Comparator Report on Patient Access to Cancer Drugs in Europe

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1 The Burden of Cancer in Europe

1.1 Summary

This chapter presents different aspects of the burden of cancer to society in terms of incidence, mortality, as well as direct and indirect costs associated with cancer. The 28 countries covered in this study are 25 of the 27 EU member states (excluding Cyprus and Malta) and the three non EU member states, Iceland, Norway and Switzerland. The following summarizes our findings.

- European cancer incidence is increasing and mortality decreasing indicating the impact of screening programs and improvements in treatments
- Survival for most cancers is improving significantly but there is great dispersion within Europe and across diagnoses
- Spending on cancer is increasing in Europe, but are still not in parity with the relative burden of cancer compared to other diseases
- There is a trend towards more ambulatory treatments, and a reduction in number of hospital-days for cancer, despite more patients treated
- The average duration per case of inability to work due to cancer is decreasing for most diagnoses

1.1.1 Study Background & Objectives

There were 2.35 million new cases of cancer diagnosed in Europe in 2006. Cancer also caused the death of 1.2 million people in Europe the same year. [1-3]. However, survival has improved for all cancers [4, 5]. The annual medical costs for cancer care in Europe were estimated to €54 billion by Wilking and Jönsson in 2005 [6]; to which the indirect costs of the disease can be added, and they are generally estimated to be more than twice the direct costs. Costs for treatment of cancer are increasing, with changes in the relative share for different categories of costs. Thus, a more detailed review of the recent evolution of the different components of the burden of cancer is presented, including an update of total cost of cancer in Europe 2007.

1.1.2 Objectives

The main purpose of this chapter is to update and extend an earlier study on the burden and cost of cancer, focusing on the European countries. Previous studies have shown that there are very limited data on the direct and indirect costs of cancer. At the same time we can see significant changes in the resources used for cancer, which makes it important to have updated figures. Data on the incidence and mortality of cancer is also far from complete for Europe, and this report also updates these data.

In particular, the objectives are to:

- Summarize the latest available data on cancer incidence, mortality and survival in Europe
- Consolidate diverse estimates and make them consistent for a cross-country comparison
- Identify commonalities and differences in patterns and evolution of cancer epidemiology across Europe
- Estimate the overall cost of the main cancer diagnoses in those countries in an aggregate and comparable way

1.1.3 The previous report (2007)

In the 2007 report, it was concluded that: cancer incidence is increasing and the reasons for this are multifactorial; mortality is falling or plateauing but is still high; the share of health care expenditure allocated to cancer is significantly lower (4-7 percent), than the share of the burden of cancer, accounting for 16.7 percent of all 'healthy' years lost in the European Union. Indirect costs account for two-thirds of the economic burden of cancer and direct health care cost and drugs account for approximately 7 percent and 13 percent respectively of all health care costs for cancer. In the present update, we review whether the current state of affairs confirms or rectifies these trends [7].

1.1.4 Methods and Materials

All the sources consulted for the previous report were revisited in search for more resent data and information, together with some new sources. Among the most relevant sources for the present study are IARC Cancer Mondial, World Health Organization (WHO), European Network of Cancer Registries (ENCR), Europa.eu and Eurostat, Organization for Economic Co-operation and

Development (OECD), IMS Health, European Cancer Health Indicator Project (EUROCHIP), Eurocare, and the national agencies of the respective countries.

Additionally, a systematic literature search was conducted through the PubMed and MD Consult databases for articles on cancer burden published between January 2006 and May 2008. The following are the search terms used: cancer AND cost OR burden OR incidence OR mortality OR survival WITH/WITHOUT Europe.

1.2 Incidence and Mortality

A comprehensive study conducted in Europe by Ferlay and colleagues in 2004 [3] -and updated in 2006 [2]- presents the latest estimation of cancer incidence and mortality in Europe defined as EU25 plus Iceland, Norway and Switzerland. To include data on Bulgaria and Romania we interpolated the growth in the number of cases in this study with respect to those that the same authors published in GLOBOCAN 2002 [1]. Even though the data collection methodology has changed slightly, and care 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.

In 2006, over 2.4 million new cancer cases were diagnosed in Europe 30, about 10 percent more than 4 years before; while the number of deaths remains practically unchanged; indicating that European all-cancers mortality rate is slowly starting to recede (see Table 1-1). As we will examine in further detail in Section 1.3, this is consistent with the positive trend in cancer survival. The available data suggests that both screening programs and new treatments may account for these trends. Nonetheless, substantial disparities remain across countries, between cancer sites and between men and women. In 2009, WHO's International Agency for Research on Cancer will publish *GLOBOCAN 2005,* with more accurate country-by-country estimations. This will allow for a more complete analysis of recent developments**.**

EU25+CH+IS+NO		Globocan 2002	Ferlay 2006	Change
All cancers but skin melanoma	No of cases	2,138,700	2,351,100	9.93%
	No of deaths	1,188,100	1,192,500	0.37%
Breast	No of cases	277,300	328,600	18.51%
	No of deaths	89,900	87,200	-2.97%
Prostate	No of cases	201,700	311,100	54.25%
	No of deaths	69,300	70,300	1.48%
Uterus	No of cases	85,900	84,900	-1.17%
	No of deaths	26,700	24,200	-9.49%
Colorectal	No of cases	283,600	307,000	8.27%
	No of deaths	142,400	142,700	0.20%
Stomach	No of cases	92,200	81,600	-11.46%
	No of deaths	70,200	58,400	-16.76%
Lung Female	No of cases	60,500	73,500	21.46%
	No of deaths	54,300	65,800	21.11%
Lung Male	No of cases	199,900	198,100	-0.86%
	No of deaths	182,100	175,200	-3.80%

Table 1-1. Number of new cancer cases and deaths in selected cancers 2002-2006

The first point to note is that there are significant differences in developments of mortality and incidence of different cancers. Breast and colorectal follow the general trend with slightly increased number of cases and similar or less deaths. The number of cases of prostate cancer, on the other hand, rose; which partly can be explained by ”wild” PSA screening [8] and an ageing population. Changes in diet and other lifestyle associated risk factors shape the sharp decline in both incidence and mortality due to stomach cancer and the spread of tobacco consumption among women accounts for the dramatic increase of lung cancer in that group.

The second divergence across Europe is geographical. As shown in Figure 1-1, Hungary’s incidence rate almost doubles that of Bulgaria, and the difference between male and female incidence is much smaller among the Nordic countries (like Denmark, Iceland or Sweden) than among Eastern and Southern Europe (like Belgium, France, Italy, Greece or Spain). Part of these disparities may still be explained by the different case-reporting systems and one can always question the accuracy of the estimates but there are also other real underlying factors influencing these outcomes. Screening programs for breast, cervical, and colorectal cancer, for example, help detect more cases earlier. Increased use of PSA may sharply raise the incidence of prostate cancer; still the biology of these “screening” detected cancers may be very different from previously diagnosed prostate cancers. In summary, different factors may increase the incidence, but if there is an effective treatment it may also lead to improved survival [9-13].

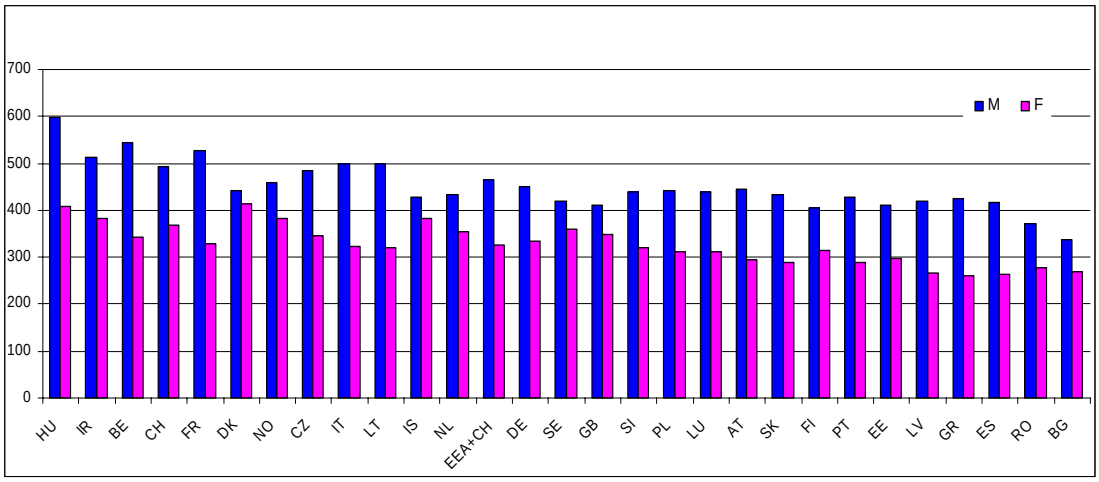

Figure 1-1. Age-standardized incidence rates, 2006 (all cancers but non melanoma) [2]

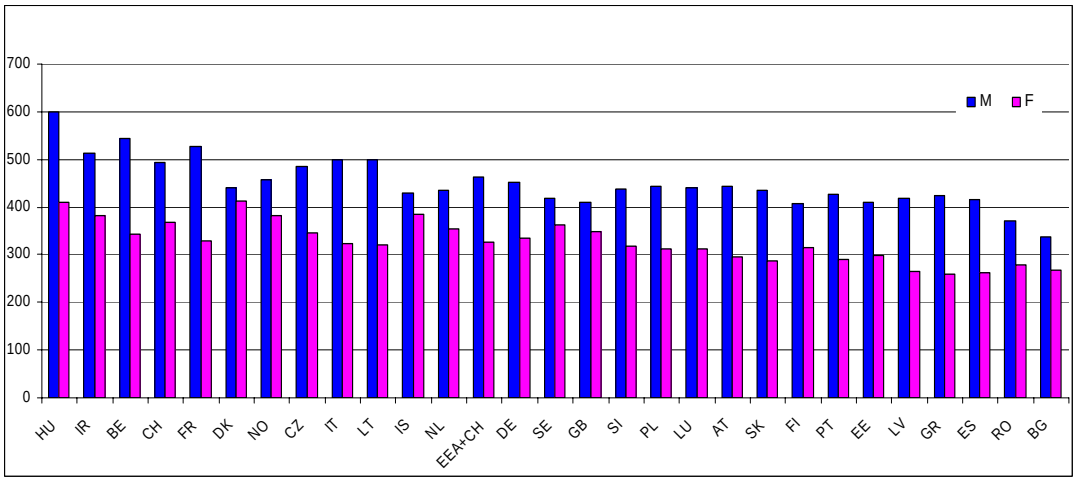

Figure 1-2. Age-standardised mortality rates, 2006 (all cancers but non-melanoma) [2]

Less drastic is the spread in mortality rates as presented in Figure 1-2. There is a clear clustering of countries in Central and Eastern Europe above the general average and the Western European countries. The differential strength of the public healthcare systems; in GDP levels and, thus, in

investment and expenditure in health policies; as well as in legal and administrative frameworks influence these results; as we will further elaborate on in Chapter 4.

1.3 Survival

Compiling data on 5-year survival presents several challenges; if not the least the difficulties to deal with the natural lag between the time treatment and analysis of survival. Nevertheless, Verdecchia and colleagues applied the period-analysis method to EUROCARE-4 data, in order to assess survival challenges in selected European countries in comparison to survival data from the United States[4].

	EUROCARE–4 mean		US SEER-13 registries	
	Relative Survival	95%CI	Relative Survival	95%CI
Testicular	97.3	[96.4–98.2]	95.4	[94.0–96.8]
Skin melanoma	86.1	[84.3–88.0]	92.3	[91.5–93.1]
Thyroid	83.2	[80.9–85.6]	93.5	[92.2–94.8]
Hodgkin's disease	81.4	[78.9–84.1]	80.6	[78.8–82.4]
Breast	79	[78.1–80.0]	90.1	[89.6–90.5]
Corpus uteri	78	[76.2–79.9]	82.3	[81.2–83.4]
Prostate	77.5	[76.5–78.6]	99.3	[98.9–99.8]
Soft-tissue	61.2	[58.3–64.2]	65.1	[62.8–67.5]
Cervix	60.4	[57.7–63.2]	65.8	[64.1–67.6]
Colorectal	56.2	[55.3–57.2]	65.5	[64.9–66.1]
Kidney	55.7	[53.6–58.0]	62.6	[61.3–63.9]
NHL	54.6	[52.7–56.6]	62	[61.0–63.0]
CM leukaemia	32.2	[29.0–35.7]	36	[33.1–39.1]
Stomach	24.9	[23.7–26.2]	25	[23.8–26.2]
AM leukaemia	14.8	[13.4–16.4]	13.9	[12.6–15.2]
Lung	10.9	[10.5–11.4]	15.7	[15.3–16.1]
All cancer Men	47.3	[46.8–47.8]	66.3	[66.0–66.6]
All cancer Women	55.8	[55.3–56.2]	62.9	[62.6–63.2]

Table 1-2. Age-adjusted 5-year relative survival for different cancers, period analysis 2000–02

As seen in Table 1-2, the relative survival is higher in the United States compared to Europe with the exception of testicular cancer, Hodgkin's disease and leukaemia, for which most European countries do consistently better than the US. However, it is important to point out that the SEER-13 data represents 13 regional cancer registries in selected parts of the US population and does not fully cover non-insured or under insured cancer patients.

The European-mean measures are disguising the real variability within the continent that the authors point out. If we consider the variability within Europe, we can appreciate that in some

countries, especially in Northern Europe, all-cancer survivals are almost at the same level as in the US. The gap in cancer survival between Northern and Western Europe compared with Eastern Europe is much more pronounced than that between both sides of the Atlantic (see Table 1-3). This geographical pattern confirms the phenomenon previously described, when examining mortality rates.

		All malignancies men	All malignancies Women
US SEER		66.3	62.9
Five Europe Best-performing	Sweden	60.3	61.7
	Iceland	57.7	61.8
	Finland	55.9	61.4
	Austria	55.4	58
	Belgium	53.2	61.6
Five Europe largest	UK	[40.2-48.1]	[48-54.1]
	Germany	50	58.8
	Italy	49.8	59.7
	Spain	49.5	59
	France	No Data	No Data
Opportunities for improvement	Poland	38.8	48.3
	Czech Republic	37.7	49.3

Table 1-3. Age-adjusted 5-year relative survival in different countries, period analysis 2000–2002 [4]

When we add the time dimension, the prospects are more encouraging. In another study -utilizing the same database- focused on the evolution over time of these survival trends, Berrino and colleagues [5] found that between 1990-1994 and 1995-1999 survival for all cancers increased and between-country differences across Europe narrowed. As can be seen in Table 1-4 the prospects of Hodgkin's disease, breast and colorectal cancer improved and survival for prostate cancer presents the most favourable evolution. The improvements in the outcome of prostate cancer most likely represents a dramatic increase in the number of cases detected by PSA "screening" and does not reflect a true major advance in the treatment of the disease.

5-year relative survival			
	1990-1994	1995-1999	Difference
Prostate	61.4	73.9	12.5
Hodgkin's disease	75.6	80.1	4.5
Colorectal	49.3	53.5	4.2
Breast	75.4	79.5	4.1
Melanoma	82.6	85.4	2.8
Ovary	32	34.2	2.2
Lung	9.2	10.2	1
Testis	94.6	95.5	0.9

Table 1-4. Evolution of 5-year age-adjusted relative survival for 8 cancers, EUROCARE pool [5]

1.4 DALYs

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 costs of treatment and losses of production when people cannot 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 most common measure of the cancer burden is Disability adjusted life years (DALYs). This is a measure combining the burden of mortality and disability, and is developed by the World Health Organization (WHO) and the World Bank. One DALY represents one lost year of 'healthy' life and the burden of disease as a measurement of the gap between actual health status and an ideal situation where everyone lives into old age free of disease and disability. As shown in Table 1-5 in 2002, cancer accounted for more than 10 million DALYs lost in the European countries of this study. On average in all countries, the cancer share is 16 percent but varies from a little more than 11 percent in Estonia to almost 18 percent in the Netherlands.

Country	All Causes ('000)	Malignant Neoplasms ('000)	Share
The Netherlands	1,869	335	17.92%
Czech republic	1,474	264	17.91%
Italy	6,789	1,202	17.70%
Germany	10,414	1,807	17.35%
Denmark	750	128	17.02%
France	7,406	1,260	17.01%
Hungary	1,779	299	16.79%
Belgium	1,358	226	16.64%
Slovenia	282	46	16.33%
Norway	520	84	16.09%
E 28	**65,551**	**10,472**	**15.98%**
Spain	4,952	785	15.86%
Poland	5,832	920	15.78%
Switzerland	799	126	15.74%
Iceland	28	4	15.66%
Sweden	977	153	15.61%
UK	7,555	1,168	15.46%
Austria	970	150	15.43%
Greece	1,393	215	15.40%
Portugal	1,415	216	15.28%
Luxemburg	55	8	14.33%
Slovakia	834	117	14.00%
Ireland	488	68	13.88%
Finland	668	86	12.87%
Lithuania	625	78	12.43%
Romania	4,106	478	11.64%
Bulgaria	1,464	168	11.45%
Latvia	482	54	11.24%
Estonia	264	29	11.15%

Table 1-5. WHO Estimated total DALys per country, 2002

As shown in Table 1-5, in 2002, cancer accounted for more than 10 million DALYs lost in the 28 countries of this study (E 28). Cancer represented 16.7 percent of all DALYs lost in the E 28, thus cancer was the third most prominent disease in terms of overall disease burden, following mental illnesses and cardiovascular disease. [14]. The proportions of Years of Life Lost (YLL) and Years Lost due to Disability (YLD) of a DALY vary considerable depending on disease group; for cancer, YLL represent over 90 percent of the DALYs lost in Europe, YLL represent 70-90 percent of DALYs lost for mental disease, cardiovascular disease and injuries, whereas for respiratory disease YLL represent less than 40 percent of DALYs lost.

	Total DALYs lost	DALY/1000 inh	%
All disease groups	58,807,846	129.7	100.0
Mental disease	14,857,720	32.8	25.3
Cardiovascular disease	10,088,093	22.2	17.1
Cancer	9,839,035	21.7	16.7
Injuries	5,099,011	11.2	8.7
Respiratory disease	3,523,243	7.8	5.9

Table 1-6. Top 5 disease groups in terms of burden of disease in EU 25 in 2002[14]

The clinical and epidemiological evolution of cancer in Europe suggests that we may expect slight changes. According to WHO Statistical Information System (WHOSIS) Query Service, an update of the country-specific DALYs estimates will be released in 2009.

1.5 Economic Burden

The burden to society can also be measured in monetary terms, both in terms of the value of production lost and in terms of resources used for treatment. Direct costs include prevention, treatment and other related costs; while indirect costs include losses of production due to inability to work caused by disease, disabilities and deaths. They may also include the so-called informal care, when relatives take care of the patient. In addition, a patient may often face costs related to the disease, for example travelling to receive treatment, prescription charges, home care and costs related to adjusting to disabilities. Parts of these costs are in some countries borne by society. So, defining the various costs and what should be included in the definition of disease-related burden is not an easy task. The picture of the economic costs of cancer becomes even more complex as it is often difficult to sort out what costs are related to cancer and what is related to other co-morbidities.

1.5.1 Direct Medical Costs

The expenditures on health care in general, and on cancer care in particular, vary greatly within and between countries. The large variations in resources available for providing treatment within and between countries, lead to great inequalities in access to treatment. Even though cancer causes a large economic burden to society, few countries have actually calculated or estimated how large these costs really are. It is often difficult to say which costs are related to cancer vis-à-vis other diseases. It is also difficult to compare the costs across countries as the burden in terms of incidence, prevalence and mortality in the approximately 200 kinds of cancer differs from country to country. The access to treatment is also unequal across countries, largely related to

resources being available, but also provision of equipment, accessibility of drugs and the organization of the provision of treatment [15]. Following more expensive treatment methods, countries adopting these methods early may have higher costs.

Jönsson and Wilking [7] estimated the average expenditure on cancer care in Europe in 2004 to €125 per capita or 6.4 percent of the total health care costs. In 2005, Bosanquet et al [16] estimated the share of total health care costs devoted to cancer care in Czech Republic, Hungary and Poland to be about 5 percent. Given the lower national expenditures on health care in these countries the amount of money spent on cancer care is far below the estimated European average. The direct costs of cancer in Czech Republic is estimated to be €72 per capita, in Hungary, €61 per capita and in Poland only €41 per capita (Table 1-7). Most of the remaining Central and Eastern European countries joining the EU in 2005 are estimated to have cancer expenditures at 3-5 percent of the total health expenditures [16]. Many of the countries in Central and Eastern Europe have even lower expenditures on health care, which naturally leads to less resource available for cancer care.

In Germany, the total health care expenditures increased with 7.8 percent between 2002 and 2006. In the same time period, cancer expenditures increased with 23.5 percent. This led to a raise in the share of cancer of the total expenditures on health care from 6.3 percent to 7.2 percent [17]. The per capita expenditure on cancer treatments also increased from €170 in 2002 to be estimated to €216 in 2007 (Table 1-7).

In Finland, the costs of cancer treatment have increased dramatically in the past ten years. From 1996 to 2004, the costs rose by 34 percent and between 2002 and 2004 by 8.9 percent, in 2004-year prices [18]. Still, the cancer share of the total health expenditures was lower than in any of the other countries we found reliable sources for, 4.3 percent. The per capita direct cost of cancer would be €93.6, with the same proportion in 2007 (Table 1- 7).

In France, the National Institute of Cancer has estimated the direct cost of cancer to ascend to €11 billion in 2004. This year additional resources were granted through the National Cancer Plan, launched by the French President in 2003. In this cancer plan €1.7 billion extra were allocated to research, prevention and treatment of cancer in France during the following two years (2003-2005). If we assume the same share of health care expenditures devoted to cancer care, the direct expenditures on cancer would have risen to €204 per capita in 2007. Considering the additional money in the cancer plan, this figure is probably an underestimation.

In the Netherlands, the total direct cost of cancer amounts to €2,477 million in 2005, which is 5.2 percent of the total costs of health care and €152 per capita. This is an 11.7 percent increase measured in 2005-year prices. The cancer share of the total health care expenditures also increased from 5.0 percent to 5.2 percent [19]. If the share of health care expenditures used on cancer remains at the same level as 2005, the per capita expenditure would increase to €170. In contrast to the UK and France, the Dutch Cancer Control Plan for 2005-2010 did not commit to any additional resources [20].

In Sweden, the direct costs of cancer rose by a little more than 40 percent between 2002 and 2004 [21]. In the same time period, the total expenditures on health care increased by 8 percent [22]. This expansion has resulted in a share in cancer of 7.2 percent of the total health expenditures, which in 2007 would mean €207 per capita.

In relation to the societal burden of cancer and large indirect costs, the resources allocated to prevention, screening and treatment of cancer are small. As we have seen in the estimates of expenditures above, we see evidence of cancer care receiving an increasing share of the total health care expenditures. We also see in other countries, where national cancer plans have been developed and implemented, that cancer care is given more attention. Although no clear budget commitments are made in most of the cancer plans, they point in a direction of higher priority to prevention, screening and treatment of cancer [23].

There are, however, also examples where reforms in cancer care have been granted additional resources in the cancer plans. In the UK, an addition of £570 million per year was allocated to cancer care by 2003/2004 and in addition £50 million a year was earmarked for palliative care in 2004. In reality the spending on cancer increased more than projected in the cancer plan, as cancer received a budget addition of £693 million (€472 million). This provided an additional budget of 27 percent. The total expenditures on cancer care is in 2005/2006 estimated to be about £4.35 billion (€3 billion) a year [24].

Large investments in cancer care were also provided in the French National Cancer Plan. Over the period of five years between 2003 and 2007, cancer care was provided with a budget addition of €1,7 billion, as mentioned above [25]. In several other countries there are also extra money directed towards specific items, often for investments in human resources and research [23].

There are not sufficient and reliable data for all countries regarding the expenditures on cancer care. For the countries with no data available we estimate that the direct costs of cancer is 6.4

percent of total health care expenditures, which is the average share of the countries with available data. The cancer share of total health expenditures in all countries together is estimated to 6.3 percent. The resources spent on treatment of cancer patients in Europe in estimated to €148 per capita (Table 1-7).

	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%*	207
Belgium	9.6	29,863	2,821	6,4%*	181
Bulgaria	7.7	5,608	730	4%[16]	29
Czech Republic	7.1	14,820	1,441	5.0%[16]	72
Denmark	9.4	15,635	2,872	6,4%*	185
Estonia	5	1,200	894	3-5 %[16]	36
Finland	7.5	11,488	2,177	4.4%[18]	95
France	11.2	196,469	3,099	6.6% [26]	205
Germany	10.7	247,058	3,001	7.2%[17]	216
Greece	10.1	27,392	2,452	6,4%*	158
Hungary	7.8	12,348	1,227	5.0%[16]	61
Iceland	9.4	936	3,042	6,4%*	195
Ireland	8.2	12,922	2,996	6,4%*	193
Italy	8.9	132,778	2,245	6,4%*	144
Latvia	6.4	2,094	918	3-5 %[16]	37
Lithuania	5.9	2,980	880	3-5 %[16]	35
Luxembourg	7.7	2,535	5,324	6,4%*	342
Netherlands	9.2	49,553	3,029	5.6% [19]	170
Norway	9.1	19,563	4,179	6,4%*	269
Poland	6.2	31,537	827	5.0%[16]	41
Portugal	10.2	20,073	1,894	6,4%*	122
Romania	5.5	11,936	553	3-5 %[16]	22
Slovakia	7.1	6,516	1,208	3-5 %[16]	48
Slovenia	8.5	3,776	1,878	3-5 %[16]	75
Spain	8.2	97,582	2,194	6,4%*	141
Sweden	9.2	26,333	2,890	7.2%[21, 22]	207
Switzerland	11.4	29,727	3,959	6,4%*	254
United Kingdom	8.2	143,223	2,356	5.6%[24]	132
Europe		1,182,725	2,336	6,3%	148

** 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, Sweden and the United Kingdom.*

Sources: 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

1.5.2 Hospitalizations

Hospitalization is the largest single item of the direct costs in cancer care. Improvements in treatment methods have reduced the length of stay for hospitalized patients. Although the absolute number of patients being hospitalized is increasing, although the total volume of yearly bed days is decreasing. In Figure 1-3 we see the example of Sweden where the number of bed-days for cancer patients per year has decreased by almost 15 percent from 1998-2006. this follows the general trend of the volume of bed days per year for all patients. In Italy we see (Figure 1-4), a similar decrease in the average length of stay; although not as dramatic as in Sweden. It should be noted that this is not to be interpreted as absolute savings in the treatment of cancer. It should rather be seen as a shift in the organization of the provision of treatment toward outpatient care. Much of the savings in average hospitalization cost per cancer patient is a result of investments elsewhere, for example newer treatment methods.

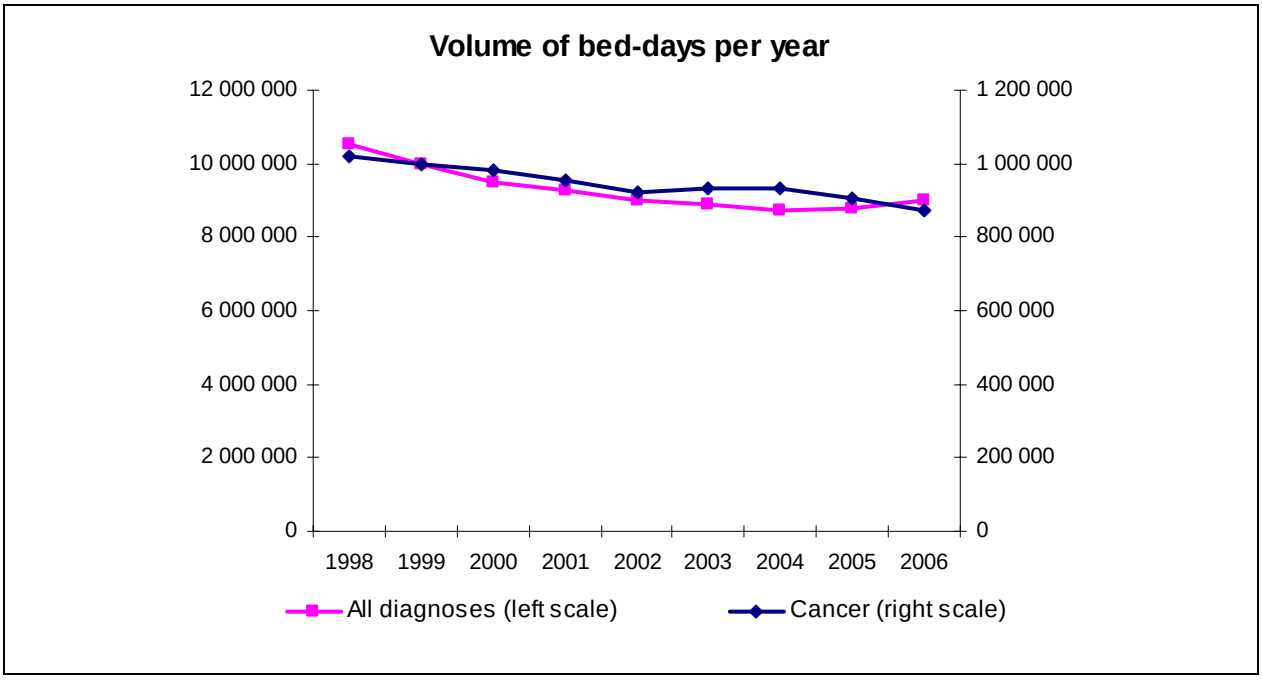

Figure 1-3. Volume in bed-days per year in Sweden, 1998-2006

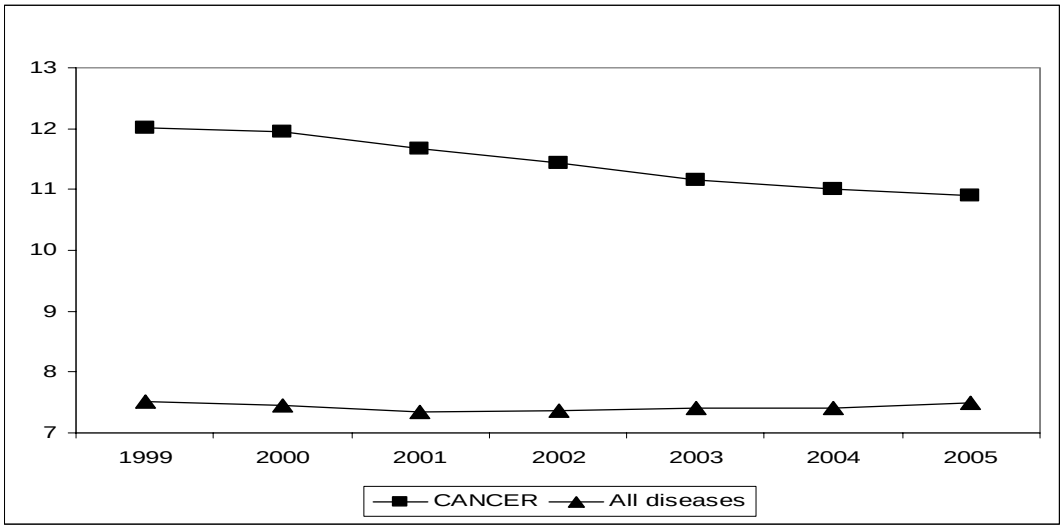

Figure 1-4. Average length of stay hospitalized in cancer versus all diseases in Italy 1999-2005

1.5.3 Drugs

The cost of drugs is making up an increasing share of the total direct costs of cancer. The primary reasons for this are the new indications for already approved drugs and the introduction of new drugs costing significantly more than most of the older cancer drugs. Although the costs of cancer drugs will continue to increase, it is not expected to be at the same pace as in the past ten years. When patents for drugs introduced in recent years will expire, generic versions will be available putting a downwards pressure on the price. Also, several new drugs are introduced in same indications as previous drugs, which may increase the number of patients treated, but first of all there will be a substitution of one drug for another at a similar, or even lower, price. In Sweden the cost of cancer drugs are expected to almost double from 2.5 billion SEK in 2007 to 4.8 billion SEK in 2022. This is to be put in a perspective of a growth rate at 15-20 percent per year in recent years (See Figure 1-5)[1].

[1] Note that not all drugs are included in the forecast presented in Figure 1-5

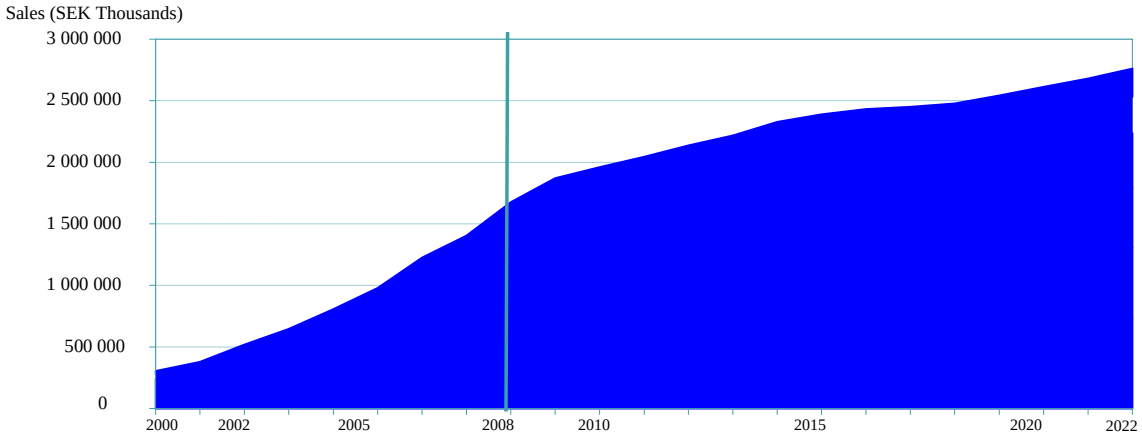

Figure 1-5 Sales and forecast of selected cancer drug sales in Sweden 2000-2022

One of the challenges in estimating and reporting comparing cost of cancer drugs in different countries is that payment system of drugs varies. For example, in some cases cancer drugs are used as hospital drugs and therefore paid through the financing of inpatient care either per diem (based on day of hospital stay), through a global hospital budget, or through a Diagnosis Related Groups (DRG) system. In the last case, the budget is allocated for hospitalisation costs based on a classification of patients in different disease categories. In other cases, drugs are used in hospital outpatient departments and reimbursed separately. In some cases costs could be reported with or without costs for distribution by wholesalers and pharmacies. In some cases taxes may also be added.

Per capita drug sales are highest in, France, Switzerland and Austria and lowest in Poland, Czech Republic and the United Kingdom (Figure 1-6). The reason for differences in the per capita sales figures may either be due to price and/or actual quantity differences.

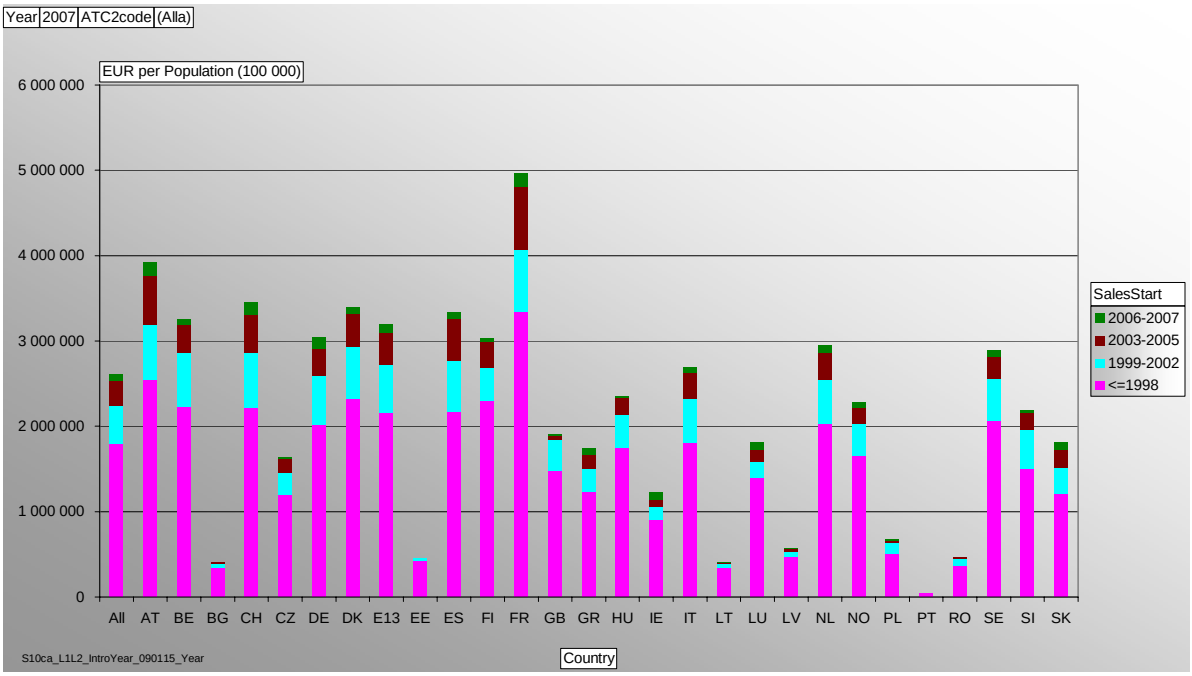

Figure 1-6. Sales of cancer drugs in 2007 in different European countries in Euros (€)/100,000 inhabitants in different European countries. Please note that for Greece, Ireland, Luxembourg and Portugal data for either hospital or retail sales are missing.

