Report

March 2017

Oncology patients' access to drug therapies in Poland in view of current medical knowledge

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The report financed
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Table of contents

Preface

Two years ago, when we ordered a report on the availability of innovative cancer drugs in Poland as compared to other European Union countries and Switzerland, we were seeking a tool that would highlight the particularly difficult situation of thousands of Polish patients. Through the commitment of many people and groups, and in particular, thanks to the open approach of the media, the issue of the availability of drugs to people suffering from cancer has become the subject of a public debate. Unfortunately, despite previous announcements, the battle against cancer has not been given priority. We find this hard to understand, particularly, as the number of patients who each year will start fighting cancer will increase by fifty percent by the end of the next decade. We therefore have a choice: shall we will plunge into stagnation, not taking any decisive actions at the government level? Or will we decide to organise chaotic actions, arranging them under a coherent strategy aiming at reaching a normal situation?

The availability of cancer pharmacotherapy is one of the most important components decisive for the success of cancer treatment. Within less than 24 months of publishing the previous report we note with concern that despite a few changes, methods used to fight cancer in Poland are frequently outdated. The several positive decisions on reimbursement made in recent months have not changed the qualitative image of the availability of cancer drugs. The challenges we face are proportional to the neglect in the past. The reimbursement system itself also appears to deviate from pro-patient orientation, condemning patients to significant uncertainty and dependence on officials' decisions and unclear regulations.

We present to you a report on a complicated and multifaceted issue. It aims at answering the question: "Are Polish patients treated in accordance with contemporary medical knowledge?" We reviewed the treatment regimen reimbursed by the National Health Fund against guidelines issued by international scientific societies representing the latest scientific knowledge. The analysis concerned 10 solid tumours and 10 haematooncologic diseases representing the most common causes of death in oncology patients in Poland. On this basis, we want to initiate a discussion on systemic changes that could improve the patients' situation. Without your support these changes cannot be implemented. Our personal experience proves that health is worth fighting for. Please join us in this fight.

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Summary of the report

Cancer in Poland versus Europe

Although the average Polish life expectancy is still lower than in many countries in Western Europe, in recent years our life expectancy has become significantly longer. With longer life, diseases whose prevalence and severity depend on the patient's age have become an increasing problem from a medical, social and economic point of view. Cancer belongs to this group of diseases.

> According to estimations, every fourth inhabitant of Poland will contract cancer during their life, and every fifth will die from it.

Considering the forecasts, in 2029 the number of new cancer cases will exceed 213 thousand. With 180.3 thousand new cases estimated in 2016 and 159.2 thousand cases of the disease noted in 2014 **experts are talking about a kind of "cancer tsunami" passing through our country**.

Despite a significant increase in the number of new cases, **Poland still remains a country with one of the lowest incidence of cancer in the whole of Europe**. A higher incidence can be observed not only in highly developed countries, including Denmark, the Netherlands, Sweden or Germany, but also in Hungary, Czech Republic and Slovakia. **Nevertheless, an average Pole has much less chance to survive 5 years with cancer when compared to citizens of other European countries**. In Sweden, Finland, or Iceland, over 60% of patients diagnosed in 2000–2007 survived for at least 5 years of being diagnosed with cancer. In the same period, in Czech Republic and Portugal, over 50% of patients were enjoying life 5 years after diagnosis. **In Poland, only 41% of patients were alive 5 years after their diagnosis.**

Poland is a country with a high number of deaths caused by cancer. In the group of economically active men cancer is the second cause of deaths, following cardiovascular diseases, and is responsible for 28% of all deaths.

> Amongst economically active women cancer is responsible for 48% of all deaths and is their first cause. A high mortality rate amongst economically active people, young and middle aged, negatively distinguishes Poland in European statistics of mortality.

Countries such as Denmark, Great Britain, Czech Republic or the Netherlands have a mortality rate in 65+ age groups higher than the one observed in Poland. However, in those countries a mortality rate for young people is significantly lower than that observed in Poland. An unfavourable position of Poland versus other countries when the mortality rate is compared in both groups, i.e. young and old people, may reflect a fact that the health care system is insufficiently prepared to cope with the problem of cancer.

The above hypothesis is confirmed by observations of changes in the mortality rates in individual countries. In 1990–2013, many aspects of cancer diagnostics and treatment changed in our country. Also, the social awareness of cancer changed. In consequence of activities undertaken, the cancer mortality rates decreased by ca. 8%,**; however, at the same time other countries managed to reduce the mortality rate to a much larger extent**. In Luxembourg, Switzerland, Belgium, and **even in the Czech Republic, the reduction in mortality rates exceeded 25%,** with an average of 17% for the whole group of OECD countries.

Epidemiology of cancer in Poland

Between 1999 and 2014, the annual incidence of cancer increased by 42%

(from less than 112 thousand to 159.2 thousand new cases a year). The number of new cases rose by 36% in men and by as much as 49% in women. **Within 16 years, about 2.1 million people in Poland had cancer, and this corresponds to a group consisting of all citizens of Warsaw and Bydgoszcz combined.**

Although in elderly people incidence rates are the highest, cancer can develop at any age. In a group of people <35 years of age, the number of new cases in 2014 was 22% higher than in 1999. The number of new cases increases faster in women versus men. In 2014, in a group of people of 35–54 years of age, the number of new cases was ca. 12% lower than in 1999, and this resulted mainly from a reduction in standardised incidence rates in men (by ca. 21%, from 198 in 1999 to 157 in 2014). In that period, the incidence rates in women increased, from 254 to 268, i.e. by ca. 5%. The number of new cancer cases in the 54+ population increased by ca. 61%. Regardless of age, **the increase in the incidence rate noted between 1999 and 2014 was 8% for men and nearly 29% for women.**

Bronchial and lung cancer still remains the cancer with the highest incidence rate. They are the first cause of disease in men and the second in women. What is worrying is the fact that for these types of cancer practically the whole increase in the absolute number of new cases results from the increased incidence in women (2014 vs. 1999 means over 3.3 thousand new cases more per annum).

The number of new cases of breast cancer is still rising. In 2014, there were nearly 6.5 thousand more new cases than in 1999. For this group of cancers, the incidence rate in 2014 was nearly 1/3 higher than in 1999. **Of 15 types of cancer characterised by the highest incidence rate, a reduction in the number of new cases was noted only for two** (stomach cancer, cervical cancer). **For all other types of cancer, an increase in the number of new cases was noted.**

Efforts undertaken to combat cancer have also brought about positive effects. Patients diagnosed in Poland in 2010–2012 had a higher possibility of survival than those diagnosed in 2000–2002. Nevertheless, **in inter-country comparisons, the 5-year survival rate with diagnosed cancer in Poland is lower than in many other countries**. **Every year, over 90 thousand people in Poland die of cancer. In 1999–2014, nearly 1.5 million people died in total. This figure represents a population corresponding to all inhabitants of Kraków and Łódź** – just as if both those cities with all their inhabitants were erased from the map of Poland in the course of those 15 years.

Bronchial and lung cancer is still the main cause of death from cancer. In 2014, nearly 4 thousand more people died of it than in 1999. However, although it can be said that the number of deaths remained at a similar level for men (15.8 thousand in 2014 vs. 15.5 thousand in 1999) with a simultaneous reduction in the standardised mortality rate by 26%, for women both those parameters increased dramatically. In women, bronchial and lung cancer was responsible for 3.6 thousand deaths in 1999 and for as many as 7.3 thousand deaths in 2014, and the standardised mortality rate rose by nearly 60% (from 11.5 in 1999 to 18.0 in 2014). Due to this increase in the number of deaths by over 100% bronchial and lung cancer became the main cause of death from cancer in women, overtaking breast cancer in this tragic list.

Despite wide-scale actions, the mortality rate for breast cancer still remains high. The fact that the standardised mortality rate for this cancer did not increase can be viewed with moderate optimism. **In 2014, in nearly each of 15 groups of cancer characterised by the highest mortality rate we observed an increase in the number of deaths**. The exceptions include stomach cancer, for which the number of deaths was nearly 750 lower in 2014 than in 1999, hepatic and cervical cancer (240 deaths less), or laryngeal cancer (nearly 130 patients less died).

Cancer and the national economy

The cancer also has an economic dimension.

In 2014, premature deaths from cancer are associated with unproduced GDP of PLN 900 million – in that one year only. This amount is equal to all funds collected by The Great Orchestra of Christmas Charity during the last 25 years.

However, the loss evaluated in terms of lost years of life of people who died of cancer in 2014 is much higher. Young people dying prematurely would have many years of economic activity before them. The value of GDP lost due to deaths in 2014 in terms of their entire expected economically active life may range from PLN 8 to 10 billion.

Financing of innovative oncology therapies in Poland

Cancer therapies are very expensive.

Cancer drugs, particularly the newest ones (targeted therapies), are so expensive that an average patient cannot afford financing treatment even by taking only one drug using their own financial resources,

and frequently the therapy is combined, involving several drugs.

In general, in Poland treatment of a patient with innovative medications can be financed through four main mechanisms:

- treatment under the public health care system;
- patient participation in clinical studies (an option available only to selected groups of patients, according to research needs of clinical trails conducted at a specific moment, and only in a few selected centres);
- support of non-governmental organisations which use obtained funds to finance treatment of patients under their care;
- with own financial resources (however, due to the cost of therapy, this option is available only to a very limited number of patients).

Public health care system

For the great majority of patients access to many safe and effective oncology drugs is only possible when they are financed by the public.

The National Health Fund (NFZ) expenditures on reimbursing of drugs begin to rise. When the new Reimbursement Act was introduced in 2012, they were significantly reduced. In 2015, the level of expenditures returned to that from before the Act, reaching PLN 11.0 billion, and in 2016 they were probably higher by PLN 400 million in total on a year-on-year basis.

It was assumed that the Reimbursement Act, apart from reducing NFZ expenditures on reimbursement, would significantly increase access of Polish patients to safe and effective drugs. **Since 2012, a certain group of previously non-reimbursable new drugs has been covered by reimbursement**. Also drugs previously reimbursed in a different way (e.g. drugs transferred to the reimbursed from a non-standard chemotherapy programme) or drugs for which less expensive generic drugs were introduced onto the market when patent protection for their reference drugs expired were also covered by reimbursement.

From a perspective of the whole NFZ reimbursement budget, currently a value of funds used for reimbursing innovative drugs announced since January 2012 does not exceed 10%. **Expenditures on innovative cancer drugs are below 2% of funds allocated by NFZ to the reimbursement budget**. In most cases the reimbursed drugs are free for oncology patients. However, this does not apply to drugs available through the pharmacy reimbursement scheme, where in 2016 patients had to co-pay PLN 49 million for these drugs (limited to L01 and L02 classes according to the WHO Classification of Medicines).

By November 2016, 51 molecules used in cancer therapies in total had been added to the reimbursement scheme. Eight new molecules used in cancer treatment, of which one was a new molecule of the innovative status, were added to reimbursed drugs available in pharmacies. Additionally, in this category of reimbursement availability, 4 new molecules in supportive treatment appeared, and as many as 3 of them can be considered as new innovative therapies. 23 new active substances were introduced to the chemotherapy catalogue, of which only 3 were innovative. Amongst the remaining new substances in the chemotherapy catalogue, 14 were previously available in other financing channels or they were transferred to the chemotherapy catalogue from a phased-out non-standard chemotherapy scheme. Further 4 drugs covered by reimbursement are generic drugs, and last 2 are not new to the reimbursement scheme. Twenty five new drugs were added to treatment programmes. It is under this category of reimbursement availability where a number of new drugs made available to patients was the largest – as many as 12. The remaining 13 molecules were previously available to patients under the non-standard chemotherapy programme or in the chemotherapy catalogue.

The inclusion of new safe and effective therapies in treatment programmes is good news for patients. To many of them drugs made available this way represent an additional therapeutic option that may improve their health and quality of life. **Less optimistic is the fact that such a large number of new drugs were added to treatment programmes – a category of reimbursement availability that, by its nature, is to ensure a strict control over NFZ expenditures on high-cost therapies, which is frequently achieved by introducing restrictive conditions qualifying a patient for a therapy, which in many cases significantly narrow a population of patients that can benefit from the treatment in relation to the registration data**. Due to the increasing number of programmes, as well as changes in criteria for qualifying patients to the previously functioning programmes, the number of patients participating in them rises. Under cancer treatment programmes drugs were administered to ca. 20.5 thousand patients in 2014 and to 20.7 thousand patients in 2015, and to 14.8 thousand already in the first six months of 2016.

Clinical studies

Clinical studies are a component of processes related to studies on a potential drug before it is made available to wide groups of patients. One of the aims of clinical studies was to give an answer to a question whether a substance being a new candidate for a drug has expected therapeutic effects. For this reason, patients are involved in those studies at their relevant stages.

For a patient, participation in clinical studies is a chance for another therapeutic option. In general, patients – due to requirements of protocols according to which studies are conducted – are monitored more closely (more laboratory and diagnostic tests, more frequent contact with a doctor). It can therefore be said that patients are provided with a super standard medical care.

From patients' point of view, clinical studies are an option for the chosen. It is estimated that in Poland no more than 1 in 25 patients with cancer participates in clinical studies, where ca. 70–80 patients participates in one study on average.

To enrol in a study:

- a patient or a doctor in charge of their case have to know that it is being held, and this is not obvious;
- a patient must meet the inclusion criteria defined in a study protocol;
- a patient must notify his willingness to participate during the recruitment phase of a study – due to high costs, once a number of patients planned to be enrolled into the study is reached, others have no chance of joining it.

Due to the above limitations, **although in some diseases clinical studies may be the only chance for a patient to have access to non-reimbursed therapy, they must be considered an interesting option for a narrow group of patients,** but they should never be considered as a significant component in the system providing access to cancer treatment.

Non-governmental organisations

Some patients will not be qualified for treatment with new drugs under treatment programmes. Drugs that could help some patients are not reimbursed in Poland. In those cases patients that cannot finance their therapy themselves are sometimes assisted by non-governmental organisations.

There are no analyses available presenting a scale at which patient therapies are co-financed by non-governmental organisations. On the basis of several examples that were identified by the authors of this report, a single organisation has under its care from a few to a little over 200 patients. Non-governmental organisations collect money for their charges which are used for drugs, consultations, diagnostics, arrivals to a treatment centre, accommodation near a treatment centre, rehabilitation equipment and medical devices. It is worth noting that many of those costs are not considered in the publicly reimbursed treatment process.

Non-governmental organisations use funds received from donors to cover the needs of their charges. They are not able to predict when and what funds they will have at their disposal. Therefore, there is no guarantee for patients, if, when and how many of them will receive this support.

Thus, similarly as in the case of clinical studies, it should be assumed that **despite the important role played by non-governmental organisations, they cannot be considered as a element replacing the public health care system in ensuring treatment of oncology patients.**

Patients co-payment for drugs at pharmacies

In general, patients in Poland have free access to the great majority of cancer drugs. However, patients have to co-pay for drugs available in pharmacies. Co-payments result from mechanisms for establishing a price, financing limits and a flat-rate fee, which are defined in the Reimbursement Act.

As a part of co-payment for cancer drugs of classes L01 and L02, in 2016 patients left PLN 49 million in pharmacies. The recently observed trend shows a significant increase in patient co-payment (from PLN 34 million in 2014 to PLN 49 million in 2016) with the volume of purchased drugs at a similar level. To some extent, the observed increase in costs borne by patients at pharmacies is associated with filling restricted prescriptions for new cancer drugs which are normally not available or available only in hospitals. This may reflect purchases made by patients that can afford financing their treatment or those receiving financial support from non-governmental organisations.

Processes associated with providing patients with access to a given drug

About 12 years usually pass before patients have access to a new therapy, and the costs of associated works are at a level of one to several billion euro. During this time a medicinal product undergoes several research and regulatory stages aiming at selecting an effective molecule and ensuring a maximum safety for patients.

Research stages of works on a new medicinal product include basic research, and preclinical and clinical studies. The works on the development of a new medicinal product conclude with drug registration, which confirms its therapeutic properties and specific safety to patients.

In Polish conditions, all stages related to including a medicinal product, particularly, a cancer drug, in the reimbursement system are of importance, as in practice only then the therapy becomes available. A pharmaceutical company is responsible for initiating a process for including a medicinal product in the reimbursement system. Due to various conditions, including prices, regulatory requirements and the international context, a pharmaceutical company introduces a medicinal product onto the Polish market only after some time of its registration in other European markets. This is a first component in a list of factors resulting in delayed access of Polish patients to therapies.

To apply for including the product in the reimbursement system, a pharmaceutical company must prepare documentation required by the Ministry of Health. Preparing required documents may take up to several months, and costs of their development and fees related to handling an application for reimbursement may be significant, particularly for medicinal products used for rare and ultra-rare diseases.

Documentation of a medicinal product submitted by a pharmaceutical company together with an application to include that medicinal product in the reimbursement system is evaluated by the Agency for Health Technology Assessment and Tariff System (AOTMiT). At the next stage of the process, the application is submitted to the Economic Commission within the Ministry of Health. Its main task is to agree final terms and conditions of reimbursement with the pharmaceutical company, including a price at which that medicinal product will be available in Poland. Negotiations conduced by the Economic Commission are difficult and responsible. On the one hand, the Commission must act as a guardian of public money allocated to health care purposes and ensure these resources are used in the best way possible, while on the other it must consider the best interest of Polish patients – when the Commission expectations cannot be met by a pharmaceutical company, it will withdraw from negotiations and its medicinal product will not be available to patients who could otherwise benefit from using it.

In this entire process, the above-mentioned balancing of payer (NFZ), patients and pharmaceutical companies interests is one of the crucial elements decisive for providing Polish patients with access to new therapies. If the payer's interests prevail during negotiations, and in discussions financial arguments significantly outweigh the substantial benefits for patients associated with the use of the medicinal product, then it is difficult to reach a consensus representing an advantageous solution for both parties to the negotiations, and to patients themselves.

The process of handling an application for including a medicinal product in the reimbursement system ends with a reimbursement decision issued by the Minister of Health. That decision can be positive or negative. That second case ends the administrative pathway. The positive decision initiates new stages on the road to making the medicinal product available to patients. New positive reimbursement decisions and valid previous decisions are published by the Minister of Health in the form of announcements every two months. This document (the announcement) is important, as only these medicinal products that are listed in it may be reimbursed by NFZ during the term of that document. The medicinal products not included in it cannot be reimbursed.

The reimbursement announcements, or rather, mechanisms underlying calculation of prices and limits, resulted in rapid changes in the levels of co-payment by patients that have affected oncology patients in recent years. On the basis of experience gained during five years of the Reimbursement Act being in force it can be seen that in many cases patients were negatively affected by significant changes in prices.

As it was mentioned above, the announcement initiates new stages on a product route to patient. For medicinal products available at pharmacies, after the announcement comes into force, the only thing a patient needs to start using a new medicinal product is a doctor's prescription. For medicinal products available within the in-patient health care system, necessary procedures must still be conducted by NFZ. The most important of them include a regulation issued by the Minister of Health and an order issued by the NFZ President implementing new medicinal products (treatment programmes) into guaranteed benefits and a tender procedure launched by NFZ branches for providing services under new treatment programmes. Individual NFZ branches announce tenders for a new treatment programme at different times. In certain cases in some branches, tender proceedings must be repeated several times before healthcare providers are selected with whom an agreement for implementation of the treatment programme is concluded. It may also occur that a given branch decides against conducting tender proceedings due to lack of sufficient financial resources. In consequence of the above situations, patients in individual voivodeships have access to medicinal products at different times, and from a legal point of view this could be perceived as an example of geographic inequality in access to treatment.

Due to all processes described above, **several to several dozen months may pass before a medicinal product is included in the reimbursement system. Several reimbursement processes in Poland took more than three years, although the statutory period is 180 (or 240) days.**

Patient access to innovative therapies

In recent years, the progress in medical knowledge has been accelerating rapidly. New medicinal products become available every year. **From the beginning of 2004 to the beginning of December 2016, the European Commission authorised introduction of 94 molecules for oncology indications into the market.**

In the report "Access to innovative cancer drugs in Poland in comparison with selected European Union countries and Switzerland", prepared to the order of the Alivia Foundation at the beginning of 2015, the availability of 30 molecules, which reached significant sales levels in the European markets, was evaluated. At that time, the analysis also indicated significant limitations towards other European countries, and particularly in comparison with the countries of Western Europe.

Out of analysed 30 substances, patients in Poland had access to only 18 (with limitations in some cases). In the Netherlands, Germany and Austria all drugs were available, while at our southern neighbours, the Czech Republic, 23 products were available. The situation in Slovakia (17), Hungary (14) and Romania (11) was worse than in Poland. Out of 18 substances available to patients in Poland, only 2 were fully available, and for 16 of them the access was limited.

When analysed in January 2017, an information important from patients' point of view is that 6 of 12 drugs not available at that time have been included in the reimbursement system. However, as those pharmaceuticals have been added to treatment programmes, only some potential patients can benefit from them.

However, expanding the list of reimbursed drugs is only a drop in the ocean of needs, as of the above-mentioned 94 new molecules registered in Europe:

- **Fifty molecules (over 53%) are not reimbursed in Poland for any oncology indications;**
- for 19 molecules (38% of non-reimbursed molecules), their manufacturers initiated actions aiming at including those products in the reimbursement system, as evidenced by orders for evaluation of applications for reimbursement submitted to the Agency for Health Technology Assessment and Tariff System;
- of 94 molecules, 32 (34%) are reimbursed under treatment programmes;
- of 94 molecules, 12 (13%) are available in the chemotherapy catalogue (pemetrexed included here is also reimbursed for another indication under a treatment programme);
- of 94 molecules, 1 (1%) is available at pharmacies.

When data for newly-registered medicinal products and a degree at which they are covered by reimbursement are analysed, it can be said that:

- for many newly-registered medicinal products their manufacturers have not yet submitted an application for reimbursement in Poland;
- in Poland drugs are included in the reimbursement programme many years after they were registered for a specific indication;
- a great majority of new cancer drugs are reimbursed under treatment programmes;
- in the event of failure, in many cases manufacturers submit new applications for the same indications.

Some arguments used in discussion about including new drugs in the reimbursement system claim that the drugs for which applications are submitted do not have the required health effects. In the light of the last point above, the arguments concerning insufficient health effects appear difficult to keep as is it possible for health effects achieved for the same medicinal product used for the same indication to differ significantly during years in which successive applications are evaluated? It seems that it is not possible. Parameters most frequently changed in successive applications include: the size of a target patient population and a price of a medicinal product, definitely having a significant effect on savings in NFZ expenditures. Unfortunately, this is at the expense of patients who did not have access to that drug while successive applications were handled.

Time to providing access to new drugs

Time is a commodity that cancer patients usually do not have – **before a new drug is reimbursed in Poland, some patients will not live to benefit from a new therapy**. Therefore, ensuring quick access to a new drug under the reimbursement system is of paramount importance.

From the moment the Reimbursement Act came into effect, i.e. from January 2012 to December 2016, AOTMiT received 397 applications for reimbursement, of which 108 concerned products used in cancer therapies. In 2016, the average time required by the Agency to evaluate the application was 86 days, and 78 days for cancer drugs. Both figures presented above exceed a limit of 60 days defined in the Act. However, it should be noted here that no information is available concerning possible delays in proceedings resulting from a need to supplement materials provided by an entity applying for reimbursement, and this aspect, when considered in the analysis, may influence its result.

In 2016, 362 days, on average, passed between a recommendation issued by the AOTMiT President for an evaluated medicine and its inclusion in the reimbursement list. When assessed for cancer drugs, this parameter was even higher -in 2016, 460 days passed between the recommendation and the announcement for the cancer drug.

These figures were influenced by "withdrawing from the reimbursement freezer" of several drugs for which reimbursement applications were already submitted in 2013 and 2014, and which were covered by the reimbursement from the second half of 2016 or were only listed in the announcement in force from January 2017.

According to the Reimbursement Act, an application for adding a product to the reimbursement system should be handled within 180 days, and when this date is prolonged due to determining of a treatment programme, within 240 days. **In this light it should be assumed that dates for handling applications are exceeded** (however, there is no data showing how many proceedings were suspended on company request).

Out of 15 cancer drugs that were included in the list of reimbursed drugs from July 2016 to January 2017, from the moment the Minister of Health sent the first order for evaluation of a given drug for a specific indication to the moment of including that drug in the announcement:

- for 5 drugs this process was shorter than 250 days (up to slightly exceeding 8 months);
- for 5 drugs this process was within a range of 251–750 days (up to slightly exceeding 2 years);
- for 5 drugs this process was within a range of 751-1322 days (up to 3.5 years).

From 1 to 4 months passes between a reimbursement announcement coming into force and a drug becoming actually available to patients. In the first month

after the announcement, NFZ bears the costs for drugs reimbursed at pharmacies. In general, the expenditures on new drugs included in the chemotherapy catalogue and new drugs included in existing treatment programmes appear in the second month of the announcement. Patients must wait as many as 4 months from the announcement coming into force for drugs included in new treatment programmes.

Therapeutic standards

Many new drugs become available in the pharmaceutical market. From the point of view of clinical practice, the following questions gain great significance for a doctor:

- is the new drug a valuable therapeutic option and should I use it?
- what is the place of that new drug in a therapy regimen?

To meet doctors' expectations and support them in making decisions on how and with products the patients should be treated, medical standards are developed. The leading centres developing standards for oncology include the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) in the U.S., as well as the European Society for Medical Oncology (ESMO). In Poland, the treatment standard for cancer were developed by the Polish Society of Clinical Oncology in 2013.

In Poland, the key parameters influencing the selection of therapies proposed to patients for specific types of cancer include: reimbursement itself (an issue of drug price availability to a patient) and rules for providing access to reimbursed medicine in individual financing channels. **Thus, to compare Polish patients' access to safe and effective treatments, it is necessary to compare principles under which individual drugs are made available with reimbursement in Poland versus the latest available guidelines for specific diseases.**

In this study, the analyses covered 10 solid tumors and 10 haematooncologic diseases with the highest mortality rates according to the latest data of the National Cancer Register. Out of the analysed therapeutic areas, only in one case the therapy was consistent with guidelines of scientific societies. Less than one in three therapeutic options were available for a relevant group of Polish patients,

	The number of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard	ESMO standard (Europe)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)			Is the treatment available in Poland compliant with the latest standard?
				Active substance available in Poland compliant with the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland compliant with the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	
Bronchial and lung (NSCLC and SCLC) cancer	14	12	13	2	3	7	2	3	8	NO
Breast cancer	8	8	7	1	2	5	1	2	4	NO
Prostate cancer	5	5	5	1	1	3	1	1	3	NO
Colon cancer Rectal cancer	7	7	7	0	3	4	0	3	4	NO
Stomach cancer	2	1	1	0	0	1	0	0	1	NO
Renal cancer	10	10	9	0	6	4	2	4	3	NO
Ovarian cancer	3	2	2	1	1	0	2	0	0	YES
Bladder cancer	1	0	1	0	0	0	0	0	1	NO
Chronic myeloid leukaemia (CML)	4	4	3	0	2	2	0	2	0	NO
Acute myeloid leukaemia (AML)	3	3	2	0	2	1	0	2	0	NO
Myeloproliferative neoplasms	2	2	1	1	0	1	1	0	0	NO
Chronic lymphocytic leukaemia (CLL)	5	5	4	0	1	4	0	1	3	NO
Diffuse large B-cell lymphomas	2	1	0	0	0	1	0	0	1	NO
Plasma cell myeloma (MM)	10	10	4	2	1	7	3	0	1	NO
Hodgkin lymphoma	2	2	1	1	0	1	1	0	0	NO
Non-Hodgkin lymphoma	3	2	1	1	0	1	1	0	0	NO
Acute lymphoblastic leukaemia (ALL)	8	8	7	4	1	3	4	1	2	NO
Summary of access to therapeutic options	89	82	68	14	23	45	18	19	31	

Less current standard – figures are in grey. For standards with the same validity status, the ESMO standard was taken into consideration in the comparison.

versus the ESMO standards, and less than one in five options when compared with the U.S. standards.

