



# **Patient Access to Cancer Drugs in Turkey**

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The authors are solely responsible for the content of the report and its conclusions.

## Executive summary

- In this study, we have assessed patient access to cancer treatment in Turkey. The burden of cancer and the introduction of new technologies in Turkey was compared with eight European countries; Czech Republic, France, Germany, Hungary, Italy, Poland, Spain and the United Kingdom.
- In Turkey, approximately 150,000 people (207/100,000 inhabitants) are diagnosed with cancer each year. Cancer is the cause of almost 60,000 deaths in Turkey annually. The burden of cancer is expected to increase as the population ages.
- Direct treatment costs in Turkey amount to €1.8 billion annually, and indirect costs are expected to be higher.
- The development of new cancer therapies has improved the survival and quality of life of cancer patients. However, the outcomes of cancer treatment are lower in Turkey than in the European countries included in our analysis.
- Cancer patients in Turkey have a limited access to the newest drug therapies in comparison to European countries.
- The process of approval and reimbursement of new drugs in Turkey is more time consuming than in European countries, delaying the patient access to treatment. Restrictions in the approved indications and reimbursement conditions also limit the patient access to the most modern treatments.
- Cost effectiveness evaluations have recently become a mandatory part of the reimbursement application for new drugs in Turkey. Health technology assessments (HTA) have been introduced recently, and are planned to play an important role in the priority setting within the health care system. The experience and use of these instruments will need to be further developed, and data collection should be improved in order to analyse the clinical and economic impact of new therapies.

- The introduction of new drugs would benefit from new ways of funding, in order to reach market. Once medicines are used in clinical practice they can be further assessed regarding clinical and economic benefits.
- The health information system in Turkey needs to be improved in order to assess the burden of cancer, and most importantly, to enable and facilitate the follow up of treatment. Without better information, it will be difficult to implement an HTA system that can produce consistent and reliable results, or to evaluate the impact of various therapeutic options.

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# 1 Introduction

Cancer is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize. Cancer affects people at all ages, with the risk for most types increasing with age. In 2008, the International Agency for Research on Cancer (IARC) estimated that there were more than 12 million new cancer cases diagnosed worldwide. This has than doubled in the last 30 years, and in 2030 it is expected that 27 million new cases will be diagnosed [1]. In 2007, cancer caused about 7.6 million deaths globally (13 percent of all human deaths) [2].

Cancer is one of the disease groups causing the most human suffering, in terms of disabilities and numbers of deaths. The possibilities of curing and prolonging life in cancer patients have grown over time for all cancers [3, 4]. These improvements result from new methods of prevention, early detection and treatment.

Significant investments in research and development are made by the pharmaceutical industry, research institutes and universities to increase understanding of the causes and development of cancer and to find new treatments. Global pharmaceutical R&D expenditure is estimated to exceed US\$90 billion (€68 billion) annually worldwide[5].

Developing new drugs is a lengthy and costly process. In 2002, the European Federation of Pharmaceutical Industries and Associations (EFPIA) highlighted the increasing costs of developing a new chemical entity (NCE) over time, by comparing four estimates of the cost of developing a NCE between 1991 and 2001[6]. The estimate for 2001 was €741 million (2005 year value). A more recent estimate by Adams and Brantner [7] estimated the total development cost per NCE to €803 million in 2005 year value).

The output of pharmaceutical industry research in terms of number of NCE is a widely discussed topic. A substantial number of NCEs are introduced each year, although not all of these provide significant therapeutic innovation, since innovation to a large extent is incremental. However, Motola and colleagues estimated that 32 percent of all new



substances introduced between 1995 and 2003 provided important therapeutic innovation[8].

All these improved treatments naturally lead to higher costs of treatment to society. The annual direct medical costs for cancer care in Europe were estimated to €54 billion by Wilking and Jönsson in 2005. The indirect costs are generally estimated to be more than twice the direct costs[9].

Access to new treatment is, however, constrained by a number of factors, such as organization of health care systems, resources available, policies and procedures regarding access and use of new technologies and economic prioritizations in health care.

New innovative drugs need to gain market access. Without market access, patients cannot benefit from their clinical effectiveness, and the opportunity to learn from its use in clinical practice is missed. There are several processes to pass before a new drug can gain market access, and lately specific requirements for pricing and reimbursement have gained increased importance. These processes, as well as the priorities for achieving timely market access, vary between countries. Therefore, we see large variations in the time it takes for drugs to reach market in different countries.

The purpose of this study is to assess patient access to cancer treatment in Turkey. More specifically, the objectives of this report are to:

- Review and assess the burden of cancer in Turkey
- Review recent progress within the field of treatments in oncology
- Review and analyze policies regarding the introduction and diffusion of medicines in Turkey
- Analyze market access of cancer drugs in Turkey and discuss the relation between patient access and treatment outcomes
- Make comparative analysis of the burden of cancer and the uptake of new cancer drugs with other countries in Europe.

The burden of cancer, treatment outcome and uptake of oncology drugs in Turkey will be compared with a number of European countries. We have chosen to compare Turkey with the five largest countries of the European Union, Germany, France, the United Kingdom, Italy and Spain. Furthermore, comparisons are also made with three other EU countries which we believe, based on our previous studies represent relevant comparators to Turkey; Poland, Czech Republic and Hungary. These countries all have lower expenditures on health than the average in the European Union. Scarce resources for health care services is a feature that is shared with most countries in the world, but the constraints in access to treatment tend to be even greater in countries having lower incomes and being less able to allocate resources to health care. This is especially important in cancer care where treatments make a large difference in the wellbeing of the patients and where the treatment is associated with high costs.

## **2 Burden of cancer in Turkey**

### **2.1 Summary**

- In Turkey, approximately 150,000 people are diagnosed with cancer each year.
- Cancer is the cause of almost 60,000 deaths in Turkey annually.
- The incidence and mortality in cancer in Turkey is significantly lower than in the EU countries.
- One reason for the low incidence is that the Turkish population is young. As the age composition of the population becomes older, the burden of cancer is expected to increase.
- Cancer is estimated to cost approximately €1.8 billion in direct treatment cost, and a larger sum in indirect costs.

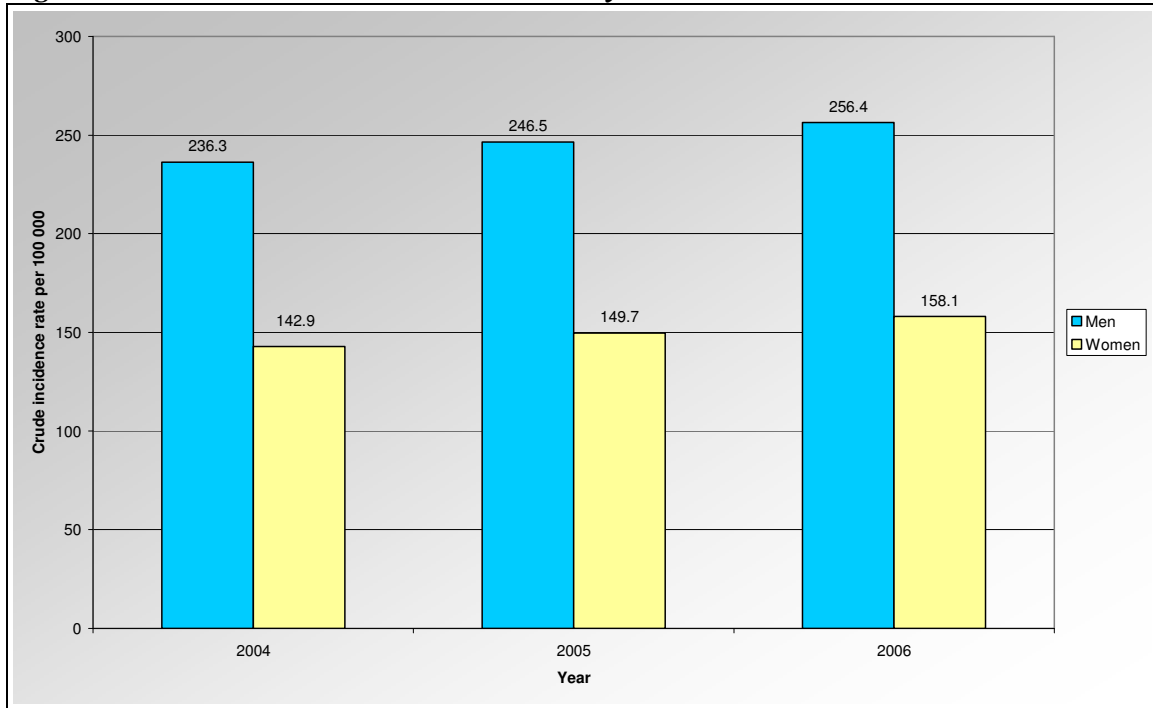
### **2.2 Incidence**

The data on cancer epidemiology in Turkey are subject to uncertainty. The history of most cancer registries is short, and the registration process has not yet matured. There are therefore, still large variations in the results of the cancer registries [10-12]. However, the reliability of the registries is under improvement, and the improvement of cancer registration is an important part of the cancer control plan in Turkey [13]. The cancer registry in Izmir, which is the oldest one in Turkey, has been used to estimate the burden of cancer in international comparisons in GLOBOCAN and in Cancer Incidence in five continents, both published by the International Agency for Research on Cancer (IARC) at the World Health Organisation (WHO). Recently, Turkey's data has been integrated to Cancer Incidence in five continents Volume IX. Additional registries in the coming years are expected to have sufficient quality for use in international comparisons.

As in most other countries, the burden of cancer is increasing in Turkey. Given a young, but ageing population, the burden is also expected to continue increasing. The latest available data on cancer incidence in Turkey is provided by the cancer control department at the Ministry of Health. The crude annual cancer incidence in Turkey is

158 per 100,000 female and 256 per 100,000 male. In total this means 150,000 new cases of cancer each year (Figure 2-1).

**Figure 2-1 Annual cancer incidence in Turkey 2004-2006**



Source: Turkish Ministry of Health

Among men, lung cancer is by far the most frequent kind of cancer, followed by prostate, skin and bladder cancer. More than one fourth of all cancers in male in Turkey are lung cancer. The natural cause of the frequency of lung cancer is smoking. The cancer incidence in female is significantly lower than in male in Turkey (Table 2-1). Among female breast cancer is the most common type of cancer followed by skin, colorectal and thyroid cancer. Almost one cancer out of five in Turkish female is breast cancer (Table 2-2).

***Table 2-1 The most common types of cancer in Turkish male (2004-2006)***

| Type                   | Annual world age standardized incidence<br>per 100 000 |
|------------------------|--|
| Trachea, Bronchi, Lung | 66,7   |
| Prostate               | 27,5   |
| Bladder                | 20,3   |
| Colorectal             | 17,0   |
| Stomach                | 14,6   |
| Larynx                 | 9,5  |
| Non-Hodgkin lymphoma   | 6,4  |
| Brain, CNS             | 5,3  |
| Kidney                 | 4,6  |
| Pancreas               | 4,5  |

Source: Turkish Ministry of Health

***Table 2-2 The most common types of cancer in Turkish female (2004-2006)***

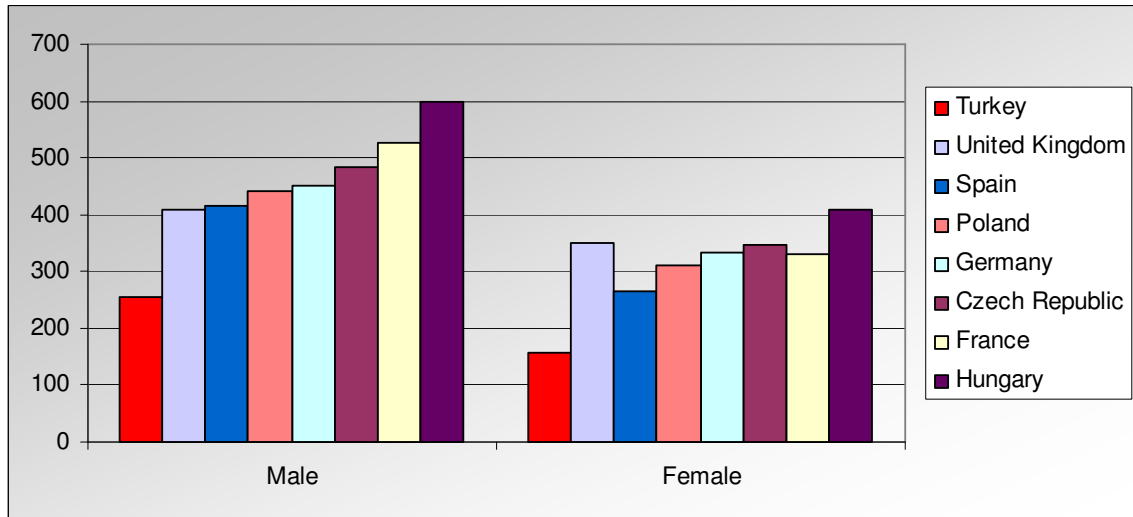
| Type                   | Annual world age standardized incidence<br>per 100 000 |
|------------------------|--|
| Breast                 | 35,8   |
| Colorectal             | 11,7   |
| Thyroid                | 9,3  |
| Uterus Corpus          | 7,7  |
| Trachea, Bronchi, Lung | 7,5  |
| Stomach                | 7,0  |
| Ovary                  | 5,8  |
| Cervix                 | 4,8  |
| Non-Hodgkin lymphoma   | 4,5  |
| Brain,CNS              | 4,1  |

Source: Turkish Ministry of Health

The latest data available allowing for cross country comparisons show that the incidence of cancer is still significantly lower in Turkey than in European countries, both among male and women. The overall incidence in 2006 in Turkey was less than half of the incidence in the European countries with the highest incidence in Italy among female and Hungary among male (Figure 2-2). This difference can also be seen in some of the most common cancer types (Figure 2-3 and Figure 2-4). The most obvious exception is lung cancer among male where the Turkish incidence is higher than Poland, Czech Republic and Germany, but still lower than in the other countries we compare with. Among the five most common cancer types among women, the Turkish rate is significantly lower than most other countries in all types except stomach cancer, where the level is higher than in France and in the UK, and at a comparable level to the rest.

It should be noted however that, the data presented in figures 2-2 to 2-4 have two different sources. The Turkish data is the latest official data from the Turkish Ministry of Health, while the data from the other countries are based on an estimation by Ferlay et al [14]. Due to different methods of collecting and processing data, it should not be read as a direct comparison.

**Figure 2-2 Age standardized cancer incidence per 100,000 inhabitants. All sites but skin (2006)**

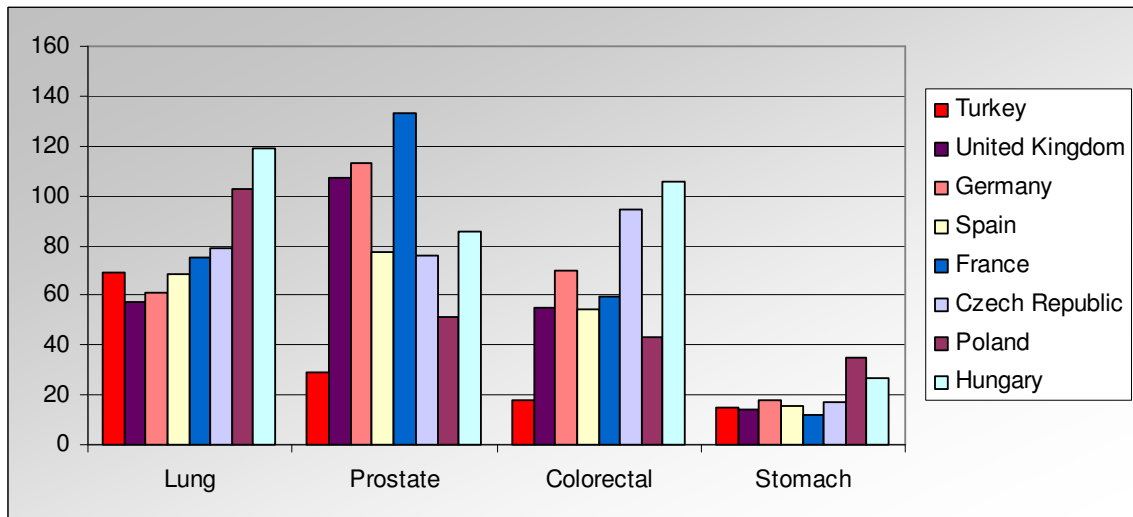


Sources:

Turkey: Ministry of Health;

All other countries: Ferlay, 2007 [14]

**Figure 2-3 Age standardized cancer incidence in selected per 100,000 male (2006)**

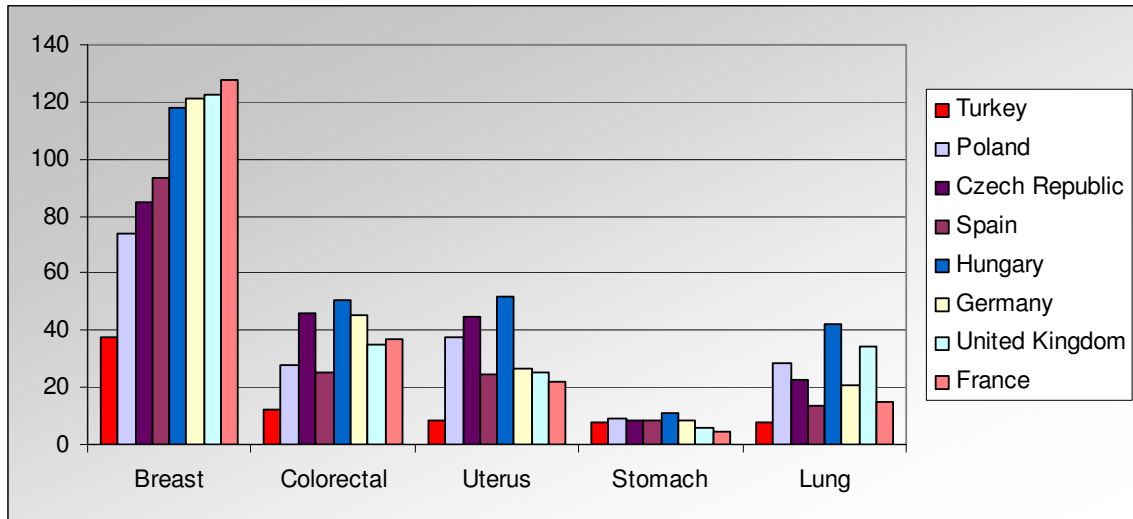


Sources:

Turkey: Ministry of Health;

All other countries: Ferlay, 2007 [14]

**Figure 2-4 Age standardized cancer incidence per 100,000 women (2006)**



Sources:

Turkey: Ministry of Health;

All other countries: Ferlay, 2007 [14]

### **2.3 Mortality**

The mortality in Turkey is also significantly lower than in Europe. The cancer types causing the most deaths in Turkey are cancers in the lung, stomach, colon and rectum. Among male these cancers, along with leukemia and prostate cancers, cause 65 percent of all cancer deaths in Turkey. Among women, breast cancer, followed by stomach and colorectal cancers, causes the largest number of deaths, in total 43 percent of all cancers (Table 2-4).