1.5.4 Indirect costs

If there is a lack of internationally comparable data on direct costs of cancer, there is even less information on what indirect costs cancer brings to society. It is difficult to estimate the indirect costs of cancer, as there are more than 200 different forms of cancer causing varying losses of production. The indirect cost of individual cancer types depends on the age distribution of the patients, since patients above retirement age do not incur cost of production loss. There are great differences in the distribution of indirect costs between different types of cancer, with breast and lung cancer being the most important in terms of working years lost in for example Germany. These two cancer types are followed by leukaemia, which often occurs in children and therefore leads to many working years lost, while prostate cancer, which mainly occurs in elderly men, is not as important in terms of lost working years.

Data from Germany show that 490,000 working life-years were lost due to cancer in 2004. This represents 11.6 percent of all life-years lost in the German working population. Multiplying the working life-years lost with the average labour cost in Germany (€45,000) gives a total of €22 billion. This is almost 30 percent higher than the estimated direct costs of cancer in Germany.

The indirect cost of cancer in Sweden was estimated to be €1.8 million in 2004; which is at the same level as the total direct costs. As shown in Table 1-8 Table 1-, the vast majority (78 percent) of the indirect costs are due to mortality.

Direct costs	€ million
Health care costs	1,572
Drug cost	218
Secondary prevention	22
Sum direct cost	***1,812***
Indirect costs	
Mortality	1,412
Sick-leave	178
Early retirement	209
Sum indirect cost	***1,799***
Sum total cost	**3,611**

Table 1-8. Direct and indirect costs of cancer in Sweden 2004 [21]

It is important to stress that the distribution of direct and indirect costs differs greatly between different kinds of cancers. An estimation of the costs of breast cancer in Sweden concluded that SEK 2.1 billion or 70 percent of the total costs of SEK 3 billion were indirect costs [28]. Both the German and the Swedish data do only take production losses into account. They exclude other indirect costs, such as informal care. Similar data is not available in the other countries of this study. However, it is important to keep in mind that the indirect costs are as high as, or even higher than the direct costs. These indirect costs must not be forgotten when assessing the economic burden of cancer to society. The improvements in cancer treatment have lead to patients having better chances of surviving and also to quicker recovery. This means that indirect costs become lower in relation to direct costs.

1.5.5 Trends in costs of cancer treatment

The costs of cancer are increasing rapidly. There are a number of reasons for this; an improved health cancer system makes people live longer, and thus increasing their risk of being diagnosed with cancer at some point in their lives. The improved treatment may lead to prolonged survival and therefore longer periods of treatment. The improved treatment methods are also becoming more and more expensive pushing costs. In many countries, cancer has received increasing attention and higher priority. This is evident as many countries have developed dedicated plans for controlling and managing cancer burden. Although most of these cancer plans do not commit to any direct budget additions, higher priorities tend to lead to increased resources.

Over the last decades we have seen enormous progress in cancer treatment, as well as within other disease areas. Probably, the most important progress has been the development of new drugs, providing opportunities for cure, prolonged live and pain relief. The development of new drugs has been enabled by large investments from both public and private sources, often in fruitful collaboration. The investments in cancer research has been remarkable in recent years [7]. These investments in cancer R&D have resulted in a number of new drugs have reached the market, often indicated for limited patient populations (at least at launch). With few exceptions these new often very innovative drugs, have come at high prices. This, in combination with better informed patients and a revolution in the way the general public can access information about new technologies through the internet, has lead to a new situation with respect to cancer treatment. The medicines share of the direct expenditures on cancer care has increased rapidly in recent years. Jönsson and Wilking estimated that drugs constituted on average 13 percent of total cancer costs in the EU in 2004 [7]. The cost of cancer drugs in France increased with almost 50 percent from 1999-2004, raising the share of cancer of the total medical costs from 19 percent to 23 percent [26]. In Sweden, cancer drug costs increased as share of all drug costs from 8.7 percent in 2002 to 12.0 percent in 2004 [21]. Similarly, in Finland, the direct costs of cancer increased with 33 percent and the costs of cancer drugs increased with 128 percent [18].

1.5.6 Budget allocation

The improvements and increased efficiency in health care and cancer treatment shift the distribution of costs. Fewer and shorter periods of hospitalisation become less important in relation to -for example- outpatient treatment and drug costs. There is also a shift towards higher direct costs in relation to the indirect costs. This is a result of improved methods of treatment reducing the risk of dying and shortening the time of disability. Still, the indirect costs, and the potential to reduce these must also be considered when assessing the economic effects of the development of new treatment methods.

The distinction between inpatient and outpatient care is becoming less interesting as drug administration, radiotherapy and surgery increasingly is performed in outpatient settings. More relevant becomes the distribution of resources between prevention, early diagnosis, curative treatment and palliative care. It is important to look at this distribution of resources for each specific type of cancer, as it differs greatly.

It is also important to observe that it is not only the cost of drugs that is increasing in cancer treatment. Investments in -for example- radiotherapy may also lead to considerable increased

cost of treatment, but may also be cost effective in the long term. New equipment may be cost effective if used for certain groups of patients, but not in others. Large investments in radiotherapy equipment may be difficult to incorporate in a short term budget.

Cost for treatment -using new drugs- must also be seen in relation to the cost of preventative measures. In Sweden the National Board of Health and Welfare has recommended inclusion of vaccination against HPV virus in the general vaccination program for girls. The cost per vaccination is SEK 3,000 each, giving a total cost of SEK 200 million per year. This should be put in relation to the hypothetic scenario that a medicine for treatment against cervical cancer with the same effect on survival is developed and proves to be more cost effective, the resources spent on vaccination is wasted. The Pharmaceutical Benefits Board has approved HPV vaccination with Gardasil and Cervarix after a cost effectiveness assessment. SBU on the other hand, is more hesitant, as the clinical effect is uncertain.

It is a critical challenge in prioritization and allocation of budget resources, not only within the health care system, but also in other parts of the welfare system and society. Investments and increased costs within one area may lead to savings in others, i.e. more efficient, but also more expensive drugs may save large costs for sick leaves as people can get back to work sooner. There is still often a so called “silo mentality“ in health care planning [29].

2 Medical review

2.1 Summary

- Cancer treatment today is characterized by multimodal treatment approach, using surgery, radiotherapy and a rapidly increasing number of available anti tumour agents. Optimal treatment requires multidisciplinary teams, including surgeons, radiotherapists, medical oncologists, diagnostic radiologists, pathologists, specialized nurses and psychosocial support.

- Most anti tumour agents are introduced in patients with late stage (metastatic) disease. In many cases, efficacy in metastatic disease translates to increased cure rates when the agent is introduced in the adjuvant setting in conjunction with surgery.

- Anti tumour agents are used as adjuvant treatment with surgery and/or radiotherapy in an increasing number of situations, improving cure rates significantly.

- Traditional anti tumour agents have been generally cell toxic, with often severe side effects. Progress in molecular medicine has enabled the development of new agents that target more disease specific mechanisms and 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 cancer 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 in some instances. Gene/protein expression analyses of tumours are likely to improve accuracy in the treatment offered to individual patients in the near future.

- New diagnostic tools including functional imaging are increasingly used in order to evaluate early response and therapy effects.

2.2 Introduction

Agents that inhibit cancer growth (chemotherapy) were first discovered in the 1940s with the alkylating agents and antimetabolites- two groups of agents still in use [30, 31]. During the 1950-70s, further classes of cell toxic agents were discovered and it became clear that chemotherapy could 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, with the aim of decreasing the risk of recurrence of the disease. The potential value of adjuvant chemotherapy after surgery was first demonstrated in 1974 in osteosarcomas [32, 33].

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. Cancer treatment has become a multimodality treatment, 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 severe side effects and the development of drug resistance of tumours.

As cancer patients 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 improved broad spectrum antibiotics has enabled intensified treatment schedules with 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 1980s, drug discovery in oncology was dominated by academia and publicly sponsored institutions like the NCI in the US. The last decade has seen a dramatic change in drug discovery and advances in biological research, enabling the identification of more specific targets of intervention and efforts can be 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 (NIH/NCI) screening programs in the 1970 and -80s,

to a major international industrial effort increasing the impetus of drug discovery and drug development in oncology. Of biotech companies in the US today, half are focussing on cancer. According to a recent review, there are about 400 new cancer agents in clinical trials[34].

The oncologic speciality has entered an exciting new phase with a rapidly expanding arsenal of new agents. In the light of recent advances, it is relevant to evaluate to what extent these advances reach their full clinical usefulness and what obstacles and factors there may be, affecting the speed of uptake of new treatments, after proving clinical efficacy and acceptable safety.

The following sections review some of the more significant advances seen in the management of cancer patients, from improvements in diagnostic techniques to advances in the medical treatment of cancer.

2.3 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 the efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980s and 1990s, such as Computerized Tomographic Scanning (CT) and Magnetic Resonance Imaging (MRI) have greatly improved the diagnostic accuracy. Other methods, such as ultrasound and bone scintigraphy also play an important role as diagnostic tools, assisting in directing local therapy, as radiotherapy. Currently, positron emission tomography (PET) in combination with CT (PET/CT) is being introduced in clinical practice with the advantage of being more sensitive than earlier alternatives in differentiating between viable and non-viable tumour tissue. The development of improved radiological techniques, with the ability to accurately tell responders from non responders after only 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. With an increasing number of high cost drugs, limiting the number of patients that receive treatment will also reduce the healthcare costs.

Advances in molecular medicine, e.g. gene- and protein profiling techniques, have contributed to increased understanding of cell and cancer biology, but 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 certain tumour-specific characteristics. In some cases it is also possible to predict if an individual tumour will respond to certain

treatments [35]. Pharmacogenomics has become an important field in cancer research and drug development. Soon, pharmacogenomics together with analyses performed on sampled tumour material, to determine potential response to treatment (chemo sensitivity tests), will be available on a larger scale in the clinical setting. This will provide a much more individualised approach to treatment, with better chances for improved outcomes.

Less than 2 percent 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 points of intervention. Already, the individual protein patterns of different types of tumours are being mapped and it has been demonstrated that patients with a specific type of cancer have certain protein patterns present in blood, indicating potential for diagnostic purposes[36].

2.3.1 The basis for recent advances in the medical treatment of cancer- understanding cell biology, tumour cells and their microenvironment

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

Some individuals are genetically predisposed to develope cancer due to altered genes that normally act as gatekeepers against cancer (tumour suppressor genes). The development of invasive cancer is a process with many steps, with an accumulation of genetic changes thought to occur over a long time period (5-20 years) [37].

Intense research during the last century has increased knowledge about the human cell and its molecular mechanisms, which has led medical oncology to a new phase in the 21st century. Increased knowledge of cancer biology has led to a clear trend where highly cell-toxic treatments are starting to give way to more disease-specific agents, targeting particular pathways in tumour development and progression.

The main areas where new agents have been developed and now are used in clinical practice:

- 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

Most chemotherapeutic agents, developed until the 1990ies, act by inhibiting DNA replication in some way and in many cases the main mechanism of action has been elucidated long after the introduction of the agent in the clinical setting. In some cases the mechanisms of action of older chemotherapeutic agents still remain unclear. In 1984, it was shown that anthracyclines, one of the most efficient class of compounds in conventional chemotherapy at the time, worked by affecting topoisomerase activity [38], fuelling the interest in finding other agents with similar mechanisms of action. In the 1990s, the topoisomerase inhibitors irinotecan and topotecan were introduced with significant clinical impact in for instance colon cancer. During the 90ies the central role of microtubules in cell division, proliferation and chemotaxis was evident, and several agents, taxans (paclitaxel and docetaxel), and vinca alkaloids (vinblastine, vincristine, and vinorelbine) derived from plant toxins were developed, affecting microtubule dynamics. Since their introduction in the 1990s, these agents have had an important impact on the treatment of cancer, with impressive responses in a wide variety of tumour forms. There are also several new agents in clinical trials with similar antitumour mechanisms, for instance a group of compounds called epothilones[39].

New antimetabolite agents have also been introduced during the last decade with an important clinical impact-gemcitabine- with efficacy in pancreatic cancer [40] and non-small cell lung cancer –pemetrexed- with a efficacy in non-small cell lung cancer [41]. Capecitabine is a drug in an oral formulation, similar to 5-FU, with a wide range of indications,, enabling many patients to take their treatment at home, resulting in increased cost effectiveness.

2.3.2 Targeting hormones, growth factors & cell signalling pathways

Cells are not static, independent units, but are interacting components that must be able to respond to a wealth of stimuli, ranging from nerve signals and hormones to signals of local tissue damage. Intracellular signal transduction pathways respond to proteins, amino acids, lipids, gases and even light. Binding to corresponding receptors activates various enzyme systems, ultimately resulting in changes in cellular behaviour or growth. Signalling pathways that are critical in cancer growth have been investigated as therapeutic targets.

2.3.3 Endocrine therapy

In many ways, the introduction of endocrine agents represents the first steps from highly toxic agents, to treatments focused on well-defined molecular targets. Interfering with the production of hormones or blocking their action through drug therapies have become cornerstones in the treatment of both breast and prostate cancer. Tamoxifen, which acts by blocking oestrogen stimulation, was the first hormonal agent to be widely used in breast cancer. Since its introduction in the 1970s, tamoxifen has proved valuable in the treatment of metastatic breast cancer, as well as in adjuvant treatment after surgery, decreasing the risk of relapse and as a preventive agent in high risk populations. The efficacy and relatively low toxicity of tamoxifen has led to the development of a large number of similar drugs. Increased knowledge of hormone synthesis and metabolism has led to the development of several new classes of hormonal agents.

In breast cancer, a number of aromatase inhibitors (e.g. anastrozole, letrozole and exemestane) have been introduced in the last decade and together with other agents with similar mechanisms of action (e.g. fulvestrant, megestrol) they constitute valuable therapeutic options in metastatic breast cancer. Aromatase inhibitors are also gaining acceptance as adjuvant treatment in postmenopausal women. In prostate cancer, anti-androgens (e.g. flutamide, bicalutamide and nilutamide) have been developed as an alternative to testicular ablation. Additionally, gonodotrophin releasing hormone analogues (e.g. goserelin, leuprolide), which block the production of testosterone, have been developed to achieve chemical castration. Recent research has also focused on the potential for hormonal agents to prevent cancer.

2.3.4 Inhibiting growth factors and signal transduction systems

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. the skin, bone marrow and intestines). Growth factors stimulate cell growth by binding to cell surface receptors, starting a cascade of activity of specific enzymes in the cell. Many cancers over express growth factor receptors or have mutations that lead to defective growth signal transduction, resulting in abnormal growth as well as invasion of normal tissue.

There are two main groups of agents that have demonstrated efficacy in interfering with growth factor signalling. Monoclonal antibodies against growth factors and/or their receptors and small molecular drugs that block the tyrosine kinases which most growth factors exert their effects through. 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 aka

HER1/erbB), vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor and insulin-like growth factor (IGF-1) receptor.

Cetuximab, a monoclonal antibody developed against EGFR, has demonstrated efficacy in metastatic colorectal cancer by increasing time to disease progression [42]. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients with advanced head and neck tumours [43] Tyrosine kinase inhibitors against the EGFR pathway have also been introduced. Erlotinib [44] has demonstrated efficacy and increased survival as monotherapy in non-small-cell lung cancer, and gefitinib [45] has demonstrated efficacy in a subset of patients with the same disease. Several clinical trials are ongoing in other tumour types. The latest drug to be approved in colorectal cancer is panitumumab. This is also a monoclonal antibody developed against the EGFR. It has been shown that therapeutic effect of this molecule, and also cetuximab, is seen in a specific subpopulation of patients i.e. those patients whose tumours express a non mutated version of the oncogene KRAS. (wKRAS) [46].

Approximately 20-30 percent of all breast cancer tumours over express the HER2 receptor, and treatment with the monoclonal antibody trastuzumab directed against the receptor has led to markedly prolonged survival in metastatic disease [47]. Patients' HER2 status is determined through a diagnostic test, thereby making testing of patients an important step in determining eligibility for treatment. Adjuvant treatment with trastuzumab results in an approximately 50 percent reduction in recurrence of the disease in patients with HER2-positive disease [48, 49].

There are now also new options available for patients that develop resistance to trastuzumab. Lapatinib, a small molecule interaction with both the HER2 and the EGF receptor has shown promising activity and is now also being tested up front in patients with HER2 positive primary breast cancer. Several other new drugs, with HER2 as target are under development.

Chronic myeloid leukaemia was the first malignant disease, for which a characteristic genetic abnormality, the Philadelphia chromosome (1960), was described[50]. In the 1980s, 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 chronic myeloid leukaemia. In the late 1990s, imatinib, an agent inhibiting BCR-ABL activity, was developed [51]. Treatment with imatinib results in complete responses in 80 percent of patients[52]. 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 [53]. Imatinib also

inhibits another cell enzyme, C-KIT, which is mutated in 95 percent of patients with gastrointestinal stromal tumours. Treatment with imatinib results in long-lasting tumour regression[54] and has been an enormous step forward, since the disease does not respond to conventional chemotherapy. For patients that has become resistant to imatinib there are now several new therapeutic options including dasatinib and nilotinib [55].

The agents that inhibit growth factors and their signal transduction pathways represent a new class of antitumour agents and their place in the clinical setting continues to evolve. In some cases like gastrointestinal stroma 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. Present data seem to 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) [56, 57]. The additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies does, however, need to be determined. Currently, data is indicating increased efficacy, but also increased side effects, when combining some of these agents.

Another key issue with these agents, as with conventional chemotherapy, is the ability 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 but 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, women and patients whose tumours had particular histological characteristics) were more likely to respond to treatment [58]. Genetic analysis has also led to the identification of mutations in the EGFR that correlate to response to gefitinib [59].

Generic name	Trade name	Drug class	Target	Year of approval
Trastuzumab	Herceptin	Antibody	HER2	1998
Imatinib	Glivec	small molecular drug	bcr-abl, ckit	2001
Erlotinib	Tarceva	small molecular drug	EGFR	2004
Cetuximab	Erbitux	Antibody	EGFR	2004
Bevacizumab	Avastin	Antibody	VEGF	2004
Sorafenib	Nexavar	small molecular drug	VEGFR, PDGFR	2005
Sunitinib	Sutent	small molecular drug	VEGFR, PDGFR	2005
Panitumumab	Vectibix	Antibody	EGFR	2007
Temsirolimus	Torisel	Small molecule drug	mTOR	2007
Everolimus		Small molecule drug	mTOR	2007
Pazopanib		Small molecule drug	VEGFR, PDGFR	2007

Table 2.1. Agents inhibiting protein kinases approved for use in oncology

2.3.5 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, strike a fine 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 [60]. We now know that tumours will not grow beyond 1-2 mm[33] if they are unable to develop 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) that were not previously known[32]. 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 [61].

Several growth factors are involved in angiogenesis but VEGF has been identified as the most important in many tumour forms. Both monoclonal antibodies against VEGF and tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed. Bevacizumab, a monoclonal antibody against VEGF, has demonstrated increased survival in patients with metastatic colon, breast and lung cancer [62-64].

In renal cancer, not responding to conventional chemotherapy, bevacizumab has extended the period of time during which the cancer is not growing [65]. Bevacizumab represents an important breakthrough in cancer therapy because it is the first agent in this new class of drugs that show impressive response and efficacy over a range of tumours. Several studies are ongoing to

investigate the effects of bevacizumab on other tumour forms, in earlier stages of disease and as an adjuvant agent, both as monotherapy and in combination with other agents. Two agents, sorafenib and sunitinib malate inhibiting tyrosine kinase targeting the VEGF receptor pathway, have recently been approved and have demonstrated efficacy in a variety of tumour forms, such as renal cancer [66, 67]. Several new agents are also in late clinical trials. It has also been shown that continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has an effect on tumour angiogenesis, thereby inhibiting tumour growth [68].

As with other new classes of agents, the final place for anti-angiogenesis treatment in the management of cancer remains to be seen. The ability to predict which patients will benefit from this type of treatment 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. Trials are also ongoing to determine the role of angiogenesis inhibition in disease prevention and in early disease stages.

2.3.6 Biotherapy

In the 1970s, the hybridoma technique [69] enabled mass production of antibodies with a single binding sites-monoclonal antibodies. 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 inefficiency of the antibodies and the development of human antibodies against murine antibodies, leading to increased elimination. The development of antibodies where the majority of the molecule is of human origin and only the binding fraction is murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of antibodies makes them attractive therapeutic options, with a number already on the market (Table 2.2) and more than a dozen in late-phase clinical trials.

Several of the antitumoural agents that have been introduced in recent years are antibodies, belonging to the class of drugs referred to as bio therapeutic agents. The development of clinically effective antibodies illustrate the difficulty in developing clinically effective agents and perhaps above all, the very long time required for a drug to be developed from the bench to the patient. As key problems have been identified and overcome, the development of a large number of new antibodies may be very rapid.

Generic name/Tradename	Indication	Year of first approval
Rituximab/MabThera	NHL	1997
Trastuzumab/Herceptin	Breast cancer	1998
Gemtuzumab /Mylotarg	Acute myeloid leukaemia	2000
Alemtuzumab/Campath/MabCampath	Chronic lymphocytic leukaemia	2001
Ibritumomab tiuxetan/Zevalin	Non-Hodgkin's lymphoma	2002
Tositumomab/Bexxar	Non-Hodgkin's lymphoma	2003
Bevacizumab/Avastin	Colorectal cancer	2004
Cetuximab/Erbitux	Colorectal cancer	2004
Panitumumab/Vectibix	Colorectal cancer	2007

Table 2.2. Monoclonal antibodies approved for use in oncology.

In 1997, the first monoclonal antibody (rituximab) was introduced in oncology, approved for the treatment of non-Hodgkin's lymphoma, fuelling renewed belief in antibodies as an important treatment option in oncology. It was not long before the first antibody for solid tumours, trastuzumab, was approved which has demonstrated impressive results in metastatic disease and as adjuvant treatment in breast cancer [47-49].

One of the challenges in developing effective antibody therapies is finding parts factors in/on the tumour cell that can be targeted, differing from normal cells. Targets other than tumour cell surface structures, have proven successful, as bevacizumab demonstrates efficacy in a broad range of solid tumour forms (colon, breast, lung and renal cancer)[62-65].

The binding of radionuclides, immunotoxins or chemotherapeutic agents to the antibody may also enhance the effect of antibodies. Ibritumomab tiuxetan, an antibody targeting CD20 with an attached radionuclide is one example.

2.3.7 Advances in supportive drug treatment

As survival rates of cancer patients have increased, the development of new classes of 'supportive drugs' has been essential. These drugs enable intensified treatment schedules and increased quality of life for patients, suffering from adverse symptoms of cancer or its 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, all of which can be ameliorated by supportive drug treatment.

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, in many cases fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but new drugs (e.g. epoetin alpha, epoetin beta, erythropoetin) that increase the production of red blood cells have been developed. In addition, chemotherapy treatment is often associated with bone marrow depression leading to anemia, neutropenia and thrombocytopenia which in turn may delay further chemotherapy treatment. The development of erythropoietin, G-CSF (filgrastim, pegfilgrastim), broad spectrum antibiotics and platelet transfusion techniques has decreased morbidity and mortality in conjunction with treatment and has also enabled intensified treatment schedules, increasing cure rates.

During the last 10 years, several new agents have been developed to prevent nausea (e.g. ondansetron, granisetron) Treatment of bone metastasis is another field where new drugs have been introduced. Bisphosphonates, reduce the risk of skeletal events (fractures) as well as providing relief from the pain caused by skeletal metastases.

2.3.8 Advances towards curing cancer

Although cancer is a common disease, affecting roughly every third person during their lifetime, approximately 50-60 percent 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 of oncology. In most tumours, stepwise and relatively modest improvements in disease management have, over time, resulted in impressive increases in the proportion of patients considered ‘cured’ of their cancer. For instance, overall breast cancer mortality in the USA and UK has been reduced by 25 percent from the 1980s to 2000 [70]. This progress is to some extent the result of screening programs, enabling earlier detection of the disease, but is also a true reduction in mortality due to improvements in adjuvant treatment. Anthracycline based polychemotherapy reduces the annual breast cancer death rate by about 38 percent for women younger than 50 years of age and by about 20 percent for those of age 50-69 years. Additional use of 5 years of tamoxifen treatment in ER-positive disease results in a reduction of the annual breast cancer death rate by 31 percent [71]. Improved chemotherapeutic regimes have increased survival further and recently, adjuvant treatment with trastuzumab in patients with HER2 positive disease

has indicated a 50 percent decreased relapse risk and a 33 percent reduced mortality risk after 3 years [48, 49]. Considerable progress has also been made in other major tumours. In colon cancer adjuvant chemotherapy have reduced mortality with 20-30 percent [72-74] and chemotherapy in the metastatic setting has four fold increased average survival, from 5 to 20 months in 15 years [62]. In other diseases like aggressive non-Hodgkin's lymphoma (NHL), the combination of CHOP plus rituximab results in a five year survival rate of 58 percent in patients over 60 years [75] and a 2-year overall survival of 95 percent in patients below 61 years [76]. In recent publications by Gondos, Brenner and Pulte significant improvements in the outcome of NHL, CML and multiple myeloma have been described based on the SEER data base in the US [77-79].

These publications represent epidemiological support for the value of innovative drugs in oncology and haematology. Similar support for treatment effects on a population has been reported by von Plessen and co-workers [80]. They reported a significant improvement in the outcome for patients with advanced non-small cell lung cancer in Norway, linked to the introduction of palliative chemotherapy.

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 percent were obtained in patients with advanced Hodgkin's disease [81]. This was a milestone in medical oncology, proving the ability to cure even in advanced stages of disease. Since then, even higher cure rates (90 percent) have been obtained using new combinations of chemotherapy [82]. In testicular cancer, the prognosis has turned from one of the worst to one of the best among oncological diagnosis. The introduction of cisplatin in the 1970s was an immediate breakthrough in the treatment of testicular cancer [83]. The addition of chemotherapy agents to surgery and local radiotherapy has further increased curative rates in patients with metastatic testicular cancer disease to approximately 90-95 percent.

However, it's important to note that breast cancer is a much more common disease; the number of patients cured of breast cancer far exceeds that of those cured of testicular cancer and Hodgkin's disease.

2.3.9 Advances towards the prevention of cancer

A number of agents that cause cancer have been brought to light. 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. Cancer can be prevented. 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 now see. The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials in women with an increased genetic risk of breast cancer who were found to benefit from treatment with tamoxifen (50 percent risk reduction) [84]. In the USA, the Food and Drug Administration (FDA) has approved the use of tamoxifen as a preventive agent in high-risk patients. However, no such licence exists in Europe.

Recently, raloxifene (an agent similar to tamoxifen) has proved as efficient as tamoxifen as a preventive agent but with less side effects [85]. There are also several ongoing studies with aromatase inhibitors, which block the production of oestrogen in post menopausal women, as preventive agents for breast cancer. Other agents that have indicated effect as preventive agents are non-steroidal anti-inflammatory drugs in colon cancer [86], finasteride in prostate cancer [87] and recently statins in breast cancer [88]. The fact that there are agents that can be used for prevention of cancer is in itself an important milestone in oncology.

The first vaccines against human papilloma virus [89] - the cause of the vast majority of cervical cancers- was introduced in 2005, but their full potential will require political decision, as it is important to include all factors for the full value of preventive measures.

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.

2.4 Conclusions

Oncology has entered an exciting phase, in which extensive research is paying dividends in the form of new treatments designed to target disease-specific mechanisms. It’s clear in some tumour forms that these agents will replace 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 more potential targets of intervention. The dividends mentioned above are, however, only realised once these drugs are adopted into routine clinical practice and reach the patients that may benefit from them.

3 Market uptake of new oncology drugs

3.1 Summary

- Total sales of oncology drugs in Europe have increased substantially over the period 1998-2007 from €4.3 per capita to €26.3 per capita.

- Drugs introduced before 1999 accounted for 68 percent, drugs introduced 1999-2002 for 17 percent, and drugs introduced 2003-2005 for 11 percent and drugs introduced in 2006-2007 for 3percent, respectively of total sales of oncology drugs in 2007.

- There are great variations between the different countries in terms of the level of uptake of new drugs, following introduction in the first country. Countries vary both in the time it takes to first sales and in the level of uptake when sales start.

- Austria, France and Switzerland are leaders in the uptake of new cancer drugs.

- The greatest differences in uptake were noted for the new colorectal and lung cancer drugs as well as drugs for renal cell cancer and liver cell cancer (bevacizumab, cetuximab, erlotinib, pemetrexed, sorafenib and sunitinib).

3.2 Oncology drugs

This chapter describes the market introduction and total sales of oncology drugs (ATC code L1, L2A and L2B) in 28 countries in Europe. The sales of these drugs in the period 1998-2007 are based on four groups of drugs: drugs launched before, or during 1998, drugs launched 1999-2002, 2003-2005 and 2006-2007. Table 3.1 lists these drugs along with year and month of first launch worldwide. Launch is here defined as the date a product or pack is first made available for general release by the manufacturer, i.e. for general prescribing and dispensing.

Drugs first launched before 1995	Date of launch	Drugs first launched 1995-1999	Date of launch
Vaccine, Bacillus Calmette-Guerin	-	Docetaxel	Apr 1995
Calcium Folinate	Jan 1942	Bicalutamide	May 1995
Methotrexate	Mar 1950	Gemcitabine	Jun 1995
Vincristine	Mar 1950	Anastrozole	Sep 1995
Cyclophosphamide	Jan 1958	Etoposide Phosphate	Jun 1996
Hydroxycarbamide	Jan 1959	Oxaliplatin	Jul 1996
Fluorouracil	Jan 1962	Topotecan	Jul 1996
Megestrol	Jan 1964	Ibandronic Acid	Oct 1996
Daunorubicin	Jan 1967	Letrozole	Nov 1996
Cytarabine	Jan 1969	Rituximab	Nov 1997
Bleomycin	Feb 1969	Capecitabine	May 1998
Doxorubicin	Jan 1971	Thalidomide	Oct 1998
Tamoxifen	Sep 1973	Trastuzumab	Oct 1998
Tegafur	Feb 1974	Temozolomide	Feb 1999
Ifosfamide	Feb 1976	Gimeracil	Mar 1999
Cisplatin	Dec 1978	Tasonermin	Sep 1999
Etoposide	Sep 1980	Exemestane	Nov 1999
Flutamide	Jun 1983	**2000-2002**	**Date of launch**
Mitoxantrone	Feb 1984	Zoledronic Acid	Oct 2000
Uracin	Mar 1984	Imatinib	May 2001
Epirubicin	Apr 1984	Alemtuzumab	Jun 2001
Leuprorelin	Aug 1984	Ibritumomab	Mar 2002
Buserelin	Sep 1984	Tiuxetan Fulvestrant	May 2002
Clodronic Acid	Mar 1985	Gefitinib	Jul 2002
Carboplatin	Dec 1985	**2003-2004**	**Date of launch**
Interferon Alfa-2A	Jun 1986	Bortezomib	May 2003
Triptorelin	Jun 1986	Cetuximab	Dec 2003
Goserelin	Mar 1987	Bevacizumab	Feb 2004
Pamidronic Acid	Mar 1987	Pemetrexed	Feb 2004
Nilutamide	Dec 1987	Erlotinib	Nov 2004
Toremifene	Jan 1989	**2005-2007**	**Date of launch**
Vinolrelbine	Jun 1989	Clofarabine	Jun 2005
Idarubicin	Feb 1990	Sorafenibe	Jul 2006
Lenograstim	Dec 1991	Sunitinib	Jul 2006
Fludarabine	Jan 1992	Dasatinib	Nov 2006
Cytarabine Ocfosfate	Dec 1992	Nelarabine	Aug 2007
Paclitaxel	Dec 1992	Trabectedine	Sep 2007
Cladribine	Mar 1993	Temoporfin	Nov 2007
Irinotecan	Apr 1994		

Table 3-1. Drug and first date of introduction worldwide

56 of the 74 cancer drugs in Table 3.1 were introduced before 2000 (defined as the first date for introduction worldwide), 6 were introduced in the period from 2000-2002, while 5 were introduced in the period 2003-2004 and 7 in the period 2006-2007.

Quarterly and annual sale statistics in the period 1998 - 2007 were obtained from IMS Health, IMS MIDAS for the following European countries: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Slovenia, Slovakia, Sweden, Switzerland and the UK. IMS data for Portugal include only a limited number of oncology drugs, thus, data from this country have only been used for the macro-evaluation and not for uptake of individual drugs. Data for the hospital products is missing for Bulgaria, Hungary, Ireland, Greece, Latvia, Lithuania, Portugal and Romania, and data for these countries are incomplete and mainly represent retail sales. The total population in the 28 European countries is 504 million [90]. The term E13 represents the average uptake of the drug in the following European countries: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the UK.

Sales from IMS Health, IMS MIDAS were based on manufacturers' prices in most countries, except in Denmark, Estonia, Finland, Greece, Latvia, Lithuania, Norway, Slovenia, Sweden, Romania, and the UK, where sales were based on trade prices (wholesaler price) and in Bulgaria, where sales were based on Public prices. 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. Costs of administration of drugs are not included. Sales are presented in nominal prices and have been converted to Euros where necessary, using the 2005 market exchange rate. IMS pharmaceutical audits report sales at either manufacturer selling price (wholesale purchase price, trade price, pharmacy purchase price/wholesales price) or public price. IMS audits in the Czech Republic, the Netherlands, Poland, Sweden and Switzerland measure sales to hospitals from wholesalers and directly from manufacturers. In Austria, Belgium, France, Italy, Germany, Spain and the UK, hospital usage is established with data from a panel of hospitals, reporting the product issues from pharmacy. These data are then projected to a national level. In certain markets with fewer hospital panels, e.g. Spain, highly specialized products may not completely represent the true market.

Differences in prices may influence the comparisons made using value terms. However, 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 we also give data based on sales in mg. A comparison of prices on most used packages reveals that some of the low uptake in UK (12 percent lower price than average) may partly be explained by a price effect. The lower than average price index in UK is explained mainly by pemetrexed (price 69 percent of comparator country) and imatinib (85 percent). France and Switzerland have on average 5 percent higher price than the comparator countries, so there is a minor effect from price here. It should also be noted that dosages can differ between countries, which may influence the interpretation of sales data as an index of number of patients treated.

3.3 Sales of new oncology drugs

The data show that total sales of oncology drugs in the selected countries have increased substantially over the period 1998-2007 from €400,000/100,000 inhabitants to €2,200,000/100,000 inhabitants (Figure 3-1). The increase in sales for oncology products over this period can partly be explained by the introduction of new innovative drugs. Sales of new drugs introduced in the period 1998 - 2007 have continuously increased, both in absolute terms and in terms of their share of total drug sales. However, it should be noted that drugs introduced before or during 1998 have increased their sales from approximately €400,000/100,000 inhabitants to approximately €1,400,000/100,000 inhabitants. This reflects a significant increase in the use of these “older” drugs, as many have become generic and that the actual number of patients being treated has increased substantially.