The access to treatment options with limitations versus the published standards was not much better.

Over fifty percent of therapeutic options were not available under the public health care system in Poland.

The assessment covered drugs approved for marketing by the European Medicines Agency (EMA) in 2004–2016 and belonging to L01 and L02 classes according to the WHO Classification of Medicines, for 20 groups of cancer. For one group, no drugs with specific indications were identified or the identified drugs did not meet the specified time criterion.

The above analysis indicates that patients in Poland have a limited access to therapeutic options, when compared to NCCN or ESMO standards. This situation results from:

- no reimbursement of many active substances included and considered in treatment algorithms specified in the guidelines;
- limitations introduced at the level of detailed record of treatment programmes, resulting in:
  - excluding a possibility to administer drugs at earlier treatment lines;
  - excluding a possibility to administer drugs at successive treatment lines in the event of failure in a therapeutic regimen under which a specific drug was previously administered.

Also one's attention is drawn to the detailed descriptions of a patient condition and diagnostic and laboratory test results that should be met to qualify a patient for treatment under a treatment programme. Usually, the standards do not contain record at that level of detail, therefore, it is not possible to evaluate to what extent the adopted parameters are consistent with current medical know-how and thus useful in patient qualification, and to what extent they are used as a factor limiting a population of patients in which that treatment can be used.

When a therapeutic standard available under the public reimbursement system is compared, it should be noted that:

- versus the NCCN standard:
  - less than a half (37/82) of therapeutic options are available to Polish patients;
  - less than one in five (14/82) of therapeutic options are available in accordance with the current standard;
  - other are available with limitations (23/82).
- versus the ESMO standard:
  - slightly more than a half (37/68) of therapeutic options are available to Polish patients;
  - less than one in three (18/68) of therapeutic options are available in accordance with the current standard;
  - other are available with limitations (19/68).

Introduction

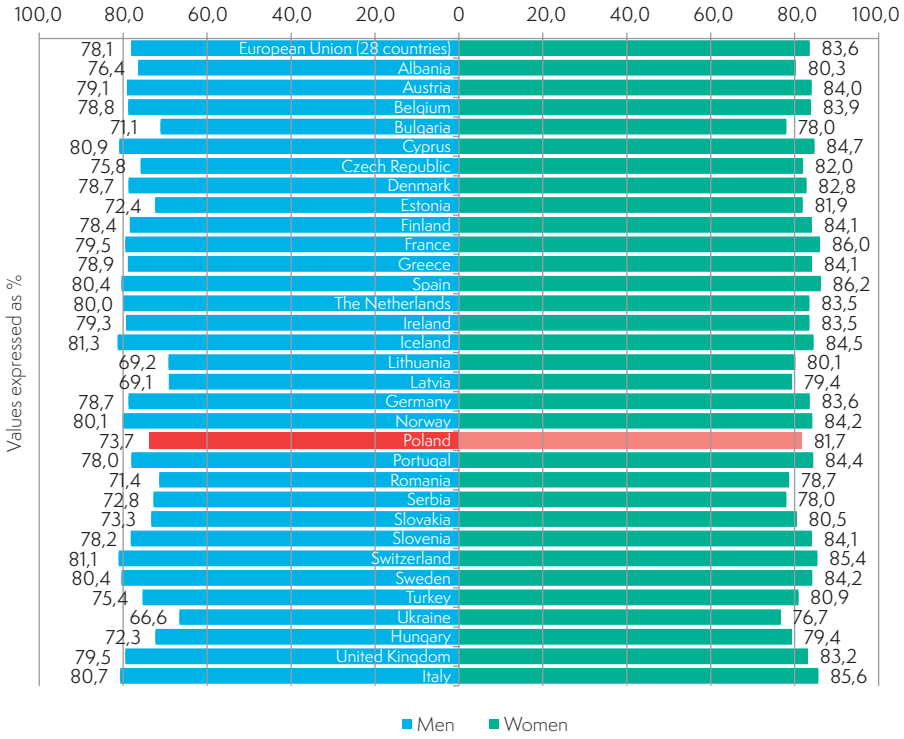

Chart 1 Life expectancy in European countries for people born in 2014. Source: Own study based on the Eurostat database, table „Life expectancy at birth by sex and age group"

Despite significant changes, life expectancy in Poland is still below the average life expectancy of many European countries.

The observed trends in increasing life expectancy in Poland and a distance separating us from the European average imply that over the next few years the life expectancy for Poles will continue to increase.

With the rising life expectancy, also increases a medical significance of diseases that decades ago were not a problem,

not because they did not exist or the medicine was unable to diagnose them, but because people did not reach the age at which those diseases occur en-masse. With an increase in the number of elderly people, the number of patients suffering from cancer, cardiovascular diseases, dementia or diabetes also increases.

According to estimations, every fourth citizen of Poland will contract cancer at some point in their life, and every fifth one will die of it (3).

From a statistical point of view this means that one person in a family of four will contract cancer at some point in their life, or one of four workers sharing a room will probably suffer from cancer. In short, everybody will come into contact with cancer at some point in their life, as a patient, care giver or an acquaintance. However, in contrast to cardiovascular diseases, dementia or diabetes, cancer kills much faster and more extensively.

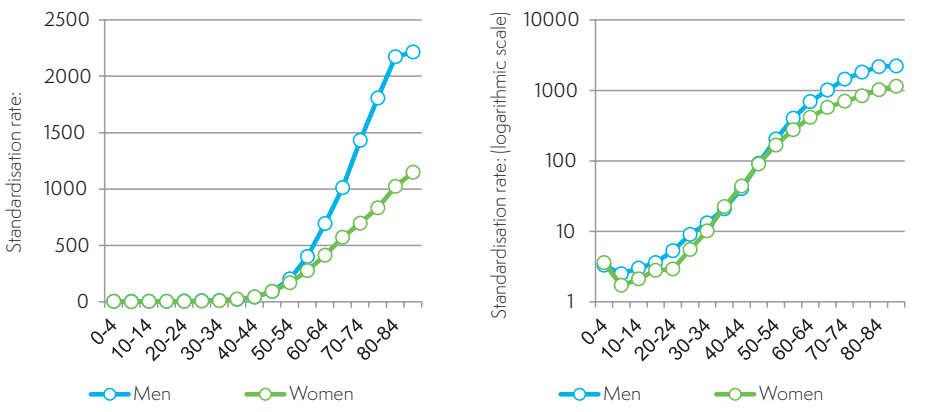

Chart 2 The relationship between a standardised mortality rate for cancer (logarithmic scale) and age, 2014
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

A problem of a significant increase in the number of cancer patients was noted, for example, as a part of discussions between the Polish Society of Oncology and the MPs in February 2016 (4). During that meeting, epidemiological data indicating that in the course of the next 5 years the number of cancer patients would increase by 15%, and by 28% in 10 years' time, were highlighted. According to the participants of that meeting, we would face a kind of a **"cancer tsunami".** According to maps of health care needs published by the Ministry of Health, considering only an isolated effect of demographic changes,

> the number of new cancer cases will increase from an estimated level of 180.3 thousand in 2016 to over 213 thousand in 2029.

Currently, cancer, similarly to other diseases of the elderly have become a particularly pressing problem for the social welfare and health care systems; they are also a factor which is very negatively affecting development prognoses for the whole economy. This mainly results from:

- increasing costs of health care provided to people suffering with these diseases;
- early withdrawal from or limited economic activity of people affected by these disease, resulting in a significant increase in costs for social care systems, and for patients suffering with these disease, significant deterioration in their living conditions – both when using a disability allowance or pension;
- reduced economic activity of families of these patients, as they have to provide care to them;
- early deaths, complications resulting in disability, treatment or chronic disease, significantly reducing the value of work that each of us contributes to the country's development.

Recent years have seen a rapid development of medical sciences (5). We know more about our body and its functional mechanisms. We can monitor it at a level of individual cells and their structures, or even go deeper to a level of molecular studies. This knowledge is used in new therapies, giving patients hope of a longer life, improvement in their health, or even complete healing. However, for those hopes to be realised, providing patients with quick and possibly extensive access to safe and effective therapies is of paramount importance.

In this report we will take a closer look at one of the areas mentioned above – cancer. For people suffering from cancer and their families, both "access to therapy" and "time" are of crucial importance, and a patient's life depends on both of them.

> On the basis of information available in the public domain, we will evaluate access to cancer therapies in Poland and will compare them against international guidelines, reflecting the current medical knowledge on diagnostics and treatment of these types of cancer.

We will also analyse the reimbursement process for new medicinal products as provided for in current legislation, highlighting elements influencing the time for which patients have to wait before they gain access to a new therapy.

Incidence and importance of cancer in Poland

Summary of the chapter

- Cancer risk factors are associated with economic development, therefore, in highly developed countries cancer prevalence is higher. Currently, in Poland cancer prevalence is lower than in the counties of Western Europe. However, our aspirations and expectations will move our economy towards that of highly developed countries. Therefore, in the future we will observe an increase in risk factors parameters in our country, and the higher cancer prevalence must also be considered.
- In recent years, every year about 160 thousand patients learn that they have been diagnosed with cancer. In the course of the last sixteen years, about 2.1 million people in Poland had cancer – this equates to all the citizens of Warsaw and Bydgoszcz combined being diagnosed with cancer!
- The number of cancer in Poland is lower than in Western Europe, yet cancer patients in Poland have a lower chance of 5-year survival. We are a country where an advantageous change in the cancer mortality rate was one of the lowest amongst European countries in 1990–2013. Our neighbour, the Czech Republic, can boast over 3.5 times larger drop in the cancer mortality rate.
- An increase in the number of elderly people in the population belongs to significant factors increasing cancer prevalence. Considering the demographic situation of Poland, it should be assumed that the number of new cases of cancer diagnosed each year will continue to rise. It is estimated that in 2029 over 213 thousand people in Poland will get cancer, thus, the number of new cases will be 1/3 times higher than in 2014.
- Cancer is a problem which is not limited to elderly people. In the population below 35 years of age, despite a low absolute number of new patients, the cancer incidence rate is growing significantly. In particular, this problem strongly affects young women.
- Throughout the years, the mortality rate for some cancer types has been reduced in Poland, yet the scale of observed changes is still far from expectations. Poland is in the group of countries where reduction in the cancer mortality rate did not exceed 10% in 1990–2013, despite progress in science and medicine. At the same time, in the group of countries that achieved the best results the cancer mortality rate ranged from 24% to over 32%.
- Cancer is also an important problem for the economy of our country. The cost of lost years of work due to the premature death of patients during only one year may reach from 8 to 10 billion zloty, and costs associated with patients' absence and lower productivity of their families represent an additional economic burden.

Cancer in Poland versus Europe

Cancer represent an important problem for public health and an enormous financial and social burden for European countries, despite a considerable progress achieved in recent years. Every year in each country hundreds of thousands of patients learn that they have been diagnosed with cancer.

Cancer incidence varies depending on the country. According to available data, Hungarians are over twice as likely to get cancer as Poles.

Also in highly developed countries, such as Denmark, the Netherlands, Sweden or Germany, the likelihood of getting cancer is significantly higher than in Poland.

Parameters indicating the probability of patient survival at least 5 years after being diagnosed with cancer also vary significantly.

On average, in Europe 54.2% of patients will live for 5 years from cancer diagnosis. However, in Sweden nearly

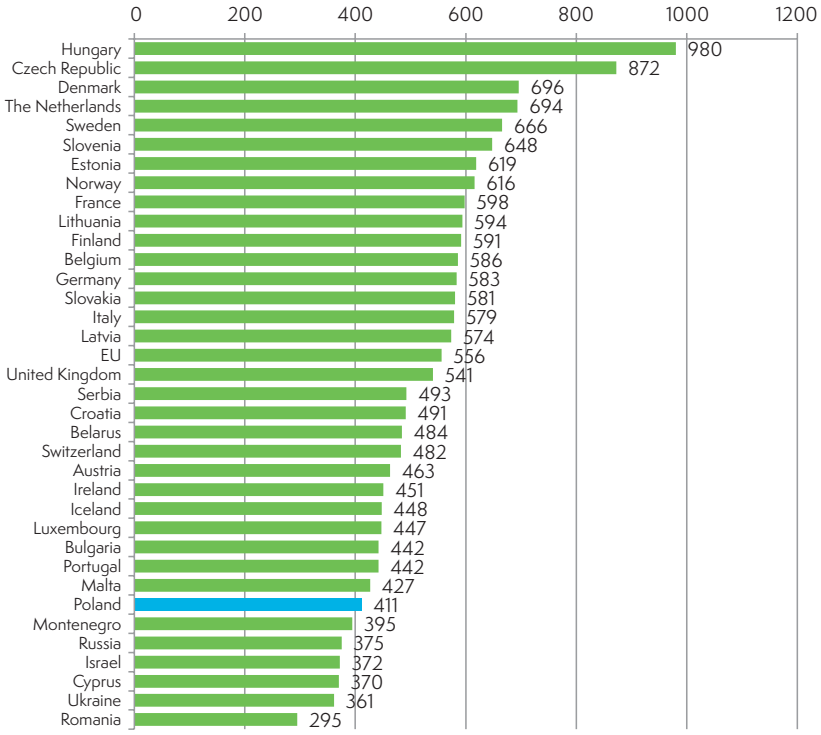

Chart 3 Cancer incidence per 100 thousand inhabitants for individual countries and for EU, the latest available data for 2012–2015 (for Poland – 2013).
Source: WHO, Regional Office for Europe, European health for all database, offline database, database from July 2016

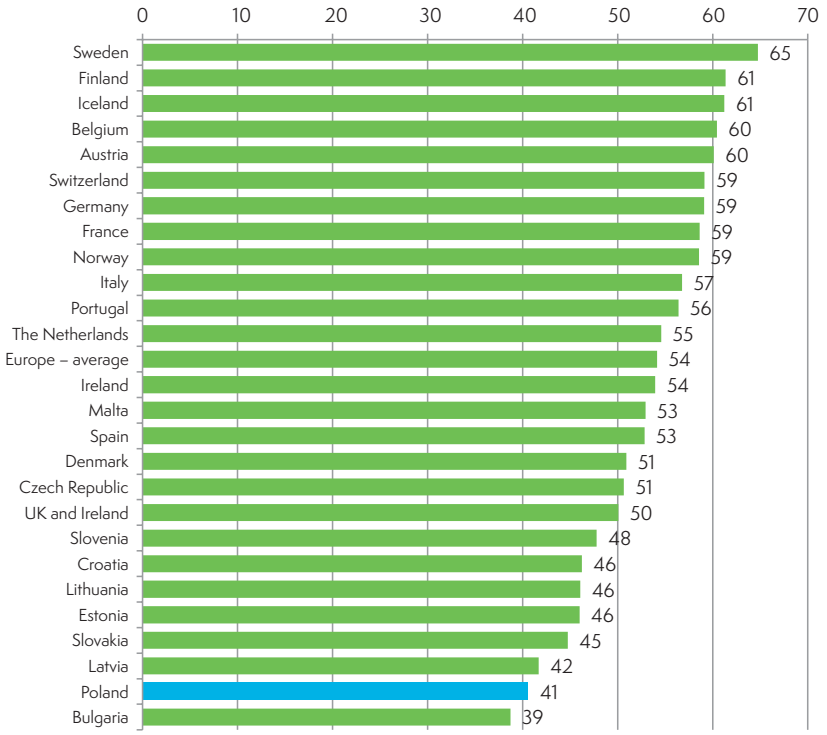

Chart 4 Standardised relative 5-year survival rate (%) for patients diagnosed in 2000–2007, all types of cancer, ICSS-Std
Source: Cancer patients' survival in Europe, EUROCARE-5 study, https://w3.iss.it/site/EU5Results/

65% can count on living for 5 years from the diagnosis. In Poland, only 41% of patients with all types of cancer will live for 5 years. This means that in Poland the number of cancer patients who will live for 5 years will be 24% lower than the European average, and nearly 37% lower than in Sweden.

According to data presented by Eurostat (6), in 2014 in Europe about 1.36 million people died of cancer, where deaths of men represented about 56% of the total number of deaths. In the same time in Poland, 95.6 thousand people died of cancer.

Deaths from cancer represent a significant proportion of all deaths registered in individual countries.

In Poland, the share of male deaths in the cancer mortality ratio was at a level of 55%. In the group of economically active men (20–64 years), cancer is the second cause of death and responsible for about 28% of them (the first cause of death in this age group are cardiovascular diseases, about 30% of deaths). Amongst economically active women (20–59 years), cancer is responsible for 48% of all deaths and in this age group it is the first cause.

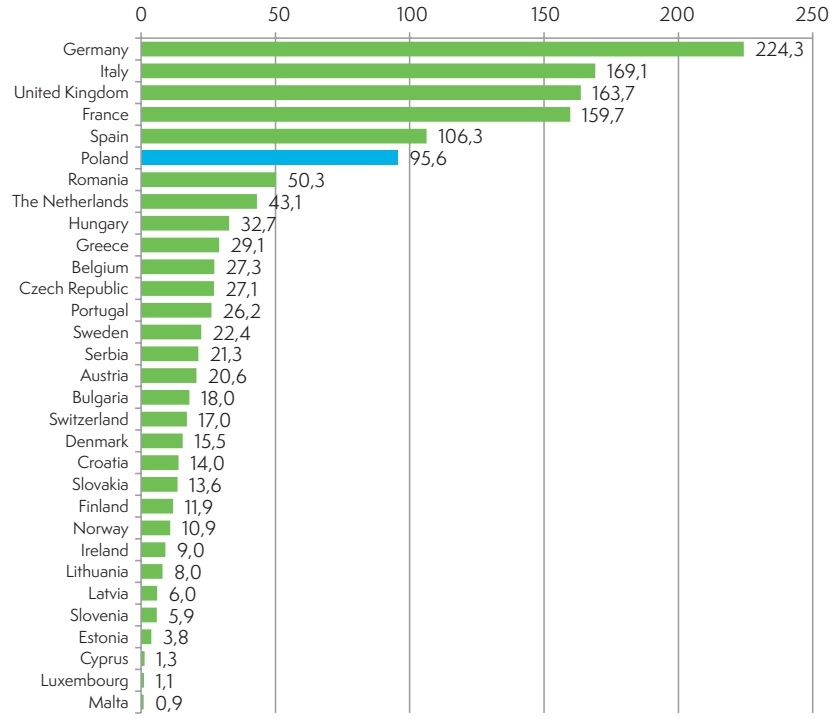

Chart 5 Number of cancer deaths in individual European countries in 2014, as thousands:
Source: Data according to Eurostat, http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics

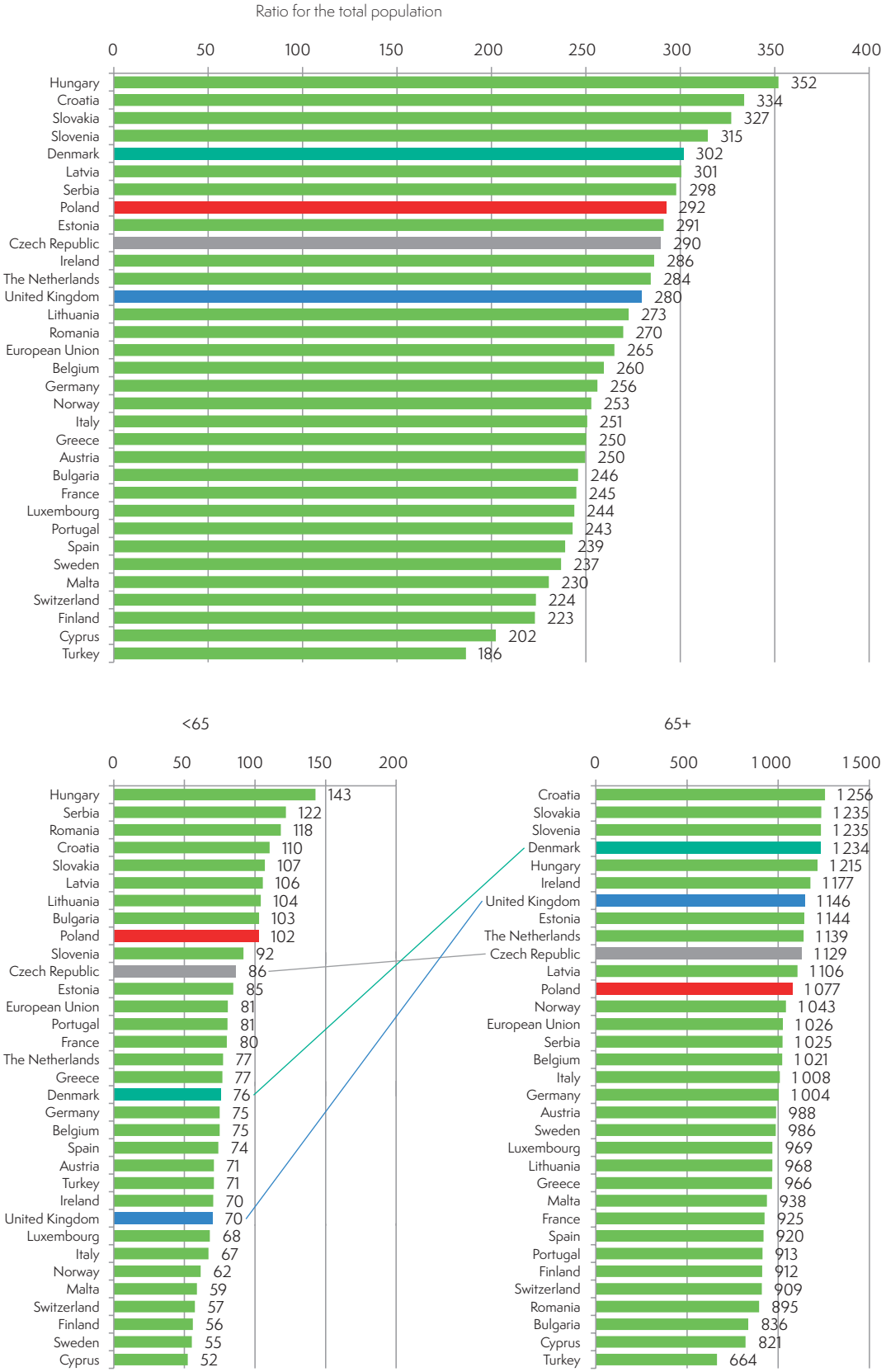

Chart 6 Cancer mortality rate in the total population, in the age group below 65 years, and in the 65+ group, 2013
Source: Data according to Eurostat, Cancer_statistics

To compare data on cancer mortality rates in individual countries of a different number of inhabitants it is necessary to analyse standardised mortality rates.

Poland takes a high place in lists where a mortality rate is expressed with a standardised rate. Highly developed countries, such as Denmark, Ireland, UK or the Netherlands, are characterised by a high cancer mortality rate amongst elderly people (in the 65+ group in Chart 5 they are above Poland), while the mortality rate amongst young people is significantly lower in these countries (in the <65 group in Chart 5 they are below Poland).

In Poland, mortality rates are high in the groups of young and elderly people alike, versus other countries.

This situation may indicate that the health care system is insufficiently prepared to cope with cancer.

Standardised cancer mortality rates have been decreasing in the majority of countries improving their health care systems. The rate of reduction in these rates in individual countries is one of the measures of effectiveness for the undertaken activities aiming at combating cancer and improving the effectiveness of its treatment. According to data made available by OECD, between 1990 and 2013 nearly all countries analysed in the OECD report managed to reduce their mortality rates. However, the extent of those changes varies depending on a country.

When the changes that occurred in Poland within that period are analysed, it must be noted that when compared to countries such as Switzerland, Belgium or our neighbour, the Czech Republic, they were rather moderate. **Particularly this last example shows a potential for improvement, as the country in a similar economic situation and at a similar level of development achieved a 3.5 times better result than Poland.**

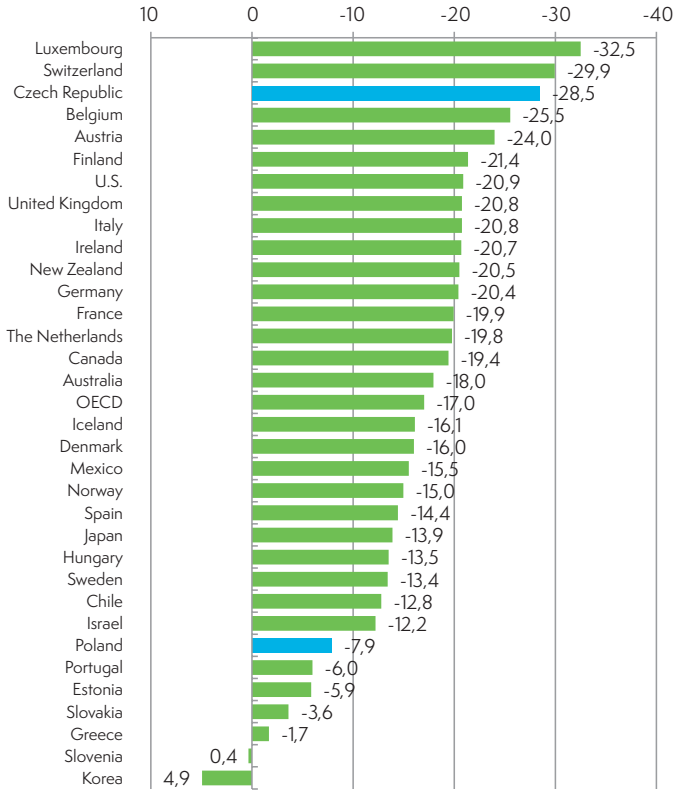

Chart 7 Change in the cancer mortality rate, 1990–2013, as %
Source: Own analysis based on data from OECD Health Statistics 2013, OECD Health Statistics 2015

Epidemiology of cancer in Poland

Before starting to discuss the epidemiology of cancer, the main sources of information for this therapeutic area should be mentioned.

In Poland, the main source of data about cancer is information collected and processed by the National Cancer Registry (NCR) operating at the Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology. An additional source of information are statistical cards for death certificates collected by the Central Statistical Office. It is estimated that the completeness of registration of new cases in Poland is about 94% and regularly improves. According to experts, there are still significant differences between voivodeships (from about 80% in Zachodniopomorskie, Podlaskie and Mazowieckie to 100% in Lubelskie, Opolskie, Podkarpackie, Pomorskie, Świętokrzyskie and Wielkopolskie voivodeships). The detailed information, for example, the estimated cancer stage, is significantly less complete, and ranges from 60% to 80% (7). Considering the above, it should be remembered that the analyses presented below may be underestimated.

