2; melanoma, multiple myeloma and NSCLC; reference diseases: Chronic Myeloid Leukaemia and HER2-positive breast cancer.

3.1 Sales of oncology drugs

Data from the IMS MIDAS database show that total sales[3] of oncology drugs in the selected countries (EU12: Austria, Belgium, Denmark, Finland, Germany, Hungary, the Netherlands, Norway, Poland, Sweden, Switzerland and the UK) have increased substantially over the period 2003-2012 from €3 billion to almost €11 billion (Figures 3.1 to 3.3).

The increase remained substantial until 2009, after which it stagnated and in some cases decreased until the end of 2012, before it increased again during 2013. Austerity measures following the recent financial crisis may be a reason for the stagnation of sales of oncology drugs in the EU12. Another explanation could be patent expirations for several drugs with large sales amounts during the last decade.

[3] By total sales we refer to the sales of all drugs in the IMS MIDAS database, based mainly on manufacturer prices, with ATC3 codes L1A, L1B, L1C, L1D, L1G, L1H, L1X, L2A, L2B, and L4X in the EU12.

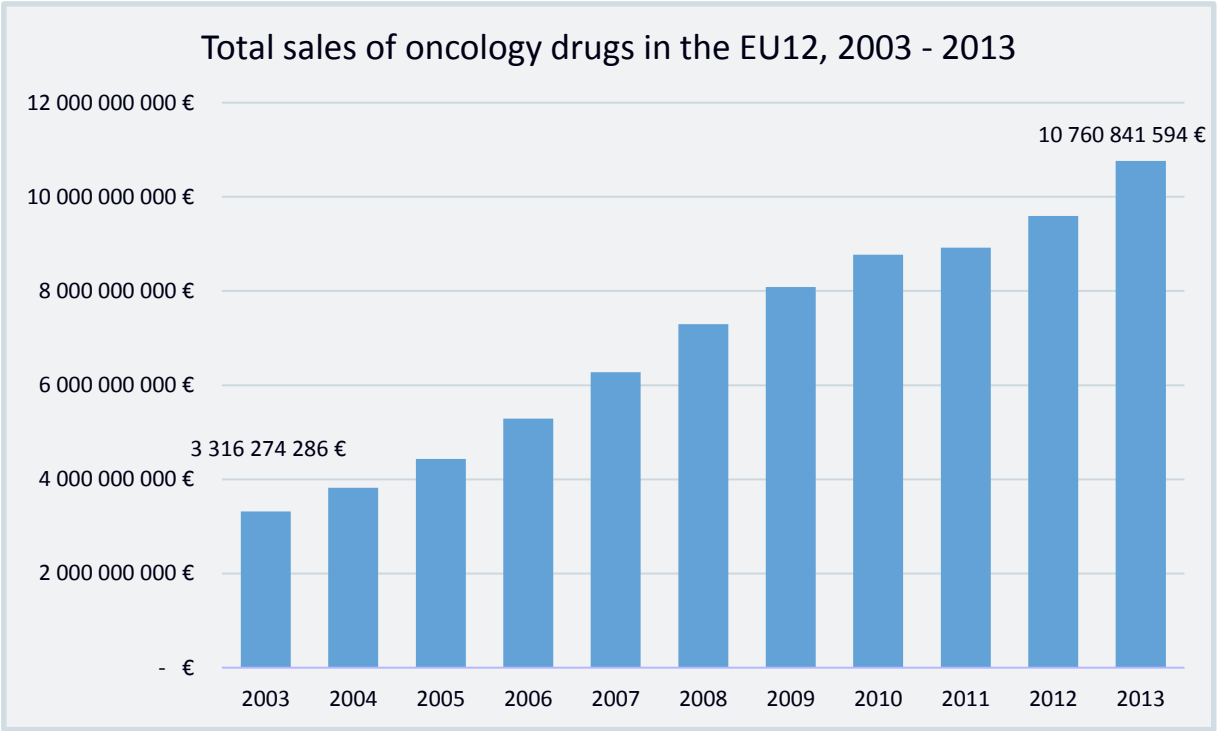

FIGURE 3.1. TOTAL SALES OF ONCOLOGY DRUGS IN THE EU12 FOR THE PERIOD 2003-2013. THE DATA CONTAIN SALES UNTIL QUARTER 3 2013, SO FOR 2013 THE SALES IN QUARTER 4 IS ASSUMED TO BE EQUAL TO SALES IN QUARTER 3.

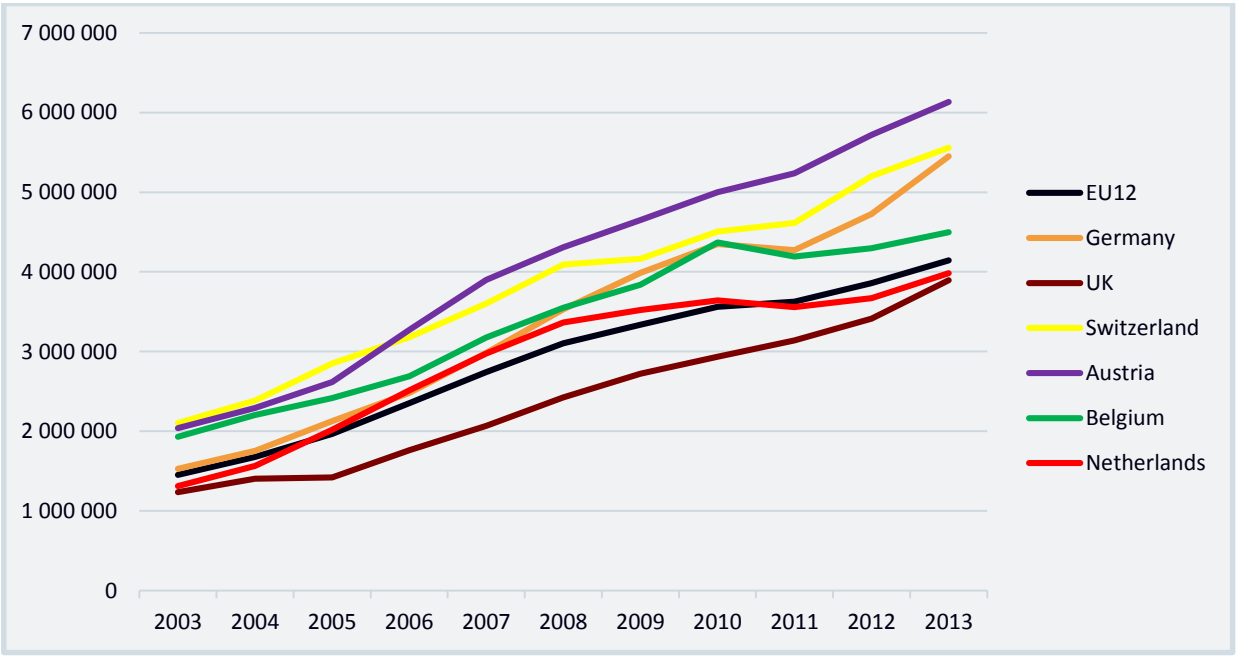

FIGURE 3.2. SALES OF ONCOLOGY DRUGS IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, PRESENTED IN € PER 100,000 POPULATION. THE DIFFERENCES TO BE NOTED SINCE 2005 ARE THAT AUSTRIA NOW HAS THE HIGHEST SALES, THAT GERMANY HAS INCREASED ITS SALES (BUT THERE MAY ALSO BE SOME DIFFERENCES IN REPORTING OVER TIME), AND THAT THE SALES IN THE UK HAS INCREASED OVER TIME. THE SUBSTANTIAL GAP BETWEEN SALES IN THE UK SEEN IN 2005, WITH SALES BEING ABOUT HALF THE SALES IN AUSTRIA, BELGIUM AND SWITZERLAND, HAVE AT THE END OF 2013 DECREASED TO ABOUT 2/3 OF SALES IN AUSTRIA AND ABOUT 3/4 OF SALES IN SWITZERLAND AND GERMANY.

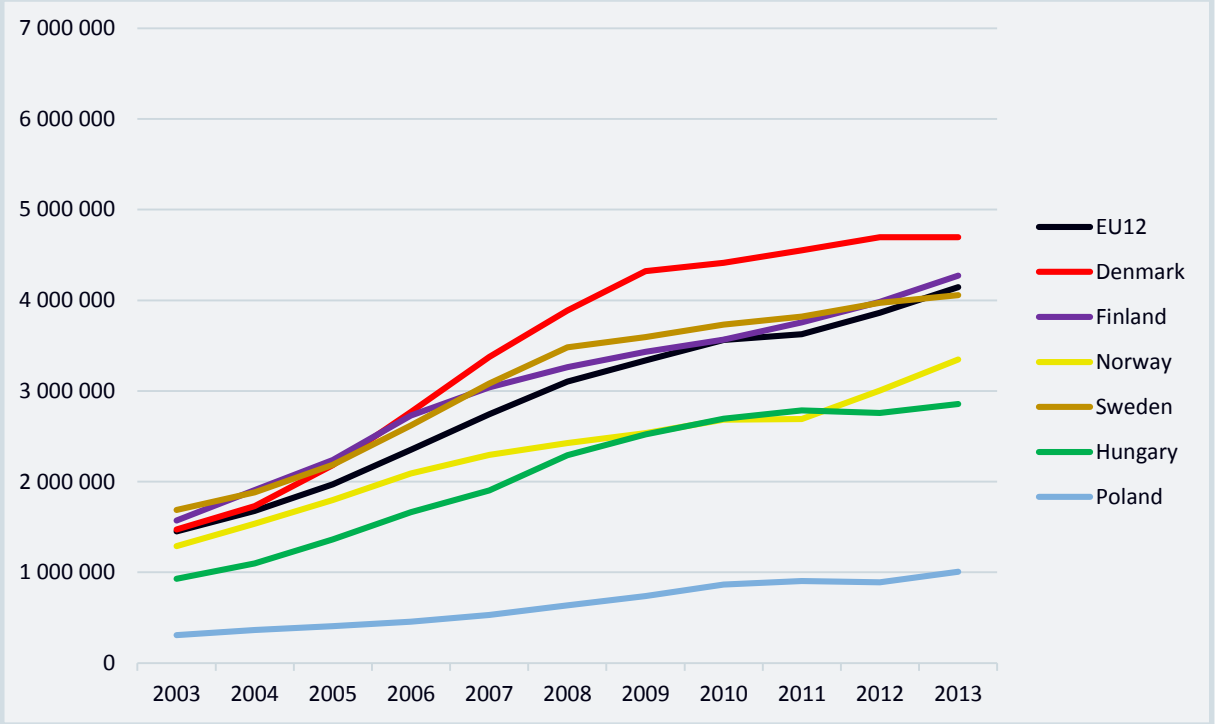

FIGURE 3.3. SALES OF ONCOLOGY DRUGS IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, PRESENTED IN € PER 100,000 POPULATION. THERE HAVE BEEN SOME CHANGES IN RELATIVE SALES SINCE 2005. DENMARK HAS INCREASED THEIR SALES, WHILE SWEDEN AND NORWAY HAVE HAD A SLOWER DEVELOPMENT OVER TIME. IN 2013, THE SALES IN NORWAY ARE SIMILAR TO THOSE SEEN IN HUNGARY. SALES IN POLAND HAVE BEEN SIGNIFICANTLY LOWER COMPARED TO THE OTHER COUNTRIES DURING THE WHOLE TIME PERIOD AND HAS STAYED RELATIVELY UNCHANGED SINCE 2008.

3.2 Selected oncology drugs

Table 3.1 lists the drugs selected for further analysis in this chapter, along with year and month of marketing authorization in the EU as well as in the US.

TABLE 3.1 DRUG AND DATE FOR EU MARKET AUTHORIZATION BY THE EMA AND MARKETING APPROVAL BY THE U.S. FOOD AND DRUG ADMINISTRATION (FDA). FOR EMA, THE MONTH AND YEAR FOR THE MARKETING AUTHORIZATION SUBMISSION BY EACH RESPECTIVE COMPANY IS GIVEN IN BRACKETS.

Molecule	Indication	Authorisation, EMA[2]	Approval, FDA[3]
trastuzumab	Breast cancer	(Feb 1999) Aug 2000	May 1998
Imatinib	Leukaemia	(Mar 2001) Nov 2001	May 2001
bortezomib	Multiple myeloma	(Jan 2003) Apr 2004	May 2003
pemetrexed	NSCLC	(Jul 2003) Sep 2004	Feb 2004
Erlotinib	NSCLC	(Aug 2004) Sep 2005	Nov 2004
lenalidomide	Multiple myeloma	(Feb 2006) Jun 2007	Jun 2006
Gefitinib	NSCLC	(May 2008) Jun 2009	May 2003[4]
ipilimumab	Malignant melanoma	(May 2010) Jul 2011	Mar 2011
vemurafenib	Malignant melanoma	(May 2011) Feb 2012	Aug 2011
crizotinib	NSCLC	(Jul 2011) Oct 2012	Aug 2011

NSCLC - Non-small cell lung cancer

[4] Gefitinib was given an accelerated approval procedure by the FDA.

Quarterly and annual sale statistics in the period 2003 to 2013 were obtained from IMS Health, IMS MIDAS. The term EU5 represents the following European countries: France, Germany, Italy, Spain and the UK. Sales from IMS Health, IMS MIDAS, were based on manufacturers' prices in most countries, except in the UK, where sales were based on trade prices (wholesaler price). Cost of distribution to the pharmacy is not included. This is mainly of importance for low priced drugs prescribed in ambulatory care, where the pharmacy margin is the highest. Cancer drugs are mainly used in the hospital setting. For the cancer drugs specifically targeted in this report ipilimumab, bortezomib and pemetrexed are used in a hospital setting and are all intravenous therapies, while vemurafenib, lenalidomide, crizotinib, erlotinib and gefitinib are all oral therapies and thus prescription drugs. Costs of administration of drugs are not included.

Sales are presented in nominal prices for the countries using the Euro (€) as the local currency. For Denmark, Hungary, Norway, Poland, Sweden, Switzerland, and the UK, sales in local currencies have been converted to Euros using the 2004 annual average of the bilateral exchange rate from the European Central Bank (ECB) [4]. By using a fixed exchange rate for the latter set of non-Euro countries this report aim to reduce the variation in sales due to exchange rate fluctuations. IMS pharmaceutical audits report sales at either manufacturer selling price (wholesale purchase price, trade price, pharmacy purchase price/wholesale price) or public price[5].

Differences in prices may influence the comparisons made using value terms. Studies show that there are price variations for branded medicines between the EU member states, with respect to both ex-factory prices and public prices [5-7]. As the EU5 – France, Germany, Italy, Spain, and the UK – are mentioned in all mentioned studies they will serve as examples of varying prices in the EU.

A price comparison of 2008 ex-manufacturer prices by the UK Department of Health for 150 pharmaceuticals among EU member states showed Germany to be the country with the highest price level, followed by the UK, Spain, France and Italy, as seen in Table 3.2 [5]. The study also highlighted the importance of exchange rates on relative prices and states that the pound sterling fell in value relative to the Euro by 17% in 2004-2008. The price indices were therefore also computed for 2008 by using the 2004-2008 average exchange rate between the Euro and the pound sterling, which is shown in the far right column of Table 3.2.

[5] The manufacturer selling price is the price for a pharmaceutical paid by a pharmacy, hospital or equivalent and consists of the ex-factory price and the manufacturer's mark-up. The public price is the official list price or the price paid by, e.g. health insurers.

TABLE 3.2 PHARMACEUTICAL PRICE INDICES FOR THE EU5, 2004-2008, USING NOMINAL BILATERAL EXCHANGE RATES.

Country	2004	2005	2006	2007	2008	2008[a]
France	84	96	89	92	108	91
Germany	106	108	105	113	142	119
Italy	78	84	78	83	101	84
Spain	80	84	85	88	109	91
UK	100	100	100	100	100	100

[a] Price indices have been computed using the five-year average exchange rate for EUR/GBP, highlighting the effect of exchange rate on price variations [5].

FIGURE 3.4. PRICE INDICES (EU5 = 100). DIFFERENCE IN EX-FACTORY PRICES AMONG THE EU5 COUNTRIES [1].

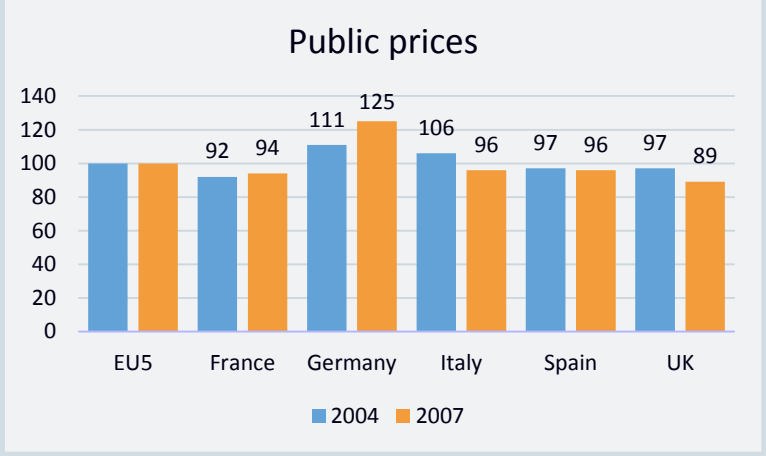

FIGURE 3.5. PRICE INDICES (EU5 = 100). DIFFERENCE IN PUBLIC PRICES AMONG THE EU5 COUNTRIES [1].

Kanavos and Vandoros compared ex-factory and public price levels for 13 branded in-patent pharmaceuticals between the US and the EU5 member states and found US ex-factory price levels to be two to three times higher than that of the EU5 member states [7]. The difference in public prices were much lower, about 20% higher than the EU5 average in 2004 and 60% higher than the

EU5 average in 2007. Figures 3.4 and 3.5 show the difference between ex-factory prices and public prices in 2004 and 2007. It shows that the UK is second to Germany when it comes to ex-factory prices but in parity with France, Italy and Spain when it comes to public prices. The authors also highlight the importance of exchange rate fluctuations in explaining variations in drug prices. For example, the aforementioned increase in US versus EU5 ex-factory prices could to 30% be explained by a depreciation of the USD in 2004-2007.

The modest difference in pharmaceutical prices between the UK and France and Germany seem to increase quite dramatically when it comes to cancer drugs. Kanavos and colleagues compared retail prices for selected cancer drugs (anastrozole, cetuximab, capecitabine, trastuzumab, lapatinib, temozolomide, sunitinib) in 2009 and found the UK to have the lowest price for all drugs except anastrozole where Hungary had a lower price [6]. Germany and France were among the countries with the highest prices and prices were generally about 40% higher compared to the UK. Even if exchange rate fluctuations may contribute to price variations, the differences for the cancer drugs in the mentioned study were still considerably lower in the UK than in France and Germany. Most of the other European countries highlighted in this report, such as Sweden, Austria, and Belgium have prices between those of Germany and the UK.

International price comparisons are problematic for a number of reasons, and it is difficult to make a precise correction for price effects. In order to avoid differences based on price effects, previous *Comparator Reports* have also reported data based on sales in milligrams. This measure was unfortunately not available in the current dataset. Based on the above information about the impact of exchange rate fluctuations on price variations we conducted a comparison of sales in milligrams (Mg) and € for bortezomib and pemetrexed in the EU5 using a previous dataset from the IMS MIDAS database. These comparisons showed that the sales in € underestimate UK sales, because of price variations and exchange rate fluctuations, but not to the extent that the cross-country comparison or analysis changes. The comparison of sales in Mg and € can be found in the Appendix at the end of Chapter 3.

3.3 Uptake of selected cancer drugs

In this section, we present the sales of the specific oncology drugs listed in the introduction of the chapter. For each drug, uptake is given as sales (in €) from the time of local introduction or first sales (a drug could have been sold under special license prior to national authorization). It should be noted that the sales data in this chapter is expressed in € and not by a volume measure. Price variations between the selected countries could therefore explain some of the variations. Data are

related to the mortality of the specific cancer and are reported as sales per case. Mortality was selected over incidence or prevalence as an indicator of the number of patients that may benefit from treatment; i.e. a measure of need. This also reflects the fact that most drugs are introduced in the metastatic non-curable setting, thus making mortality the most relevant number to relate sales to. For the measure of sales of each selected oncology drugs per case the mortality rate for 2012 of each respective cancer type was used, as retrieved and defined in the European Conservation Action Network (EUCAN) in 2012 [8]. For Melanoma the mortality rate for "Melanoma of the skin" was used; for Multiple Myeloma the mortality rate for "Multiple Myeloma" was used; for NSCLC the mortality rate for "Lung cancer" was used. For the reference case of imatinib the mortality rate for "Leukaemia" was used and for the reference case of trastuzumab the mortality rate for "Breast cancer" was used.

The selected drugs are distributed on the different tumour types as below:

- Melanoma: ipilimumab and vemurafenib
- Multiple Myeloma: bortezomib and lenalidomide
- Non-Small Cellular Lung Cancer (NSCLC): crizotinib, erlotinib, gefitinib and pemetrexed

In addition to the selected cancer drugs we also include the uptake of imatinib and trastuzumab as reference cases.

3.3.1 Reference cases

Imatinib, granted an EU marketing authorisation in 2001, and trastuzumab, granted an EU marketing authorisation in 2000, are two well established therapies for the treatment of, mainly, Chronic Myeloid Leukemia (CML) and HER2-positive breast cancer, respectively. Both drugs represent major and uniformly accepted breakthroughs in the treatment of cancer and now form the backbone of treatment for the two diseases.