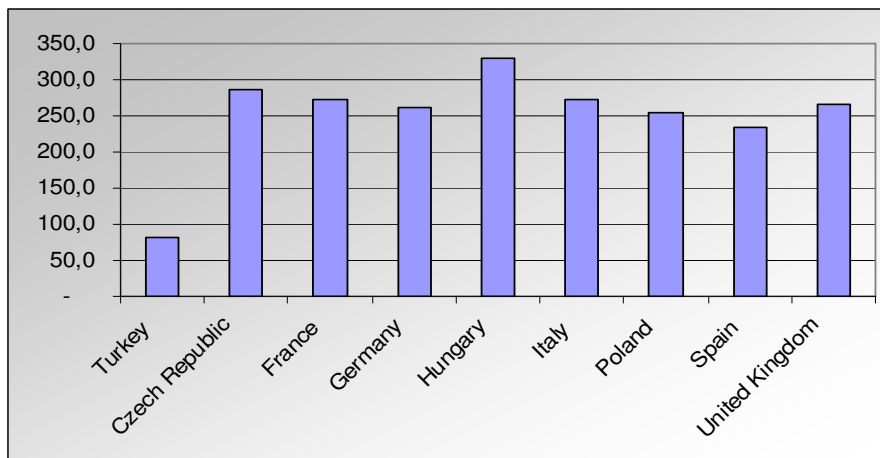


**Table 2-3 World age standardized cancer mortality in Turkey, 2004**

|                       | Male  | Female | Total |
|-----------------------|-------|--------|-------|
| Lung                  | 44.1  | 4.9    | 24.5  |
| Stomach               | 10.4  | 5.4    | 7.9   |
| Colon and rectum      | 5.8   | 5.4    | 5.6   |
| Leukemia              | 5.0   | 4.1    | 4.6   |
| Brain, nervous system | 3.8   | 3.2    | 3.5   |
| Bladder               | 6.0   | 0.9    | 3.5   |
| Larynx                | 4.8   | 0.3    | 2.6   |
| Non-Hodgkin lymphoma  | 2.7   | 2.2    | 2.5   |
| Liver                 | 2.5   | 1.4    | 2.0   |
| Pancreas              | 2.3   | 1.6    | 2.0   |
| Esophagus             | 2.0   | 1.4    | 1.7   |
| Oral cavity           | 1.7   | 0.9    | 1.3   |
| Kidney etc.           | 1.4   | 0.9    | 1.2   |
| Multiple myeloma      | 0.7   | 0.6    | 0.7   |
| Thyroid               | 0.3   | 0.7    | 0.5   |
| Melanoma of skin      | 0.5   | 0.4    | 0.5   |
| Nasopharynx           | 0.6   | 0.3    | 0.5   |
| Hodgkin lymphoma      | 0.5   | 0.3    | 0.4   |
| Other pharynx         | 0.3   | 0.2    | 0.3   |
| Prostate              | 5.0   |        |       |
| Testis                | 0.5   |        |       |
| Breast                |       | 9.7    |       |
| Cervix uteri          |       | 2.4    |       |
| Corpus uteri          |       | 2.0    |       |
| Ovary etc.            |       | 3.4    |       |
| All sites but skin    | 107.8 | 58.7   | 83.3  |

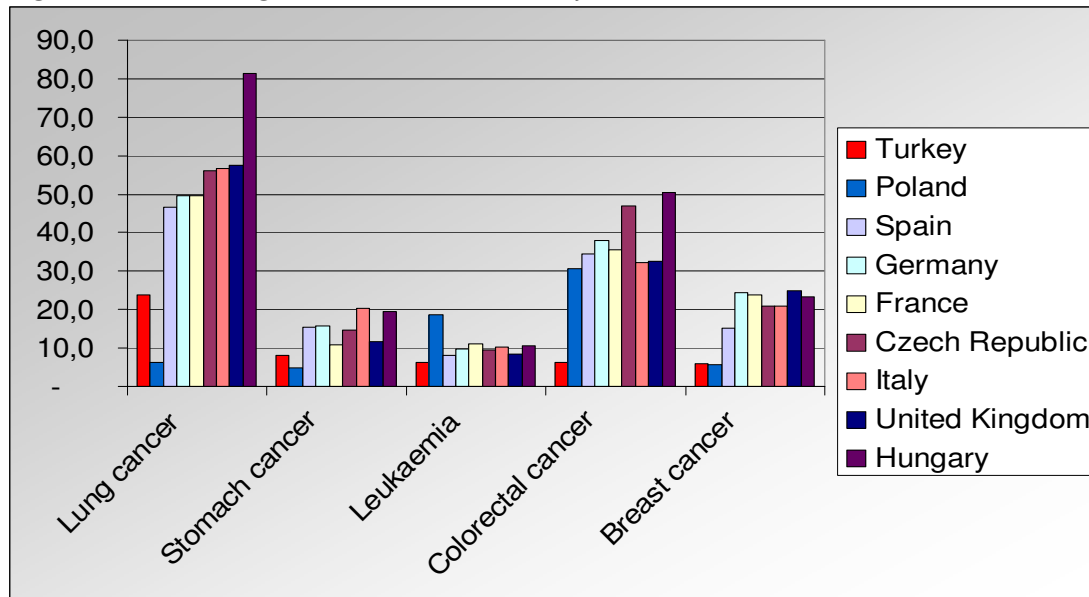
Source: Turkish Ministry of Health, Department of Cancer Control, 2008

**Figure 2-5 World age standardized cancer mortality in selected countries, 2004**



Source: WHO Global burden of disease database

**Figure 2-6 World age standardized mortality in selected cancers, 2004**



Source: WHO Global burden of disease database

## **2.4 Disability adjusted life years lost due to cancer**

The difference in burden of cancer in Turkey compared to European countries is also apparent in the number of Disability Adjusted Life Years lost (DALYs). DALY is a measure of overall disease burden. Originally developed by the World Health Organization (WHO), it includes equivalent years of “healthy” life lost by virtue of being in states of poor health or disability. This measure combines mortality and morbidity into a single, common metric. DALYs lost in cancer is significantly lower in Turkey, as one could expect due to the comparably low incidence rates. The cancer share of all DALYs lost is also much lower in Turkey than in other countries. Only 6.7 percent of all DALYs lost are due to cancer in Turkey while the same share for European countries is between 12 percent and 15 percent (Table 2-5).

**Table 2-4 World age standardized DALYs lost in cancer and as a proportion of total DALYS lost per 100.000 inhabitants (2004).**

|                | Total DALYs lost | DALYs lost in cancer | Cancer share of DALYs lost |
|----------------|------------------|----------------------|----------------------------|
| Turkey         | 16 246           | 1 088                | 6,7%                       |
| Czech Republic | 11 439           | 1 723                | 15,1%                      |
| France         | 10 666           | 1 514                | 14,2%                      |
| Germany        | 10 114           | 1 387                | 13,7%                      |
| Greece         | 9 927            | 1 229                | 12,4%                      |
| Hungary        | 14 665           | 2 097                | 14,3%                      |
| Italy          | 9 256            | 1 286                | 13,9%                      |
| Poland         | 13 057           | 1 787                | 13,7%                      |
| Slovakia       | 13 463           | 1 677                | 12,5%                      |
| Slovenia       | 11 674           | 1 554                | 13,3%                      |
| Spain          | 9 786            | 1 309                | 13,4%                      |
| United Kingdom | 10 616           | 1 331                | 12,5%                      |

Source: WHO Global burden of disease database (2009)

The burden of cancer in Turkey in terms of the number of annual new cases and deaths appears to be much lower than in European countries. The data published in the different cancer registries differs significantly. Comparing the data with that of other countries also indicates that there is a high level of under registration of the number of cases. This could either be due to the fact that there *are* actually significantly less number of cancer cases in Turkey, or that there is an under registration of cancer patients. It may be the case that a smaller share of the patients come to the attention of medical services compared to European countries.

The short history of the active Turkish cancer registries may have led to a lack of accurate statistics on the epidemiology of cancer in Turkey.

#### 2.4.1 Expectations of the future burden of cancer in Turkey

One of the main drivers behind the increasing number of cases of cancer in the world is an ageing population, since most cancers appear in older ages. The population in Turkey is significantly younger than in European countries, partly due to low life expectancy, and partly due to a larger number of births. The life expectancy at birth is eight years lower in Turkey than in some European countries (Table 2-6). As seen in Figure 2-7, there have been steadily large birth cohorts in Turkey in the past 30 years, whereas Poland as many other European countries have also had several cohort with fewer births.

***Table 2-5 Life expectancy at birth 2007***

|                |      |
|----------------|------|
| Turkey         | 73,4 |
| Hungary        | 73,3 |
| Poland         | 75,4 |
| Czech Republic | 77,0 |
| United Kingdom | 79,5 |
| Germany        | 80,0 |
| France         | 81,0 |
| Spain          | 81,0 |
| Italy          | 81,4 |

Source; OECD Health data 2009

The life expectancy is however increasing, and the ageing of the large birth cohorts in the past 30 years is leading towards an ageing population (Figure 2-7). In fifteen years time, the earliest large birth cohorts of the past 30 years are approaching the middle ages. Looking even further, these cohorts will in a few years approach their 60s and 70s, an age where the risk of having cancer is escalating. The two most important factors leading to cancer, smoking and poorly balanced diet, are also expected to rise in Turkey [13].

Even if there may be a degree of uncertainty in the available cancer statistics, it is fair to expect that the burden of cancer will increase substantially in the years to come. As in other countries that have been in this phase of rapid growth of cancer cases, it is expected that the economic burden of cancer will increase rather dramatically in Turkey in the coming years. This poses tremendous challenges in how to provide these patients with access to the most appropriate treatment. This treatment may be very costly, whereas the resources available for health care are scarce. This is additional to the challenges European countries with substantially larger health care expenditures have faced [6, 9, 15].

Figure 2-7 Population composition in Turkey 2009

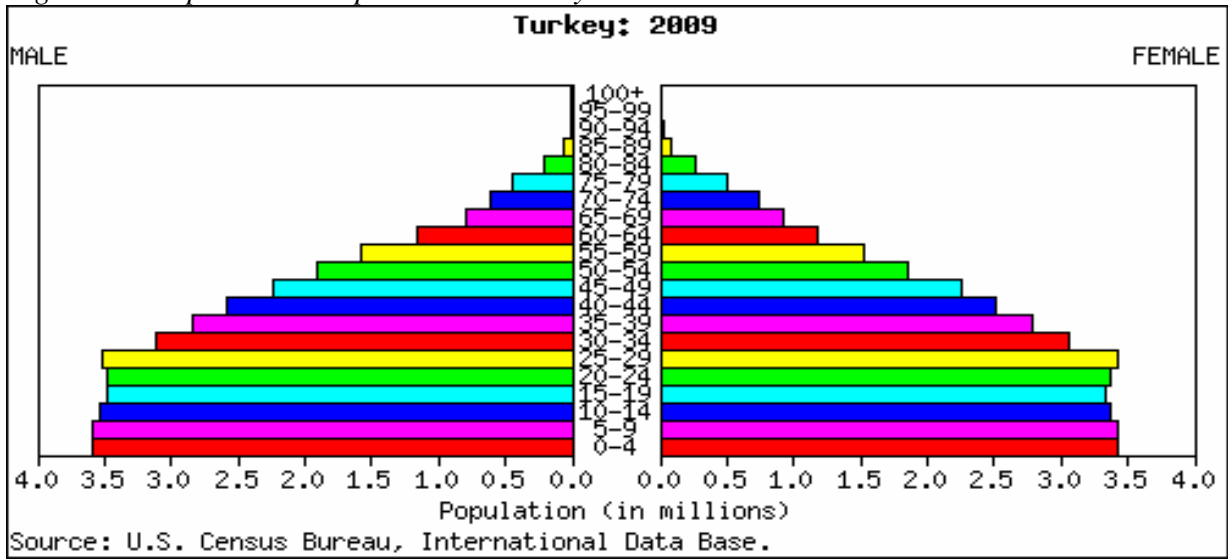
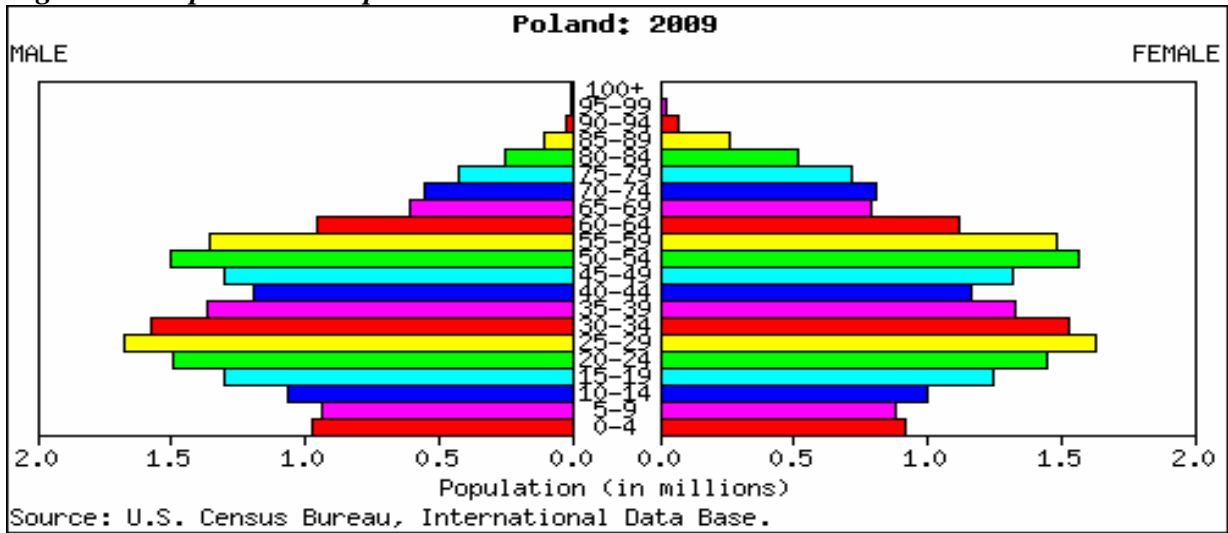
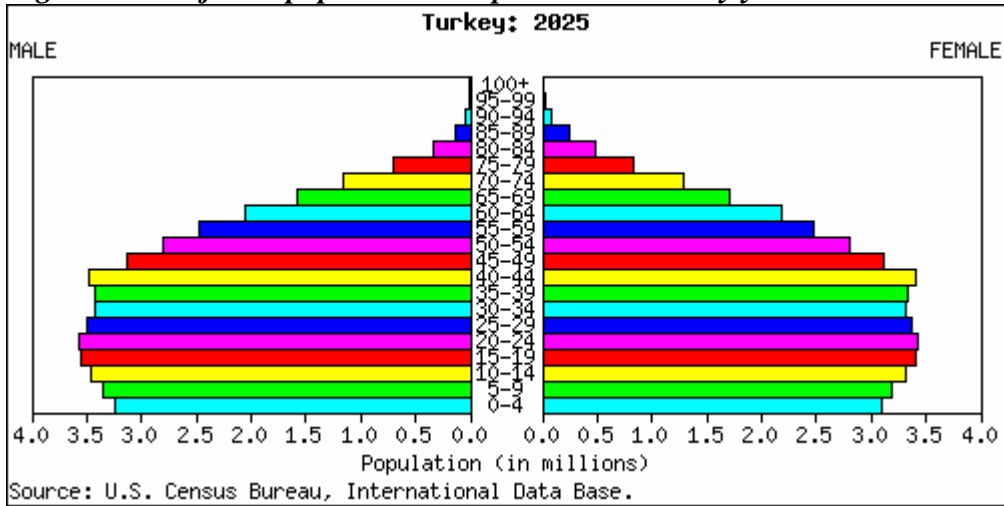


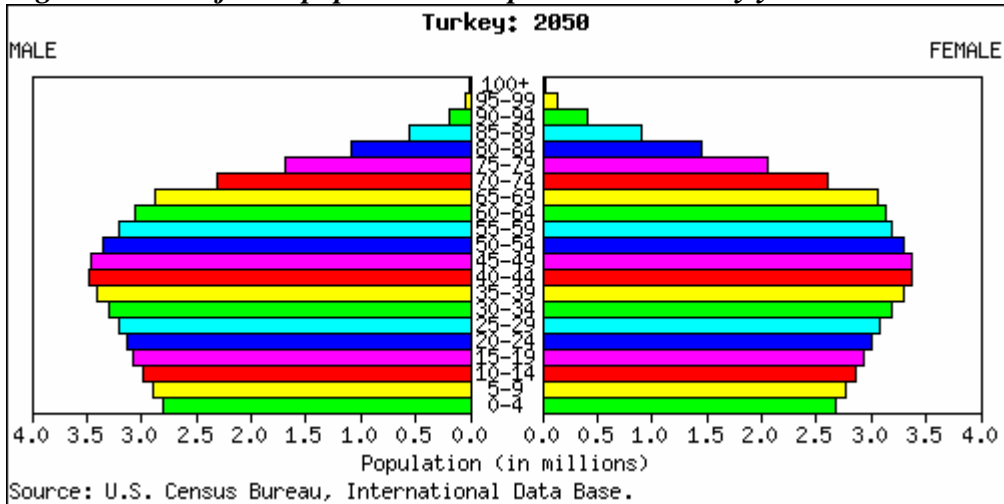
Figure 2-8 Population composition in Poland 2009