Cancer affects people of different ages. Every year in Poland over 150 thousand people are diagnosed with cancer.

From 1999 to 2014, the number of new cases rose by over 42%, where the increase in the number of new cases was at a level of over 36% for men and 49% for women. Within 16 years, about 2 million 102 thousand

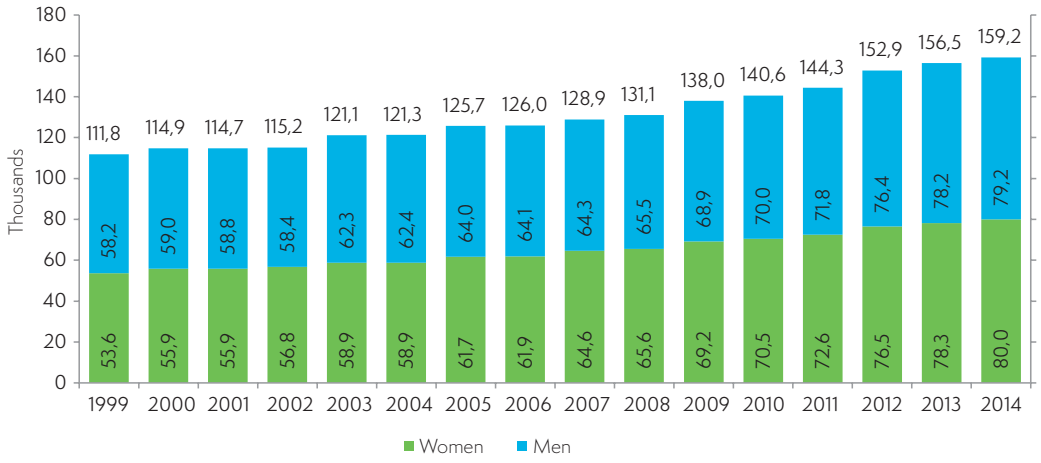

Chart 8 Annual cancer incidence rate in Poland
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

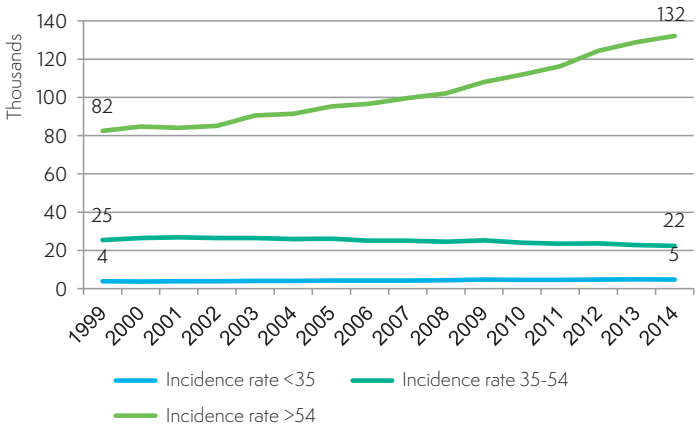

Chart 9 Cancer incidence rate according to age groups, absolute numbers as thousands
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

people in Poland developed cancer. **This number of people who had cancer is larger than the total number of people inhabiting Warsaw and Bydgoszcz** (6).

Although the number of cancer patients is the highest in the elderly population, yet – as the statistics show – the disease may occur at any age.

The steep rise in the number of new cases a year in the 54+ population is partly influenced by demographic changes observed in the population. With the increasing number of elderly people the number of cancer patients also increases, as this group of diseases is strongly correlated with age. However, an increase in the number of new cases a year in the group of young people, below 35 years old, is also noticeable, rising from 4 thousand to nearly 5 thousand cases (by nearly 22%). The increased incidence is observed not only for absolute data, but also for standardised rates The higher dynamics in the incidence increase in young women versus young men is noticeable.

In the age group of 35–54 years, a strong differentiation in trends characterising rates for women and for men is noticeable. This means that women in this group are at a higher risk of cancer than males of the same age.

In the course of 16 years, the standardised incidence rate for men has decreased significantly (by about 21%). Within the same period, that ratio for women increased by about 5%.

The cancer incidence rate is the highest in the 54+ group. In this age group, the standardised incidence rates have increased both for men and for women. The incidence rate increased by ca. 8% (2014 vs. 1999) for men, while for women it rose by nearly 29% within the same period.

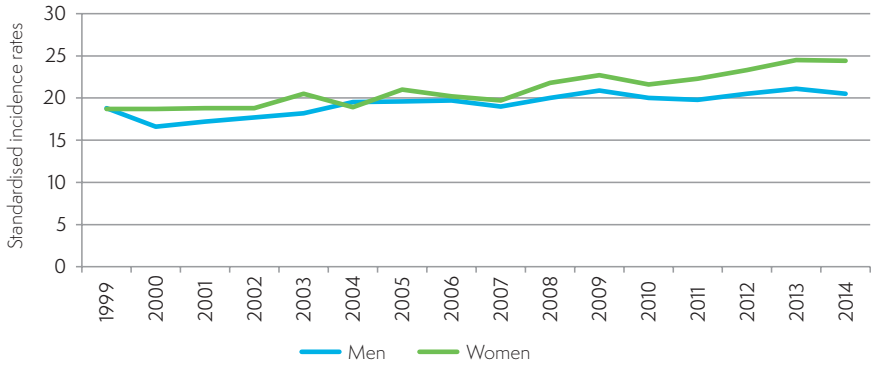

Chart 10 Standardised incidence rates by sex, <35 years group
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

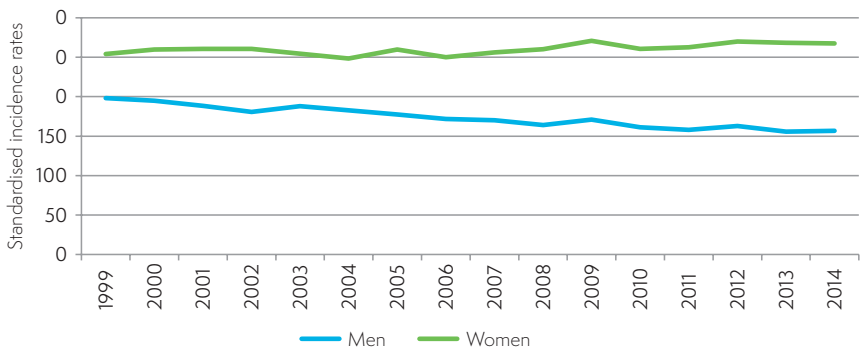

Chart 11 Standardised incidence rates by sex, 35–54 years group
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

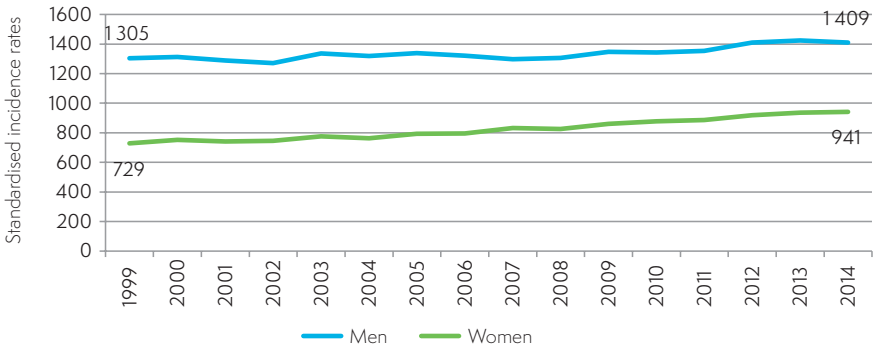

Chart 12 Standardised incidence rates by age groups, >54 years group
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

Fifteen most common groups of cancer were responsible for 76% of new cases in 2014.

The highest incidence rate is still observed for bronchial and lung cancer. They are the first cause of disease in men and the second in women. What is worrying is the fact that for these types of cancer practically the whole increase in the absolute number of new cases results from the increased incidence in women (2014 vs. 1999 means over 3.3 thousand new cases more per annum). This increased incidence amongst women is also observed at the level of the standardised incidence rate (an increase by nearly 45%), and this means that **the increase in the number of new cases would be noted regardless of any changes in the structure of female population.** In men, the standardised incidence rate dropped by 31%. Thus, despite changes in the demographic structure, the number of new cases of bronchial and lung cancer was reduced by 1.1 thousand a year (2014 vs. 1999).

The number of new cases of breast cancer is still rising. In 2014, nearly 6.5 thousand more new cases were noted than in 1999. The incidence rate for this group increased by nearly 1/3 from 1999 to 2014.

A rapid growth in the incidence is observed for cancers from the following groups: "skin cancers other than melanoma" and "prostatic cancer". In this first case, nearly 8.5 thousand more new cases were noted in 2014 (an increase by over 162%). Nearly 8 thousand more new cases of the prostatic cancer were recorded in 2014 versus 1999, and this means an increase in its incidence by 180%.

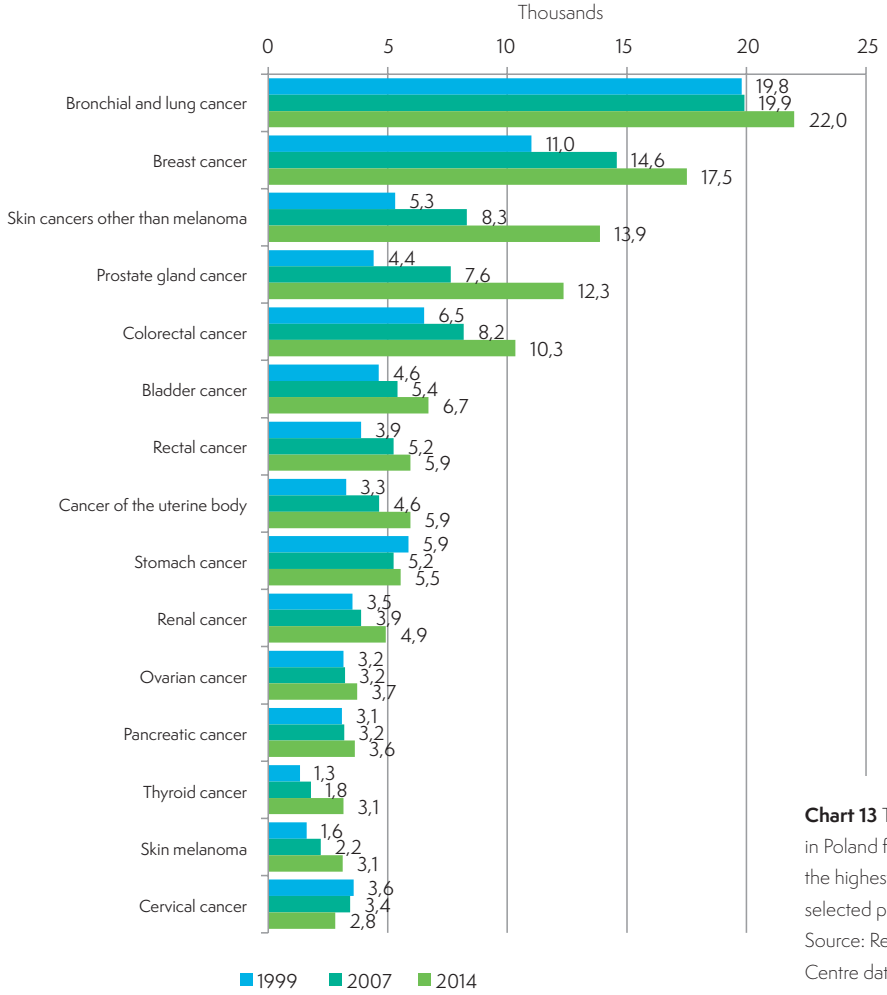

Chart 13 The number of new cancer cases in Poland for 15 cancers characterised by the highest incidence rate in 2014, and in selected previous years
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

Out of 15 cancers characterised by the highest incidence rate, the exceptions are stomach cancer (over 300 less new cases in 2014 vs. 1999) and cervical cancer, for which the annual incidence rate was lower by over 750 cases in 2014 than in 1999. For all other types of cancer, an increase in the number of new cases was noted.

Apart from an increase in the incidence, a significant increase in the cancer mortality rate is also observed. An analysis of data adjusted for population changes shows that the increase in the number of deaths for many cancers is observed for men and women alike. The efforts undertaken to combat cancer, leading to an increased probability of patient survival – usually estimated as a likelihood of living for 5 years from cancer diagnosis – act as a counterweight to the increase in the incidence rate.

The high mortality rate is characteristic for cancers (8). In Europe, nearly a half of cancer patients will not be alive 5 years after the diagnosis. In well-developed countries, this is second most common cause of death, after cardiovascular diseases. For many years, both the cancer incidence rate and the number of deaths where cancer was the main cause, had continued to increase. This situation resulted from demographic changes and from an increased exposure to factors that may contribute to cancer development. Only in recent years these trends have been reversed.

Unfortunately, according to the forecasts, in this decade cancer may become the leading cause of death in Poland (9). Despite a significant improvement in treatment outcomes for cardiovascular diseases (the standardised mortality rate decreased by half in 1990–2010), the effectiveness of oncology treatment has changed only slightly (and much less than in other countries).

Cancer group	Patients diagnosed in 2000–2002	Patients diagnosed in 2010-2012
Lip		66%
Mouth		37%
Salivary gland		57%
Nasal cavity and sinuses		34%
Oesophagus	5%	11%
Upper gastrointestinal tract	13%	23%
Large intestine	36%	51%
Anus and rectum		49%
Liver	8%	16%
Gallbladder	7%	14%
Pancreas		9%
Larynx	45%	51%
Lung	10%	17%
Melanoma	61%	72%
Breast	69%	79%
Cervix	51%	60%
Body of the uterus	70%	77%
Ovary	39%	53%
Prostate	48%	74%
Testicle	85%	84%
Kidney	46%	63%
Urinary bladder	46%	54%
Central nervous system	23%	33%
Thyroid	83%	91%

Table 1 Likelihood of 5-year survival from a cancer diagnosis
Source: Map of health care needs for oncology in Poland, Ministry of Health, 2015 12, http://www.mz.gov.pl /wp-content/uploads/2015/12/MPZ _onkologia _Polska.pdf

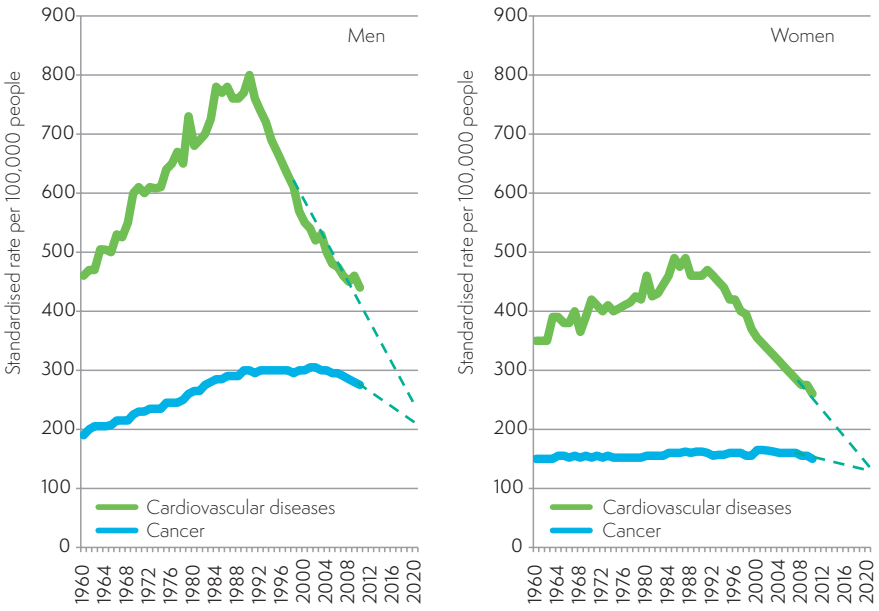

Chart 14 Cancer and cardiovascular disease mortality rates
Source: Witold Zatoński, Rak, dieta - wyzwania, 2012; Standardised mortality rates (for European population) per 100 thousand people

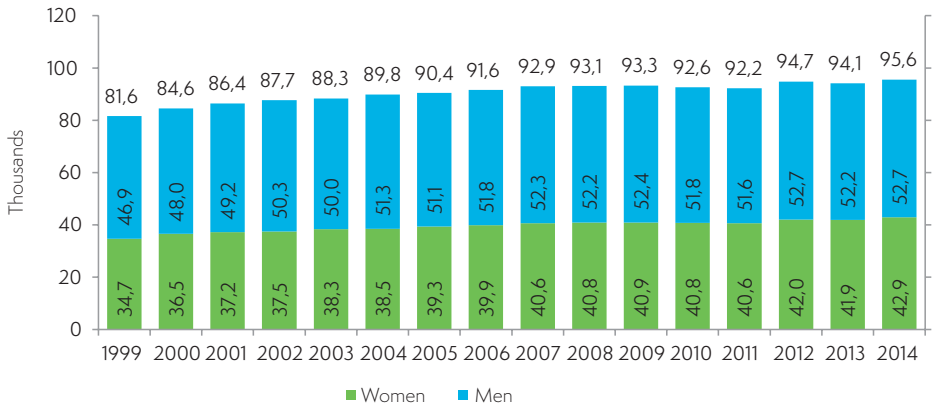

Chart 15 Annual number of deaths from cancer in Poland
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

Every year over 90 thousand people die of cancer in Poland. **In 1999–2014, 1 million 450 thousand people died in total. This figure represents a population corresponding to all inhabitants of Kraków and Łódź** (10)- just as if both those cities with all their inhabitants were erased from the map of Poland within these 15 years.

In the absolute numbers, the number of deaths increases. In 1999, 82 thousand cases were noted, while in 2014 this number was 17% higher. What is important, the number of deaths increased by nearly 24% for women, and by slightly above 12% for men.

Fifteen most common groups of cancer are responsible for 78% of all deaths from cancer in Poland.

Bronchial and lung cancer is still the main cause of death from cancer. Nearly 4 thousand more people died of this group of diseases in 2014 than in 1999. However, although it can be said that the number of deaths remained at a similar level for men (15.8 thousand in 2014 vs. 15.5 thousand in 1999) with a simultaneous reduction in the standardised mortality rate by 26%, for women both those parameters increased dramatically. In women, bronchial and lung cancer was responsible for 3.6 thousand deaths in 1999 and for as many as 7.3 thousand deaths in 2014, and the standardised mortality rate rose by nearly 60% (from 11.5 in 1999 to 18.0 in 2014). Due to this increase in the number of deaths by over 100%, bronchial and lung cancer became the main cause of death from cancer in women, overtaking breast cancer in this tragic list.

Despite wide-scale actions, the mortality rate for breast cancer remains high. The fact that the standardised mortality rate for this cancer did not increase can be viewed with moderate optimism.

In 2014, in nearly each of 15 groups of cancer characterised by the highest mortality rate an increase in the number of deaths was observed. The few exceptions include stomach cancer, for which the number of deaths was nearly 750 lower in 2014 than in 1999, hepatic and cervical cancer (240 deaths less), or laryngeal cancer (nearly 130 patients less died).

A reduction in the number of deaths from cervical cancer is a real success. The standardised mortality rate for this cancer amounted to 6.4 deaths/100 thousand inhabitants in 1999, and 4.5 deaths/100 thousand inhabitants in 2014, representing nearly a 30% improvement. This success results from an extensive programme of cytological examinations and diagnosing cancer at its early stages, providing an opportunity to undertake effective treatment.

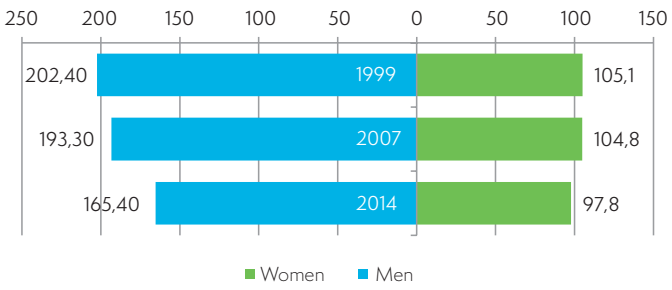

Chart 16 Standardised cancer mortality rates
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

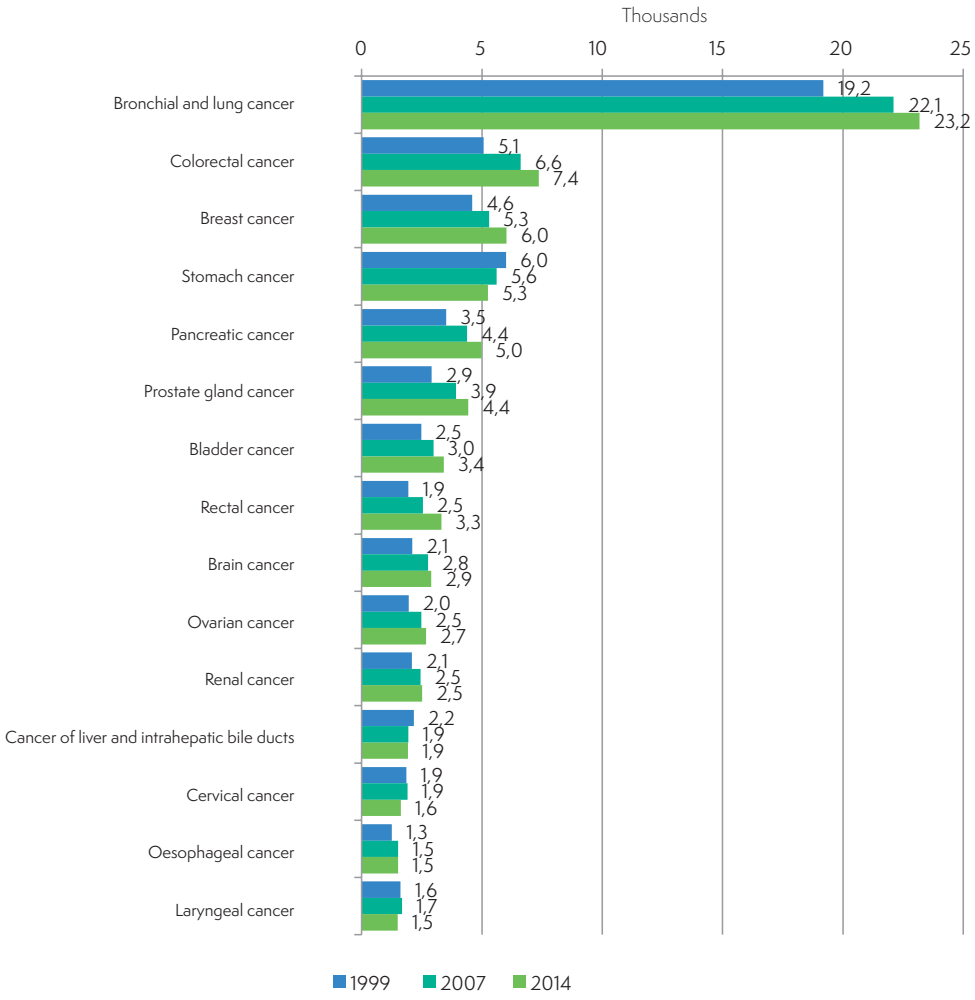

Chart 17 The number of deaths from cancer for 15 cancers characterised by the highest mortality rate in 2014, and in selected previous years
Source: Reports based on the Oncology Centre data, http://85.128.14.124/krn/

Cancer and the national economy

Premature deaths from cancer are a problem that affects not only patients and their families, health care or social care systems. This is also a significant challenge to our national economy resulting from lost productivity of these people.

> The value of unproduced GDP for one year by people who died of cancer in 2014 amounts to nearly 900 million zloty, and this corresponds to all funds collected by the Great Orchestra of Christmas Charity during the last 25 years.

However, the loss resulting from productivity of people who died of cancer should be evaluated from the point of view of their entire expected economically active life.

Considering:

- the number of deaths from cancer in 2014;
- the age structure;
- sex;
- a period of the economic activity between 20 and 60 years of age for women and 20 and 65 years of age for men, and assuming the constant value of GDP per capita as recorded in 2015 throughout their economic activity, it can be assumed that the value of GDP lost due to premature deaths of people who died in 2014 was over 8 billion zloty. In the variant of the analysis considering the average annual growth in GDP at the level of 3% throughout the analysed period, the value of GDP lost amounts to nearly 11 billion zloty. This lost value of work of people who died prematurely in 2014 throughout their expected economically active life represents from 0.5% to 0.6% GDP produced in our country in 2015.

The above analysis does not consider economic costs related to absenteeism, i.e. absence from work of those who are ill. It also does not consider economic costs associated with reduced productivity of families, supporting cancer patients during the disease. Therefore, it should be emphasised that the total costs of cancer for the economy of our country are significantly higher than those presented above.

Thus, an earlier cancer diagnosis, increasing treatment effectiveness, and providing wide groups of patients with access to effective therapies should be of importance not only for patients and doctors, but also for the Minister of Development, as cancer is and will remain one of the components having a negative effect on development

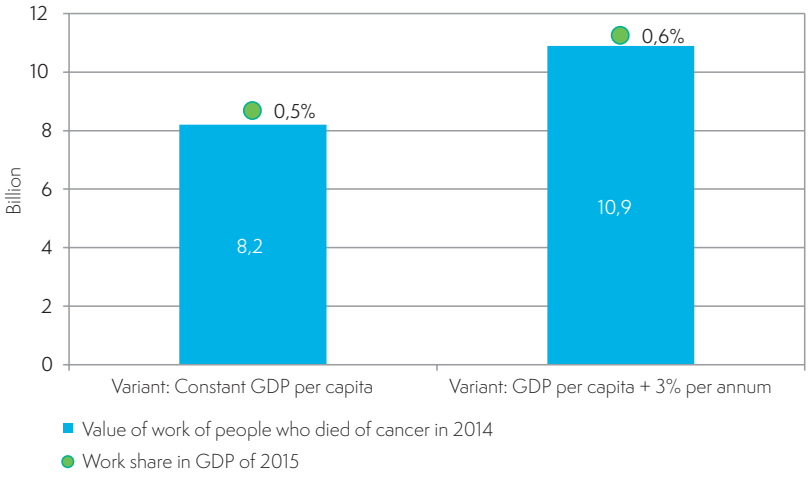

Chart 18 Analysis of the value of GDP lost due to premature deaths from cancer in 2014
Source: Own analysis based on KRN and GUS data

opportunities for our economy. The financial resources allocated to health care and cancer treatment should therefore be treated as an investment whose outcomes are measurable also from an economic point of view. In oncology, the progress in effectiveness of cancer treatment results mainly from early diagnosis, better diagnostic methods, and access to safe and effective therapies, improving chances for patient survival and healing.