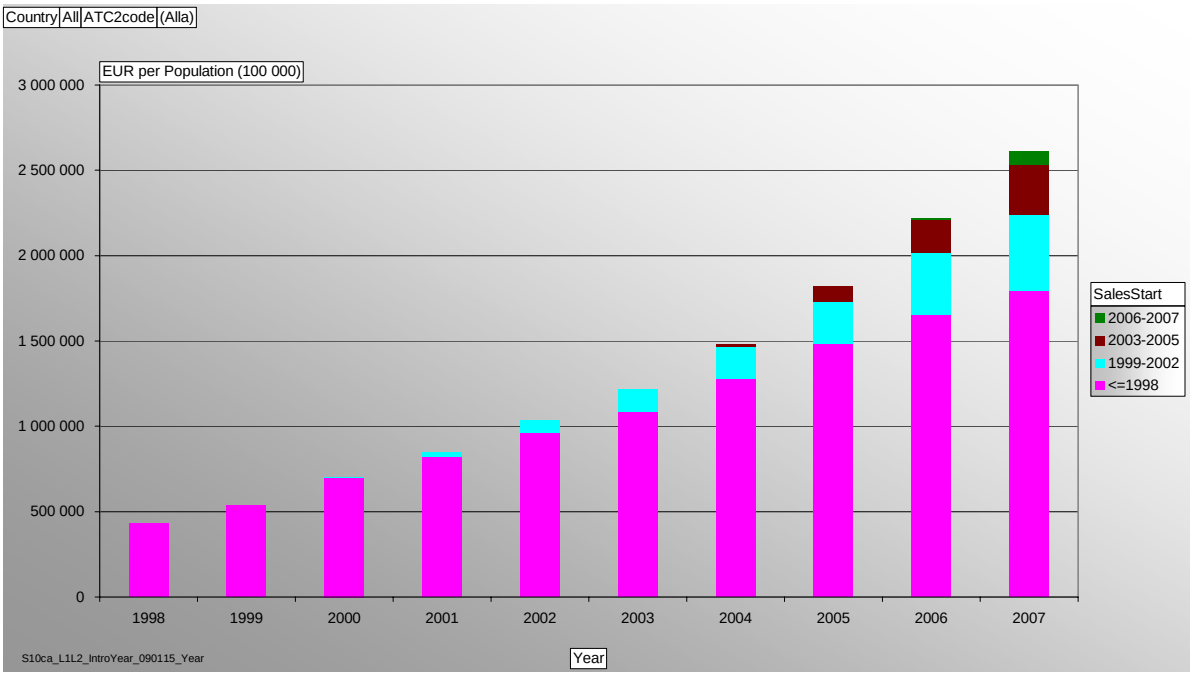

Figure 3-1. Sales of cancer drugs in 1998-2007 in Euros (€)/100,000 inhabitants in Europe.

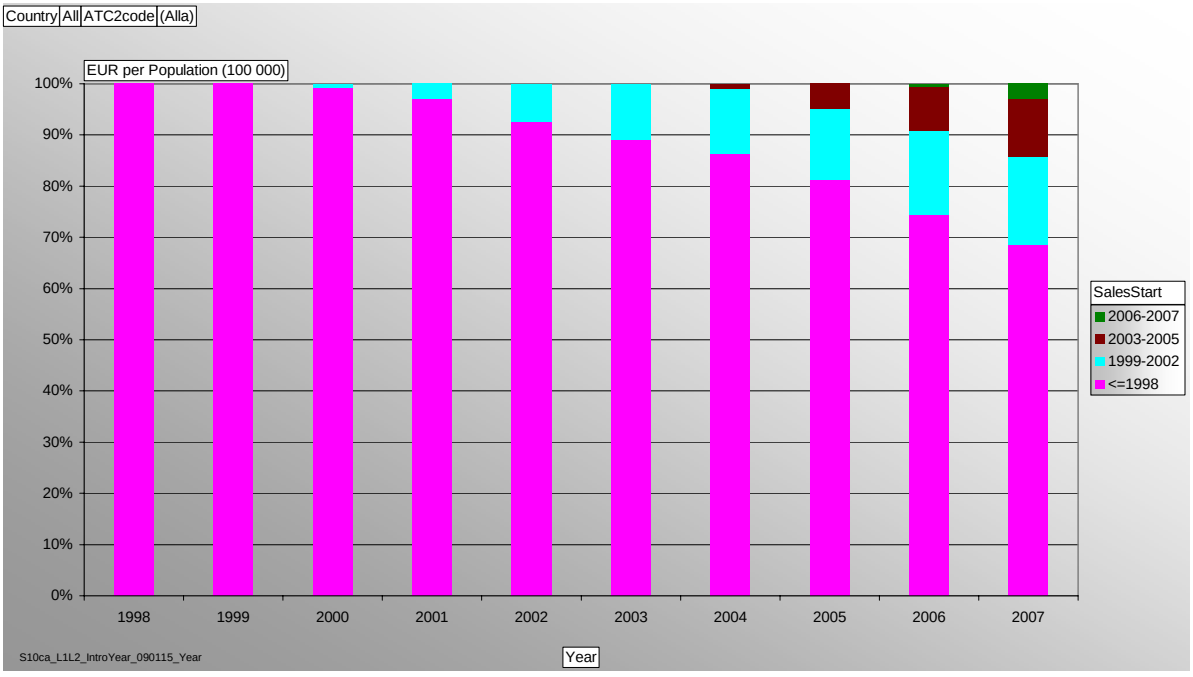

Figure 3-2. The portion of total sales of cancer drugs in 2007 by time period of launch in Euros (€)/100,000 inhabitants in Europe.

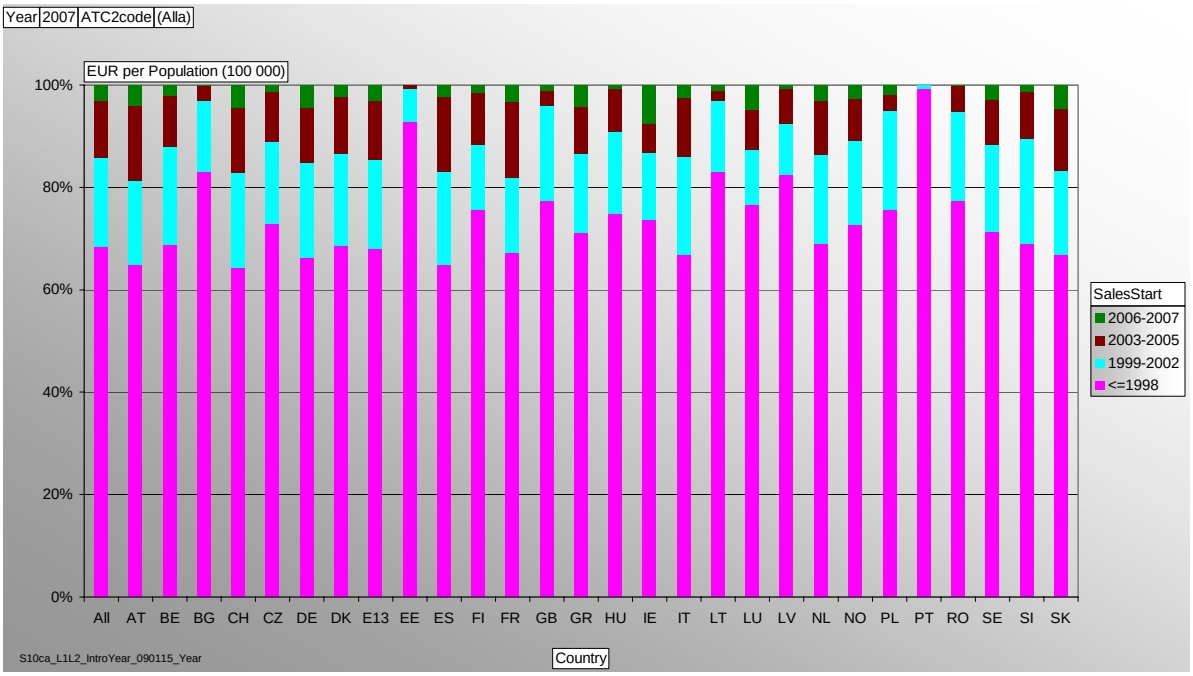

Figure 3-3. The portion of total sales of cancer drugs different European countries in 2007 by time period of launch. Please note that for Greece, Ireland, Luxembourg, and Portugal data for either hospital or retail sales are missing.

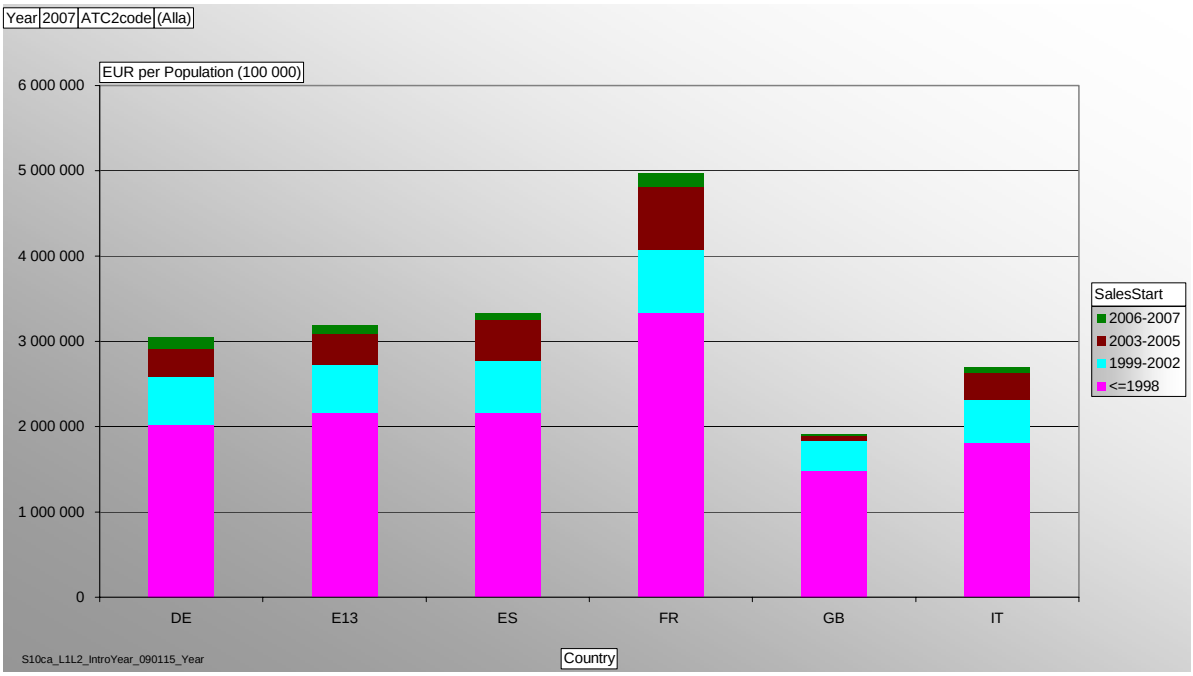

Figure 3-4. Sales of cancer drugs in 2007 in E13, France, Germany, Italy, Spain and the UK given in (€)/100,000.

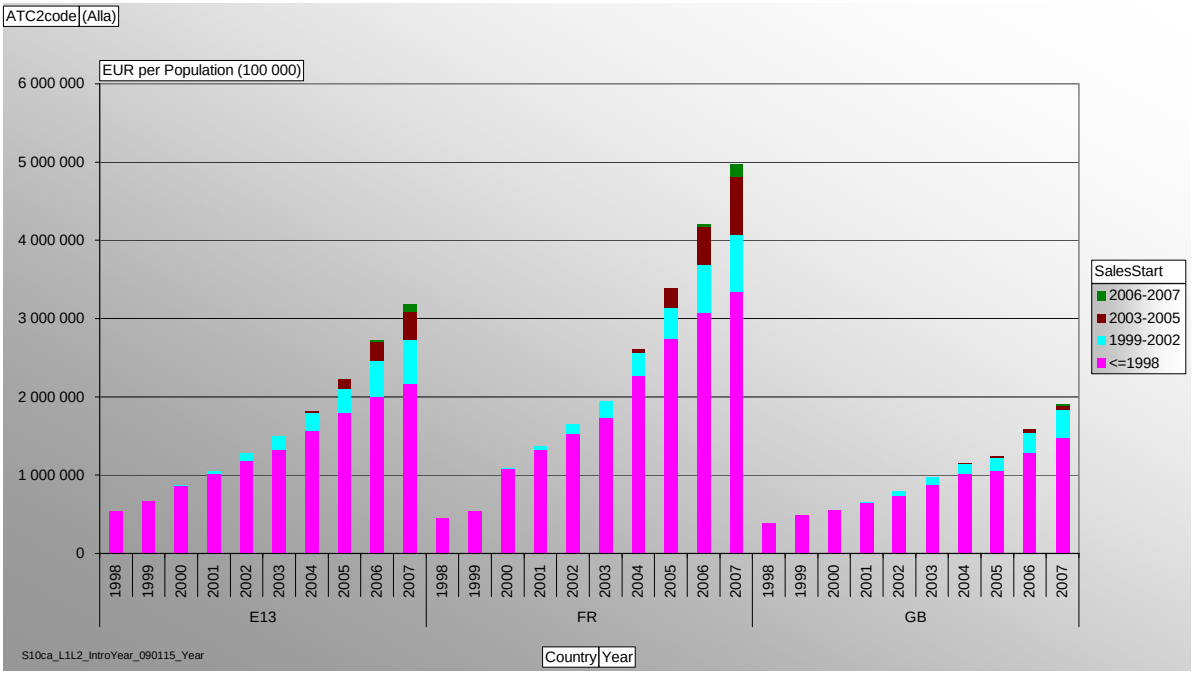

Figure 3-5. Sales of cancer drugs in 1998-2007 in E13, France and the UK in Euros (€)/100,000 inhabitants in Europe

3.4 Uptake of selected cancer drugs.

In this section of the report, we present the uptake of a number of specific oncology drugs. For each drug, uptake is given as sales (in € or mg) from the time of local introduction or first sales (a drug could have been sold under special license prior to national authorization). Data are sales per 100,000 inhabitants, or are related to the mortality of the specific cancer. This was done do exclude the effects of variation in mortality rates for some cancers in the countries studied. In the comparisons of uptake we use the term E13, as previously described. We have selected drugs in order to have representation of the major tumour areas discussed in previous chapters. These are:

- Brain tumours: temozolamide;
- Breast cancer: docetaxel, paclitaxel, trastuzumab and the aromatase inhibitors; anastrazole, exemestane and letrozole;

- Colorectal cancer: capecitabine, irinotecan, oxaliplatin, bevacizumab and cetuximab;
- Non-small cell lung cancer (NSCLC): gemcitabine, vinorelbine, erlotinib and pemetrexed;
- Chronic myeloid leukaemia , CML, as well as non-Hodgkin's lymphoma, NHL: imatinib and rituximab
- Renal cell cancer and liver cell cancer: sorafenib and sunitinib.

3.4.1 Brain tumours

The therapeutic options for patients with malignant brain tumours like glioblastoma and astrocytoma have until recently been surgery and radiotherapy. Recent studies have shown that the addition of a chemotherapeutic agent, temozolamide can significantly prolong survival. The drug is approved for the treatment of adult patients with newly diagnosed glioblastoma multiforme, concomitant with radiotherapy and as maintenance treatment, as well as for treatment of adult patients with refractory anaplastic astrocytoma, i.e. patients who have disease progression on other drugs [91].

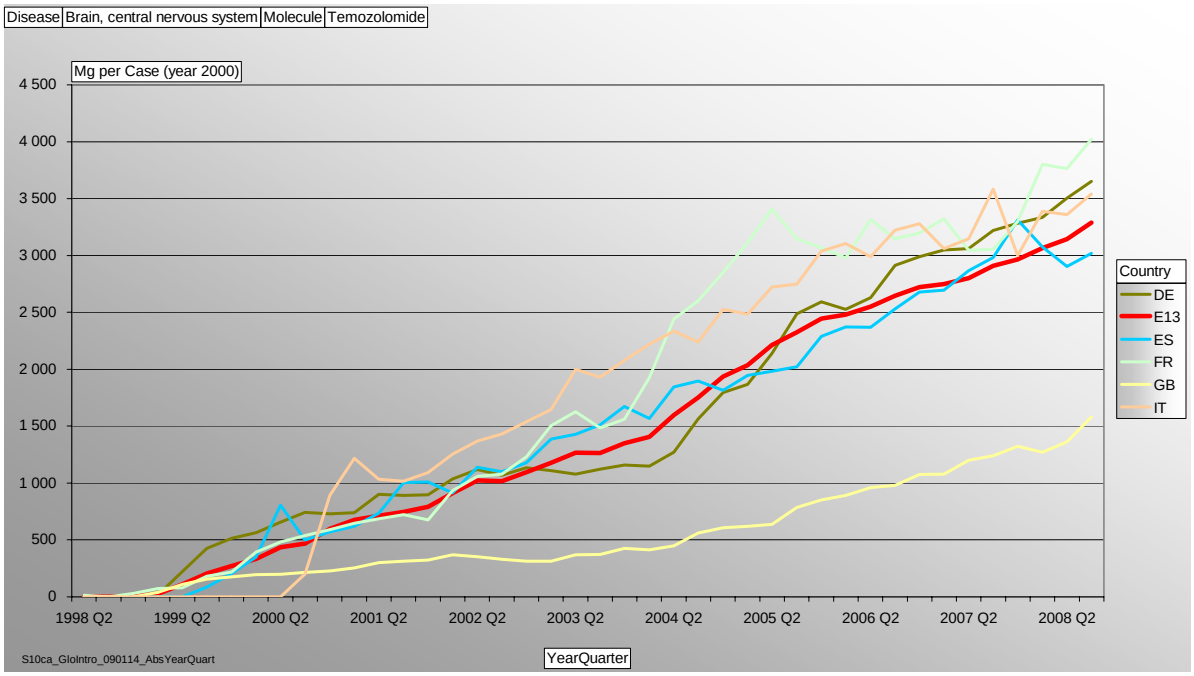

Figure 3-6..Usage of temozolamide expressed as mg/case (related to mortality in brain tumours in 2000) in E13, France, Germany Italy, Spain and the UK.

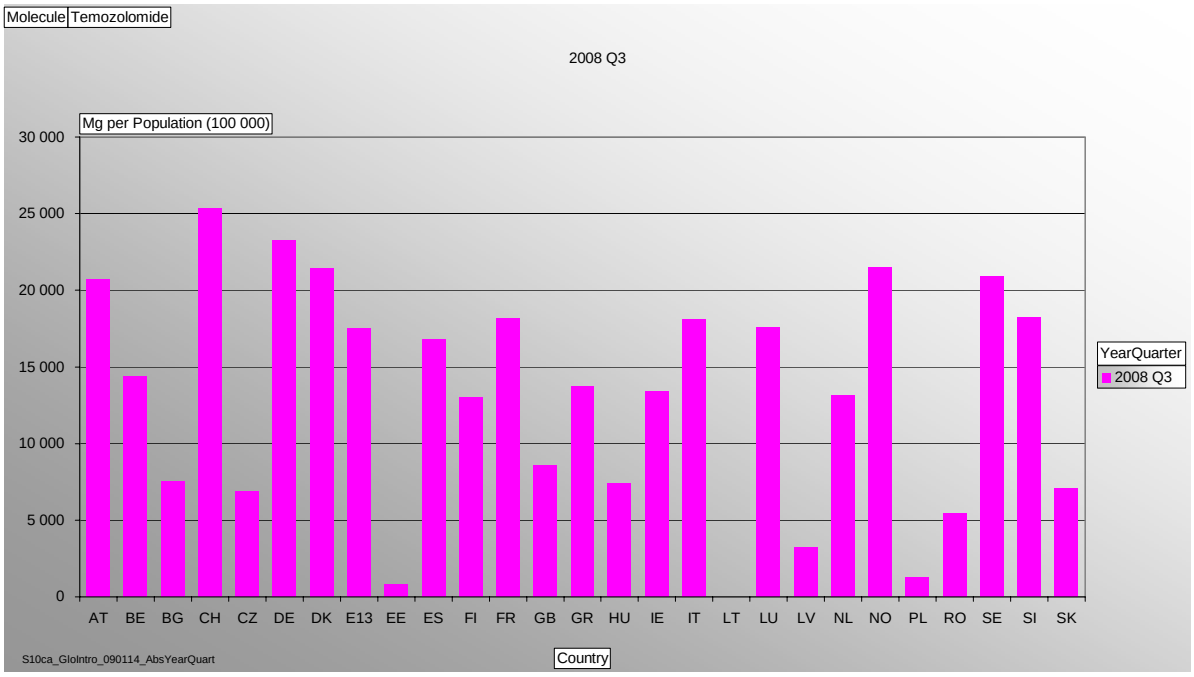

Figure 3-7. Usage of temozolamide expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries.

3.4.2 Breast cancer

Breast cancer is the most drug-intensive area, when it comes to treatment of solid tumours. In early breast cancer the use of adjuvant therapy in conjunction with surgery has become the cornerstones of the multimodal approach to the disease. Adjuvant medical treatment in breast cancer has evolved over a 30-40 years period. However, it was not until the mid 1980ies that the value of adjuvant therapy was recognized. A key factor in the evaluation of adjuvant therapy has been the overview met analysis process led by Sir Richard Peto and the EBCTCG group [92]

In this process data of almost 200,000 women have been collected and the value of adjuvant radio therapy, chemo therapy and hormonal therapy has been evaluated.

Hormonal therapy of breast cancer started with tamoxifen and later also included the aromatase inhibitors (AIs).Tamoxifen was launched in 1975 and initially considered a costly treatment with limited effect, has established itself as the most cost-effective cancer treatment to date. Its broad indication in the treatment of advanced disease and as adjuvant treatment (and prevention in the USA), represents a major breakthrough in the treatment of breast cancer. With more than 15 years of follow up the value of tamoxifen versus no tamoxifen is clear in hormone receptor positive breast cancer patients. Mortality decreases from 35 to 25 percent at 15 years [93] Newer, innovative drugs (aromatase inhibitors (AI); anastrazole, exemestane and letrozole) are now replacing, in part, tamoxifen, both in the treatment of advanced disease and in the adjuvant setting. The added value with respect to survival benefit still remains low (1.5-3 percent) related to if AIs are used alone or in sequence with tamoxifen.

The first generation adjuvant chemotherapy evolved during the 1970ies, starting with combinations including alkylating agents and anti metabolites (CMF). CMF gave improvement in relative survival compared to no chemotherapy with 32 percent. The addition of antracyclines (doxorubicine or epirubine) added further more to survival. The most recent development with third generation adjuvant chemotherapy includes taxanes (docetaxel or paclitaxel). The addition of taxanes in the adjuvant therapy adds another 6 percent in relative survival[92].

The marked reduction we have seen in breast cancer mortality (25 percent overall and almost 50 percent in women younger than 70 years of age) [93] is based on the progress that we have seen, both in adjuvant medical therapy and improvement in early diagnosis through screening programs, implemented in most parts of Europe since the mid 1980s.

The biological therapy – trastuzumab - entered breast cancer therapy in the late 1990ies, has dramatically changed the outcome for women with HER2 over expressing breast cancer (15 percent of early breast cancer (BC) and 20-30 percent of advanced BC). Trastuzumab, a HER2 receptor antibody, has become important in the treatment of patients with advanced breast cancer over expressing HER2, and has also been approved in many countries for the adjuvant treatment, based on recent strong clinical data [94].

Diagnostic testing is required to determine whether a patient is candidate for hormonal treatment, or for trastuzumab treatment. This is an important factor to consider in the budgeting of new treatments.

We illustrate the adoption of new drugs in breast cancer with the uptake of taxanes (docetaxel and paclitaxel), trastuzumab as well as the combined uptake of aromatase inhibitors (anstrazole, letrozole and exemestane) in different countries.

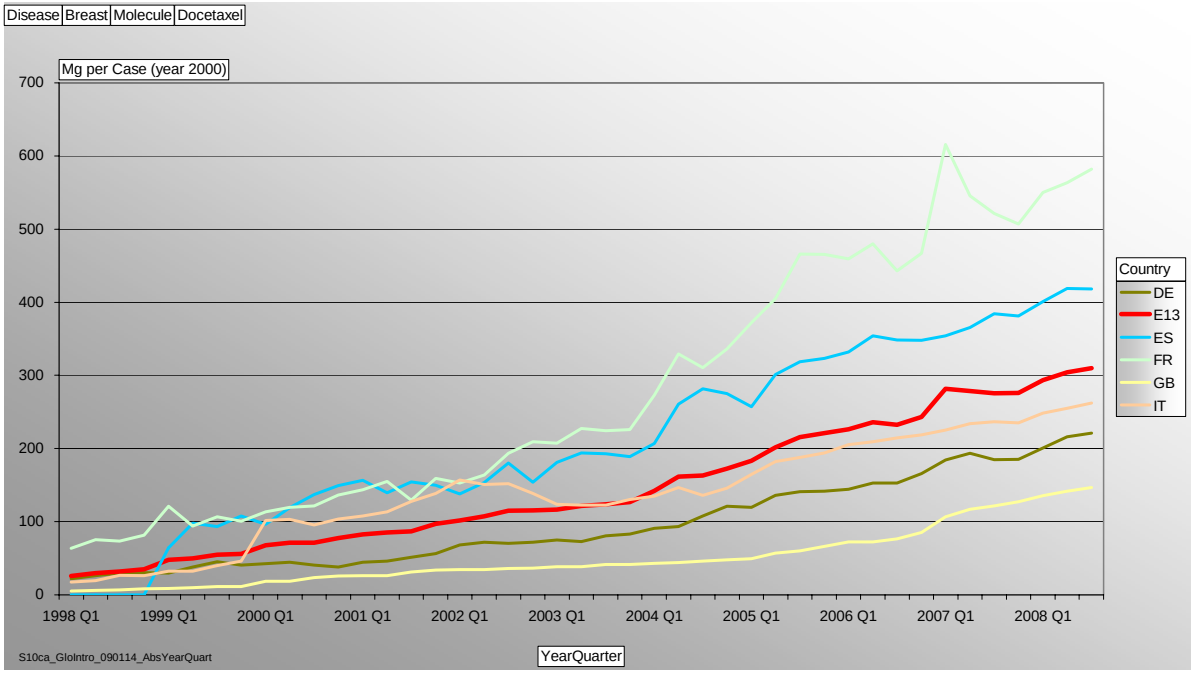

Figure 3-8. Usage of docetaxel expressed as mg/case (related to mortality in breast cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that docetaxel also have other indications like lung-, prostate- and gastric cancer.

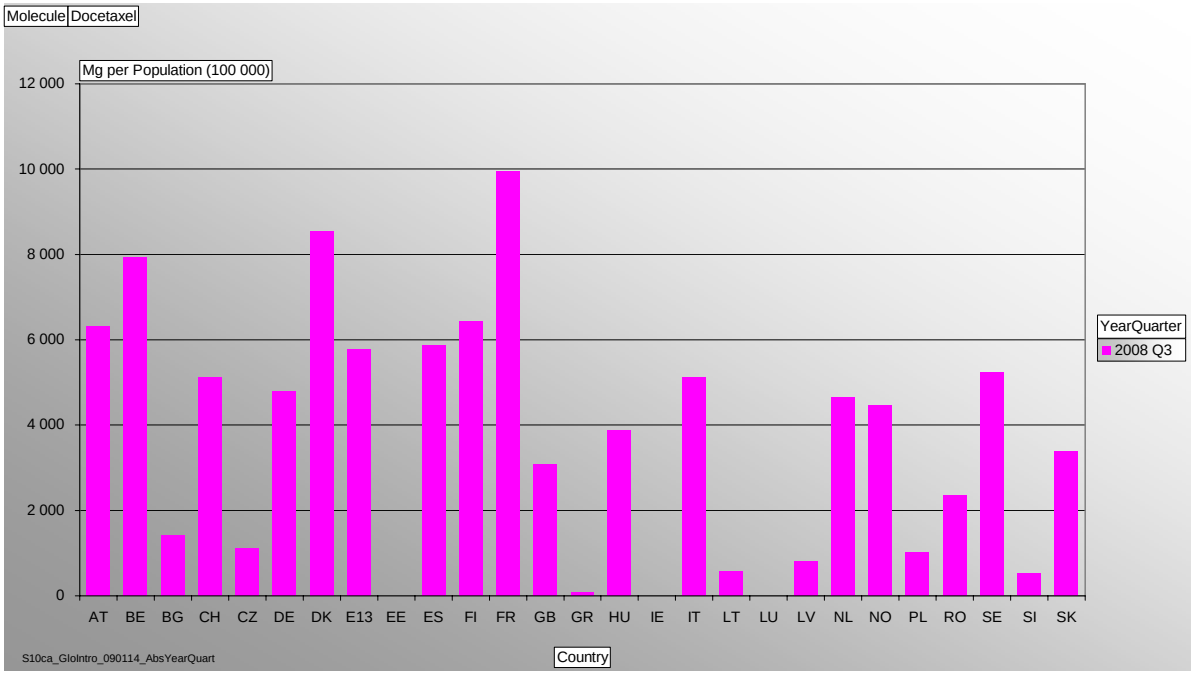

Figure 3-9. Usage of docetaxel in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries. Please note that docetaxel also have other indications like lung-, prostate- and gastric cancer.

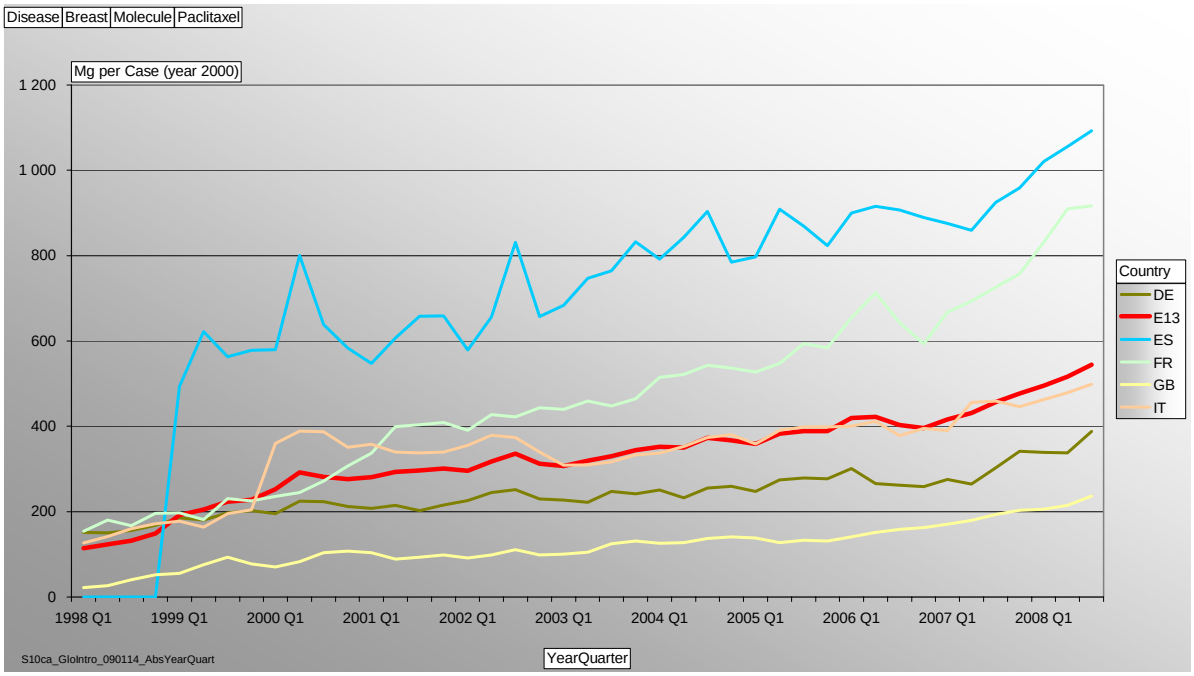

Figure 3-10.Usage of paclitaxel expressed as mg/case (related to mortality in breast cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that paclitaxel also have other indications like lung- and ovarian cancer.

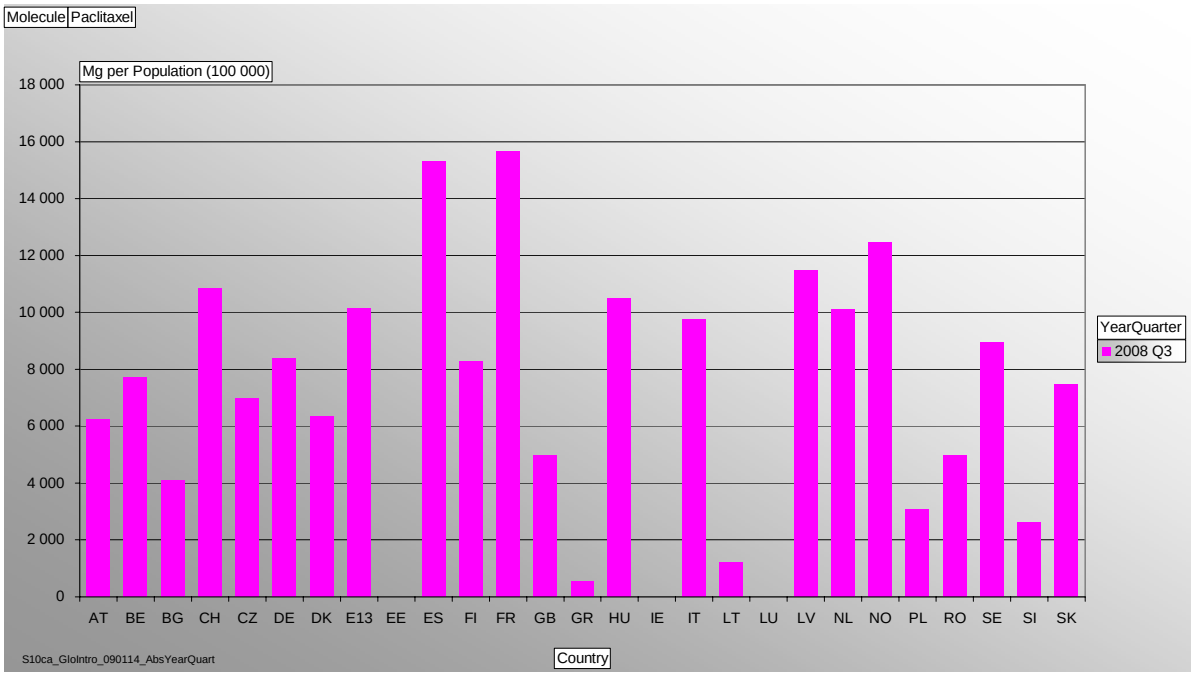

Figure 3-11.Usage of paclitaxel in 2007 expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries. Please note that paclitaxel also have other indications, like lung- and ovarian cancer.

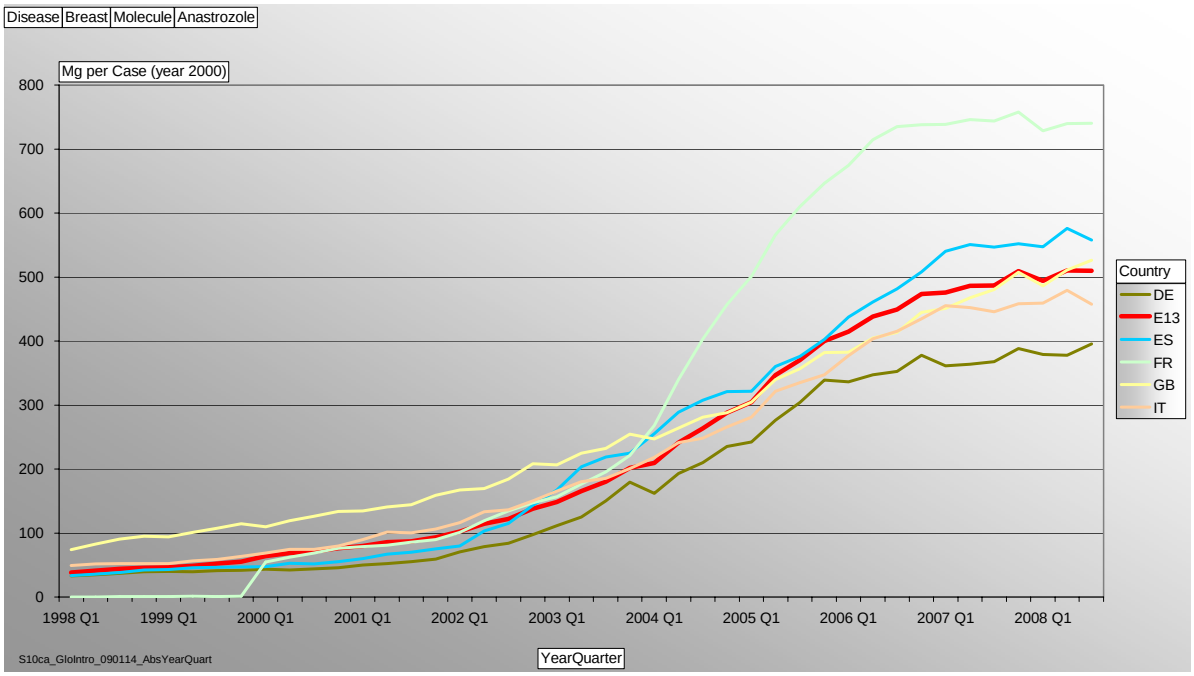

Figure 3-12. Usage of anastrozole expressed as mg/case (related to mortality in breast cancer in 2000) in E13, France, Germany Italy, Spain and the UK.