**Figure 2-9 Projected population composition in Turkey year 2025**



**Figure 2-10 Projected population composition in Turkey year 2050**



## ***2.5 Outcome of cancer treatment in Turkey***

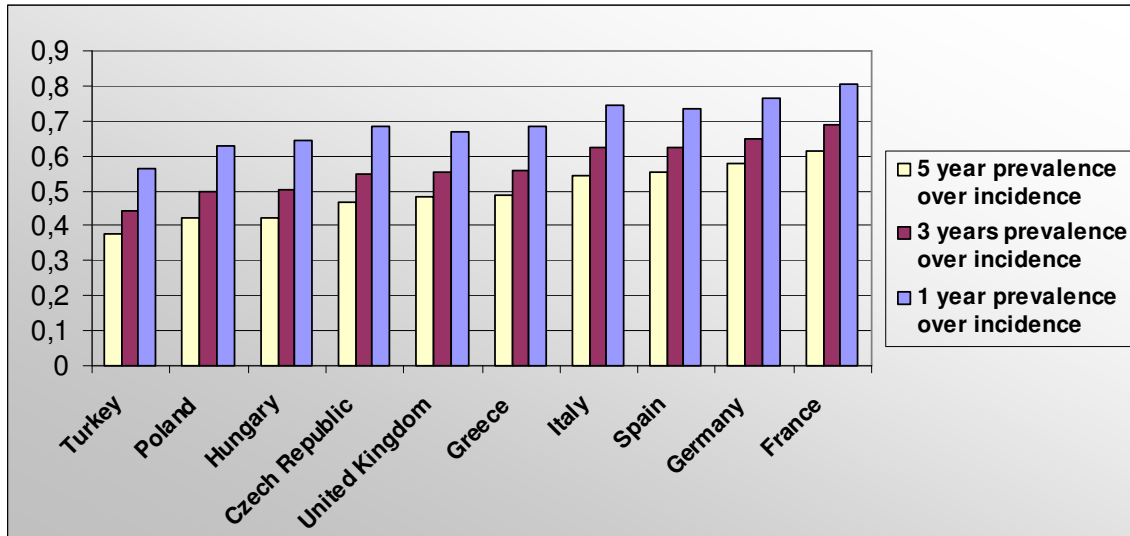
As there is scarce information on the survival of cancer in Turkey, it is challenging to assess the outcome of cancer treatment and the impact of access to treatment. It is also difficult to compare the outcome of treatment in Turkey with other countries. One way to compare the outcome is to use the relation between prevalence and incidence. In this study we have used the data available in the GLOBOCAN 2002 database to compare the prevalence/incidence ratio in Turkey with a selection of European countries. The prevalence in the GLOBOCAN database is calculated by multiplying the incidence with the expected survival.

The outcome measure is calculated by dividing the prevalence (the overall number of cases) by the incidence (the number of new cases) multiplied by the number of years of prevalence. The 5-year prevalence/incidence ratio is then the 5-year prevalence divided by the incidence multiplied by 5. The 5-year prevalence is the number of new cases in the past 5 years still being alive.

The reason for using the prevalence/incidence measure is to be able to compare the outcome of treatment in Turkey with other countries in a short, medium and long term. They are the best comparable figures available for such a large number of countries.

In Figure 2-2 we can see that the outcome of cancer care is much lower in Turkey than in the European countries included in the comparison. This estimate of the outcome of cancer treatment has its limitations, and it should not be interpreted as a direct measure of cancer survival. It serves more as an indication that cancer patients in Turkey do not have as high a chance of surviving cancer as in Europe. There are several factors influencing the survival, which could explain the differences across countries e.g. late diagnosis, treatment practice applied, availability of treatment options, country specific causes of cancer, patient characteristics etc. In this report we primarily look at factors related to patient access to treatment.

**Figure 2-11 Outcome of cancer treatment in selected countries**



Source: GLOBOCAN 2002 [16]

## **2.6 The cost of cancer treatment in Turkey**

The burden of cancer 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.

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. Access to treatment is also unequal across countries, largely related to the availability of resources, 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.

In Europe, countries with lower expenditures per capita on health tend to have a smaller share of the health care resources devoted to cancer. Given that the level of health expenditures in Turkey is lower than in other European countries, we also expect the resources available for cancer treatment to be low. Comparative European countries with lower incomes also tend to have a smaller share of the total health expenditures devoted to cancer treatment. In the central and eastern European countries, approximately 3-5 percent of health care expenditures are used on cancer[18].

As in most European countries, there is a great uncertainty in the estimations of the costs of cancer treatment in Turkey [17]. According to the Ministry of Health, the direct expenditures on cancer treatment are approximately 2.5 billion USD (€1.8 billion). This would mean that the cancer share of all health expenditures would be 6 percent based on a total health expenditure of €30 billion (PPP adjusted) in 2007 [19]. This would mean that the total expenditure per capita on cancer treatment would be €25. This is to be compared to the average in Europe at €148 per capita, and the expenditures in Poland and Hungary where the cancer costs are €41 and €61 per capita respectively [15]. The Turkish expenditures compared to a selection of European countries are found in Table 2-7.

**Table 2-6 Expenditures on cancer in selected countries (2007)**

|                | Cancer share of health expenditures | Direct costs of cancer per capita in € PPS |
|----------------|-------------------------------------|--|
| Czech Republic | 5.0%                                | 72   |
| France         | 6.6%                                | 205  |
| Germany        | 7.2%                                | 216  |
| Hungary        | 5.0%                                | 61   |
| Italy          | 6,4%                                | 144  |
| Poland         | 5.0%                                | 41   |
| Spain          | 6,4%                                | 141  |
| United Kingdom | 5.6%                                | 132  |
| Turkey         | 6.0%                                | 25   |

Source: Wilking et al [15]

In an estimate of the economic burden of lung cancer in Turkey, Cakir Edis and Karlikaya [20], estimated the total cost of diagnosis and treatment at 81 million USD (€65 million) in 2004. Given national health expenditures of 23 billion USD (€18 billion) in 2004, the direct costs of lung cancer would consume 0.3 percent of the total health care budget. The corresponding figures for some European countries are higher. In Sweden, the lung cancer share of total health expenditures is 0.6 percent, in Germany 0.5 percent, in the Netherlands 0.3 percent and in France 0.5 percent [21].

Recent efforts in improving the efficiency of resource utilization in Turkey has also led to a number of cost effectiveness studies on specific diseases [22]. Such studies have for example included breast cancer screening [23]. This study estimated the cost of breast cancer treatment in Turkey to be YTL 162 million (€90 million) excluding costs of screening of YTL 100 million (€56 million). Without screening, the total cost of breast cancer treatment was estimated to be YTL 224 million (€125 million).

## ***2.7 Conclusion***

A lack of data makes it difficult to provide a clear picture of the burden of cancer in Turkey. In order to enable sound decisions on priorities in health care it is necessary to know what the challenges are in terms of current and future needs of treatment. It is also necessary to know where the resources are spent in order to assess whether they are efficiently utilized.

The epidemiology data on cancer in Turkey has its limitations, and it is expected to underestimate the true burden of cancer. The most recent data on cancer epidemiology has improved significantly, and this will facilitate the analysis of the burden of cancer and outcome of treatment. There is still a lack of data to analyze the current situation and to determine the best strategies to manage the challenges of today and in the future. It will still take a few more years before long term trends of the developments in cancer treatment can be analyzed.

The department of cancer control at the Ministry of Health has in recent years made efforts in mapping the burden of cancer both in terms of epidemiology, costs and cost effectiveness of treatment.

## **3 The health care system in Turkey**

### **3.1 Summary**

- The Turkish health care system is facing new challenges with an ageing population, increasing the burden of resource-consuming diseases such as cancer, and constrained budgets.
- The Turkish health care system has been restructured in recent years to improve access to treatment and equity.
- The reforms have also included the processes of approval and reimbursement of new drugs. Efforts have been made to make these processes shorter, more transparent and support e cost containment in a constrained health care budget.

### **3.2 Introduction**

Turkey is a large country both in terms of geographical space and population. In terms of population, the 73 million inhabitants make Turkey larger than most European countries. The population of Turkey is young in comparison with most European countries. The life expectancy at birth in Turkey is, as seen in the previous chapter, lower than in EU countries, but is, rising rapidly. In the years 1995 to 2007 it rose from 67.1 years to 73.4 years [19].

The Turkish economy has been growing rapidly in recent years, despite a major set back experienced during the economic and financial crisis in 2001, and more recently, like many other countries, the recent global financial crisis. The growing economy has also increased the resources available for health care. For low and middle income countries, increased resources for health care also provide opportunities to use more modern technologies. Every health care system faces a challenge in providing health care services matching diverse needs of the population with limited resources. The limited resources lead to a need to make choices and prioritizations. With greater resources, the health care system can move further beyond merely basic needs.

The Turkish health care system has in recent years gone through major reforms, both regarding the provision and financing of services. In 2003, a new reform program for the health care system was launched, with the aim of improving the access to health care. In

2002, the World Bank stated that the health status of the Turkish population and the ability of the health care system to provide adequate services to the population were lower than in comparable middle income countries [22]. With that in mind, the Turkish government initiated a study to assess the burden of disease and cost effectiveness of the delivery of health care services. In 2003 the Ministry of Health launched a ten year Health Transformation Programme (HTP). The HTP also aims to address a number of problems in the Turkish health sector, including health outcomes lagging behind other OECD countries; inequities in access to health care and the fragmented financing and delivery of health services and poor quality of care [24] .

One of the cornerstones of the reform program was the establishment of a Universal Health Insurance (UHI) system combining the previously separate health insurance funds in one Social Security Institute (SSI). The enrolment in the UHI is mandatory, with contribution rates proportional to the ability to pay and all beneficiaries entitled to the same benefits package. Contributions for those deemed unable to pay premiums are paid from public funds on the basis of a means-tested system. SSI is the only purchaser of health services contracting public and private providers [25].

The expenditures on health in Turkey are lower than most European countries, following a low overall level of GDP. The per capita expenditures on health are less than one fifth of the level in Germany and France. Like in many European countries with lower than average health expenditures, the use of pharmaceuticals is relatively high in relation to health expenditures (Table 3-1). One of the major reasons is that the cost of pharmaceuticals is higher in relation to other costs in countries with lower incomes, such as salary levels and hospitalization costs etc.

*Table 3-1 Expenditures on Health in Turkey and selected comparator countries, 2007*

|                | GDP per capita USD PPP | Expenditure on health per capita USD PPP | Expenditure on health as a share of GDP | Pharmaceutical expenditure per capita USD PPP * | Pharmaceutical expenditure as a share of expenditure on health |
|----------------|------------------------|--|---|---|--|
| Turkey         | 11 535                 | 591                                      | 5,7 %                                   | 143   | 24 %   |
| Poland         | 14 674                 | 843                                      | 6,2 %                                   | 236   | 28 %   |
| Hungary        | 18 155                 | 1 440                                    | 8,5 %                                   | 391   | 27 %   |
| Czech Republic | 22 042                 | 1 447                                    | 7,1 %                                   | 402   | 28 %   |
| Greece         | 27 232                 | 2 283                                    | 9,0 %                                   | 651   | 29 %   |
| Spain          | 29 383                 | 2 260                                    | 8,3 %                                   | 332   | 15 %   |
| Italy          | 32 002                 | 2 496                                    | 8,9 %                                   | 376   | 15 %   |
| Germany        | 31 949                 | 3 251                                    | 10,7 %                                  | 326   | 10 %   |
| France         | 31 316                 | 3 306                                    | 11,1 %                                  | 429   | 13 %   |
| United Kingdom | 32 961                 | 2 580                                    | 8,2 %                                   | 316   | 12 %   |

\*2006

Source: OECD

### **3.3 Organization of cancer care in Turkey**

In Turkey, the majority of the oncologists work in large centers. In 2005, there were 44 cancer diagnosis and treatment units or centers. The vast majority, 28 of them, were university-based. Six of them were run by the Ministry of Health, 6 were old social security establishments, 3 were private hospitals and one was based in a private university. Most of these centers had some of the main oncology disciplines, medical oncology, pediatric oncology and pathology. In 29 of the units, radiation oncology was provided. Only 4 had surgical oncology. About one third of the centers had a research laboratory. Some of the institutions thus lacked a multi-disciplinary structure of oncology treatment.

In 2005, there were three dedicated cancer institutes in Turkey. The oncology institutes in Hacettepe University and Istanbul University were established in 1982, and the oncology institute in Dokuz Eylül University was established in 1992 [26].

In recent years, efforts have been put in on early detection and screening[27]. Cancer Early Diagnosis and Screening Centers (KETEM – Kanser Erken Teshis, Tarama ve Eđitim Merkezleri) have been established in order to execute population based screening programs in breast, cervical and colorectal cancer. The Ministry of Health has established 88 such centers throughout the country. In addition to providing screening, the KETEMs also train health personnel in raising the awareness of cancer in the public. The KETEMs also refer diagnosed cancer patients to appropriate treatment centers, and

to provide social, psychological and medical support. In total, 280 KETEMs are planned to be in operation in 2015. By 2011, it is expected that 70 percent of the target population will be screened [28]. The provision of services in these KETEMs is limited by a shortage of staff. The number of staff is only about one third of the actual needs [29].

Cancer control in Turkey is coordinated by the department of cancer control at the Ministry of Health. In 2009, a first national cancer plan was released. The cancer program is largely focused on prevention and screening of cancer, in order to reduce the new cases and to detect cancers earlier. Regarding treatment, there are five main objectives set out in the cancer program;

- Improvements in human resources
- Improvements in technological and physical infrastructure
- Development of a national policy in diagnosis, treatment and medication
- Establishing a national organization structure in cancer
- Establishing a delivery chain structure in diagnosis, treatment and research

It is planned to establish a national cancer institute with the purpose of coordinating cancer treatment in Turkey [28].

A primary aim of the cancer control strategy in Turkey is also to establish accurate and reliable cancer registries[13].

In the work of the national cancer program a number of needs are specified. Many objectives address the issue of availability of cancer treatment to the entire population. One of the main barriers identified is the lack of a clear structure of the organization of cancer treatment and a lack of coordination between different actors. Many objectives will require large investments in infrastructure, training, staffing costs, medications etc. However, the program does not specify how the reforms should be financed.

### ***3.4 Introduction of new health care technologies in Turkey***

In Turkey, the market authorization of new drugs is granted after evaluation of safety, efficacy and quality. The market approval process is under the responsibility of the General Directorate of Pharmaceuticals and Pharmacy (GDPP) at the Ministry of Health. The GDPP is the main authority for market authorization, pricing, legal classification and inspection of pharmaceuticals. The directorate is supported by a number of commissions. These commissions comprise pharmacologists, clinicians, other related experts and representatives of the Ministry and other related organizations. The commissions evaluate the documents provided by pharmaceutical manufacturers and their decisions form the basis for marketing and approval. The market authorization process includes four stages. First the application is reviewed by the Advisory Commission for Authorization of Medicinal Products for Human Use. This process takes in general 3-4 months. For oncology products a subcommittee with four members (oncologists/hematologists) also reviews the product, which extends the process.

After approved by the first commission the application is also reviewed by the Advisory Commission for Technology and Pharmacology which evaluates the technical aspects of the product. The technical commission also reviews the applications approved by FDA in the US and EMA in the EU. This review takes 6-8 months before approval. Following reforms in 2005, the registration process has become more standardized and transparent.

At the third stage in market approval process, the application is assessed by the commission for bio-equivalence (for generic products) and bioavailability (for original products). Pricing is also a part of the market authorization process. The price is set by the Department of Pricing under the GDPP, based on an international reference pricing scheme. The price can be submitted either during the registration process or after the registration process is completed. The pricing procedure usually takes 2-6 months. For generic products, the registration process is shorter as they do not require going through the main committee. After the registration and price approval, a sales permit from the Ministry of Health (MoH), is also required to complete the marketing authorization process. This takes approximately two weeks. The entire process for new products needs 12-18 months to be completed. According to the Ministry of Health, the marketing approval process should not exceed 210 days [25]. In reality, however, the average

approval time is between 12 and 24 months [30]. A recent survey by the Association of Research Based Pharmaceutical Companies (AIFD), documented that the average time to authorization for oncology products is 655 days. These delays are not limited to oncology medicines. AIFD has documented the time required to register, price and reimburse new medicines in general to be on average 2-3 years.

A recent measure introduced by the Health Ministry, concerning the provision of Good Manufacturing Practice (GMP) certificates, is contributing to significant delays in the registration of new medicines, and hence, lengthening the time for patient access to those treatments. At the time of this writing, some 250 dossiers are held up as manufacturers and Ministry of Health officials discuss a way to mitigate the impact of this new measure on patients.

In contrast, within the EU, there is a centralised procedure for this authorization. The producer submits an application to the regulatory body, the European Medicines Agency (EMA). 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. The centralised procedure in the EU may help to speed up the market access for new drugs in EU member states that would otherwise endure time-consuming authorization processes, and there are precedents where countries linked their approvals with the EU centralized procedure during their pre-accession period.

#### 3.4.1 Pricing and reimbursement of medicines in Turkey

As in most other countries the expenditures on medicines has increased at a higher pace than the general health expenditures in Turkey. In order to address this, the government in 2004 launched a reform to control the rising pharmaceutical expenditures. An important component of this reform has been to reduce the price of the drugs.

In the past, prices of pharmaceuticals were determined upon the application of the firm based on a cost-plus approach. However, increasing concerns about the share of pharmaceutical expenditures in total health care expenditures have led to increasing regulations of the pricing and reimbursement [25].