Access to innovative cancer drugs in Poland

Summary of the chapter

- Recent years have brought about a rapid progress in knowledge on pathomechanisms underlying each cancer, and on cancer as such, and this contributed to many new drugs and new therapies launched onto the market.
- Public expenditures on drugs in Poland are the lowest in Europe. When calculated per capita, our expenditures on drugs are low when compared not only with large countries in Western Europe (nearly 5.5 times less than in Germany and 4 times less than in France), but also with countries such as Hungary (2.3 times less) and Czech Republic (2.2 times less).
- In recent years, many new drugs from various therapeutic areas were included in the reimbursement system. Some of them were innovative drugs.
- The National Health Fund spends less than 10% of resources allocated to co-payment for drugs on reimbursement of innovative drugs. Expenditures on innovative cancer drugs are below 20% of the funds allocated to all new innovative therapies.
- Innovative cancer drugs are very expensive. Only a very small number of patients can pay their full price. Clinical studies are available to a narrow group of patients meeting the inclusion criteria for projects being currently in progress. Therefore, to provide access to cancer drugs for a wide group of patients, they must be included in the reimbursement system.
- Only some (less than 50%) of new drugs registered for oncology indications in Europe after 2004 were included in the reimbursement system in Poland.
- Frequently, several years pass between registering a drug in Europe and providing access to it to the Polish patients. Many causes contribute to this delay, and they are attributable to decision makers in the reimbursement system in Poland, companies owning individual medicines, and to procedures defined in the system alike.
- Contracting procedures, and, in particular, the freedom the individual NFZ Branches have in deciding about dates for announcing tenders for providing services under new treatment programmes may lead to a situation where in some voivodeships patients already have access to treatment, while in others it is still unavailable, and this implies a discrimination due to a place of residence/treatment.
- In Poland, cancer patients have access to a lower number of therapeutic options for the majority of analysed cancers than specified in current American and European guidelines. Additionally, for the majority of drugs, limitations are introduced at a level of provisions governing the reimbursement system (in particular, criteria for qualification to treatment programmes), and in consequence a drug can only be used in selected groups of patients and only at specific stages of the therapeutic process – frequently this group is narrower than specified in the recommendations. Only 20–30% of safe and effective innovative drugs are available in Poland in accordance with recommendations of the international scientific societies.

Financing of innovative oncology therapies in Poland

Cancer therapies are very expensive.

Cancer drugs, particularly the latest ones, helping to combat cancer in patients with specific genetic mutations (targeted therapies) or used in cancer immunotherapies, are effective but so expensive that an average patient cannot afford financing treatment even with one drug using their own financial resources – and such therapy is usually combined and long-term.

In general, in Poland treatment of a patient with safe and effective drugs can be financed through four main mechanisms:

- treatment under the public health care system;
- support of non-governmental organisations which use obtained funds to finance treatment of patients under their care;
- with own financial resources (however, due to the cost of therapy, this option is available only to a very limited number of patients);
- patient participation in clinical studies (an option available only to selected groups of patients, according to research needs of clinical trials conducted at a specific moment, and only in a few selected centres).

	Average official sales price, PLN
Crisantaspase	14 580
Crizotinib	26 018
Lanreotide	4 014
Lenalidomide	17 261
Nivolumab	4 472
Obinutuzumab	16 408
Olaparib	21 172
Paclitaxelum albuminatum	1 241
Pembrolizumab	8 047
Pertuzumab	12 096
Rituximab	7 824
Ruxolitinib	15 588
Temsirolimus	3 909
Trastuzumab	7 290
Vismodegib	20 241

Table 2 An average official sales price calculated as a mean of official sales prices for all packages of a drug according to the announcement 2017-01 (cancer drugs covered by the reimbursement from July 2016 to January 2017)

Public health care system

For any cancer patient in Poland, the basic therapeutic path leads through services financed from public resources by the National Health Fund. For the vast majority of patients, access to cancer drugs, and particularly, to new therapies is only possible when they are financed by the public payer.

Public expenditures on drugs in Poland, that is those financed by NFZ, belong to the lowest in Europe, and are relatively low amongst the OECD countries, both when expressed at their nominal value and in relation to GDP.

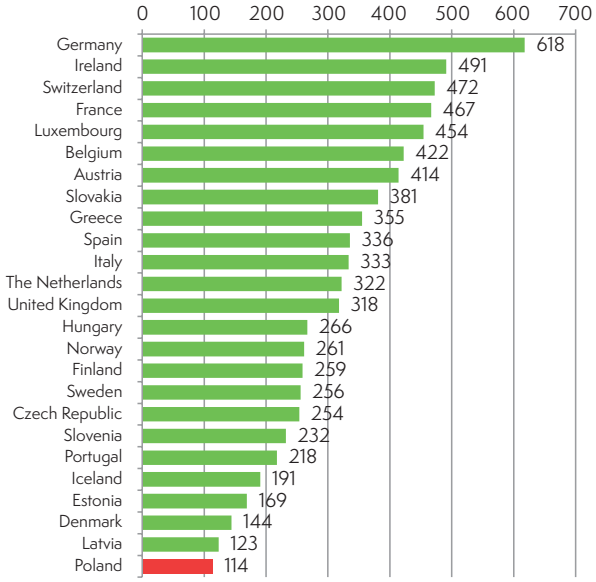

Chart 19 Public expenditures (government and from an obligatory health insurance system) on drugs and other perishable medical goods in European OECD countries per capita in 2014, USD PPP (expressed as U.S. dollars, with purchase power parity considered)
Source: OECD Health Statistics 2016;

Drugs are financed by NFZ through several financing channels:

- financing by reimbursement of drug costs in the following reimbursement availability categories:
  - prescription drugs available at a pharmacy;
  - drugs used under a treatment programme;
  - drugs used for chemotherapy;
- financing by settlement of hospital services under Uniform Patient Groups (UPGs) – drugs that patients receive during their stay at a hospital, but excluding drugs available to a patient under the Chemotherapy Catalogue or treatment programmes.

In 2015, expenditures on pharmaceutical products settled under UPGs reached the level of ca. 1.5 billion zloty. However, from the cancer patients' point of view, they are of lesser significance, because cancer therapies, particularly modern ones, are mainly financed under treatment programmes.

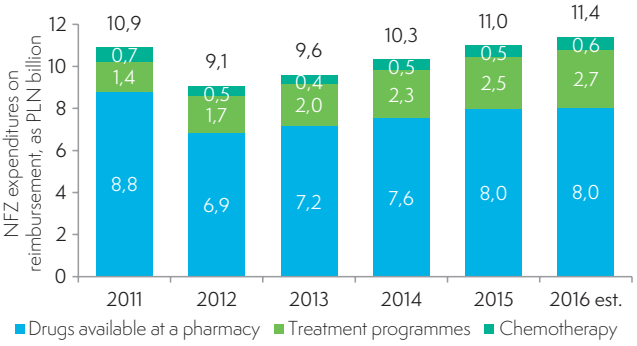

Chart 20 NFZ expenditures on reimbursement in 2011-2016
Source: Own analysis based on data published by NFZ

In 2015, expenditures on reimbursement reached a level of 11 billion zloty, for the first time exceeding the level from before the Reimbursement Act came into force. In 2016, they will possibly amount to ca. 11.4 billion zloty.

One of the main objectives of the Reimbursement Act introduced in 2012 was to increase access of Polish patients to safe and effective therapies. This was to be reflected by introducing new drugs to the reimbursement system. However, not all drugs introduced as new into the reimbursement system can be included in the innovative drugs category. New drugs in individual categories include drugs previously reimbursed through a different financing channel (e.g. drugs transferred to reimbursed channels from a non-standard chemotherapy programme) or drugs in the case of which their original producer failed in its efforts to obtain reimbursement, and only their less expensive generic drugs, introduced onto the market when patent protection for their reference drugs expired, obtained a consent for reimbursement from public funds.

Reimbursement expenditures on innovative therapies1 increase, but still they represent less than 10% of NFZ reimbursement expenditures.

In 2015, expenditures on innovative cancer drugs represented less than 20% of the total NFZ expenditures on innovative drugs. The list below clearly shows that **the main financing channel for this group of drug therapies are treatment programmes.**

[1] Innovative therapies (original, innovative, or reference drug) – the first drug with a new active substance launched onto the market and granted marketing authorisation due to its therapeutic efficacy, quality and safety documented on the basis of clinical studies, versus other products used for the same indication.

million PLN	2012		2013		2014		2015		2016	
	implementation		implementation		implementation		implementation		implementation, July 2016	
total reimbursement budget, including:	**9 062**		**9 592**		**10 317**		**11 011**		**6 505**	
reimbursed new original active substances	14	0,2%	118	1,2%	354	3,4%	593	5,4%	490	7,5%
expanding reimbursement indications of original drugs	0	0,0%	18	0,2%	71	0,7%	132	1,2%	90	1,4%
total	**14**	**0,2%**	**136**	**1,4%**	**425**	**4,1%**	**725**	**6,6%**	**580**	**8,9%**
leki stosowane w programach lekowych	**1 731**		**2 002**		**2 258**		**2 481**		**1 494**	
reimbursed new original active substances	0	0,0%	82	4,1%	230	10,2%	358	14,4%	345	23,1%
expanding reimbursement indications of original drugs	0	0,0%	8	0,4%	33	1,5%	77	3,1%	48	3,2%
total	**0**	**0,0%**	**90**	**4,5%**	**263**	**11,7%**	**435**	**17,5%**	**394**	**26,4%**
drugs used for chemotherapy	**468**		**406**		**508**		**542**		**330**	
reimbursed new original active substances	0	0,0%	0	0,0%	6	1,2%	17	3,2%	10	3,1%
expanding reimbursement indications of original drugs	0	0,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%
total	**0**	**0,0%**	**0**	**0,0%**	**6**	**1,2%**	**17**	**3,2%**	**10**	**3,1%**
reimbursement at pharmacies	**6 863**		**7 184**		**7 551**		**7 988**		**4 682**	
reimbursed new original active substances	14	0,2%	36	0,5%	117	1,6%	218	2,7%	135	2,9%
rozszerzenie wskazań refundacyjnych leków oryginalnych	0	0,0%	10	0,1%	38	0,5%	56	0,7%	42	0,9%
total	**14**	0,2%	**46**	**0,6%**	**155**	**2,1%**	**274**	**3,4%**	**176**	**3,8%**

Table 3 NFZ reimbursement expenditures on new innovative drugs
Source: PEX PharmaSequence own analysis based on data published by NFZ, an innovative drug status assigned to a product throughout the analysed period

It should also be mentioned that in the treatment of cancer patients, NFZ reimburses drugs that can be collectively called supportives in cancer therapies. In 2015, the cost of NFZ expenditures on financing new medicines in this group of products were below 40 million zloty, and in the period from January to July 2016, slightly above 13 million.

million PLN	2012	2013	2014	2015	up to July 2016
reimbursement at pharmacies	**0,1**	**2,5**	**2,1**	**3,5**	**2,8**
reimbursed new original active substances	0,1	2,5	2,1	3,5	2,8
expanding reimbursement indications of original drugs	0,0	0,0	0,0	0,0	0,0
drugs used for chemotherapy	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
reimbursed new original active substances	0,0	0,0	0,0	0,0	0,0
expanding reimbursement indications of original drugs	0,0	0,0	0,0	0,0	0,0
drugs used under treatment programmes	**0,0**	**25,3**	**88,5**	**134,5**	**94,2**
reimbursed new original active substances	0,0	17,6	58,6	71,4	48,3
expanding reimbursement indications of original drugs	0,0	7,7	30,0	63,1	46,0
Total	**0,15**	**27,79**	**90,67**	**137,99**	**97,12**
(share in NFZ expenditures on innovative drugs)	**1,05%**	**20,44%**	**21,33%**	**19,03%**	**16,75%**

Table 4 NFZ reimbursement expenditures on new innovative drugs used for cancer (excluding supportive drugs used in cancer therapies)
Source: PEX PharmaSequence own analysis based on data published by NFZ, an innovative drug status assigned to a product throughout the analysed period

Drugs issued to patients with reimbursement at pharmacies

Patients have extensive access to cancer drugs available at pharmacies. As they are used by patients themselves, they must be characterised by safety of therapy.

Drugs in "oncology classes" according to the international classification of medicinal products (ATC) are mainly:

- Alkylating agents [L01A].
- Antimetabolites [L01B].
- Plant alkaloids and other natural products [L01C].
- Cytotoxic antibiotics [L01D].
- Other antineoplastic agents [L01X].
- Hormones and related agents [L02A].
- Hormone antagonists and related agents [L02B].

In 2015, the NFZ costs of reimbursement of drugs from the above groups (class L01 and L02) reached nearly 280 million zloty.

In the period from July 2012 to November 2016, 8 oncology molecules became eligible for reimbursement at retail pharmacies. One molecule can be considered a new innovative drug introduced in reimbursement announcements under reimbursement at pharmacies.

Additionally, one of the introduced molecules (exemestan) can be considered as a new one in the reimbursement system, but the reimbursement covers only

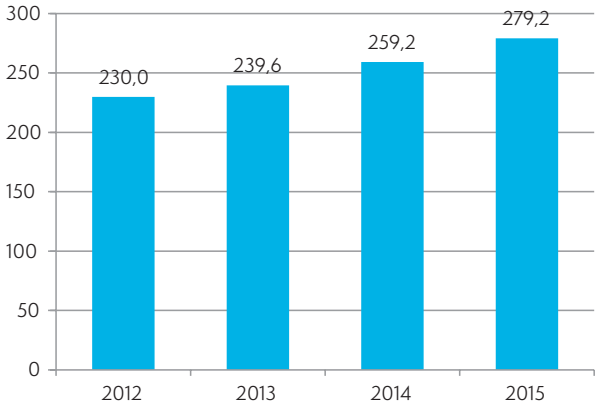

Chart 21 NFZ reimbursement value for medicines from L01 and L02 classes available at retail pharmacies.
Source: PEX PharmaSequence own study based on information on reimbursement of drugs in out-patient health care, published by NFZ

products being less expensive equivalents of the reference drug. Other molecules (triptorelinum, busulfanum, chlorambucilum, melphalanum, tioguaninum) were previously available in the chemotherapy catalogue, and cyclophosphamidum was included in reimbursement lists before the Reimbursement Act came into force (before 2012).

Announcement date	Molecule
Nov 2012	Degarelixum

Table 5 A list of new innovative cancer molecules introduced into the pharmacy reimbursement in 2012-2016
Source: Own study based on reimbursement announcements of the Minister of Health

Four new molecules used in supportive cancer therapy were also added to pharmacy reimbursement.

Additionally, zoledronic acid (acidum zoledronicum) was also covered by reimbursement, and it should be considered a new drug in the pharmacy reimbursement system, however, the formulation covered by reimbursement was also a generic drug.

Announcement date	Molecule
Nov 2014	Oxycodoni hydrochloridum + Naloxoni hydrochloridum
May 2014	Posaconazolum
March 2014	Lipegfilgrastimum

Table 6 A list of new innovative molecules used in supportive therapy introduced into the pharmacy reimbursement in 2012-2016
Source: Own study based on reimbursement announcements of the Minister of Health

Chemotherapy catalogue

Drugs from the chemotherapy catalogue are available to all patients diagnosed with cancer whose code is included in appendices to a reimbursement announcement in the list of cancer allocated to a given drug. The chemotherapy catalogue covers cancer therapies and supportive therapies. According to NFZ data, in 2015 nearly 127 thousand people used services associated with chemotherapy, and during the first half of 2016 that number reached 90 thousand.

In the period from July 2012 to November 2016, 23 molecules were added to the chemotherapy catalogue. Only 3 of these molecules are considered as new innovative drugs introduced into reimbursement announcement under the chemotherapy catalogue.

All the above molecules are classified as supportive cancer therapies.

Further 14 innovative molecules introduced into the chemotherapy catalogue during that period were previously reimbursed under other reimbursement financing channels or were transferred to the chemotherapy catalogue from a non-standard chemotherapy catalogue

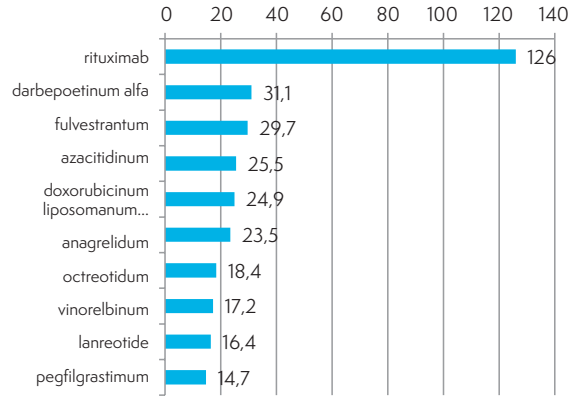

Chart 22 Top 10 active substances generating the highest costs within chemotherapy scopes in 2015 (PLN, million)
Source: A report on National Health Fund operations for 2015

(tioguaninum, melphalanum, chlorambucilum, busulfanum, clofarabinum, arsenicum trioxidum, arepitantum, bendamustinum, azacitidinum, anagrelidum, nelarbinum, brotezomib, denosumab, crisantaspasum). Four molecules introduced into the chemotherapy catalogue were new generic medicines (isotretinoinum, acidum zoledronicum, voriconazol, mitoxantron). The last 2 molecules were not new in the reimbursement system, and products that were added to the chemotherapy catalogue were equivalents of a reference drug (temozolamidum, imatinibum).

Announcement date	Molecule
May 2014	Posaconazolum
May 2014	Plerixaforum
March 2014	Lipegfilgrastimum

Table 7 A list of new innovative molecules added to the chemotherapy catalogue by the Ministry of Health from 2012 to November 2016.
Source: PEX PharmaSequence own study based on reimbursement announcements of the Minister of Health

Non-standard chemotherapy programme

A characteristic feature of the non-standard chemotherapy programme was a need to submit an individual application for a specific patient, and meeting the requirements specified in AOTMiT President's recommendation concerning a given medicinal product for a relevant indication.

Currently, as it is not possible to include new patients in the programme, this mechanism of access to the therapy is irrelevant from a point of view of new people diagnosed with cancer.

Year	Number of applications submitted	Number of approvals issued	Value of approvals (PLN)
2012	8 848	7 961	195 636 185
2013	6 536	5 960	159 748 253
2014	2 749	2 387	56 606 456
2015	793	790	19 403 573

Table 8 Access to drugs under a procedure "Treatment programme for non-standard chemotherapy"

During the last 2 years, only 2 groups of patients had access to non-standard chemotherapy (12):

- patients continuing therapies initiated before 1 January 2015 under a procedure "Treatment programme for non-standard chemotherapy" for a given drug, a relevant indication in a given patient;
- patients who received an approval for a non-standard chemotherapy for applications submitted at a voivodeship NFZ branch by 31 December 2014.

A number of approvals issued for individual molecules shows that only some individual patients used that channel of access to cancer drugs in 2015

Treatment programmes

Treatment programmes are a basic mechanism to provide patients with access to high-cost drug therapies. Descriptions of individual treatment programmes:

- define patient populations that can be covered by a given programme;
- specify criteria to be met by a patient to be provided treatment under a treatment programme;
- specify criteria that would result in excluding a patient from a programme should they occur, meaning that drug(s) they received under that programme would be discontinued.

Active substance	Number of approvals issued
Lenalidomide	155
Everolimus	148
Sorafenib	57
Erlotinib	57
Dasatinib	39
Cetuximabum	14
Sunitinib	25
Pazopanib	31
Bexarotene	43

Table 9 Substances responsible for the highest costs of non-standard chemotherapy together with the number of approvals issued, for 2015
Source: A report on National Health Fund operations for 2015

Coordinating teams, operating at NFZ, are established for some treatment programmes. A decision to include a patient in the programme is not made in that programme by a doctor in charge of that patient's case, but by team members (also on the basis of criteria defined in the programme).

NFZ financed treatment of patients under 22 cancer treatment programmes by the end of 2014, 23 programmes in 2015, and 21 programmes in the first half of 2016. A reduction in the number of cancer treatment programmes in 2016 results from moving molecules from treatment programmes to the chemotherapy catalogue (bendamustine for all reimbursed indications is financed under the chemotherapy catalogue since July 2015, bortezomib was transferred to the chemotherapy catalogue in September 2015).

The question that has remained unanswered to date is whether treatment programmes guarantee access to drugs to all patients that may benefit from a given therapy. Let us consider breast cancer. In 2014, nearly 17 thousand more new cases of cancers from this group were noted. Statistically, every fourth patient has cancer with overexpression of HER2 receptors, and this means that there were 4.3 thousand new patients of this type in 2014. The number of new patients who were alive in 2014, but became ill in 2012 and 2013 with HER2-positive cancer may reach 7.5 thousand. In total, for the years 2012–2014, the estimated number of patients that may require therapy under a treatment programme offering drugs against breast cancer with HER2 overexpression was 11.8 thousand. In 2015, only 5.1 thousand patients were treated under the treatment programme.

Name of treatment programme	2014	2015	First half of 2016
bexarotene treatment for mycosis fungoides or Sézary syndrome		61	63
bendamustine treatment for indolent non-Hodgkin lymphomas resistant to rituximab	130	94	
treatment for malignant lymphomas	1 908	2 119	1 417
treatment for patients with advanced ovarian cancer	389	653	543
dabrafenib treatment for skin melanoma		24	124
Ipilimumab treatment for skin or mucosal melanoma	97	262	159
treatment for skin melanoma	447	466	222
dasatinib treatment for acute lymphoblastic leukaemia with Philadelphia chromosome (Ph+)		50	48
treatment for brain glioma	309		
treatment for soft tissue sarcomas	161	232	164
treatment for essential thrombocytosis	930		
treatment for non-small-cell lung carcinoma	1 609	1 467	893
treatment for non-small-cell lung carcinoma with afatinib		45	85
treatment for gastrointestinal stromal tumours (GISTs)	786	921	874
treatment for castration-resistant prostate cancer	575	904	687
treatment for squamous cell carcinoma of head and neck organs combined with radiotherapy for locally advanced disease	57	60	45
treatment for chronic myeloid leukaemia	2 369	1 071	927
treatment for kidney cancer	2 218	2 333	1 892
treatment for breast cancer	4 558	5 112	3 880
treatment for hepatocellular carcinoma	238	291	212
treatment for plasma cell myeloma (multiple myeloma)	1 041	1 172	
treatment for well-differentiated pancreatic neuroendocrine tumour	52	67	47
treatment for advanced colorectal cancer	1 735	1 969	1 498
treatment for advanced stomach cancer	62	140	109
treatment for advanced dermatofibrosarcoma Protuberans (DFSP)	9		
lenalidomide in treatment of patients with resistant or recurrent multiple myeloma	873	1 208	919
Number of patients in cancer treatment programmes	20 553	20 721	14 808

Table 10 Number of patients included in cancer treatment programmes
Source: Own analysis based on the NFZ quarterly report on operations

In the period from July 2012 to November 2016, 25 molecules were introduced in the cancer treatment programmes. From this number, 12 molecules belong to a group of new innovative drugs.

The remaining 13 molecules were previously available to patients under a non-standard chemotherapy programme or in the chemotherapy catalogue (bexarotenum, ipilimumabum, lenalidomidum, bendamustinum, pazopanibum, bevacizumabum, cetuximabum, docetaxelum, erlotinibum, gefitynibum, panitumumabum, pemetreksedum, trabectedinum).

Announcement date	Molecule
Nov 2016	Crizotinib
Nov 2016	Temsirolimus
Sept 2016	Olaparib
July 2016	Obinutuzumab
July 2016	Pertuzumab
July 2016	Nivolumab
July 2016	Pembrolizumab
May 2016	Brentuximabum vedotinum
July 2015	Dabrafenib
Nov 2014	Afatinib
March 2014	Axitinibum
March 2013	Wemurafenib

Table 11 A list of new innovative drugs added to treatment programmes by the Ministry of Health from 2012 to November 2016.
Source: PEX PharmaSequence own study based on reimbursement announcements of the Minister of Health

Clinical studies

The role of clinical studies in the process of development of a new drug will be discussed in detail further below. This part of the study focuses on their role from the point of view of patients and their access to therapy.

Clinical studies are a research process involving patients or healthy volunteers. It is conducted in accordance with a precisely specified protocol, monitored by expert, specially trained health care personnel, supervised by people acting as a clinical study monitor. Strict adherence to the study protocol, including monitoring of patients' health using tests provided for in its course (whose scope is usually much more extensive than for a patient undergoing a standard therapy) and a multi-step supervision over the study ensure maximum safety of patients participating in the study.

From the patients' point of view, the most important are phase 2 and 3 studies, as ill people participate in them. It should be highlighted that participation in a clinical study is not a 100% guarantee that a patient will receive a new studied drug. To evaluate the actual efficacy of a drug, it is necessary to conduct a study using an alternate therapy, representing a reference for the studied drug. To simplify, it can be assumed that a half of patients in the study receive the new drug, and the other half receive the reference therapy. As the studies are conducted according to the "double blind trial", i.e. a doctor does not know what drug they give to a patient, and patient does not know what drug they receive, and it is not possible to say which patient is in which group – results are compared only at a level of a central entity conducting the study.

For a patient, participation in a clinical study may be a chance to undergo a therapy according to a completely new therapeutic regimen or an option for another stage of treatment when standard therapeutic options available under the health care system have already been exhausted. Frequently, this is the only chance for prolonging the life of patients at terminal stages, to whom an available register therapy or the reimbursement system cannot offer anything. As it was mentioned above, clinical studies require the monitoring of patients' health. In general, their scope is far more extensive than a scope of diagnostic tests and the number of contacts with a doctor foreseen in a standard therapeutic approach. Therefore, it can be assumed that a patient participating in a clinical study is offered a better standard of care.

In Poland, about 4% of cancer patients participate in clinical studies (12).

On average, in Poland about 70–80 patients participate in a study concerning one drug. When the total number of those in need is considered, this is a proverbial "drop in the ocean of needs". However, from a point of view of expenditures on treatment, clinical studies' contribution into financing of patients' treatment is disproportionally large, as usually they involve the latest therapies. According to estimations for 2014, the actual value of treatment financed from the budget for clinical studies could have reached as much as 600 million zloty, corresponding to about 11% of the total NFZ budget for oncology (12).

However, it is not that easy to take advantage of the treatment options offered by clinical studies.

First, knowledge about studies conducted in Poland is not well disseminated between doctors and patients. This information, to a limited extent, is published at generally accessible websites – http://www.badaniaklinicznewpolsce.pl/baza-badan-klinicznych/, https://pto.med.pl/badania_kliniczne. However, in many cases the published information does not include contact data. Thus, doctors cannot contact a research centre to confirm that their patient meets the inclusion criteria of a given programme and to agree options for transferring that patient under the care of the research centre. Lack of contact data also prevents patients who are actively seeking therapeutic options from contacting such centres on their own.

Secondly, not every person willing to participate in clinical studies can be enrolled into them. A candidate for a clinical study must meet the inclusion criteria and cannot meet exclusion criteria. Both groups of criteria are precisely defined for each study and – although the final decision is made by a study doctor – yet when any factors limiting participation occur in a patient, this practically excludes their participation in the study.

Clinical studies are very expensive. Therefore, the number of patients participating in a study is precisely defined. When a specified number of patients is reached during recruitment into a study, qualification of new participants is stopped, and in practice this path is closed for any new patients.

Should clinical studies be treated as a method for cancer treatment? Due to a limited number of patients they cannot replace health care financed from public resources. As clinical studies are conducted for specific needs, it cannot be guaranteed that a patient with a specific type of cancer will find in Poland a study concerning their disease, as such study may simply not be conducted.