3.3.1.1 Trastuzumab

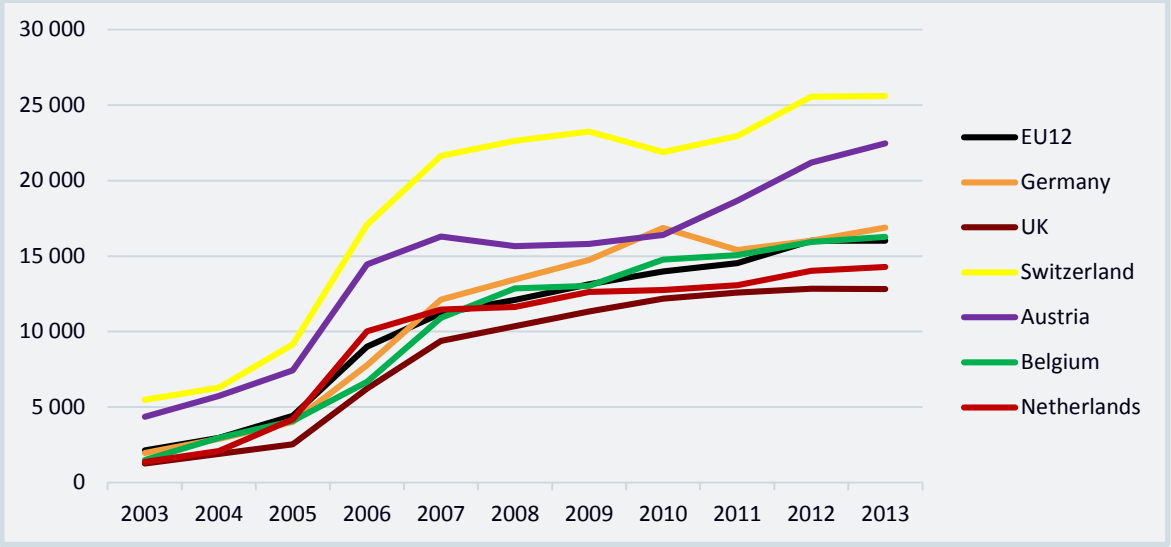

FIGURE 3.6. SALES OF TRASTUZUMAB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THERE ARE STILL MAJOR DIFFERENCES IN THE USE OF TRASTUZUMAB. THE USE IN SWITZERLAND IS TWICE THE USE IN THE UK. SALES IN AUSTRIA HAS ALSO INCREASED MUCH MORE THAN THE SALES IN COMPARATIVE COUTRIES WHO HAVE HAD RELATIVELY STABLE SALES FROM 2008/2009 AND ON. IT IS FROM A MEDICAL POINT OF VIEW DIFFICULT TO EXPLAIN THE HIGH SALES IN SWITZERLAND AND AUSTRIA. MOST WESTERN EUROPEAN COUNTRIS HAVE SALES RELATIVELY CLOSE TO THE EU12 AVERAGE. THE UK AND ESPECIALLY HUNGARY AND POLAND HAVE LOWER SALES WHICH MAY REPRESENT DIFFERNCES IN MEDICAL OPINION OF TRASTUZUMAB'S ROLE IN HER2-POSITIVE BREAST CANCER, BUT WHICH MOST LIKELY IS LINKED TO ECONOMIC FACTORS IN THE DIFFERENT HEALTH CARE SYSTEMS. DUE TO LACK OF VOLUME DATA, WE CANNOT SEPARATEE PRICE EFFECTS.

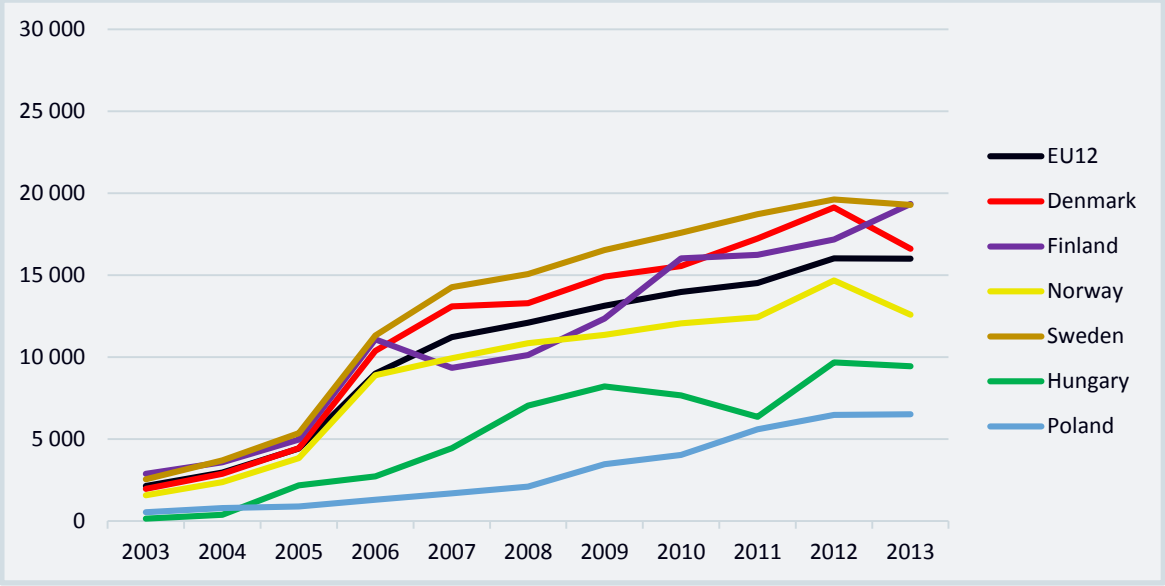

FIGURE 3.7. SALES OF TRASTUZUMAB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. SWEDEN CONTINUES TO HAVE HIGH SALES IN RELATION TO OTHER NORDIC COUNTRIES ALTHOUGH THE DIFFERNCE VERSUS DENMARK AND FINLAND HAS SHRUNK. SALES IN HUNGARY AND POLAND ARE STILL LOW AND CANNOT REFLECT THE MEDICAL NEED IN THESE COUNTRIES.

3.3.1.2 Imatinib

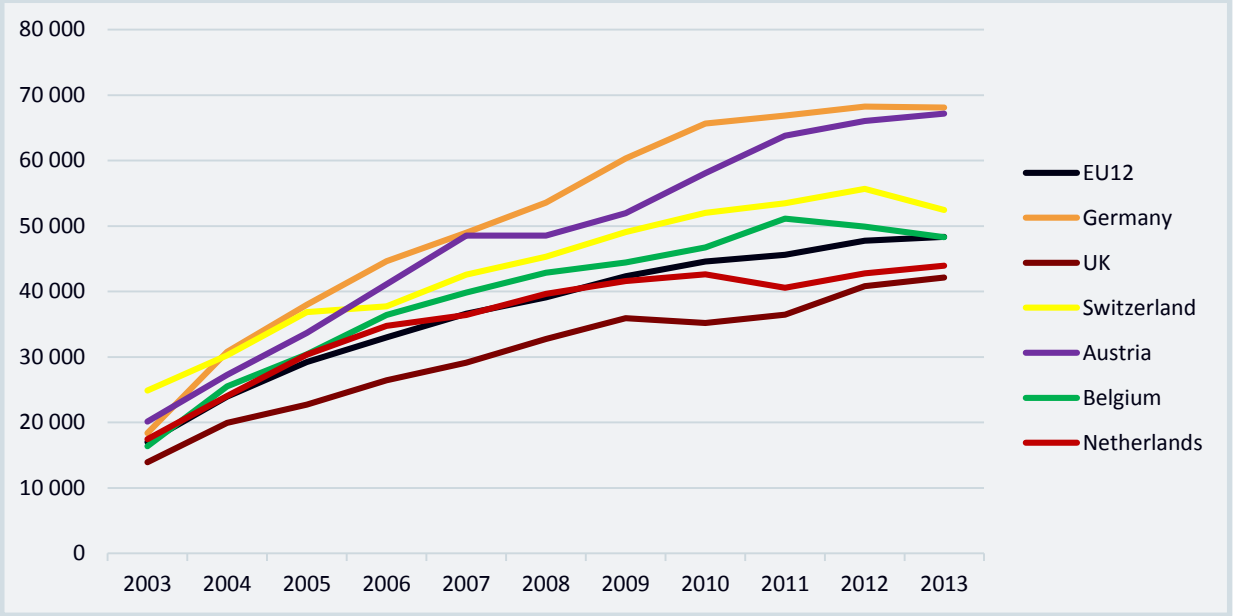

FIGURE 3.8. SALES OF IMATINIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THE BETWEEN-COUNTRIES DIFFERENCE IN IMATINIB SALES HAVE DIMINISHED OVER TIME. STILL, NOW DIFFERENCES ARE MORE PROMINENT. FOR THE MOST RECENT YEARS THIS MAY BE A REFLECTION OF NEWLY INTRODUCED DRUGS IN CML LIKE NILOTINIB AND DASATINIB. IT IS STILL STRIKING TO NOTE THAT SALES IN FOR EXAMPLE UK ARE JUST ABOUT 60% OF THOSE IN AUSTRIA AND SWITZERLAND.

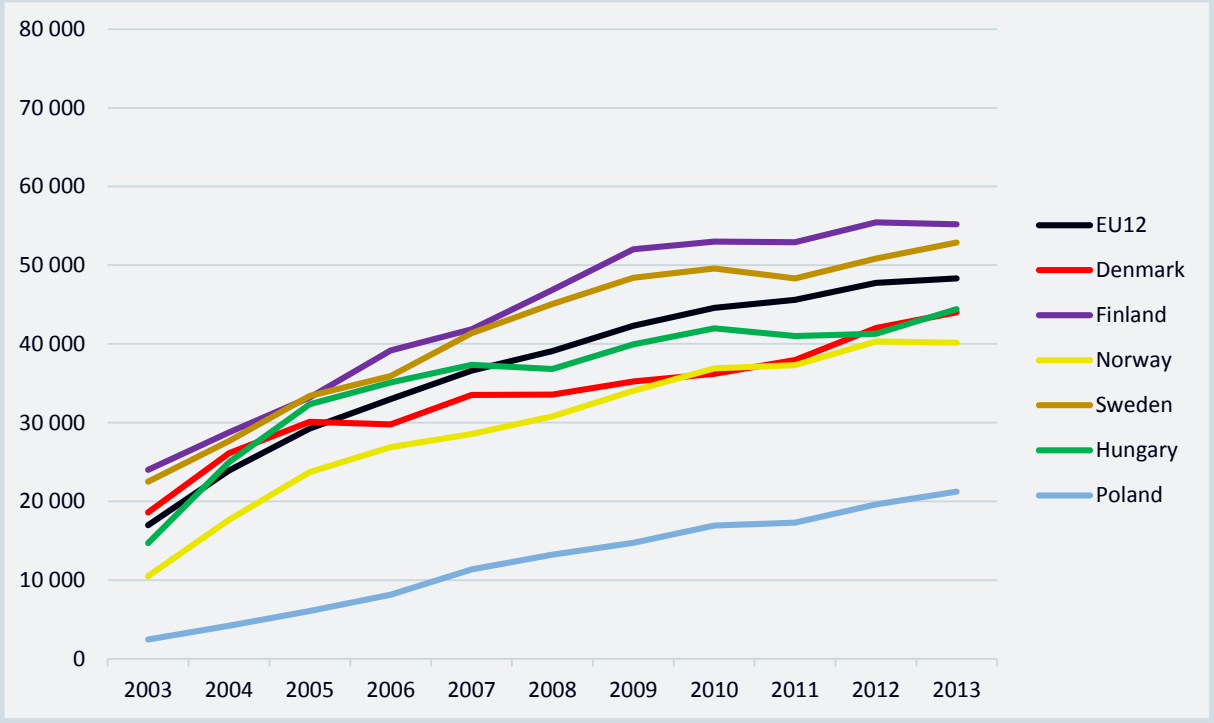

FIGURE 3.9. SALES OF IMATINIB IN € PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. WHAT STANDS OUT IN THIS COMPARISON IS THAT SALES IN POLAND STILL LAG BEHIIND WHICH MUST REFLECT AN UNDER TREATMENT OF PATIENTS WITH CML.

3.3.2 Non-small lung cancer

3.3.2.1 Pemetrexed

Pemetrexed is a chemotherapy drug and a multi target anti-folate. Its indications are the treatment of pleural mesothelioma and NSCLC, mainly then of adenocarcinoma type.

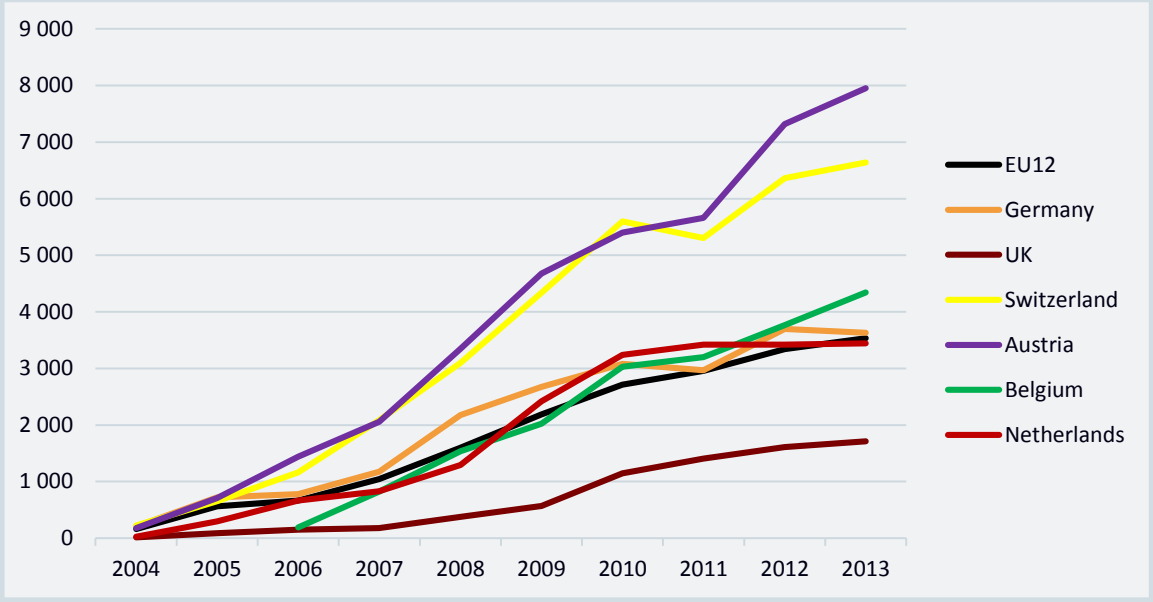

FIGURE 3.10. SALES OF PEMETREXED PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 EUCAN MORTALITY DATA [8]. SALES OF PEMETREXED DIFFER BY A FACTOR 4-5 (AUSTRIA AND SWITZERLAND VS. THE UK). FROM A MEDICAL POINT OF VIEW THIS IS VERY DIFFICULT TO UNDERSTAND. FOR THE OTHER COUNTRIES IN THIS COMPARISON, SALES ARE MORE OR LESS UNIFORM AND AT THE EU12 LEVEL. IT IS ALSO INTERESTING TO NOTE THAT BELGIUM AND THE UK HAD SALES AT A SIMILAR LEVEL IN 2006, BUT THAT SALES IN BELGIUM ARE NOW MORE THAN TWICE AS HIGH COMPARED TO THE UK.

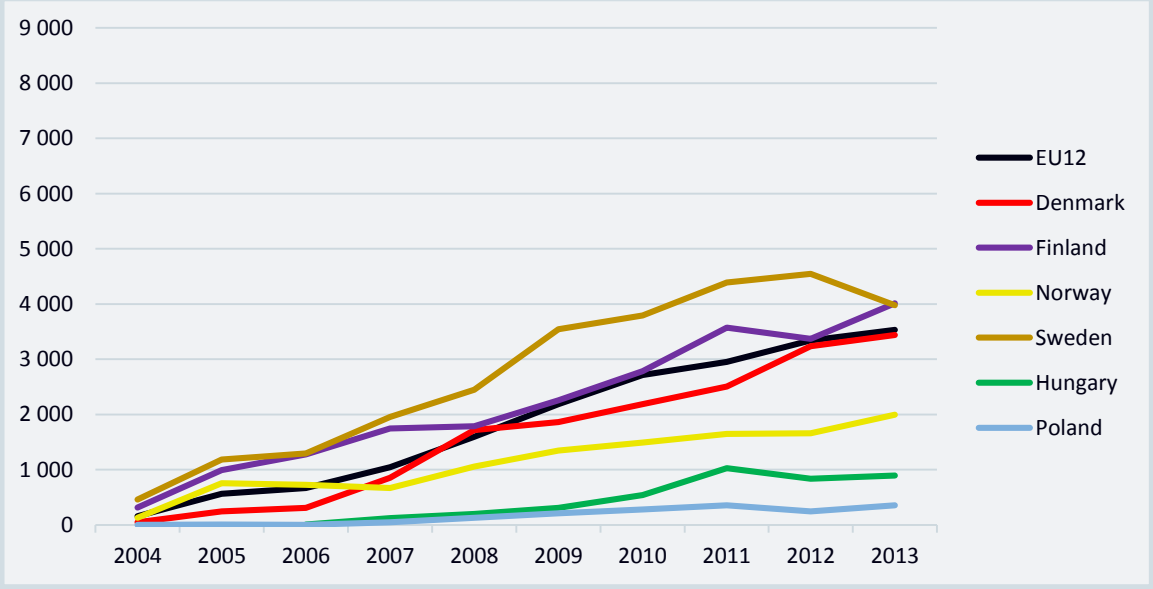

FIGURE 3.11. SALES OF PEMETREXED PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 EUCAN MORTALITY DATA [8]. SWEDEN STARTED ABOVE, BUT HAS RETURNED TO THE EU12 LEVEL WHERE THEY ARE ACCOMPANIED BY DENMARK AND FINLAND. NORWAY STILL HAS SIGNIFICANTLY LOWER SALES COMPARED TO EU12 AND THE NORWEGIAN SALES ARE DIFFICULT TO EXPLAIN AS PEMETREXED SALES WERE RELATIVELY HIGH IN NORWAY DURING THE FIRST YEARS AFTER INTRODUCTION. BOTH HUNGARY AND POLAND HAVE LOW SALES OVER TIME.

3.3.2.2 Erlotinib

Erlotinib hydrochloride is a drug used mainly in NSCLC and pancreatic cancer. It is a reversible tyrosine kinase inhibitor, which acts on EGFR.

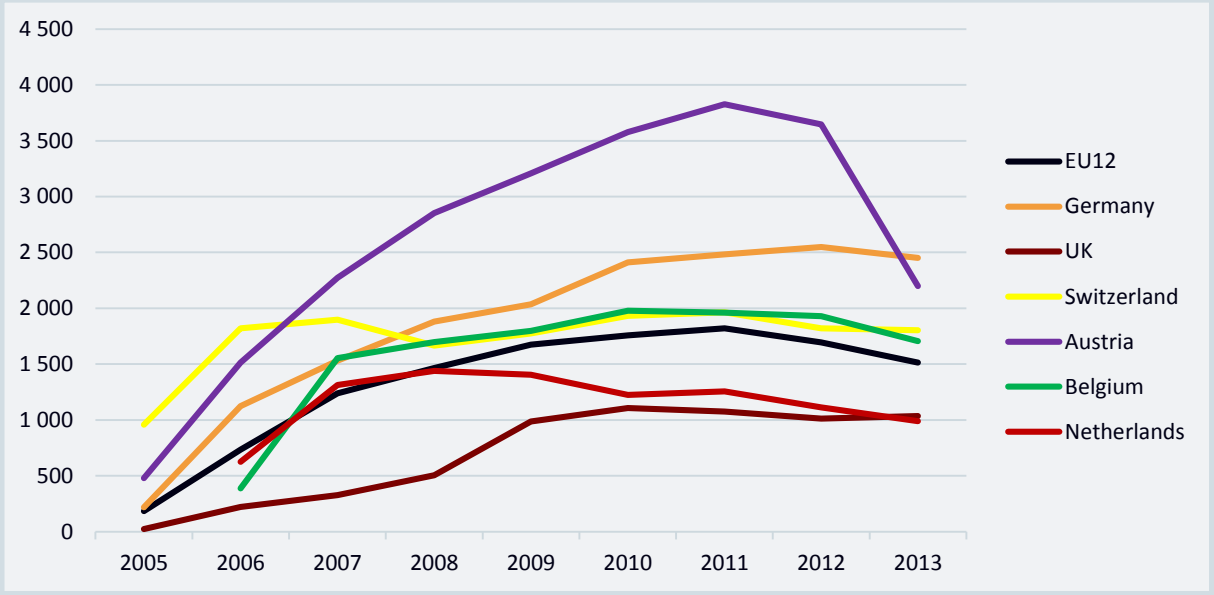

FIGURE 3.12. SALES OF ERLOTINIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THE VERY HIGH SALES IN AUSTRIA SEEMS TO HAVE SHIFTED FROM ERLOTINIB TO GEFITINIB. THE TWO FOLD VARIATION DETECTED IS DIFFICULT TO EXPLAIN FROM A MEDICAL PERSPECTIVE, BUT IT MAY REFLECT A LOW RATE OF MOLECULAR TESTING IN SOME COUNTRIES.

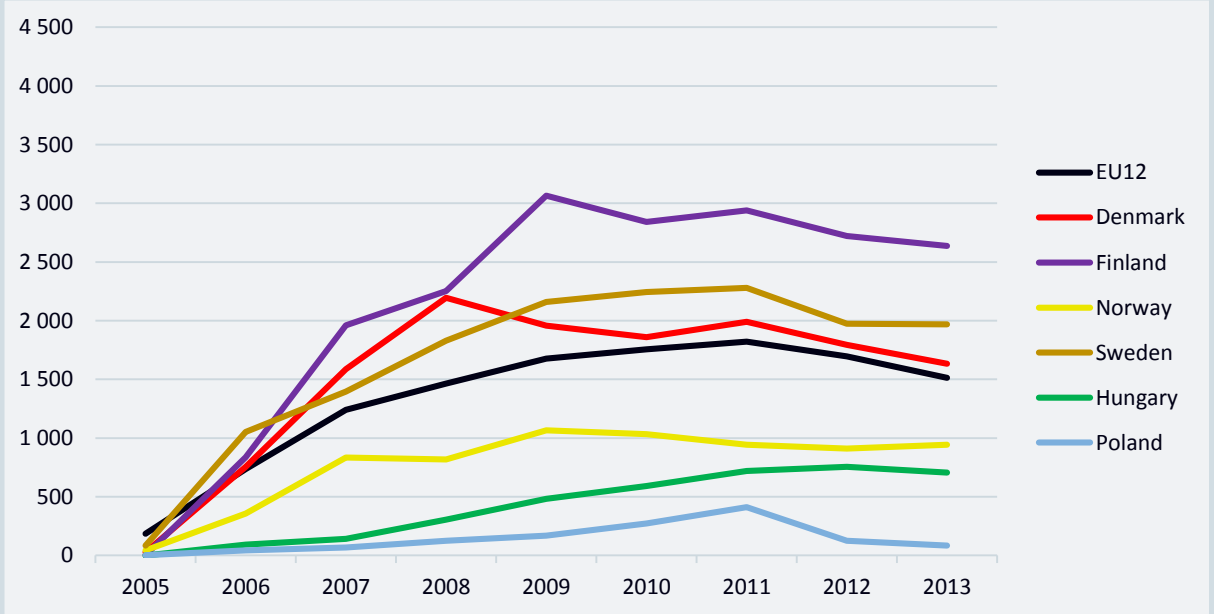

FIGURE 3.13. SALES OF ERLOTINIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. IN THIS COMPARON SIMILAR DIFFERENCES ARE SEEN. SALES ARE LOW IN NORWAY, HUNGARY AND POLAND. SOME OF THE DIFFERENCES SEEN MAY REFLECT A SHIFT TO GEFITINIB.

3.3.2.3 Gefitinib

Gefitinib, is a drug used mainly in the treatment of lung cancer. Gefitinib is an EGFR inhibitor which interrupts cell signalling.