As a starting point of reforms, the Turkish government applied an international reference price system for pharmaceuticals in 2004. Under the new government pricing legislation, the reference price of original product is determined according to lowest price among



five countries from an established list of up to ten EU reference countries. The list may be altered every year. Currently, the five reference countries are France, Italy, Spain, Portugal and Greece. The country, where the product is released and shipped, also serves as another reference. This price is the ceiling price for the original product.

Both original and generic prices are capped at 66 percent of reference price with the first generic entry of any original molecule.

The Turkish reimbursement system has been revised several times in the past ten years. Since 2005 there is a positive list of reimbursed products. In 2008 a new reimbursement guideline was introduced. It included defined timelines for reimbursement, and improved the transparency of the process. From 2009, pharmacoeconomic evaluations are mandatory.

The Turkish reimbursement process is separated from the market approval and pricing process. Companies apply to the Social Security Institution (SGK), for reimbursement new medicines. The written request should be supported by

- The FDA marketing authorization and New Drug Application (NDA) number, the EMA marketing authorization and co-marketing certificate, if any, for original (innovator) products and for first-time listing of new molecules
- Regulatory and reimbursement status within OECD countries
- Clinical data
  - Safety
  - Efficacy
- Pharmacoeconomic data
  - The pharmacoeconomic analysis shall be performed and must be annexed with the appropriate sensitivity analysis.
  - The comparison should be with the most commonly used alternative
  - Cost Minimization, Cost Effectiveness, Cost utility (may be submitted by the applicant as an annex to the pharmacoeconomic analysis).

- Budget impact model from payer perspective

The other stakeholders involved in the reimbursement evaluation process alongside the SGK are the Ministry of Finance (MoF), the Ministry of Health (MoH), the State Planning Organization, the Under secretariat of Treasury, Key opinion leaders and industry representatives.

The submitted products are primarily evaluated by the Medical & Economic Evaluation Commission and the final decision is given by Reimbursement Commission. The final revised list is announced after the official approval of the Head of SGK.

Health technology assessments have also been introduced, but are not yet fully adopted. Several changes have also been introduced to reduce the cost of drugs. These include for example higher discounts, therapeutic referencing for some treatment areas, payback system and more restrictions on prescription. The reimbursement level is 100% for chronic diseases approved by SGK.

There is a minimum mandatory discount of 23 percent for reimbursed original products until there are generic alternatives available. The reimbursement level is 100 percent for chronic diseases approved by SGK. Maximum reimbursement price is determined using “active ingredient based equivalent groups”, whereby 15 percent above the cheapest (after mandatory discounts) drug available in the same group.

First and subsequent generics can be priced equal to or less than the previously launched products in the same equivalent group. Generic products whose unit prices are 5 percent lower than that of the drug with the lowest unit price in the same equivalent group are taking advantage of fast track reimbursement approval within a week. As a result, the lower price entries can substantially lower the reimbursement price for existing original products.

During last years, several changes have also been introduced to reduce the cost of drugs. The last one, having a major impact on innovative pharmaceuticals came with the Medium Term Fiscal Plan (2010-2012) of the government. This long term fiscal plan aims at controlling the pharmaceutical budget against the overall government healthcare expenditure.

As of December 2009, the mandatory institutional discount increased from 11 percent to 23 percent for the reimbursed original products until first generic entry to the market.

The rising cost of pharmaceuticals has been addressed in most countries by various market regulations. Strategies to keep the prices down have included direct price controls, profit controls, reference pricing schemes and other agreements between authorities and the industry. All countries in the EU except for Germany and the UK apply direct price controls to drugs on patent. In France, drugs defined as new and innovative may also be exempted.

Some countries, like Austria, France, Spain and Sweden have negotiated price-volume trade-off agreements with individual producers. Prices may be set according to expected or realized volume. If the actual consumption is higher than this value, the price may be cut or the companies may have to repay the purchaser.

The price control mechanisms have kept drug prices in Turkey at a lower level than in almost all OECD countries. The average retail price of drugs is less than 70 percent of the OECD average. The price level is approximately at the level of that in Poland, and Czech Republic [31].

The time from application for reimbursement to a final decision in Turkey is usually up to one year [30], which is also a cause of delay of market access.

## 4 Medical review

### 4.1 Summary

- Cancer treatment today is characterized by a multi-modal 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.
- New treatments appear to have been important in generating cancer survival gains.
- 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. Also histology based outcome predictions in case of using a certain molecule has been proven.
- New diagnostic tools including functional imaging are increasingly used in order to evaluate early response and therapy effects.

## **4.2 Introduction**

Agents that inhibit cancer growth (chemotherapy) were first discovered in the 1940s. These are the alkylating agents and antimetabolites- and are still in use [32, 33]. 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 [34, 35].

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[36].

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.

### ***4.3 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 [37]. 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[38].

#### 4.3.1 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 develop 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) [39].

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 1990s, 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 [40], 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 90s the central role of microtubules in cell division, proliferation and chemotaxis was evident, and several agents, taxanes (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[41].



New antimetabolite agents have also been introduced during the last decade with an important clinical impact-gemcitabine- with efficacy in pancreatic cancer [42] ovarian cancer, metastatic breast cancer, bladder cancer and non-small cell lung cancer – pemetrexed- with an efficacy in malign pleural mesothelioma and nonsquamous histology of non-small cell lung cancer [43]. 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.

Despite all new targeted agent developments, chemotherapy still remains the backbone of treatment in cancer treatment. Now there is also an important improvement in the area of NSCLC. 10 years there were still discussions on whether advanced NSCLC should be treated or not. In 1995 a meta analysis showed 5.5 m median survival in this patient population [44]. In 10 years time there was a significant improvement. With addition of biologicals to chemotherapy in NSCLC median survival is now around 12 months [45].

#### 4.3.2 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.

#### 4.3.3 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 is an estrogen receptor antagonist, 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 unique mechanisms of action (e.g. fulvestrant, megestrol) they constitute valuable therapeutic options in metastatic breast cancer. Aromatase inhibitors have already gained 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, gonadotrophin 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.

#### 4.3.4 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 [46]. In combination with radiotherapy, cetuximab has also demonstrated efficacy in patients

with advanced head and neck tumours [47]. Similar to locally advanced H&N tumors, cetuximab has also shown increase survival, proven to prolong progression free survival, increase response rates in recurrent/metastatic Head & Neck tumors when it is used in combination with platinum-based chemotherapy [48]. Tyrosine kinase inhibitors against the EGFR pathway have also been introduced. Erlotinib [49] has demonstrated efficacy and increased survival as monotherapy in non-small-cell lung cancer. Recent studies in lung cancer with gefitinib showed efficacy only in EGFR mutation positive patients [51]. 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) [52].

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 [53]. 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 [54, 55]. Trastuzumab has now also been approved (December 2009) by EMA for the treatment of HER2 over-expressing advanced gastric cancer.

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[56]. 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 [57]. Treatment with imatinib results in complete responses in 80 percent of

patients[58]. 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 [59]. 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[60] 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 sunitinib, dasatinib and nilotinib [61].

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 stromal tumours and renal cancer, for which there are no active chemotherapy alternatives they are first-line options. In other tumour forms it remains to be seen if these agents will replace conventional chemotherapy as first-line treatment. 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) [62, 63]. 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. [64]. The reason behind this is found to be related to EGFR mutation status of the patients. Later studies with gefitinib demonstrated superiority to doublet chemotherapy in terms of progression-free survival which shows that the analysis of EGFR mutation status was a strong predictive biomarker for the effect of gefitinib. Progression-free survival was significantly longer in mutation positive patients receiving gefitinib as first-line treatment compared

with mutation negative patients [51]. These data indicate a subgroup of patients that will benefit from this targeted therapy the most, which may lead to optimal use of resources.

**Table 4-1 Agents inhibiting protein kinases approved for use in oncology**

| Generic name | Trade name | Drug class           | Target        | Year of approval |
|--------------|------------|----------------------|---------------|------------------|
| Trastuzumab  | Herceptin  | Antibody             | HER2          | 1998             |
| Imatinib     | Glivec     | small molecular drug | bcr-abl, ckit | 2001             |
| Gefitinib    | Iressa     | small molecular drug | EGFR          | 2009*            |
| Erlotinib    | Tarceva    | small molecular drug | EGFR          | 2004             |
| Cetuximab    | Erbix      | 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   | Afinib     | Small molecule drug  | mTOR          | 2007             |
| Pazopanib    |            | Small molecule drug  | VEGFR, PDGFR  | 2007             |

\* EMA approval

#### 4.3.5 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 [65]. We now know that tumours will not grow beyond 1-2 mm[35] 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[34]. 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 [66].

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 [67-69].

Progress in understanding the molecular basis of renal cell carcinoma, especially related to genetics and angiogenesis, has been achieved mainly through of the study of von

Hippel-Lindau disease. A great variety of active agents have been developed and tested in metastatic renal cell carcinoma (mRCC) patients. New specific molecular therapies in metastatic disease are presently being introduced in clinical practice. Sunitinib and bevacizumab increase the progression-free survival when compared to cytokines. Sorafenib is another multi kinase inhibitor that increases progression-free and overall survival after cytokines as a second line treatment. Other agents targeting the mTOR pathway, everolimus and temsirolimus, have also been approved in renal cancer [70, 71]. 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 [72]. Hepatocellular cancer (HCC) is another malignancy with new treatment options. HCC is the fifth most common malignancy worldwide and third leading cause of cancer death [73]. Sorafenib is the first systemic treatment with proven efficacy approved for the treatment of advanced and metastatic HCC [74, 75]. Sorafenib has extended treatment options for patients with HCC, and is now established as the standard of care for Child-Pugh A-patients with HCC not amenable to surgery or loco-regional treatment.

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.

#### 4.3.6 Biotherapy

In the 1970s, the hybridoma technique [76] 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 4-2) 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.

***Table 4-2 Monoclonal antibodies approved for use in oncology***

| Generic name/Trade name        | 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/Erbix                | Colorectal cancer             | 2004                   |
| Panitumumab/Vectibix           | Colorectal cancer             | 2007                   |

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 [53-55].

One of the challenges in developing effective antibody therapies is finding parts factors in/on the tumour cell that can be targeted and that differ 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)[67-69, 77].

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.

#### 4.3.7 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, rythropoietin) 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.

#### 4.3.8 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 [78]. 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, and adjuvant use of an aromatase inhibitor has shown additional reductions [79]. 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 [54, 55]. Considerable progress has also been made in other major tumours. In colon cancer adjuvant chemotherapy have reduced mortality with 20-30 percent [80-82] and chemotherapy in the metastatic setting has four fold increased average survival, from 5 to 20 months in 15 years [67]. 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 [83] and a 2-year overall survival of 95 percent in patients below 61 years [84]. 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 [85-87].

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 [88]. 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 [89]. 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 [90]. 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 [91]. 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.

The survival benefit of improvements in treatment has also been studied in a number of cancer sites in 1988-2000 in the US by Sun et al. They found that treatment advances could explain 83 percent of the survival improvements in breast cancer, 85 percent in lung cancer, 76 percent in colorectal cancer, 100 percent in pancreatic cancer and 96 percent in non-Hodgkin's lymphoma. The survival benefits came in a time when several new treatments were introduced while improvements in screening and early detection of these cancers were small [92].

#### 4.3.9 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) [93]. 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 [94]. 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 [95], finasteride in prostate cancer [96] and recently statins in breast cancer [97]. 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 [98] – the cause of the vast majority of cervical cancers- was introduced in 2005. The introduction of vaccination requires political decision, as it is important to include all factors for the full value of preventive measures. The vaccination has also been introduced on a broad scale in many European countries.

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.

#### **4.4 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.



## **5 Market Access for Cancer Drugs and the Role of Health Economics**

### **5.1 Summary**

- Pharmacoeconomic evaluations have recently become a mandatory part of the reimbursement application for new drugs in Turkey.
- Health technology assessment are planned to play an important role in the priority setting within the health care system in coming years. The lack of necessary data puts limitations to such analyses.
- The introduction and use of new innovative drugs will require better evidence on cost effectiveness
- The introduction of new drugs would benefit from new ways of funding, in order to assess the clinical and economic effects in practice.

### **5.2 Introduction**

The development of new health technologies leads to greater opportunities for more efficient delivery of health services and improvements in treatment outcomes. Studies have shown a relationship between early access of new cancer drugs and survival, both in general and for specific cancers [88, 99].

As new technologies often come at a higher price, it is important to assess whether the higher costs are motivated by improvements in outcomes. As health care budgets become increasingly stretched, a greater emphasis is placed 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, including the cost-effectiveness analysis, is often termed “the fourth hurdle” to market access for new drugs, after safety, efficacy and quality. The regulatory approval process and the reimbursement approval system in Turkey was described earlier in section 3.1.

In the formal approval and reimbursement processes there are several factors that could hinder or limit market entry. First, and most obvious, a new drug might not be approved or reimbursed at all. The processes could also be time consuming and delay market

entry. Market access for new drugs may also be restricted by limitations in the approved indication or by restrictions in reimbursement. As will be discussed in chapter 6, new drugs are facing longer processes for approval and reimbursement in Turkey than in other countries. A new drug may not be available until several years later in Turkey due to so called launch lags. This is also confirmed in other studies [25].

Many drugs are also not reimbursed for their full indication in the market approval file.

### ***5.3 Health technology assessments***

In order to accommodate new technologies and to evaluate the clinical and economic value, Health Technology Assessments (HTA) has become an increasingly used tool in many countries. HTA is a multidisciplinary approach to policy analysis, studying the medical, social, ethical, and economic implications of development, diffusion, and use of health technology. The extent of the use of HTAs to evaluate new technologies varies between countries, and also what strategies are focused on [100]. In Europe, the UK, Germany and France are considered leading the development and application of HTAs. In most countries in Central and Eastern Europe the experience and application of HTAs is limited. This is also the case in Turkey. In order to make use of HTAs, knowledge and competence in both undertaking and evaluate HTAs in public authorities, providers and payers of health care systems and in the industry are required. This competence in the field of HTAs is scarce in Turkey [100] as it also is in many European countries [15].

Published reports on HTA are often used as a point of reference in countries other than the one for which they were developed. This may provide support for decision makers, but it is also important to make the analysis for the specific conditions in each country. What is considered cost effective in one country may not be the best option in other countries having other resources available and a different burden of disease.

Health economics and pharmacoeconomics have recently been introduced in the Turkish reimbursement system. Cost minimisation and budget impact is still emphasized in the new reimbursement decisions. There is still a lack of experience and knowledge both among companies and authorities within these fields. Cost effectiveness criteria are not used in a systematic and consistent way in the reimbursement process. Pharmacoeconomic assessments are strictly required but not always considered to be adequate for the pricing and reimbursement decisions. There is also a severe problem of

availability of data to use in economic evaluations. Even if such information would be available, authorities still lack the capacity to assess the results, which limits the use of health economic evidence [25].

#### **5.4 How can new drug therapies be funded?**

The limited budget available for health care is the main obstacle for market access of new drugs. It is important to have a long term perspective on cost effectiveness.

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 in the budgets for medicines in hospitals and ambulatory care settings. 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?

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 [102].

Another option being explored, and applied in several European countries, with regards to uptake of new drugs, has been the concept of 'risk sharing' between the

pharmaceutical company and the payer[103]. 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 proven to be as efficient as expected, the price of the drug may be reduced, or the manufacturer may pay back part of the cost of the drug. If there are possibilities to make post market follow up of a drug, the value of the use of can be proved [104]. This facilitates a price setting that is based on the therapeutic benefit of the drug.

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 market authorization, it should not be necessary to undertake another safety and efficacy appraisal of the new drug in order to make reimbursement decisions. The reimbursement decision is thus related to whether the drug should be reimbursed or not and hence available through the national healthcare system or other payers. In Turkey the pharmacoeconomic requirements are somewhat diffuse. One of the reasons is that this has not been required until recently, and thus a lack of tradition in making these assessments.

## **5.5 Conclusions**

Increasingly stretched healthcare budgets are faced with growing needs and demands of the population for modern cancer treatment. New drug treatments 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 in importance for decisions making in market access and reimbursement. This raises the question of 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, although there are indications that this will change.

Equally important will be the question on whether health care systems will be able provide budgetary space for new innovative technologies, if they are assessed to provide benefits to patients and society outweighing the costs. It is important to have a societal perspective on the costs and economic benefits taking not only the direct medical costs into account, but also indirect cost savings due to inabilities to work and the value of patient well-being.

## **6 Uptake of new oncology drugs in Turkey**

### **6.1 Summary**

- The sales of oncology drugs in Turkey is significantly lower than in most other of our comparative countries
- The drugs covered in this study are reaching the market later in Turkey than in other countries.
- Many drugs have restricted reimbursement conditions in Turkey.
- The late introduction and low use of new oncology drugs, means that the access to treatment for cancer patients is limited.

### **6.2 Oncology drugs**

This chapter describes the market introduction and total sales of selected oncology drugs (ATC code L1, L2A and L2B) in Turkey and in comparison with a number of countries in Europe. The drugs analysed in this report is listed in (Table 6-1).

In (Table 6-1) we also see the date of first launch worldwide, and when it was first sold in Turkey. First 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. The sales start in Turkey is in most instances delayed several years, especially the older drugs. There are also a number of drugs that are approved by EMA, reimbursed and used in many EU countries, but not approved and used in Turkey. This is the case of for example cetuximab clofarabine, etoposide phosphate, gefitinib, nilotinib, panitumumab and tasonermin. A number of drugs has been approved but is not yet granted reimbursement in Turkey; sorafenib, erlotinib and ibritumumab.