Therefore, although in some diseases clinical studies may be the only chance for a patient to have access to an effective therapy, they must be considered an interesting option for a narrow group of patients, but they should never be considered as a significant component in the system providing access to cancer treatment. From the patients' point of view, such access must be ensured by a public payer cooperating with pharmaceutical companies – suppliers of drugs.

Non--governmental organisations

In general, it is possible to finance from public resources new drug therapies included in the reimbursement system. Treatment as a part of clinical studies is possible when studies on a specific medicinal product that has not yet received a marketing authorisation as a drug to be used in patients, or which expands a scope of its registration (indication) or safety control. **Between these two situations there is also a group of reasons, due to which a new drug that could be effective in the treatment of a patient is not available to them:**

- **a drug is available in other countries in the world, its position in a therapeutic process may be well established, as proved by including it in guidelines for doctors developed for specific types of cancer, but it is not registered in Poland;**
- **a drug is registered in Poland, but is not included in the reimbursement system with a decision on reimbursement of the Minister of Health, therefore a patient wishing to use it would have to cover full costs of the therapy (and usually they cannot afford this);**
- **a drug is included in the reimbursement system, but a patient does not meet the criteria for inclusion in the treatment programme, and thus they cannot receive a therapy using drugs included in therapeutic regimes of the programme under the reimbursement system.**

Frequently in this situation the only option for a patient to receive treatment with a drug that may be a drug of "last resort" to them is to obtain private financing for their therapy.

As it was mentioned above, treatment with new cancer drugs is very expensive. Therefore, patients' own funds or funds they can obtain from their families are usually insufficient to cover the costs of the entire therapy.

For several years now, the needs of these patients have been met by non-governmental organisations. Many foundations operating within areas associated with cancer obtain financial resources from 1% of the personal income tax (PIT) scheme or by organising collections from other donors, and then use them to finance therapies for patients under their care. However, due to available resources, this assistance cannot be very common.

No analyses are available which present a scale at which patient therapies are co-financed by all non-governmental organisations in Poland. No information is also available at a national level showing which therapies were co-financed. Therefore, situations described below are only a few examples that authors of this study were able to find.

Under the "Skarbonka" (Money-box) programme maintained by the Alivia Foundation, 510 people in total have applied for financial assistance since 2010. In 2016 alone, financial assistance provided to patients by the Foundation amounted to PLN 3 million. These resources were used to purchase drugs, to pay for consultations, diagnostics, cost of travel to treatment centres, of accommodation near a treatment centre, rehabilitation equipment and medical devices (13).

In 2015, the "Rak'n'Roll – Wygraj Życie" Foundation helped its 36 charges to collect nearly 1 million zloty for their fight with cancer. From the beginning of its operations, over 100 patients have received support from the Foundation (14).

The "Na Ratunek Dzieciom z Chorobą Nowotworową" Foundation ("Help for Children with Cancer") financed costs of young patients' treatment abroad, including in Italy, Germany and the UK. The Foundation also purchased drugs required for treatment which were not reimbursed by NFZ (15).

The Professor Grzegorz Madej Memorial Foundation "Wygrajmy Zdrowie" ("Let's win our health" Foundation) provided nearly 120 thousand zloty for treatment of 11 patients in 2015 (16).

Under the programme "Pomoc Dzieciom z Chorobami Nowotworowymi i ich Rodzinom" ("Help for Children with Cancer and their Families"), in 2015 the "Krwinka" ("Blood cell") Foundation provided financial support to its charges reimbursing drugs for children with cancer or haematologic diseases (17).

As it was mentioned above, similar programmes are maintained by other non-governmental organisations operating in the health care area. This activity supports patients that are not eligible for financing of their therapy from public funds. However, the number of patients that can be supported in their therapeutic process by non-governmental organisations are limited. To a considerable extent this limitation results from financial capacities of these organisations, as they depend on donors' charity. This specific "randomness" of financing does not guarantee maintaining the support on a stable level, and this may result in significant differences in the number of patients benefiting from support granted by an individual organisation each year.

Patients co-payment for cancer drugs at pharmacies

Patients can use many cancer drugs available to them at pharmacies. Some of these drugs have a direct effect on cancer therapy, some alleviate side effects associated with basic drugs, other are used to strengthen a patient's body, while others are used to treat other diseases of the patient. The analyses below are limited to groups of drugs belonging to the following classes according to WHO ATC classification:

- Alkylating agents [L01A].
- Antimetabolites [L01B].
- Plant alkaloids and other natural products [L01C].
- Cytotoxic antibiotics [L01D].
- Other antineoplastic agents [L01X].
- Hormones and related agents [L02A].
- Hormone antagonists and related agents [L02B].

The majority of drugs from the above groups available at pharmacies are covered by the reimbursement system, and thus available to patients against partial payment. The main dominant payment categories are "free of charge" and "flat rate", i.e. by default, a drug is available to a patient for free or at a flat rate price of PLN 3.20. However, specific conditions of the reimbursement system operating in Poland mean that not always "free of charge" means no payment, and "flat rate" a cost of PLN 3.20.

A default payment category is applicable up to a financing limit specified for a given therapy by the Minister of Health, according to algorithms provided in the Reimbursement Act. A patient buying a drug belonging to the "free of charge" category at a price equal to or below the financing limit will receive that drug for free. A patient buying a drug at a price higher than a financing limit specified for a given therapy will have to cover the difference between that drug price and the financing limit from their own resources.

The situation is even more complicated for drugs available to patients at a flat rate price. To determine the amount covered by the patient, additionally, a number of

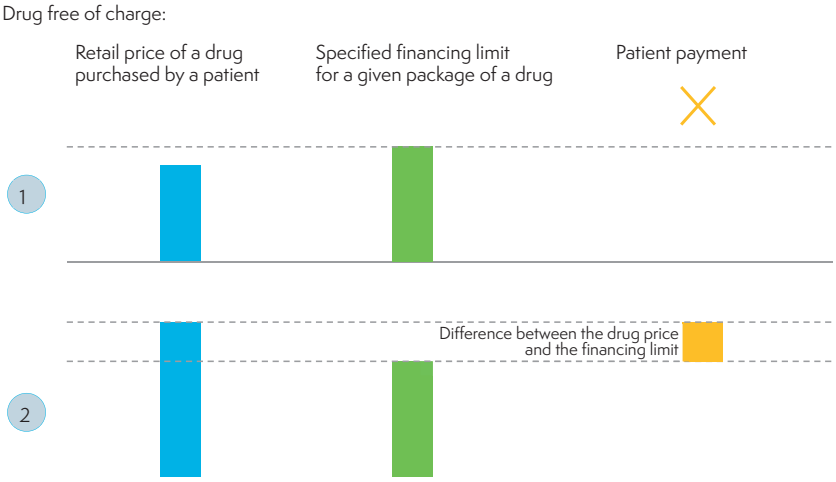

Chart 23 Rules for determining the amount paid by a patient for a reimbursed drug from the "free of charge" category
Source: PEX PharmaSequence own study.

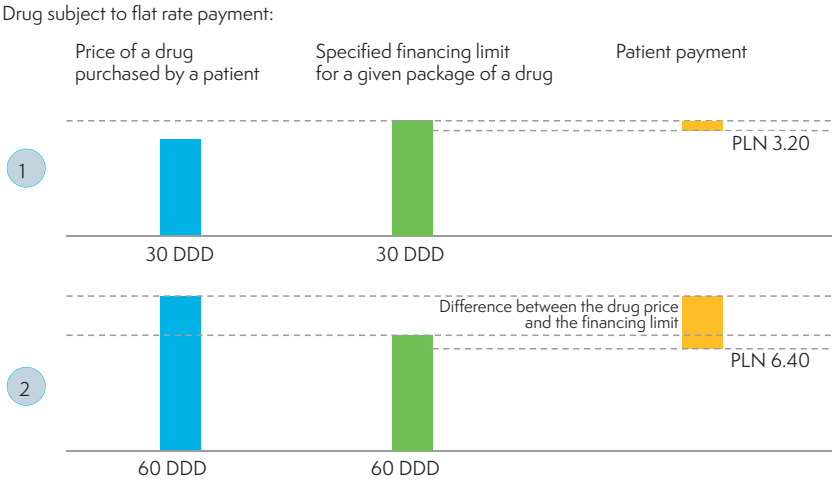

Chart 24 Rules for determining the amount paid by a patient for a reimbursed drug from the "flat rate" category
Source: PEX PharmaSequence own study.

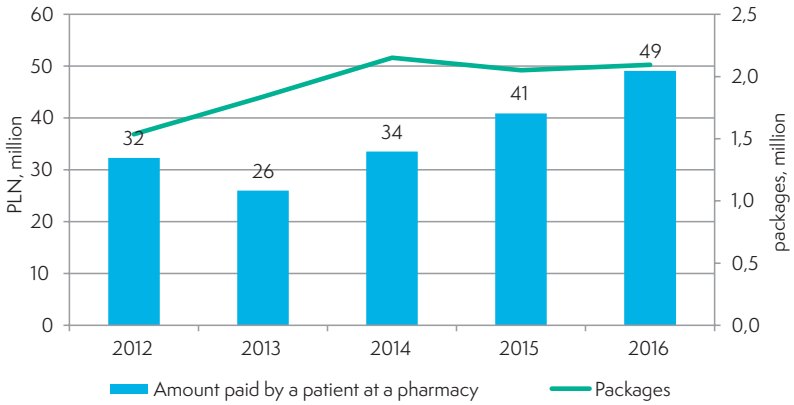

Chart 25 Evolution of amounts paid by patients and volumes for drugs from selected therapeutic classes
Source: PEX PharmaSequence sell-out data.

days of therapy for which a given package of drug is sufficient when used at a standard drug daily dose (DDD) specified by WHO are considered, and the flat rate payment increases proportionally following the relation between a number of therapy days in a given package and 30 days assumed in an algorithm of its calculation.

As shown in the diagrams above, the level of the financing limit significantly influences the amount paid by a patient. Mechanisms influencing that level will be discussed in more detail further below, however, we should mention here that they may result in abrupt reductions in that limit, and in consequence, the amount paid by a patient for a given medicine will increase, while the retail price of the drug used by the patient may remain the same.

The above rules influence the costs of therapy borne by patients for drugs from the analysed ATC classes purchased at pharmacies. An increase in the amounts covered by patients in 2014–2016 with a relatively stable sales volume (quantities of packages of drugs sold) is quite worrying.

To some extent, the observed increase is associated with filing at retail pharmacies of restricted prescriptions for new cancer drugs which are normally not available or available as part of in-patient health care. Despite their negligible volume, by covering the full price of drugs, the patients spent nearly 3.4 million zloty in 2016.

	Number of packages purchased at pharmacies in 2016
ABIRATERONUM	6
BEVACIZUMAB	95
BORTEZOMIB	111
CRIZOTINIB	8
DASATINIB	30
ENZALUTAMID	24
EVEROLIMUS	12
IMATINIBUM	53
IPILIMUMABUM	4
LAPATINIB	11
NILOTINIB	37
NIVOLUMAB	69
OLAPARIB	11
PANITUMUMAB	7
PAZOPANIBUM HYDROCHLORIDUM	39
PERTUZUMAB	2
REGORAFENIBUM	14
RUXOLITINIB	3
SORAFENIB	28
SUNITINIB	18
TRASTUZUMAB	62

Sales of innovative cancer drugs to patients at pharmacies in 2016, Source: Sell-out data (sales to patients in retail pharmacies) PEX PharmaSequence.

Processes associated with providing patients with access to a given drug

Nowadays, very rarely a new drug is discovered by accident. The vast majority of medicinal products are developed by painstaking work conducted by large numbers of scientists under research programmes aiming at providing doctors with means to fight a given disease. Those programmes may be conducted at laboratories of large pharmaceutical companies, laboratories operating at state universities, or at laboratories of small entities where a group of enthusiasts strives to find a solution to a scientific challenge. Increasingly often these activities are conducted as part of various forms of public private partnership (e.g. Innovative Medicines Initiative (18)), to use all available resources in the best way and to develop an effective drug as soon as possible.

On average, about 12 years passes between inventing a chemical (or biological) substance that may become a medicinal product in the future and its introduction into therapy standards or sets of drugs reimbursed by the state, and the costs associated with those works amount to ca. € 1 billion (19). During that time, the studied substance goes through specific stages (20), in general, consisting of:

- basic research;
- pre-clinical studies;
- clinical studies (phase 1, 2 and 3);
- process of approving the product for use in humans (drug registration);
- clinical studies (phase 4);
- process of including the drug in the reimbursement system.

Due to the nature of this study, the initial stages of this process will not be discussed in detail, however, they should be at least described in brief.

Basic research

At this stage of works, a chemical compound or a biological substance which is to be an effective tool combating a specific disease is isolated (or designed).

Pre-clinical studies

During pre-clinical studies tests are conducted under laboratory conditions to confirm whether a given substance is characterised by mechanisms having a desired therapeutic effect. Its physical and chemical parameters must also be confirmed, and its toxicity established. At this stage, the risk of passing a substance that may be harmful to humans to further studies must be minimised. As the studies must be conducted in conditions as close to those present in a human body as possible, works are conducted in vitro on cell lines, and on animals.

Of about 8 thousand substances being candidates for medicinal products, only about 5 substances pass through pre-clinical studies with a positive result (19).

Clinical studies (21)

Clinical studies are one of the crucial components of a process for developing a substance being a candidate for a medicinal product, and a process of deciding whether to make it available to patients – as a medicinal product – for a specific indication. The main aim of a clinical study is to confirm that a medicinal product provided to doctors and patients is safe and effective (12).

In general, four phases of clinical studies are distinguished. The number of subjects participating in individual phases of the study varies:

- phase 1 study: 50–100 healthy volunteers;
- phase 2 study: 300–600 patients suffering with a specific disease or ailments;
- phase 3 study: from about 1000 up to even several thousand patients;
- phase 4 study: studies conducted after a medicinal product was approved for use.

The aim of the phase 1 study is to verify the safety of a studied substance and to determine its doses. Usually, several dozens of healthy volunteers participate in the works. When studies on preparations used to treat cancer are conducted, in some cases phase 1 is combined with phase 2, so healthy volunteers are not exposed to very toxic substances.

Phase 2 studies aim at proving the efficacy of the substance in a specific group of patients and confirming its safety. At this stage, the efficacy of the new medicinal product is verified against placebo or against a medicinal product previously used to treat a given disease. To ensure the complete objectiveness of the results, usually the "double blind trial" method is used, as was already mentioned above. It should also be mentioned that phase 2 clinical studies also include the so-called "one-arm" clinical studies, without a control group, where all patients are treated with the same substance. When phase 2 demonstrates that benefits associated with the use of a given substance significantly exceed the risks resulting from its administration, then the substance can be passed to phase 3.

Phase 3 of clinical studies is to finally confirm the substance efficacy for a specific clinical indication. Groups consisting of several thousand to several dozen thousand patients, located in centres all over the world, participate in the study. Therefore, this phase of the clinical study is time-consuming (may take as long as several years) and requires significant financial expenditures. Similarly as in phase 2, "double blind trial" methods are typically used in this phase, and patients are randomly assigned to a group taking studied medicinal product or to a group taking a control formulation.

When clinical studies are discussed, phase 4 studies must also be mentioned, which are conducted after the drug receives a marketing authorisation. Their aim is to further monitor the efficacy and safety of the drug, as well as to evaluate possible side effects not identified in previous studies.

Drug registration

Research material collected at previous stages of the proceedings forms medicinal product documentation submitted to offices responsible for approving the substance for use. At the European level, an application for marketing authorisation is handled by the European Medicines Agency (EMA), and a marketing authorisation is granted by the European Commission. In Poland, these two operations are conducted by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. A substance approved by a relevant office becomes a medicinal product and can be used in humans to treat diseases and groups of patients indicated in the registration documentation.

From the patients' point of view, information about the registration of a new medicinal product for a disease from which they are suffering is good news, although their joy may be short-lived. Usually, new therapies are too expensive for a patient to finance from their own resources. Thus, a patient can only get access to that drug when it is covered by reimbursements by a payer for health care services – in Poland, in general, this is associated with introducing the medicinal product into the reimbursement system.

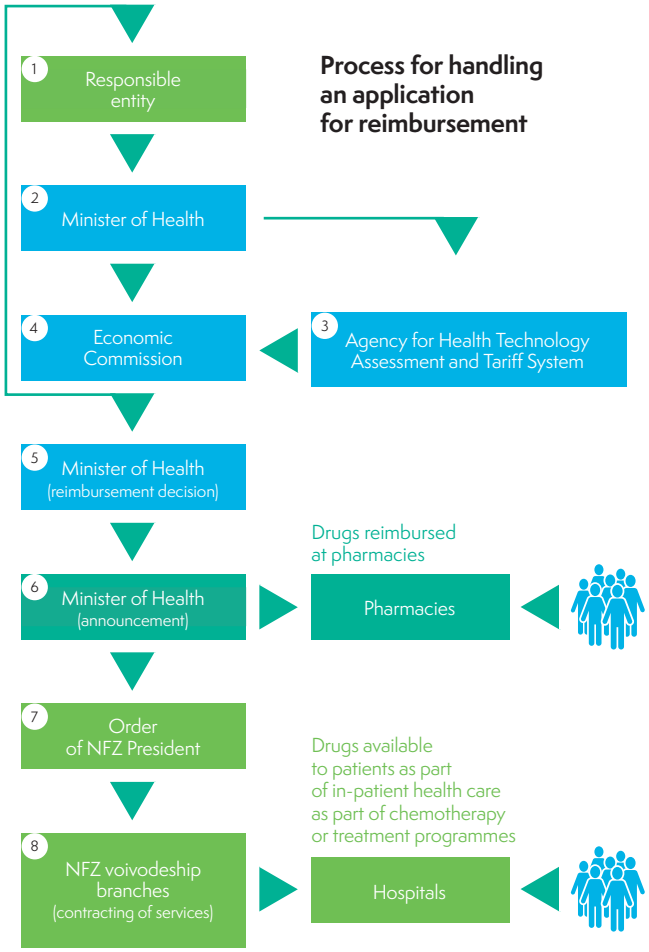

Chart 26 Simplified flowchart of a process of applying for including an innovative drug in the reimbursement system in Poland.
Source: Own study.

Including a drug in the reimbursement system

While procedures related to registration of a new therapy can be conducted at the European Union level and, following relevant administrative steps, patients in individual member states can be provided access to that drug automatically, the procedures associated with determining the level of co-financing from public funds for a given drug remain under control of individual states.

In many cases, including a drug in the reimbursement system means patients are provided with access to a new therapy. New drugs are simply too expensive for patients to pay for them themselves, or for a hospital to include a therapy with that drug under rates contracted for previously provided services. In Poland, decisions about including new therapies in the reimbursement system are made later than in other European countries. For this reason, this study will focus on the reimbursement processes in more detail.

From 1 January 2012, the provisions of the Act on Reimbursement of Medicines, Foodstuffs for Particular Nutritional Purposes and Medical Devices of 12 May 2011 came into force in Poland (22). This Act defines the stages of proceedings to include a product in the reimbursement system, and roles of individual entities in this process.

The chart below presents the main stages of the process of applying for reimbursement for a new drug.

Re 1–2. Responsible entity ▶ Minister of Health: submitting an application for reimbursement

A process for including a drug in the reimbursement system is initiated by an entity owning rights to that drug in Poland or holding a relevant authorisation granted by an owner of such rights. A pharmaceutical company, after preparing required documents, submitting a relevant application and paying fees required by the law, initiates proceedings to include the drug in a programme of reimbursement from public funds. There are many declared reasons why a pharmaceutical company may delay initiation of proceedings to include its new product in the reimbursement system in Poland. The most important ones include those associated with the price, a risk of parallel export and unprofitability of initiating the process due to a small population of patients in which a given drug can be used.

Regardless of the reasons, the situations related to delaying the introduction of a given product onto the market or delaying the application for including it in the reimbursement system are not good from the patients' point of view. However, the Reimbursement Act includes mechanisms allowing addressing at least some of them effectively – risk sharing agreements (23). This mechanism was initially foreseen for other purposes; however, it allows to maintain a high official price with simultaneous significant reduction in the price effectively paid by a payer.

A specific case, already mentioned above, are drugs used for rare and ultra-rare diseases, and for those for some types of cancer. Frequently, these therapies are very expensive and they cannot meet cost the effectiveness criteria established in the Reimbursement Act, that is, they exceed the "cost-effectiveness threshold".

The cost-effectiveness threshold is a result of calculations, showing that for income of our country (expressed as GDP) the maximum cost of a new therapy to be associated with achieving a unit health effect (1 LYG – one life year gained or 1 QALY – one quality-adjusted life year gained) versus therapies already available should not exceed three times the GDP (gross domestic product) per capita. The cost-effectiveness threshold estimated for 2016 was PLN 125,995 (3 x PLN 41,985) (24). It should be mentioned here that the ratio of costs to health effects does not estimate or determine the quality of life, but only allows estimating and selecting on this basis a therapy ensuring the best possible use of currently available financial resources (24).

Coming back to the process of handling the reimbursement application it should also be mentioned that at the first stage the application is verified against formal requirements, and any deficiencies found may stop the entire process at this stage.

Re 2-3. Minister of Health ▶ Agency for Health Technology Assessment and Tariff System: recommendation of the Agency President concerning the inclusion of a drug in the reimbursement system

Without undue delay, the Minister of Health passes the complete set of documents together with the submitted application to the Agency for Health Technology Assessment and Tariff System (AOTMiT), and within 60 days the Agency President sis obliged to present a recommendation concerning the inclusion of the drug in the reimbursement system.

The Agency conducts a verification during which it:

- ▶ evaluates the analyses attached to the submitted application;
- ▶ presents recommendations from other countries concerning the reimbursement of the analysed drug, analyses grounds and detailed conditions for including it in the reimbursement system;
- ▶ specifies a threshold price for the drug at which the "cost-effectiveness threshold", mentioned above, is met.

On the basis of the conducted analyses, the Transparency Board at AOTMiT issues its opinion on including the drug in the reimbursement system. The opinion, together with the verification, forms a basis for a recommen-

dation issued by the Agency President. Multiple stages of this process are to ensure that the opinion issued about the drug is objective and independent, and considers only substantial criteria.

When the role of the Agency and its recommendation in the reimbursement process is discussed, it should be emphasised that they are not binding for the Minister of Health. This approach seems to be justified, as changes may occur at successive stages of the proceedings (e.g. during discussions with the Economic Commission, a pharmaceutical company may decide to adjust a price of the drug), which, should that be known to the Agency during its works, could have a considerable influence resulting in a different recommendation.

It should also be noted that the process of evaluation of the application for reimbursement at the Agency for Health Technology Assessment and Tariff System is the only stage in the entire process of handling the reimbursement application whose details are available to any interested person in the Public Information Bulletin of the Agency. It provides dates on which orders from the Minister of Health for drug evaluation related to submitted reimbursement applications were received, together with the relevant documentation attached (excluding information which constitutes the company secret of the applicant), a verification conducted by the Agency and recommendations prepared by the Transparency Board and by the Agency President.

Re 4. Economic Commission: negotiations with a marketing authorisation holder

The AOTMiT President's recommendation, together with the complete documentation, is then sent back to the Ministry of Health and is delivered to the Economic Commission.

The Economic Commission is an entity operating at the Minister of Health, and its tasks include negotiations with applicants concerning:

- determining an official sales price – i.e. a price at which a pharmaceutical company may sell its product in Poland when it is included in the reimbursement system;
- reimbursement level – this is one of the factors determining the amount paid for that drug by a patient in a pharmacy;
- specifying indications when the drug is to be reimbursed – i.e. for which diseases a patient can receive a drug with reimbursement (when used to treat diseases not specified as covered by reimbursement, the patient must pay the full price of a drug);
- establishing risk sharing instruments – i.e. the use of tools described in the Reimbursement Act to secure the payer for drugs – the National Health Fund – against excessively high costs of drug reimbursement (as it was mentioned before, these mechanisms also allow to maintain a high official price of a drug while reducing its effective price, and thus a pharmaceutical company can hide an effective price from regulatory bodies in other European markets).

Negotiations conducted by the Economic Commission are difficult and responsible. On one hand, the Commission must act as the guardian of public money allocated to health care purposes and ensure these resources are used in the best way possible (when expenditures on reimbursement of a given drug are high, this may have a potentially negative effect on the NFZ budget and result in lack of funds for other health care services), while on the other it must consider the best interest of Polish patients – when the Commission expectations cannot be met by a pharmaceutical company, it will withdraw from negotiations and its medicinal product will not be available to patients who could otherwise benefit from using it.

In the entire process, the above-mentioned balancing of payer (NFZ), patients and pharmaceutical companies' interests is one of the crucial elements decisive for providing Polish patients with access to new therapies. When the payer's interests prevail during negotiations, and in discussions financial arguments significantly overweight the substantial benefits for patients associated with use of the medicinal product then it is difficult to reach a consensus representing an advantageous solution for both parties to the negotiations, and to patients.

For this reason, any attempts aiming at increasing the transparency of a negotiation process conducted by the Economic Commission should be encouraged. These include changes resulting from the regulation introduced by the Minister of Health on 28 January 2016 (30), changing the rules of the Commission's functioning and including:

- a need to develop a negotiation strategy before negotiations are initiated and obliging the Commission negotiation teams to implement it;
- a duty to provide grounds for resolutions passed by the Commission, previously not required, and which was frequently mentioned by pharmaceutical companies.

Re 5. Minister of Health: issuing the reimbursement decision

When the negotiations are completed, the Economic Commission presents their results to the Minister of Health. It is the Minister who makes the final decision about including the product in the reimbursement system. The positive conclusion of the process of handling the reimbursement application is confirmed with a reimbursement decision issued by the Minister of Health to a marketing authorisation holder.

According to Article 11 of the Reimbursement Act, the reimbursement decision contains:

- reimbursement availability category, and for drugs that will be available under treatment programmes - a programme description;
- level of patients' co-payment for the drug;

- official sales price;
- date of coming into force and term of the reimbursement decision;
- when specified, description of agreed risk-sharing instruments;
- specification of the limit group.

Some of components forming the decision proved impractical from the patients' and the payer point of view. An example of that component is the description of a treatment programme included in the decision. To introduce a new drug into a treatment programme, current legislation requires amendments to decisions issued for all drugs that have been in that program so far. Entities holding issued decisions may, but do not have to, agree to such an amendment. Lack of their consent makes amendments in the programme records impossible, and the new drug cannot be used in it.

Re 6. Minister of Health: publication of the announcement

Issuing of the reimbursement decision does not mean that the drug can be reimbursed. The decision must be made public. It is done through the publication of newly issued and already valid reimbursement decisions in announcements published by the Minister of Health. From January 2012, such announcements have been published regularly every 2 months. Regularity and frequency of announcement publications should be noted for two reasons:

- before the Reimbursement Act came into force, the Minister of Health was obliged to publish the reimbursement list every quarter, yet there were years when only one reimbursement list was published;
- as announcements are published every two months, patients can be sure that a new drug for which a reimbursement decision was issued will be available to them in the shortest time possible. With the current procedure for announcement publication, a drug that received a positive reimbursement decision in January of a given year, may be included in the announcement, and thus be reimbursed, already in March. When the announcements are published at longer intervals, the time between the decision and the announcement will be longer, and patients will have to wait longer for the drug (it should also be noted that publication in the announcement is not always tantamount to a drug being available to a patient, but this will be discussed further below).