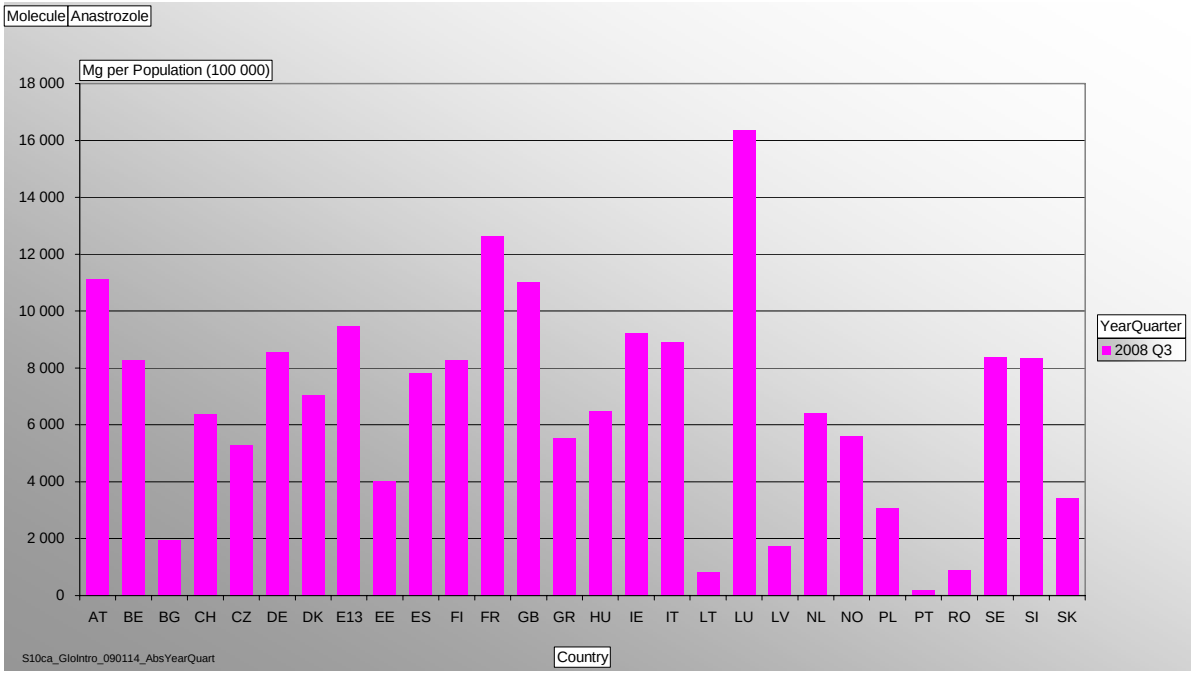

Figure 3-13. Usage of anastrozole in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 27 European countries

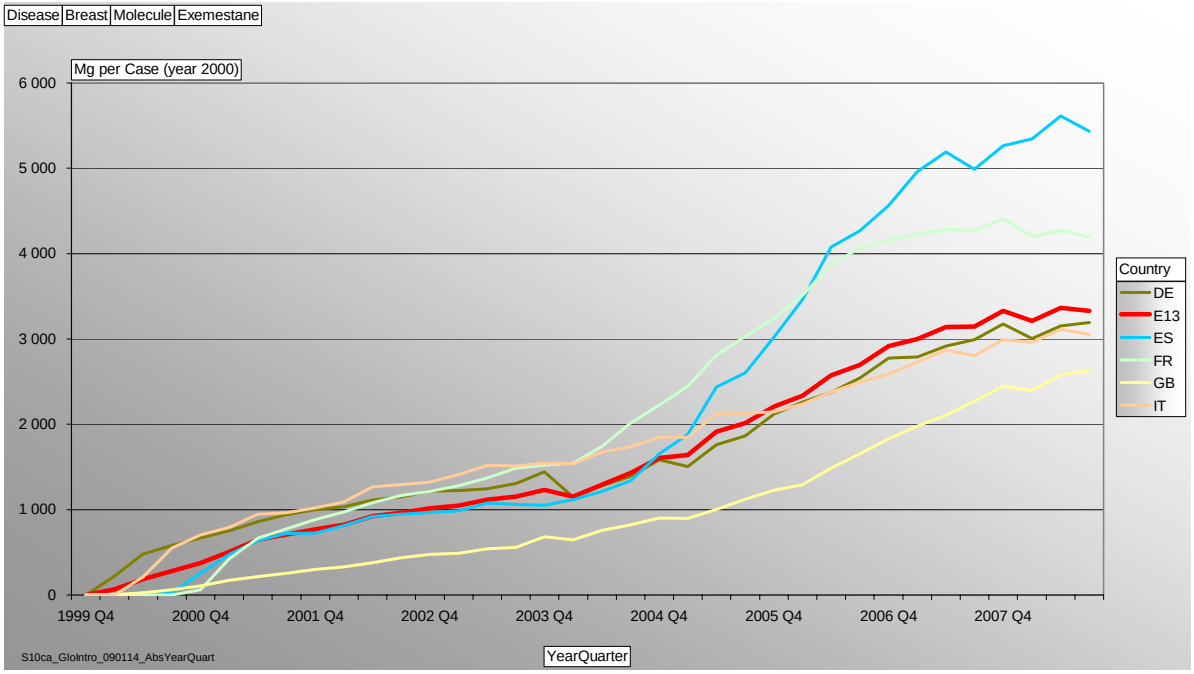

Figure 3-14. Usage of exemestane expressed as mg/case (related to mortality in breast cancer in 2000) in E13, France, Germany Italy, Spain and the UK

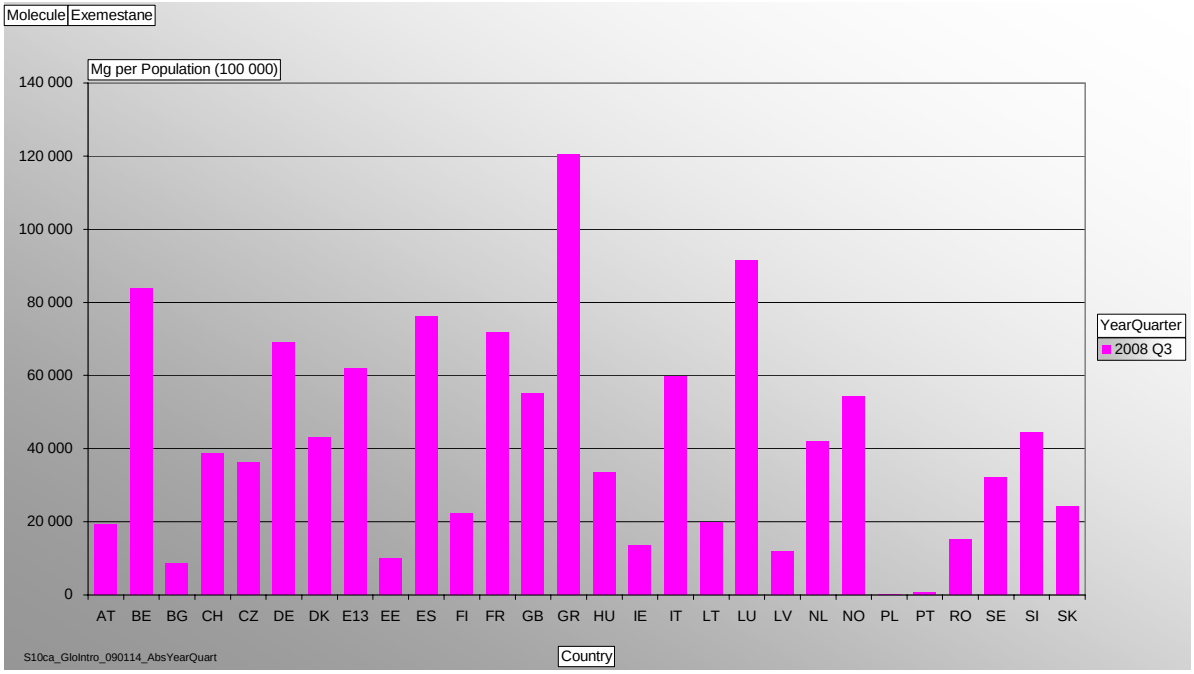

Figure 3-15. Usage of exemestane in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 27 European countries

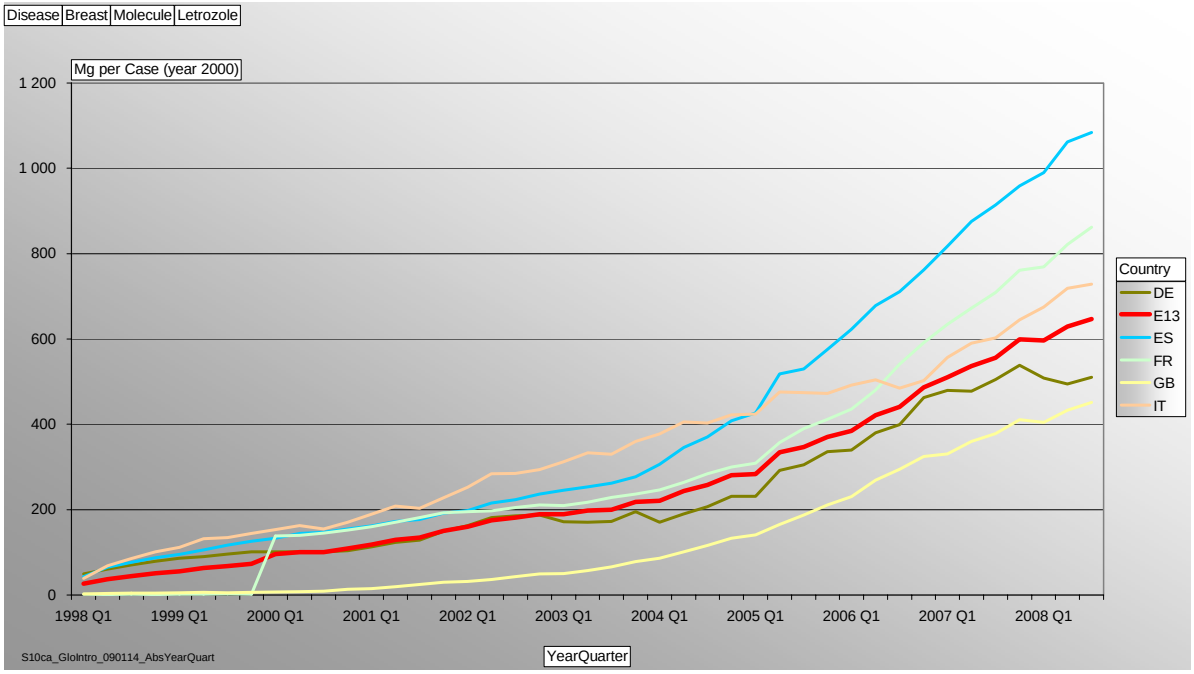

Figure 3-16. Usage of letrozole expressed as mg/case (related to mortality in breast cancer in 2000) in E13, France, Germany Italy, Spain and the UK.

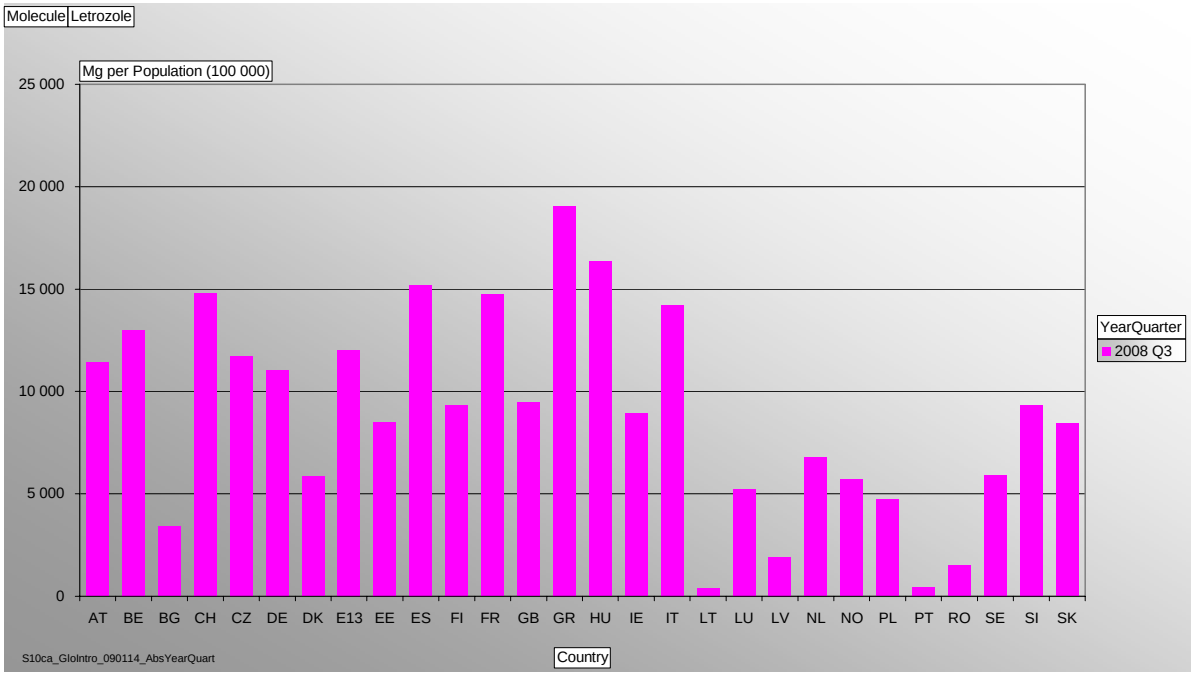

Figure 3-17. Usage of letrozole in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 27 European countries

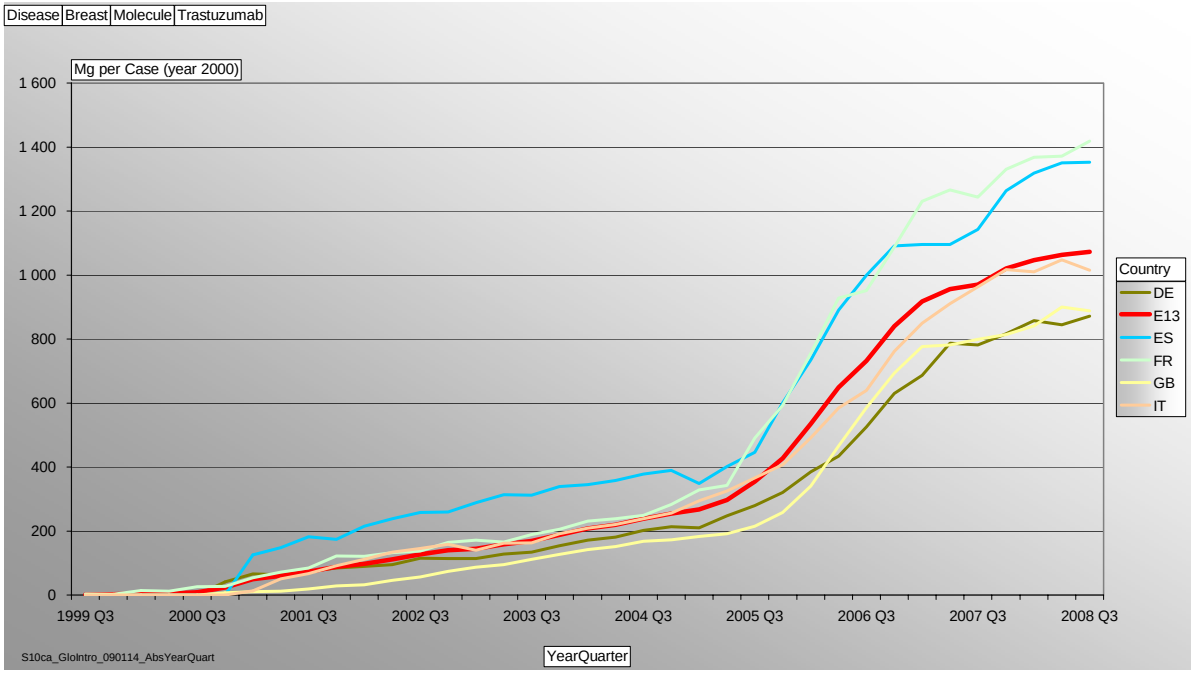

Figure 3-18. Usage of trastuzumab expressed as mg/case (related to mortality in breast cancer in 2000 in E13, France, Germany Italy, Spain and the UK.

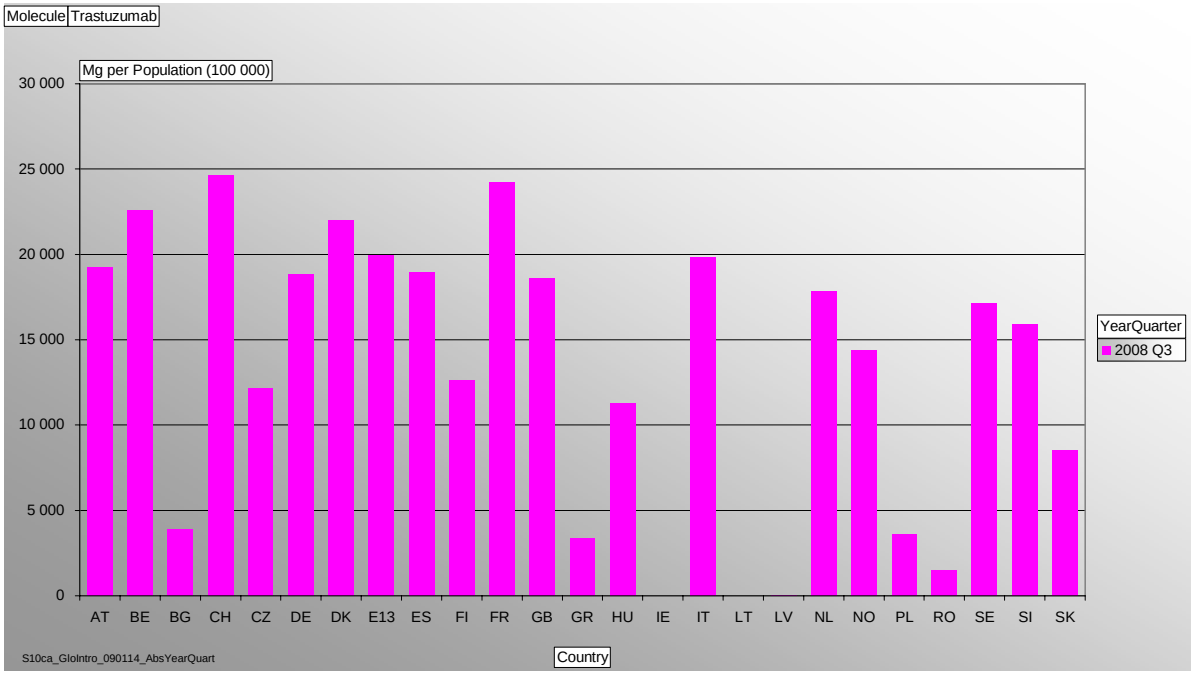

Figure 3-19. Usage of trastuzumab in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 24 European countries.

3.4.3 Colorectal cancer

Until the end of the 1980s, colorectal cancer remained a therapeutic area in which medical treatment was considered to have little or no effect. Developments in diagnostic and surgical techniques were major contributors to outcome improvement. With the publication of the adjuvant data on modulated 5-fluorouracil (5-FU)-based therapy in the late 1980s and mid 1990s, colorectal cancer rapidly became an area for further drug development. In the mid 1990s, both irinotecan and oxaliplatin became established agents added to modulated 5-FU, which was still the cornerstone of treatment for both early and advanced colorectal cancer. Adjuvant 5FU based therapy, now also with 5FU available as an oral drug; capecitabine, with the addition of oxaliplatin in high risk individuals, has markedly improved outcome for stage III disease patients, while the value for patients with intermediate risk disease, stage II, is still uncertain and surgery alone remains standard for stage I disease patients [95]. Recently, two new drugs -bevacizumab and cetuximab- have been approved for the treatment of advanced colorectal cancer, representing a breakthrough in the treatment of the disease. Bevacizumab, is an anti-angiogenesis drug, with indication in first line treatment of advanced colorectal cancer [96].

Cetuximab, which interacts with the epidermal growth factor (EGF) receptor, at present indicated as 2nd or 3rd line drug in metastatic disease, but will most likely soon be approved also for first line treatment [97].

The most recent development in colorectal cancer is the identification of the subgroups of patients with wild type KRAS, more likely to respond to EGFr blockade. The most recent EGFr drug, panitumumab, is approved in this patient population (wKRAS) [98]. This now also applies to cetuximab.

We illustrate drug uptake in colorectal cancer through sales of capecitabine, irinotecan, oxaliplatin, bevacizumab and cetuximab in the different markets.

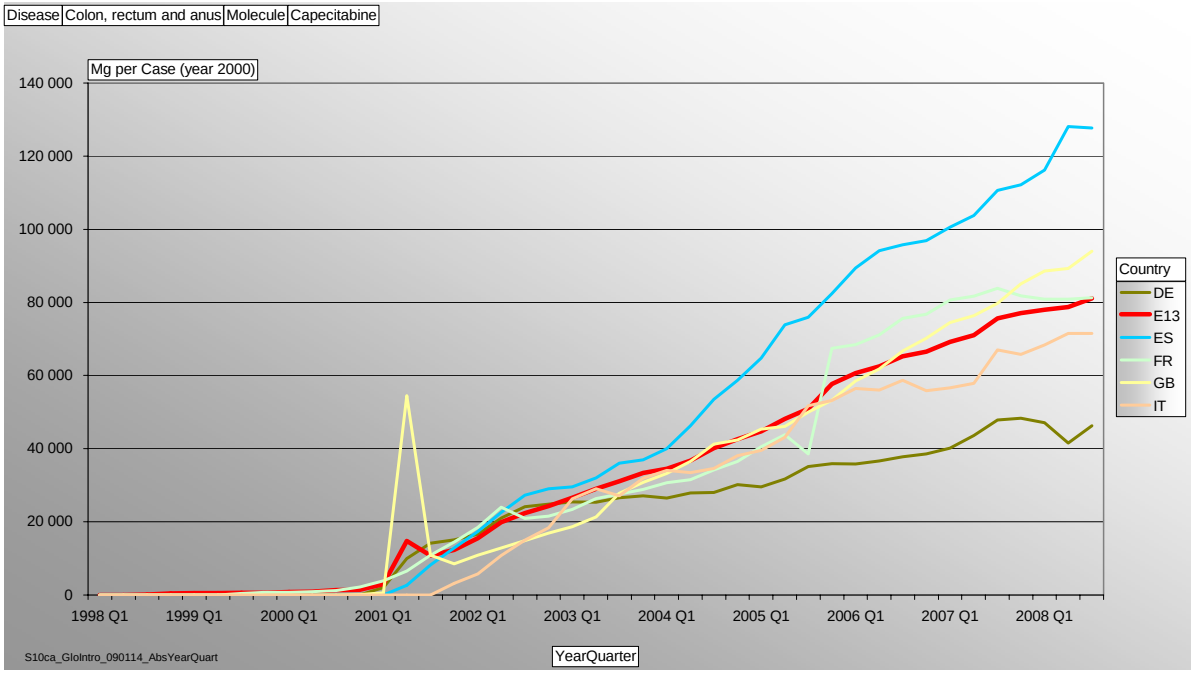

Figure 3-20. Usage of capecitabine expressed as mg/case (related to mortality in colorectal cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that capecitabine is also indicated in breast- and gastric cancer

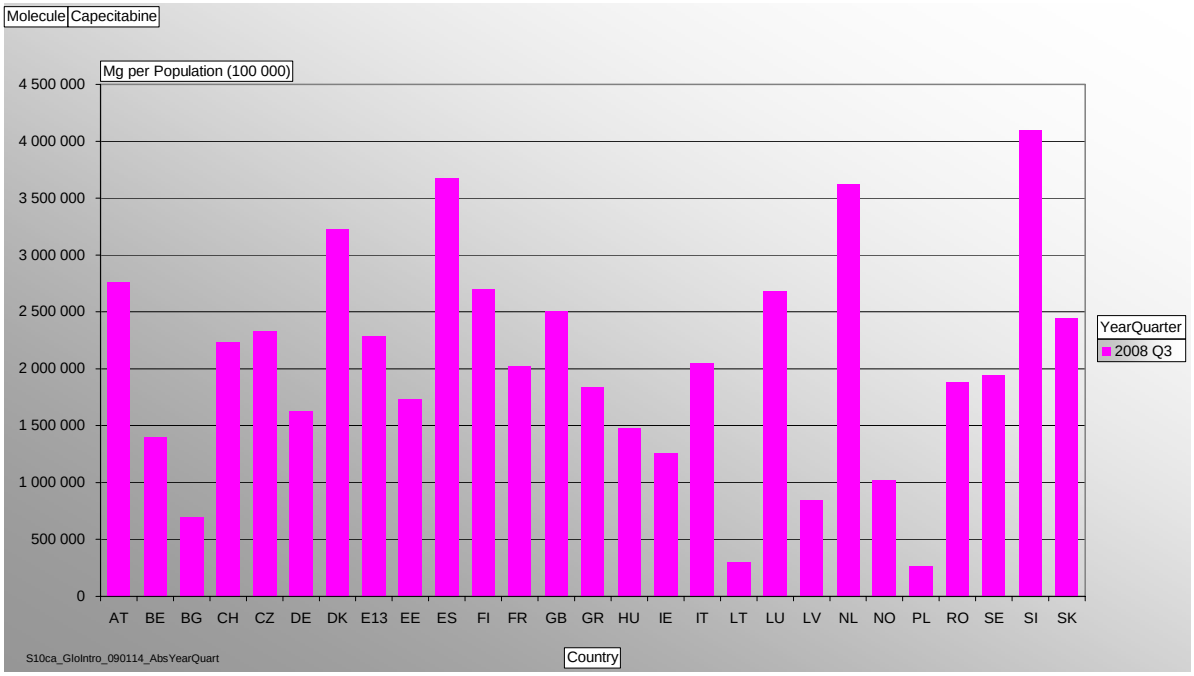

Figure 3-21. Usage of capecitabine in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries. Please note that capecitabine is also indicated in breast- and gastric cancer.

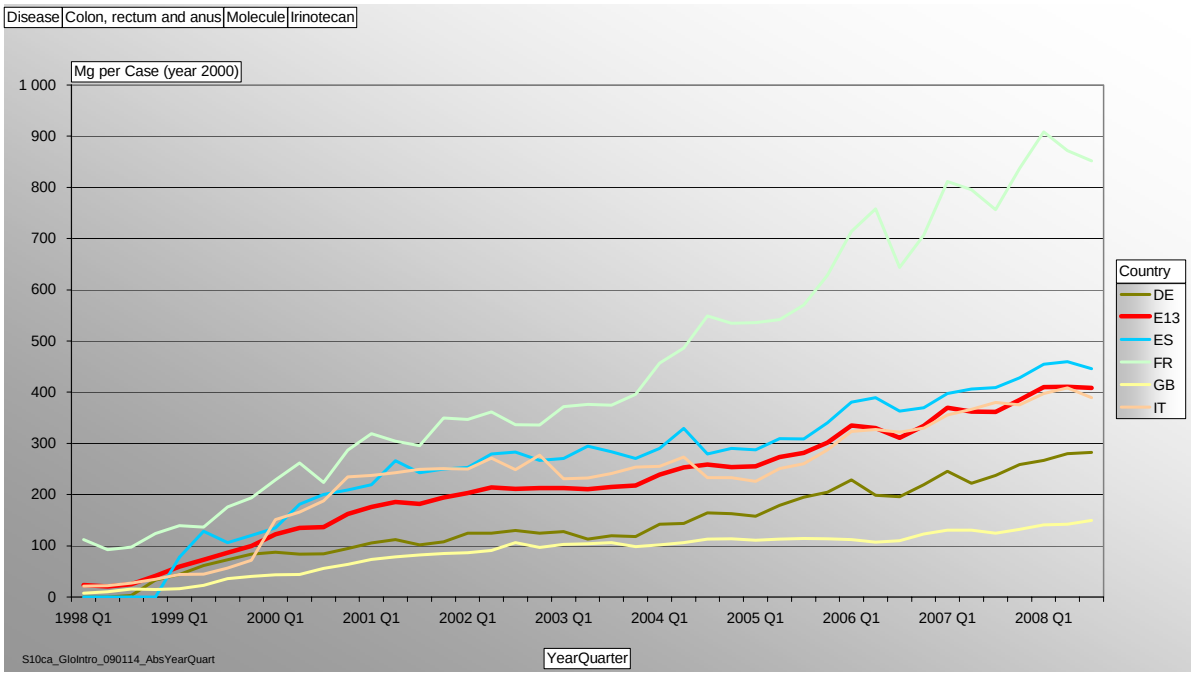

Figure 3-22. Usage of irinotecan expressed as mg/case (related to mortality in colorectal cancer in 2000) in E13, France, Germany Italy, Spain and the UK.

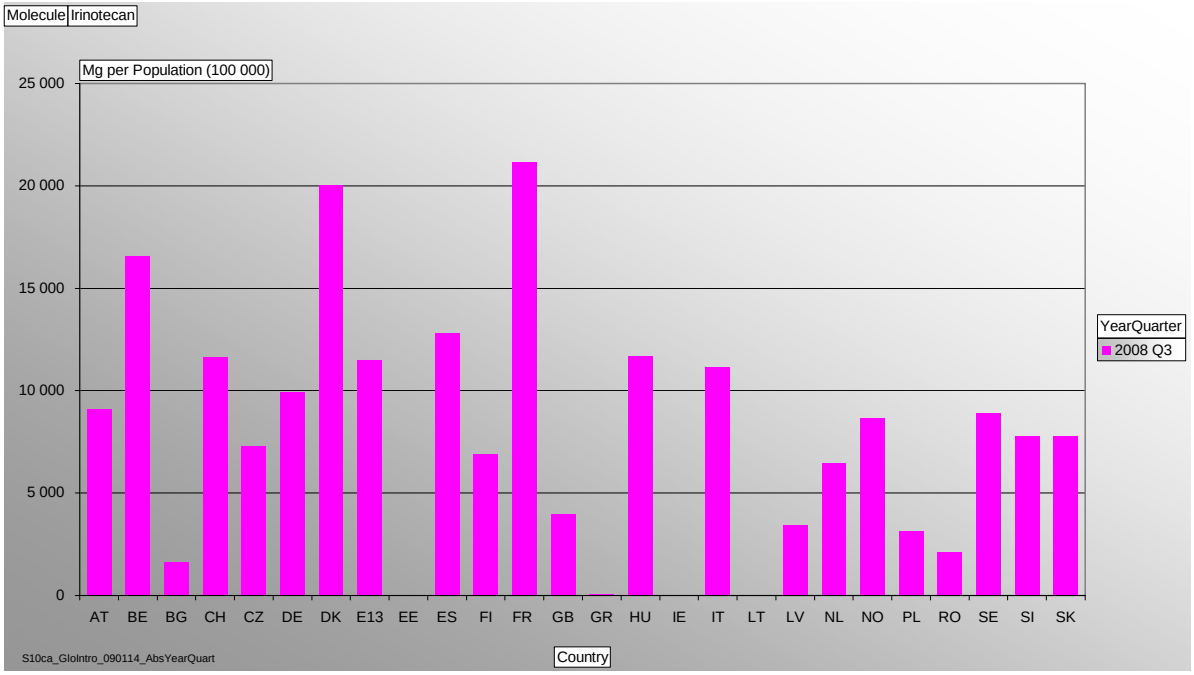

Figure 3-23. Usage of irinotecan in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 25 European countries.

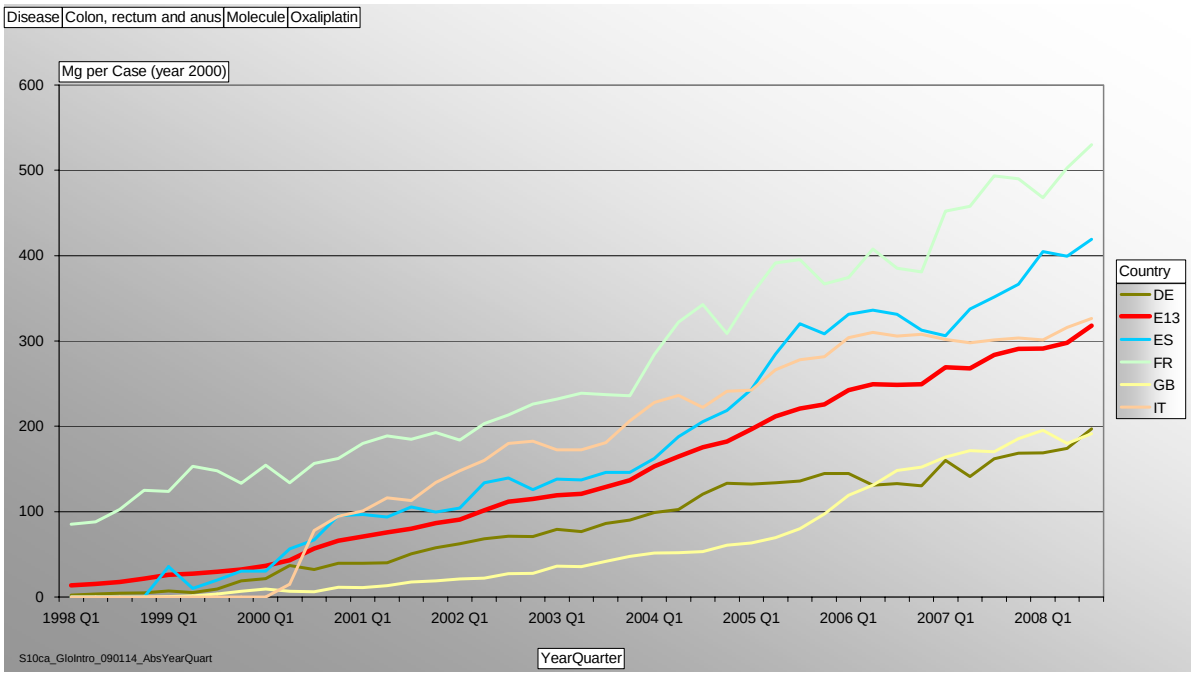

Figure 3-24. Usage of oxaliplatin expressed as mg/case (related to mortality in colorectal cancer in 2000) in E13, France, Germany Italy, Spain and the UK.