One reason of the delay of the sales start in Turkey is the long processes of approval and reimbursement. In the case of many of the drugs included in this study, the registration process from submission of application to approval, has often taken less than six months in the US and in the EU. In Turkey the process for the same drugs are often 18-24 months. The reimbursement process for these drugs in Turkey has often taken up to twelve months or more from submission of application to reimbursement

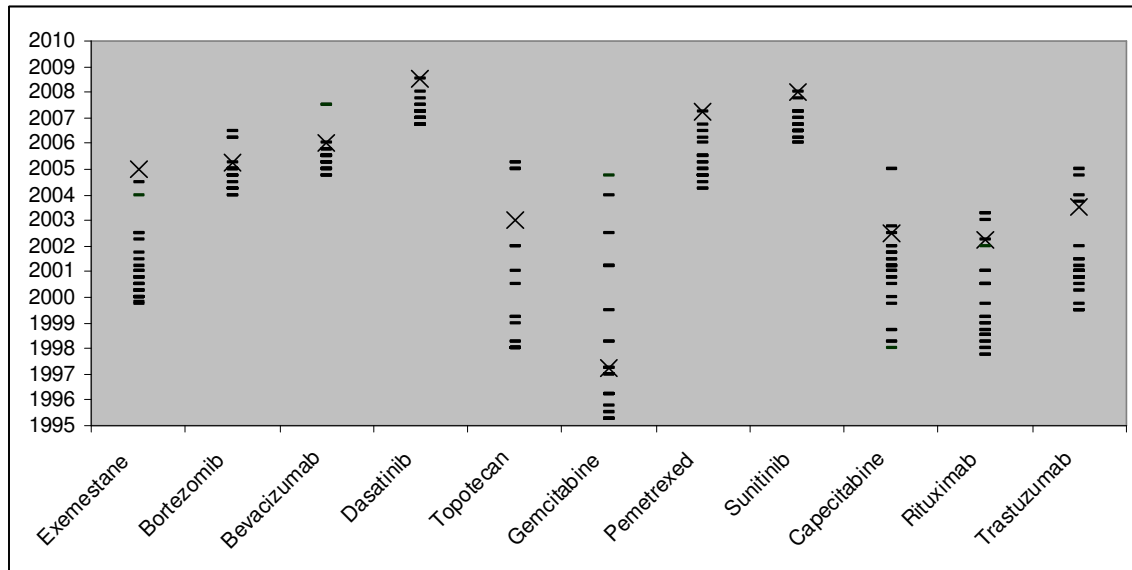
approval. This means that many new medicines are delayed by up to 3-4 years after approval in Europe or in the US.

***Table 6-1 List of drugs included in study, data of launch and first sales in Turkey***

| <b>Generic name</b> | <b>Brand name</b> | <b>Date of first launch</b> | <b>Date of first sale in Turkey</b> |
|---------------------|-------------------|-----------------------------|-------------------------------------|
| Anastrozole         | Arimidex          | September 1995              | October 1998                        |
| Docetaxel           | Taxotere          | April 1995                  | 1998                                |
| Capecitabine        | Xeloda            | May 1998                    | 2002                                |
| Exemestane          | Aromasin          | November 1999               | February 2005                       |
| Fulvestrant         | Faslodex          | May 2002                    | December 2006                       |
| Letrozole           | Femara            | July 1997                   | March 1999                          |
| Trastuzumab         | Herceptin         | October 1998                | August 2003                         |
| Oxaliplatin         | Eloxatin          | July 1996                   | 2004                                |
| Bevacizumab         | Avastin           | February 2004               | February 2006                       |
| Bicalutamide        | Casodex           | May 1995 (50mg)             | January 1997 (50mg)                 |
|                     |                   | June 1999 (150mg)           | October 2004 (150mg)                |
| Gemcitabine         | Gemzar            | June 1995                   | August 1997                         |
| Pemetrexed          | Alimta            | February 2004               | May 2007                            |
| Topotecan           | Hycamtin          | July 1996                   | 2003                                |
| Sunitinib           | Sutent            | July 2006                   | January 2008                        |
| Temsirolimus        | Torisel           | May 2007                    | November 2007                       |
| Bortezomib          | Velcade           | May 2003                    | June 2005                           |
| Rituximab           | Mabthera          | November 1997               | May 2002                            |
| Imatinib            | Glivec            | May 2001                    | March 2002                          |
| Dasatinib           | Sprycel           | November 2006               | August 2008                         |

The delay of sales of a selection of drugs in Turkey compared to other European countries is also presented in Figure 6-1. The lines represent the first sales of countries in the EU, Norway and Switzerland and the crosses represent Turkey. We see in most cases that there is a long time from first sales in the early countries until the first sales in Turkey.

**Figure 6-1 Time of first sales of selected oncology drugs in Turkey and in Europe**



### **6.3 Sales of selected drugs in Turkey and selected European countries**

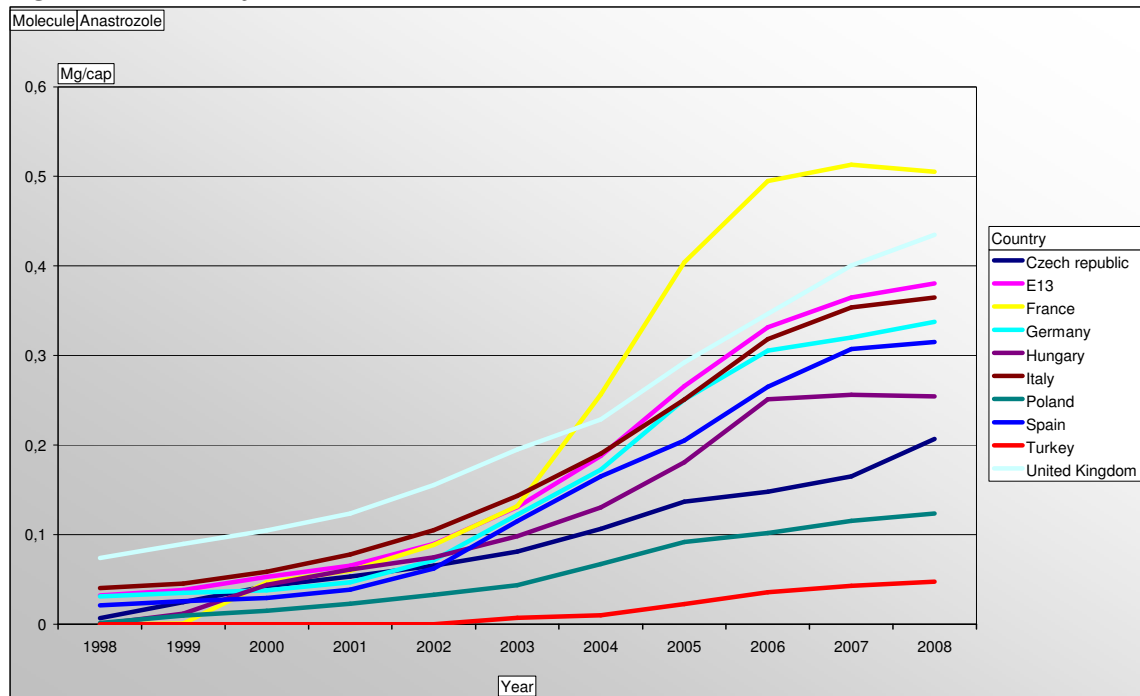
The Turkish sales of drugs analyzed in this report is compared to a number of European countries. The five largest EU countries, Germany, France, Spain, the UK and Italy as well as three countries in central and eastern Europe facing similar challenges in funding new drugs due to lower resources available in the health care system. In addition to these countries we also compare the Turkish sales with a basket of European countries, named E13, including the following countries, Austria, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the UK.

### 6.3.1 Drugs mainly used in breast cancer

#### Anastrozole

In Turkey, anastrozole (Arimidex®) is approved for treatment of advanced breast cancer in postmenopausal women, and for treatment of postmenopausal women with hormone receptor positive early breast cancer. In the EU anastrozole was first sold in 1995, and in the US it was approved in 1995 and first sales were registered in 1996. In Turkey it was granted market approval and reimbursement first in 1998. The sales per capita in Turkey are much lower than in our comparative European countries (Figure 6-2),

**Figure 6-2 Sales of anastrozole**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

#### Docetaxel

In Turkey, Docetaxel (Taxotere®) is indicated for locally advanced squamous cell carcinoma of head and neck, advanced gastric adenocarcinoma, breast cancer, Non Small Cell Lung Cancer (NSCLC), prostate cancer and ovarian cancer. For advanced gastric adenocarcinoma it is approved for patients who have not received prior

chemotherapy. In breast cancer, it is approved in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer;

As monotherapy, docetaxel is approved for locally advanced or metastatic breast cancer after failure of any prior chemotherapy cytotoxic therapy including an anthracycline or an alkylating agent.

In combination with Doxorubicin, docetaxel is approved for treatment of patients with locally advanced or metastatic Breast Cancer who have not previously received cytotoxic therapy for this condition. In combination with trastuzumab for treatment of patients with metastatic Breast Cancer whose tumors over express HER2 and who previously have not received chemotherapy for metastatic disease.

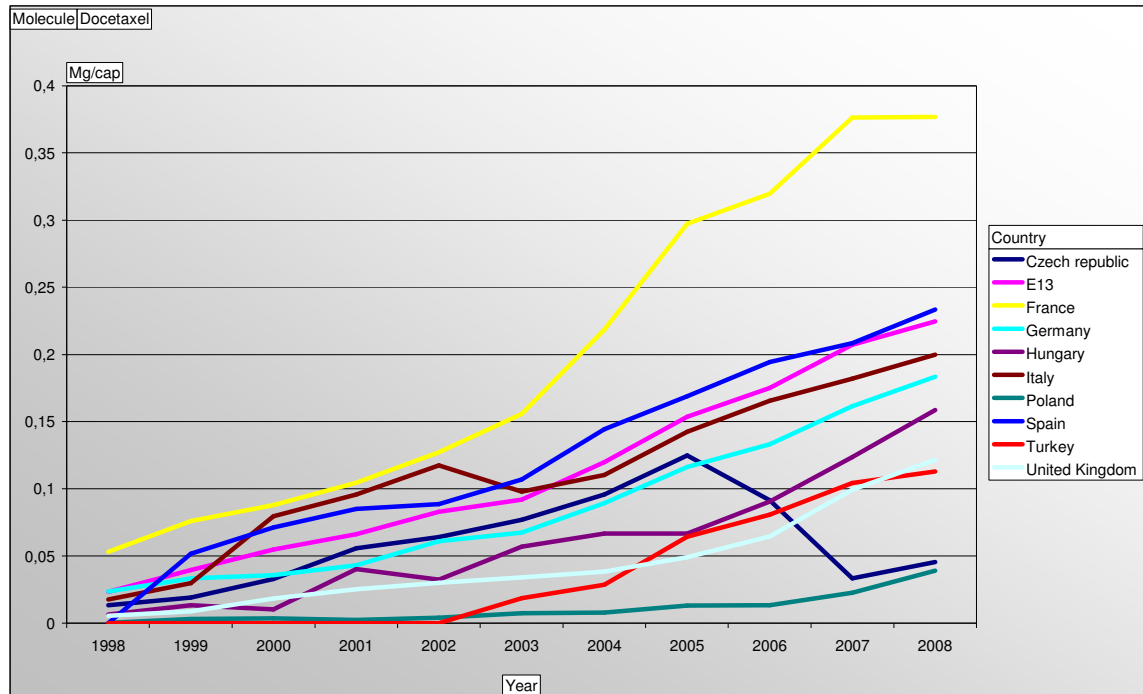
In combination with capecitabine, docetaxel is indicated for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

In NSCLC, docetaxel is approved as single agent for patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy as well as in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition. In prostate cancer, docetaxel is indicated in combination with prednisone for patients with androgen independent (hormone refractory) metastatic prostate cancer.

The indications of docetaxel in Turkey correspond to the indication in the EU and in the US. Docetaxel is reimbursed according to the approved indications, but a health commission report is required. In addition docetaxel may also be used in off label setting for third-line chemotherapy in combination with gemcitabine for soft tissue sarcomas.

Docetaxel was approved in Turkey in 1998, two years later than in the US and three years later than in the EU. The sales of docetaxel were in 2008 higher than many countries in the EU, e.g. United Kingdom, Poland, Hungary and the Czech Republic. It was, however, lower than in for example Germany, France and in the E13 (Figure 6-3).

**Figure 6-3 Sales of docetaxel**



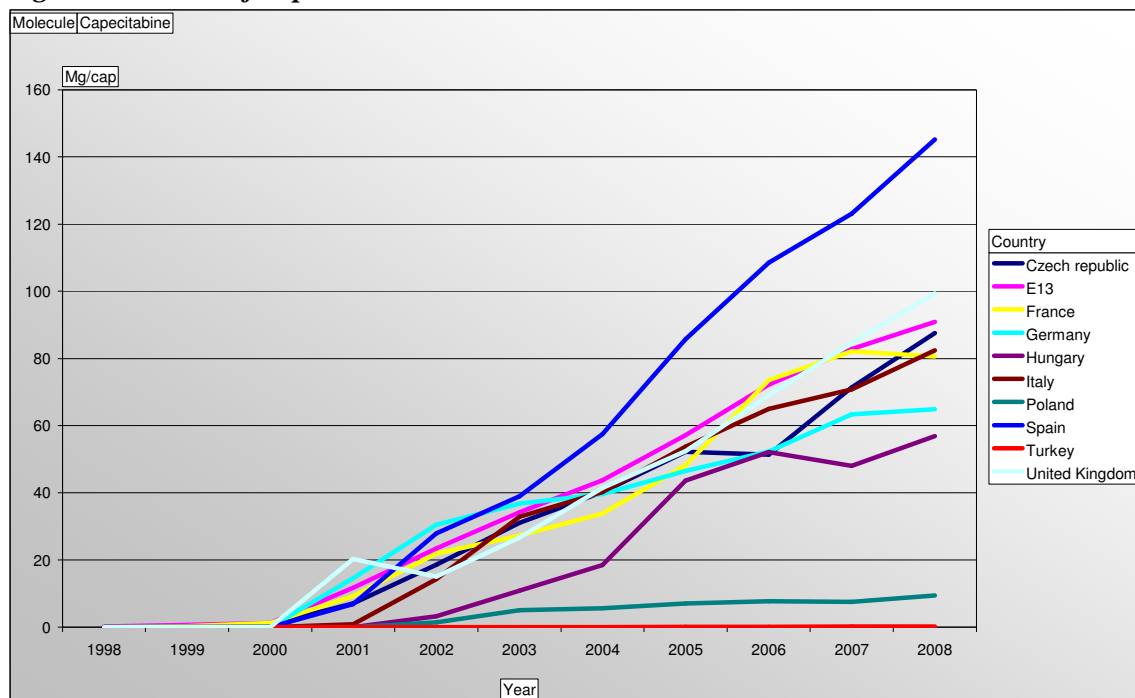
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Capecitabine

Capecitabine (Xeloda®) has been on the global market since 1998. In Turkey, it is indicated for first-line treatment of patients with metastatic colorectal carcinoma. Capecitabine is indicated for locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy in combination with taxanes or as monotherapy after failure of a taxane and an anthracycline-containing chemotherapy regimen. In the EU it is also indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

It was first approved in the US for metastatic breast cancer in April 1998. In the US and in the EU it was first sold in June 1998, while it was not used in Turkey until 2002 when it was also first approved for registration and reimbursement. Capecitabine is reimbursed as per approved indication. In Figure 6-4 the sales in Turkey are very low in relation to the other comparator countries.

**Figure 6-4 Sales of capecitabine**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Exemestane

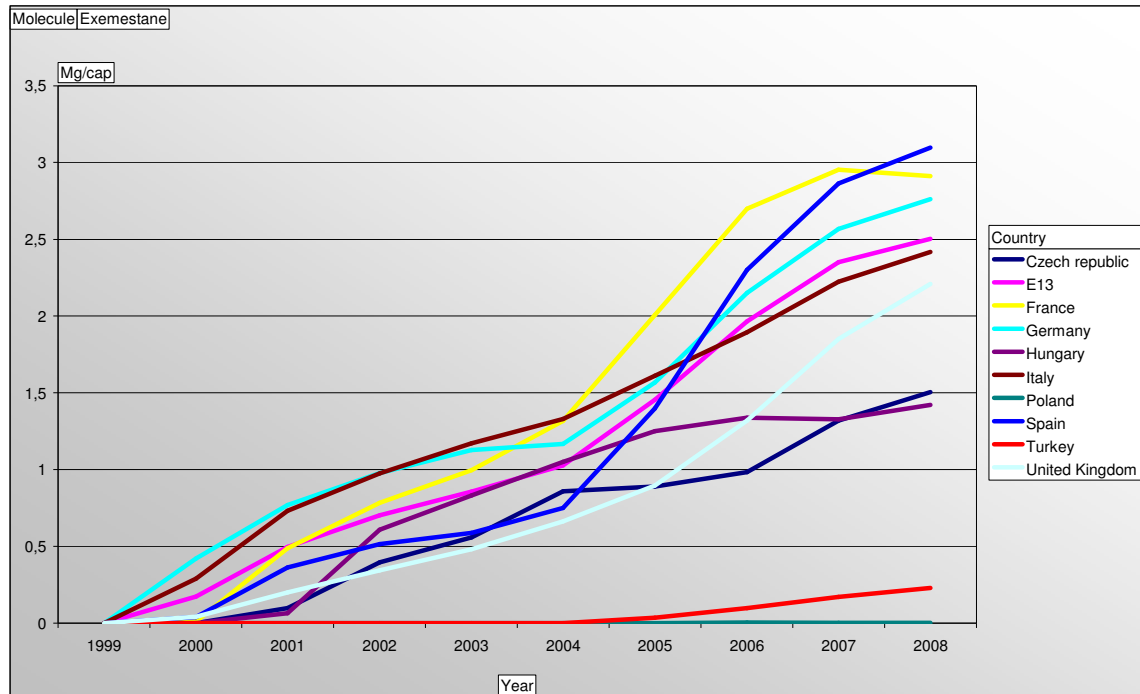
Exemestane (Aromasin®) is indicated for the patients with postmenopausal (estrogen and/or progesterone receptor) hormone receptor positive early breast cancer, following 2 – 3 years of tamoxifen therapy to complete a total of 5 years of hormonal therapy.

It is also indicated for the treatment of patients with postmenopausal (estrogen and/or progesterone receptor) hormone receptor positive advanced breast cancer and in patients whose disease has progressed following endocrine therapy. This corresponds to the indications in the EU and in the US. It was approved for registration in December 2004 and for reimbursement in February 2006. In the EU it was first approved in 1998 and in the US in 1999. Exemestane is reimbursed according to the approval indication.