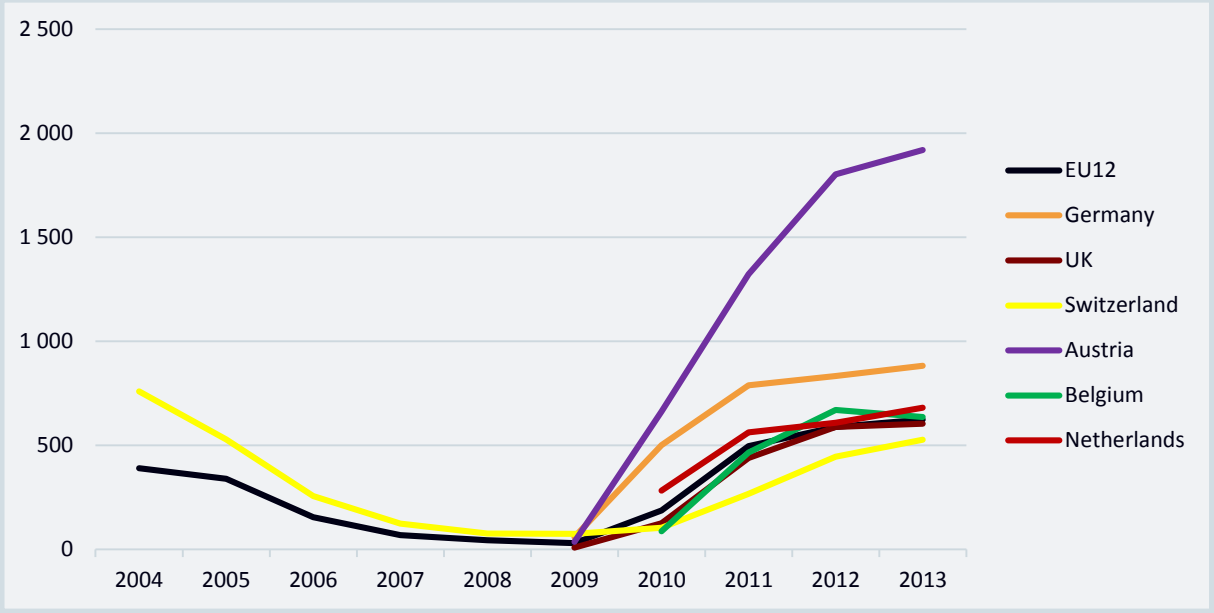

FIGURE 3.14. SALES OF GEFITINIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. UPTAKE OF GEFITINIB SEEMS TO BE BY FAR HIGEST IN AUSTRIA, FOLLOWED BY GERMANY. THE OTHER COUNTRIES HAVE SIMILAR, BUT LOWER, UPTAKE.

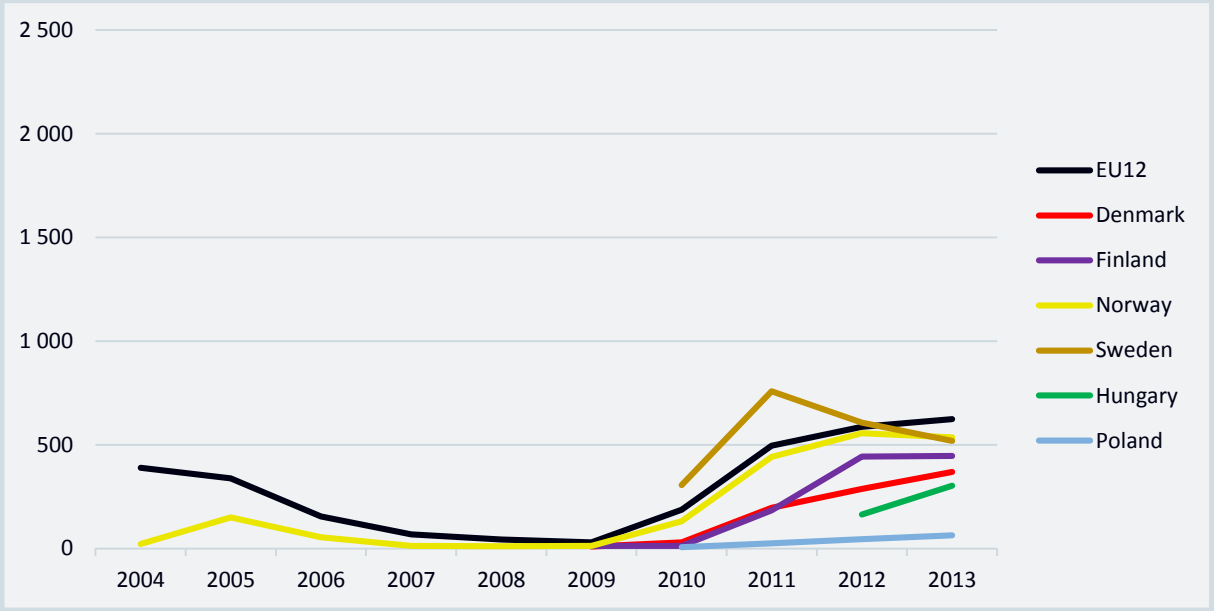

FIGURE 3.15. SALES OF GEFITINIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. SALES IN THIS COMPARISON TO SOME EXTENT REFLECT SHIFTS FROM ERLOTINIB TO GEFITINIB. AGAIN, SALES IN POLAND ARE VERY LOW.

3.3.2.4 Crizotinib

Crizotinib is an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor, approved for treatment of patients NSCLC expressing the ALK fusion protein. The patient population is small (<5% of patients with lung cancer expressing the ALK fusion protein).

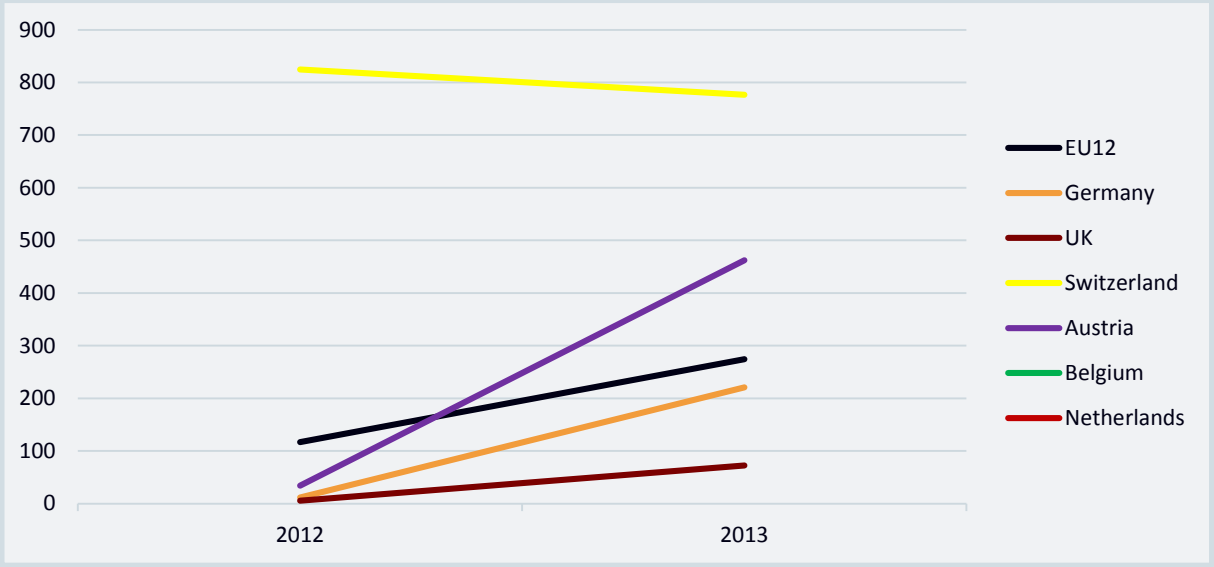

FIGURE 3.16. SALES OF CRIZOTINIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THERE ARE NO SALES REGISTRED IN BELGIUM AND THE NETHERLANDS, WHICH PROBABLY REFLECTS THE DISCUSSION REGARDING REIMBURSEMENT OF CRIZOTINIB IN SEVERAL COUTRIES DURING 2012-2013. SALES MAY ALSO REFLECT A LACK OF TESTING OF THE TARGET FOR CRIZOTINIB AS ONLY 3-5% OF PATIENTS WITH NON-SMALL CELL LUNG CANCER EXPRESS THIS TARGET.

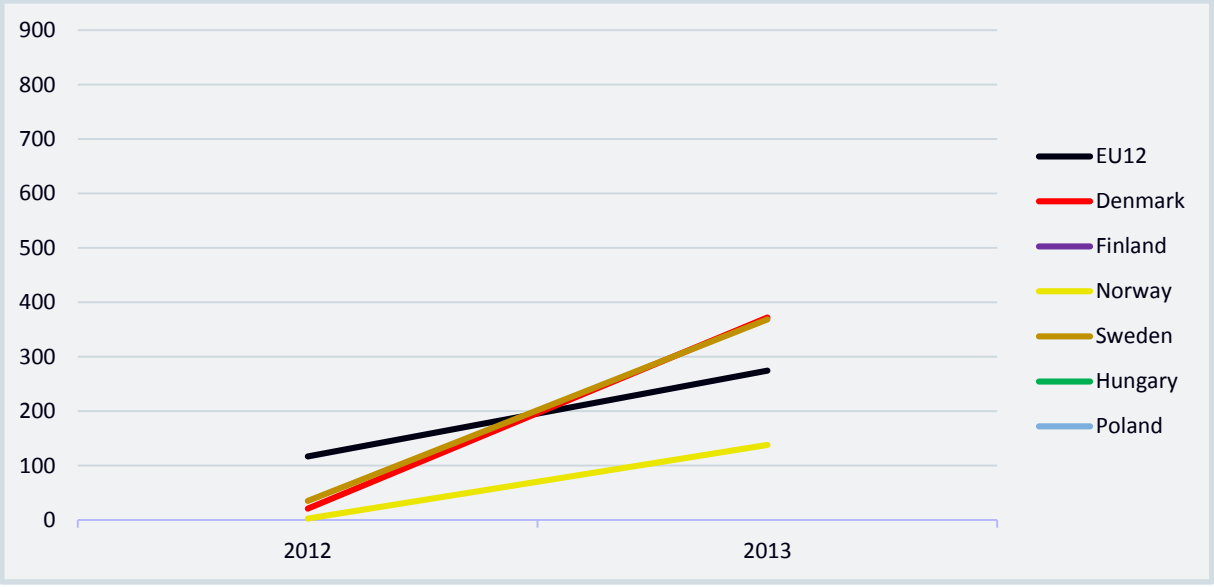

FIGURE 3.17. SALES OF CRIZOTINIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. AS IN FIGURE 3.16, SEVERAL COUNTRIS HAD NOT YET STARTED TO USE CRIZOTINIB BY THE TIME OF DATA CLOSURE IN THIS STUDY (END OF 2013).

3.3.2.5 Combined sales of pemetrexed, erlotinib, gefitinib and crizotinib

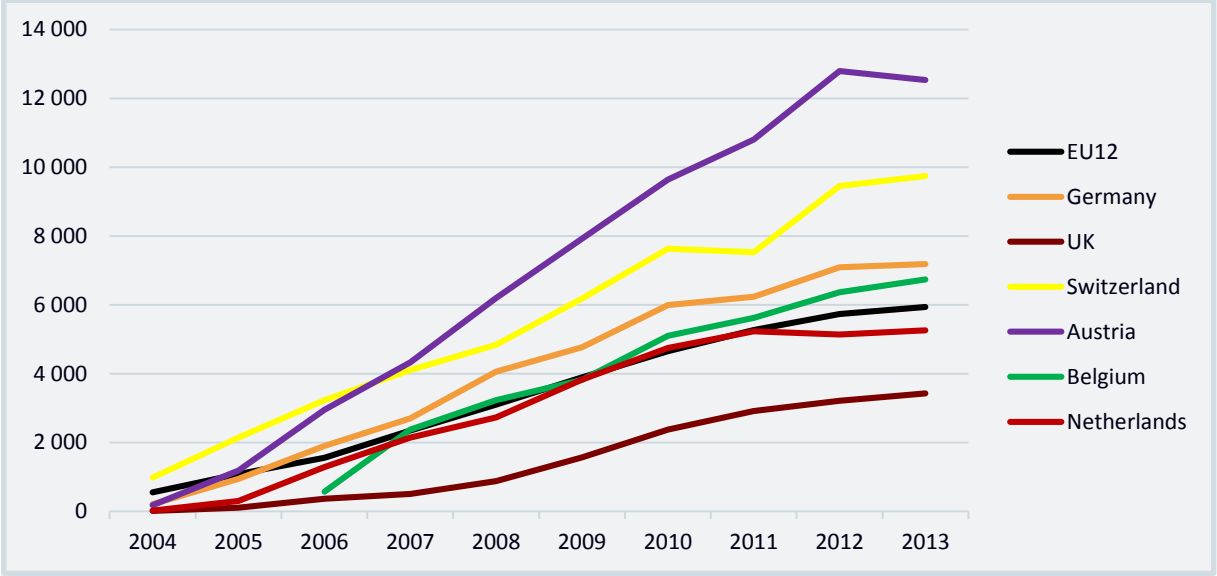

FIGURE 3.18. COMBINED SALES OF PEMETREXED, ERLOTINIB, GEFITINIB, AND CRIZOTINIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. AS IN THE COMPARISON IN FIGURE 3.16, SEVERAL COUNTRIES HAD NOT YET STARTED TO USE CRIZOTINIB BY THE TIME OF DATA CLOSURE FOR THIS STUDY (END OF 2013). THERE ARE LARGE VARIATIONS IN THE SALES OF "NEW" DRUGS FOR THE TREATMENT OF LUNG CANCER. AUSTRIA AND SWITZERLAND ARE BY FAR THE "EARLY ADOPTERS" WHILE THE UK HAS A MUCH LOWER UPTAKE OF THESE DRUGS.

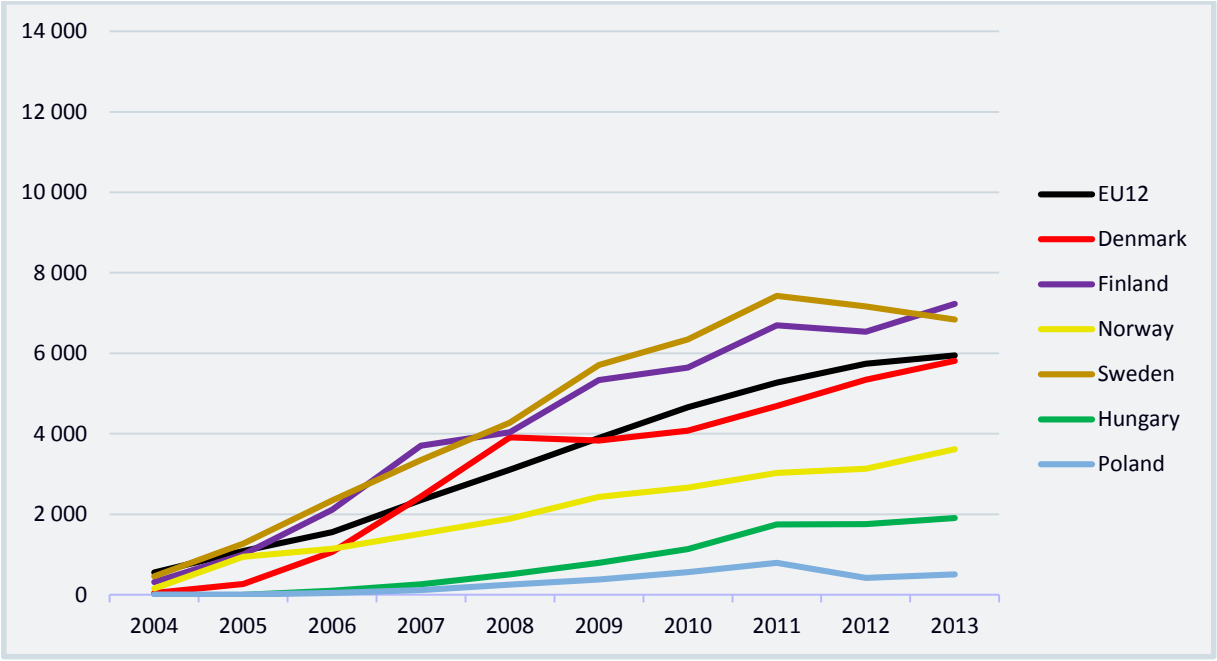

FIGURE 3.19. COMBINED SALES OF PEMETREXED, ERLOTINIB, GEFITINIB, AND CRIZOTINIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. AS SEEN IN THE COMPARISON IN FIGURE 3.17, SEVERAL COUNTRIES HAD NOT YET STARTED TO USE CRIZOTINIB BY THE TIME OF DATA CLOSURE FOR THIS STUDY (END OF 2013). AS IN FIGURE 3.18 WE NOTE LARGE VARIATIONS IN SALES OF "NEW" LUNG CANCER DRUGS. SALES IN NORWAY ARE JUST ABOUT 2/3 OF SALES IN THE EU12 AND THERE SEEMS TO BE A VERY LOW ACCESS IN BOTH HUNGARY AND POLAND.

3.3.3 Multiple Myeloma

3.3.3.1 Bortezomib

Bortezomib is the first therapeutic proteasome inhibitor. It is approved for treating relapsed multiple myeloma (MM) and mantle cell lymphoma. In MM, complete clinical responses have been obtained in patients with refractory and advanced disease.

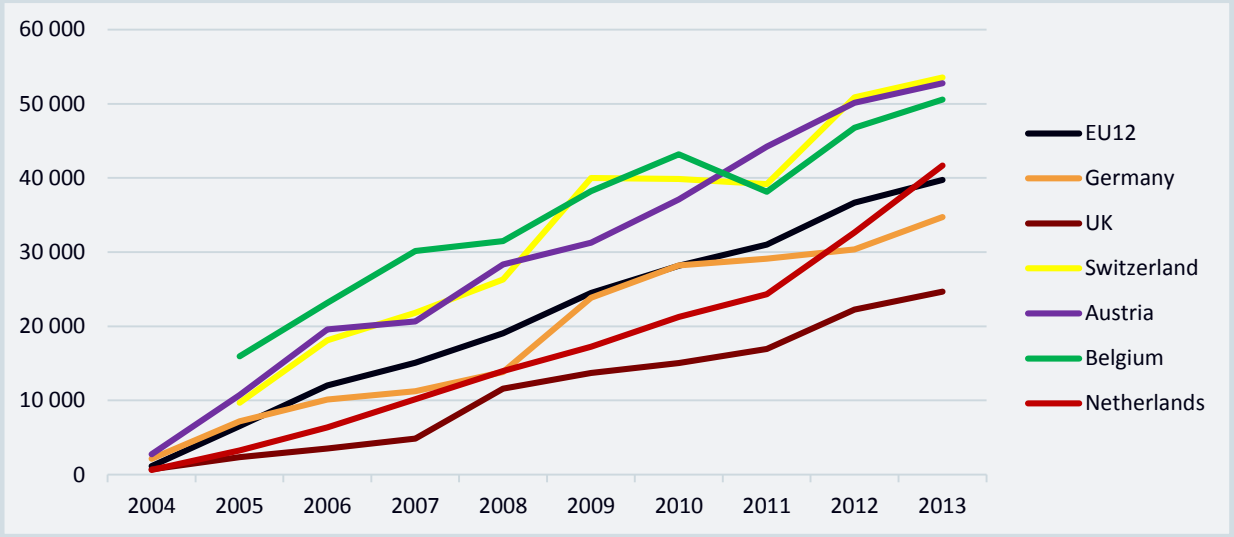

FIGURE 3.20. SALES OF BORTEZOMIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. MOST COUNTRIES ARE AT THE EU 12 LEVEL OR ABOVE, WITH THE EXCEPTION OF THE UK.

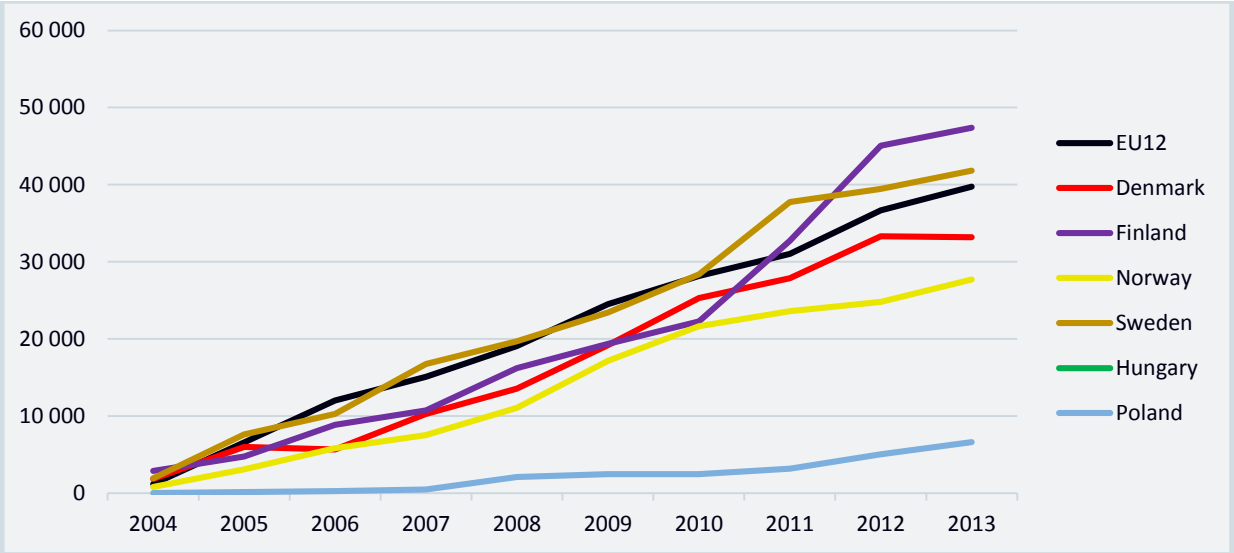

FIGURE 3.21 SALES OF BORTEZOMIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. NOTE THA SALES FOR HUNGARY HAS BEEN EXCLUDED DUE TO DATA INCONSISTENCIES. SALES ARE, WITH THE EXCEPTION OF NORWAY AND POLAND, RELATIVELY UNIFORM IN THIS COMPARISON WHICH REFLECTS A SIMILAR VIEW ON MEDICAL NEED AND ADHERENCE TO GUIDELINES.

3.3.3.2 Lenalidomide

Lenalidomide, a derivative of thalidomide, was introduced in 2004. Lenalidomide has significantly improved overall survival in MM. Lenalidomide has also shown efficacy in myelodysplastic syndromes (MDS).