The announcement is valid from the date of its coming into force to a date of publication of a new announcement. For drugs purchased at pharmacies, prices and distribution margins specified in the announcement are "fixed". This means that in every pharmacy in Poland during the term of a given reimbursement announcement a patient will pay exactly the same price for the same reimbursed drug. For drugs used in hospitals (drugs used for chemotherapy and drugs used in treatment programmes), unlike the rules adopted for pharmacies, prices and distribution margins provided in announcements are maximum ones (meaning that a hospital cannot purchase a drug at a price higher than specified in the announcement, but it can purchase it at a lower price following tender proceedings).

In 2016, patients, particularly those suffering from cancer, on several occasions were faced with significant changes in the amounts they had to pay for drugs purchased at pharmacies. This situation resulted not from an increase in the prices of drugs for which patients had to co-pay more after the announcement was amended, but from reductions in the prices of drugs from other manufacturers which, according to mechanisms provided in the Act, influenced the level of the financing limit, i.e. the amount to which the public payer (NFZ) covers part of the drug price.

The Act defines several mechanisms which, together with changes in drug prices, result in significant changes in amounts paid by patients. The most important of them include:

- an option for the Minister of Health to create limit groups consisting of drugs containing different active substances (molecules). Using formulas provided in the Act, a financing limit, that is the amount of reimbursement paid by NFZ, is calculated for such limit groups; when the limit group contains older drugs with a low price and their market share is large enough to determine the financing limit, then when new drugs, usually more expensive, are added to the same group, the specified NFZ reimbursement limit for these drugs will be low and patients will have to pay more for them;
- a pharmacy margin share in the amount representing the financing limit for a given drug may be different than a pharmacy margin share in a retail price of that drug. Changes in the amount paid for a drug by a patient resulting from the above situation are particularly visible in limit groups based on one molecule. To simplify, let us assume that in the discussed example the limit group contains only several packages of one drug, and individual packages differ significantly in a number of defined daily doses (DDD, i.e. standardised amount of an active substance in one packaging of that drug). When manufacturer's prices for individual packages are proportional to DDD and fixed, but the number of relevant packages of that drug sold in successive months changes – resulting in a change in the drug packaging on the basis of which the financing limit is calculated – then the amount paid by a patient will change. When the packaging being the basis for the limit changes from small to large, the patients will pay more for all drugs, and when the large package is changed to small, the patients will pay less for that drug;
- applying the "first equivalent" principle. The legislator's intent was to introduce a mechanism ensuring that when a second drug based on the same molecule (that is, the first equivalent of a drug being already included in the reimbursement system), the price is automatically decreased. Thus, a principle was implemented that a price of the first equivalent (not only in a "drug-drug", but also

in a "drug for indication" combination) should be lower by 25% from the price of the drug previously included in the list. Additionally, this drug automatically becomes the basis for the limit, and in the future, when a price of that drug is reduced, the financing limit will follow that change. This principle is very effective and, from the public finances point of view, it should be considered as well justified. However, from the patients' point of view, there is a problem, as other companies with their drugs in that limit group cannot foresee when such "first equivalent" will appear and what its price will be. Thus, they are not able to adjust their prices to the changing financing limit in advance, and this usually results in large and rapid changes in amounts paid by patients. As during the term of the announcement companies cannot sell drugs at prices other than those published in the announcement, for a period of two months the patients must pay larger amounts for all drugs included in a given limit group (what is important – for each drug, even those based on a different active substance);

- parameters considered in mathematical algorithms for calculating a financing limit are not publicly available, and thus companies cannot prepare simulations and make decisions about possible price adjustments in advance.

An algorithm used to determine the financing limit is based on two parameters:

- the number of drug packages reimbursed by NFZ for 3 months preceding the month for which the financing limits are calculated;
- prices of individual products.

However, the problem is that:

- data on quantities of reimbursed drugs are published by NFZ cumulatively (from the beginning of a year to the end of a given month), thus volumes in individual months can only be approximated;
- drug prices considered in calculations of the limit have not functioned publicly (that is, submitted proposals for changes in prices versus a current announcement), and combination of these two factors significantly hinders any forecasts for changes in the limit. It should be mentioned here that according to announcements from the Ministry of Health, it can be expected that published information about reimbursement will be limited solely to the reimbursement value. When this change is introduced for drugs reimbursed at pharmacies, precise adjustment of prices will be very difficult and, regardless of the market segment in which it is introduced, it will practically be impossible to verify the correctness of calculations made by the Ministry of Health.

As it can be seen from examples presented above, an amount paid for drugs by patients depends not only on pharmaceutical companies, but also on regulatory mechanisms created by the legislator. Using experience gained during 5 years of the Reimbursement Act being in force, it would be worthwhile to analyse cases of changes in prices most problematic to patients, and then amend the Act to minimise the risk of their recurrence in the future.

Re 7-8. Procedures at the National Health Fund level

Drugs that patients can receive at pharmacies are available to them on conditions specified in the announcement on the day of that announcement coming into force. However, for drugs available under chemotherapy or in treatment programmes, this situation is completely different. NFZ bodies must conduct additional activities for these drugs, including:

- changes in relevant orders made by the NFZ President, resulting in the introduction of new drugs/services to a catalogue of products contracted by NFZ;
- for new treatment programmes, conducting tender proceedings to select entities with which agreements for the implementation of new programmes will be signed.

Individual NFZ branches announce tenders for a new treatment programme at different times. In certain cases in some branches, tender proceedings must be repeated several times before healthcare providers are selected with whom an agreement for implementation of the treatment programme is concluded. It may also occur that a given branch decides against conducting tender proceedings due to lack of sufficient financial resources. In consequence of the above situations, patients in individual voivodeships have access to drugs at different times, and from a legal point of view this could be perceived as an example of inequality in access to treatment.

Only after passing the above stages at the level of NFZ branches and hospitals, drugs become available to patients. In general, drugs introduced into the chemotherapy catalogue and drugs added to the already existing treatment programmes are available earlier, while drugs available in new treatment programmes are available much later.

Patient access to innovative therapies

In recent years, great progress has been made in medical sciences. Nowadays, studies focus on the molecular structure of receptors. There are hundreds, or even thousands of them located on the membrane of an individual cell, forming a signalling system with which it communicates with its environment. Achievements of the molecular biology open previously unknown possibilities for determining causes of diseases. This way, researchers have been given powerful tools for development of new drugs.

Oncology medicine is one of the main beneficiaries of that progress. Developments in molecular biology have formed foundations for the creation of targeted therapies. An example of such a therapy are drugs used for breast and stomach cancers, destroying cancer cells with an excessive number (overexpression) of the human epidermal growth factor receptor 2 (HER2).

New medicinal products become available every year. From the beginning of 2004 to the beginning of December 2016, the European Commission authorised the introduction of 94 molecules for oncology indications into the market.

In the report "Access to innovative cancer drugs in Poland in comparison with selected European Union countries and Switzerland", prepared to the order of the Alivia Foundation at the beginning of 2015, the availability of 30 molecules which reached significant sales levels in the European markets, was evaluated. At that time, the analysis also indicated significant limitations versus other European countries, and in particular, versus countries of Western Europe.

Out of 30 molecules analysed, patients in Poland had access to only 18. In the Netherlands, Germany and Austria, all drugs were available, while at our southern neighbours, the Czech Republic, 23 products were available. The situation in Slovakia (17), Hungary (14) and Romania (11) was worse than in Poland.

Active substance	Evaluation of availability, as of Jan 2015
pemetrexed	available (reimbursed)
azacitidine	available (reimbursed)
cetuximab	available (reimbursed) with limitations
bevacizumab	available (reimbursed) with limitations
erlotinib	available (reimbursed) with limitations
sorafenib	available (reimbursed) with limitations
sunitinib	available (reimbursed) with limitations
dasatinib	available (reimbursed) with limitations
trabectedin	available (reimbursed) with limitations
nilotinib	available (reimbursed) with limitations
panitumumab	available (reimbursed) with limitations
lapatinib	available (reimbursed) with limitations
gefitinib	available (reimbursed) with limitations
everolimus	available (reimbursed) with limitations
pazopanib	available (reimbursed) with limitations
ipilimumab	available (reimbursed) with limitations
vemurafenib	available (reimbursed) with limitations
axitinib	available (reimbursed) with limitations
nab-paclitaxel	not available (not reimbursed)
cabazitaxel	not available (not reimbursed)
eribulin	not available (not reimbursed)
ruxolitinib (as phosphate)	not available (not reimbursed)
decitabine	not available (not reimbursed)
crizotinib	not available (not reimbursed)
brentuximab vedotin	not available (not reimbursed)
aflibercept	not available (not reimbursed)
pertuzumab	not available (not reimbursed)
dabrafenib	not available (not reimbursed)
regorafenib	not available (not reimbursed)
trastuzumab emtansine	not available (not reimbursed)

Table 12 A list of 30 drugs evaluated in January 2015 for their availability to Polish patients
Source: EY Polska, to the order of the Alivia Oncology Foundation, Access to innovative cancer drugs in Poland in comparison with selected European Union countries and Switzerland

Out of 18 molecules available to patients in Poland, only 2 were fully available, and for 16 of them the access was limited

From the perspective of January 2017, the information important from the patients' point of view is that 6 of 12 drugs not available at that time have been included in the reimbursement system.

- **nab-paclitaxel:** Pancreatic adenocarcinoma, Jan 2017, treatment programme;

- **ruxolitinib:** Primary myelofibrosis and secondary myelofibrosis in the course of polycythaemia vera and essential thrombocytosis, Jan 2017, treatment programme
- **crizotinib:** Non-small-cell lung carcinoma, Nov 2016, treatment programme;
- **brentuximab vedotin:** Resistant and recurrent forms of CD30+ lymphomas (Hodgkin lymphoma, other and unspecified T-cell lymphomas), May 2016, treatment programme;
- **pertuzumab:** Breast cancer, July 2016, treatment programme;
- **dabrafenib:** Skin melanoma, July 2015, treatment programme.

Less hopeful information for patients is that all these drugs were included in treatment programmes, under which, as a reimbursement financing channel, therapies are made available to populations of patients meeting specified criteria. In general, the adapted criteria significantly limit the group of patients in which a relevant drug can have an advantageous effect.

The table below presents a complete list of drugs authorised by the European Commission from 2004 to 2016, together with information about the availability of that drug to patients in Poland.

Of 94 molecules listed below:

- **Fifty molecules (over 53%) are not reimbursed in Poland for any oncology indications;**
- for 19 molecules (38% of non-reimbursed molecules), their manufacturers initiated actions aiming at including those products in the reimbursement system, as evidenced by orders for evaluation of applications for reimbursement submitted to the Agency for Health Technology Assessment and Tariff System;
- of 94 molecules, 32 (34%) are reimbursed under treatment programmes;
- of 94 molecules, 12 (13%) are available in the chemotherapy catalogue (pemetrexed included here is also reimbursed for another indication under a treatment programme);
- of 94 molecules, 1 (1%) is available at pharmacies.

Table 13 A list of new active substances granted marketing authorisation in the EU in 2004–2016 in oncology, together with their therapeutic areas, and therapeutic areas in which these products are reimbursed in Poland or were analysed by AOTMiT.
Source: Own study based on data published in the AOTMiT Public Information Bulletin, information on marketing authorisations published at EMA website, Minister of Health reimbursement announcement in force as of Jan 2017, report "Access to innovative cancer drugs in Poland in comparison with selected European Union countries and Switzerland", April 2015

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
ibritumomab tiuxetan	16/01/2004	Follicular lymphoma B-cell non-Hodgkin lymphoma (NHL)		(under the order 127/2014, 10 June 2014, AOTMiT verifying its removal from non-standard chemotherapy for non-Hodgkin lymphomas, negative recommendation 7 July 2014)	
fulvestrant	10/03/2004	Breast cancer	Breast cancer (Chemotherapy catalogue)		
cladribine	14/04/2004	Hairy cell leukaemia	Histiocytosis Follicular non-Hodgkin lymphoma Diffuse non-Hodgkin lymphoma Peripheral and skin T-cell lymphoma Other non-Hodgkin lymphomas Malignant immunoproliferative diseases Lymphocytic leukaemia Myeloid leukaemia Monocytic leukaemia (...) (Chemotherapy catalogue)		
bortezomib	26/04/2004	Multiple myeloma Mantle cell lymphoma	Multiple myeloma Plasma cell leukaemia Waldenstrom macroglobulinemia Other amyloidosis (Chemotherapy catalogue)		
mitotane	28/04/2004	Adrenocortical carcinoma (ACC)	Adrenal cancer Malignant neoplasm of other endocrine glands and related structures (Chemotherapy catalogue)		
cetuximab	29/06/2004	EGFR+ colorectal cancer Squamous cell carcinoma of head and neck	Colon cancer Squamous cell carcinoma of head and neck (Nov 2013) (treatment programme)		available (reimbursed) with limitations

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
pemetrexed	20/09/2004	Malignant pleural mesothelioma Non-small-cell lung carcinoma	Non-small-cell lung carcinoma (treatment programme) Pleural mesothelioma (chemotherapy catalogue)		available (reimbursed)
bevacizumab	12/01/2005	Colorectal cancer (MCRC) Breast cancer Non-small-cell lung carcinoma (NSCLC) Renal cell carcinoma Ovarian, fallopian tube or peritoneal cancer Cervical cancer	Colon cancer Ovarian cancer (March 2013) (treatment programmes)	110/2016, 28 April 2016, Cervical cancer, Negative recommendation, 8 July 2016	available (reimbursed) with limitations
erlotinib	19/09/2005	Non-small-cell lung carcinoma (NSCLC) Pancreatic cancer	Non-small-cell lung carcinoma (treatment programme)		available (reimbursed) with limitations
clofarabine	29/05/2006	Acute lymphoblastic leukaemia (ALL)	Acute lymphoblastic leukaemia (March 2013) Langerhans cell histiocytosis otherwise unclassified (Jan 2015) Acute myeloid leukaemia (Jan 2015) (Chemotherapy catalogue)		
sorafenib	19/07/2006	Hepatocellular carcinoma Renal cell carcinoma Differentiated thyroid carcinoma	Hepatocellular carcinoma Kidney cancer Gastrointestinal stromal tumours (GISTs) (Nov 2014) (treatment programmes)	280/2014, 9 Dec 2014, Thyroid cancer, Negative recommendation, 9 Feb 2015	available (reimbursed) with limitations
sunitinib	19/07/2006	Gastrointestinal stromal tumours (GISTs) Metastatic renal cell carcinoma Pancreatic neuroendocrine tumours	Gastrointestinal stromal tumours (GISTs) Kidney cancer Well-differentiated pancreatic neuroendocrine tumours (Nov 2013) Treatment for soft tissue sarcomas (Sept 2014) (treatment programmes)		available (reimbursed) with limitations
dasatinib	20/11/2006	Chronic myeloid leukaemia (CML) Ph+ acute lymphoblastic leukaemia (ALL PH+)	Chronic myeloid leukaemia Ph+ acute lymphoblastic leukaemia (Jan 2015) (treatment programmes)		available (reimbursed) with limitations
docetaxel	20/04/2007	Breast cancer Non-small-cell lung carcinoma Prostate cancer Gastric adenocarcinoma Cancer of head and neck	Use in numerous cancers (Chemotherapy catalogue)		
lenalidomide	14/06/2007	Multiple myeloma Myelodysplastic syndromes Mantle cell lymphoma	Multiple myeloma (treatment programme, Nov 2013, previously non-standard chemotherapy) Myelodysplastic syndromes (treatment programme, Jan 2017)	under an order 113/2014, 5 May 2014, AOTMiT verifying its removal from non-standard chemotherapy for diffuse non-Hodgkin lymphoma, positive recommendation 30 June 2014	
nelarabine	22/08/2007	T-cell acute lymphoblastic leukaemia T-cell lymphoblastic lymphoma	Acute lymphoblastic leukaemia Diffuse small-cell non-Hodgkin lymphoma Diffuse lymphoblastic non-Hodgkin lymphoma (chemotherapy catalogue, Jan 2015)		
trabectedin	17/09/2007	Soft tissue sarcoma Ovarian cancer	Soft tissue sarcomas (treatment programmes)		available (reimbursed) with limitations
nilotinib	19/11/2007	Ph+ chronic myeloid leukaemia (CML) in chronic phase	Chronic myeloid leukaemia (treatment programmes)		available (reimbursed) with limitations
temsirolimus	19/11/2007	Renal cell carcinoma Mantle cell lymphoma	Kidney cancer (Nov 2016) (treatment programmes)		
panitumumab	03/12/2007	Colorectal cancer without KRAS mutation (wild type)	Colorectal cancer (treatment programmes)		available (reimbursed) with limitations
nab-paclitaxel	11/01/2008	Breast cancer Pancreatic adenocarcinoma Non-small-cell lung carcinoma	Pancreatic adenocarcinoma (Jan 2017) (treatment programmes)		not available (not reimbursed)
thalidomide	16/04/2008	Multiple myeloma	-	082/2012, 20 Aug 2012, Multiple myeloma, Positive recommendation, 12 Nov 2012	
lapatinib	10/06/2008	HER2+ breast cancer	Breast cancer (treatment programmes)		available (reimbursed) with limitations

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
histamine dihydrochloride	07/10/2008	Acute myeloid leukaemia (AML)	---	---	
azacitidine	17/12/2008	Myelodysplastic syndrome (MDS) Chronic myelomonocytic leukaemia (CMML) Acute myeloid leukaemia (AML)	Myelodysplastic syndromes Acute myeloid leukaemia Chronic myelomonocytic leukaemia (chemotherapy catalogue, Nov 2013)		available (reimbursed)
degarelix	17/02/2009	Prostate cancer	Prostate cancer (pharmacy, Nov 2012)		
mifamurtide	06/03/2009	Osteosarcoma		058/2013, 7 April 2013, Osteosarcoma, Negative recommendation, 1 July 2013	
gefitinib	24/06/2009	EGFR+ non-small-cell lung carcinoma (NSCLC)	Non-small-cell lung carcinoma (treatment programme)		available (reimbursed) with limitations
topotecan	24/07/2009	Small-cell lung carcinoma (SCLC) Cervical cancer Ovarian cancer	Bronchial and lung cancer Ovarian cancer Malignant neoplasm of heart, mediastinum and pleura Malignant neoplasm of peripheral nerves and the autonomic nervous system Malignant neoplasm of connective tissue and other soft tissues Cervical cancer Adrenal cancer (Chemotherapy catalogue)		
everolimus	03/08/2009	HR+, HER2+ breast cancer Pancreatic neuroendocrine tumour Neuroendocrine tumours of gastrointestinal tract or lungs Renal cell carcinoma	Kidney cancer Pancreatic neuroendocrine tumour (Nov 2013) (treatment programmes)	105/2013, 8 May 2013, Breast cancer, Negative recommendation, 22 June 2013	available (reimbursed) with limitations
vinflunine	21/09/2009	Transitional cell carcinoma of the urinary tract			
ofatumumab	19/04/2010	Chronic lymphocytic leukaemia (CLL)			
pazopanib	14/06/2010	Renal cell carcinoma Soft tissue sarcomas	Kidney cancer (March 2013) Soft tissue sarcomas (March 2014) (treatment programmes)		available (reimbursed) with limitations
tegafur / gimeracil / oteracil	14/03/2011	Stomach cancer		023/2013, 20 Feb 2013, Stomach cancer, Negative recommendation, 27 May 2013	
cabazitaxel	17/03/2011	Prostate cancer			not available (not reimbursed)
eribulin	17/03/2011	Breast cancer Liposarcoma		112/2013, 15 May 2013, Breast cancer, Negative recommendation, 29 July 2013	not available (not reimbursed)
ipilimumab	13/07/2011	Melanoma	Skin or mucosal melanoma (treatment programme, March 2014)		available (reimbursed) with limitations
abiraterone acetate	05/09/2011	Prostate cancer	Prostate cancer (treatment programmes, Jan 2014)		
vandetanib	17/02/2012	Medullary thyroid cancer (MTC)			
vemurafenib	17/02/2012	BRAV-V600+ melanoma	Skin melanoma (treatment programme, March 2013)		available (reimbursed) with limitations
6-mercaptopurine monohydrate	09/03/2012	Acute lymphoblastic leukaemia (ALL)			
pixantrone dimaleate	10/05/2012	B-cell non-Hodgkin lymphoma (NHL)		149/2016, 10 June 2016, Malignant lymphoma, Negative recommendation, 26 Aug 2016	
ruxolitinib (as phosphate)	23/08/2012	Myelofibrosis	Primary myelofibrosis and secondary myelofibrosis in the course of polycythaemia vera and essential thrombocytosis (treatment programmes, Jan 2017)		not available (not reimbursed)
axitinib	03/09/2012	Renal cell carcinoma	Kidney cancer (treatment programmes, March 2014)		available (reimbursed) with limitations
decitabine	20/09/2012	Acute myeloid leukaemia (AML)			not available (not reimbursed)

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
crizotinib	23/10/2012	ALK+ non-small-cell lung carcinoma (NSCLC)	Non-small-cell lung carcinoma (treatment programmes, Nov 2016)		not available (not reimbursed)
brentuximab vedotin	25/10/2012	Hodgkin lymphoma (HL) Systemic anaplastic large cell lymphoma (sALCL)	Resistant and recurrent forms of CD30+ lymphomas (Hodgkin lymphoma, other and unspecified T-cell lymphomas) (treatment programmes, May 2016)		not available (not reimbursed)
aflibercept	01/02/2013	Colorectal cancer (MCRC)		068/2014, 20 March 2014, Colorectal cancer, Positive recommendation, 26 May 2014	not available (not reimbursed)
pertuzumab	04/03/2013	HER2+ breast cancer	Breast cancer (treatment programme, July 2016)		not available (not reimbursed)
bosutinib (as monohydrate)	27/03/2013	Ph+ chronic myeloid leukaemia (CML PH+)		194/2016, 21 Sept 2016, Chronic myeloid leukaemia (until 31 Jan 2017 without a recommendation of the AOTMiT President)	
enzalutamide	21/06/2013	Prostate cancer		222/2014, 9 Sept 2014, Prostate cancer, Partly positive recommendation, 24 Nov 2014 083/2015, 29 May 2015, Prostate cancer, Negative recommendation, 11 Aug 2015 008/2017, 5 Jan 2017, Prostate cancer, (until 31 Jan 2017 without a recommendation of the AOTMiT President)	
ponatinib	01/07/2013	Chronic myeloid leukaemia (CML) Ph+ acute lymphoblastic leukaemia (ALL PH+)		104/2016, 9 April 2016 Ph+ acute lymphoblastic leukaemia, Partly positive recommendation, 6 July 2016 134/2016, 19 May 2016, Acute lymphoblastic leukaemia, Partly positive recommendation, 5 Aug 2016	
vismodegib	12/07/2013	Basal cell carcinoma	Basal cell carcinoma (treatment programme, Jan 2017)		
pomalidomide	05/08/2013	Multiple myeloma			
dabrafenib	26/08/2013	BRAV-V600+ melanoma	Skin melanoma (treatment programme, July 2015)		not available (not reimbursed)
regorafenib	26/08/2013	Colon cancer Gastrointestinal stromal tumours (GISTs)		004/2015, 12 Jan 2015, Gastrointestinal stromal tumours (GIST), Negative recommendation, 23 March 2015 (in 2012 under the order 109/2012, 12 Nov 2012, AOTMiT analysed grounds for a consent to reimburse the medicinal product for colorectal cancer indications, Negative recommendation, 3 Dec 2012)	not available (not reimbursed)
afatinib	25/09/2013	EGFR+ non-small-cell lung carcinoma (NSCLC)	Non-small-cell lung carcinoma (treatment programmes, Nov 2014)		
radium Ra223 dichloride	13/11/2013	Prostate cancer		015/2015, 26 Jan 2015, Prostate cancer, Negative recommendation, 30 March 2015	
trastuzumab emtansine	15/11/2013	HER2+ breast cancer			not available (not reimbursed)
cabozantinib	21/03/2014	Medullary thyroid cancer (MTC)		53/2015, 27 March 2015, Medullary thyroid cancer, Negative recommendation, 8 June 2015	
siltuximab	22/05/2014	Castleman's disease			
trametinib	30/06/2014	BRAV-V600+ melanoma	---	115/2016, 5 May 2016, Melanoma, Negative recommendation, 22 July 2016	
obinutuzumab	23/07/2014	Chronic lymphocytic leukaemia (CLL) Follicular lymphoma (FL)	Chronic lymphocytic leukaemia (treatment programme, July 2016)		
idelalisib	18/09/2014	Chronic lymphocytic leukaemia (CLL) Follicular lymphoma (FL)			

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
ibrutinib	21/10/2014	Mantle cell lymphoma (MCL) Chronic lymphocytic leukaemia (CLL) Waldenstrom macroglobulinemia (WM)		056/2016, 22 Jan 2016, Chronic lymphocytic leukaemia, Negative recommendation, 11 April 2016 174/2016, 28 July 2016, Chronic lymphocytic leukaemia (until 31 Jan 2017, no documents on the AOTMiT website) 204/2016, 25 Oct 2016, Mantle cell lymphoma, Negative recommendation, 13 Jan 2017	
nintedanib	21/11/2014	Non-small-cell lung carcinoma (NSCLC)		131/2015, 22 Sept 2015, Non-small-cell lung carcinoma, Negative recommendation, 2 Feb 2016	
olaparib	16/12/2014	BRCA+ ovarian cancer BRCA+ fallopian tube cancer BRCA+ peritoneal cancer	Ovarian cancer Fallopian tube cancer Primary peritoneal cancer (treatment programmes Sept 2016)		
ramucirumab	19/12/2014	Stomach cancer Adenocarcinoma of the gastroesophageal junction Colorectal cancer Non-small-cell lung carcinoma (NSCLC)		132/2016, 17 May 2016, Stomach cancer, Negative recommendation, 13 July 2016	
ceritinib	06/05/2015	ALK+ non-small-cell lung carcinoma (NSCLC)			
lenvatinib mesylate	28/05/2015	Thyroid cancer			
nivolumab	19/06/2015	Melanoma Non-small-cell lung carcinoma (NSCLC) Renal cell carcinoma	Skin or mucosal melanoma (treatment programme, July 2016)	107/2016, 26 April 2016, Non-small-cell lung carcinoma, Negative recommendation, 12 July 2016 186/2016, 8 Sept 2016, Kidney cancer, Negative recommendation, 22 Nov 2016	
pembrolizumab	17/07/2015	Melanoma PD-L1 + non-small-cell lung carcinoma (NSCLC)	Skin or mucosal melanoma (treatment programme, July 2016)		
dinutuximab	14/08/2015	Neuroblastoma			
sonidegib diphosphate	14/08/2015	Basal cell carcinoma			
Panobinostat lactate anhydrous	28/08/2015	Multiple myeloma		146/2016, 8 June 2016, Multiple myeloma, Negative recommendation, 26 Aug 2016	
carfilzomib	19/11/2015	Multiple myeloma		-	
cobimetinib hemifumarate	20/11/2015	BRAV-V600+ melanoma		181/2016, 11 Aug 2016, Melanoma, Positive recommendation, 26 Oct 2016	
blinatumomab	23/11/2015	Ph acute lymphoblastic leukaemia (ALL Ph)		191/2016, 19 Sept 2016, Ph+ acute lymphoblastic leukaemia, Partly positive recommendation, 29 Nov 2016	
talimogene laherparepvec	16/12/2015	Melanoma			
asparaginase	14/01/2016	Acute lymphocytic leukaemia (ALL)			
pegaspargase	14/01/2016	Acute lymphoblastic leukaemia (ALL)	Lymphomas Leukaemias (incl. ALL) (Chemotherapy catalogue)		
osimertinib mesylate	02/02/2016	EGFR T790M+ non-small-cell lung carcinoma (NSCLC)			
necitumumab	15/02/2016	EGFR+ non-small-cell lung carcinoma (NSCLC)			
Dexamethasone (40mg)	16/03/2016	Multiple myeloma	(recommended dose is not reimbursed)		
trifluridine / tipiracil hydrochloride	25/04/2016	Colorectal cancer (MCRC)			
elotuzumab	11/05/2016	Multiple myeloma			
daratumumab	20/05/2016	Multiple myeloma			

Active substance	Date of marketing authorisation in EU	EMA registration indication	Reimbursement indication in Poland according to the announcement of Jan 2017 (financing channel, date of including in the reimbursement system)	When not reimbursed, if an order was placed with AOTMiT (order #, order date, indication, recommendation, recommendation date)	Evaluation of availability, as of Jan 2015, according to the "Access" report
lenvatinib mesilate	25/08/2016	Renal cell carcinoma			
cabozantinib s-malate	09/09/2016	Renal cell carcinoma			
irinotecan hydrochloride trihydrate	14/10/2016	Pancreatic adenocarcinoma	Numerous cancers, including pancreatic cancers (Chemotherapy catalogue)		
olaratumab	09/11/2016	Soft tissue sarcoma			
palbociclib	09/11/2016	HR+, HER2- breast cancer			
ixazomib citrate	21/11/2016	Multiple myeloma			
venetoclax	05/12/2016	Chronic lymphocytic leukaemia (CLL)			

When the above list is analysed, several issues are noted:

- for many drugs that received a marketing authorisation after December 2015 an order for an analysis of a reimbursement application was not sent to AOTMiT, and this may mean that Poland is not in the group of countries in which drug manufactures first apply for a marketing authorisation and for the inclusion in the reimbursement system of new cancer drugs;
- for a large group of drugs, in Poland a relevant indication was included in the reimbursement system many years after that drug was approved for use for that indication in the European market; for example, ruxolitinib was granted a marketing authorisation with a decision of 23 Aug 2012, but it was included in the reimbursement system in Poland only in January 2017, i.e. after 1592 days; however, although the drug was included in the reimbursement system in January, it does not mean that the first patient will receive the drug in that month (time in reimbursement processes will be discussed further below), thus the actual time of providing access to that therapy will be even longer;
- the great majority of new drugs is introduced into the reimbursement system on the basis of the reimbursement availability category "treatment programme"; in general, this category allows a regulatory body limiting a population of patients who can receive a given therapy (due to established criteria for inclusion in a programme), and this is advantageous from the Ministry of Health's point of view, as it allows controlling of NFZ reimbursement expenditures, but from the patients' point of view it is not a good solution, because it limits access to that therapy for some patients;
- in many cases a manufacturer submitted reimbursement applications in successive years for the same therapeutic indication, and only the nth application resulted in a positive reimbursement decision.