The sales of exemestane are very low in Turkey compared to most of the comparator countries. It is hardly visible in the charts next to the larger European countries. Only Poland had lower sales in the past four years (Figure 6-5).



**Figure 6-5 Sales of exemestane**

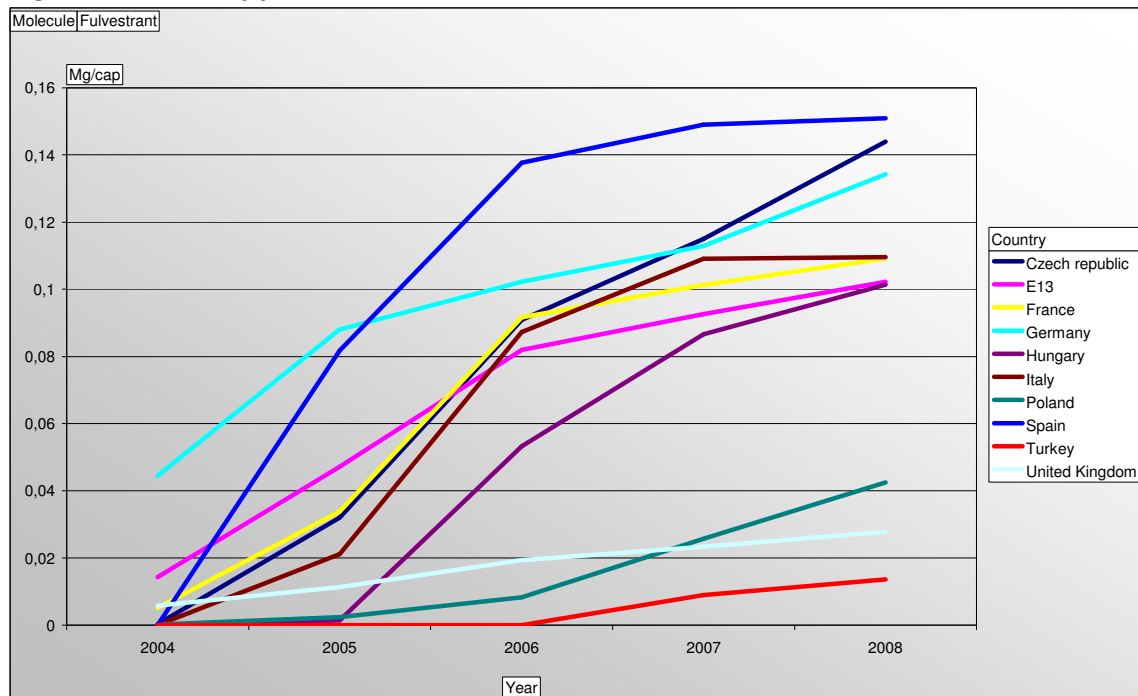


\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Fulvestrant

Fulvestrant (Faslodex®) is in Turkey indicated for the treatment of locally advanced or metastatic breast cancer in women with natural or induced postmenopausal status whose disease has progressed following endocrine therapy. This is similar to the indication in the US and in the EU. In the US it was first approved in 2002 whereas it was approved in the EU in 2004. In Turkey it was not approved until 2005 and reimbursed in December 2006. The Turkish reimbursement is restricted to patients already treated with tamoxifen and then AIs (anastrozole, exemestane, letrozole). The sales in Turkey started later than in the other comparator countries and the sales volume is also lower (Figure 6-6).

**Figure 6-6 Sales of fulvestrant**



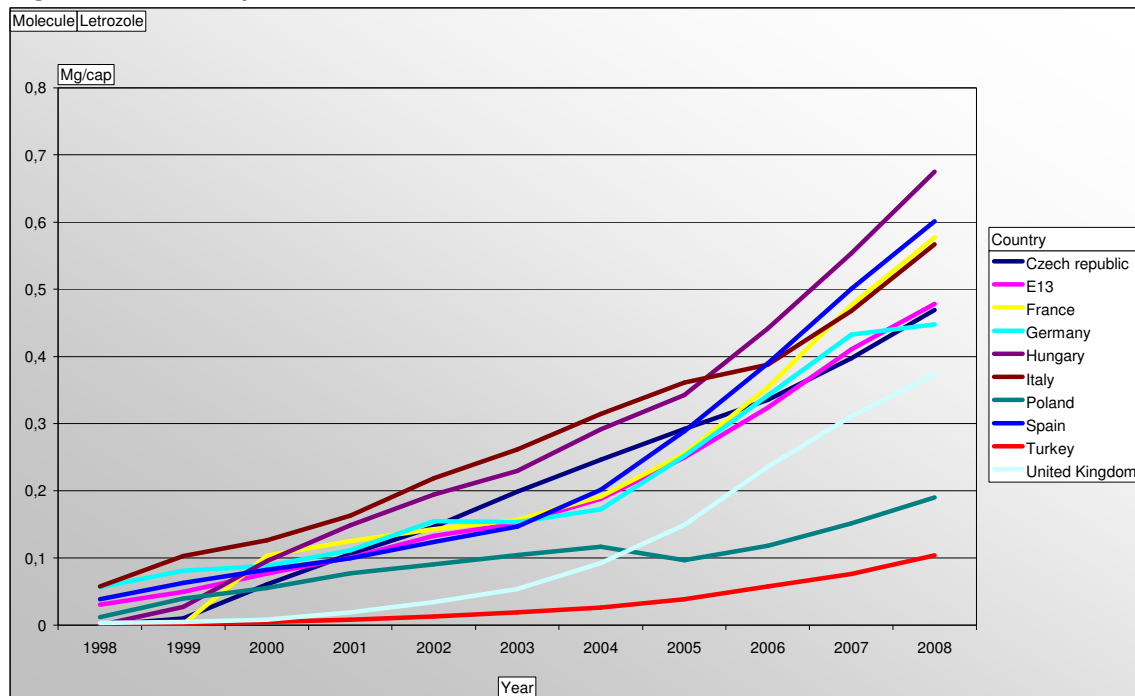
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Letrozole

The Turkish indication for letrozole (Femara®) follows that of FDA and EMA; Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer, extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy, first-line treatment in postmenopausal women with hormone-dependent advanced breast cancer, treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens, and pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery. There are no reimbursement restrictions applied to letrozole in Turkey. Letrozole was approved in both the US and in several European countries in 1997. This was before the EU-wide EMA approval. In Turkey, letrozole was

approved for use in 1999. The per capita sales of letrozole are the lowest in the countries we compare with in this study (Figure 6-7).

**Figure 6-7 Sales of letrozole**



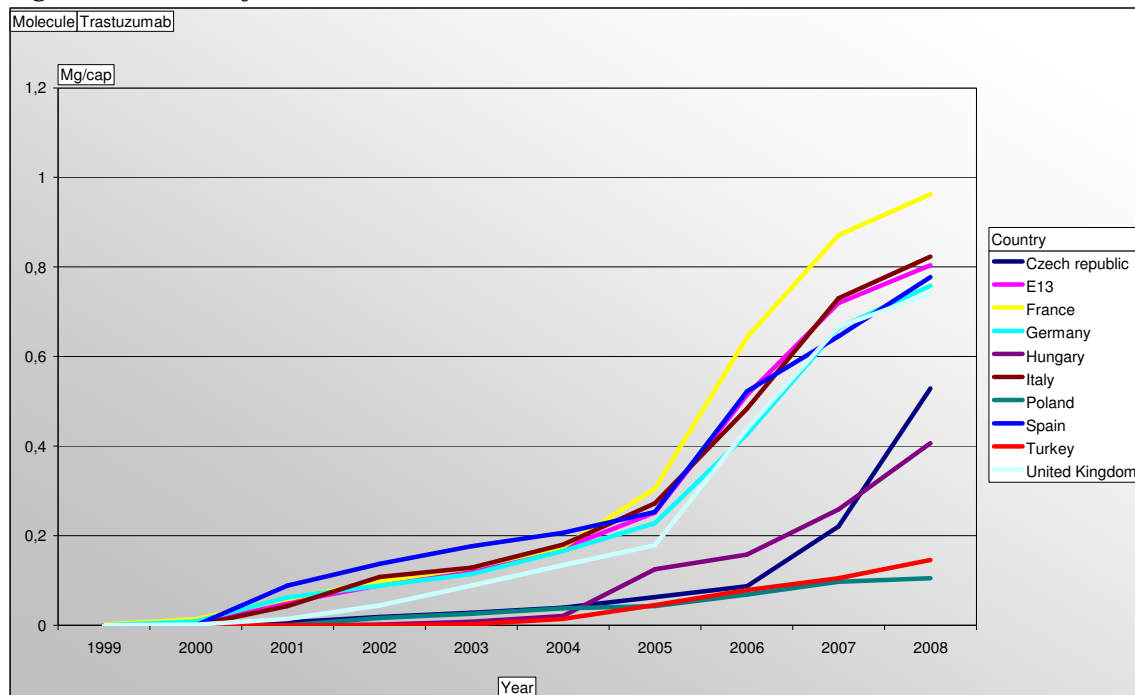
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Trastuzumab

Trastuzumab (Herceptin®) is indicated for the treatment of patients with metastatic breast cancer who have tumors that over express HER2 (determined by immunohistochemistry 3+ or FISH+), either as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease or in combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. In the EU it is also indicated for treatment in combination with an aromatase inhibitor for postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab. Since December 2009, trastuzumab is also approved by EMA for HER2-positive metastatic gastric cancer.

Trastuzumab was first approved in the US in 1998, followed by the EU in year 2000 and Turkey in 2003. Trastuzumab is reimbursed as per product label in Turkey. The sales per capita of trastuzumab are higher in Turkey than in Poland, but lower than in the other countries included in this comparison (Figure 6-8).

**Figure 6-8 Sales of trastuzumab**



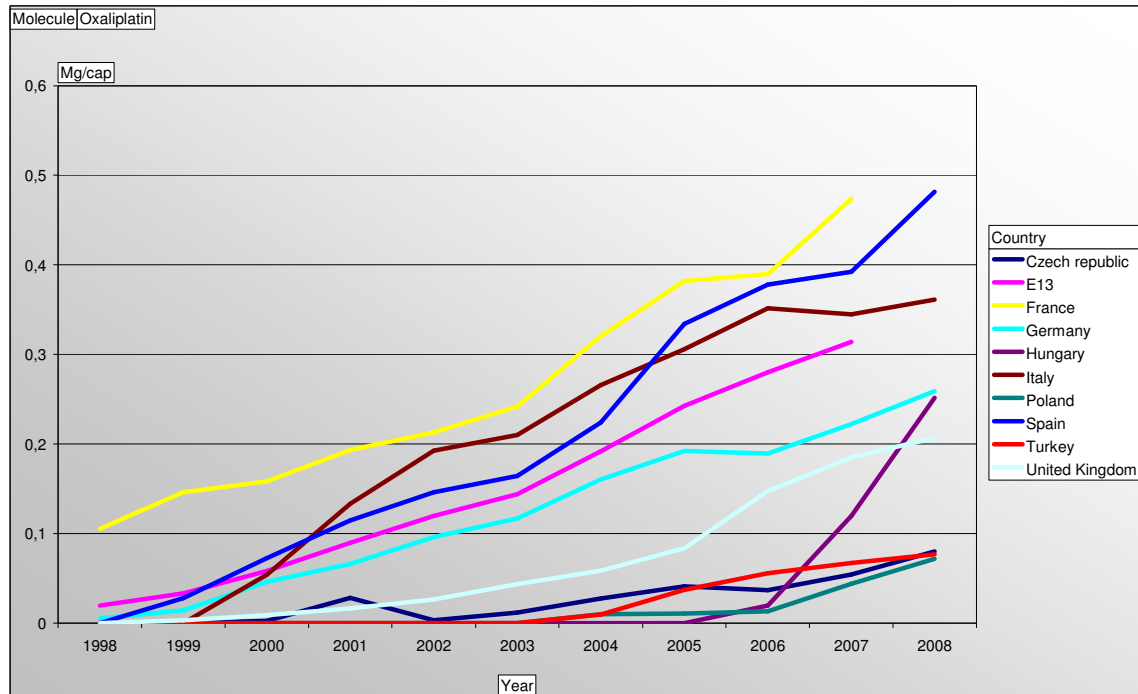
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### 6.3.1 Drugs mainly used in colorectal cancer

#### Oxaliplatin

Oxaliplatin (Eloxatin®) has the same indication in Turkey as in the EU and in the US; Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor, treatment of metastatic colorectal cancer in combination with 5 fluorouracil (5 FU) and folinic acid (FA). It was first approved for registration in the EU in 1996 and in Turkey 2001. Oxaliplatin is reimbursed according to the approved indications. The sales of oxaliplatin are in Turkey at the same level as in Poland and the Czech Republic and slightly lower than in the UK, but significantly lower than the remaining comparator countries (Figure 6-9).

**Figure 6-9 Sales of oxaliplatin**



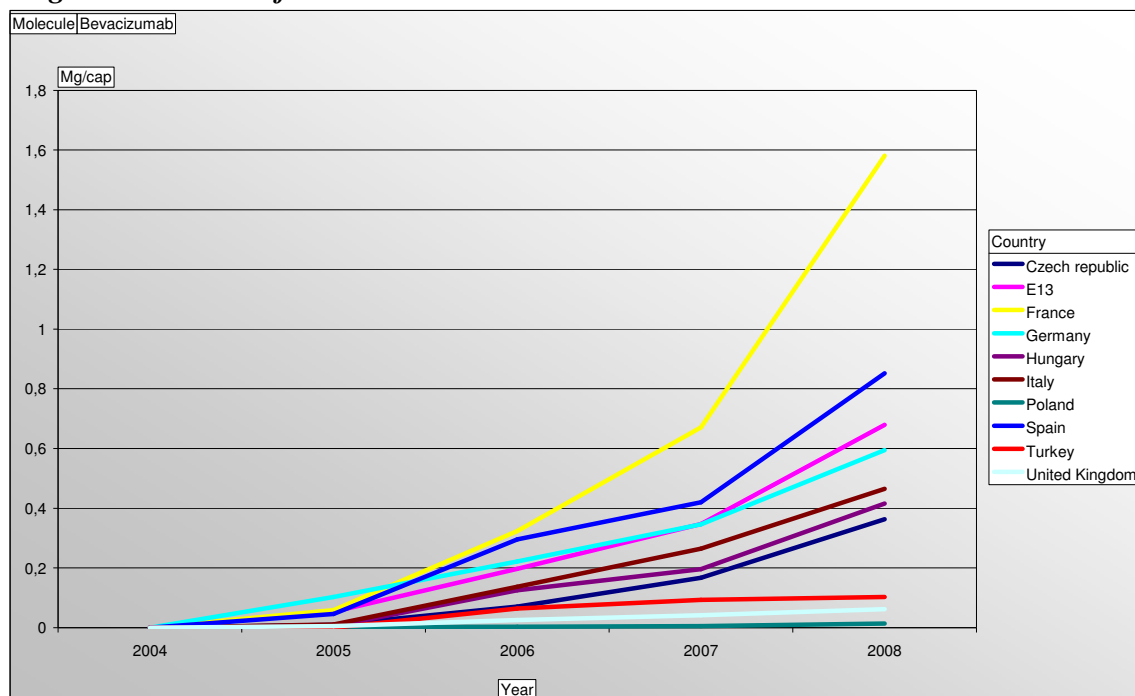
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## Bevacizumab

Bevacizumab (Avastin®) is indicated in Turkey for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with 5-fluorouracil/folinic acid or 5-fluorouracil/folinic acid/irinotecan. It is also indicated for second-line or third-line treatment in the same combinations if not previously used. In the EU and in the US bevacizumab is in addition to colorectal cancer also indicated for first-line treatment of patients with metastatic breast cancer in combination with paclitaxel; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology, in addition to platinum based chemotherapy and for metastatic/advanced renal cell cancer in combination with interferon alfa-2a. Bevacizumab was first approved in Turkey in December 2005 and approved for reimbursement in March 2006. In the EU it was approved in January 2005 and in the US in February 2005. First sales in Turkey were seen in February 2006, while it was first sold in the US in March 2004 and in the EU January 2005. Bevacizumab is reimbursed according to the approved indication in Turkey.

Measured in terms of mg per capita the sales in Turkey are lower than in most other countries, excluding the UK and Poland. In the E13 the uptake is more than four times higher per capita (Figure 6-10).

**Figure 6-10 Sales of bevacizumab**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

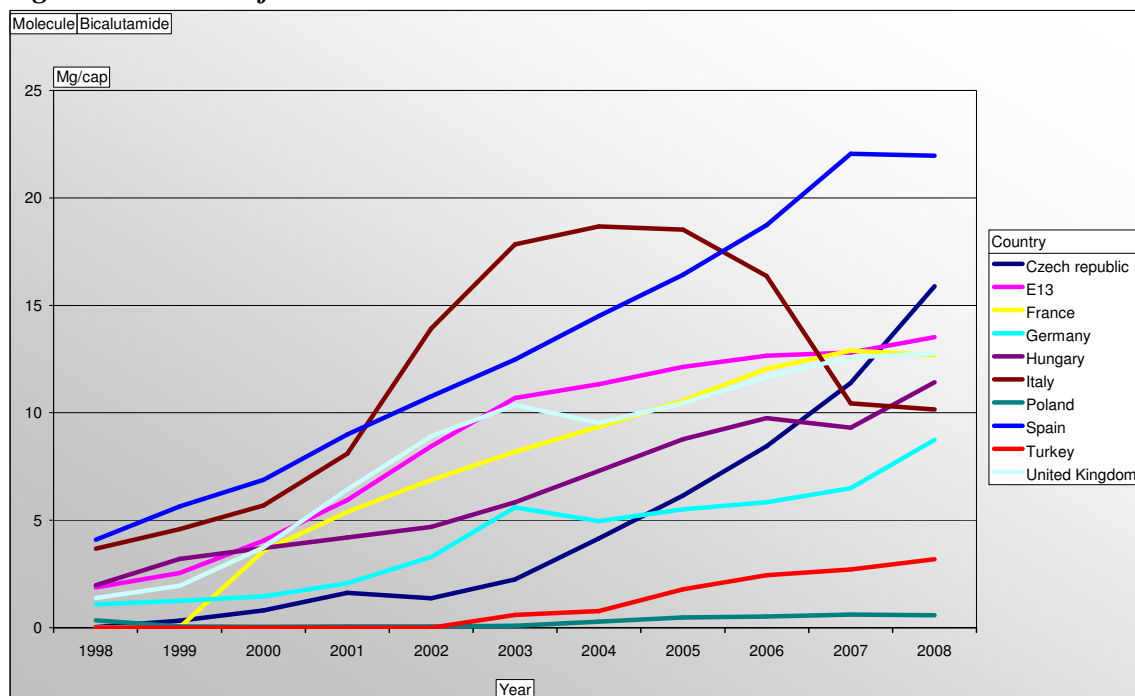
### 6.3.2 Drugs mainly used in prostate cancer

#### Bicalutamide

Bicalutamide (Casodex®) 150 mg is indicated for early hormonal treatment as either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer. It is also approved for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable. Bicalutamide 50 mg is indicated for the treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration. 50 mg was first approved in Turkey in 1996, the year after it was first approved in the US. Bicalutamide 150 mg was first sold in Turkey in 2004, but Bicalutamide 50 mg was first sold in 1997.