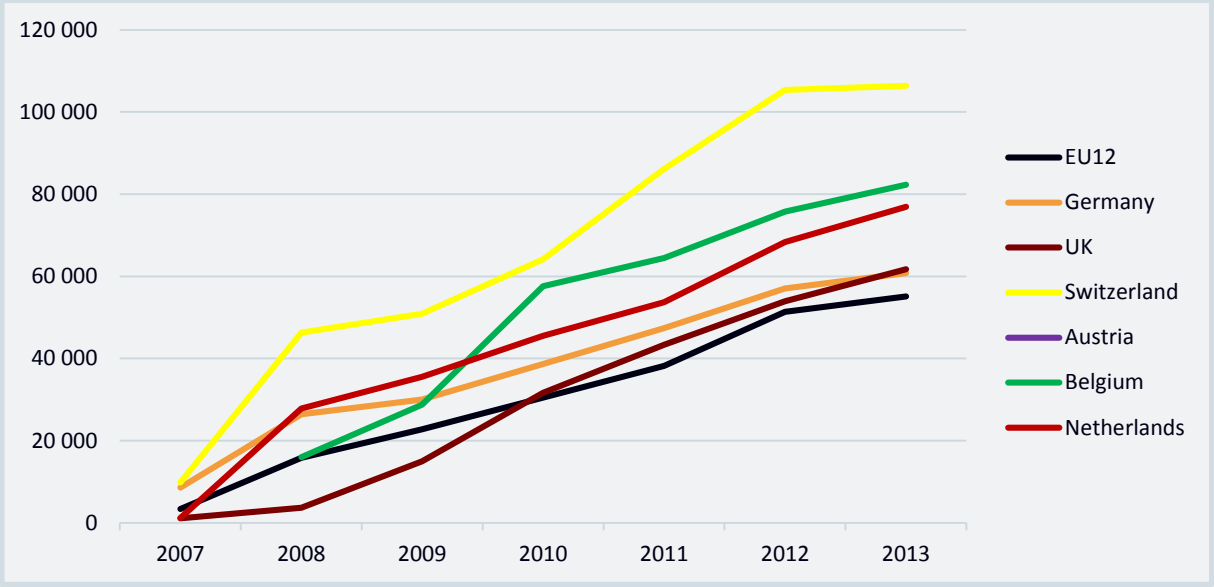

FIGURE 3.22. SALES OF LENALIDOMIDE PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. NOTE THAT SALES FOR AUSTRIA HAS BEEN EXKLUDED DUE TO DATA INCONSISTENCIES. THE UPTAKE IS VERY HIGH IN SWITZERLAND, BELGIUM AND NETHERLANDS. EVEN THE UPTAKE IN THE UK IS HIGHER THAN USUAL WITH NEW INNOVATIVE DRUGS.

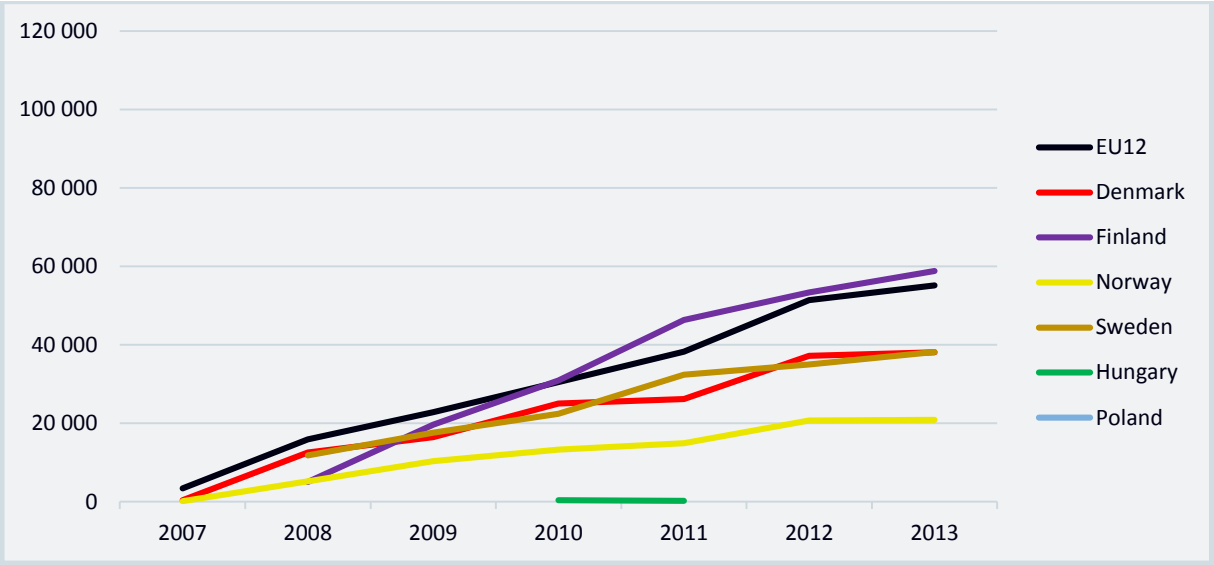

FIGURE 3.23. SALES OF LENALIDOMIDE PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8].THE NORDIC COUNTRIES, EXCEPT FINLAND, HAVE A LOWER UPTAKE THAN OTHER WESTERN EUROPEAN COUNTRIES. IN ADDITION, THE UPTAKE IS VERY LOW IN HUNGARY AND THERE IS NO UPTAKE AT ALL IN POLAND.

3.3.3.3 Combined sales of bortezomib and lenalidomide

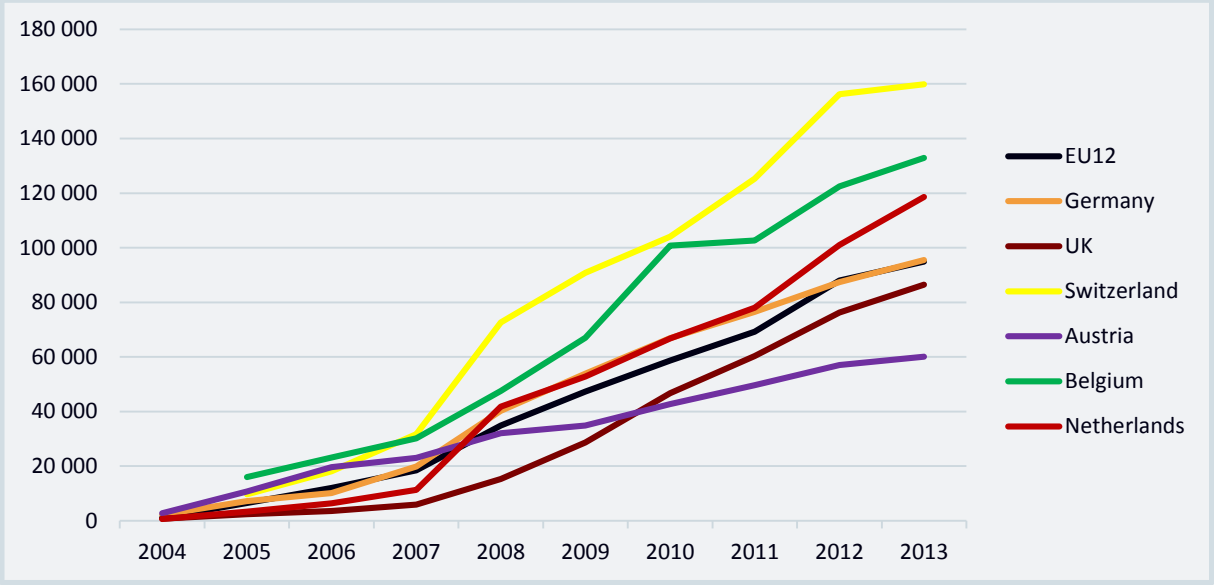

FIGURE 3.24. COMBINED SALES OF BORTEZOMIB AND LENALIDOMIDE PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. NOTE THAT SALES OF LENALIDOMIDE FOR AUSTRIA ARE NOT INCLUDED THUS MAKING THE UPTAKE OF MYELOMA DRUGS BEING SIGNIFICANTLY UNDERESTIMATED. THE HIGH SALES IN SWITZERLAND AND BELGIUM AS WELL AS THE RAPID INCREASE IN THE NETHERLANDS SHOULD BE NOTED.

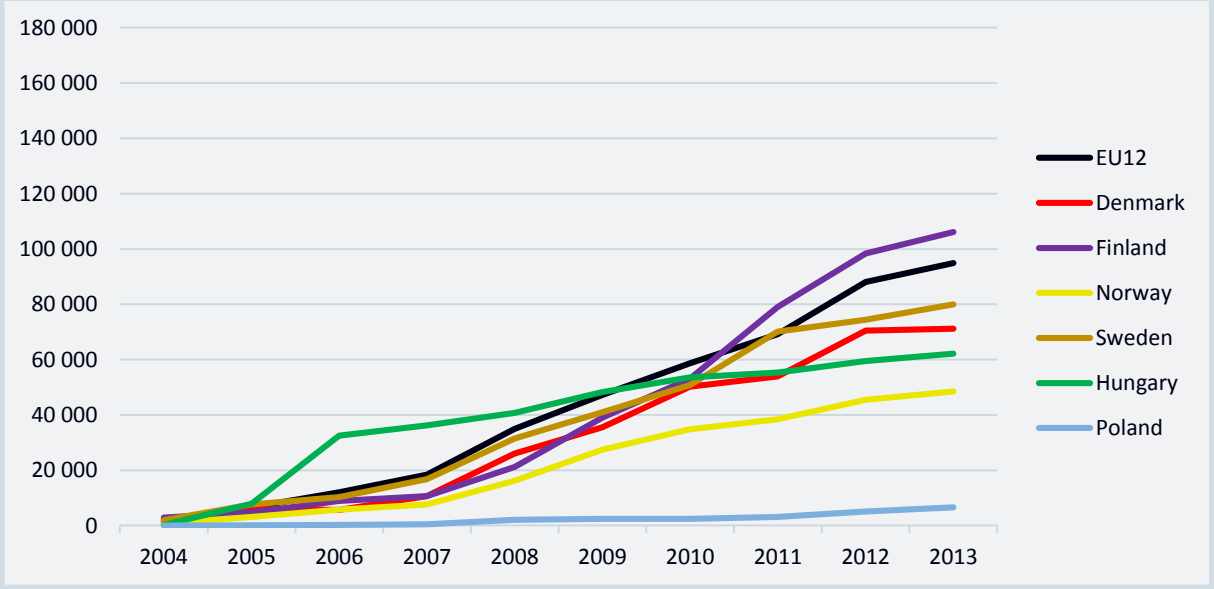

FIGURE 3.25. COMBINED SALES OF BORTEZOMIB AND LENALIDOMIDE PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. AGAIN, NOTE THAT THE UPTAKE IN POLAND IS VERY LIMITED.

3.3.4 Melanoma

3.3.4.1 Ipilimumab

Ipilimumab, a fully human monoclonal antibody which blocks cytotoxic T-lymphocyte-associated antigen-4, became the first agent approved in the EU for the treatment of adult patients with unresectable or metastatic melanoma who have received prior therapy that showed an overall survival benefit in a randomised phase III trial. The drug is now also approved as first line therapy.

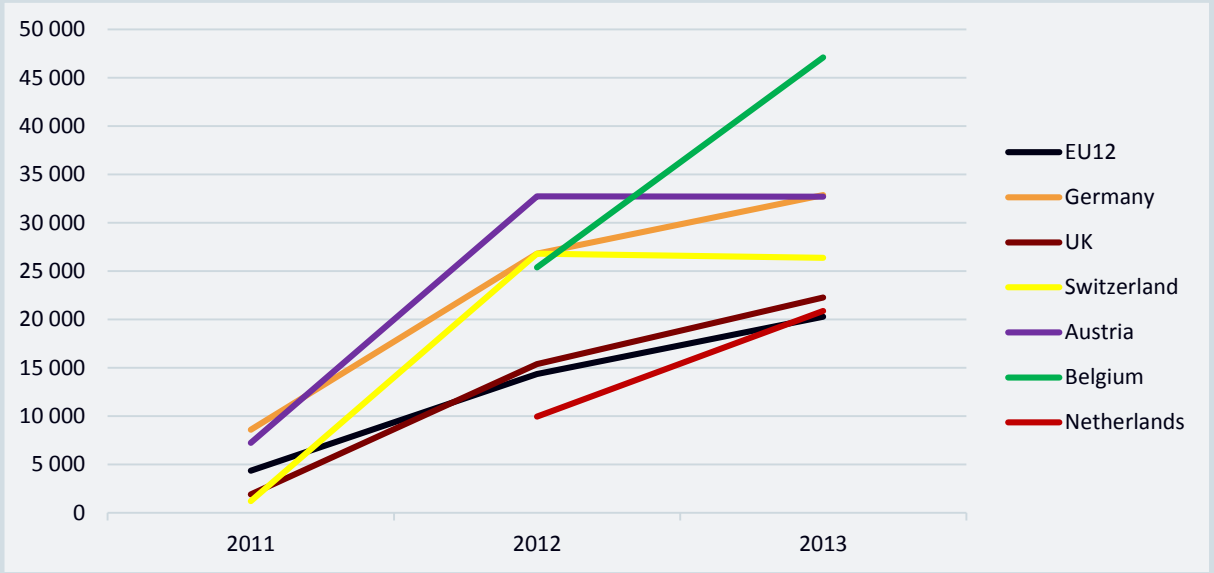

FIGURE 3.26. SALES OF IPILIMUMAB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. ALL COUNTRIES IN THIS COMPARISON HAS AN UPTAKE ABOVE THE AVERAGE EU12 LEVEL. A VERY RAPID AND HIGH UPTAKE IS SEEN IN BOTH AUSTRIA, SWITZERLAND, AND GERMANY BUT MOST OF ALL IN BELGIUM. EVEN THE UK HAS AN UPTAKE ABOVE THE EU12 LEVEL.

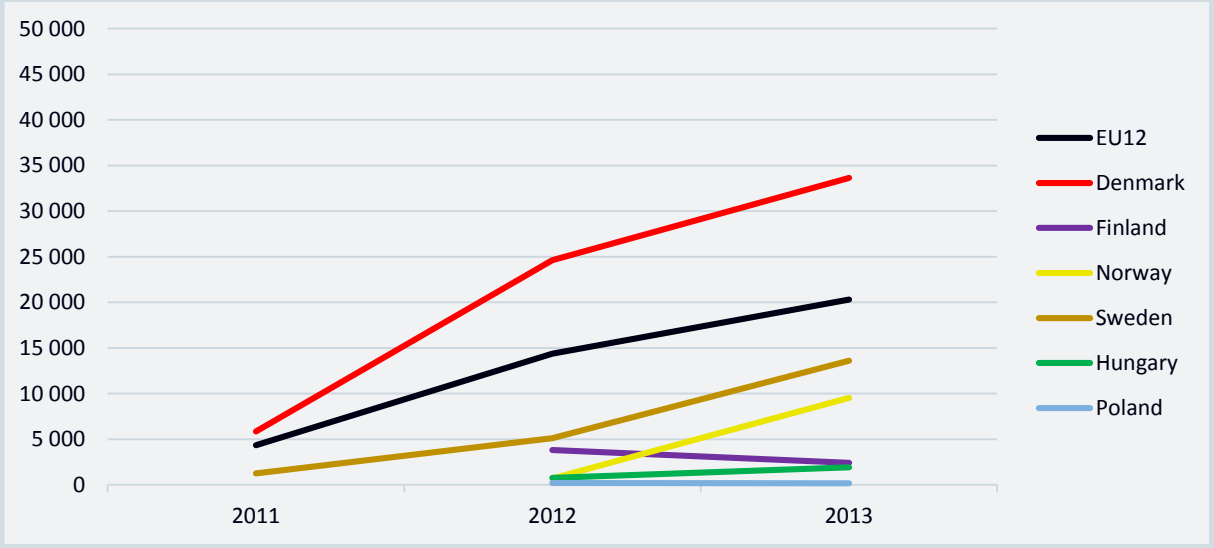

FIGURE 3.27. SALES OF IPILIMUMAB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THE UPTAKE IN THE NORDIC COUNTIRES (DENMARK EXCLUDED) HAS BEEN SLOW AND RELATIVELY LOW. A VERY LOW UPTAKE IS SEEN IN HUNGARY AND POLAND.

3.3.4.2 Vemurafenib

Vemurafenib is approved for the treatment of late-stage melanoma, making it the first drug designed using fragment-based lead discovery to gain regulatory approval. EMA has approved vemurafenib as a monotherapy for the treatment of adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma, the most aggressive form of skin cancer.

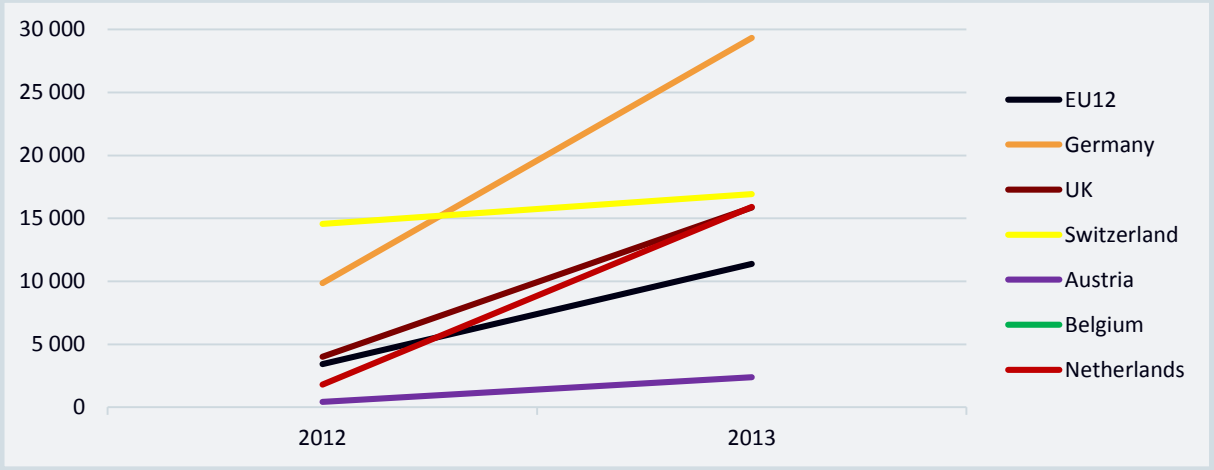

FIGURE 3.28. SALES OF VEMURAFENIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THERE ARE VERY LARGE VARIATIONS IN THE UPTAKE OF VEMURAFENIB. GERMANY HAS A RAPID AND HIGH UPTAKE WHILE SWITZERLAND HAS A STEADY UPTAKE. NETHERLANDS AND UK ALSO HAVE RAPID UPTAKES, WHILE THE UPTAKE IS VERY LOW IN AUSTRIA AND LACKING IN BELGIUM.

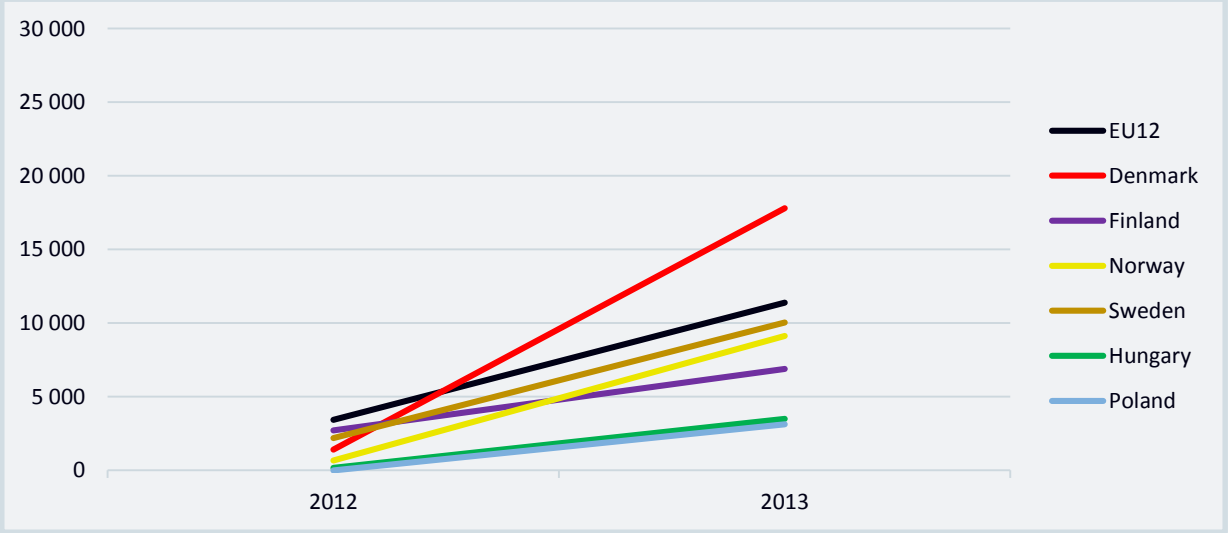

FIGURE 3.29. SALES OF VEMURAFENIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. SALES OF VEMURAFENIB ARE HIGHER COMPARED TO IPILIMUMAB. SALES ARE SEEN IN ALL COUNTRIES IN THIS COMPARISON AND THE UPATKE FOLLOW A SIMILAR PATTERN BUT WITH A RAPID UPTAKE IN DENMARK, A LOWER AND SLOWER UPTAKE IN FINLAND AND A LOW UPTAKE IN BOTH POLAND AND HUNGARY.

3.3.4.3 Combined sales of ipilimumab and vemurafenib

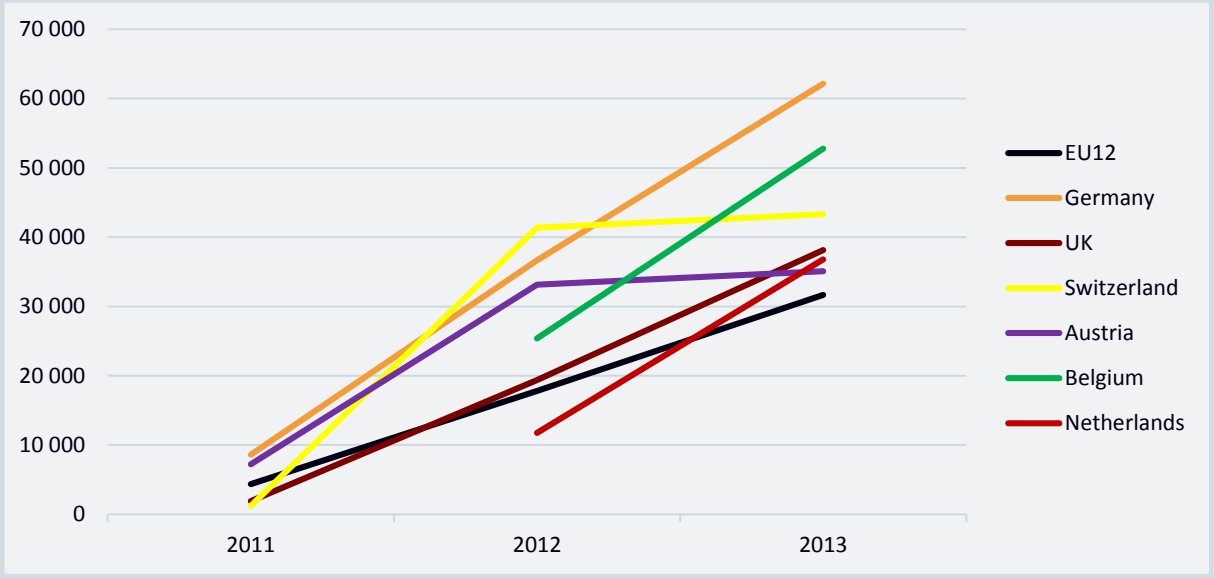

FIGURE 3.30. COMBINED SALES OF IPILIMUMAB AND VEMURAFENIB PER CASE IN EU12, AUSTRIA, BELGIUM, GERMANY, THE NETHERLANDS, SWITZERLAND AND THE UK IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. THERE IS A LARGE VARIATIONS IN THE TOTAL UPTAKE OF NEW MELANOMA DRUGS. A VERY HIGH UPTAKE IS FOUND IN GERMANY AND BELGIUM (THEN ONLY OF IPILIMUMAB) AND THE UPTAKE IN THE UK IS AT THE AVERAGE EU12 LEVEL.