Some arguments used in the discussion about including new drugs in the reimbursement system claim that drugs for which applications are submitted do not have the required health effects. In the light of the last point above, the arguments concerning insufficient health effects appear difficult to prove, as is it possible for health effects achieved for the same medicinal product used for the same indication to differ significantly during the years in which successive applications are evaluated? It seems that it is not possible. The parameters most frequently changed in successive applications include: the size of the target patient population and a drug price, which definitely has a significant effect on savings in NFZ expenditures. Unfortunately, this is at the expense of patients who did not have access to that drug while successive applications were handled.

Time to providing access to innovative drugs

In a given disease, a new drug may be a breakthrough therapy which considerably prolongs a patient's life. Time is a commodity that cancer patients usually do not have – before a new drug is reimbursed in Poland, some patients will not live to benefit from a new therapy. Therefore, ensuring cancer patients' quick access to a new drug under the reimbursement system is of paramount importance. Thus, the analysis will now focus on the time in processes of including new drugs in the reimbursement system.

A pharmaceutical company (authorisation holder) decides about initiating a process for including the product in the reimbursement system. Due to numerous conditions, this decision can be deferred or even suspended. From the patients' point of view, this is a disadvantageous situation, because when the company defers its decision to launch its product onto the Polish market or to include it in the reimbursement system, this is the first component influencing the time in which that therapy will be available to a patient.

The reimbursement application cannot be submitted straight away. Polish legislation requires a manufacturer to provide a whole set of information and analyses to its reimbursement application. The list of required appendices includes:

- an analysis of a decisive problem;
- an analysis of clinical efficacy;
- an economic analysis;
- an analysis of an influence on the health care system;
- a rationalisation analysis.

These documents must meet requirements specified by the Minister of Health, and their content will be verified at the further stages by AOTMiT. Thus, they must represent a high level of competence, approach the discussed problem comprehensively, and be based on the latest knowledge in a given therapeutic area. Therefore, it takes many months to prepare such analyses. It is also relatively expensive, and in combination with fees for handling reimbursement applications, it may substantiate a decision not to submit a reimbursement application in the case of manufacturers of drugs used for rare or orphan diseases.

An analysis of time passing between the submission of a reimbursement application and the first reimbursement expenditures from NFZ can be conducted (with some limitations discussed below) on the basis of data available in the public domain.

The main source of information about a process for handling reimbursement applications is information provided on the website of the Agency for Health Technology Assessment and Tariff System (in its Public Information Bulletin), data in reimbursement announcements of the Minister of Health, and NFZ reports on its expenditures on reimbursement.

Precision of evaluation of individual process stages results from quality of data available at each source. For example, for parameters concerning expenditures on reimbursement, a date of reimbursement cannot be presented with precision higher than +/- 30 days, as these details are published cumulatively as monthly lists. Additionally, in the case of reimbursement expenditures, data can be adjusted. As reimbursement data is presented cumulatively, it is not possible to identify when the adjustment was made, as well as to assign it to a relevant month it concerned. These adjustments may appear with a considerable delay in relation to reported data, for example, adjustment of data for 2014 was published on the NFZ website on 24 June 2015, while adjustment of data for 2015 was published on 21 June 2016.

The process can be halted between its individual stages on request of the entity applying for reimbursement. This information is not always generally available – in practice, information about suspended processes is available only when the application is verified by AOTMiT.

Finally, one of the stages includes negotiations

between the Ministry and the authorisation holder. When their positions differ significantly, they may take many rounds, thus significantly influencing the process duration.

Therefore, the data provided below, concerning the duration of individual stages in the process of handling reimbursement applications, and in particular, the last stage of the process (from the announcement to making a payment) should be treated as estimates.

Number of submitted applications for reimbursement

When a completed application for including a drug in the reimbursement system is received, the Minister of Health, in accordance with provisions of the Reimbursement Act, should immediately provide that application to the Agency for Health Technology Assessment and Tariff System. For the needs of the analysis below we will assume that the date of receiving the Minister of Health's order for evaluation to be performed by the Agency, published on the AOTMiT website, is the same as the date of submitting the application for reimbursement, and all applications concerning products are transferred to the Agency.

The definition of an innovative drug according to the Reimbursement Act should be noted. Under the Reimbursement Act, an innovative drug should be understood as any drug that does not have its equivalent for a given indication in a reimbursement announcement in force as of a date of submitting the application. Therefore, it can be a drug based on a new, innovative molecule, as well as a drug being an equivalent of an innovative drug (a generic drug) when no application for reimbursement has been submitted for the innovative drug or it has not been included in the reimbursement system despite undertaken efforts.

The number of orders submitted by the Ministry of Health to the Agency reflects the activity of pharmaceutical companies concerning introduction of new products onto the Polish market. From the beginning of 2012, i.e. from changes in the system introduced in the Reimbursement Act, 397 applications for including drugs in the reimbursement system have been received by the Agency.

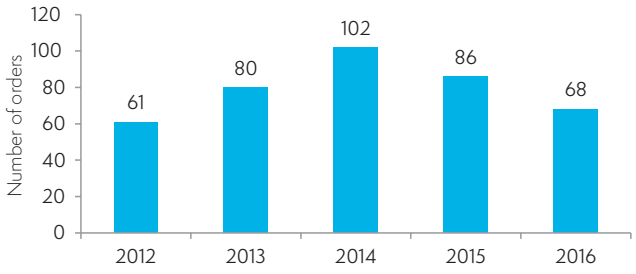

Chart 28 Number of orders by order year
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

As it can be seen in the chart above, the lowest number of applications for reimbursement of innovative products was received in 2012 – only 61. It is understandable, considering the fact that the new reimbursement rules for treatment programmes and chemotherapy came into force on 1 July 2012, and to that day introduction of new drugs in those reimbursement categories had been suspended. The number of applications rose in 2012–2014, and then in next 2 years it was considerably lower. In 2016, during which no significant events that could negatively affect decisions about initiating a reimbursement process were noted, the number of submitted applications was nearly at the same level as in 2012, and this corresponds to 1/3 drop versus 2014, when the number of applications was the highest.

The largest number of submitted applications concerned cancer – 108, i.e. over 27% of all applications.

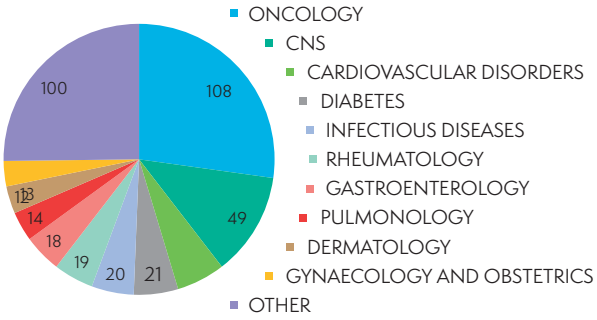

Chart 29 Number of orders by the rapeutic areas
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

Other areas, in which a significant number of reimbursement applications was placed included diseases of the nervous system (CNS), for which 49 applications were placed, cardiovascular disorders (23 applications), diabetes (21 applications), infectious diseases (20 applications), rheumatology (19 applications), gastroenterology (18 applications), pulmonology (14 applications), dermatology (13 applications) and gynaecology and obstetrics (12 applications).

As it was mentioned above, from 2012, as many as 108 applications have been placed for reimbursement of cancer products used for cancer.

The number of applications submitted in individual years was 18 (nearly 17% of all applications) in 2012, as many as 27 (about 25% of all applications) in 2013, and 21 (over 19%), 18 (about 17%) and 24 (about 22% of submitted applications) in 2014, 2015, and 2016, respectively.

However, it should be noted that some "oncology" reimbursement applications concerned transfer to the reimbursement system of drugs previously available under a non-standard chemotherapy programme.

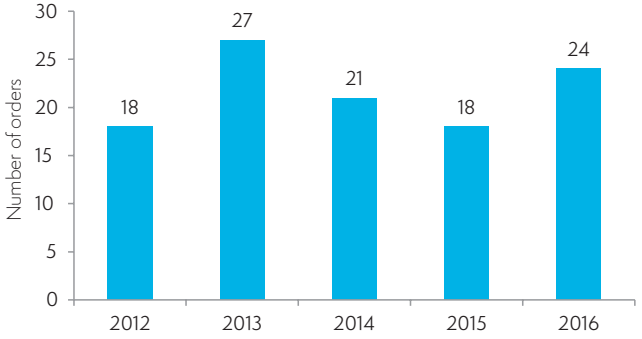

Chart 30 Number of orders for evaluation of products applying for reimbursement in cancer areas, by order year
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

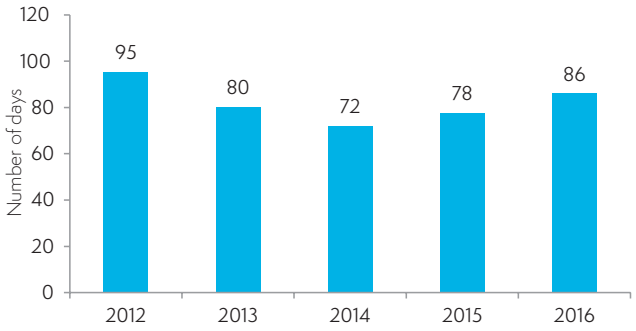

Chart 31 An average number of days from an order to the issuance of a recommendation by the AOTMiT President
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

The following drugs underwent such evaluation and were finally included in the reimbursement system:

- tocilizumabum, treatment programme, announcement in Jan 2013;
- pazopanibum, treatment programme, announcement in March 2013;
- arsenicum trioxidum, chemotherapy catalogue, announcement in March 2013;
- clofarabinum, chemotherapy catalogue, announcement in March 2013;
- bendamustinum hydrochloridum, chemotherapy catalogue, announcement in July 2013;
- bendamustinum hydrochloridum, treatment programme, announcement in July 2013 (from July 2015, the bendamustinum molecule is available only in chemotherapy);
- lenalidomide, treatment programme, announcement in Nov 2013;
- azacitidinum, chemotherapy catalogue, announcement in Nov 2013;
- abirateroni acetas, treatment programme, announcement in Jan 2014; ipilimumabum, treatment programme, announcement in March 2014;
- nelarbinum, chemotherapy catalogue, announcement in Jan 2015;
- bexarotenum, treatment programme, announcement in Jan 2015;
- crisantaspasum, chemotherapy catalogue, announcement in July 2016.

An average number of days from submission of an application by Ministry of Health to the issuance of a recommendation by the AOTMiT President

Under Article 35(8) of the Reimbursement Act, the Agency President provides a recommendation to a minister in charge of health issues no later than within 60 days of the order date.

In 2012–2014, the average time of handling an application for drug reimbursement by the Agency was shortened from 95 days to 72 days, i.e. by ca. 24%. This resulted probably from increased experience of pharmaceutical companies in preparing required documentation, as well as from increased skills in its evaluation of the Agency personnel. Unfortunately, in 2015–2016 that time increased again to 86 days, and this probably should be associated with other orders that the Agency had to perform at that time (pricing of services).

When statutory deadlines (60 days) and the result of the analysis are considered, it must be said that the average time exceeds that specified by the legislator. However, it should be noted here that no information is available concerning possible delays in proceedings resulting from a need to supplement materials provided by an entity applying for reimbursement, and this aspect, when considered in the analysis, may influence its result.

For cancer drugs, both a similar trend and a time needed by AOTMiT to handle applications are observed in successive years.

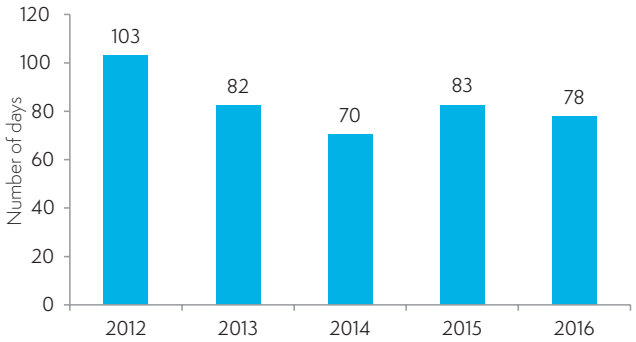

Chart 32 An average number of days from an order to the issuance of a recommendation by the AOTMiT President for products applying for reimbursement in the oncology area, by year of issuing a recommendation
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

Number of positive recommendations of the AOTMiT President

According to the Act, when preparing a recommendation, the AOTMiT President should consider an opinion of the Transparency Board. During the verification, the President should:

- decide whether that drug should be financed from public funds;
- specify detailed conditions for including the drug in the reimbursement system (medical indications for which that drug should be reimbursed, the level of patient's co-payment for the drug, a limit group into which that drug should be classified);
- address any comments or proposals concerning a structure of a treatment programme or recommended risk-sharing instruments that may appear during works conducted at the Agency;
- prepare grounds for their recommendation, under which they will:
  - list scientific evidence forming a basis for their decision and present a comparison of the evaluated drug against other, alternate therapies;
  - indicate and discuss clinical recommendations;
  - address a cost-effectiveness threshold specified in the Act and specify a price of a drug meeting that criterion;
  - evaluate the effect of the decision to reimburse the drug on NFZ expenditures.

As it can be seen from above information, the President's opinion should be a competent one, focusing on two areas:

- a competent, evidence-based evaluation of clinical efficacy of that drug;
- evaluation whether cost-effectiveness criteria are met and of their influence on expenditures.

In 2013–2016, during one month, the AOTMiT President issued about 7 recommendations for drugs for which reimbursement applications were submitted, on average. A reduction in the number of recommendations issued in 2015–2016 visible in the chart below results from a reduced number of orders for evaluation of applications for reimbursement of drugs submitted to the Agency.

In the same period, on average, less than 4 recommendations issued by the President were positive.

However, this average does not reflect a significant change that occurred at the beginning of 2015, when the number of positive recommendations in the period 2015–2016 dropped to about 1.5 recommendations a month. This situation was also reflected in the number of applications with a positive decision for cancer. In the analysed period, the Agency President issued 88 recommendations for cancer drugs.

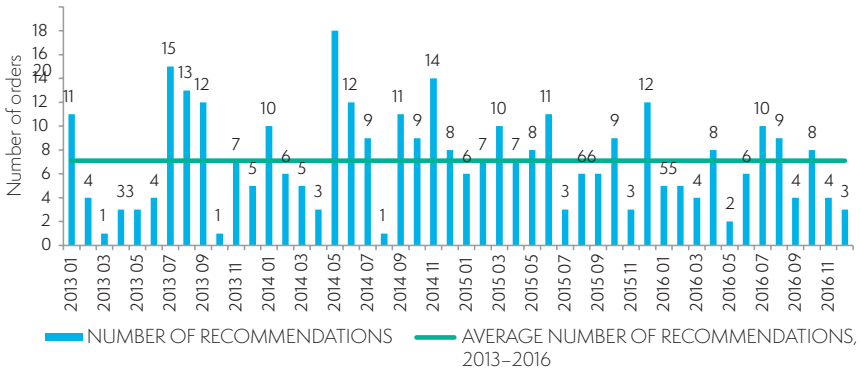

Chart 33 Number of the AOTMiT President recommendation, by month
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

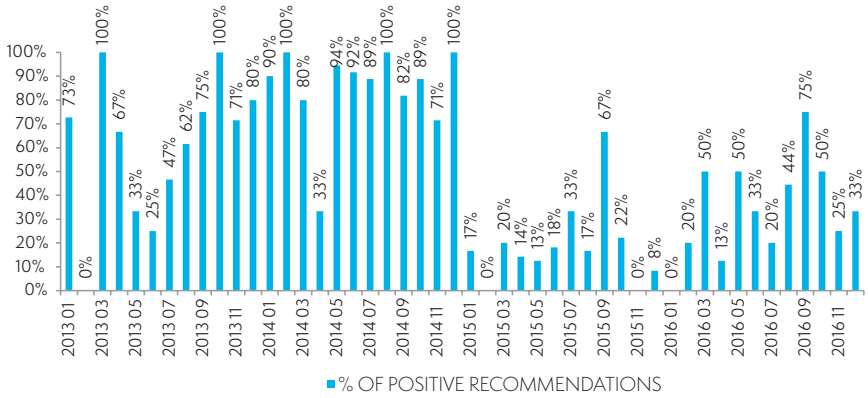

Chart 34 Share of positive recommendations of the AOTMiT President in the total number of recommendations, by month
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

The AOTMiT President issued 45 positive recommendations for cancer drugs, i.e. a slightly more than every second (51%) application was evaluated positively. However, a significant disproportion between 2013–2014 and 2015–2016 should be noted.

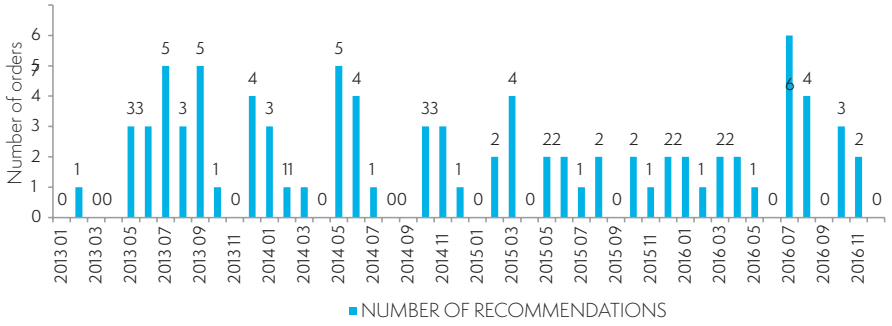

Chart 35 Number of the AOTMiT President recommendations for products applying for reimbursement in cancer areas, by month
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

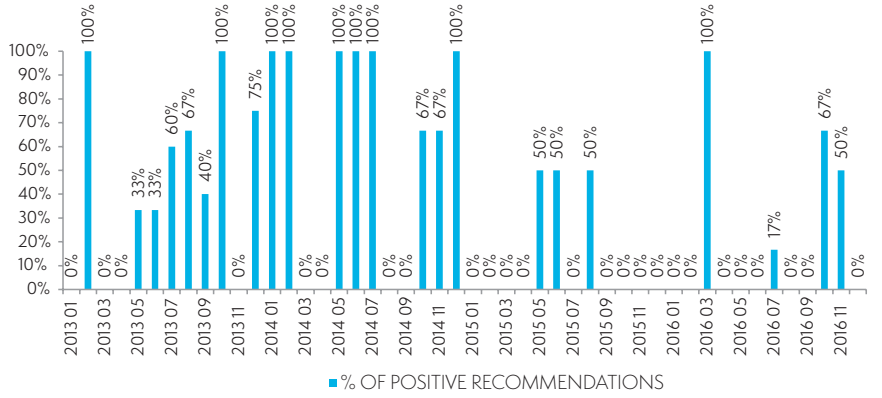

Chart 36 Number of positive recommendations of the AOTMiT President for products applying for reimbursement in cancer areas, by month
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin

Average number of days from a recommendation of the AOTMiT President to including a product in the reimbursement system

An indication for including the product in the reimbursement system is the date of coming into force of the first reimbursement announcement in which this new product was included. However, for that to happen, the application for reimbursement of a new drug must undergo further stages of the process at the Ministry of Health level. The first step are the price negotiations between an entity applying for reimbursement and the Economic Commission. At the next step, the Minister of Health becomes acquainted with the complete process documentation and makes a decision about issuing a reimbursement decision.

An issue rising concerns is the fact that the time from the issuance of the AOTMiT President's recommendation and the announcement gets extended.

In 2016, reimbursement decisions were issued for several products which received a recommendation of the AOTMiT President in previous years, so the process of handling the application at the Ministry of Health level took very long. As for analyses concerning the year, the long time during which products are kept in a kind of suspension included in the announcement burdens the years of 2016–2017. However, it should be mentioned that the time from the recommendation to the announcement may be influenced both by decisions made by the Minister of Health, and by an entity applying for reimbursement. Certainly, this time is also influenced by deadline for considering applications for including a product in the reimbursement system under treatment programmes. For these applications, the proceedings are prolonged by the time necessary to determine the contents of a treatment programme, where this time should not exceed 60 days.

According to the Reimbursement Act, an application for adding a product to the reimbursement system should be handled within 180 days, and when this date is prolonged due to determining of a treatment programme, within 240 days. In this light it should be assumed that deadline for considering applications is exceeded (however, there is no data showing how many proceedings were suspended on a company request). From the patient's point of view this situation is very disadvantageous, as their costs (financial or health) are transferred onto patients who

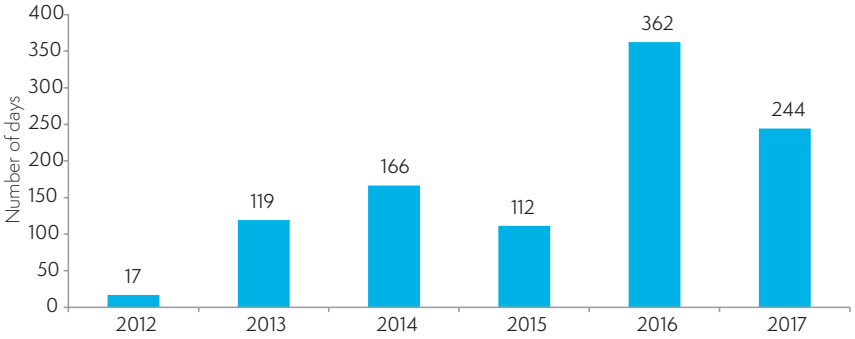

Chart 37 An average number of days from a recommendation of the AOTMiT President to publication in the Ministry of Health announcement, by year of including in the announcement
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin and dates at which the Minister of Health's reimbursement announcements came into force

do not have access to optimum treatment under the public health care system during that time.

From the first announcement that came into force on 1 January 2012, to the announcement that came into force on 1 January 2017, 64 new molecules were included in the reimbursement system as drugs available at pharmacies. From July 2012 to January 2017, 23 new drugs were added to the chemotherapy catalogue, while at the same time 57 new drugs appeared in treatment programmes. Of those new drugs included in the reimbursement system, 8 products were products used in cancer treatment (triptorelinum, degarelixum, busulfanum, chlorambucilum, melphalanum, tioguaninum, exemestanum, cyclophosphamidum), and 25 new drugs were added to the treatment programmes (crizotinibum, temsirolimusum, olaparibum, obinutuzumabum, pertuzumabum, nivolumabum, pembrolizumabum, brentuximabum vedotinum, dabrafenib, bexarotenum, afatinib, ipilimumabum, axitinibum, lenalidomidum, bendamustinum hydrochloridum, wemurafenib, pazopanibum, bevacizumabum, cetuximabum, docetaxelum, erlotinibum, gefitynibum, panitumumabum, pemetreksedum, trabectedinum).

For oncology molecules, time intervals that passed from the issuance of recommendation by the AOTMiT President to publication in the announcement were longer. In this respect, a difference for 2016 was 71 days, and for drugs included in the reimbursement system in January 2017 it was 89 days more, on average.

For cancer drugs, in 75% of cases a positive decision of the AOTMiT President resulted in including the product in the reimbursement system. In 38% cases of a negative opinion of the AOTMiT President, the Minister of Health was of a different opinion and the product was included in the reimbursement system. Concerning the above results, it should be remembered that no information is available publicly how many of proceedings that were not included in the announcements are in progress, and how many were definitely completed. Therefore, the above results should be treated as approximations.

Considering the dates for handling reimbursement applications at individual stages of the process provided above, and deadlines specified in the Reimbursement Act (180 days, with an option for increasing to 240 days when provisions of a treatment programme must be specified), it should be said that they are exceeded, yet both the government agencies and the entities applying for reimbursement may be responsible for reasons underlying this situation.

Average number of days from publication in the announcement to the appearance of NFZ expenditures

In general, a drug that was included in the reimbursement announcement can be named as available to specific populations of patients. However, in practice on a day of the reimbursement announcement coming into force, patients have access to reimbursed products only at retail pharmacies. For drugs available in the chemotherapy catalogue and in treatment programmes, NFZ must conduct additional activities that will allow hospitals to use new products (adding a drug to the products dictionary, publishing of necessary orders of the NFZ President, preparing tender proceedings for new treatment programmes). Due to all these actions, a few more months pass before a drug becomes available to a patient.