The per capita sales of bicalutamide in Turkey is lower than in all other comparator countries, except Poland (Figure 6-11). It should be noted that the patent for bicalutamide expired in Europe in 2008.

**Figure 6-11 Sales of bicalutamide**



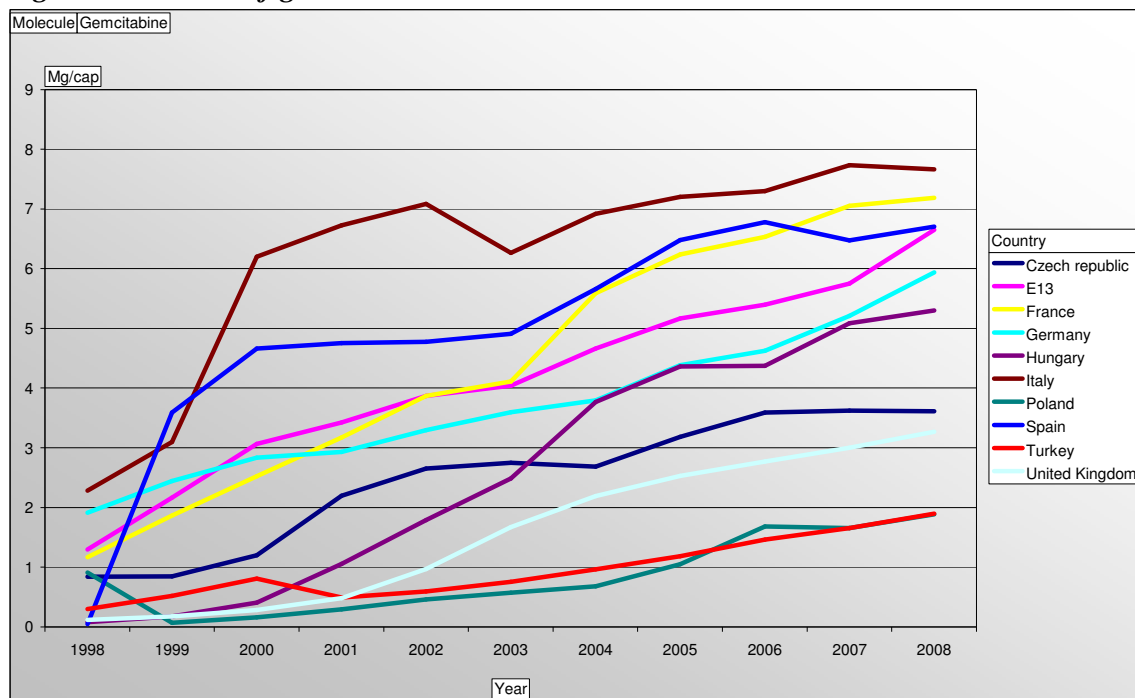
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### 6.3.3 Drugs mainly used in lung cancer

#### Gemcitabine

Gemcitabine (Gemzar®) was first approved in 1997 for NSCLC. In addition to NSCLC, it is in Turkey also indicated for bladder cancer, ovarian cancer, pancreatic cancer and breast cancer. These indications follow the indications in the EU and in the US. It was first launched in Europe in 1995 and in the US in 1996. In Turkey Gemcitabine is approved as per indication. In Turkey, the sales in mg per capita is at the level of the sales in Poland, but significantly lower than in the remaining European comparator countries (Figure 6-12). The patent on gemcitabine expired in 2009.

**Figure 6-12 Sales of gemcitabine**



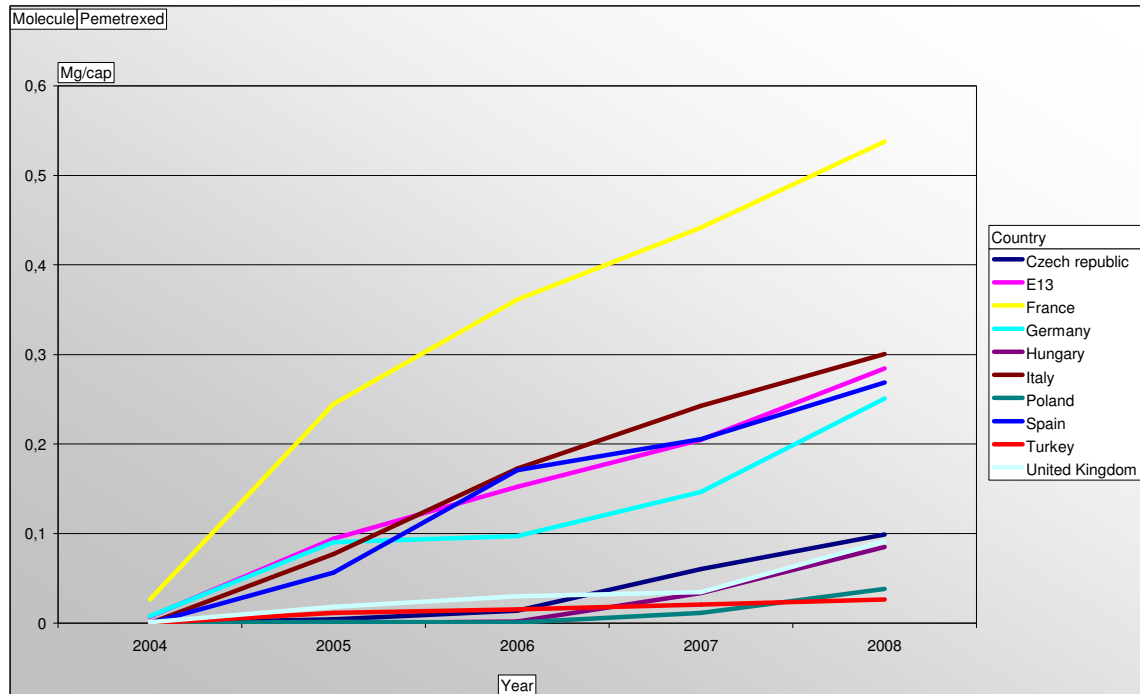
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### Pemetrexed

Pemetrexed is indicated only for mesothelioma and 2<sup>nd</sup> line treatment of non-squamous NSCLC in Turkey. In the US and in the EU it is also licensed for first- and second-line treatment of non small cell lung cancer (NSCLC) patients who are non-squamous histology. Recently pemetrexed has been approved by the EMA in May 2009 and FDA in July 2009 for the maintenance of NSCLC patients in non-squamous histology who had not progressed after first-line therapy. In most countries in the EU, Pemetrexed is also reimbursed for use in mesothelioma and first- and second- line treatment of NSCLC, whereas it is reimbursed only for mesothelioma in Turkey. The sales of pemetrexed in Turkey is at the same level as in Poland, and slightly lower than in Hungary, the UK and in the Czech Republic (Figure 6-13).



**Figure 6-13 Sales of pemetrexed**

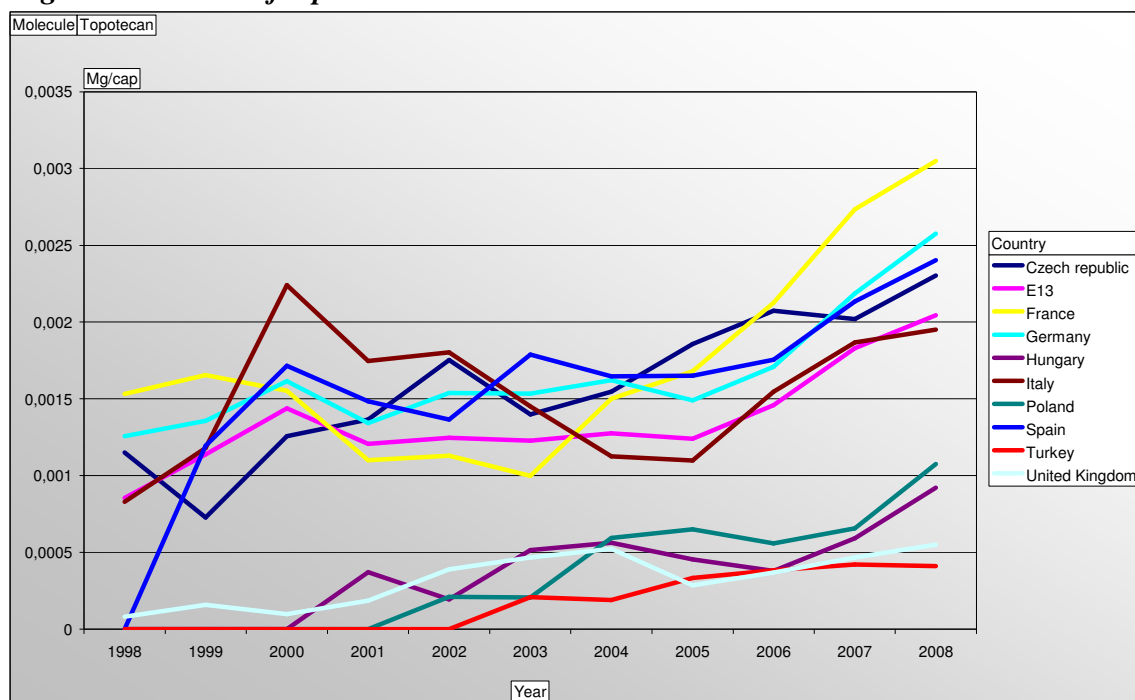


\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### Topotecan

Topotecan (Hycamtin®) is approved for treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy and for patients with small cell lung cancer after failure of first-line chemotherapy, in Turkey, the US and in the EU. In the EU and in the US it was approved in 1996, but in Turkey not until 2002. Topotecan is approved for reimbursement as per approved indication in Turkey but restricted to specialists. A health report is also required for prescription. The mg per capita sales in Turkey is at the same level as in the UK, and slightly lower than in Poland and Hungary (Figure 6-14).

**Figure 6-14 Sales of topotecan**

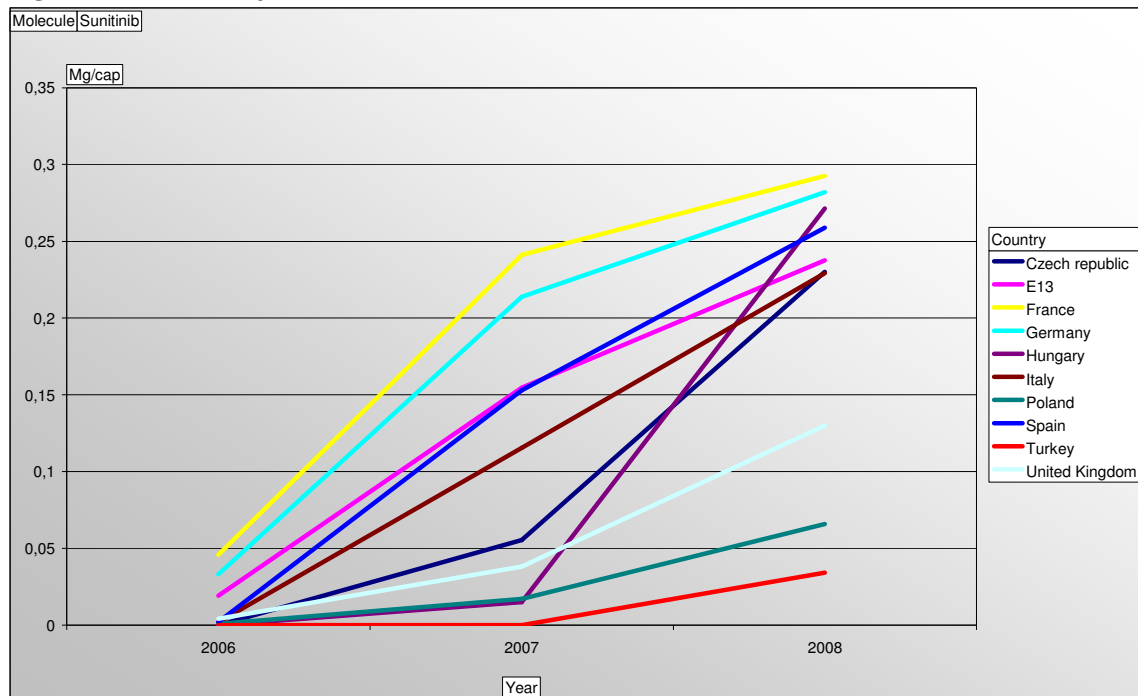


\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

#### 6.3.4 Drugs mainly used in renal cancer Sunitinib

Sunitinib (Sutent®) is a rather recent drug, approved in Turkey, the EU and the US for the treatment of advanced and/or metastatic renal cell carcinoma (mRCC). It is also indicated for treatment of unresectable metastatic gastrointestinal stromal tumour (GIST) resistant to imatinib mesylate treatment. In the US it was approved in 2006. In Turkey it was first registered for both indications in 2007, one year after EU. In the US, UK, France, Germany, Italy and Hungary, Sunitinib is reimbursed in first-line RCC treatment. The mRCC reimbursement in Turkey is restricted to second-line therapy after cytokines. In GIST, the reimbursement in Turkey is second-line treatment after imatinib failure as indicated. The per capita sales of sunitinib in Turkey are, as seen in Figure 6-15 lower than in the countries of comparison, but any long term trends can not yet be seen.

**Figure 6-15 Sales of sunitinib**

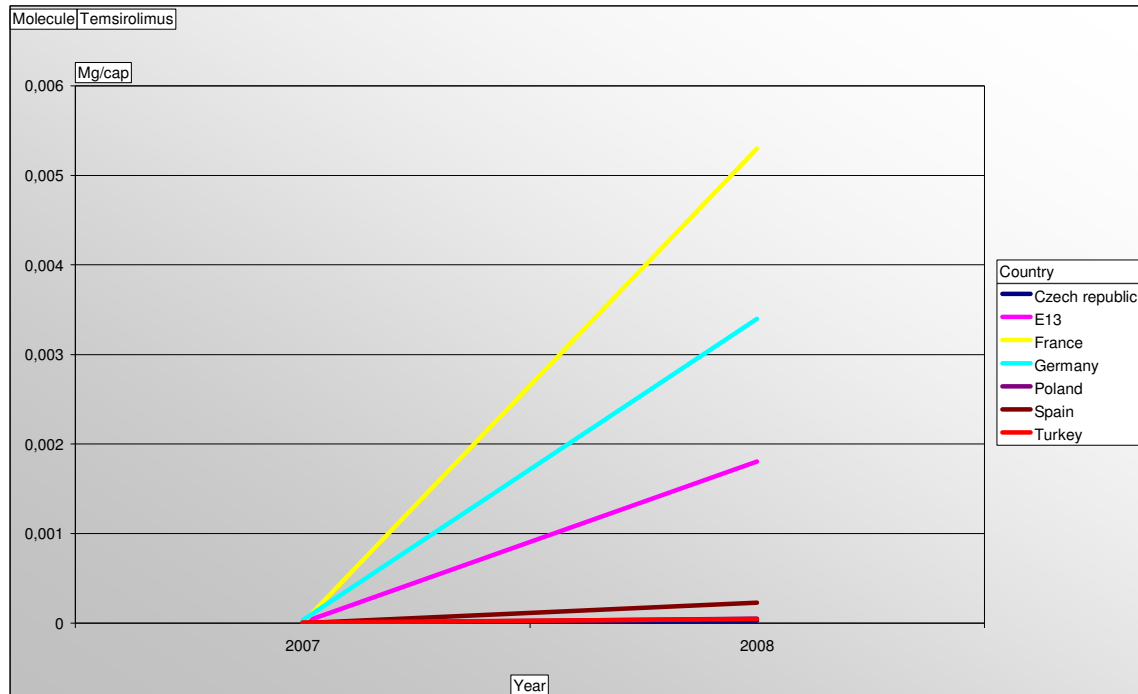


\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### Temsirolimus

Temsirolimus (Torisel®) is also a new drug, approved in Turkey in December 2008, and got inclusion into the positive list of reimbursement in November 2009. It was first approved in the US in May 2007 and in the EU in November the same year. US indication is advanced renal cell carcinoma and in EU Torisel is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors. The indication in Turkey is metastatic renal cell carcinoma, but reimbursement is restricted to poor prognostic patients and after cytokine treatment on contrary to its indication. The use is still low in Turkey as it is in the other countries of comparison (Figure 6-16).