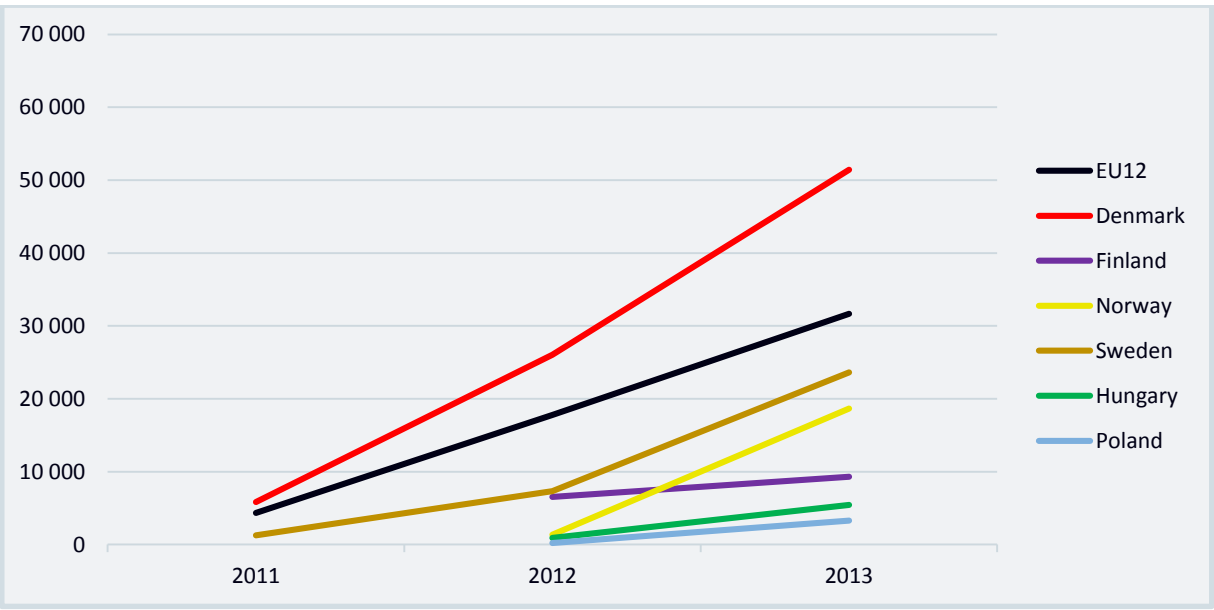

FIGURE 3.31. COMBINED SALES OF IPILIMUMAB AND VEMURAFENIB PER CASE IN EU12, DENMARK, FINLAND, NORWAY, SWEDEN, HUNGARY AND POLAND IN 2003-2013, BASED ON 2012 MORTALITY DATA FROM EUCAN [8]. WITH THE EXCEPTION OF DENMARK, THE UPTAKE OF NEW MELANOMA DRUGS ARE LOW IN THE NORDIC COUNTRIES AS WELL AS IN POLAND AND HUNGARY.

3.4 Chapter summary

There are large variations in the uptake and use of cancer drugs in different countries. In general there is a more rapid uptake and higher level of use in Western Europe compared to Eastern Europe. Highest overall use is found in Austria, Switzerland and Germany and lowest in Hungary and Poland. Table 3.3 summarizes the results and gives a "ranking" of overall sales as well as in the specific disease areas described in this chapter

TABLE 3.3 SUMMARIZES "RANKING" OF UPTAKE OF ALL CANCER DRUGS AS OF 2013 AS WELL AS SELECTED CANCER DRUGS BY INDICATION IN THE COUNTRIES IN FOCUS FOR THIS REPORT.

Country	Total sales	Lung cancer	Multiple myeloma	Malignant melanoma
Austria	1	1	9 [a]	7
Belgium	5	5	2	2
Denmark	4	7	8	3
Finland	6	3	4	10
Germany	3	4	5	1
Hungary	11	11	12 [a]	11
Netherlands	8	8	3	6
Norway	10	9	10	9
Poland	12	12	11	12
Sweden	7	6	7	8
Switzerland	2	2	1	4
UK	9	10	6	5

[a] Indicates incomplete data for one of the drugs within the group.

Appendix Chapter 3

A3.1 Comparison of sales in milligrams (Mg) and Euros (€)

Measuring the sales of oncology drugs in monetary values instead of using a volume measure may, at least in theory, come with some drawbacks and limitation. Differences in drug prices, price levels and exchange rates could all over- or understate drug sales in cross-country comparisons. In order to size any impacts of differences in prices, price levels or exchange rates, we compared the sales of selected drugs using an earlier dataset.

Figures A3.1 and A3.2 show the sales of bortezomib in the EU5, 2004-2009. When comparing sales in € with sales in Mg it is clear that sales using 5 underestimates the sales for the UK compared to the rest of the EU5 countries, which is most plausibly caused by exchange rate fluctuations. The general trends and the following analysis, however, remains the same irrespective of € or Mg are used for the cross-country comparison. In other words, price variations among the EU5 does not seem to significantly affect sales in a cross-country comparison and the use of sales data in € is still seen as a valid approach for cross-country comparisons of the EU5. The sudden drop in French sales, measured in €, between Q3 2009 and Q4 2009 could be explained by the data for, especially, the last quarter in the IMS dataset not being complete for all countries and pharmaceuticals. When comparing 2010 and 2014 IMS data, it is sometimes seen that data for the last quarter(s) of the 2010 data have been somewhat revised in the 2014 data.

Figures A3.3 and A3.4 presents sales for pemetrexed in € and Mg in the EU5 during 2004-2009. As in the case of bortezomib, exchange rate fluctuations and price variations among the EU5 underestimate the UK sales but does not change the overall picture or analysis.

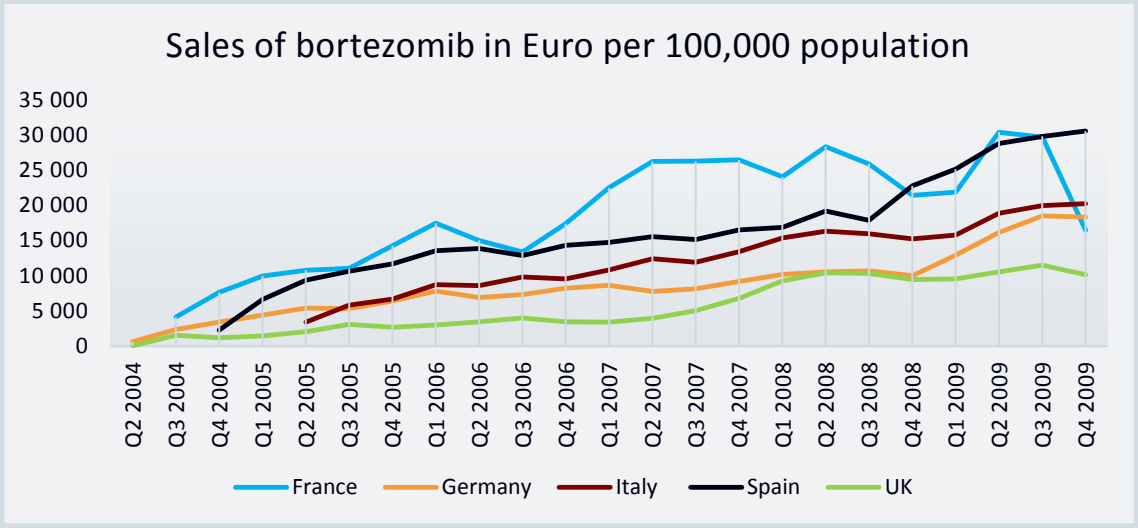

FIGURE A3.1. SALES OF BORTEZOMIB IN € PER 100,000 POPULATION, 2004-2009 IN THE EU5.

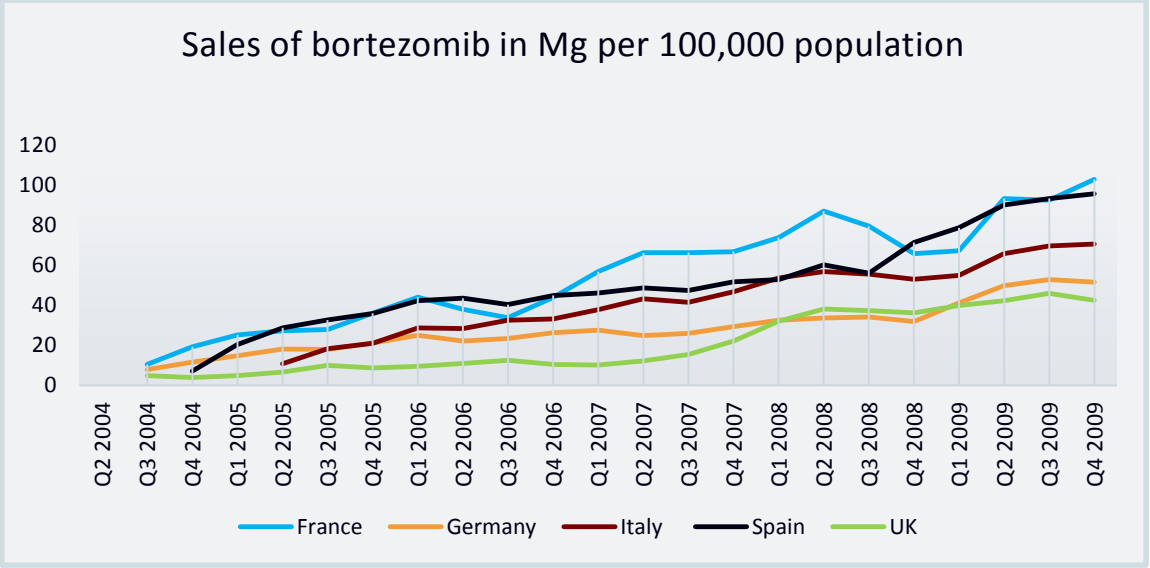

FIGURE A3.2. SALES OF BORTEZOMIB IN MG PER 100,000 POPULATION, 2004-2009 IN THE EU5.

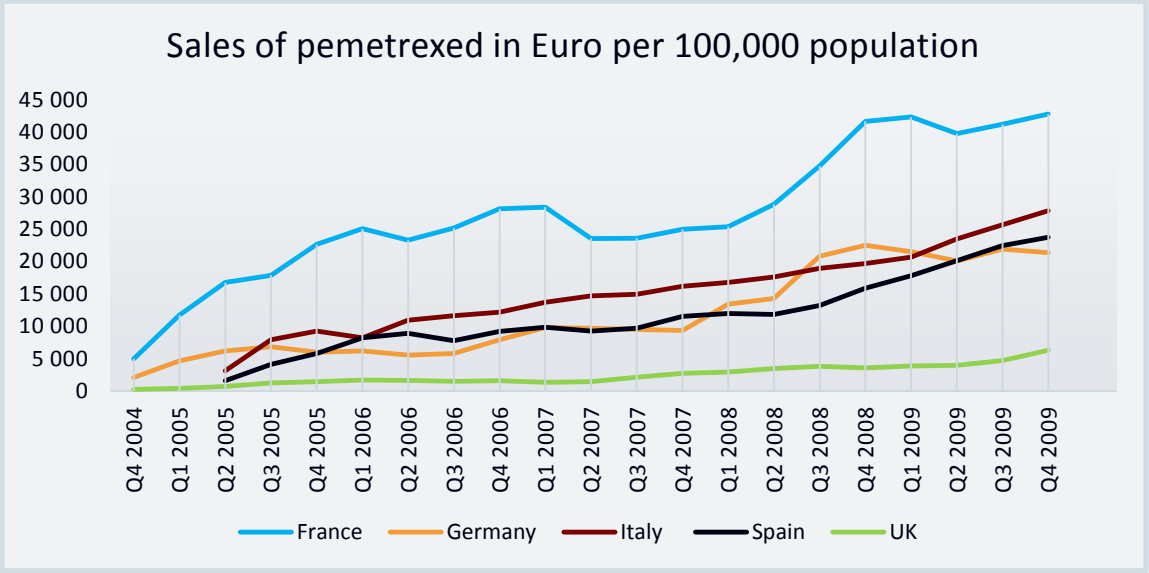

FIGURE A3.3. SALES OF PEMETREXED IN € PER 100,000 POPULATION IN THE EU5, 2004-2009.

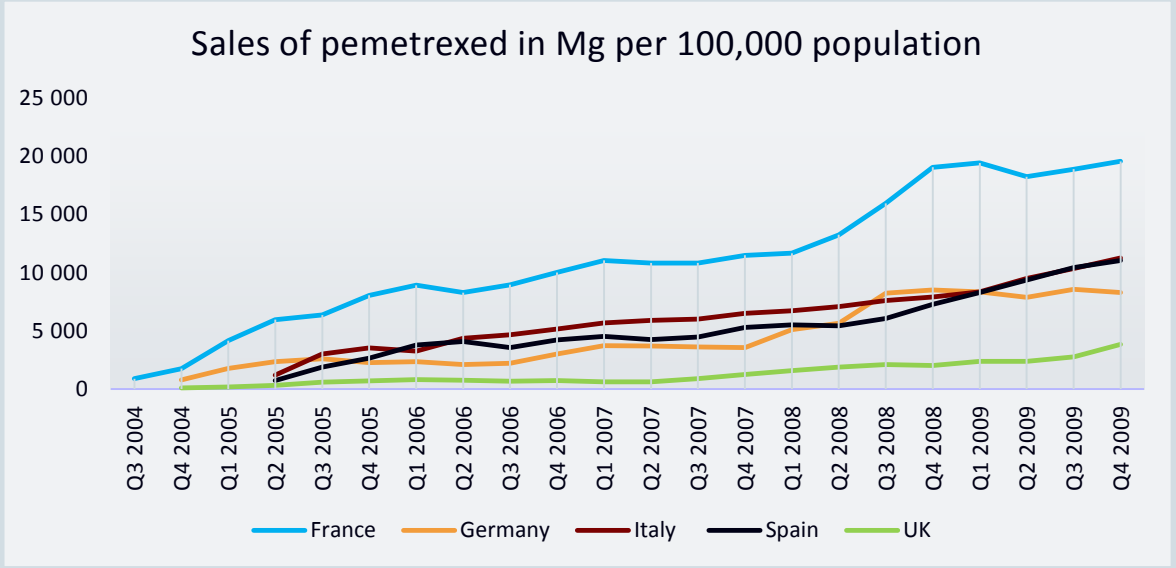

FIGURE A3.4. SALES OF PEMETREXED IN MG PER 100,000 POPULATION IN THE EU65, 2004-2009.

References Chapter 3

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4. Market access for cancer drugs – the policy issues

All EU member states saw a sudden drop in GDP per capita in 2009, following the 2008 financial crisis. In general, the northern and western EU member states had a relatively fast recovery while the eastern and southern member states had a hard time recovering in the aftermath of the financial crisis.

Drug budgets in the EU are the responsibility of public health care systems with the payer being either a national or local government, as in Italy or Sweden, or by a statutory health insurance, as in Germany. Prices for new drugs are in most cases regulated within the health care system and prices for new drugs are subject to negotiations between the payer and the manufacturer. The development and introduction of new health technologies leads to greater opportunities for more efficient delivery of health services and improvements in treatment outcomes. As new technologies often come at a high cost, it is important to assess whether the higher costs are motivated by improvements in outcomes.

The UK and Sweden are the only EU countries where a value-based pricing system (VBP) is in use where prices are explicitly related to the value of a drug, in a formal assessment of its cost-effectiveness. In these countries reimbursement or treatment guidelines/recommendations, not only prices, is what is being determined or negotiated between the payer and the manufacturer.

This chapter reviews the policy issues related to market access to new cancer drugs focusing on the countries, diseases and drug classes covered in this report. But since policy issues to a large extent are similar for all European countries and for all types of cancer, the review will sometimes extend to, and be relevant for, a broader range of countries, diseases, and health care interventions.

We start with a review of regulatory aspects and times for approval by EMA for European countries in relation to that by the FDA and other jurisdictions. This is followed by a review of the policy issues related to reimbursement. Reimbursement decisions are focused on pricing for prescription drugs, while many drugs are used in the hospital setting where the pricing and reimbursement decisions are different.

International reference pricing is a common measure aimed at controlling costs, which has consequences for access to new cancer drugs in different countries. However, the dysfunctional aspects of the system are obvious, and it is possible to observe how different countries try to introduce policies that circumvent it. Thus this system is replaced by more flexible payment systems

for pharmaceuticals, which for example allows price discrimination between countries and indications.

The scientific development in cancer research makes it possible to make earlier and more accurate predictions of what drugs work for different groups of patients. But that also means that new drugs come to the market with less evidence for assessment of clinical value, which increases the uncertainty in decisions on pricing, reimbursement and use. Policies for management of uncertainty thus are becoming a new important policy area for cancer drugs.

The chapter concludes with a summary and conclusions.

4.1 Pharmaceutical regulation and market access in the EU

The European Medicines Agency (EMA) grants marketing authorisation of medicines in the EU after evaluation of safety, efficacy and quality by the Committee for Medicinal Products for Human Use (CHMP). For cancer drugs, and for new drugs treating several other diseases, this is done through a centralised procedure where the producer submits an application to the EMA and is granted a single marketing authorisation for all EU member states, as well as for Iceland, Lichtenstein and Norway. The EMA also grants authorisation for new therapeutic indications for already existing medicines. The formal decision of granting marketing authorisation is taken by the European Commission (EC).

Certain drugs that are of major interest for public health or which are therapeutic innovations may be subject to an accelerated approval procedure. This has been the case for about 5% of the cancer drugs assessed by the EMA. For ordinary applications the time frame is 210 evaluation days compared to 150 evaluation days in the accelerated approval procedure. The time frames does not include the time for the producer to review any draft of a CHMP opinion, in which case the evaluation days stop counting.

Hartmann et al. evaluated the EMA approval rate for all applications of anticancer drugs submitted in 2006-2011. In that time period 46 applications were submitted, out of which 29 received a positive opinion and marketing authorization by the CHMP. This means that 63% of the applications received an authorization (or 74% if counting on the fact that 10 applications were withdrawn prior to a first opinion by the CHMP), i.e. the approval rate for cancer drugs was 63% [1]. For non-cancer drugs the approval rate was 73% (133 out of 183 applications were given a marketing authorization). The approval rate for all applications submitted in 2006-2011 was 71%.

EMA has a time frame of 210 evaluation days, i.e. the days they are responsible for the application, not including the time it takes the manufacturer to review drafts or answer questions. For the cancer drugs targeted in this report the average time from the EMA receiving the application to the manufacturer receiving marketing authorization was 414 days, as is seen in Table 4.1. This is almost twice the number of evaluation days targeted by the EMA and may in large be explained by each application being subject for re-reviews, questions by the EMA and for the time elapsing between a positive opinion by the EMA and the formal decision by the EC. Trastuzumab had, by far, the greatest time elapse of 564 days while imatinib had the smallest, 251 days.

TABLE 4.1. TIME ELAPSED BETWEEN APPLICATION AND MARKETING APPROVAL IN THE EU FOR A SELECTED SET OF CANCER DRUGS. THE TIME ELAPSED IS THE DIFFERENCE BETWEEN THE DATE WHEN THE EMA RECEIVED THE APPLICATION TO THE DATE THE EC GAVE A MARKETING AUTHORIZATION.

Molecule	Application for marketing authorization	Authorization date	Time elapsed
Trastuzumab	1999-02-11	2000-08-28	564
Imatinib	2001-03-01	2001-11-07	251
Bortezomib	2003-01-31	2004-04-26	451
Pemetrexed	2003-07-29	2004-09-20	419
Erlotinib	2004-08-26	2005-09-19	389
Lenalidomide	2006-02-28	2007-06-14	471
Gefitinib	2008-05-06	2009-06-24	414
Ipilimumab	2010-05-05	2011-07-13	434
Vemurafenib	2011-05-04	2012-02-17	289
Crizotinib	2011-07-28	2012-10-23	453
Average			414

Shah et al. compared the approval times of antineoplastic tyrosine kinase inhibitors between the EMA/EC and the FDA (the US equivalent of EMA) [2]. For the EMA/EC the average time from submission of application to a decision by the EC were 410 days, very much in line with the average time elapsed for the drugs reported in Table 4.1. The EMA had on average 225 active evaluation days if the time it took to validate the application before the evaluation procedure started is included. This means that slightly less than half of the evaluation days were due to administration of application before starting the EMA evaluation (24 days), time for the manufacturer to complete the application (69 days) and the time elapsed between the EMA opinion and the EC decision (91 days), a total of 184 days. Applications to the FDA were, on average, submitted 31 days prior to the submission to EMA. The average (total) time from submission to approval of an application by the FDA was 205 days, i.e. almost exactly half the number of days compared to the EMA/EC. When comparing active evaluation days between the FDA and the EMA/EC, however, the difference shrinks to about 20 days. The FDA have a procedure called priority review for drugs believed to provide major advances in treatment or for drugs targeting diseases lacking treatment options. The time elapse for drugs under priority review were 167 days while the time elapse for drugs under

standard review were 320 days. A majority of the cancer drugs compared were evaluated using priority review by the FDA while a standard review were used by the EMA.

The difference in time elapse from submission to authorization between the FDA and the EMA/EC is in large explained by the FDA being mandated to make binding decisions while the EMA represents all EU member states with the EC making the formal binding decision. Shah et al. comment on the institutional difference between the FDA and the EMA by saying "Inevitably, the system in the EU, compared with the system at the FDA, has to be more complex, given that EC is accountable to the citizens of the entire Union of sovereign MS (Member States). While it has the drawback of some potential delay, it also has the advantage of an application receiving a detailed and rigorous scrutiny through different perspectives of the 27 expert members of the CHMP" [2]. The FDA comparison does however show that there is room for improvement of the evaluation procedure, e.g. by using priority reviews or by shortening the time the application is not under review.

A new review from The Centre for Innovation in Regulatory Science (CIRS) of the time needed by agencies to approve new medicines confirm the results above [3]. CIRS has analysed the trends in new medicines' approval between 2004 and 2013 by six regulatory authorities including Health Canada, Swissmedic, Australian TGA, EMA, the US FDA and Japanese PMDA. Review times continue to decrease in the majority of jurisdictions allowing an earlier licensing of important new medicines. Underlying factors influencing the overall time it takes for a new medicine to be submitted and then approved by an agency include company strategy, the conduct and the type of the review process, the type of the product and its therapeutic area. There is also a convergence in approval times between the different agencies.