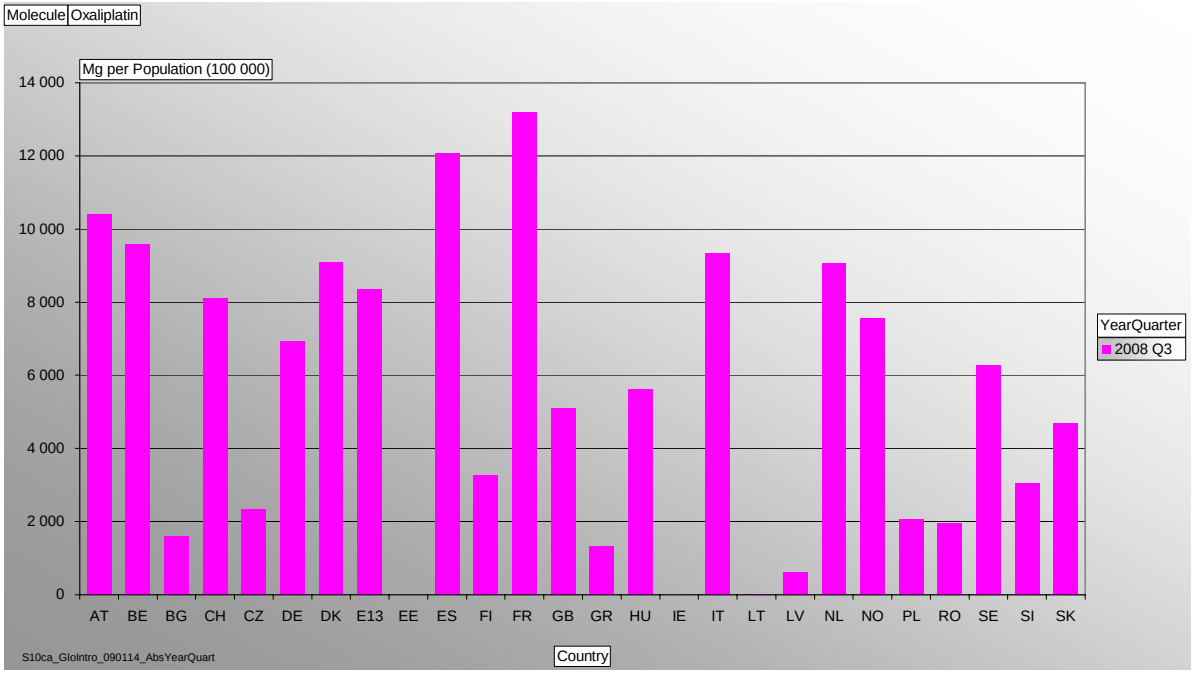

Figure 3-25. Usage of oxaliplatin in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 25 European countries.

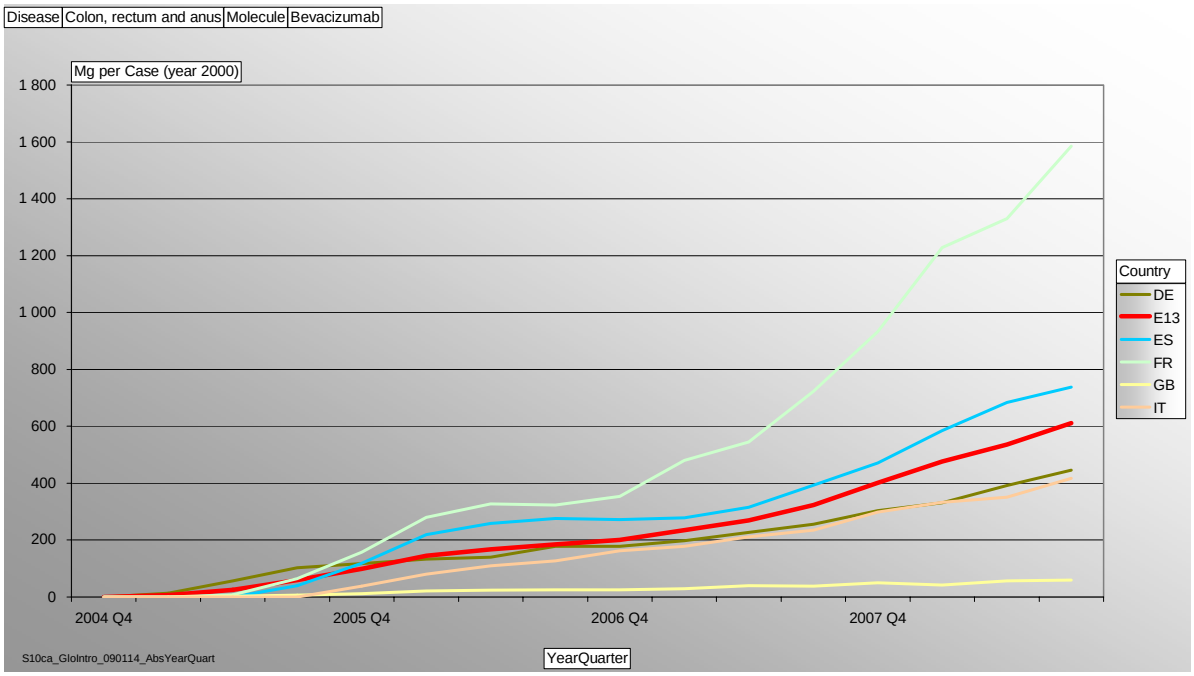

Figure 3-26. Usage of bevacizumab expressed as mg/case (related to mortality in colorectal cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that bevacizumab is also indicated for breast-, lung- and renal cell cancer.

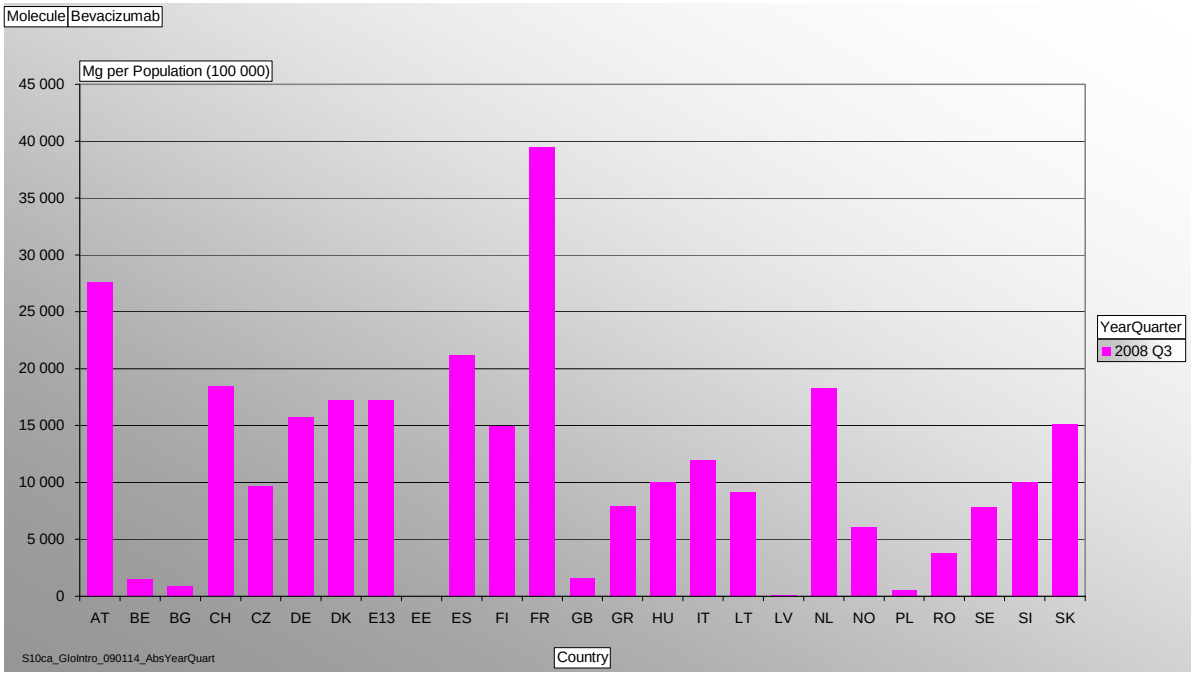

Figure 3-27. Usage of bevacizumab in 2007, expressed as sales in mg/100,000 inhabitants in E13 as well as 24 European countries. Please note that bevacizumab is also indicated for breast-, lung- and renal cell cancer.

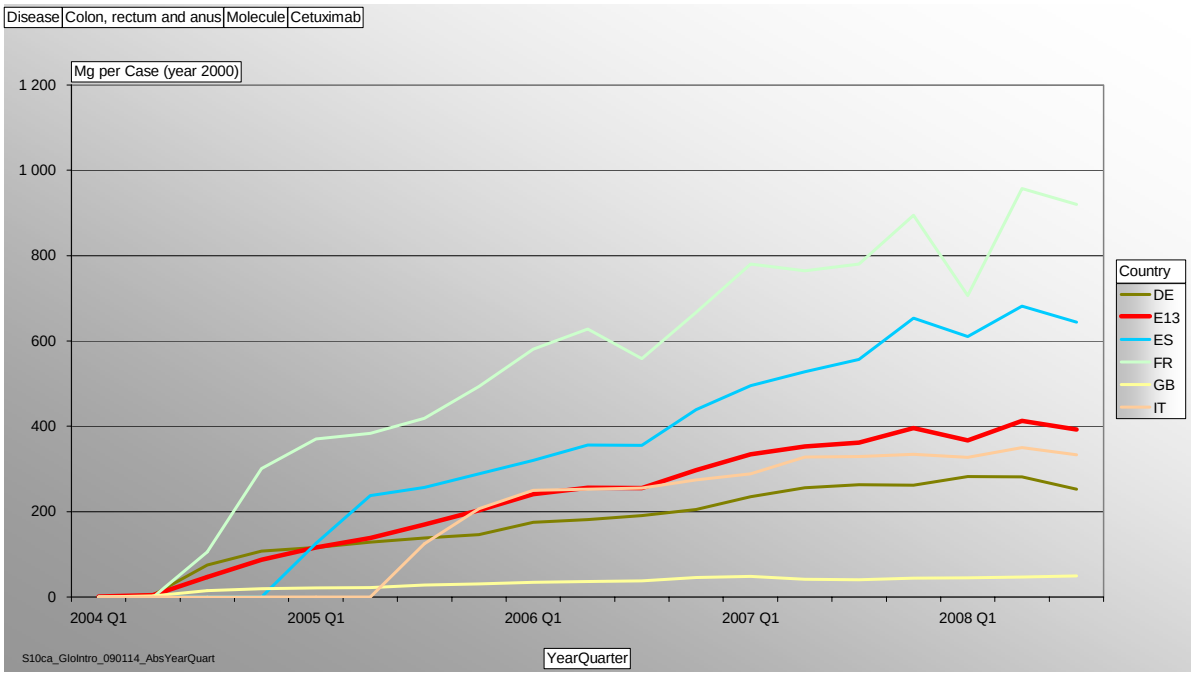

Figure 3-28. Usage of cetuximab expressed as mg/case (related to mortality in colorectal cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that cetuximab is also indicated for head and neck cancer.

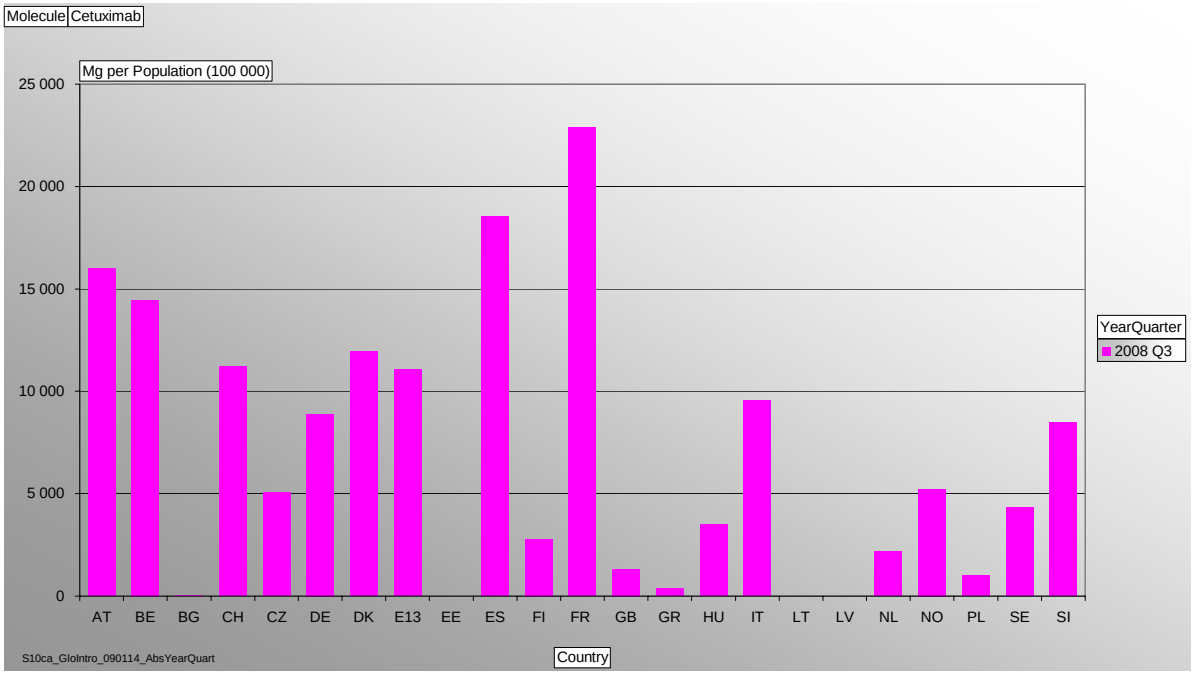

Figure 3-29. Usage of cetuximab in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 22 European countries. Please note that cetuximab is also indicated for head and neck cancer.

3.4.4 Chronic myeloid leukaemia (CML), Non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM)

Drug development in CML, NHL and MM represents major innovations, as described in the medical review. Imatinib in CML has fundamentally changed the outcome in CML as well as gastro intestinal stromal tumours (GIST). This is reflected in recent epidemiological reports, showing a dramatic improvement in outcome [78]. There are now also new small molecules (dasatinib and nilotinib) indicated for patients with CML that become resistant to imatinib.

NHL represents another malignant disease in which major breakthroughs have been seen that have fundamentally impacted outcome, as been reported in recent epidemiological reports [77]. Rituximab is an important new drug in the treatment of NHL and has, with expanding indications, become a key component in the treatment of NHL. The drug has, like imatinib in CML, changed the outcome of NHL.

The outcome for patients with MM has also changed incrementally. The therapeutic progress has been closely linked to innovations in medical therapy [79].

Here we report on the uptake of imatinib, rituximab and bortezomib.

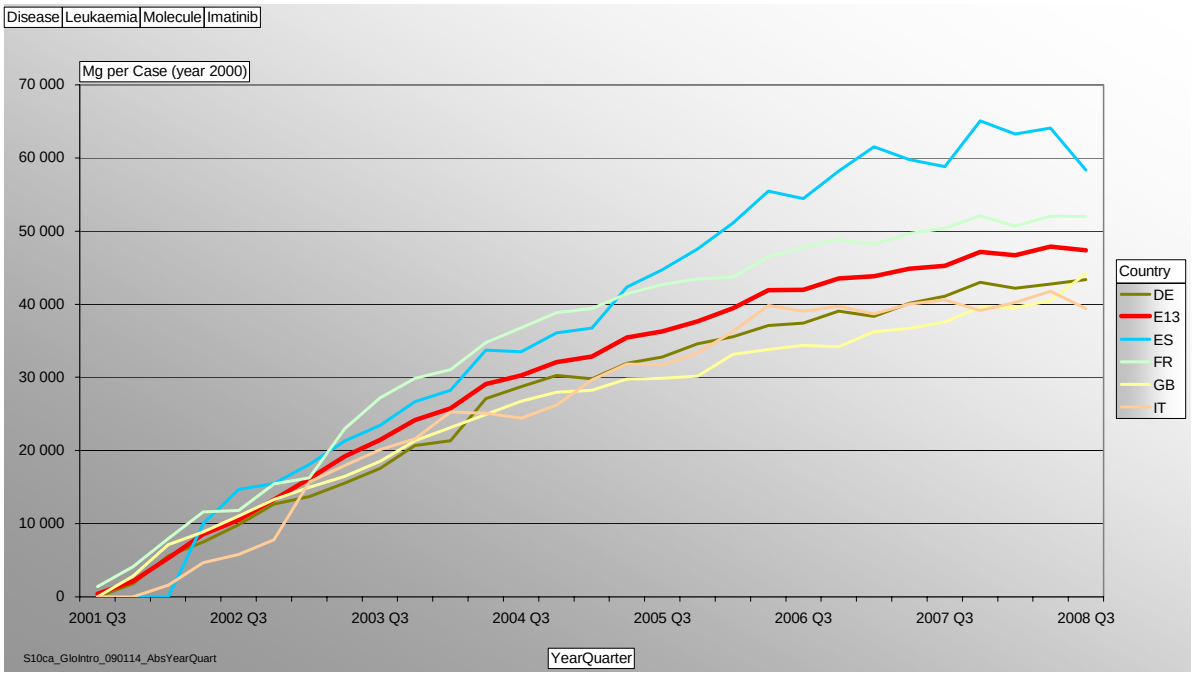

Figure 3-30. Usage of imatinib expressed as mg/case (related to mortality in leukaemia in 2000) in E13, France, Germany Italy, Spain and the UK.

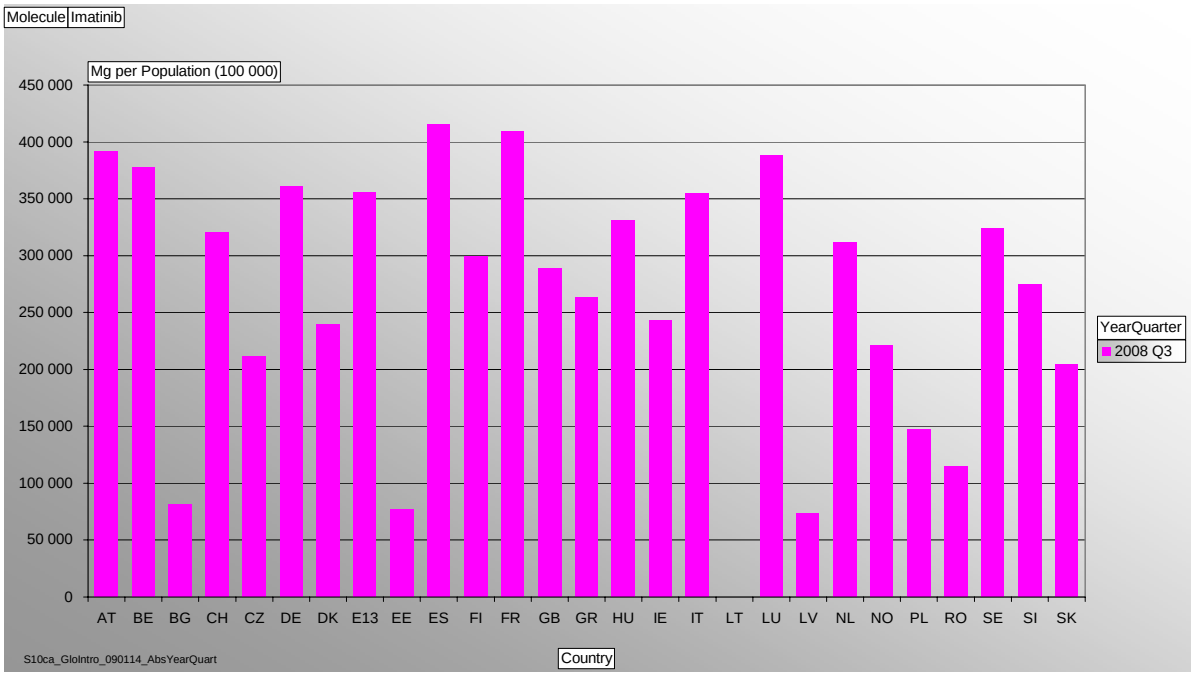

Figure 3-31. Usage of imatinib in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries.

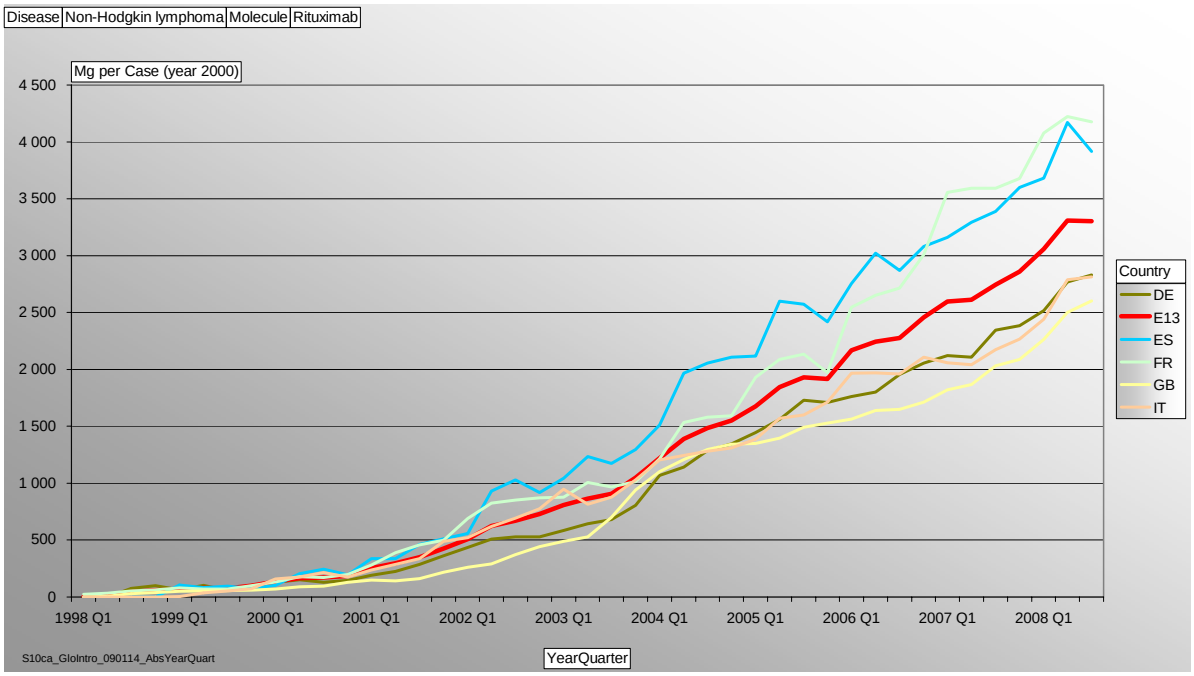

Figure 3-32. Usage of rituximab expressed as mg/case (related to mortality in NHL in 2000) in E13, France, Germany Italy, Spain and the UK.

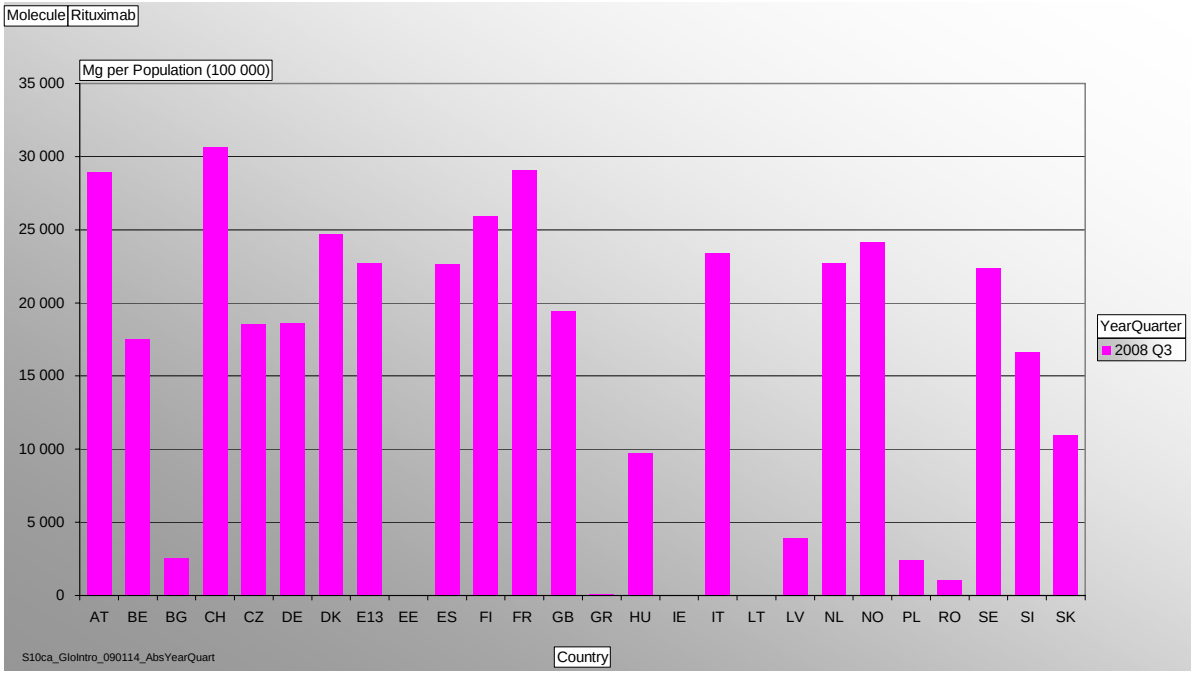

Figure 3-33. Usage of rituximab in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 25 European countries.

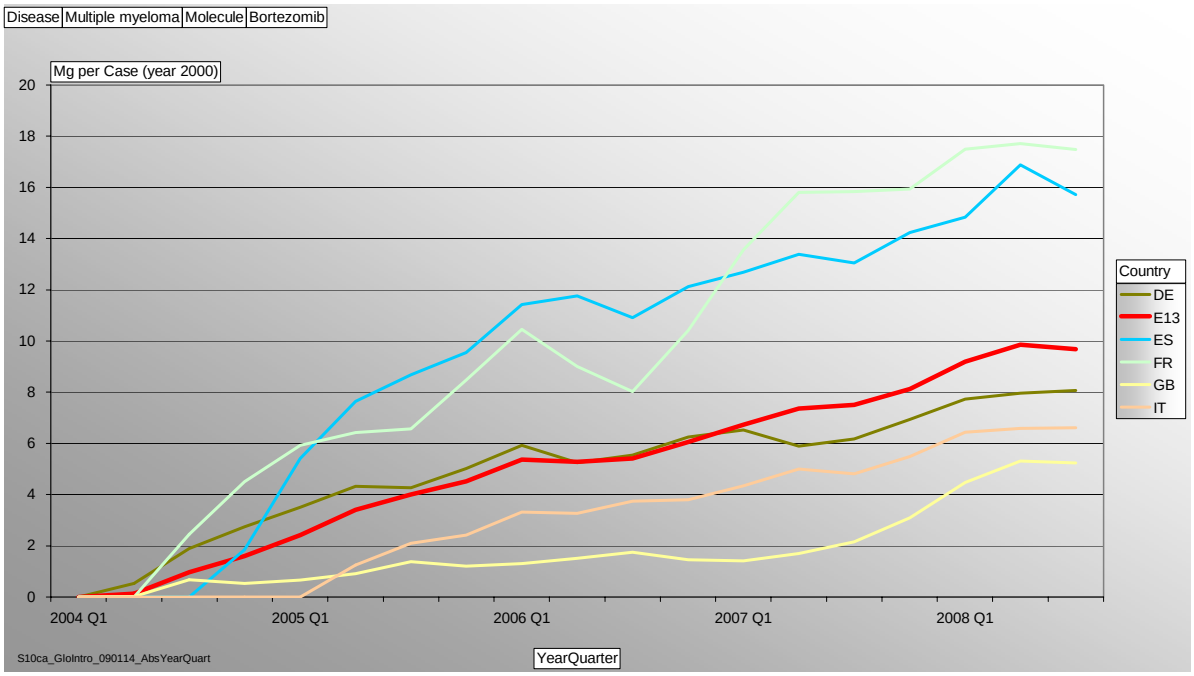

Figure 3-34. Usage of bortezomib expressed as mg/case (related to mortality in multiple myeloma in 2000) in E13, France, Germany Italy, Spain and the UK.

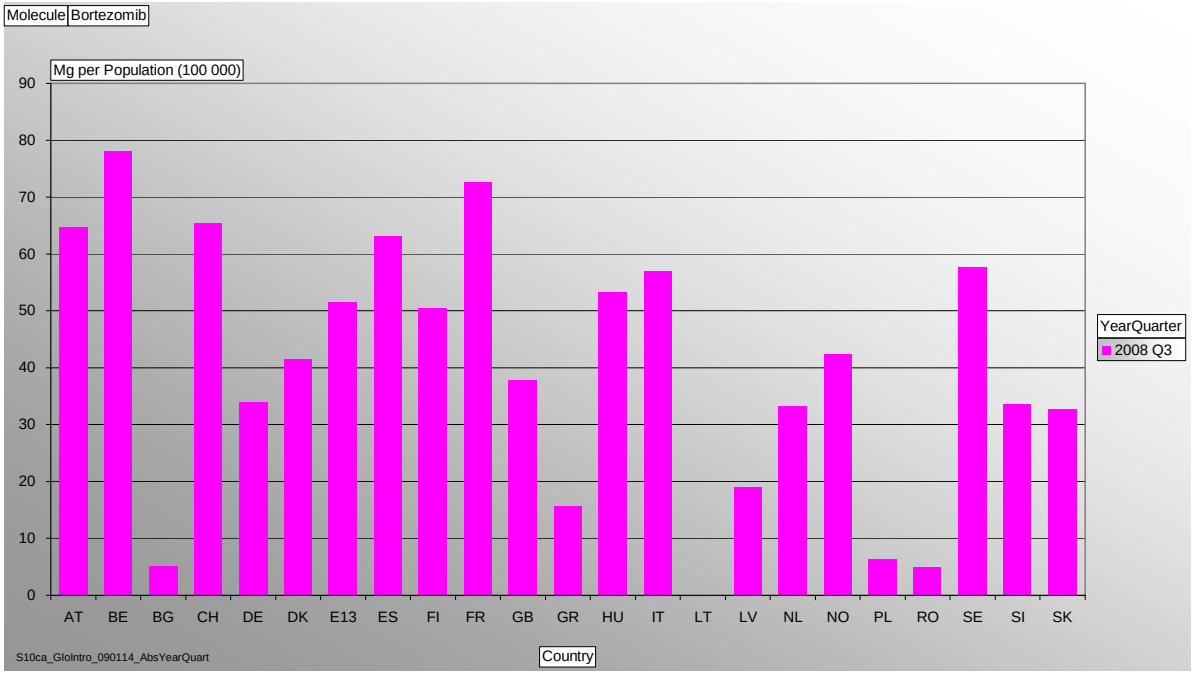

Figure 3-35. Usage of bortezomib in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 22 European countries.

3.4.5 Non-small cell lung cancer (NSCLC)

NSCLC has long been an area of therapeutic nihilism in many countries. It was not until a decade ago, when platinum-based chemotherapy was shown to provide a clear benefit for patients with advanced disease, that the development of modern chemotherapy in this area of oncology escalated. We now also have solid clinical evidence that adjuvant chemotherapy will also give substantial benefit in selected patient groups. During the 1990s new chemotherapy agents, like taxanes (docetaxel, paclitaxel), gemcitabine and vinorelbine came into use in combination with cisplatin or carboplatin. There are new therapeutic options in NSCLC, including EGFR-targeting agents, such as gefitinib and erlotinib, and chemotherapy with pemetrexed. The efficacy of both gefitinib and erlotinib has been linked to specific patient subgroups with different EGFR mutations [99].

The efficacy of pemetrexed has also been linked to specific pathological subgroups of non-small cell lung cancer [100].

In the following graphs we show uptake of gemcitabine, vinorelbine, erlotinib and pemetrexed. The sales are related to lung cancer mortality.

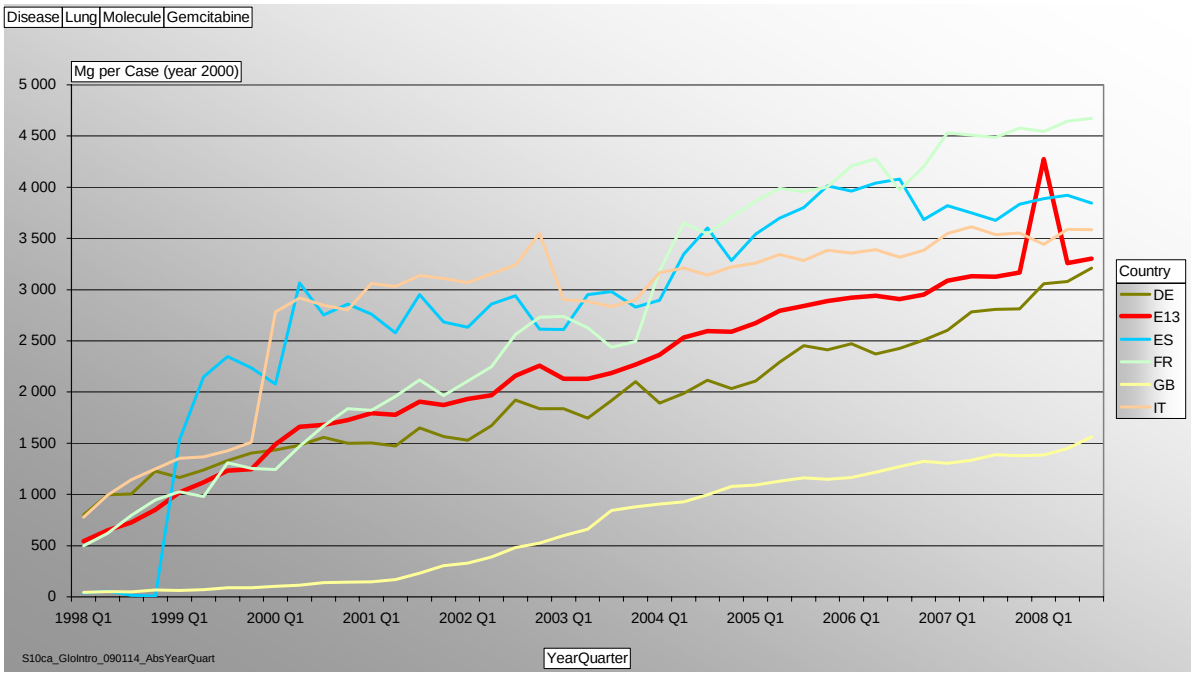

Figure 3-36. Usage of gemcitabine expressed as mg/case (related to mortality in leukaemia in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that gemcitabine is also approved in pancreatic- and breast cancer.

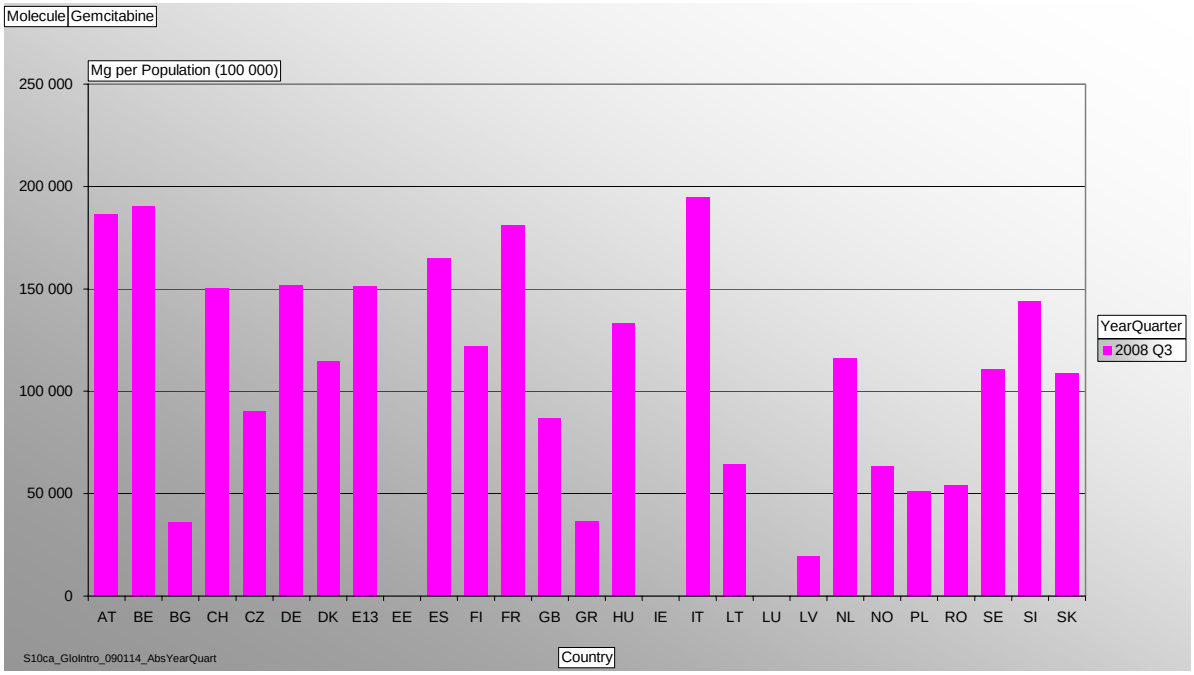

Figure 3-37. Usage of gemcitabine in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 26 European countries. Please note that gemcitabine is also approved in pancreatic- and breast cancer.