**Figure 6-16 Sales of temsirolimus**



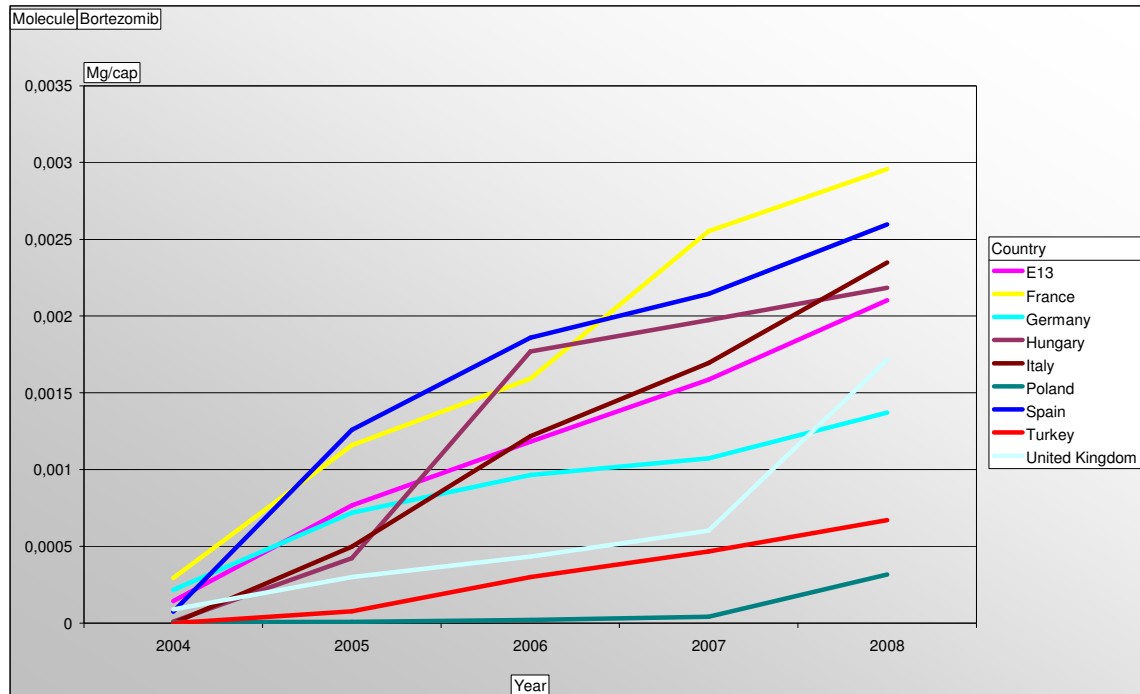
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### 6.3.5 Drugs mainly used in multiple myeloma

#### Bortezomib

Bortezomib (Velcade®) is in Turkey approved for first line treatment of multiple myeloma patients, who are older than 65 and do not have the chance for bone marrow transplantation and has deletion 13q as well as for treatment of mantle cell lymphoma who have received at least one prior therapy. In the EU and in the US, bortezomib is also indicated for frontline and relapse/refractory multiple myeloma. Bortezomib was launched in May 2003 (US), and first sold in Turkey in June 2005. The sales per capita are significantly lower than in most other comparator countries with the exception of Poland (Figure 6-17).

**Figure 6-17 Sales of bortezomib**



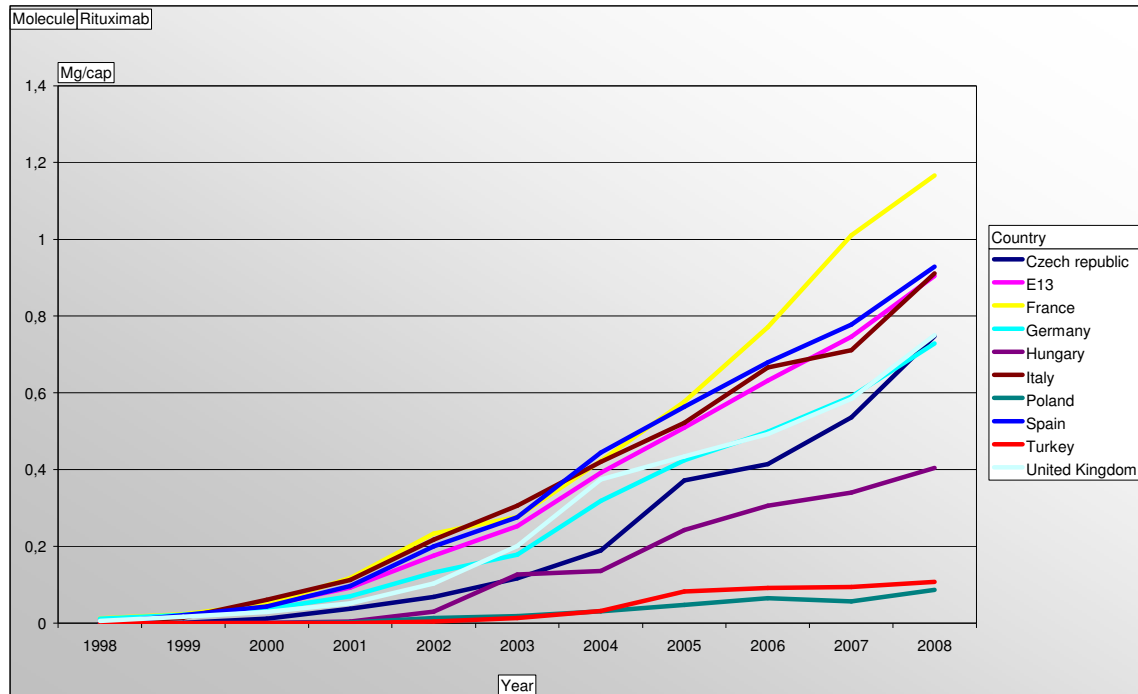
\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

### 6.3.6 Drugs mainly used in lymphoma

#### Rituximab

Rituximab (Mabthera®) is indicated for the treatment of stage III-IV Follicular Non-Hodgkin's Lymphoma, diffuse large B-cell Non-Hodgkin's Lymphoma like in the EU and in the US. Also, Rituximab (Mabthera®) is not approved in first-line and second-line treatment in chronic lymphocytic leukemia in Turkey whereas it has been approved by EU in February 2009 and in September 2009 respectively. Rituximab was first approved for treatment in 2002 in Turkey, four years later than in the EU, and five years later than by the FDA in the US. It is not reimbursed in maintenance treatment of Follicular Non-Hodgkin's Lymphoma in Turkey, unlike in the EU and in the US. Otherwise, rituximab is reimbursed according to the approved indication. The sales of rituximab in Turkey is higher than in Poland, but much lower than in the remaining countries we compare with here in terms of mg per capita (Figure 6-18).

**Figure 6-18 Sales of rituximab**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

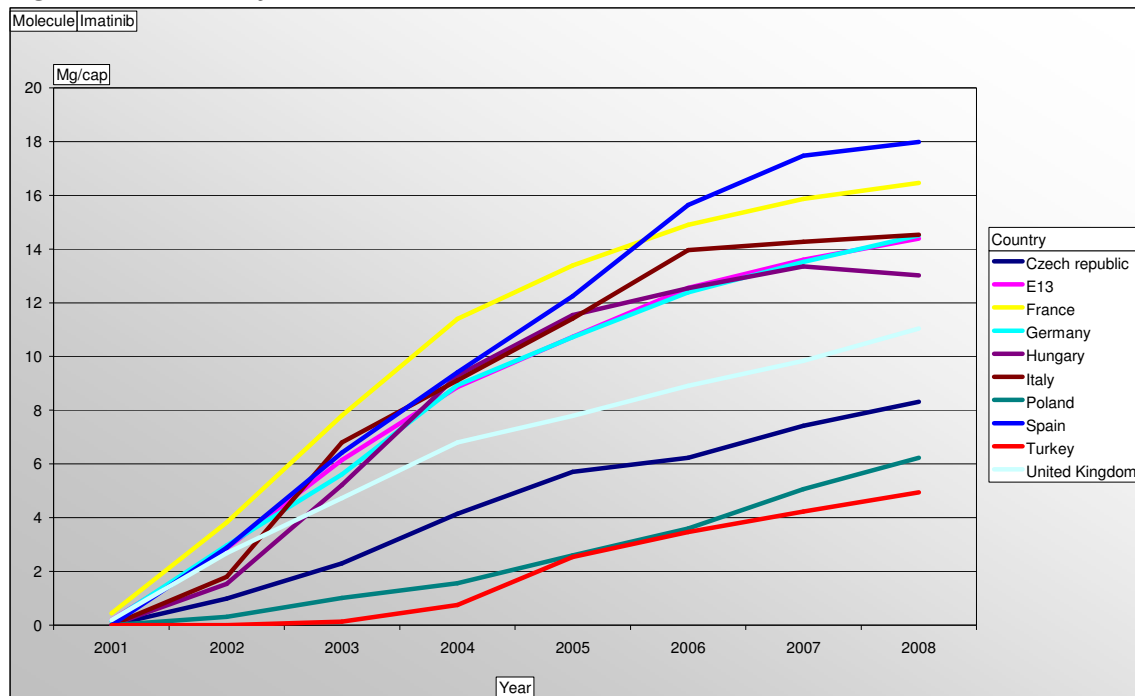
### 6.3.7 Drugs mainly used in chronic myeloid leukemia (CML)

#### Imatinib

Imatinib (Glivec®) is indicated for patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML), either newly diagnosed, in accelerated phase, or in blastic phase, or are refractory to or have become Philadelphia chromosome negative with other therapies. Therapy with imatinib is also approved in adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) with C-kit receptor. Adult patients with newly diagnosed or relapsed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in combination with multiple-agent chemotherapy regimens with proven benefit for induction of remission may also be treated with imatinib. Imatinib is also indicated for patients with hypereosinophilic syndrome and systemic mastocytosis demonstrated by FIP1L1-PDGFR $\alpha$  fusion gene laboratory investigations. In the EU and in the US imatinib is also approved for adjuvant treatment of GIST, but this indication is not yet approved in Turkey. There are no restrictions in reimbursement or prescription in Turkey compared

to approved indication and doses. The sales of imatinib in Turkey are lower than in the other countries included in this comparison (Figure 6-19).

**Figure 6-19 Sales of imatinib**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

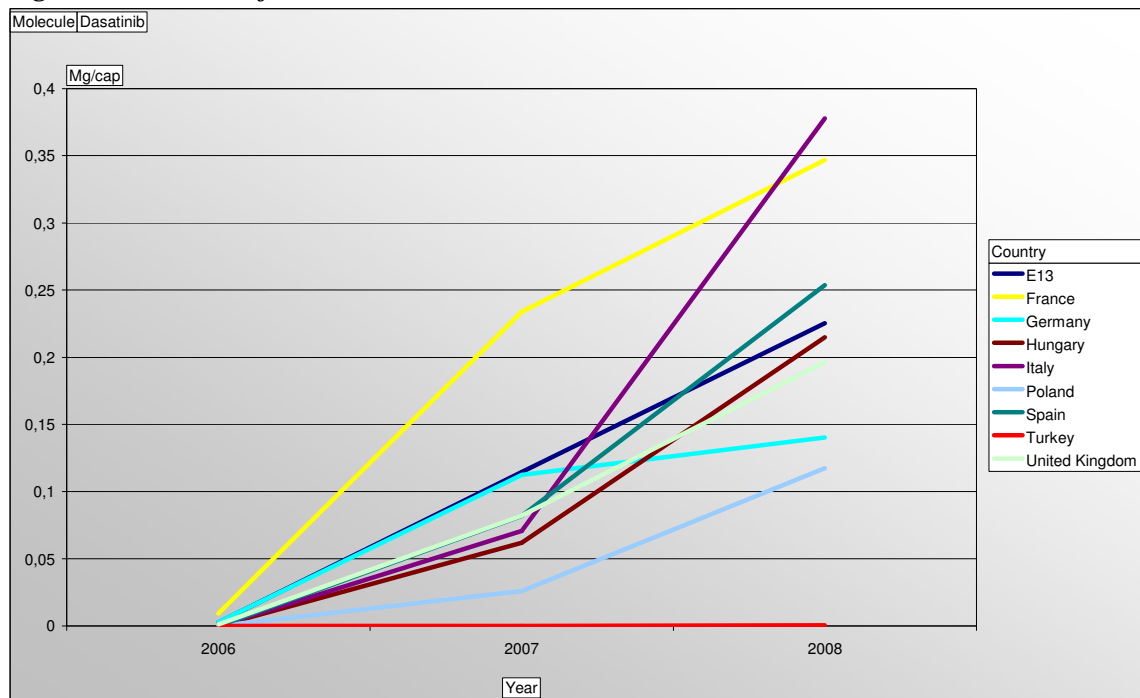
## Dasatinib

Dasatinib (Sprycel®) is in Turkey indicated for chronic myeloid leukaemia (CML) who do not respond to or do not tolerate imatinib, with loss of complete hematologic or cytogenetic response or who develops additional new cytogenetic abnormalities. It is also indicated for remission induction in adults with relapsed/refractory Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and indicated for accelerated, myeloid or lymphoid blast phase (advanced phase) CML and in adult patients with CML who entered the blastic or accelerated phase under imatinib treatment. This corresponds to the indication in the EU and in the US.

Dasatinib was first approved by FDA in June 2006 and by EMA November 2006. In Turkey, registration approval was obtained in December 2007 and reimbursement approval was obtained in August 2008. The reimbursement of Dasatinib in advanced phase CML and PH+ALL patients in Turkey was first limited to 100 mg daily but this limitation was abolished in July 2009.

First sales in US and Europe appeared in the third quarter of 2006. First sales of dasatinib in Turkey were registered in August 2008. In Figure 6-20, we can see the development of the sales per capita in the EU countries. The Turkish sales is for obvious reasons very low in 2008.

**Figure 6-20 Sales of dasatinib**



\*Note: For all countries but Turkey, the fourth quarter of 2008 is extrapolated based on the fourth quarter share of yearly sales in earlier years.

## 6.4 Conclusions

The late entry into the market and low levels of use of new oncology drugs provides limitations to patient access to cancer treatment in Turkey. The long processes for registration and reimbursement of new drugs lead to long delays in market launch.



Together with the scarce resources this has negative implications for the patient's access to cancer treatment.

The sales of oncology drugs in Turkey should also be seen in the light of a significantly lower incidence and prevalence of cancer in Turkey. The lower use of cancer drugs cannot, however, be explained only by a lower burden of cancer only.

## 7 Discussion and policy recommendations

Although the available statistics on the burden of cancer are still subject to some uncertainty, the incidence and mortality in cancer is lower than in the European countries included in this comparison.

The resources available for health care in general and also more specifically in cancer treatment are highly constrained in Turkey. In comparison with EU countries, small resources available for health care limits the introduction and use of cost consuming modern technologies in Turkey. The per capita use of cancer drugs is significantly lower in Turkey than in European countries.

For several of the drugs analysed in this report, there are restrictions in the approved indications and in the reimbursement conditions in Turkey. Compared to the approval documents in many European countries certain drugs are not approved for all indications or doses in Turkey. Reimbursement may also be restricted by the indication, doses and what medical specialists have the right to prescribe and use certain drugs. The regulatory approval and reimbursement processes in Turkey are much longer than in most European countries. Compared to the US or some EU countries, this causes market entry delays in Turkey for up to four years for new drugs.

When new products are launched it is important that they reach the market and come into use, to enable patient access to treatment. The long processes for marketing approval and reimbursement of new drugs constrain the access to treatment in Turkey. Most drugs being evaluated for market approval in Turkey have been assessed in the US, in Europe or elsewhere. It is of great importance that the experiences of authorities in other countries are also applied in Turkey in order to speed up the processes for market approval and reimbursement, and shorten the launch delays.

With health care budgets becoming increasingly stretched, a greater emphasis is put on how to use the limited resources in the most efficient way. The development of new health technologies leads to greater opportunities for more efficient provision of health services and improvements in treatment outcomes. As new technologies often come at a higher price, it is important to assess whether the higher costs are motivated by

improvements in outcomes measured both in terms of survival, and in the well-being of cancer patients.

In Europe the great costs of treatment are increasingly putting a perspective of the overall economic impact on the society. Resources spent on direct treatment, may be justified by savings made on indirect costs. Such a societal perspective on cost effectiveness would be necessary to establish basis for priority-setting in Turkey. This will be necessary to be able to maximize the utilization of resources and to provide cancer patients with access to necessary treatment.

Given the scarce resources allocated to health care and cancer treatment, the priorities in the Turkish health care system are likely to be different from most European countries. Larger investments in modern and often expensive treatment may be difficult to accommodate in the existing budgets.

In Europe, new treatments having higher clinical value are also consuming an increasing share of health care resources. In order to provide patients with access of modern and the most appropriate treatment to cancer patients in Turkey, resources needs to be set aside budgets in both inpatient and outpatient setting. Providing a separate funding for new cancer drugs during the first years on the market may facilitate earlier market entry, and provide patients with access to modern treatment.

In order to accommodate new technologies and to evaluate the clinical and economic value, Health Technology Assessments (HTA) has become an increasingly used tool in many countries. New technologies need to be assessed in terms of clinical and economic benefits so that treatments having the potential to save lives and money and to improve quality of life of cancer patients are in regular use. In many European countries, primarily in the Central and Eastern parts, the application of HTAs is limited. This is also the case in Turkey. In order to make use of HTA, knowledge and competence in both undertaking and evaluate HTAs in public authorities, providers and payers of health care systems and in the industry are required. In order to make clinical and economic evaluations of new drugs, there needs to be data available, and an infrastructure to collect data to support such analyses.

Often there is still a degree of uncertainty in the clinical and economic impacts of new drugs until it is used in regular clinical practice. In post market follow up studies, further

data on the effects of the drug can be collected, which may provide better basis for deciding what patients should have access to certain treatments.

Evaluations of the economic benefits of new treatments require sufficient and reliable health information data. This includes for example information on burden of disease, utilization of health care services, costs of treatment. Such information necessary to make sound decisions on priorities of available resources needs to be improved in Turkey. It is also important to develop a health information system facilitating the collection of clinical data in order to make post market evaluations of new drugs. Such a system includes efficient collection of clinical data and organisation of cancer registries allowing for retrospective studies. Without having reliable and long term data it is not possible to assess the effects of new treatments and how to make priorities with scarce resources. The true costs of cancer treatment must also be systematically analysed. Without knowing the economic impact of introducing new therapies, the cost effectiveness of these can not be assessed.

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