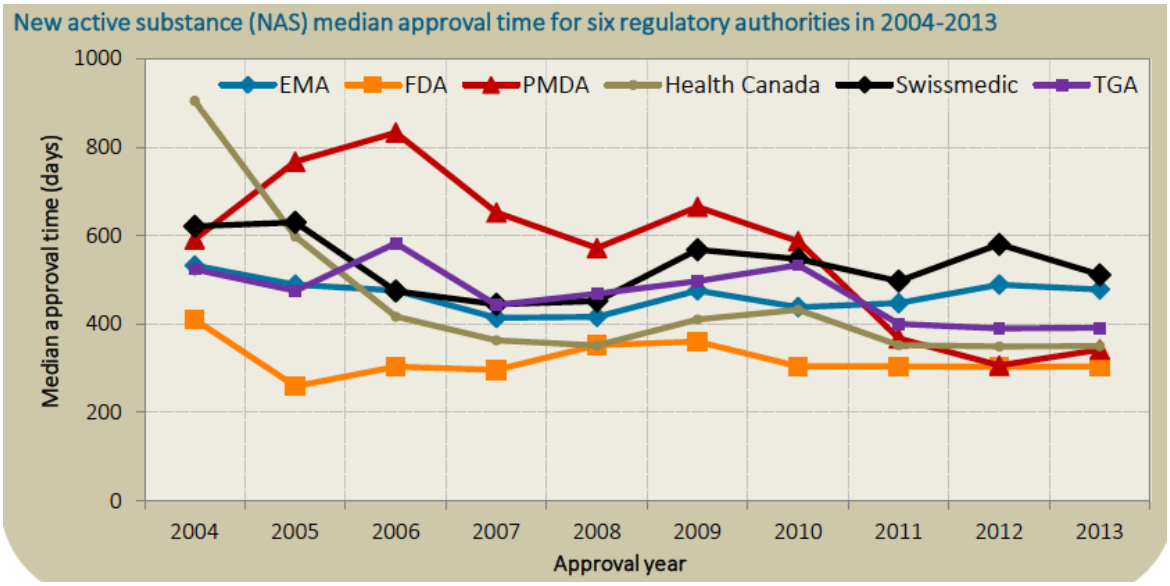

FIGURE 4.1 NEW ACTIVE SUBSTANCE (NAS) MEDIAN APPROVAL RATES FOR SIX REGULATORY AUTHORITIES 2004-2013. SOURCE: CIRS (2014) [3].

Figure 4.1 above also show that the difference in median approval times between EMA and FDA persists into 2013. The last five years have seen a large increase in the approval of anti-cancer and immunomodulator New Active Substances (NAS), which account for nearly a third of all approvals. The anti-cancer and immunomodulator approvals were characterised by short approval times, which may reflect the use of expedited review pathways within these jurisdictions. In 2009-2013, median approval times for anti-cancer and immunomodulator therapies were fastest compared with other therapeutic areas across four agencies – EMA, FDA, Swissmedic and TGA – but equally rapid for PMDA and Health Canada [3]. Median approval time (days) for anti-cancer and immunomodulator NSAs were 450 days in EMA and 240 at FDA, as seen in Figure 4.2 below.

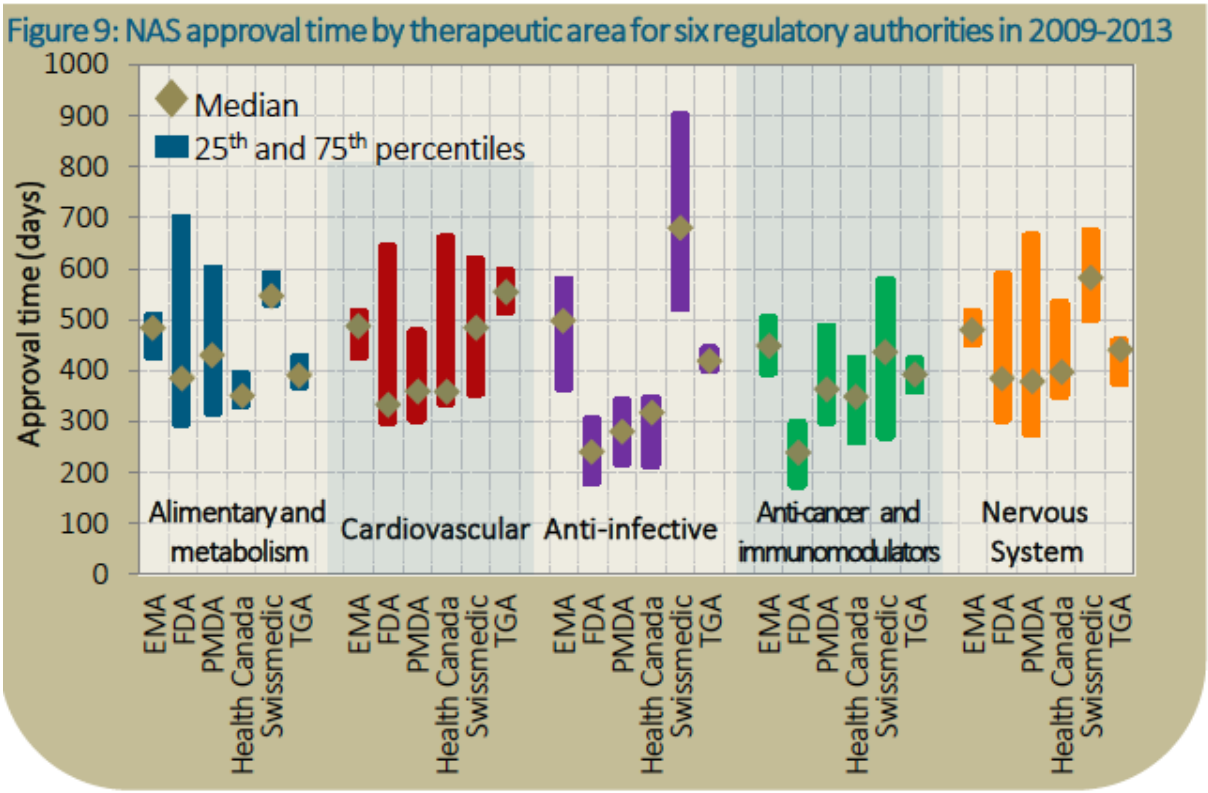

FIGURE 4.2 NAS APPROVAL TIMES BY THERAPEUTIC AREA FOR SIX REGULATORY AUTHORITIES 2009-2013. SOURCE: CIRS (2014) [3].

4.2 Pricing and reimbursement of pharmaceuticals

The time to marketing authorization in the EU depends on the time it takes the EMA to assess a drug, the time it takes the company behind the submission to answer questions or to come up with additional data or evidence and finally the time between the positive opinion by the EMA and the final decision taken by the EC.

Once an EU marketing authorization is granted further actions are needed in order to get market access in each of the EU member state. This step include administrative processes with national medical product agencies and HTA agencies such as NICE in the UK and IQWIG in Germany. Such agencies require evidence on the added benefit or the cost-effectiveness of a drug, which are used in the pricing and reimbursement process. The latter part of the process is described in more detail in the next section of this report, but is also depicted in Table 4.2.

The table shows the rate of availability of new drugs receiving an EMA marketing authorization 2008-2010 and the average time between marketing authorization and patient access to the drugs, as measured by the "number of days elapsing from the date of EU marketing authorization to the day of completion of post-marketing authorization administrative processes". As can be seen in the table the Northern- and Western European countries in general have a higher rate of availability and fewer days elapsed between EMA marketing authorization and patient access for new drugs [4].

TABLE 4.2. DELAY AFTER MARKETING AUTHORIZATION ACCORDING TO EFPIA'S PATIENTS W.A.I.T INDICATOR 2011 [4]

Country	Average number of days elapsed between date of EU marketing authorization and "accessibility" date
Austria	122
Belgium	371
Denmark	116
Finland	248
Germany	0
Hungary	N/A
Netherlands	209
Norway	160
Poland	N/A
Sweden	272
Switzerland	140
UK	118

The time elapse shown in Table 4.2 is dependent on the regulatory, pricing and reimbursement processes of individual EU member states. This, however, cannot explain all of the time elapsed in each respective country as pricing and market access strategies of manufacturers' may also contribute. In chapter 3 it was seen that several cancer drugs were introduced earlier in some countries, usually Germany and the UK, and later in other countries, such as France, Italy and Spain. The decision on if and when to launch a specific drug in a specific country is made by the manufacturer, and thus also reflects commercial factors; for example rich countries with a large pharmaceutical market (in EU-terms) have earlier launches. The use of external reference pricing, as an example, also provides incentives for manufacturers to launch a drug in e.g. UK before launching the same drug in Spain.

Waiting time for reimbursement is generally shorter than the time for marketing authorization, but in some countries, for example Belgium, it can take up to a year. The numbers in Table 4.2 are not specifically for cancer drugs, they are based on a small sample of drugs, and the definition of "reimbursement" is not standardized between countries. Reimbursement may mean different things in different countries, and is not a guarantee for actual use.

Let us consider the example of Sweden. A formal reimbursement decision is only required for oral drugs, which are a minority of the cancer drugs. The county councils can purchase oral drugs without a formal reimbursement decision by The Dental and Pharmaceutical Benefits Agency (TLV), the national reimbursement authority in Sweden. In addition, the county councils may put in restrictions for use for budgetary reasons, even if the TLV has made a positive decision. Thus reimbursement is not only a matter of timing, but also include the price and other conditions that the new cancer drugs are available under. There is free pricing of hospital drugs in Sweden but most new hospital drugs will be subject to an evaluation by TLV (since 2011). There may be a price agreement based on, in some cases, undisclosed discounts on a national level. Still, the drug may be subject to restrictions in use on regional or local levels.

Drugs used in ambulatory care require formal decisions on reimbursement and pricing in most countries, while those used in hospitals often are covered by the general hospital budget. Drugs used in oncology are most often used in the hospital setting which is true for the majority of the oncology drugs selected for review in this report.

Most of the countries in Europe have formal procedures for making national reimbursement decisions, while in for example the UK, there are no specific procedures before the drug may be prescribed under the reimbursement system [5]. For countries with formal decision processes, the reimbursement decisions often include price negotiations and estimates of the forecasts of sales. Although UK lacks overt restrictions on pricing, it does not mean that the authorities do not intervene to control prices and costs. In the UK, the Pharmaceutical Price Regulation Scheme (PPRS) of the Department of Health controls company profits and can ask for price cuts and paybacks from companies.

In Germany free pricing was allowed for new pharmaceuticals until the 2011 Act on the Reform of the Market for Medical Products (Arzneimittelmarkt-Neuordnungsgesetz – AMNOG), which was introduced as a cost containment measure for pharmaceuticals [6,7]. List prices are still set freely by pharmaceutical companies for new and innovative drugs during the first year following market launch. During that year a benefit assessment, very much like the evaluation of additional benefit

in France, is undertaken and the price and reimbursement rate of a drug is thereafter set accordingly [6-8].

In for example Belgium, Finland, the Netherlands, Norway, Portugal, Sweden and the UK the formalized decision-making process requires an economic evaluation, and the issue of cost-effectiveness plays an important role. For Denmark, Switzerland, Germany and several other European countries the role of economic evaluation and cost-effectiveness is not a formalized part of the decision-making process, but the producer may submit supportive data of economic benefits, which may facilitate a positive decision. Reimbursement of pharmaceuticals are in most cases publically funded, through income tax (e.g. in the UK, Spain and Italy) or through statutory health insurance (e.g. in Germany and France). In addition, a varying proportion of health care funding is paid for out-of-pocket. The proportion is usually small in EU member states but larger and more common in less developed parts of the world. The amount/proportion of reimbursement often differ depending on whether the drug in question is in- or off-patent, the type and seriousness of the disease it treats and the level of additional benefit the drug deliver compared to already existing comparators.

4.3 Hospital budgets, pricing and patient access

Most cancer drugs are used in hospitals, and for such drugs it is not necessary to apply for reimbursement in many countries. The rationale for this is that drug costs are part of the overall hospital costs and the hospital pays for the drug from its revenues which may be received in different ways; as payment per patient treated (Diagnosis Related Groups, DRG), a fixed budget or as a separate payment for the drugs used. The method for payment will influence the use of the drugs.

For the drugs studied in this report the number of drugs used in a hospital setting and out-of-hospital are equal (Table 4.3). For the drugs used in a hospital setting some are used in ambulatory care, i.e. health care centres or the equivalent, while others are administered in a hospital.

TABLE 4.3. PLACE OF ADMINISTRATION OF THE SELECTED ONCOLOGY DRUGS [9]. IN-HOSPITAL REFERS TO INTRAVENOUS ADMINISTRATION IN EITHER INPATIENT OR OUTPATIENT CARE WHILE OUT-OF-HOSPITAL REFER TO ORAL ADMINISTRATION IN THE PATIENTS' HOME.

Molecule	Type of administration	Place of administration
trastuzumab	Intravenous or subcutaneous	In-hospital
imatinib	Oral	Out-of-hospital
bortezomib	Intravenous	In-hospital
pemetrexed	Intravenous	In-hospital
erlotinib	Oral	Out-of-hospital
lenalidomide	Oral	Out-of-hospital
gefitinib	Oral	Out-of-hospital
ipilimumab	Intravenous	In-hospital
vemurafenib	Oral	Out-of-hospital
crizotinib	Intravenous	In-hospital

If drugs used in hospitals are financed outside the regular hospital budget system, administrative rules and regulations for price and volume may apply. Since new cancer drugs may be used in the hospital setting initially, and transferred to ambulatory use at a later stage, it is sometimes unclear how they should be handled in the reimbursement process.

Hospital budgets are often more rigid than the budgets of ambulatory care, and it is necessary to plan several years in advance, in order to make budgetary space for new treatment alternatives for inpatient care. Therefore, the ability of patients to access cancer drugs is highly dependent on the allocation of appropriate and adequate funding and the availability of financial resources within the healthcare systems. In some cases hospital-administered drugs are paid for through the financing of inpatient care on a per diem basis through the hospital budget (based on per day of hospital stay) or through a DRG (Diagnosis Related Groups) system, where budget is allocated for hospitalisation costs based on a classification of patients in different disease categories. If a new more costly drug should be financed within a given DRG reimbursement, the hospital has to save in other areas, or face a budget over-draft.

Another issue for hospital budgets is the persistence of what has been called '*budget silos*', which prevents the shift of money from one budget to another (at least in the short term) [10]. The introduction of a new drug could increase hospital costs but could also produce additional benefits to patients, as well as result in savings in ambulatory care, or hospitalization cost, or savings in social insurance payments. If payments to hospitals from governments, health authorities or healthcare trusts are not flexible, the introduction of new drugs will be delayed as there is no budget for new treatments, even if shown cost-effective.

Systems where drugs used at care centres or hospital outpatient clinics are financed separately may improve patient access to new therapies. There may be a delay in the definition of drugs authorized for separate financing, but when that decision is made, patients will have access to the drug. However, such "open-ended" systems have to be appropriately managed to avoid over utilization, which could lead to cost-containment policies with unintended consequences on access.

In addition to the challenges in funding new cancer therapies in a hospital setting, there are certain systemic barriers that further inhibit patient access. For example, an oral version of 5-FU, capecitabine, is available to cancer patients undergoing treatment for colorectal or breast cancer and offers an effective, cost-effective and convenient way of treatment. Yet, some healthcare systems, such as that in Germany, provide payment incentives for physicians to use a hospital-based intravenous administration. In the UK, hospitals would lose revenue by shifting from intravenous administration (which is counted as an '*in-patient stay*', a factor in determining overall hospital funding) to an oral therapy. Situations providing economic or structural incentives to use a specific formulation of therapy, neither cost-effective nor beneficial to patients, beg further scrutiny.

Therefore, to resolve the issue of inequity in-patient access to cancer drugs, the issue of adapting healthcare budgets in general, and hospital budgets in particular, to the introduction of new cancer drugs must be immediately addressed.

Resource allocation to new cancer drugs should not be dependent on whether the drug is financed through the hospital budget for inpatient care, through a drug budget used for hospital outpatients, or if the drug is prescribed for self-medication and paid for through the drug reimbursement system. Therapeutic alternatives should be compared and evaluated related to their total and marginal cost and benefit to avoid sub-optimal decisions, due to economic incentives to select certain forms of administration.

4.4 External reference pricing

External Reference Pricing (ERP), also known as international reference pricing or international price comparison[6], is defined by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies as "The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" [11,12]. This usually involves collecting the

[6] In the remainder of this report we will use external reference pricing, or its abbreviation ERP.

price of a given drug from a selected number of countries, e.g. from a basket of four reference countries in France to more than twenty reference countries in e.g. Austria and Italy [13,14].

According to a recent study by Vogler and colleagues 25 of the current 28 EU member states apply an ERP system, with Denmark, Sweden and the UK being the exceptions. The paper by Vogler et al. on external reference pricing from the European Federation of Pharmaceutical Industries and Associations (EFPIA), ERP is used informally in Denmark, leaving Sweden and the UK as the only non-ERP practitioners in the EU. Germany has recently begun to use ERP in price negotiations [15].

The countries applying an ERP system differs somewhat among studies on the matter. A plausible explanation for this is seen in Table 4.4 where the characteristics of ERP systems in our selected countries are listed. Formal ERP is the classic way of using the price of a given drug in a basket of reference countries in order to set the domestic price. Informal ERP refer to the use of ERP to negotiate, but not formally determine, a domestic price.

"It is important to note in this context that EPR is often only one of the several pricing and reimbursement tools available to countries and very frequently provides a benchmark or a starting point for negotiations between industry and health insurance organizations (e.g. Austria or the Netherlands, where it applies). In other countries (e.g. Czech Republic or Greece) EPR has a significant impact on the ex-factory price, as it is the key price-setting methodology" [16].

TABLE 4.4. EXTERNAL REFERENCE PRICE RULES IN EUROPE. BASED ON DATA AND INFORMATION FROM IMS HEALTH, CREATIV-CEUTICAL AND EFPIA MEMBERS [13].

Country	ERP used	Formal/ Informal	Calculation used	Price referenced	Medicines	Frequency of re-referencing (months)	Number of reference countries (Basket)	Number of times the country is referenced
Austria	Y	F	Average	MNF	Reimbursed	-	26	16
Belgium	Y	I	Average	MNF	Reimbursed	Undefined	6	16
Denmark	Y	I	Average	PPP	Hospital-only	-	9	15
Finland	Y	I	No calculation scheme	PPP	Reimbursed	Up to 60	29	14
Germany	Y	I	Not defined	MNF	Innovative Med	-	15	17
Hungary	Y	F	Lowest	PPP	Reimbursed	12	30	14
Netherlands	Y	F	Average	PPP	POM	6	4	15
Norway	Y	F	Average 3 lowest	PPP	POM	12	9	3
Poland	Y	I	Benchmark in negotiations	MNF	Reimbursed	24	30	13
Sweden	N	-	-	-	-	-	-	13
Switzerland	Y	F	Average	MNF	-	36	6	-
UK	N	-	-	-	-	-	-	-

Stargardt and Schreyögg evaluated the impact of a marginal price reduction in Germany on the cross-reference pricing schemes in the EU15 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and the UK) [17]. Each country's cross-reference pricing scheme was classified and an analytical model was built to simulate the effect, both direct and indirect, in the EU15 of a € 1.00 price reduction in Germany. The direct effect is the effect in a given country of the price reduction in Germany. The indirect effect is that created by the interrelations of cross-reference pricing schemes, i.e. Austria uses Italy as one of their reference countries and Italy, in turn, uses Austria as a reference country. This creates a '*ripple effect*' when the price reduction in Germany leads to price reductions in e.g. Austria and Italy, leading to even further price reductions caused by the interrelationship between cross-reference pricing schemes. In other words, the price in a given country influences prices in other EU member states.

The UK is one of the most widely referenced countries in relation to pharmaceutical prices. Therefore, although the UK pharmaceutical market accounts for just over 3 percent of global sales, pharmaceutical prices in the UK likely impact on prices in countries that reference their prices to the UK [18].

Figure 3.4: Overview of countries that reference to the UK

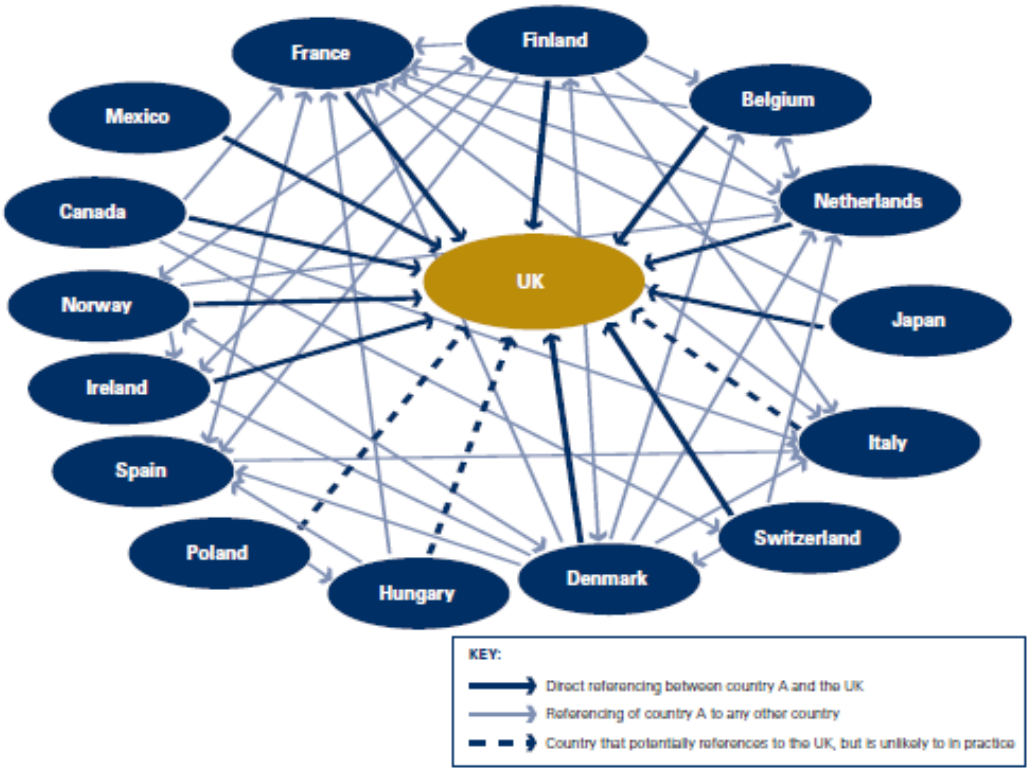

FIGURE 4.3. OVERVIEW OF COUNTRIES USING THE UK AS A REFERENCE COUNTRY, DIRECTLY AND INDIRECTLY. [19]

ERP is mainly seen as an instrument to reduce expenditures through reduction of unit prices. However, achieving cost-containment through ERP is limited due to several factors [14].