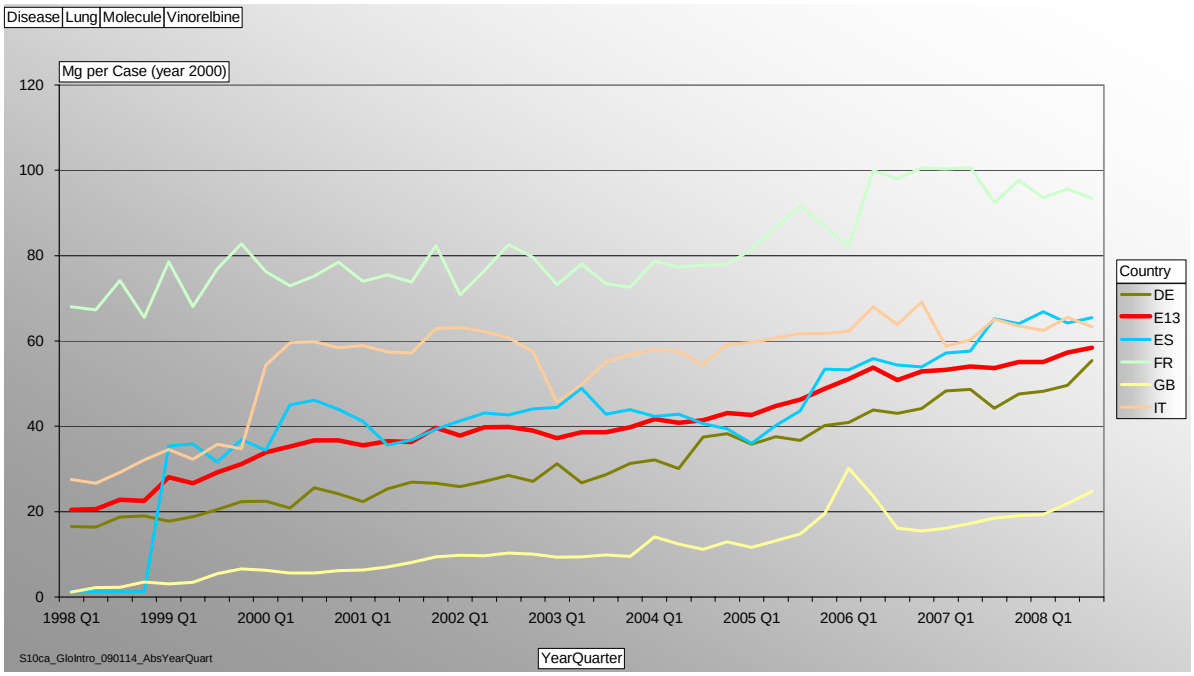

Figure 3-38. Usage of vinorelbine expressed as mg/case (related to mortality in lung cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that vinorelbine was approved in 1989.

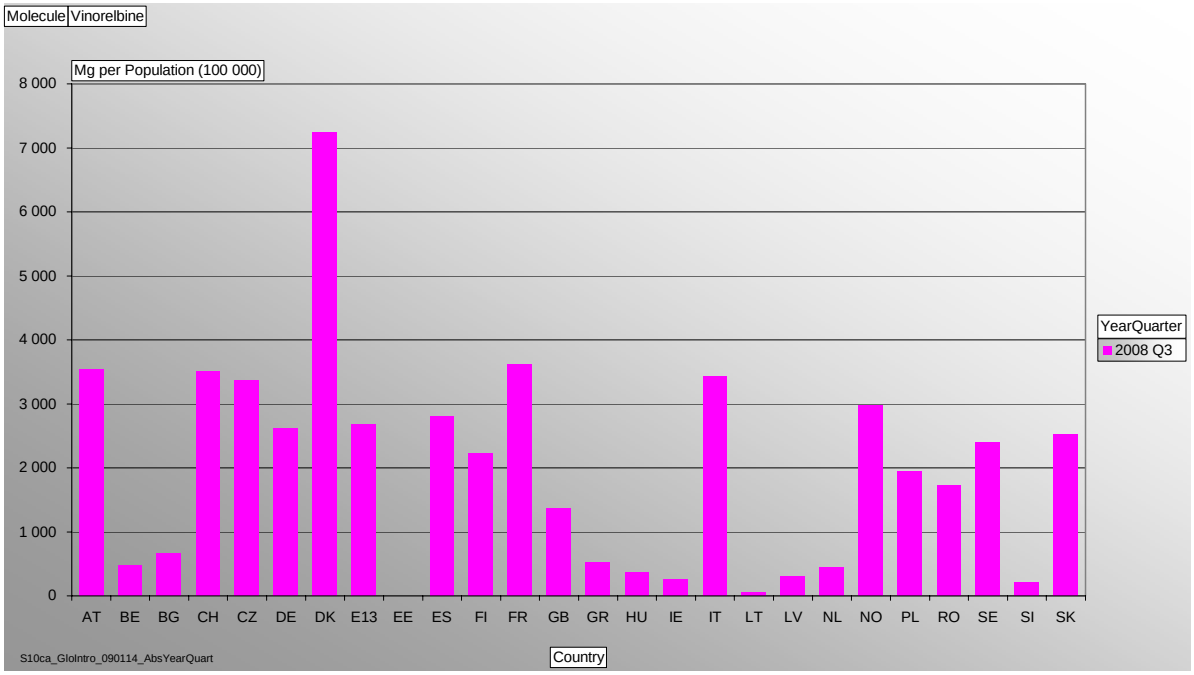

Figure 3-39. Usage of vinorelbine in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 25 European countries. Please note that vinorelbine was approved in 1989.

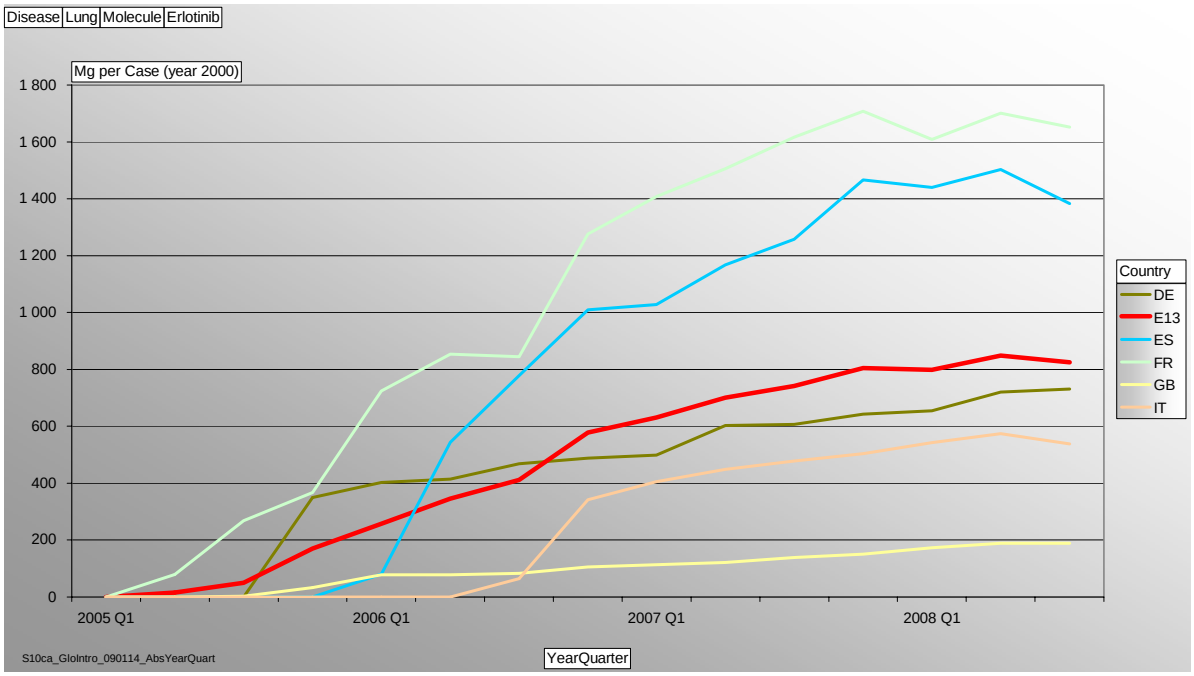

Figure 3-40. Usage of erlotinib expressed as mg/case (related to mortality in lung cancer in 2000) in E13, France, Germany Italy, Spain and the UK. Please note that erlotinib is also approved in pancreatic cancer.

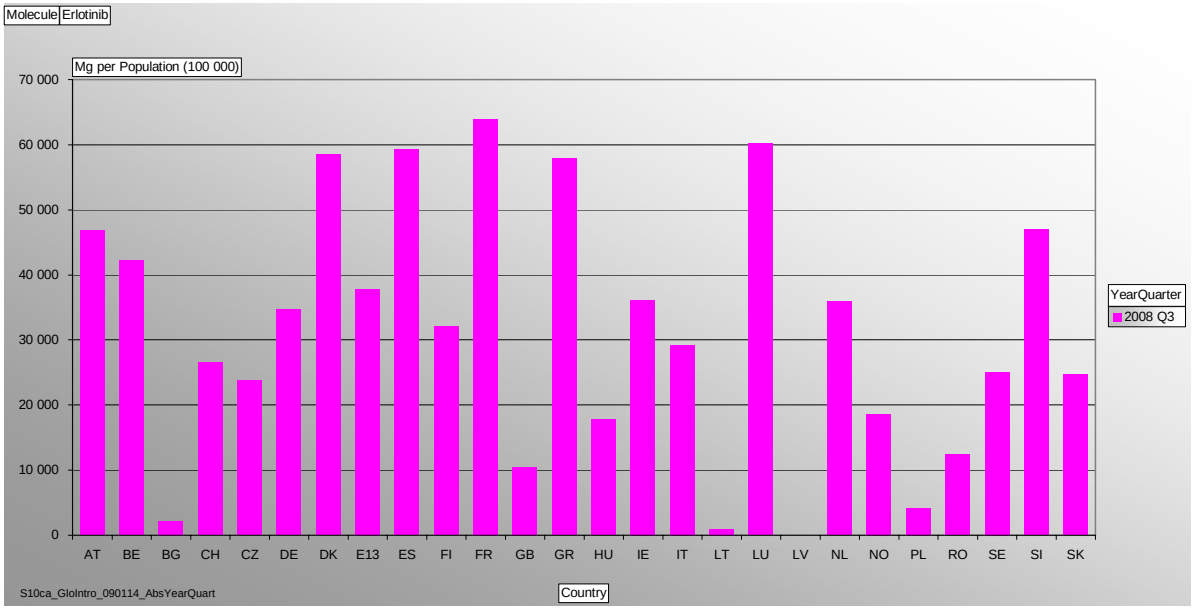

Figure 3-41. Usage of erlotinib in 2007, expressed as sales in mg/100,000 inhabitants in E13 as well as 25 European countries. Please note that erlotinib is also approved in pancreatic cancer.

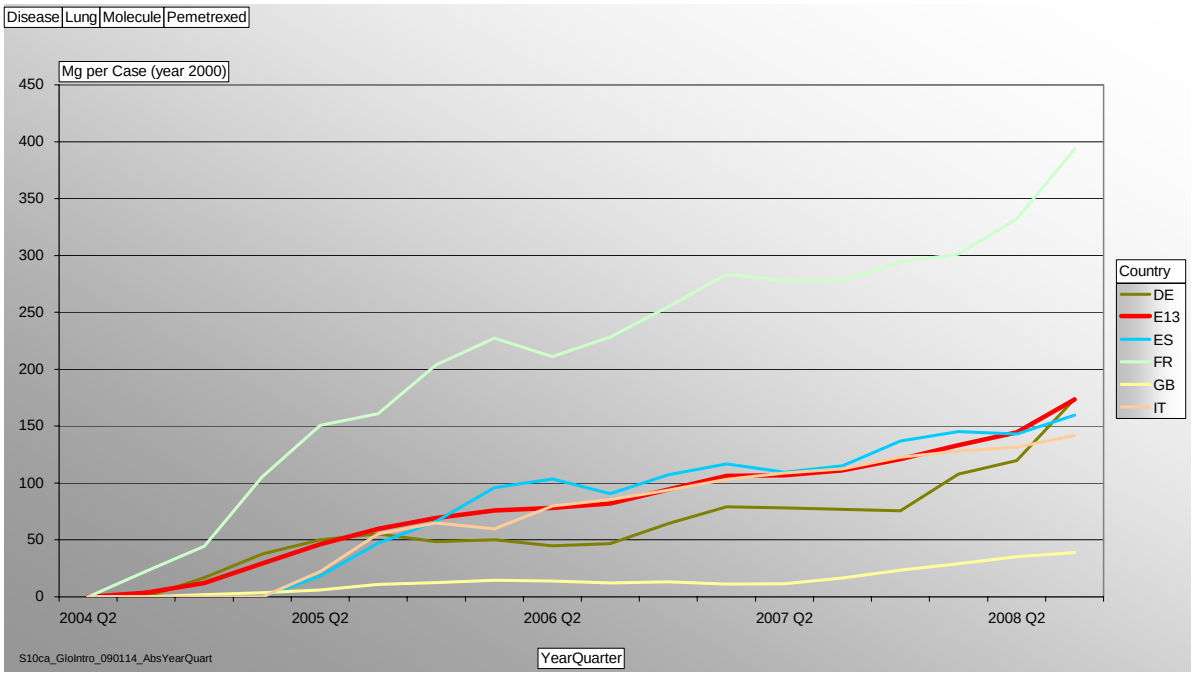

Figure 3-42. Usage of pemetrexed expressed as mg/case (related to mortality in lung cancer in 2000) in E13, France, Germany Italy, Spain and the UK.

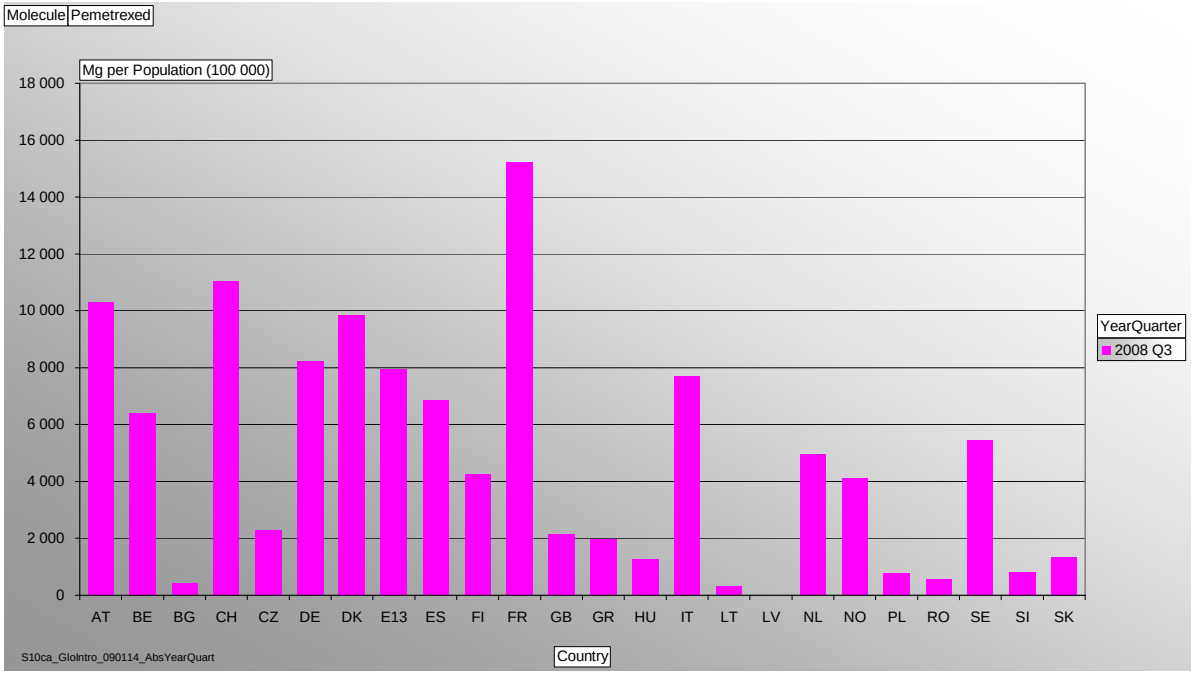

Figure 3-43. Usage of pemetrexed in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 23 European countries.

3.4.6 Renal cell cancer (RCC) and liver cell cancer (LCC)

Renal cell cancer accounts for 2-3 percent of cancer incidence and results in over 100.000 annual deaths worldwide. In developed countries the average age-adjusted incidence of RCC is approximately 12/100,000 in men and 5/100,000 in females. It is the most lethal urological cancer and the sixth leading cause of cancer deaths in the developed countries. For unknown reasons there has been an incidence increase of 3 percent over the last 30 years. Surgery remains the only curative therapy, and so far medical treatment has not been successful. Chemotherapy has been more or less ineffective and until recently the only effective treatment was cytokine-based immunotherapy with interferon or interleukin with relatively low response rates (~15 percent) and high toxicity. Over the last couple of years several new targeted therapies have been approved for treatment of renal cancer, including small TKIs, like sorafenib and sunitinib, as well as bevacizumab, the mTOR inhibitors temsirolimus (CCI-779) and everolimus (RAD001) [101].

Hepatocellular carcinoma (HCC, also called hepatoma) is a primary malignancy (cancer) of the liver. Most cases of HCC are secondary to either a viral infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis). Liver cancer is relatively uncommon in Europe, but represents a major health problem as one of the most common cancers in countries with a high incidence of hepatitis [102].

In RCC we present the use by sorafenib and sunitinib. Please note that sorafinib is also approved for primary liver cell cancer.

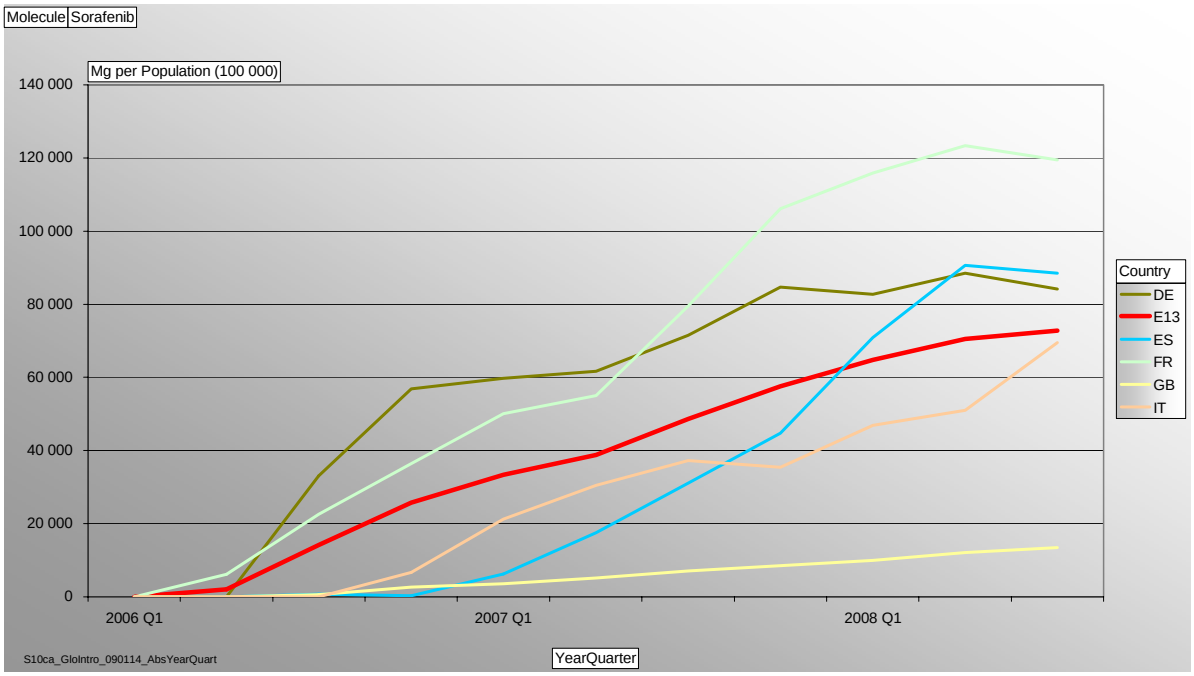

Figure 3-44. Usage of sorafenib expressed as mg/100,000 inhabitants E13, France, Germany Italy, Spain and the UK.

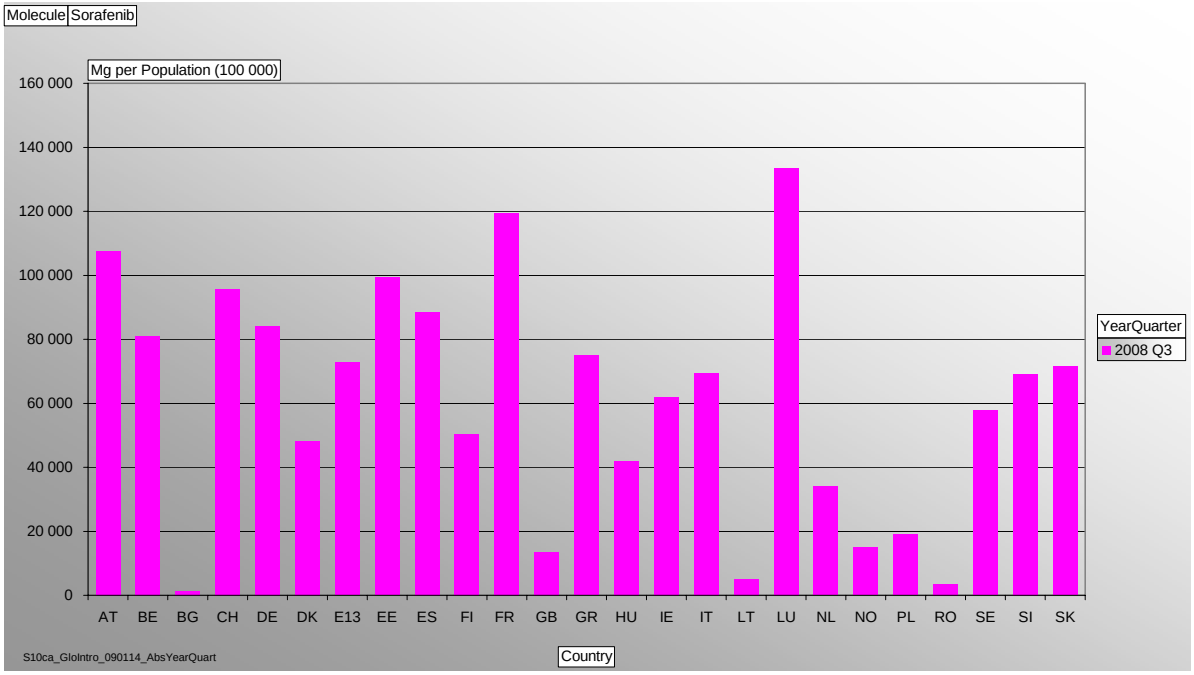

Figure 3-45. Usage of sorafenib in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 24 European countries.

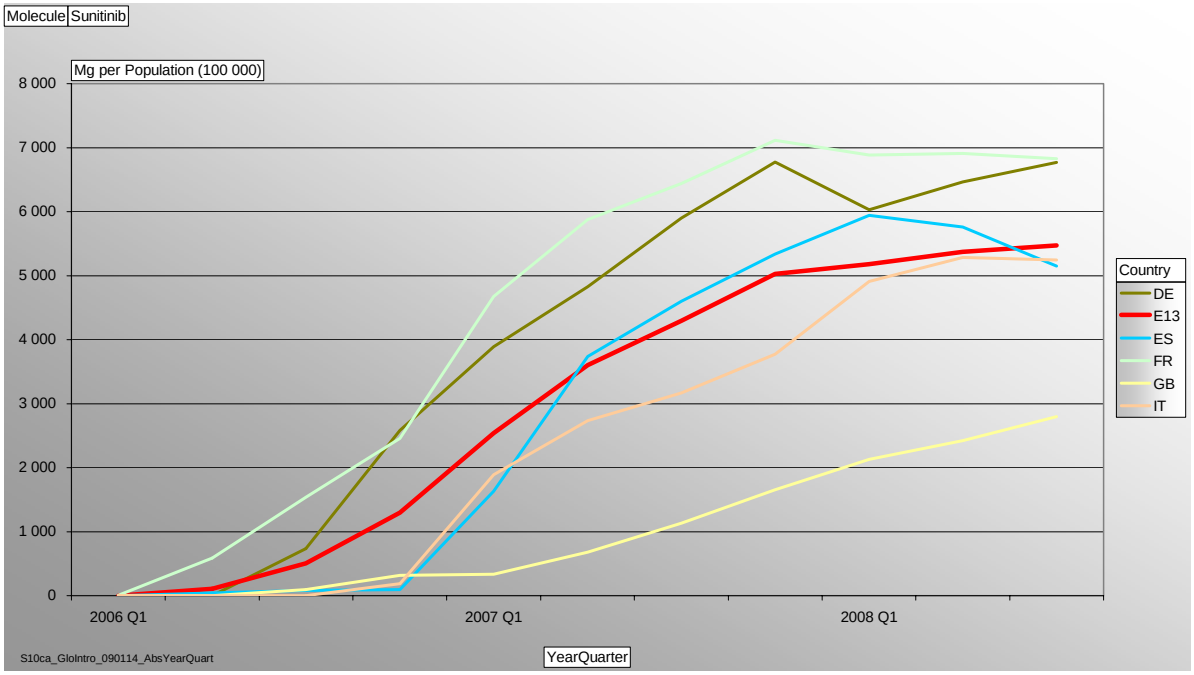

Figure 3-46. Usage of sunitinib expressed as mg/100,000 inhabitants in E13, France, Germany Italy, Spain and the UK

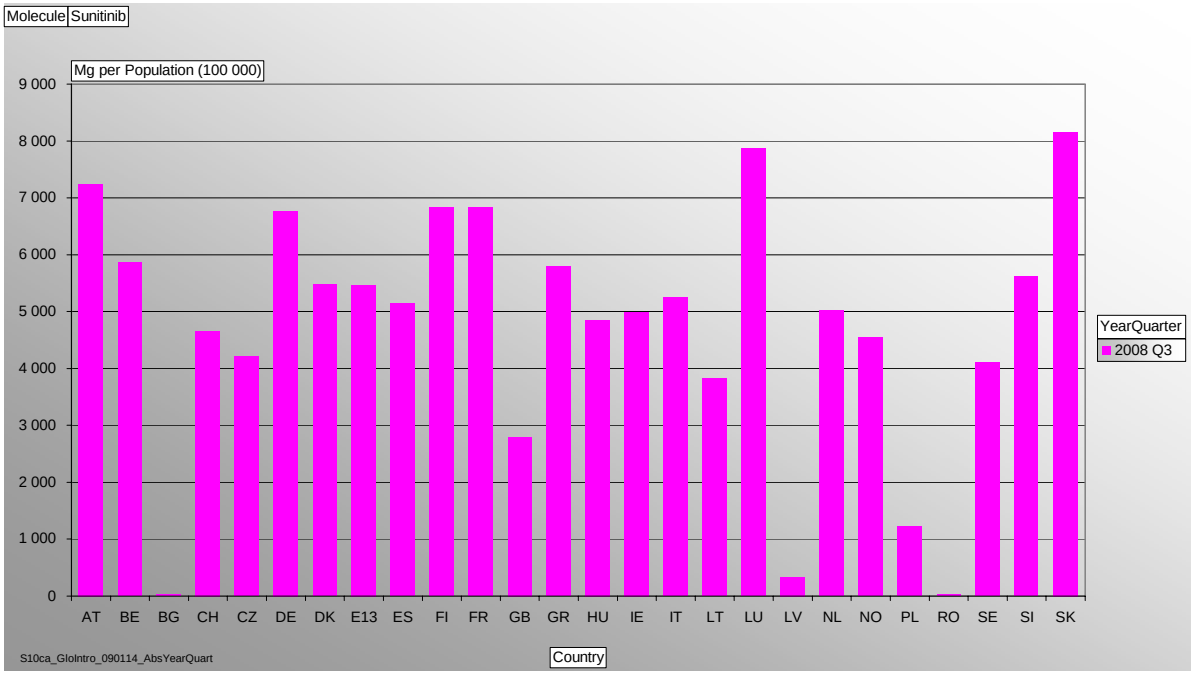

Figure 3-47. Usage of sunitinib in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 25 European countries

3.5 Conclusions

The number of available cancer drugs has increased substantially over the last 10-15 years. It is likely that further increase in the number of drugs will be seen over the next 5 years. The number of cancer drugs approved in 1995-2005 was around 25 and it is expected that the number of cancer drugs approved during the period 2007-2012 will be 50. (communication from IMS Health)

The cost of cancer drugs has increased about 5-6 times in the period 1998-2007. This increase is higher, but not dramatically different from the overall increase in the cost of cancer care. The cost is expected to increase at the same rate over the next 5 years, but will then gradually slow down, due to patent expirations and increased competition. (communication from IMS Health). It is also important to note that the cost increment is not only related to the introduction of new drugs. Actually, 2/3 of the costs for cancer drugs in 2007 came from drugs approved before 1999. The increase of these drugs, from €4.3 to €26.3 per capita is the major part of the increase in costs of cancer drugs during this time period. Thus, it seems that the differences in uptake of cancer drugs do not only reflect different opinions about the medical value and value for money for the most recent drugs, but also in general reflects the attitude to medical treatment of cancer patients. Countries with rapid uptake of new drugs also seem to have a high usage of all types of cancer drugs.

As shown in this chapter, there are great variations, both in the level of uptake and in the speed of uptake for all drugs included in the analyses. This highlights the inequality in access to cancer drugs. It also shows that the ability to access new cancer drugs depends on where the patient lives. Countries with lower income per capita have a slower uptake, despite the fact that drugs account for a large part of total health care spending in these countries.

4 Market Access for Cancer Drugs and the Role of Health Economics

The development 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 price, it is important to asses whether the higher costs are motivated by improvements in outcomes. With health care budgets becoming increasingly stretched, a greater emphasis is put on how to use the limited resources in the most efficient way. Health technology assessment (HTA) is a multidisciplinary approach to policy analysis, studying the medical, social, ethical, and economic implications of development, diffusion, and use of health technology. HTA, and the cost-effectiveness analysis that is a part of HTA, is often termed “the fourth hurdle” to market access for new drugs, after safety, efficacy and quality.

4.1 Pharmaceutical regulation and market access

Market authorization of new drugs is granted after evaluation of safety, efficacy and quality. Within the EU, there is a centralised procedure for this authorization. The producer submits an application to the regulatory body, the European Medicines Agency (EMEA). The Committee for Medical Products for Human Use (CHMP) grants market authorisation for the entire EU. CHMP also grants authorisation for drugs to be used in new indications.

Certain drugs may be given a simplified or accelerated approval procedure. These are usually drugs for serious and life-threatening illnesses, without existing effective treatments. Such exceptional circumstances often apply to drugs for rare cancers or cancers with high mortality. Since 2005 this simplified procedure has applied to some new oncology drugs.

Authorisation for the 20 anti-cancer drugs assessed from 1995 to 2005 took an average of 418 days. Almost 30 per cent of this time was used for administration, not related to the approval process itself [103]. By comparison, the average review time for all standard drugs in the US in 2004 was 387 days, and 180 days for priority drugs.

Drugs used in ambulatory care require in most countries formal decisions on reimbursement and pricing, while those used in hospitals are often to be covered by the general hospital budget. Drugs used in oncology are most often used in the hospital setting.

Most of the countries in Europe have formal procedures for making national reimbursement decisions, while others (mainly UK and Germany), there have no specific procedures before the drug may be prescribed under the reimbursement system [104]. For countries with formal decision processes, the reimbursement decisions include price negotiations and estimates of the forecasts of sales.

Although UK and Germany lack overt restrictions on pricing, it does not mean that the authorities in these countries do not intervene with drug 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, there are also reimbursement restrictions in place, as physicians have a greater responsibility for the use of drugs and have accountability against their own office budget.

In for example Belgium, Finland, the Netherlands, Norway, Portugal and Sweden the formalised decision-making process requires an economic evaluation, and the issue of cost-effectiveness plays an important role. For Denmark and Switzerland 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.

4.2 Hospital budgets and patient access to drugs

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 budget, which takes into consideration the number and type of patients treated. Budget impact will then be more important than cost effectiveness in a societal perspective, when a decision is made on the availability of a drug.

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 later transferred to ambulatory use, it is sometimes unclear how they should be handled in the reimbursement process.

Hospital budgets are 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. Regardless of whether payments are based on fixed per diem or on DRG systems, it is necessary to have budget flexibility when new drugs come to market. If a new and expensive drug should be financed within a given DRG reimbursement, the hospital will run a deficit, and thus has to save in other areas, or face the situation with 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) [29]. 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 day care centres or at 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 challenges in funding new cancer therapies in a hospital setting, certain systemic barriers also exist, further inhibiting 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 effictive, 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, this very significant issue of adapting healthcare budgets in general and hospital budgets in particular to the introduction of new cancer drugs must be immediately addressed, if the issue of inequity in patient access to cancer drugs is to be resolved.

Appropriate resources should be allocated independently of 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 cost and benefit to avoid sub-optimal decisions, due to economic incentives to select certain forms of administration.

4.3 Pricing of pharmaceuticals

There are several factors influencing the pricing of pharmaceuticals. First, the price that a pharmaceutical company sets must cover expenses, associated to the research and development process, resulting in the drug. The considerable investment in drug development is a sunk cost at the time of launch and drug prices are negotiated. This is in strong contrast to the marginal cost of producing additional units, which is generally very low. Patent protection is one of the regulations of the drug market, aimed at providing incentives for research and development and at the same time controlling society's costs for drug treatments. The patent system provides a mean for pharmaceutical companies to gain a monopoly-like position on the market during a certain time period following the launch of a new drug, which allows the recuperation of R&D investments before permitting competitors to enter the market with generic copies.

A generic drug is a bioequivalent drug which may be marketed after patent protection of the original has expired. Generics are usually priced much lower than the original product. The prices of many of the high-priced oncology drugs introduced during the last decade may therefore be expected to be reduced considerably as their patents expire.

The government is often the dominant buyer on the national pharmaceutical market; a position that allows them to negotiate prices with manufacturers. In addition, various other methods may be used to control and regulate drug prices. A study by the US Department of Commerce [13], compared pharmaceutical price controls of 11 OECD countries to the US, and found that principal methods of price control in the countries studied were reference pricing, procedural barriers, restrictions on dispensing and prescribing, and reimbursement.

Danzon and Furukawa [105] compared manufacturers' prices in 8 countries (Canada, Chile, France, Germany, Italy, Japan, Mexico, and the United Kingdom) relative to prices in the United States. In the countries with strict price regulations, generic penetration of the market tended to be lower than in less regulated markets. In price-regulated markets, original products might be priced lower while on patent, but are able to better defend their market share after patent expiry, since generic competition in weaker. This is partly a consequence of other policies to encourage use of generics, such as compulsory licensing policies and incentives for pharmacists to substitute generics.

Comparing prices and costs of pharmaceuticals between different countries by using a common currency unit is problematic. Exchange rates do not reflect the relative purchasing power across countries and moreover bias may be introduced, due to exchange rate fluctuations. Danzon and Furukawa concluded that variations in drug prices are approximately in line with income differences in high-income countries. Moreover, the study also concluded that any currency fluctuations, following the pricing of certain pharmaceuticals greatly contributed to price differences across countries. International variations in pharmaceutical prices were lower than for other medical interventions. In addition, not only the relative income differs between countries, but also other relative prices, for example between different therapeutic alternatives, may differ from country to country, making it difficult to interpret the consequences of a certain average price level for pharmaceuticals.

There seems to be a trend towards convergence of prices between countries for new innovations. A consequence of this is that the relative costs of, for example, new drugs for cancer may vary from country to country with different levels of income. This may contribute to differences in use of a drug, as low income countries cannot afford drugs at the same price as in the high income countries. Diversified prices may give a more equal access, but this policy is dependent on measures to control parallel imports and re-sale to high price countries. Producers' restrictions on parallel imports are prohibited by EU regulations.

4.4 How can new drug therapies be funded?

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 and Germany), separate lists of innovative drugs exist. These may include special funding for the drugs to be accessed outside of the hospital systems or

enabling hospitals to apply to get new cancer drugs placed on the list, allowing them to switch to innovative drugs, within the restrictions of their hospital budgets. 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 [106].

However, in order to facilitate faster patient access to new cancer medicines, there may be a number of options to consider:

- Can a policy of separate funding for new cancer drugs be introduced 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?

It is important to distinguish between regulatory decisions regarding (1) the availability of the drug in the national market, (2) the reimbursement of a new drug, and (3) health technology assessments by government agencies. Guidance from medicine agencies in various countries indicates that a new drug therapy should be available within certain time limit, e.g. within 180 days in the EU. Following the granting of the license, it should not be necessary to undertake another safety and efficacy appraisal of the new drug in order to make reimbursement decisions. The national decision is related to whether the drug should be reimbursed or not and hence available through the national healthcare system or other payers. As we explain later in this section, the requirement for health technology assessments within this reimbursement process differs from one country to another.

4.5 Impact of reimbursement decisions on drug availability

In the 1980s and 1990s, discussions regarding access to new drugs focused on the time lag between application and granting of marketing authorization. This delay was identified as the first barrier for patient access to new medicines. Additional barriers have since been identified in the form of country specific negotiations for price approval and the granting of reimbursement.

The European Federation of Pharmaceutical Industries and Associations (EFPIA), approached IMS to prepare a database to be used to analyse delays in market access for pharmaceuticals in Europe[107]. The database is used to measure total time delays from marketing authorisation of a new drug to the availability of this drug to patients in Europe. It records the average delay between marketing authorisation and availability of all new substances for each country, as well as the rate of availability (measured by the numbers of approved products available to patients under normal reimbursement conditions). Delays due to launch delays are not included.

For each country, all products with an identified first marketing authorisation date during the study period of January 2003 to December 2006 have been included. Products included in the calculation are those for which the appropriate pricing, reimbursement and/or publication dates have been identified. If pricing, reimbursement and/or publication dates are not available, products have been excluded. This includes products awaiting a pricing or reimbursement decision. The database covers 22 European countries and the result of the latest update is shown in Table 4-1.

As the time from market access to availability to patients varies widely between hospital and ambulatory setting, a separate analysis has been performed for a number of countries as shown in table 4-2.

Country	No of products	No of products accessible to patients	Average time Delay between approval and market access	Maximum time Delay between approval and market access	Minimum time Delay between approval and market access
Austria	83	46	397	1111	0
Belgium	84	48	478	1186	28
Czech Republic	67	48	270	1131	0
Denmark	81	25	74	1043	0
Estonia	63	11	235	433	97
Finland	86	56	167	940	0
France	84	47	326	636	69
Germany	80	80	0	0	0
Greece	83	56	239	867	20
Hungary	85	34	317	791	0
Ireland	72	57	82	384	0
Italy	73	48	335	817	59
Netherlands	78	59	188	721	0
Norway	85	37	147	766	0
Poland	78	5	214	731	0
Portugal	87	29	196	969	0
Slovakia	72	48	422	1308	35
Slovenia	63	28	281	579	0
Spain	82	44	282	742	24
Sweden	85	57	169	805	0
Switzerland	79	51	194	1292	20
UK	77	77	0	0	0

Table 4-1. Average time delays in days between marketing authorization and effective market access (hospital and retail combined) – all products (marketing authorization 1 January 2003 to 31 December 2006). Status 30 June 2007 [108].

We can see in table 4-1 that Germany and the UK have no reimbursement delay. The figure given for the UK is, however, somewhat misleading as we know that there are significant delays in reimbursement and availability of new drugs, due to the impact of NICE reviews. France, Hungary and Italy demonstrate a delay of almost one year due to the time it takes for the formal reimbursement decision. The average time from market authorisation to patient access in Austria, Belgium and Slovakia is well over a year. This is significantly longer than the 180 days stipulated by EU regulation.

It should also be noted that this measure of patient delay, while applicable to cancer drugs, is not exactly the same. The formal reimbursement process for cancer drugs is not applicable to all countries in the report. In Austria, Finland, the Netherlands and Sweden for example, cancer drugs used in hospitals are immediately available once the marketing authorization is granted.

Country		Number accessible to patients	Average time to access (days)	Minimum delay (days)	Maximum delay (days)
Austria	Retail	34	538	178	1111
	Hospital	12	0	0	0
Belgium	Retail	40	495	28	1186
	Hospital	8	392	256	581
Finland	Retail	36	259	38	940
	Hospital	20	0	0	0
France	Retail	31	334	69	636
	Hospital	16	299	155	434
Greece	Retail	44	224	26	685
	Hospital	12	295	20	867
Ireland	Retail	40	116	27	384
	Hospital	17	4	0	61
Italy	Retail	14	344	122	644
	Hospital	34	331	59	817
Netherlands	Retail	50	221	38	721
	Hospital	9	0	0	0
Norway	Retail	17	306	0	766
	Hospital	20	11	0	224
Portugal	Retail	22	246	0	969
	Hospital	7	39	0	271
Spain	Retail	25	317	159	742
	Hospital	19	236	24	556

Table 4-2. Average time delays in days between marketing authorisation and effective market access in hospital and retail setting – all products (marketing authorisation 1 January 2003 to 31 December 2006). Status 30 June 2007 [108].

In table 4-2 we see that the differences in delay are large in many countries, with hospital based use is generally accessible earlier, compared to drugs used in outpatient setting. Still, the delays from market authorization to accessibility in hospital are very long in Belgium, France, Greece, Italy and Spain. In Greece the delay is actually even longer for hospital based use than for drugs used in outpatient setting.

Still, the decisive factor for the availability of new innovative cancer drugs to cancer patients is the availability and allocation of budget within the hospital sector. Thus, there are clearly opportunities for procedural improvements with regards to access to cancer drugs to potentially address some of the current imbalance. A number of possible options are presented below:

- Expediting the review time for the marketing authorization of new innovative cancer drugs, e.g. through the Centralized Procedure in the EU.

- Ensuring that, once a cancer drug has obtained its marketing authorization, it is then available at the national level without further delays due to price and reimbursement negotiations or additional restrictions.

- Ensuring that any economic evaluation/health technology assessment regarding a new cancer drug is done expeditiously to facilitate (as opposed to delay) patient access.

- Ensuring that appropriate and adequate funding for new innovative cancer drugs is included in healthcare systems and hospital budgets preferably on a proactive and not reactive basis.

4.6 Some policy issues in the allocation of resources for new drugs

When considering whether or not to grant reimbursement or allocate budgetary resources for a new drug or other treatment, one issue arising is the uncertainty regarding long-term consequences of the use of new drugs. Currently, clinical trial data are used to evaluate the use of new drugs and its use is extrapolated to long term use/follow-up. Payers do express uncertainty, however, regarding the 'real life' usage and the future potential of these new drugs.

The Swedish national HTA agency, SBU, assesses new cancer drugs based on costs and benefits. 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 assess future benefits. One example is the vaccination against Human Papilloma Virus, 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, especially as new targeted drugs will increase in the number of strategies [109].

A cancer drug is often first used for very limited indications and severe disease status, where the medical need is high. Later the use is extended to other indications, such as in 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 [14]. 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.

While HTA and economic evaluations are helpful in assessing the value of new drug therapies in relation to costs, the allocation of appropriate budgetary resources is a real issue. Costs of new drugs are concentrated to the budgets for medicines in hospitals and ambulatory care settings. Patients will not experience the potential benefits of these new innovative cancer treatments, unless budgets are made available. A European study of the influence of economic evaluation in health-care decision making was recently undertaken. The main conclusion from the study is that economic evaluations are used differently in different healthcare systems. There is no clear and consistent pattern, even if many European countries have introduced economic evaluations in health policy making. Clearly economic evaluations are country-specific, due to country specific costs[110]. It is also clear that different government agencies use economic evaluations for different policy decisions. In Sweden, for example, the pharmaceutical benefits board (LFN) uses economic evaluations as one piece of information for reimbursement decisions, the health technology assessment agency (SBU) use them as part of technology assessments and the National Board of Health and Welfare (Socialstyrelsen) use such studies for treatment guidelines.

4.7 The role of health technology assessments

4.7.1 HTA Agencies

Health technology assessments in Europe are increasing in importance and public agencies are established in most countries. Most of these are national, but in some countries, for example in Spain and Italy the most important ones are at a regional level.

It is expected that the decisions made by the leading agencies, for example those in the UK, Germany, and France, are likely to have an impact on the rest of the countries in Europe. NICE in the UK has for example been approached to share its processes and guidance internationally. They are also known to have high visibility within, and outside of Europe, which is facilitated by the appraisals and that the decision making process is transparent and the results are publicly accessible on their web site.

In Italy, no national HTA agency existed until 2007, when *La Società Italiana di* Health Technology Assessment (SIHTA) was established, There are however a number of regional agencies emerging. In Spain there are several regional HTA agencies, serving regional health care services, responsible for provision of health care and also for the financing of drugs. Their work is coordinated at the national level of *Agencia de Evaluación de Tecnologias Sanitarias* (AETS).

In the Central and Eastern European countries, there is no tradition of the use of HTA and requirements of economic evidence in the formal reimbursement and pricing decisions. However, in recent years most of these countries have established national HTA agencies. Examples of these are *AHTAPol* in Poland, and *HUNHTA* in Hungary. In Slovenia, the public health Institute *Institut za varovanje zdravja Republike Slovenije* has established a department with the responsibility to perform HTAs.

There are also international networks of HTA agencies, aiming at exchanging knowledge and methods across countries. In 2004 the European Commission and Council of Ministers defined targeted HTA as a political priority. As a response to that, the *European network for Health Technology Assessment* (EUnetHTA), was founded in 2006 with the aim of coordinating the work of HTA organizations in Europe. The objectives are to:

- reduce overlap and duplication of efforts and hence promote a more effective and efficient use of resources.

- increase the HTA output and input to decision-making in the member states and hence increase the impact of HTA.

- strengthen the link between HTA and healthcare policy making in the EU and member states.

EUnetHTA has 63 public funded partner organizations in 32 countries, including all EU member states, except Slovakia and Bulgaria, as well as Norway and Switzerland in Europe and four other countries outside Europe. Among the partner organizations are national/regional agencies, universities and research institutes.

Table 4-3 shows the European members of the two largest international HTA networks, INAHTA and EUnetHTA. All countries but Bulgaria and Czech Republic are represented in at least one of the two networks. Although the role of the HTA agencies vary from country to country, the membership in these organizations show that there are agencies involved in international collaboration. It should be noted that some of the EUnetHTA member agencies are not associated partners financially and technically contributing, but have more of an advisory role, for example the agencies in Poland, Portugal, Romania, and Italy.

Country	Members in EUnetHTA	Members in INAHTA
Austria	Ludwig Boltzman Institute of HTA Austrian Health Institute Hauptv. der Österr. Sozialversicherungstr.	Ludwig Boltzman Institute of HTA
Belgium	KCE – Belgian Health Care Knowledge Centre	KCE – Belgian Health Care Knowledge Centre
Denmark	DACEHTA – Danish Centre for Evaluation and HTA DSI- Danish Institute for Health Services Research Center for Applied Research and Technology Assessment, University of Southern Denmark HTA and Health Service Research, Center of Public Health	DACEHTA - Danish Centre for Evaluation and Health Technology Assessment DSI - Danish Institute for Health Services Research
Estonia	University of Tartu, Dept of Public Health	
Finland	FinOHTA - Finnish Office for HTA	FinOHTA - Finnish Office for HTA
France	HAS - French National Authority for Health CEDIT - Commitee for Evaluation and Diffusion of Innovative Technologies	HAS - Haute Autorité de Santé CEDIT - Commitee for Evaluation and Diffusion of Innovative Technologies
Germany	DAHTA@DIMDI- German Agency for HTA IQWIG - Institute for Quality and Efficiency in Health Care University of Lübeck, Institute for Social Medicine Technische Universität Berlin University of Bremen, Interdisciplinary Centre for HTA German HTA Association (CP) Public Health Genomics European Network (PHGEN), German Center for Public Health Genomics (DZPHG) (CP)	DAHTA @DIMDI - German Agency for HTA IQWiG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Hungary	HunHTA - Unit of Health Economics and Health Technology Assessment	
Ireland	HIQA – Health Information and Quality Authority	
Italy	ASSR Regione Emilia-Romagna - Agenzia Sanitaria e Sociale Regione Emilia-Romagna Age.na.s.- Agenzia Nazionale per i Servizi Sanitari Regionali Università Cattolica del Sacro Cuore, Policlinico universitario “A. Gemelli”, Health Technology Assessment Unit and Laboratory of Health Economics (Institute of Hygiene) Regione Veneto	
Latvia	VSMTVA - Health Statistics and Medical Technology State Agency	VSMTVA - Health Statistics and Medical Technologies State Agency
Lithuania	StaHeCCA - State Health Care Accreditation Agency under the Ministry of Health	StaHeCCA - State Health Care Accreditation Agency under the Ministry of Health

Table 4-3. HTA agency memberships in EUnetHTA and INAHTA by country 2008 (cont)

(Continued)

Country	Members in EUnetHTA	Members in INAHTA
Poland	Agency for HTA in Poland, AHTAPol (CP) CEESTAHC - Central and Eastern European Society for Technology Assessment in Health Care	AHTAPol - Agency for Health Technology Assessment in Poland
Portugal	Institute of Molecular Medicine (CP)	
Romania	National School of Public Health and Health Services Management (CP from 2007)	
Slovenia	Institute of Public Health of the Republic of Slovenia	
Spain	AETS - Agencia de Evaluación de Tecnologias Sanitarias AETSA - Andalusian Agency for Health Technology Assessment CAHTA - Catalan Agency for Health Technology Assessment and Research Galician Agency for Health Technology Assessment OSTEBA - Basque Office for Health Technology Assessment Servicio Canario de la Salud UETS - Unidad de Evaluación de Tecnologías Sanitarias	AETS AETSA - Andalusian Agency for Health Technology Assessment AVALIA-T - Galician Agency for Health Technology Assessment CAHTA - Catalan Agency for Health Technology Assessment and Research OSTEBA - Basque Office for Health Technology Assessment UETS - Unidad de Evaluación de Tecnologías Sanitarias
Sweden	SBU - Swedish Council on Technology Assessment in Health Care	SBU - Swedish Council on Technology Assessment in Health Care
The Netherlands	CVZ - College voor zorgverzekeringen ZonMw	CVZ - College voor Zorgverzekeringen ZonMw GR - Gezondheidsraad
The United Kingdom	NICE - National Institute for Health and Clinical Excellence NCCHTA - National Coordinating Centre for HTA CRD - Centre for Reviews and Dissemination, University of York (CP)	NHS QIS – Quality Improvement Scotland NCCHTA - National Coordinating Centre for Health Technology Assessment CRD - Centre for Reviews and Dissemination, University of York IAHS - Institute of Applied Health Sciences NHSC - National Horizon Scanning Centre
Iceland	Directorate of Health	
Norway	NOKC - Norwegian Knowledge Centre for the Health Services	NOKC - Norwegian Knowledge Centre for the Health Services
Switzerland	SNHTA - Swiss Network for Health Technology Assessment (CP)	MTU-SFOPH - Medical Technology Unit - Swiss Federal Office of Public Health

Table 4-3 (continued). HTA agency memberships in EUnetHTA and INAHTA by country 2008

Health technology assessments are based on knowledge and expertise from different countries, which opens for international collaboration between HTA agencies. An assessment in one country may benefit from studies in another country by adapting these with national data. This may be one option in countries where resources available for HTA are limited or where there is a

limited tradition of applying such assessments [27]. All countries may not need to assess all technologies. Assessments already done in other countries may indicate when it is useful to perform a local HTA.

4.8 Review of databases on health technology assessments

Cost-effectiveness information is an important part of HTA reports published by HTA agencies. The evaluation involves the study of the medical, social, ethical and economic implications of the development, distribution and use of a health technology, classified as prevention, rehabilitation, vaccines, pharmaceutical drugs and devices, and other medical and surgical procedures. Reports produced by HTA agencies supporting decision-making in healthcare aim at improving the quality and cost-effectiveness of the use of health technologies. They are intended for those who make choices regarding healthcare options (including professional caregivers, healthcare administrators, planners and health policy-makers). Therefore, HTA assessments can be expected to have a strong influence on market access. In many cases there is also a direct link between the assessment by the HTA agency and funding for the technology appraised. For example, in the UK there is a direct link between the issuance of a positive guidance on a new drug therapy by NICE and budget allocated for the reimbursement of this new therapy by the National Health Service (NHS). We have performed a review of three databases containing HTA information to answer questions regarding the role of HTAs on patient access to new cancer drugs:

- How many economic evaluations related to cancer drugs have been published between 1991 and 2007, and has the number of these reports increased over time?
- In which countries were these reports prepared?
- What drugs have been evaluated

The databases scanned to address these questions are the HTA database of the International network of Agencies for Health Technology Assessments (INAHTA); the Health Economic Evaluation Database (HEED) (both from 1991 to 2007) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) database (from 1998 to 2007).

4.8.1 The INAHTA health technology assessment database

The HTA database is produced in collaboration with the INAHTA Secretariat, based at the Swedish Council on Technology Assessment in Health Care (SBU) in Sweden. The INAHTA was established in 1993 to promote cooperation and information sharing between the many organisations throughout the world, assessing healthcare technology. The database contains records of ongoing projects being conducted by members of the INAHTA as well as publications reporting completed technology assessments carried out by INAHTA members and other HTA agencies. The abstracts in the database are descriptive and give information on year of publication, HTA agency, country and sometimes study purpose and type of intervention. All records in the HTA database consist of publications and projects from nationally funded HTA organisations. INAHTA has 60 member agencies in 20 countries. Of the 60 agencies, 32 (53 percent) are based in Europe.

A total of 6462 HTA reports were published in the period 1991-2007. In principle, the number of reports has increased steadily over the years. Figure 4-1 and Table 4-4 show the number of HTA reports on cancer (1991-2007). A total of 797 HTA reports on cancer were identified in the period 1991-2007. The number of reports increased significantly up to 2002, but has since been rather stable, except for a peak in 2006. It should be remembered that the published HTA reports do not represent all HTA studies made in the healthcare systems in different countries. Providers and drug formulary committees undertake more or less ambitious studies, or ask the companies providing technologies or drugs to provide such studies, as a basis for decisions.

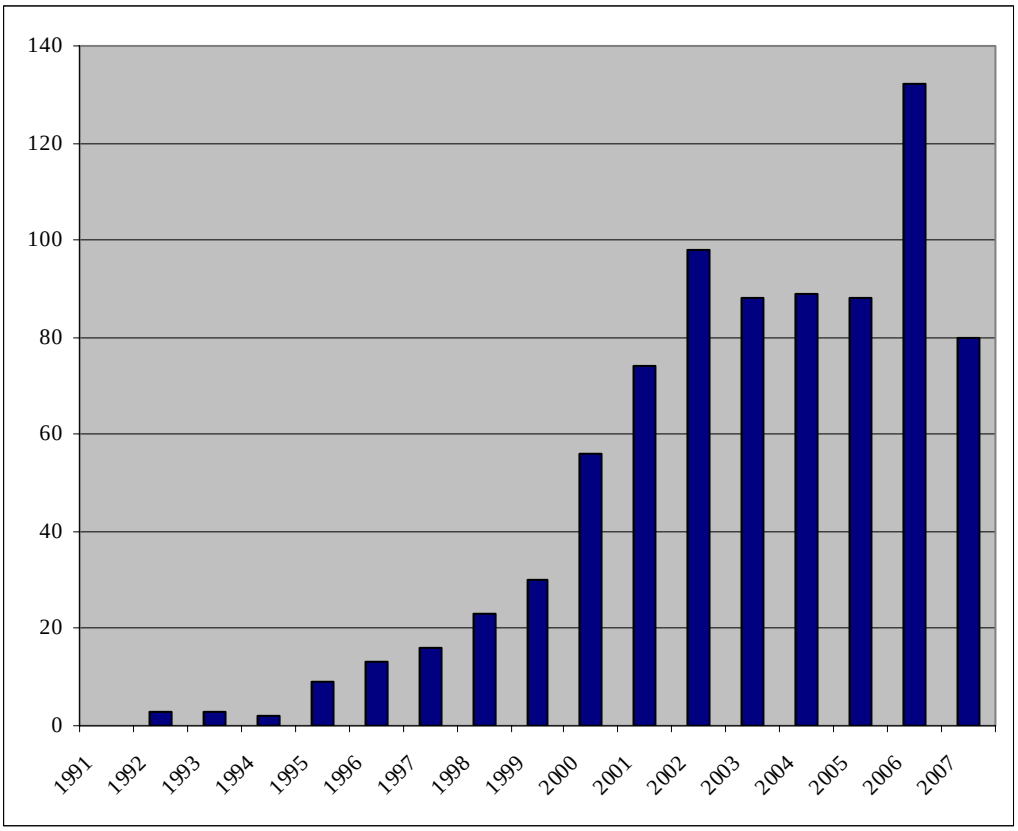

Figure 4-1. Number of HTA reports regarding cancer between 1991 and 2007

The number of HTA reports focusing on cancer registered in the INAHTA database increased rapidly in a few years in the late 1990s. Breast cancer contributes with the largest number of studies and was also dominating the increase in the 1990s. The level of reports seems to have somewhat stabilized in the past years, although is should be noted that the database is still being updated with studies published in previous years. The total number of studies registered for the latest years may then expect to increase.

Of the 158 reports listed in the INAHTA database, about one third were published by HTA agencies in the UK, primarily NICE, Scottish Medicines Committee (SMC), National Horizon Scanning Centre (NHSC), and the HTA program within National Institute for Health Research (NIHR). Among the other countries, Spain, the Netherlands, Sweden, Denmark and France are among the most active countries, measured by publications in the INAHTA network. Less than half of the countries had any reports published by HTA agencies registered in the database in the years 1990-2007. It should be noted that the studies presented here are only prepared by member organizations in INAHTA. As we saw earlier, some countries did not have any member

agencies of this organization. Nevertheless, the data presented in Table 4-4, indicates limited importance of economic evaluations and Health technology assessments in many countries.

Country	Total	1990-1995	1996-2000	2001	2002	2003	2004	2005	2006	2007*
United Kingdom	**103**	0	**10**	**8**	**20**	**12**	**10**	**11**	**19**	**13**
Spain	**12**	**2**	1	**1**	0	0	**2**	**3**	**3**	0
Netherlands	**8**	0	**2**	**2**	**1**	0	0	0	**1**	**2**
Sweden	**8**	0	**2**	**2**	**1**	**1**	0	**2**	0	0
Denmark	**7**	0	0	**1**	**1**	0	0	**2**	**2**	**1**
France	**7**	1	**2**	0	**1**	0	**1**	**2**	0	0
Finland	**4**	0	**2**	0	0	0	0	0	**1**	**1**
Austria	**3**	0	0	0	0	**1**	0	0	0	**2**
Germany	**2**	0	2	0	0	0	0	0	0	0
Norway	**2**	0	0	**1**	0	**1**	0	0	0	0
Belgium	**1**	0	0	0	0	0	0	0	**1**	0
Hungary	**1**	0	0	**1**	0	0	0	0	0	0
Estonia	**0**	0	0	0	0	0	0	0	0	0
Ireland	**0**	0	0	0	0	0	0	0	0	0
Italy	**0**	0	0	0	0	0	0	0	0	0
Latvia	**0**	0	0	0	0	0	0	0	0	0
Lithuania	**0**	0	0	0	0	0	0	0	0	0
Poland	**0**	0	0	0	0	0	0	0	0	0
Portugal	**0**	0	0	0	0	0	0	0	0	0
Romania	**0**	0	0	0	0	0	0	0	0	0
Slovenia	**0**	0	0	0	0	0	0	0	0	0
Switzerland	**0**	0	0	0	0	0	0	0	0	0
Total	**158**	**3**	**21**	**16**	**24**	**15**	**13**	**20**	**27**	**19**

*Note that all studies in the most recent years may not yet be registered in the database.

Table 4-4. Number of published HTA reports on selected drugs by country and year the INAHTA HTA Database 1990-2007

In Table 4-5, we see the number of reports regarding cancer drugs listed in the INAHTA database. The drug having the most studies is Docetaxel with 14 reports followed by imatinib with 12 reports, trastuzumab (11), capecitabine (10) and gemcitabine (10). Docetaxel, imatinib, capecitabine and gemcitabine are reviewed for several indications and docetaxel and gemcitabine in combination with other drugs. Trastuzumab are reviewed in five countries. These facts may partly explain the relatively large number of reports in this database. It should be noted that there is a delay in reporting studies to the database. The database is still updated with studies several years back in time.

Drugs	2000-2001	2002-2003	2004-2005	2006-2007	Total
Docetaxel	5	1	3	5	14
Imatinib	0	7	5	0	12
Trastuzumab	2	2	2	5	11
Capecitabine	0	5	1	4	10
Gemcitabine	5	2	0	3	10
Cetuximab	0	1	0	7	8
Oxaliplatin	1	3	2	2	8
Rituximab	0	6	2	0	8
Topotecan	2	0	2	3	7
Bevacizumab	0	0	3	3	6
Temozolomide	2	0	0	3	5
Bortezomib	0	1	1	1	3
Exemestane	0	0	1	2	3
Pemetrexed	0	1	0	2	3
Sorafenib	0	0	0	3	3
Alemtuzumab	0	1	0	1	2
Letrozole	0	0	0	2	2
Sunitinib	0	0	0	2	2
Trabectedin	0	1	0	1	2
Anastrozole	0	0	0	1	1
Clofarabine	0	0	0	1	1
Dasatinib	0	0	0	1	1
Erlotinib	0	1	0	0	1
Ibritumomab	0	1	0	0	1
Nelarabine	0	0	0	1	1
Nilotinib	0	0	0	1	1
Panitumumab	0	0	1	0	1
Thalidomide	0	1	0	0	1
Bicalutamide	0	0	0	0	0
Etoposide phosphate	0	0	0	0	0
Fulvestrant	0	0	0	0	0
Gefitinib	0	0	0	0	0
Gimeracil	0	0	0	0	0
Ibandronic acid	0	0	0	0	0
Tasonermin	0	0	0	0	0
Zoledronic acid	0	0	0	0	0
Total	*17*	*34*	*23*	*54*	*128*

*Note that all studies in the most recent years may not yet be registered in the database.

Table 4-5. Number of published HTA reports on selected drugs by year in the INAHTA HTA Database 1990-2007

4.8.2 The Health Economic Evaluation Database

The HEED has been developed as a joint initiative between the Office of Health Economics and the International Federation of Pharmaceutical Manufacturers' Associations. It contains information on cost-effectiveness studies and economic evaluations of medicines and other treatments and medical interventions. Figure 4-3 presents the number of studies in the HEED, related to cancer, 1991-2007. In total, 3,500 cancer studies were identified in the period (11 percent of all studies in the database), with a peak in 1997. It is difficult to say if the decline in the number of studies in recent years reflects a decline in the number of studies undertaken or just a decline in the number of studies published. One problem with publications is the long time lag from completion of a study until publication. It may, therefore, be that sponsors of studies have found other ways of making the results available. The database may be updated with studies from the most recent years not yet registered.

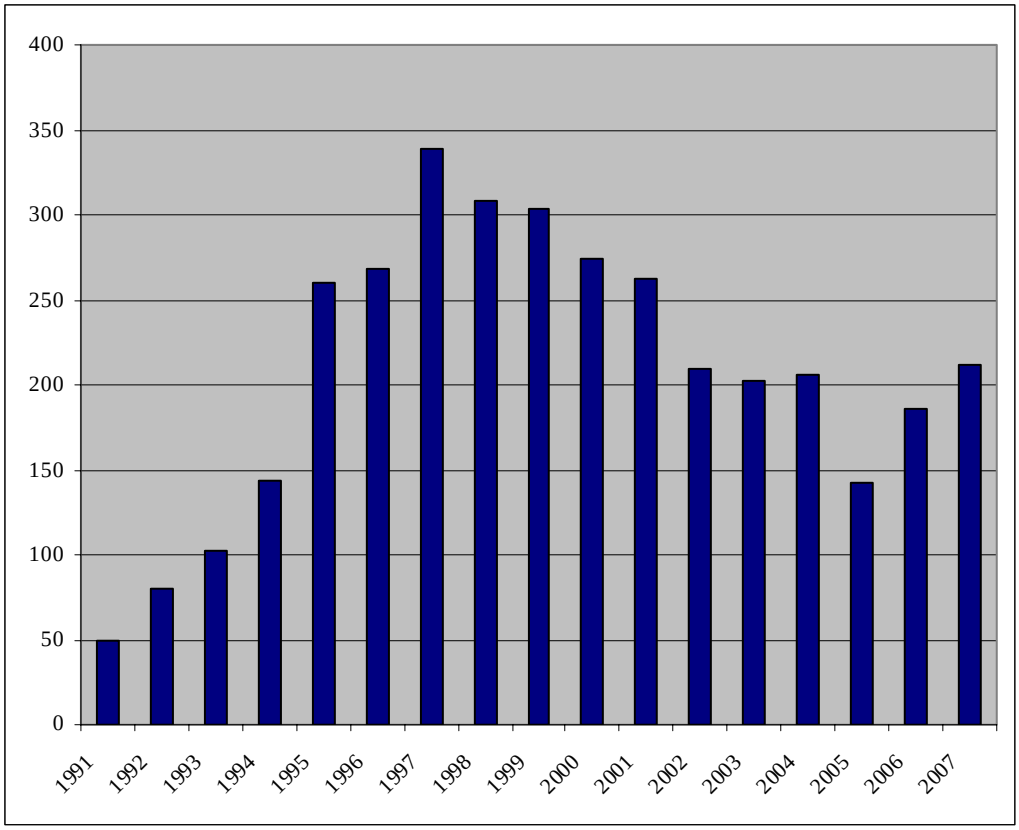

Figure 4-2. Studies in the HEED related to cancer published 1991-2007

In the HEED database there are a total of 70 economic evaluations for 15 of the 36 cancer drugs covered in this report. Docetaxel was the focus of 13 (18 percent) of these evaluations, while 8 studies (11 percent) reviewed gemcitabine and 7 reports (10 percent) covered capecitabine. The number of economic evaluations has increased with time; from 7 studies published during 1995-1997 to 22 studies published during 2004-2006 and 22 studies published in 2007 alone.

Drugs	1995-1997	1998-2000	2001-2003	2004-2006	2007	Total
Docetaxel	4	5	1	2	1	13
Gemcitabine	3	2	2	1	0	8
Capecitabine	0	0	2	2	3	7
Trastuzumab	0	0	0	4	2	6
Letrozole	0	1	1	3	0	5
Oxaliplatin	0	0	1	2	2	5
Anastrozole	0	0	0	2	2	4
Bevacizumab	0	0	0	0	4	4
Temozolomide	0	1	0	1	2	4
Zoledronic acid	0	0	0	3	1	4
Cetuximab	0	0	0	1	2	3
Exemestane	0	0	2	0	1	3
Rituximab	0	0	1	1	0	2
Erlotinib	0	0	0	0	1	1
Gefitinib	0	0	0	0	1	1
Total	**7**	**9**	**10**	**22**	**22**	**70**

Table 4-6. Number of Published Reports in HEED Database for Cancer Drugs 1995-2007

The United Kingdom is by far the most active country in producing health economic evaluations for cancer drugs, according to the HEED database. The 34 studies is more than one third of all studies on cancer drugs. Among the other countries the most cancer related studies are produced in the Netherlands (10 studies), followed by France Germany and Spain with 9 studies each (Table 4-7). Some of these evaluations were conducted in multiple countries, which explain the larger number in Table 4-7 compared to Table 4-6.

Country	1995-1997	1998-2000	2001-2003	2004-2006	2007	Total
United Kingdom	4	5	7	10	8	34
Netherlands	0	0	1	1	8	10
France	1	2	2	2	2	9
Germany	2	0	1	2	4	9
Spain	2	1	2	2	2	9
Belgium	0	0	1	3	3	7
Italy	2	0	1	0	4	7
Norway	1	0	0	3	2	6
Sweden	1	1	0	0	1	3
Finland	0	0	0	2	0	2
Austria	0	0	0	0	1	1
Switzerland	0	0	0	0	1	1
Total	***13***	***9***	***15***	***25***	***36***	***98***

Table 4-7. Number of Published Reports in the HEED Database for Cancer Drugs by Country 1995-2007

4.8.3 The International Society for Pharmacoeconomics and Outcomes Research

ISPOR represents healthcare researchers and practitioners (including pharmacists, physicians, economists, nurses and researchers from academia, the pharmaceutical industry, government, managed care, health research organisations and purchasers of healthcare). ISPOR promotes the science of pharmacoeconomics and health outcomes research. The mission of ISPOR is to translate pharmacoeconomics and outcomes research into practice, to ensure that society allocates healthcare resources wisely, fairly and efficiently. Since 1998 ISPOR hold two large international meetings each year, one in the USA and one in Europe. Two Asia-Pacific conferences have been held, in 2003 and in 2006. In 2007, the first in American conference was held in Cartagena, Colombia. The research papers presented at these meetings (covering 1998-2007) are collated in the ISPOR Research Digest electronic database. From 1998-2007, 8738 studies were presented. Figure 4-8 illustrates that the number of ISPOR abstracts related to cancer presented in the European ISPOR conferences has increased from 11 in 1998 to 88 presented in 2007. More than half of the studies related to cancer are presented in Europe. Between 1998 and 2007, about 10 percent of all studies presented in Europe were related to cancer.

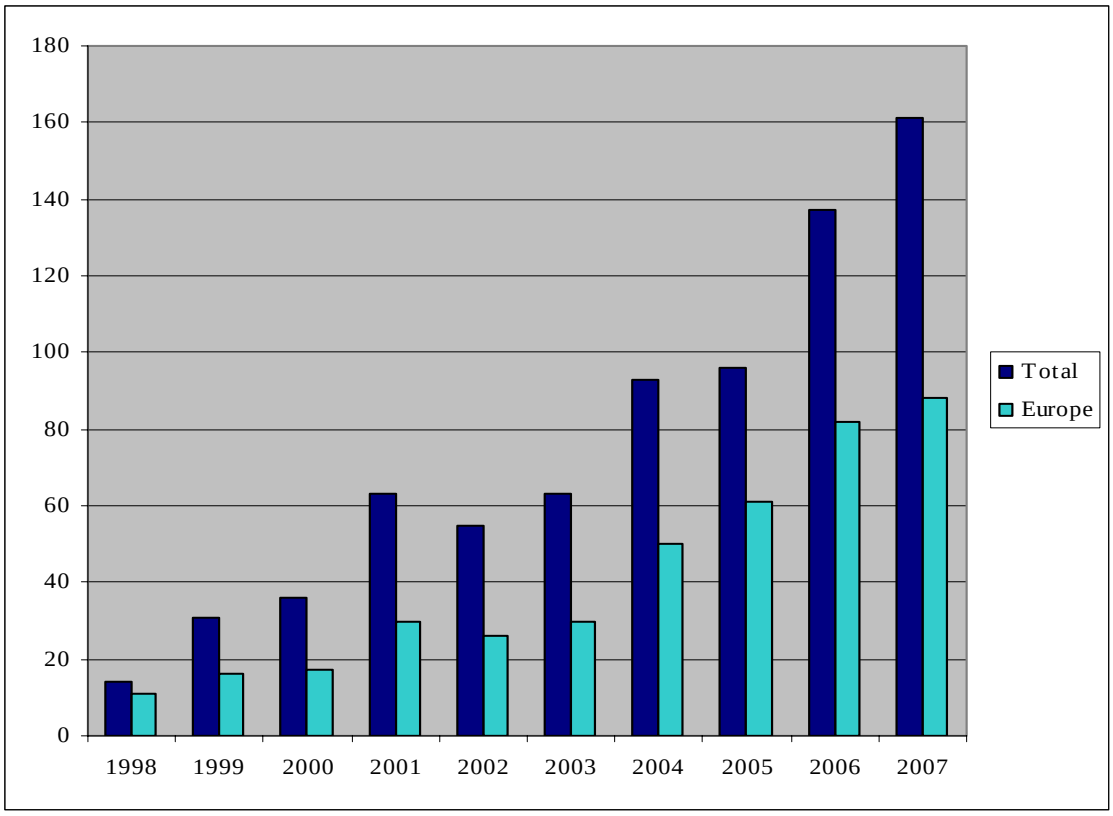

Figure 4-3. Studies related to cancer presented at ISPOR conferences in Europe, in total 1998-2007

Like in the case of the total number of cancer studies, the studies specifically related to cancer drugs are also increasing. As presented in Table 4-8, there were in total 117 reports related to the cancer drugs presented on the ISPOR meetings in 1998-2007. The number of studies in European countries presented each year have increased from two in the year 2000 to 30 in 2007. In the years 2004-2006, the average number was just under 20 per year. The drugs covered in most studies are Docetaxel with 17 studies, Capecitabine (14 studies) and Gemcitabine (13 studies). These are all drugs that have been on the market for several years and studies of these were presented at ISPOR meetings in 2001 or earlier. Capecitabine and Docetaxel were still among the most studied drugs in 2007. Drugs gaining market access in the most recent years may be subject to studies in the years to come.