Firstly, comparing pharmaceutical prices is difficult because published list prices may differ substantially from effective prices. This is due to different pricing regimes and little price transparency. Profit margins for pharmacists and wholesalers and the value-added tax on pharmaceuticals differ across countries. Also, the industry negotiates discounts with distributors of pharmaceuticals, which are not communicated to the public and leave listed prices unaffected. Pay-back mechanisms may lower the effective prices of pharmaceuticals ex-post, but their impact on price levels is not published. Also, parallel trade may lower effective prices in high price countries. Packaging also differs across countries, making price comparisons partially invalid.

Secondly, the industry may adapt strategically and continuously to ERP, partially eroding the potential for cost-containment. The industry can launch products in countries with high pharmaceutical prices first (e.g. Germany). Thereby, prices may increase in all other countries, which directly or indirectly refer to high-price countries. Moreover, the industry may avoid competition on prices and rather competes on discounts, which benefit wholesalers and pharmacies rather than consumers. These adaptation strategies result in list-price inflation and cross-country convergence of prices. Consequently, ERP may lead to prices being too high and not reflecting national market conditions. [20]

Thirdly, the increased use of non-disclosed discounts reduces the availability of public prices to be used for ERP.

In addition, ERP has an impact on both drug prices and on the uptake of pharmaceuticals even in countries not using ERP [14]. For instance, in May 2012 TLV, Sweden, denied reimbursement for abiraterone (Zytiga®), a new drug for the treatment of prostate cancer. TLV considered Zytiga® a safe and effective drug, but the public price claimed by the manufacturer was higher than TLV could accept. The health care providers, too, considered abiraterone to be an attractive treatment. However, the manufacturer was not interested in reducing the list price in the relatively small Swedish market as it would jeopardize the price in larger European markets through the ERP system. In the end, the manufacturer and health care providers closed their own agreements, including confidential discounts and performance based agreements, in order to by-pass the national authority who is unauthorized to make agreements on confidential prices. Three years later, in May 2015, TLV granted Zytiga® reimbursement and the drug was included in the national

reimbursement scheme. By then, the public prices in Europe of Zytiga® had decreased to a level acceptable for TLV.

ERP, as well as parallel trade, tend to reduce the scope for price discrimination and the use of different markets' price sensitivity. We now see manufacturers and payers develop several types of payment models, including risk sharing schemes, payback arrangements, coverage with evidence development, confidential discounts, etc. The development is driven by the quest is to avoid the impact of ERP in the pricing and reimbursement process and by the strive to speed up the uptake of new innovative pharmaceutical treatments [14].

4.5 How should new cancer drugs be paid for?

4.5.1 Private versus public payment – the role of co-payments

Private out-of-pocket payments still plays a significant role for the funding of pharmaceuticals. As shown in Figure 4.4 below, the share of public payment is lower for medical products than for medical services. While 75% of all medical services are paid by public budgets, the public pays only just over 50% of expenditures for medical goods. For prescription pharmaceuticals, the share is higher, about 75% in many countries, such as Denmark, Germany and Sweden, while the coverage rate for hospital services is close to 100%.

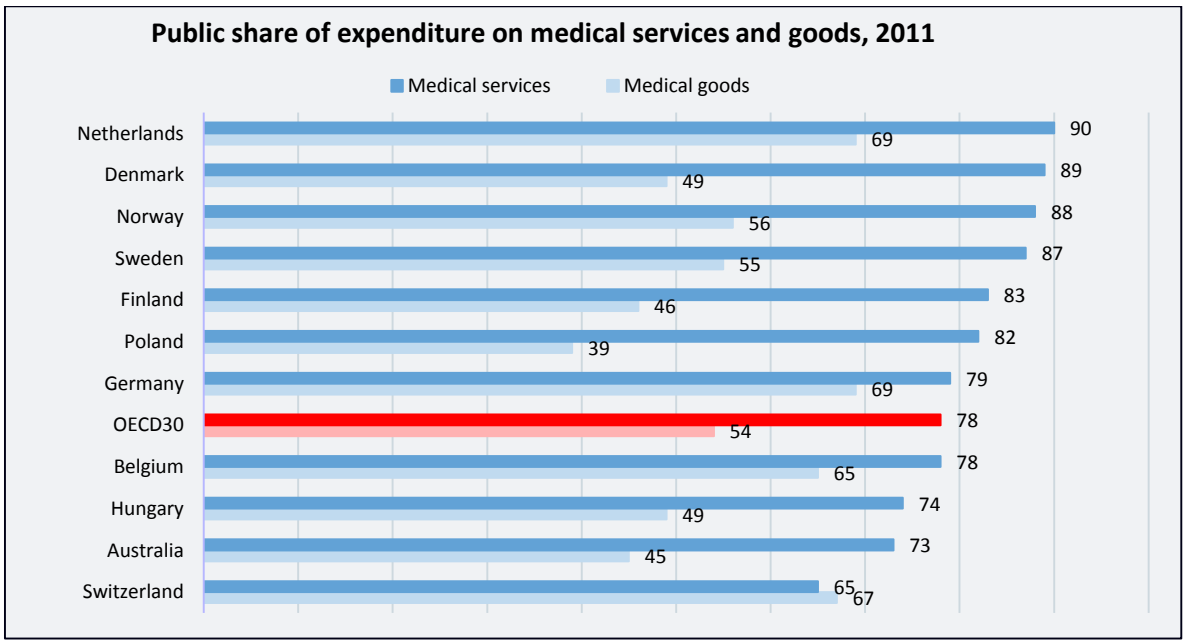

FIGURE 4.4. PUBLIC SHARE OF EXPENDITURE ON MEDICAL SERVICES AND GOODS, 2011 (OR NEAREST YEAR) [21]. THE OECD 30 REFERS TO AUSTRALIA, AUSTRIA, BELGIUM, CANADA, CZECH REPUBLIC, DENMARK, ESTONIA, FINLAND, FRANCE, GERMANY, GREECE, HUNGARY, ICELAND, ISRAEL, ITALY, JAPAN, KOREA, LUXEMBURG, THE NETHERLANDS, NEW ZEALAND, NORWAY, MEXICO, POLAND, PORTUGAL, SLOVAK REPUBLIC, SLOVENIA, SPAIN, SWEDEN, SWITZERLAND, AND THE UNITED STATES. THERE WAS NO INFORMATION REPORTED FOR THE UK.

Most co-payments are for medicines that are inexpensive, for example drugs that are off patent. For such drugs, where the costs are low and the alternatives many, co-payments have a role to play, since they increase consumer choice and contribute to funding. However, for modern cancer medicines the costs are more equal to hospital services and payments from patients' plays a small role. Experiences from the US shows that even minor co-payment rates, usually around 20%, can lead to financial problems for patients as well as health problems due to lacking adherence to treatment based on said financial problems [22,23].

4.5.2 Value based pricing and payment methods

Value based pricing based on either clinical data alone or a combination of clinical data and formal assessments of cost-effectiveness has developed as the main principle for reimbursement during the last 25 years. The practices differ between countries, and this principle is often combined with other principles, such as exernal reference pricing.

The development of new cancer medicines has challenged the practices of value based pricing for mainly two reasons. The first is that new cancer medicines comes to the market with limited data for assessing the value, which may be far ahead in an uncertain future. While improvement in median survival is a clear indication that the drug works, the value is dependent on mean survival benefit, which may not be estimated with uncertainty when some patients have a long-term survival. The way cancer drugs are developed – first for patients with advanced non-curable disease, and later for adjuvant treatment – and often used in combination and sequence makes the value differ significantly between different indications and patients.

This calls for flexibility in pricing. There has also been flexibility in pricing if we take a long term perspective. Price discrimination according to ability to pay was the rule before the creation of the common European market for pharmaceuticals. Non-disclosed price discounts and price-volume agreements have also been a feature of many pharmaceutical markets for a long time.

But the increased focus from payers on value, in combination with demands for transparency of decisions on pricing and reimbursement has changed market conditions. There is a need for a more rational approach to pricing and payment according to value.

4.5.3 Pricing and value – at the margin versus the total

Formal estimates of value for money, such as ratios of cost per Life Year Gained (LYG) and cost per Quality Adjusted Life Year (QALY) usually include a price per unit of the drug used in the treatment process. For cancer drugs, this price is often the most important element in the estimate of the cost. Since there is only one price, the assessment of value for money is reduced to an attempt to identify the users (patients) for which the ratio is below a certain level. The higher the price, the fewer patients will qualify, even if the price may have no relation to the cost involved in an increased use of the drug. The cost per extra unit, the marginal cost, is in all cases with a significant part of fixed costs in the development and production process, much lower than the average cost.

For the payer, it is the total costs and the total benefits that matter. A total cost, or budget impact, is the price multiplied with the total number of units used. The total value is the sum of the value for all patients treated, illustrated by the area under the value curve in Figure 4.5 below. The difference between total value and total cost is called the consumer surplus. The difference between the total costs, equal to the total revenue, and the marginal cost of production is called the producer surplus. The producer surplus should pay for the fixed costs of R&D and production.

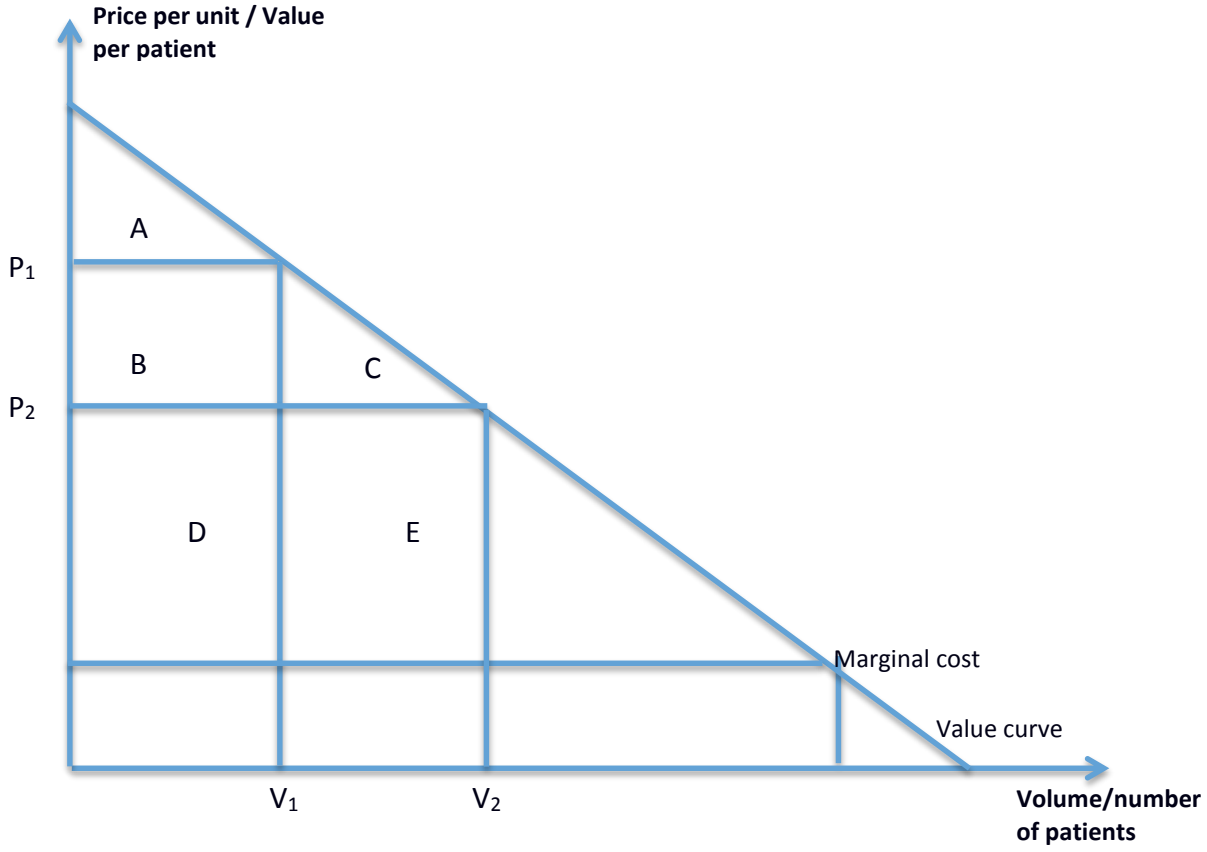

FIGURE 4.5. MARGINAL AND TOTAL VALUE

It is often claimed that payers are not interested in cost-effectiveness but rather budget impact. If that is correct, Figure 4.5can illustrate that the same budget impact could be achieved with a lower price and a higher number of patients treated. That will increase the consumer surplus, revenue minus costs, but the effect on producer surplus depends on the slope of the curve. It is possible to create a win-win situation where both the consumer and the producer surplus is increasing if price can be varied between patient groups. This is shown in Figure 4.5, where a reduction in price for a second group of patients (from P_1 to P_2), increases both the consumer surplus, the triangle above the price line (from A to A+B+C), and producer surplus, the rectangle between the marginal cost and the price for the new volume V_2 (from B+D to D+E).

The methods for pricing and payment is thus important in relation to access for patients, reward for innovation to payers, and the value created through the use of the new medicines. In practice, there are different payment mechanisms for drugs used in the hospital and drugs prescribed for use in the ambulatory care setting.

For drugs used in hospital inpatient care, payment is included in the payment for the hospital stay. For most countries in Europe, hospitals are paid by a per diem, or a fixed rate per admission/discharge according to DRG groups. This was not a major issue when drugs accounted for only a few percent of hospital expenditures. But with a growing pressure on hospital finances, and the use of budgeting and reimbursement at the level of a clinical departments, the cost of cancer drugs are now a significant part of the total cost for the department of oncology (e.g. around 30 percent in Sweden). There is thus a need for new mechanisms to pay for cancer drugs used in the hospital.

For drugs prescribed and used in ambulatory care, and distributed through pharmacies, a specific reimbursement system is in place in most countries. Since the 1990s decisions about reimbursement of prescription drugs have been increasingly guided by formal assessment of cost-effectiveness. After a positive reimbursement decision was made, the involvement of the payer was limited, and the prescribing physicians and the patient made decisions about use. Total costs were controlled through co-payment, combined with ad hoc cost-containment measures. As explained above, these measures did not work for new cancer drugs, which prompted a more close involvement by the payer in the volumes prescribed.

4.5.4 Pricing versus payment

Traditionally price has been defined in relation to units of substance, vials or packages used for treatment. However, this way of paying for new treatments has a number of problems. One is that it is often difficult to assess the value of new cancer drugs when they first come to the market. Different approaches to link reimbursement and price decisions to observed outcome have been developed under different names; coverage by evidence development, risk-sharing agreements, pay-for performance etc. Other new payment mechanisms based on the observation that value may differ between indications and patients have also be introduced; pay for responders only, differential price per indication, and cap on the total payment for a defined period. This form of differential pricing has been introduced to optimize the value of new cancer drugs, at the same time as the reward to the innovator increases.

There is thus a link between price and value, and next section will focus on the development of new mechanism for payment for innovative cancer drugs, that may be of benefit for both payers and providers.

4.5.5 Separate funding for cancer drugs

There are a number of ways in which different countries have attempted to address the issues of funding new drugs:

In some countries, such as France, a separate list of innovative drugs exists. These drugs are funded outside of the hospital financing systems (DRG), which means that they can be used outside the hospital budget restriction.

In other countries, there are special budgets available for new medicines such as the decision in Denmark in 2005 to allocate DKK200 million (€27 million) for new cancer drugs, or the separate “Cancer fund” in the US. The UK set up the Cancer Drugs Fund (CDF) in 2010, providing separate funding for and patient access to cancer drugs that is not routinely provided by the NHS, and in many cases not seen as cost-effective by NICE. The CDF provides £200m annually of additional funding for cancer drugs on a separate list, implying that funding outside the hospital budget restriction is possible also in the UK [24].

After five years, there is a proposal that England's Cancer Drugs Fund will now be managed by NICE. NHS wants the CDF to become a 'managed access' fund for new cancer drugs, with “clear entry and exit criteria”. The CDF would be used to resource drugs that appear promising, but where NICE indicates that there is insufficient evidence to support a recommendation for routine

commissioning, and where additional evidence would be likely to enable a more informed NICE appraisal decision. Instead of a simple failure to recommend, the drug would be given 'conditional approval' by NICE and provided through the CDF for a defined period, whilst further evidence from real world use was collected. At the end of this period, the drug would go through an abbreviated NICE appraisal, using this additional evidence and the company's offer price, and then either attract a positive recommendation from NICE at which point it would move out of the CDF into mainstream commissioning, or a negative NICE recommendation at which point it would move out of the CDF and become available only on the basis of individual patient referral [25].

Separate funding for new medicines can be one way to improve access, but it may also cause problems elsewhere and may distort treatment decisions. While it most certainly will increase access for selected patients to the specific drugs in question, it may also limit access for other patient groups. In a health care system using value based pricing and measures of cost-effectiveness to allocate appropriate resources for drug funding, such as Sweden or the UK, bypassing the cost-effectiveness requirements severely limits the use of value based pricing. It would also ascertain more value to certain diseases, making the pricing and reimbursement environment less transparent. Separate funding also raises questions on which drugs should be included, for which period of time and of the size of the budget.

There are a number of questions that may be asked:

- Can a policy of separate funding for new cancer drugs be introduced in a more systematic way and on a wider scale?
- Can access to separate funding be combined with the collection of relevant data in the market place to help further define the optimal number of patients who could benefit from the treatment?
- As indications for usage of new cancer drugs change over time, as more evidence is gathered, can a separate funding mechanism be established to cover the cost for new cancer drugs during their first three years on the market while data on '*real life*' usage are gathered?
- How should a payment system that optimizes the value for patients of new cancer drugs be designed?

4.6 Managing uncertainty about value – Market-access agreements for anti-cancer drugs

When considering whether or not to grant reimbursement or allocate budgetary resources for a new drug or other treatments, one issue arising is the uncertainty regarding long-term consequences of the use of new drugs. Currently, clinical trial data are used to assess the value of

new cancer drugs [26,27]. But those data have limitations for predicting '*real life*' usage and for assessment of the future potential value of these new drugs.

HTA agencies assess new cancer drugs based on the relative effectiveness and costs. The goal is to evaluate the drug as early as possible, to be able to provide guidelines for decisions before any treatment praxis is established. The problem is that it is difficult to predict future benefits. One example is the vaccination against Human Papilloma Virus (HPV), which can cause cervical cancer. It is difficult to assess the future risk reduction as there are several factors to consider other than the vaccination.

Not only the clinical benefits of new technologies may be difficult to assess, but also costs related to treatment. When introducing a new drug, there are direct costs related to the use, but the drug is also part of a broader treatment strategy. This leads to further complications in assessing costs of new technologies. New targeted drugs and immune-oncology drugs will increase in the number of potential treatment strategies [28]. An issue of specific importance is how to describe the value of therapies with curative potential, where it will take very long time before the final data are available [29].

A cancer drug is often first used for very limited indications and in patients with advanced disease, where the medical need is high. Later the use is extended to other indications, such as the adjuvant setting or for preventive purposes. The cost-effectiveness is often low for the first indication, but increases with a broader use. It is therefore important to recognise that new innovative drugs are introduced for limited indications where the economic benefits are not easy to project.

It is important to have a long-term perspective on cost-effectiveness. The treatment cost per patient may be very high at the introduction, but when the patent of a drug is running out, the cost will be much lower, as generics will enter the market. The introduction of a new technology may therefore involve risks for the payer. For a limited hospital budget it is difficult to spend large sums with hope of higher return in future savings that could not be guaranteed.

One option being explored with regards to uptake of new drugs, has been the concept of '*risk sharing*' between the pharmaceutical company and the payer [30]. Here the provision of additional effectiveness documentation in different indications would be done by the manufacturer (when additional indications are granted by the medicine agency) in exchange for appropriate budgetary allocation by the payer, to make the drug available to patients in the new indications. The payer

and the manufacturer share the economic risk of introducing the new drug. If it is not proved to be as efficient as expected, the price of the drug is reduced.

4.6.1 Uncertainty and risk-sharing agreements

Uncertainty is inherited in the drug development process, but decision must be made both by the company developing the drug, the authorities responsible for market authorization and reimbursement agencies, payers, providers and patients. Information about the new drug will be accumulated over time, and one option is to wait with a decision until a later point in time. This strategy will reduce the probability to make wrong decisions, to use an ineffective or harmful drug, but will also increase the probability that patients that can benefit from a valuable drug will be denied this opportunity. The rate of increase in information about potential benefits and harms can be influenced by investments, but these are costly and must therefore be carefully assessed in terms of costs and benefits. Towse and Garison [31] define a performance-based agreement as one between a payer and a pharmaceutical, device or diagnostic manufacturer where the price level and/or revenue received is related to the future performance of the product in either a research or a real-world environment. This is broadly comparable to de Pouvourville's definition of '*risk-sharing'* as "a contract between two parties who agree to engage in a transaction in which one party has sufficient confidence in its claims that it is ready to accept a reward or a penalty depending on the observed performance" [30].

While performance based agreements are mainly used for handling uncertainty about value, such agreements can also be undertaken for non-cost-effectiveness reasons; for managing budgets and for hiding discounts.

Towse and Garrison provide an overview of the risk-sharing landscape from a payer perspective, presented in Figure 4.7.

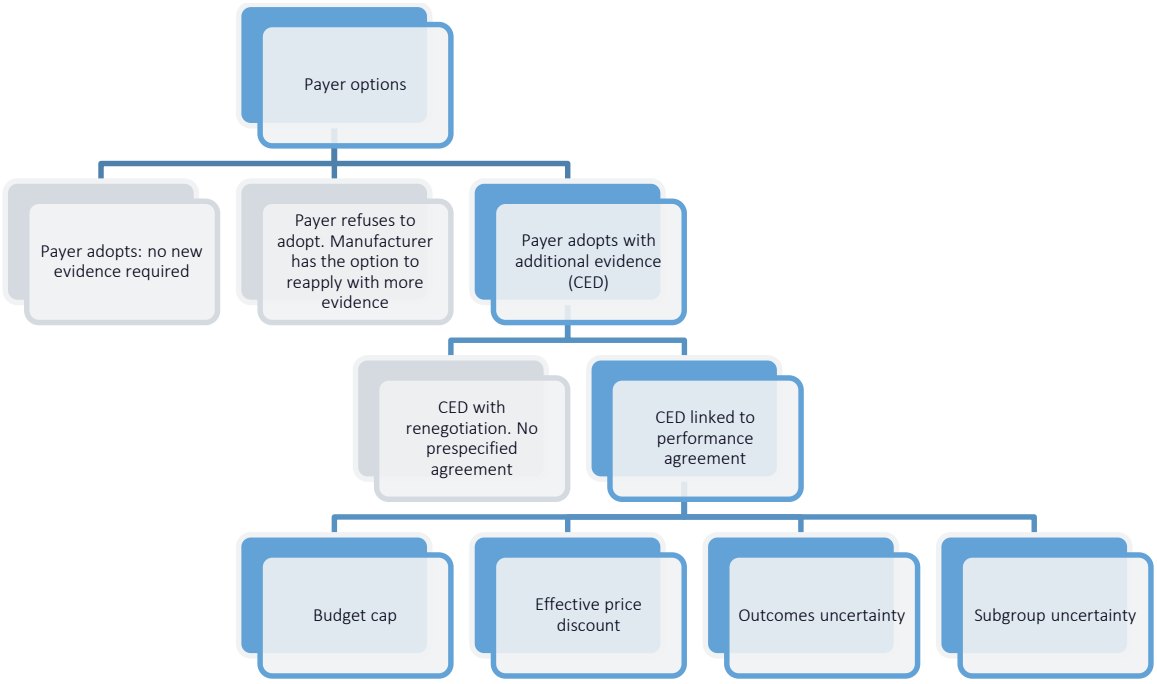

FIGURE 4.7. OVERVIEW OF THE RISK-SHARING LANDSCAPE [31].
CED – COVERAGE WITH EVIDENCE DEVELOPMENT.