Drugs	1998-2000	2001-2003	2004-2006	2007	Total
Docetaxel	1	7	5	4	17
Capecitabine	1	4	4	5	14
Gemcitabine	0	7	6	0	13
Anastrozole	0	3	5	0	8
Erlotinib	0	0	6	2	8
Oxaliplatin	0	1	2	4	7
Rituximab	0	1	3	2	6
Trastuzumab	0	0	3	3	6
Exemestane	0	0	3	2	5
Pemetrexed	0	1	3	1	5
Cetuximab	0	0	3	1	4
Fulvestrant	0	0	3	0	3
Gefitinib	0	0	2	1	3
Ibandronic acid	0	0	3	0	3
Imatinib	0	1	2	0	3
Letrozole	0	1	2	0	3
Zoledronic acid	0	0	2	1	3
Sunitinib	0	0	0	2	2
Alemtuzumab	0	0	0	1	1
Dasatinib	0	0	0	1	1
Sorafenib	0	0	1	0	1
Temozolomide	0	0	1	0	1
Tasonermin	0	0	0	0	0
Total	***2***	***26***	***59***	***30***	***117***

Source. ISPOR Research Digest

Table 4-8. Number of Reports in ISPOR Database for Cancer Drugs 1998-2007

In Table 4-9, we present the number of reports presented at ISPOR meetings by country of study. The numbers here are larger than in Table 4-8, as there may be more than one country included in one study. The countries most often represented at the ISPOR meetings are the, by population, largest countries. The United Kingdom are represented in a little more than one fourth (37 reports) of the reports followed by France with 29 reports in the period 2001-2007. In the middle range, Germany is represented in 15 studies, Spain in 13 studies and Italy in 11 studies. A large share of the increased number of reports in 2007 came from countries having none or few studies before 2007 (Austria, Czech Republic, Finland and Sweden) or countries with relatively few reports in previous years (Italy and Poland).

Country	1998-2000	2001-2003	2004-2006	2007	Total
United Kingdom	1	9	20	7	37
France	0	11	12	6	29
Germany	0	5	7	3	15
Spain	0	3	8	2	13
Italy	0	3	1	7	11
Poland	0	1	2	3	6
Belgium	0	1	2	2	5
Netherlands	0	2	2	0	4
Finland	0	0	0	2	2
Greece	0	0	2	0	2
Hungary	0	0	1	1	2
Sweden	0	0	0	2	2
Austria	0	0	0	1	1
Czech Republic	0	0	0	1	1
Denmark	0	0	1	0	1
Total	***0***	***35***	***58***	***37***	***131***

Source: ISPOR Research Digest

Table 4-9. Number of published reports in ISPOR database for cancer drugs by country 1998-2007

4.9 Assessing the impact of HTA on decision making

This review has shown that a significant number of health economic evaluations related to cancer have been published, in particular in the mid and later part of the period 1991-2005. These evaluations have been undertaken by publicly funded agencies, established to evaluate and provide information on new medical technologies, by health economists employed in the pharmaceutical industry and by independent researchers often funded by government and/or industry. This activity must be seen as a sign of the growing importance of economic evaluation and cost-effectiveness for decisions regarding market access.

Europe plays a major role in the production of HTA reports and economic evaluations. In particular, the UK is the leader in terms of the number of HTA reports produced and in terms of being the country for which a majority of economic evaluation studies are undertaken. This reflects the leading role the UK has had in development of health economics in Europe and, in particular, the methodology of economic evaluation.

One other explanation of the UK's leading role in the HTA area is NICE, the driving force behind the majority of the HTA reports being produced. Although NICE was only established in 1999, it

has rapidly gained a strong position in producing guidance to the NHS on the use of new and existing drug therapies in England based on clinical and economic evidence [16].

The National Institute for Health and Clinical Excellence (NICE) issues guidance for England; the Scottish Medicines Consortium (SMC) issues guidance for Scotland and the All Wales Medicines Strategy Group issues guidance for Wales. Currently NICE produces guidance in four areas:

1. Technology appraisals - guidance on the use of new and existing medicines and treatments within the NHS in England

2. Clinical guidelines - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England

3. Interventional procedures - guidance on whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use in England

4. Public health

Referral of a drug to NICE for appraisal can take up to 18 months. Once a product is referred for NICE's review and guidance, the actual time required is at a minimum of 62 weeks. In contrast, the actual time required for a review by the SMC is 3 months.

NICE has been approached to share its process and guidance internationally. All information on NICE decisions is available on the internet and there is an obvious (though difficult to measure) impact on the decisions made by NICE on other countries.

The impact of a review and issuance of NICE guidance regarding a product or class of products is significant. For example, there are indications that the taxanes achieved more rapid uptake in the UK, due to the positive NICE assessment and guidance provided to the NHS. While a positive NICE review may lead to a more rapid uptake and faster patient access to treatments, there is an issue with the capacity of NICE to undertake such reviews in a timely fashion. Also, during the period of the NICE review , no resources are allocated by the NHS. This leads to a delay in drug introduction and availability to patients, commonly referred to as the 'NICE blight'.

In Europe, in addition to the UK, the Netherlands, Spain and Sweden are also active producers of HTA reports. In Sweden, SBU (the Swedish Council on Technology Assessment in Health Care)

was established in 1987 and has played an important role in starting the international network of HTA agencies.

NICE has appraised 21 technologies related to cancer since 2001. Five of these were related to breast cancer and three to colorectal cancer. The guidance on trastuzumab for use in early breast cancer was released in August 2006, only three months after the drug was licensed by the regulatory authorities for use in early breast cancer, and recommended trastuzumab to be offered as a treatment option for women with early-stage HER2-positive breast cancer. A draft guidance on bevacizumab and cetuximab of August 2006 states that the two drugs are not recommended for first- respective second-line treatment of metastatic colorectal cancer, as they are not considered compatible with the best use of NHS (National Health Service) resources. Earlier technology appraisals on breast cancer treatments include guidance of trastuzumab for use in metastatic breast cancer, as well as for the use of capecitabine, vinolrebine and the taxanes docetaxel and paclitaxel. For colorectal cancer NICE has published technology appraisals for the use of capecitabine/oxaliplatin, capecitabine/tegafur uracin, and irinotecan/oxaliplatin/raltitrexed.

Swedish SBU has published 24 reports on cancer. The majority of these relate to cancer screening and non-medical cancer treatments. Three reports on medical treatments have been published, regarding aromatase inhibitors and trastuzumab for breast cancer, and imatinib for chronic myeloid leukaemia. The reports present the clinical and cost-effectiveness data that is available about the treatments, but do not give any explicit recommendations regarding whether the drugs shall be funded or not.

HTA are taken into account by decision-makers to various extent in different countries. The structure of HTA and its impact on decision making is largely dependent of the nation's health care system and its regulatory mechanisms, economic incentives for health care providers, and influence of opinion leaders, patients and the media. An assessment of the influence of HTA on decision-making in the G-7 countries conducted by Health Canada[111] appraises that although there is generally little evidence on the direct impact of HTA results on policy making, HTA is recognised as an instrument to assist in health care expenditure decision making and HTA agencies appear to have good connection with decision makers in particular in Canada, UK and France, while in the USA and Japan the interest in HTA has been relatively limited.

Observations in relation to the adoption of particularly expensive health technologies in different nations indicate that in the USA, Japan, and in some cases in France, expensive technologies

have generally been adopted early and have quickly diffused. while in the UK and most Scandinavian countries, technologies have been adopted at a later stage and are gradually diffused[111]. These observations suggest that HTAs are more appraised in countries that are normally not first in line when it comes to adoption of new health technologies. It is important to have information about cost-effectiveness as one of the basis for treatment recommendations, but it is also important that requirements for economic evaluations do not delay patient access to new drug therapies. This means that there is a trade-off between access to reliable evidence and a fast up take of new treatments.

In Table 4-10, we see that the leading HTA agencies NICE and SMC not only review the vast majority of new cancer drugs for different indications. In most cases they also recommend the introduction and use of these drugs. Still, as we have shown in chapter 3 of this report, the introduction and volume of uptake of these drugs in the UK is surprisingly low.

Drug Names	Recommendation		In-progress
	NICE	SMC	NICE
Anastrozole	✓ Breast cancer	✓ Breast cancer	-
Bevacizumab	× Metastatic colorectal cancer, NSCLC, Metastatic breast cancer	× Metastatic colorectal cancer, metastatic carcinoma of the colon or rectum & NSCLC	✓ Renal cell carcinoma
Bortezomib	✓ Multiple myeloma	✓ Multiple myeloma	-
Capecitabine	✓ Breast cancer, Colon cancer & Colorectal cancer	✓ Breast cancer & Stage III colorectal cancer	-
Cetuximab	× Metastatic colorectal cancer ✓Head and Neck Cancer	× Metastatic colorectal cancer; ✓Head and Neck Cancer	✓ 1st line Colorectal cancer & NSCLC
Clofarabine	-	✓ Acute lymphoblastic leukaemia	-
Dasatinib	-	✓ Chronic myeloid leukaemia × Acute lymphoblastic leukaemia	✓ acute lymphoblastic leukaemia & chronic myeloid leukaemia
Docetaxel	✓ Breast cancer, NSCLC & Prostrate cancer	✓ Breast cancer & NSCLC	-
Erlotinib	-	✓ NSCLC	✓ NSCLC
Etoposide phosphate	-	-	-
Exemestane	✓ Breast cancer	✓ invasive early breast cancer	-
Fulvestrant	-	× Metastatic breast cancer	-
Gefitinib	-	-	✓NSCLC
Gemcitabine	✓ Breast cancer, pancreatic cancer, NSCLC	✓ Breast cancer	-
Ibandronic acid	-	✓ Breast cancer	-
Imatinib	✓ chronic myeloid leukaemia & gastro-intestinal stromal tumours	× Philadelphia chromosome positive acute lymphoblastic leukaemia	-
Letrozole	✓ Breast cancer	✓ Breast cancer	-
Nelarabine	-	✓ T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL)	-
Nilotinib		✓Chronic myeloid leukaemia	✓ chronic myeloid leukaemia
Oxaliplatin	✓ Colorectal cancer & Colon cancer	✓ Stage III colon cancer	-
Panitumumab	-	× metastatic colorectal carcinoma	-

Pemetrexed	✓ malignant pleural mesothelioma; × NSCLC	✓ unresectable malignant pleural mesothelioma; × NSCLC	-
Rituximab	✓ NHL, follicular lymphoma, relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma	✓ NHL	-
Sorafenib	-	× Renal cell carcinoma & Hepatocellular carcinoma	✓ Renal cell carcinoma & advanced and metastatic hepatocellular carcinoma
Sunitinib	-	× Gastrointestinal stromal tumour & Advanced/metastatic renal cell carcinoma	✓Renal cell carcinoma
Temozolomide	✓ Brain cancer & Newly diagnosed glioblastoma multiforme	✓ Newly diagnosed glioblastoma multiforme	✓advanced and metastatic melanoma
Ibritumomab/ Tiuxetan	-	× NHL	-
Topotecan	✓ Ovarian cancer	✓ Carcinoma of the cervix × Relapsed small cell lung cancer	✓small cell lung cancer
Trabectedin	-	× Advanced soft tissue carcinoma	-
Trastuzumab	✓ Breast cancer	✓ Early breast cancer; × Metastatic breast cancer	-
Zoledronic acid	-	✓ Breast cancer	-

✓- iRecommended
× - Not recommended

Table 4-10. Recommendations of NICE and SMC in the United Kingdom

4.9.1 Relations between HTAs and patient access to cancer drugs

While most of HTA agencies agree that the benefits should be measured in terms of improvements in quality-adjusted life years (QALYs), there is a lack of general agreement on which costs to include: Sweden, Germany and the Netherlands uses a societal cost perspective. In France and Spain the perspective is related to the aim of the study [26].

Another potential issue to consider with QALYs is the threshold value used to determine whether a drug is cost-effective. Different countries may use different QALY values, which are either published or recognised unofficially. For example, the Netherlands has an unofficial threshold cost per QALY gained of €18,000, while NICE's threshold cost is acknowledged to be £20,000-£30,000 per gained QALY. In the US, $50,000/QALY gained is a figure that has been widely

quoted as a cost-effectiveness ratio [112]. A different approach in setting cost-effectiveness thresholds proposed by the World Health Organisation [15], is that interventions costing less than three times GDP per capita for each Disease Adjusted Life Year (DALY) saved would be considered cost-effective.

It is important to consider whether these thresholds are still applicable to the evaluation of new cancer drugs and whether the same threshold should be used for cancer drugs as for other interventions, such as cardiovascular drugs. Nadler and colleagues [113] recently published a survey, assessing if oncologist in the US believed that new cancer drugs offer good value for money. A survey was sent to 139 medical oncologists at two hospitals in Boston. A little less than one out of five, 78 percent of the respondents thought that patients should have access to “effective” care regardless of costs. An implied cost-effectiveness threshold was calculated to about $300,000 per QALY gained.

Perhaps more controversially we could ask whether economic evaluations and cost-effectiveness have a role with regards to cancer drugs and whether there is another way to evaluate the cost benefit of these drugs.

Activities are now underway in Europe to establish a more formal European network of HTA agencies, EUnetHTA, as mentioned earlier in this chapter. Since technology assessment is based on a common pool of scientific studies, there are possible advantages of collaboration over national borders, at least in the collection and assessment of available scientific information. It can be expected that different countries may draw different conclusions from the results. However, it is a safe prediction that there will be more international cooperation in this field in the future.

In Sweden, the Pharmaceutical Benefits Board, LFN makes decision on reimbursement. LFN has only assessed a small number of cancer drugs. In part because LFN was not founded until 2002, but also because they do not assess drugs for in patient use only.

The drugs assessed by LFN are listed in Table 4-11.

New drug (NCE)

Velcade is used for second line treatment of multiple myeloma (MM). Treatment cost SEK 270,000 per patient, for a prolonged survival of one year. Health economic study gave 400,000-600,000 SEK/QALY. First decision is a limited reimbursement, and thereafter renewed reimbursement.

Iressa. License prescription for lung cancer on selected patients. Documented medical need for individual patients. No health economic assessment.

Onsenal (Celebra cox 2 inhibitor). Reduced risk of colon cancer for selected patients. Orphan drug. Eight patients a year. Prevalence 300 a year. Treatment cost SEK 13,000a year. No health economic assessment.

Procren Depot . Leuprorelinacetat, a gonadotropinreleasing hormone analogue (GnRH-analogue), given subcutaneous for prostate cancer in advanced stage. New administration form at the same price as before. Treatment cost SEK 14,000 a year.

Sprycel. For treatment of Cronic Myeloid Leukaemia (CML). Global incidence is one to two cases per 100,000 inh. a year globally Number of cases in Sweden are about 80 a year. Median age is 60 years, and 10 percent of patients are less than 20 years old. Used for patients with resistance or intolerance against imatinib. Treatment cost SEK 670,000 a year. Unclear health economic documentation.

Tasigna. Tasigna is an orphan drug for treatment of adults with Cronic Myeloid Leukaemia (CML). Standard treatment is today Glivec. Treatment with Glivec is interrupted if patient is resistant or intolerant. Newer tyrosine kinase inhibitors like Sprycel (dasatinib) have indication for use when Glivec resistant.

Tarceva. New mechanism and administration (pills). The indication is ”locally advanced or metastatic non small cell lung cancer which have failed in at least one chemotherapy treatment. Other entities in Sweden with the same use in Sweden is pemetrexed (Alimta) and docetaxel (Taxotere), both of which are infusion solutions. About 1,000 patients a year may be treated. Treatment cost is SEK 15,000 a month for patients with a relatively short expected survival. Prolonged survival is four months. Cost effectiveness is estimated to be similar to docetaxel.

Revlimid. An orphan drug for treatment of multiple myeloma. The drug contains the active substance lenalidomid, and inhibits the growth of cancer cells. Treatment cost with Revlimid is considerably higher than for Velcade, but the clinical effect is similar. LFN has therefore decided that Revlimid is only an option if patient should not be treated with Velcade. The treatment cost is SEK 63,277 per cycle for the highest recommended dose. The cost of Velcade is lower, SEK 44,068 per cycle.

Targretin. Orphan drug with few patients with cutaneous T-cell Lymphoma (CTCL) no health economic documentation. 100 capsules cost SEK 13,000 kronor.

Nexavar. Nexavar contains sorafenib, and is used for treatment of advanced kidney cancer. Orphan drug for licence prescription. No health economic study. The price is SEK 37,720 for 120 pills.

Sutent is an orphan drug for treatment of Gastrointestinal stromal tumours (GIST) and renal cell cancer. Sutent is used for treatment of non resectable tumours and/or have metastasised when other treatment has no effect due to resistance or intolerance. Sutent is also used for treatment of metastatic renal cell cancer (MRCC) if interferon alfa eller interleukin-2 has no effect. Estimated costs for GIST in 2003 years prices SEK 179 million of which the drug cost is SEK 55 million. Corresponding figure for MRCC is SEK 178 million. Drug cost is generally within the hospitalization cost. The estimated cost per QALY is about SEK 1 million for patients with GIST and SEK 550,000 for patients with MRCC. The estimated survival effects in renal cancer are not clear.

Metvix contains metylaminolevulinat and is used in photodynamic treatment of different types of neoplasms in the skin photodynamic treatment with Metvix is a cost effective alternative to surgery or freezing treatment when these are not suitable.

Cervarix and Gardasil are vaccines reducing the risk of HPV infection associated with cervical cancer. The cost is SEK 3,000-3,300 plus administration costs and follow ups.

New administration form
Glivec, Navelbine, UFT, Eloxatin

New generics
Etoposid (MEDA) and Metotrexade (Europharma)

New Prices
Large number, not analysed

Tabell 4-11. Cancer drugs granted access by the Swedish Pharmaceutical Benefits Board

4.10 Conclusions

Increasingly stretched healthcare budgets are faced with growing needs and demands of the population, leading to increasing use of cancer drugs. New drugs also bring higher costs compared to older drugs. The cost of cancer drugs may then be expected to grow significantly. The increased costs of cancer drugs creates a need for better clinical and economic evaluations for decision makers and are required to be able to balance patients' needs within a limited budget. At the same time there is a need to balance short term budget constrains and long term savings from using cost effective treatment methods. Cancer patients are dependent on reimbursement and publicly funded healthcare that function well and allocate appropriate budgetary resources to existing and new drug therapies.

Variations in the use of new drugs in different countries have increased the focus on the development of policies regarding the use of new medical technologies and, in particular, new drugs. HTA and economic evaluations have increased importance for decisions making in market access and reimbursement. This does raise the question about the role of economic evaluation on the availability of new innovative cancer drugs. The evidence of any systematic impact of such studies on uptake of new drugs is still lacking. There are indications that this will change, and it will be interesting to follow the implications of recent decisions about -for example- trastuzumab, if positive recommendations will result in a more equal uptake between and within countries. In the UK, NICE and SMC are the most active producers of HTA reports in Europe. Their recommendations are also, in most cases, positive regarding cancer drugs. Nevertheless, as we saw in chapter 3, the uptake of cancer drugs in the UK is far below the European average.

It will also be interesting to follow the use of HTAs in countries with none or little tradition of including such studies in the decision making process. Equally important will be the question on whether health care systems will be able provide budgetary space for new innovative technologies.

References

1. J. Ferlay, F.B., P. Pisani and D.M. Parkin *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*, in *IARC CancerBase No. 5 version 2.0*. 2004, IARC CancerBase No. 5 version 2.0, IARCPress.
2. Ferlay, J., et al., *Estimates of the cancer incidence and mortality in Europe in 2006.* Ann Oncol, 2007. **18**(3): p. 581-92.
3. Boyle, P. and J. Ferlay, *Cancer incidence and mortality in Europe, 2004.* Ann Oncol, 2005. **16**(3): p. 481-8.
4. Verdecchia, A., et al., *Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data.* Lancet Oncol, 2007. **8**(9): p. 784-96.
5. Berrino, F., et al., *Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study.* Lancet Oncol, 2007. **8**(9): p. 773-83.
6. Wilking, N. and B. Jönsson, *A pan-European comparison regarding patient access to cancer drugs*. 2005, Karolinska Institutet and Stockholm School of Economics: Stockholm.
7. Jönsson, B. and N. Wilking, *A global comparison regarding patient access to cancer drugs.* Annals of Oncology, 2007. **18**(Supplement 3): p. iii1-iii77.
8. *Health Statistics. Athas on Mortality in the European Union*. 2003, Office for Official Publications of the European Communities.
9. Shapiro, S., et al., *Breast cancer screening programmes in 22 countries: current policies, administration and guidelines. International Breast Cancer Screening Network (IBSN) and the European Network of Pilot Projects for Breast Cancer Screening.* Int J Epidemiol, 1998. **27**(5): p. 735-42.
10. Schroder, F.H., *Detection of prostate cancer: the impact of the European Randomized Study of Screening for Prostate Cancer (ERSPC).* Can J Urol, 2005. **12 Suppl 1**: p. 2-6; discussion 92-3.
11. Gutierrez-Ibarluzea, I., J. Asua, and K. Latorre, *Policies of screening for colorectal cancer in European countries.* Int J Technol Assess Health Care, 2008. **24**(3): p. 270-6.
12. Hackshaw, A., *EUSOMA review of mammography screening.* Ann Oncol, 2003. **14**(8): p. 1193-5.
13. Feig, S.A., *Screening mammography: a successful public health initiative.* Rev Panam Salud Publica, 2006. **20**(2-3): p. 125-33.
14. de Pouvourville, G., *Risk-sharing agreements for innovative drugs - A new solution to old problems.* The European Journal of Health Economics, 2006. **7**(3): p. 155-157.
15. Wilking, N., et al., *Benchmarking report on lung cancer care in selected countries*. 2008, Stockholm: Available at www.comparatorreports.se.
16. Bosanquet, N., J. Attridge, and K. Sikora, *Can the new EU members catch up in cancer care?* Eurohealth, 2005. **11**(1).
17. Statistisches Bundesamt, *Gesundheit - Krankheitskosten, 2002, 2004 und 2006*. 2008, Wiesbaden: Statistisches Bundesamt.
18. Cancerorganisationerna, *Kostnader för Cancer*. 2006, Tampere: Cancerstiftelsen.
19. Poos, M., et al., *Cost of Illness in the Netherlands 2005*. 2008, Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu.

20. NPK, *National Cancer Control Programme*. 2004, The Hague: NPK Steering Group.
21. Cancerfonden, *Cancerfondsrapporten 2006*. 2006, Stockholm: Cancerfonden.
22. Socialstyrelsen, *Statistik över kostnader för hälso- och sjukvården*. 2007, Stockholm: Socialstyrelsen.
23. Atun, R., *National Cancer Control Programmes in Europe*. 2008, Ljubljana: Slovenian Presidency of the EU
24. National Health Services, *Cancer Reform Strategy*. 2007, London: Department of Health.
25. République Francaise, *Plan Cancer: 2003-2007*. 2003, Paris: Direction générale de la Santé
26. Institute National de Cancer, *Analyse Économique des Coûtes du Cancer en France*. 2007, Paris: Institute National de Cancer.
27. Gulácsi, L., I. Boncz, and M. Drummond, *Issues for countries considering introducing the "fourth hurdle": the case of Hungary*. Int J Technol Assess Health Care, 2004. **20**(3): p. 337-341.
28. Lidgren, M., N. Wilking, and B. Jonsson, *Cost of breast cancer in Sweden in 2002.* Eur J Health Econ, 2007.
29. Garrison, L. and A. Towse, *The drug budget silo mentality in Europe: an overview.* Value Health, 2003. **6 Suppl 1**: p. S1-9.
30. Goodman, L.S., et al., *Landmark article Sept. 21, 1946: Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. By Louis S. Goodman, Maxwell M. Wintrobe, William Dameshek, Morton J. Goodman, Alfred Gilman and Margaret T. McLennan.* Jama, 1984. **251**(17): p. 2255-61.
31. Farber, S., et al., *Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin).* . N Engl J Med, 1948. **238**: p. 787-793.
32. Black, W.C. and H.G. Welch, *Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy.* N Engl J Med, 1993. **328**(17): p. 1237-43.
33. Jaffe, N., et al., *Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma.* N Engl J Med, 1974. **291**(19): p. 994-7.
34. Pharmaceuticals Research and Manufacturers of America, *New Medicines in Development for Cancer: 395 New Medicines in Development Offer Hope in the War on Cancer*. 2003, Washington: PhRMA.
35. Hofmann, W.K., et al., *Relation between resistance of Philadelphia-chromosome-positive acute lymphoblastic leukaemia to the tyrosine kinase inhibitor STI571 and gene-expression profiles: a gene-expression study.* Lancet, 2002. **359**(9305): p. 481-6.
36. Petricoin, E.F., et al., *Use of proteomic patterns in serum to identify ovarian cancer.* Lancet, 2002. **359**(9306): p. 572-7.
37. Hanahan, D. and R.A. Weinberg, *The hallmarks of cancer.* Cell, 2000. **100**(1): p. 57-70.
38. Tewey, K.M., et al., *Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II.* Science, 1984. **226**(4673): p. 466-8.
39. Wartmann, M. and K.H. Altmann, *The biology and medicinal chemistry of epothilones.* Curr Med Chem Anticancer Agents, 2002. **2**(1): p. 123-48.

40. Rothenberg, M.L., et al., *A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer.* Ann Oncol, 1996. **7**(4): p. 347-53.
41. Hanna, N., et al., *Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.* J Clin Oncol, 2004. **22**(9): p. 1589-97.
42. Lenz, H., et al., *Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin.* J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition): 22, 14S (July 15 Supplement), abs 3510, 2004.
43. Bonner, J., et al., *Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: A phase III study of high dose radiation therapy with or without cetuximab.* J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition): 22, 14S (July 15 Supplement), abs 5507, 2004.
44. Shepherd, F., et al., *A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial.* . Proc Am Soc Clin Oncol Late-Breaking Abstracts Booklet 2004; 23: 18, abs 7022., 2004.
45. Kris, M.G., et al., *Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial.* Jama, 2003. **290**(16): p. 2149-58.
46. Di Nicolantonio, F., et al., *Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer.* J Clin Oncol, 2008. **26**(35): p. 5705-12.
47. Slamon, D., et al., *Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.* N Engl J Med 2001; 344: 783-792, 2001.
48. Romond, E.H., et al., *Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.* N Engl J Med, 2005. **353**(16): p. 1673-84.
49. Piccart-Gebhart, M., et al., *Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.* N Engl J Med. 2005 Oct 20;353(16):1659-72.
50. Nowell, P.C., *The minute chromosome (Phl) in chronic granulocytic leukemia.* Blut, 1962. **8**: p. 65-6.
51. Druker, B.J. and N.B. Lydon, *Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia.* J Clin Invest, 2000. **105**(1): p. 3-7.
52. O'Brien, S.G., et al., *Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia.* N Engl J Med, 2003. **348**(11): p. 994-1004.
53. Shah, N.P., et al., *Overriding imatinib resistance with a novel ABL kinase inhibitor.* Science, 2004. **305**(5682): p. 399-401.
54. Demetri, G.D., et al., *Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.* N Engl J Med, 2002. **347**(7): p. 472-80.
55. Gora-Tybor, J. and T. Robak, *Targeted drugs in chronic myeloid leukemia.* Curr Med Chem, 2008. **15**(29): p. 3036-51.
56. Herbst, R.S., et al., *Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor*

receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol, 2005. **23**(11): p. 2544-55.
57. Hainsworth, J., et al., *evacizumab, erlotinib, and imatinib in the treatment of patients (pts) with advanced renal cell carcinoma (RCC): A Minnie Pearl Cancer Research Network phase I/II trial.* B J Clin Oncol (Meeting Abstracts) 2005; 23: 388s, abs 4542.
58. Miller, V.A., et al., *Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer.* J Clin Oncol, 2004. **22**(6): p. 1103-9.
59. Lynch, T.J., et al., *Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.* N Engl J Med, 2004. **350**(21): p. 2129-39.
60. Folkman, J., *Tumor angiogenesis: therapeutic implications.* N Engl J Med, 1971. **285**(21): p. 1182-6.
61. Hanahan, D. and J. Folkman, *Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis.* Cell, 1996. **86**(3): p. 353-64.
62. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. **350**(23): p. 2335-42.
63. Miller, K.D., et al., *Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.* J Clin Oncol, 2005. **23**(4): p. 792-9.
64. Sandler, A., et al., *Randomized phase II/III Trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial - E4599.* Proc Am Soc Clin Oncol 2005; 23: abs 4.
65. Yang, J.C., et al., *A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer.* N Engl J Med, 2003. **349**(5): p. 427-34.
66. Motzer, R., et al., *Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC).* J Clin Oncol (Meeting Abstracts) 2005; 23: 380s, abs 4508.
67. Escudier, B., et al., *Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC).* J Clin Oncol (Meeting Abstracts) Late Breaking Abstracts 2005; 23: 1093s, abs 4510.
68. Wang, J., et al., *Paclitaxel at ultra low concentrations inhibits antiangiogenesis without affecting cellular microtubule assembly.* Anticancer Drugs 2003; 14: 13-19.
69. Kohler, G. and C. Milstein, *Continuous cultures of fused cells secreting antibody of predefined specificity.* Nature, 1975. **256**(5517): p. 495-7.
70. Peto, R., et al., *UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years.* Lancet, 2000. **355**(9217): p. 1822.
71. *Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **365**(9472): p. 1687-717.
72. Wolmark, N., et al., *The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03.* J Clin Oncol, 1993. **11**(10): p. 1879-87.

73. *Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators.* Lancet, 1995. **345**(8955): p. 939-44.
74. Andre, T., et al., *Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.* N Engl J Med, 2004. **350**(23): p. 2343-51.
75. Feugier, P., et al., *Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol, 2005. **23**(18): p. 4117-26.
76. Pfreundschuh, M., et al., *Randomized intergroup trial of first line treatment for patients <= 60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab - early stopping after the first interim analysis.* Proc Am Soc Clin Oncol 2004; 23: 556, abs 6500.
77. Pulte, D., A. Gondos, and H. Brenner, *Ongoing improvement in outcomes for patients diagnosed as having Non-Hodgkin lymphoma from the 1990s to the early 21st century.* Arch Intern Med, 2008. **168**(5): p. 469-76.
78. Brenner, H., A. Gondos, and D. Pulte, *Recent trends in long-term survival of patients with chronic myelocytic leukemia: disclosing the impact of advances in therapy on the population level.* Haematologica, 2008. **93**(10): p. 1544-9.
79. Brenner, H., A. Gondos, and D. Pulte, *Recent major improvement in long-term survival of younger patients with multiple myeloma.* Blood, 2008. **111**(5): p. 2521-6.
80. von Plessen, C., et al., *Effectiveness of third-generation chemotherapy on the survival of patients with advanced non-small cell lung cancer in Norway: a national study.* Thorax, 2008. **63**(10): p. 866-71.
81. Devita, V.T., Jr., A.A. Serpick, and P.P. Carbone, *Combination chemotherapy in the treatment of advanced Hodgkin's disease.* Ann Intern Med, 1970. **73**(6): p. 881-95.
82. Diehl, V., et al., *Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease.* N Engl J Med, 2003. **348**(24): p. 2386-95.
83. Einhorn, L.H. and J. Donohue, *Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer.* Ann Intern Med, 1977. **87**(3): p. 293-8.
84. Fisher, B., et al., *Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.* J Natl Cancer Inst, 1998. **90**(18): p. 1371-88.
85. Vogel, V.G., et al., *Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.* Jama, 2006. **295**(23): p. 2727-41.
86. Thun, M.J., M.M. Namboodiri, and C.W. Heath, Jr., *Aspirin use and reduced risk of fatal colon cancer.* N Engl J Med, 1991. **325**(23): p. 1593-6.
87. Thompson, I.M., et al., *The influence of finasteride on the development of prostate cancer.* N Engl J Med, 2003. **349**(3): p. 215-24.
88. Kochhar, R., et al., *Statins reduce breast cancer risk: a case control study in US female veterans.* Proc Am Soc Clin Oncol 2005; 23: abs 514.
89. Villa, L.L., et al., *Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial.* Lancet Oncol, 2005. **6**(5): p. 271-8.

90. Eurostat, *Eurostat population and Social Conditions. Available at: http://epp.eurostat.ec.europa.eu*.
91. Nieder, C., M. Adam, and A.L. Grosu, *Combined modality treatment of glioblastoma multiforme: the role of temozolomide.* Rev Recent Clin Trials, 2006. **1**(1): p. 43-51.
92. Clarke, M., et al., *Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials.* Lancet, 2008. **371**(9606): p. 29-40.
93. Peto, R., *The worldwide overview: new results for systemic adjuvant therapies. For the Early Breast Cancer Trialists' Collaborative Group University of Oxford, Oxford, United Kingdom, San Antonio Breast Cancer Symposium.* 2007.
94. Mariani, G., et al., *Trastuzumab as adjuvant systemic therapy for HER2-positive breast cancer.* Nat Clin Pract Oncol, 2008.
95. Benson, A.B., 3rd, et al., *American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.* J Clin Oncol, 2004. **22**(16): p. 3408-19.
96. Chase, J.L., *Clinical use of anti-vascular endothelial growth factor monoclonal antibodies in metastatic colorectal cancer.* Pharmacotherapy, 2008. **28**(11 Pt 2): p. 23S-30S.
97. Bokemeyer, C., et al., *Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer.* J Clin Oncol, 2008.
98. Heinemann, V., et al., *Clinical relevance of EGFR- and KRAS-status in colorectal cancer patients treated with monoclonal antibodies directed against the EGFR.* Cancer Treat Rev, 2008.
99. Heist, R.S. and D. Christiani, *EGFR-targeted therapies in lung cancer: predictors of response and toxicity.* Pharmacogenomics, 2009. **10**(1): p. 59-68.
100. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. **26**(21): p. 3543-51.
101. Heng, D.Y. and R.M. Bukowski, *Anti-angiogenic targets in the treatment of advanced renal cell carcinoma.* Curr Cancer Drug Targets, 2008. **8**(8): p. 676-82.
102. Roxburgh, P. and T.R. Evans, *Systemic therapy of hepatocellular carcinoma: Are we making progress?* Adv Ther, 2008. **25**(11): p. 1089-104.
103. Netzer, T., *European Union centralised procedure for marketing authorisation of oncology drugs: an in-depth review of its efficiency.* Eur J Cancer, 2006. **42**(4): p. 446-55.
104. EUROMET 2004, *The Influence of Economic Evaluation Studies on Health Care Decision-Making - A European survey*. 2005, Amsterdam: IOS Press.
105. Bossard, N., et al., *Survival of cancer patients in France: A population-based study from The Association of the French Cancer Registries (FRANCIM).* European Journal of Cancer, 2007. **43**(1): p. 149-160.
106. Indenrigs- og Sundhedsministeriet, *Aftale mellem regeringen og Dansk Folkeparti om forbedring af behandlingen af kræft*, ed. Finansministeriet. 2005, Copenhagen.
107. Lofthus, C.M., et al., *Epidemiology of distal forearm fractures in Oslo, Norway.* Osteoporos Int, 2008. **19**(6): p. 781-6.
108. IMS Global Consulting, *Phase 8 Report November 2007. PATIENTS W.A.I.T. Indicator Commissioned by EFPIA.*
109. Jönsson, B. and N. Wilking, *Läkemedelsutvecklingen inom cancerområdet. LIF report 2008:6*. 2008, Stockholm: LIF.

110. *EUROMET 2004: The Influence of Economic Evaluation Studies on Health Care Decision-Making - A European survey. Report, IOS Press, Amsterdam.* 2005.
111. Roehrig, C. and K. Kimberley, *Health technology assessment in Canada and the G-7 countries: A comparative analysis of the role of HTA agencies in the decision making process.* . Health Care System Division Working Papers, 2003.
112. Hirth, R.A., et al., *Willingness to pay for a quality-adjusted life year: in search of a standard.* Med Decis Making, 2000. **20**(3): p. 332-42.
113. Nadler, E., B. Eckert, and P.J. Neumann, *Do oncologists believe new cancer drugs offer good value?* Oncologist, 2006. **11**(2): p. 90-5.