Risk sharing and performance based agreements requires collection of data. Such agreements as part of a reimbursement decision are also called coverage by evidence development. As shown in Figure 4.7, evidence can be used for a renegotiation, an approach applied by for example TLV in Sweden, or directly linked to different economic performance indicators. For example, payment could be capped to a fixed sum (budget), price could be linked to the volume of sales, or payment could be linked to an outcome indicator (responders, survivors), or to sales in specific subgroups of patients. The different payment models can also be combined.

4.6.2 Current trends in risk-sharing

Based on the taxonomy and description of risk sharing or performance based agreements (Figure 4.8), Carlson et al. conducted a review of performance-based risk-sharing agreements between 1993-2013 [32].

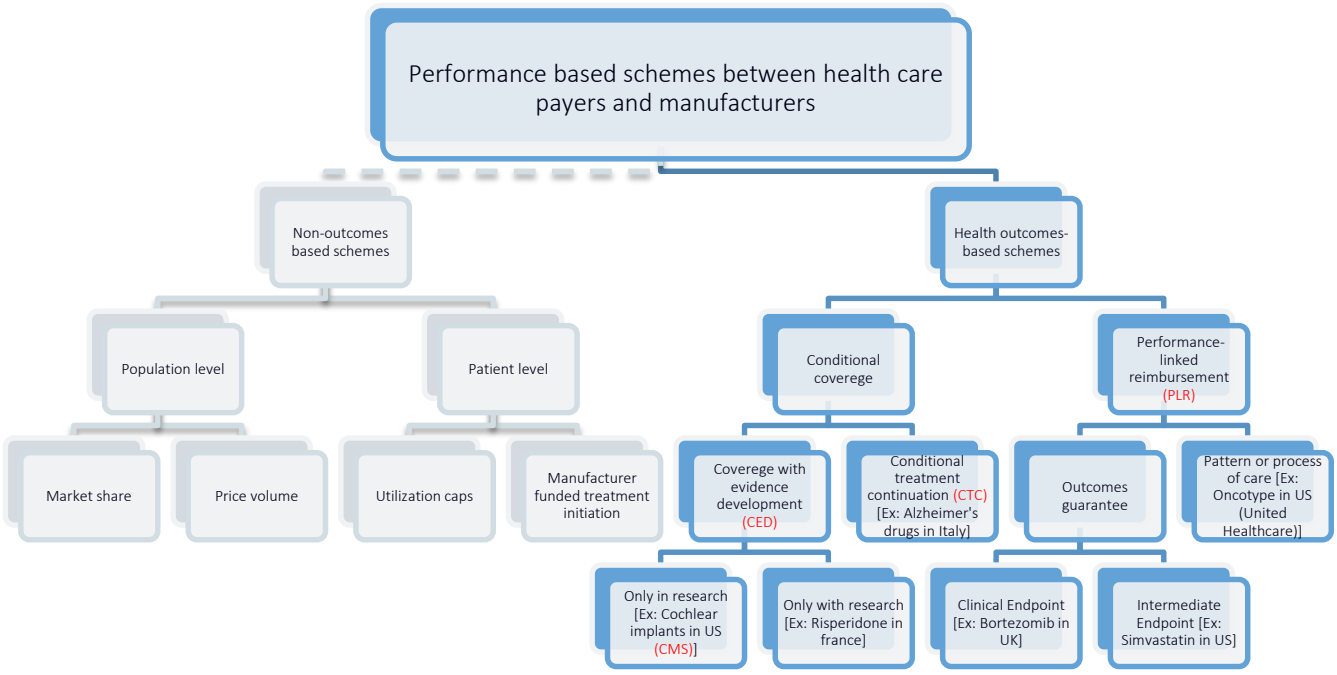

FIGURE 4.8. TAXONOMY OF RISK-SHARING ARRANGEMENTS ACCORDING TO CARLSON ET AL. [32].

Carlson et al. makes a distinction between non-outcome and outcome based schemes or agreements. The non-outcome based arrangements designed solely for budgetary purposes, i.e. arrangements based on market share, price/volume, utilization caps and manufacturer funded treatment initiation [32].

Performance based schemes are divided into conditional coverage and performance based reimbursement. Carlson et al. identified 148 such schemes, with the vast majority taking place 2007-2011 [33]. The results of their review are presented in Figure 4.

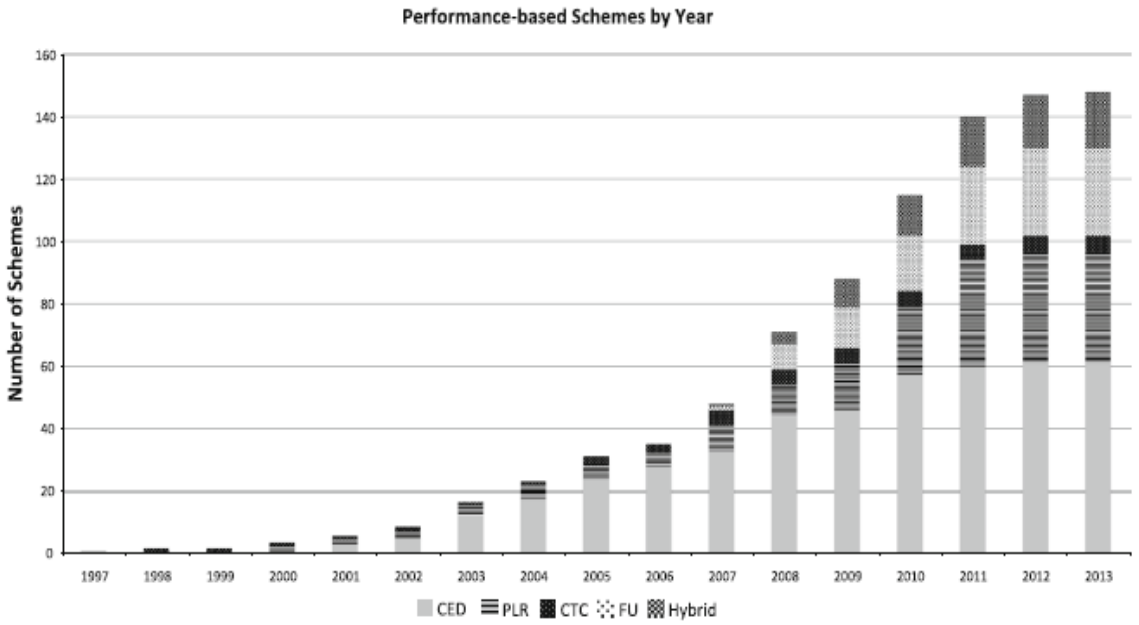

FIGURE 4.9. NUMBER OF PERFORMANCE BASED ARRANGEMENTS BY YEAR. THE IDENTIFIED ARRANGEMENTS WERE CATEGORISED ACCORDINGLY; CED, PLR, FU, CTC AND HYBRID ARRANGEMENTS (PLR|CTC; PLR|FU; PLR|CTC|FU; CED|PLR; CED|PLR|FU) [33].
CED – COVERAGE WITH EVIDENCE DEVELOPMENT
CTC – CONDITIONAL TREATMENT CONTINUATION
FU – FINANCIAL/UTILIZATION
PLR – PERFORMANCE-LINKED REIMBURSEMENT

Europe continues to dominate the number of arrangements implemented. The increase in the number of agreements has levelled off during the last year. This may be attributed to some previously active countries moving away from the use of Performance-Based and Risk-Sharing Agreements (PBRSAs) in favour of simpler arrangements, e.g. the UK's move toward confidential discounts. These discounts meet the needs of payers in terms of cost containment and cost-effectiveness as well as the needs of the manufacturer for getting early market access and avoiding the negative consequences of external reference pricing. However, they do nothing to ensure that the right patients are receiving, and staying on, the drug of interest. Thus, simpler agreements do not address effectiveness uncertainty, nor do they provide an incentive to manufacturers to focus on improved real-world value [33].

The most common therapeutic area for arrangement development was oncology. The reason may be the increasing number of new oncology drugs, high disease related costs, and the availability of validated, mutually acceptable, short-term response measures. Arrangements that utilize existing administration systems, which include reasonable proxies for clinical outcomes and cost-effectiveness has replaced complicated data collection projects. For example, the UK implemented

an arrangement to provide gefitinib for patients with locally advanced or metastatic non-small cell lung cancer in which gefitinib is supplied at a single fixed cost of £12,200 per patient, irrespective of the duration of treatment [23]. In addition, the UK Department of Health is not charged until the third month that treatment is supplied, which means that a patient who receives less than 3 months of treatment will not incur a charge. This arrangement uses the dispensing of the drug as a proxy for progression-free survival, which is feasible in cancer as most drugs are treat-to-progression or unacceptable toxicity. Essentially, if the patient progresses before three monthly prescriptions have been provided, there is no cost to the payer. If the patient is benefiting (i.e., not progressing or stable), they can continue to receive the drug, the payer pays one fixed price and is then shielded from the cost exposure of long-term users. This arrangement can meet the needs of all parties with early access, a shadow discount, management of subgroup uncertainty, patient access, and low administrative burden [33].

Market access agreements are tools that can be used by countries and manufacturers to help solve access problems. Payers benefit through cost containment, ensuring more efficient use of resources (i.e. value for money) and improved access, with the potential for improved outcomes for their covered population. Manufacturers benefit by securing market access at or near launch, and through achieving more efficient global pricing strategies. The long-term viability and growth of these arrangements will rest in the ability of the parties to develop mutually beneficial arrangements that entail minimal administrative burden in their development and implementation. These arrangements continue to evolve in individual systems and countries, and will ultimately be judged on their ability to meet the needs of the key players—payers, manufacturers, and patients [33].

Neumann et al. has a more sceptic perspective on the use of risk-sharing agreements and, amongst many, mentions high transaction costs and administrative burden as potential barriers for a wide implementation of said agreements [34]. Risk sharing could gain traction as payers and product manufacturers acquire experience with the concept and as information systems and measurement tools improve. But they conclude that in the foreseeable future, risk sharing seems more likely to remain the exception, as payers and manufacturers continue to use established pricing models and experiment with new forms of rebates and discounting that are unconnected to data collection or performance measures.

4.6.3 Reviews of risk-sharing and oncology

EExamples of oncology agents reimbursed under risk-sharing agreements with NICE [35] are presented in Table 4.5. The common features of risk-sharing schemes are that there is either persistent discount or discount applied at the onset or maintenance phase of the treatment; (1) there is a cap for amount of reimbursed product, (2) there are strict criteria for treatment eligibility under an approved indication along with criteria for response, non-response and treatment discontinuation, and (3) there is often free provision of the drug in some circumstances. The free provisions may be triggered not only by pressure from payers but also by manufacturers' willingness to collect long-term efficacy and safety outcomes (e.g., registries or post-marketing safety studies) requested by regulatory authorities.

TABLE 4.5. OUTCOME-BASED PRICING AGREEMENTS FOR ONCOLOGY PRODUCTS IN THE UK [36].

DRUG	INDICATION	COMPANY	PAYER	MARKET	DESCRIPTION
Gefitinib (Iressa)	EGFR-active mutant positive non-small cell lung carcinoma	AstraZeneca	NHS	UK	AZ will provide the product free for patients requiring less than three months of treatment. NHS will pay a fixed sum per patient for those requiring more than three months of treatment.
Pazopanib (Votrient)	Renal cancer	GSK	NHS	UK	GSK reduces price of Votrient to bring it into line with Pfizer's Sutent and will give NHS a partial rebate if Votrient to match Sutent in clinical trials.
Panitumumab (Vectibix)	KRAS-wild type positive colon cancer	Amgen	AIFA	Italy	In cases of therapeutic failure during the second month of treatment, Amgen will pay 50% of the cost, after which Amgen is not liable to pay treatment costs.
Bortezomib (Velacade)	Mylenoma	Takeda, J&J	NHS	UK	The scheme is open for patients treated with Velcade at 1st relapse only. The maximum number of Velcade 3.5 mg vials per patient covered by the Scheme is 18. Strictly defined criteria for response and non-response in different types of myeloma. Prior to checking response for scheme eligibility purposes, all patients should receive 4 cycles of treatment unless toxicities prevent treating to 4 cycles. If, within the first 4 cycles, treatment has to be stopped because of tolerability reasons, the scheme only applies if the patient showed no response or a minor response to treatment.
Erlotinib (Tarceva)	EDFR-active mutant positive non-small cell lung carcinoma	Roche	NHS	UK	Discounted scheme is under negotiation with NICE.
Trabectedin (Yondelis)	Soft-tissue sarcoma	Zeltia, J&J	NHS	UK	Under the scheme, the hospital will be responsible for the cost of the first five treatment cycles of the Product. If a Patient continues to demonstrate benefit (as determined by their treating physician) after five treatment cycles, the cost of the Product for "ongoing" treatment (i.e., from treatment cycle six onwards) will be provided "free-of-charge".
Lapatinib (Tyverb)	Metastatic breast cancer	GSK	NHS	UK	A 12 week discounted scheme was enacted under approved indication.
Nilotinib (Tasigna)	Chronic myeloid leukemia (imatinib intolerant/ resistant)	Novartis	NHS	UK	A discounted scheme was agreed between NICE and manufacturer.
Mifamurtide (Mepact)	High-grade non-metastatic osteosarcoma	Takeda	NHS	UK	A patient access scheme has been agreed whereby the manufacturer will make mifamurtide for the treatment of osteosarcoma available at a reduced cost to the NHS. The nature of this cost reduction is confidential.

Espin et al. investigated the use of oncology risk-sharing schemes (RSS) in the EU and found that six European countries stated that they are using new innovative contracting instruments for oncology medicines: France, Italy, Lithuania Portugal, Slovenia and the UK [35]. Italy and the UK reported more RSS experiences than the others; furthermore, a greater amount of literature on this subject can be found for both these countries. Other countries that did not answer the survey have implemented RSS, e.g. Belgium, the Netherlands and Germany. However, it is not possible to know whether or not the RSS they have implemented focus on oncology products.

Most of the RSS are financially based schemes since outcome-based schemes are more complex to implement. Italy and the UK have the most experience with these schemes. The authors conclude that the use of RSS in Europe on oncology products is a new and growing trend that is based on the need for new ways to finance high-cost medicines whose effectiveness remains uncertain. Nonetheless, no common approach exists across countries to deal with these new schemes for financing oncological medicines. An effort must be made to estimate the real opportunity costs implicit in implementing these new risk-sharing schemes and there is a need to evaluate how RSS have been implemented and what the consequences are.

Van de Vooren et al. have compared the market access agreements for anti-cancer drugs in Italy and England [37]. These schemes are called Market Entry Agreements (MEA) in Italy and Patient Access Schemes (PAS) in England and Wales. A summary of the number and types of the schemes is shown in table 4.6 below.

TABLE 4.6. NUMBER AND TYPES OF MARKET ACCESS SCHEMES IN ONCOLOGY IN ITALY AND ENGLAND/WALES.

	FINANCIAL-BASED SCHEMES	OUTCOME-BASED SCHEMES
MEA	Cost-sharing (13)	Risk-sharing (2)
		Payment-by-result (22)
PAS	Simple discount (12)	Response scheme (1)
	Free stock (2)	
	Dose cap (2)	
	Rebate (1)	
	Single fixed price (1)	

MEA – Managed Entry Agreement
PAS – Patient Access Scheme

Italy has more outcome-based schemes while England and Wales have shifted towards only financial based schemes. The major, common concern around these schemes is their burdensome administration, mainly borne by the local health professionals involved in compiling patient data and applying for money back from the pharmaceutical companies. The lack of transparency in the commercially confidential PASs is another critique.

The experience with the current performance based schemes in Italy, particularly the burdensome and small refund, €121million out of a total of €3696 million paid, prompted Navarria et al. to suggest an alternative model for risk sharing called *Success fee* [38]. The main feature of this model is an ex post payment made by the NHS to the manufacturer for those patients who received a real benefit from treatment. This model thus avoids the administrative complications of a payback system, but there is still a need for an agreement and data collection to allow payments for "real patient benefit". Success fee represents, according to the authors, an effective strategy to promote value-based pricing making available to patients a rapid access to innovative and expensive therapies, with an affordable impact on drug expenditure and, simultaneously, ensuring third-party payers to share with manufacturers the risk deriving from uncertain safety and effectiveness.

4.7 Chapter summary

The rapid introduction of new, effective cancer drugs during the last ten years has challenged the traditional system to pay for drugs. Since cancer drugs are administered in hospitals, at hospital outpatients departments, by freestanding specialists in ambulatory care, and are prescribed to patients for use at home it is no longer rational to have separate systems for payment dependent on the type of administration. There is a need for co-ordination, and consistent decision making, to meet the goals of efficient and equitable use. Pharmaceuticals and devices have traditionally had lower rates of public payment than services, but new pharmaceuticals and diagnostics are now an integral part of the delivery of comprehensive cancer services. There is thus an ongoing process of integrating medical products into systems of bundled payments which can be related to outcome and quality of care.

However, the transformation to a new payment system is not merely technical and administrative. There are other aspects of new cancer drugs and diagnostics that need to be taken into account in order to optimize the value of the new therapeutic opportunities. The scientific development towards targeted therapies changes the development, and it is possible to make shorter and smaller trials to find out if new treatments work for different types of patients. Patients and the health care system are also interested to have an opportunity to use these treatments early on, particularly in situations where there are few effective alternatives. Decisions about market authorization and reimbursement must thus be made under great uncertainty about risk-benefit and value. The development of instruments like adaptive licensing and coverage by evidence development requires complementary decision about how new pharmaceuticals should be paid for while evidence is developed. A number of approaches to payment based on the collection of data

about outcome, i.e. risk sharing schemes, have been tried. These have often developed as a response to a specific decision problem rather than carefully planned and designed in advance.

But the management of uncertainty is not the only issue. It is well known that the way health care providers are paid has an important impact on the services provided, and thus outcome and quality of care. A payment system for new cancer drugs should be designed also with the objective of optimal use of the new drugs. That requires attention to the fact that the value is not only uncertain but may also differ between users, e.g. for different types of cancer or line of treatment. Another complicated factor is that combination therapies will be increasingly common, and that the increasing incidence of cancer among the elderly makes it necessary to take co-morbidities into account in designing optimal intervention strategies.

Common for all potential solutions to the problem is the need for collection of data on resource utilization and outcome. Decisions must increasingly be based on objective and verifiable criteria, which require careful attention to what data should be collected, and how the data should be analysed and interpreted. The development of payment systems based on prospective outcome data will thus be integrated with the scientific development of new cancer drugs. The payment system will be one of the factors determining access to new therapies, and will indirectly influence what type of therapies developed in the future.

It is not possible to define the perfect payment system for cancer drugs, in the same way that it is not possible to design the perfect payment system for hospital care or physician services. These are long-standing issues in health economic research. It is easier to see the shortcomings in prevailing systems. But there are a number of “models” that can be used for reference when designing a new payment system.

One model is to have a separate budget for new innovative cancer drugs during a limited period when they are introduced in clinical practice, and there is a need to collect further data for assessment of value.

A second model is payment of a “fixed fee” for treatment of a predicted number of patients during the coming year. This model has the advantage that it gives the innovator a fixed revenue related to the total potential value of using the drug for a specific population or jurisdiction. It includes optimal pricing since the social marginal cost of the use of more doses of the drug is close to zero. The use of this model is problematic when several drugs are used for one patient, which all

contribute to the outcome. However, algorithms for this can be worked out, and the problem remains if the objective is to set a value based price for each individual drug.

A third model should be payment per patient/year with different payment for different patients. This has the same advantages as price discrimination, and can be combined with additional payments, based on quality and/or outcome data such as responders, survivors etc.

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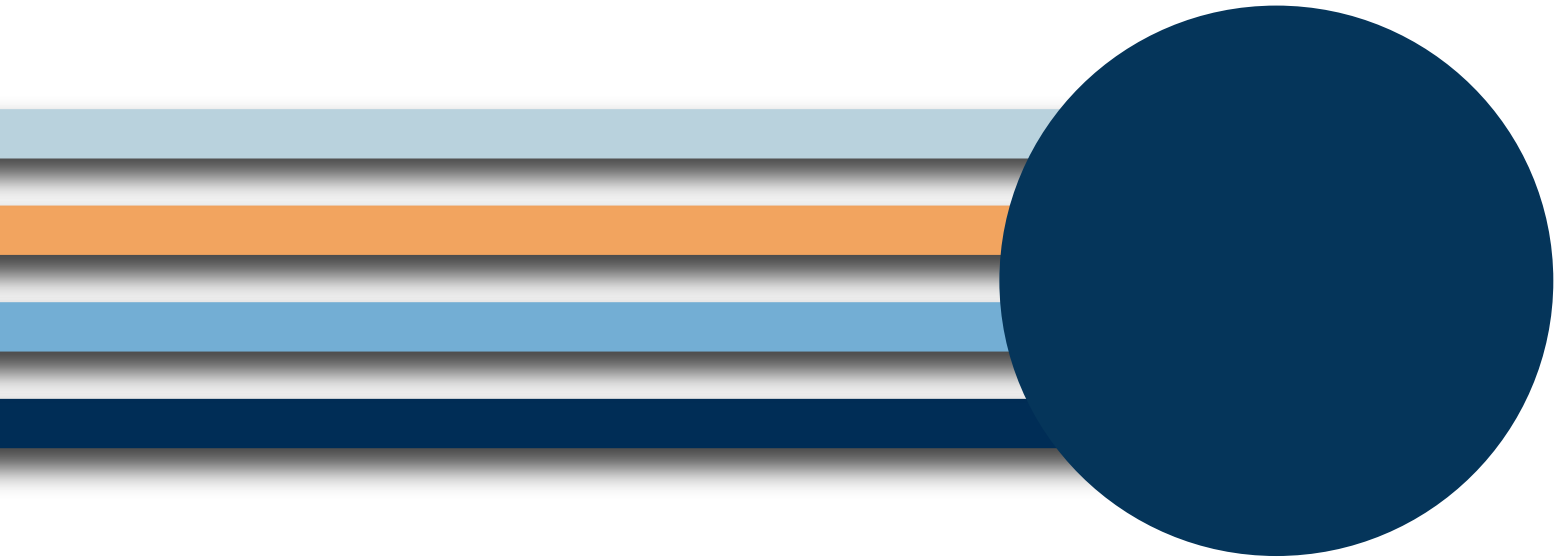

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