A month in which NFZ reimbursement expenditures appear may be approximately treated as the moment at which a new therapy became available. As it was mentioned before, for drugs to which patients have access under the reimbursement system at pharmacies, they are available from the moment a reimbursement announcement comes into force. Usually, the first expenditures

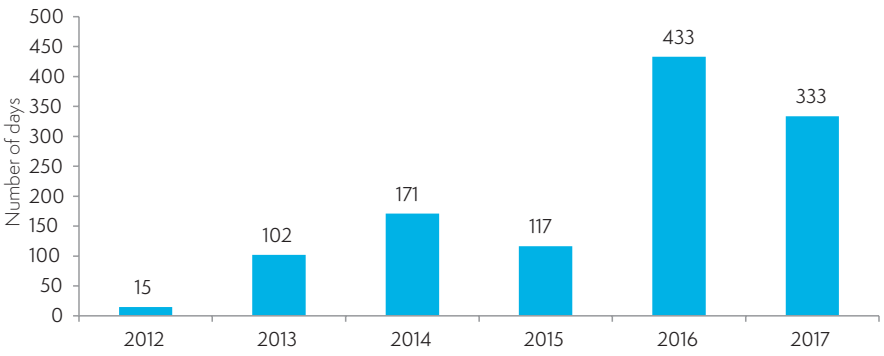

Chart 38 An average number of days from a recommendation of the AOTMiT President to publication in the Ministry of Health announcement, by year of including in the announcement – only oncology products.
Source: Own study on the basis of data published in AOTMiT Public Information Bulletin and dates at which the Minister of Health's reimbursement announcements came into force

appear in the first month of the announcement coming into force. For drugs available in the chemotherapy catalogue and new drugs added to treatment programmes, the time from appearing in the announcement to first NFZ reimbursement expenditures is about 1 month. For drugs available under new treatment programmes, where a tender must be conducted for provision of services, this time is 4 months on average, and the drug availability in individual NFZ branches may differ significantly.

	INCLUDING IN THE REIMBURSEMENT SYSTEM	
AOTMiT PRESIDENT RECOMMENDATION	NO	YES
NEGATIVE	62%	38%
POSITIVE	25%	75%

Table 14 The relationship between a type of the AOTMiT President's recommendation and including a product in reimbursement announcements, 2012–2016, by orders for evaluation of drug reimbursement applications
Source: Own study on the basis of data published in the AOTMiT Public Information Bulletin and dates of coming into force of the reimbursement announcements of the Minister of Health (the analysis covers a period from 2012 to 2016, due to a change in the practice of issuing recommendations by the AOTMiT President observed since 2015 results of the above analysis for 2012–2014 and 2015–2016 may differ significantly).

For oncology products, the dates when therapies are made available to patients are close to the average dates for individual availability categories as presented above.

Let us take a closer look at several products used in oncology which have been recently added to the reimbursement system (new drugs/drugs with new indications in oncology from announcements from July 2016 to January 2017, in the order from the last announcement).

Lenalidomide

From the announcement in force from 1 January 2017, lenalidomide is reimbursed under a treatment programme "treatment for patients with transfusion-dependent anaemia in the course of myelodysplastic syndromes with low or moderate risk 1, associated with a cytogenetic mutation in the form of isolated 5q deletion (d46)" (it is a new indication for a product that was previously included in the reimbursement system for a different indication).

An order for evaluation of the application for including the product in the reimbursement system was received by AOTMiT on 14 January 2015 (8/2015). After 75 days from placing the order, on 30 March, the AOTMiT President issued a negative recommendation to the reimbursement application.

As many as 718 days (nearly 2 whole years) passed from the date of sending the order to the publication in the announcement, confirming the product was included in the reimbursement system.

Vismodegib

Vismodegib is available from January 2017 under a treatment programme "vismodegib treatment for patients with basal cell carcinoma".

An order for evaluation of the application for including this product and indications in the reimbursement system was placed with AOTMiT on 5 August 2015 (109/2015). On 15 December 2015, the AOTMiT President issued a negative recommendation for the submitted application. Thus, the process of the application evaluation at the Agency took 132 days.

As many as 515 days (1 year and 5 months) passed from the order for evaluation of the application to the day of including the product in the reimbursement system.

Paclitaxelum albuminatum (nab-paclitaxel)

Nab-paclitaxel has been reimbursed under a treatment programme "treatment for patients with metastatic pancreatic adenocarcinoma" since January 2017.

An order for evaluation of the application for including the product in the reimbursement system was received by AOTMiT on 20 August 2015 (118/2015). After 77 days from placing the order, on 5 November 2015, the AOTMiT President issued a negative recommendation for the application.

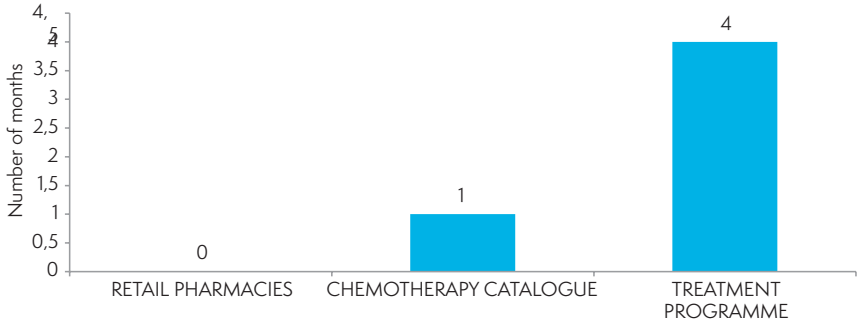

Chart 39 An average number of months from publication in the Ministry of Health announcement to NFZ expenditures, by financing channels (only products not reimbursed before)
Source: Own study based on dates of coming into force reimbursement announcements of the Minister of Health and communications on reimbursement expenditures published by NFZ.

As the product appeared in the reimbursement system from 1 January 2017, it means that 500 days (1 year 5 months) passed from the order to the announcement coming into force.

Ruxolitinib

The ruxolitinib molecule has been available in the reimbursement system since 1 January 2017, for indication "treatment of primary myelofibrosis and secondary myelofibrosis in the course of polycythaemia vera and essential thrombocytosis".

The first order for evaluation of the application for including this product in the reimbursement system and for this indication was placed with AOTMiT on 5 March 2014 (47/2014). On 12 May 2014, after 68 days, the AOTMiT President issued a positive recommendation for the submitted application.

On 19 May 2015, the Agency once again received an order from the Minister of Health requesting evaluation of the application for including the product in the reimbursement system for the same indication (135/2016). Another positive recommendation of the AOTMiT President was issued after 78 days, on 5 August 2016.

As many as 227 days passed from sending the second order to AOTMiT to including the product in the reimbursement system. However, when the first order placed with AOTMiT is considered then the process from the request for the application evaluation to including the product in the reimbursement system took 1033 days (nearly 2 years and 10 months).

Crizotinib

The product has been reimbursed from the announcement in force as of 1 November 2016 under a treatment programme "treatment of non-small-cell lung carcinoma".

On 13 June 2013, AOTMiT received an order from the Minister of Health requesting evaluation of the application for including the product in the reimbursement system (151/2013). On 9 September 2013, after 88 days from the order placement, the AOTMiT President issued a negative recommendation.

As many as 1237 days (nearly 3 years and 4 months) passed from the placement of the order with AOTMiT to the day of including the product in the reimbursement system.

Temsirolimus

The product has been reimbursed from the announcement in force as of 1 November 2016 under a treatment programme "treatment of kidney cancer".

An order for evaluation of the application for including the product in the reimbursement system for this indication was received by AOTMiT on 20 March 2013 (042/2013). On 27 May 2013, after 68 days, the AOTMiT President issued a negative recommendation for the analysed application.

On 3 April 2015, the Minister of Health sent an order to AOTMiT requesting it to get acquainted with new HTA analyses for that drug (58/2015). Unfortunately, no documentation summing up results of the analysis conducted by the Agency is available on the AOTMiT website.

As many as 1322 days (3 years and 7 months) passed from the order for evaluation of the reimbursement application to the day of including the product in the reimbursement system.

Olaparib

This product has been available in the reimbursement system since 1 September 2016 under a treatment programme "maintenance therapy with olaparib for patients with advanced platinum-sensitive recurrent ovarian cancer, cancer of fallopian tube or primary peritoneal cancer".

An order for evaluation of the application for including the product in the reimbursement system was received by AOTMiT on 11 January 2016 (2/2016). On 1 April 2016, after 81 days from receiving the order, the AOTMiT President issued a negative recommendation for the submitted application.

The product appeared in the reimbursement announcement on 1 September 2016, and this means that 234 days (nearly 8 months) passed from the order to including the product in the reimbursement system.

Lanreotide

Together with the announcement in force as of 1 September 2016, indications for this product were expanded. The product's availability under the pharmacy list and chemotherapy was expanded with gastrointestinal and pancreatic neuroendocrine tumours, GEP-NET G1 and some G2 (maximum Ki67 index 10%) of the middle section of the archenteron or of the pancreas, excluding primary foci in at the end section of the archenteron, in adult patients with locally advanced inoperable tumours or with metastases.

An order requesting evaluation of the application for including the product in the reimbursement system for this additional indication was received by AOTMiT on 18 January 2016 (55/2016, the requested reimbursement category included the chemotherapy catalogue). On 18 March 2016, after 60 days from the order placement, the AOTMiT President issued a positive recommendation for the submitted application.

As many as 227 days (nearly 8 months) passed from the order placement to the day of including the product with the specified indication in the reimbursement system.

Trastuzumab (subcutaneous)

A drug containing trastuzumab in a subcutaneous form has been reimbursed since 1 July 2016 and was added to a treatment programme "treatment of breast cancer".

An order for evaluation of the application for including this product in the reimbursement system was placed with AOTMiT on 11 March 2014 (50/2014). On 19 May 2014, after 69 days from receiving the order, the AOTMiT President issued a positive recommendation for the evaluated application.

As many as 843 days (2 years and 4 months) passed from the order to the day of including the product in the reimbursement system.

Rituximab (subcutaneous)

A drug containing rituximab in a subcutaneous form has been reimbursed since 1 July 2016 and has been added to a treatment programme "treatment of malignant lymphomas".

An order for evaluation of the application for including this product in the reimbursement system was placed with AOTMiT on 28 August 2014 (201/2014). A negative recommendation of the AOTMiT President was issued after 67 days, on 3 November 2014.

The product appeared in the reimbursement announcement on 1 July 2016, that is, after 673 days (1 year and 10 months) from placing the order requesting evaluation with the Agency.

Obinutuzumab

Obinutuzumab was included in the reimbursement system with the announcement in force as of 1 July 2016 under a treatment programme "treatment of chronic lymphocytic leukaemia with obinutuzumab".

An order with request for evaluation of the application for including obinutuzumab in the reimbursement system was received by the Agency on 7 April 2015. On 6 July 2015, after 90 days, the AOTMiT President issued a negative recommendation for the product.

The drug was included in the reimbursement announcement after 451 days (1 year and 3 months) from placing the order with AOTMiT.

Pertuzumab

A drug containing the active substance pertuzumab was included in the reimbursement announcement in force as of 1 July 2016 and was added to an existing treatment programme "treatment of breast cancer".

The first application for including the product in the reimbursement system for treatment of advanced breast cancer was submitted by the manufacturer in 2013. An order for evaluation of the application for including the product in the reimbursement system was placed with AOTMiT on 3 November 2013 (334/2013). On 17 December 2013, after 43 days from the order, the Agency President issued a positive recommendation for the evaluated application.

On 3 March 2014, the Agency received an order 43/2014, in which the Minister of Health requested "analyses verifying the influence on the payer's budget in the event of including the medicinal product in the reimbursement system and conducting analyses with a division into direct costs resulting from reimbursement of active substances and indirect costs". Documents summing up performance of this order are not available on the AOTMiT website.

On 27 October 2015, the Agency received another order from the Minister of Health requesting evaluation of the application for including pertuzumab in the reimbursement system. This time, on 30 December 2015, after 64 days of analysing the provided material the Agency President issued a negative recommendation.

Pertuzumab was included in the reimbursement announcement in force as of 1 July 2016. As many as 248 days passed from the last order, but 970 days, that is, 2 years and 8 months, passed from the first order received by AOTMiT.

Pembrolizumab

Pembrolizumab was introduced into the reimbursement system with an announcement coming into force as of 1 July 2016, under a treatment programme "treatment of skin or mucosal melanoma".

The first order for evaluation of the application for including the product in the reimbursement system was delivered to AOTMiT from the Ministry of Health on 15 September 2015 (130/2015). However, this order was withdrawn with a letter of 17 September 2015.

Another request for evaluation of the application for including pembrolizumab in the reimbursement system was placed with the Agency on 3 November 2015 (148/2015). On 7 January 2016, the Agency's President issued a negative recommendation for including the product for the requested indication (the treatment programme "treatment of skin or mucosal melanoma"), but at the same time recommended including the product in the reimbursement system, provided a single treatment pro-

gramme was created to include all therapies for advanced melanoma financed at that time (a new limit group for PD-1 inhibitors).

As many as 241 days (8 months) passed from the date of sending the second order, which in this case should be treated as the beginning of the process, to including pembrolizumab in the reimbursement system.

Nivolumab

A medicine with an active substance nivolumab was included in a reimbursement announcement coming into force as of 1 July 2016, under a treatment programme "treatment of skin or mucosal melanoma".

The Ministry of Health submitted to the Agency an order for evaluation of the reimbursement application on 5 November 2015. On 8 January 2016 (after 64 days) the Agency President issued a recommendation analogous to that quoted above for pembrolizumab.

As many as 239 days (8 months) passed from sending the order to the Agency to the announcement coming into force.

Crisantaspase

The crisantaspase molecule was included in the reimbursement system in an announcement that came into force as of 1 July 2016 under the chemotherapy catalogue for the indication acute lymphoblastic leukaemia when used in combination with other chemotherapeutics for treatment of patients, mainly paediatric, with hypersensitivity to pegylated E.coli L-asparaginase.

An order for evaluation of the application for including this product in the reimbursement system was placed with Agency on 8 January 2016 (1/2016). A positive recommendation was issued after 76 days from receiving the order (on 24 March 2016).

The product was included in the reimbursement announcement after 175 days (6 months) from placing the order for application evaluation with the Agency.

As it can be seen from the above examples, the time required for including a product in the reimbursement system in Poland differs significantly in individual cases.

Of the presented examples, the shortest time to conduct procedural stages within the specified scope was less than six months. At the other end of the scale are products that needed over 3.5 years to go through the process.

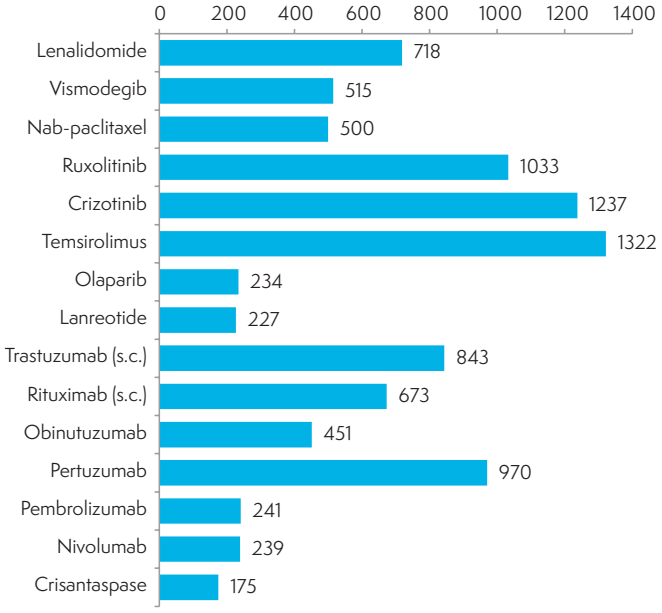

Chart 40 Number of days from the Minister of Health submitting the first order for evaluation of the application for including a given product for a given indication in the reimbursement system with the Agency for Health Technology Assessment and Tariff System to coming into force a reimbursement announcement in which the new drug or the new indication was listed for the first time.
Source: Own study based on dates of coming into force reimbursement announcements of the Minister of Health and communications on reimbursement expenditures published by NFZ.

Therapeutic standards

A lot of new drugs become available on the pharmaceutical market. From the point of view of clinical practice, the following questions gain great significance for a doctor:

- is the new drug a valuable therapeutic option and should I use it?
- what is the place of that new drug in a therapy regimen?

These questions can be answered by observational studies conducted at different centres across the world. Such studies are usually conducted according to all principles allowing a statistical evaluation of observations made. However, due to variable characteristics of studied populations, differences in study protocols, a need to analyse statistical descriptions of findings and multitude of such studies conducted through the years, a single doctor is not able to manage this flood of information and process it. Frequently, they simply do not have access to sources, and by focusing on patients and on the daily fight for their health and lives, they do not have the time to study numerous scientific reports.

To meet doctors' expectations and support them in making decisions in how and with what products the patients should be treated, medical standards are developed (medical guidelines, therapeutic guidelines, guideline procedures, standard procedures, etc.).

Medical standards are written sets of recommendations that may refer to all components of a diagnostic-therapeutic-rehabilitation process in a given area of medicine, usually concerning a specific disease or a group of diseases. Thus, standards may cover subjects of preventive actions, i.e. what should be done and how to prevent a disease. They may describe tests to be performed to diagnose a disease, monitor its progress or evaluate treatment efficacy. Medical standards can also describe therapeutic options that can be used for a given disease (e.g. drugs, surgery, radiotherapy), patients in which they are effective, in which sequence they should be used to achieve the best result, and for drugs – doses at which they should be administered.

Medical standards are usually developed by scientific societies, or teams of experts in individual branches of medicine – usually in the form of sets of recommendations or guidelines. They are not the law, so there is no obligation to use them. However, considering they:

- are based on the latest medical knowledge;
- include information being an essence of knowledge of the global community of doctors specialising in a given disease;
- are based on experience resulting from treating hundreds or even thousands of patients;

they should be considered as a valuable guideline in the daily work of any doctor.

Medical standards are also developed for cancer.

In Poland, treatment standards for cancer were developed by the Polish Society of Clinical Oncology in 2013 ["Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych" ("Guidelines for diagnostic and therapeutic procedures in malignant neoplasms") are available at http://onkologia.zalecenia.med.pl/]. Some of these standards were updated in 2014 and 2015. Although these studies are recent, with the rapidly changing medical knowledge in the area of cancer and launching new therapeutic options onto the market, for some issues they may have become outdated over time.

The leading centres developing standards for oncology include the National Comprehensive Cancer Network (NCCN, www.nccn.org) in the U.S. and the European Society for Medical Oncology (ESMO, www.esmo.org).

NCCN is a non-profit organisation, in which 27 leading American oncology centres operate. The aim of the Society is to improve quality and effectiveness of the care

provided to cancer patients so they can enjoy a better quality of life. To fulfil this ambitious task, using extensive scientific and clinical experience of its members, NCCN prepares studies representing valuable guidelines for patients, doctors and entities which are payers for medical services.

NCCN Clinical Practice Guidelines in Oncology are one type of documents developed by NCCN. NCCN guidelines are characterised by frequency of their updating – to follow a fast-changing knowledge in the area of oncology; as a rule, they are updated nearly immediately after any important event occurs. In consequence, several updates to guidelines for a specific disease are published every year. Due to this frequency of updating, NCCN studies can be considered as reflecting the latest medical knowledge.

ESMO is a leading European organisation specialising in medical oncology. It associates 15 thousand specialists from over 130 countries. In Europe ESMO is considered as a reference organisation for education and information in oncology. Joint efforts of the organisation members result in activities aiming to continuously improve clinical practice standards in cancer. These activities are reflected in the Clinical Practice Guidelines published by ESMO. Documents published by ESMO are updated regularly; they also consider a registration situation on the European market (some drugs may already be registered on the American market for a relevant medical indication, but are yet unavailable on the European market). Therefore, the ESMO guidelines are a good European indicator of the latest treatment options and regimens for their use.

In Poland, key parameters influencing the selection of therapies proposed to patients for specific types of cancer include: reimbursement itself (an issue of drug price availability to a patient) and rules for providing access to reimbursed medicine in individual financing channels.

In brief, the importance of reimbursement for innovative drugs in oncology can be summed up as follows.

- when a cancer drug available to a patient at a pharmacy is not reimbursed, then possibly only a negligible group of patients can afford it;
- if a cancer drug used in in-patient health care (hospitals) is not reimbursed, then no hospital will purchase that drug and give it to a patient, as it will be too large a burden to its finances;

while rules for making drugs available can be summed up as follows:

- a cancer drug available with reimbursement at retail pharmacies can be used according to medical knowledge in every patient whose disease conforms to the scope of indications covered by reimbursement (note: the scope of indications covered by reimbursement can be less/more extensive than the scope of registered indications);
- a cancer drug available in the chemotherapy catalogue can be used according to medical knowledge in every patient whose disease is included in a list of indications covered by reimbursement for a given active substance (note: the scope of indications covered by reimbursement can be less/more extensive than the scope of registered indications);
- a cancer drug available under treatment programmes can be used:
  - in a patient with relevant diseases, meeting specified requirements concerning their clinical condition and being at a specified stage of a therapeutic process;
  - drugs covered by the programme can be used at a stage of the therapeutic process described in a treatment programme description.

Thus, to compare Polish patients' access to innovative drug therapies, it is necessary to compare principles under which individual drugs are made available with reimbursement in Poland versus the latest available guidelines for specific diseases.

This comparison is presented below. It was prepared using the following methods:

- The analysis focused on active substances registered under a central procedure available in lists published on the EMA website, and which registered indications include an indication for a relevant cancer (access to EMA databases as of 3 Feb 2017).
- They were registered in 2004 or later.
- In general, they are included in therapeutic classes L01 and L02 according to WHO ATC classification.
- In this study, the analyses covered the following therapeutic areas (ten solid tumors and ten haematooncologic diseases with the highest mortality rates according to the latest data of the National Cancer Register):
  - Solid tumors
    - Bronchial and lung cancer
    - Breast cancer
    - Prostate gland cancer
    - Colon cancer
    - Bladder cancer
    - Rectal cancer (analysed together with colon as colorectal cancers)
    - *Cancer of the uterine body*
    - Stomach cancer
    - Renal cancer
    - Ovarian cancer
  - Haematooncology
    - Chronic myeloid leukaemia
    - Acute myeloid leukaemia
    - Polycythaemia vera (considered as myeloproliferative neoplasm)
    - Essential thrombocytosis (considered as myeloproliferative neoplasm)
    - Primary myelofibrosis (considered as myeloproliferative neoplasm)
    - Chronic lymphocytic leukaemia
    - Diffuse large B-cell lymphomas
    - Plasma cell myeloma/Multiple myeloma
    - Hodgkin lymphoma
    - Non-Hodgkin lymphoma
    - Acute lymphoblastic leukaemia

For therapeutic areas marked in italics in the above list:

- no drugs were identified whose registration indications would include an indication for a given disease;

- or the identified drugs did not meet the time criterion (were registered before 2004).

Examples of therapy limitations do not exhaust a subject of problems with patients' access to a given drug. Certainly, specialists in a given therapeutic area providing practical care to patients will be able to specify considerably more provisions, with which conditions for administering a given drug specified in reimbursement requirements differ from the current medical knowledge.

Bronchial and lung (NSCLC and SCLC) cancer

Of 14 drugs registered in Europe with indications to be used for bronchial and lung cancers, nearly all are included in current NCCN and ESMO guidelines. In Poland, only two drugs are reimbursed in accordance with ESMO and NCCN guidelines. Eight formulations are not reimbursed for these indications.

The main limitations in the scope of availability for drugs covered by reimbursement in Poland concern the treatment line. Practically in all cases, according to the guidelines, drugs listed as "available with limitations" can also be used at other stages of the treatment process than those for which they are approved for use in Poland according to provisions of a treatment programme.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
pemetrexed	√	√		√			√	
bevacizumab	√	√			√			√
erlotinib	√	√	√			√		
gefitinib	√	√	√			√		
everolimus	√				√			
crizotinib	√	√		√			√	
afatinib	√	√		√			√	
nintedanib		√						√
ramucirumab	√	√			√			√
ceritinib	√	√			√			√
nivolumab	√	√			√			√
pembrolizumab	√	√			√			√
osimertinib mesylate	√	√			√			√
necitumumab		√						√
14	12	13	2	3	7	2	3	8

Breast cancer

Of 8 drugs registered in Europe with indications to be used for breast cancers, all are included in current NCCN standards, and 7 are included ESMO guidelines. In Poland, less than half of these drugs are available in accordance with the standard, and 5 out of 8 drugs are not included in the reimbursement system.

Fulvestrant is reimbursed under the chemotherapy catalogue. Breast cancers are in a list of ICD-10 codes assigned in the catalogue to that molecule, thus use of this molecule is under control of a doctor in charge of a case.

For lapatinib, programme provisions deviate from NCCN guidelines. The ESMO standard indicates that lapatinib can be used in selected patients as part of anti-HER2 therapy instead of trastuzumab, while under a treatment programme lapatinib can be administered to patients previously treated with trastuzumab.

According to provisions of the treatment programme, pertuzumab can be used in patients in whom local treatment (surgery, radiotherapy) is ineffective or permanently impossible to use. In NCCN and ESMO guidelines, pertuzumab can be used in a therapy before surgery.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
fulvestrant	√	√	√			√		
bevacizumab	√	√			√			√
lapatinib	√	√		√			√	
everolimus	√	√			√			√
eribulin	√	√			√			√
pertuzumab	√	√		√			√	
trastuzumab emtansine	√				√			
palbociclib	√	√			√			√
8	8	7	1	2	5	1	2	4

Prostate gland cancer

Of 5 drugs registered in Europe with indications to be used for prostate gland cancers and included guidelines only one is reimbursed in accordance with indications specified in the international standards. Another one is available with limitations, and 3 are not reimbursed in Poland.

Degarelix is available to patients under reimbursement at retail pharmacies for the indication: advanced hormone-dependant prostate cancer. In NCCN and ESMO standards, it is one of the components of the androgen deprivation therapy (ADT), representing an element of therapeutic algorithms in treatment of prostate cancer.

For abiraterone, the treatment programme provides for its use in patients with disease progression during or after chemotherapy with docetaxel. According to the standards, this drug can be used regardless of previous treatment with docetaxel..

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
degarelix	√	√	√			√		
cabazitaxel	√	√			√			√
abiraterone	√	√		√			√	
enzalutamide	√	√			√			√
radium Ra223 dichloride	√	√			√			√
5	5	5	1	1	3	1	1	3

Colorectal and rectal cancer

Out of 7 drugs registered in Europe with indications to be used for colorectal and rectal cancers, all are included in current NCCN and ESMO guidelines.

None of these drugs is financed in Poland according to these standards. 4 out of 7 drugs are not reimbursed for the analysed indication, and a possibility to use other 3 is limited versus standards. Both NCCN and ESMO guidelines accept the use of these drugs as a first line therapy, while provisions of the treatment programme allow their use in a second or third line.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
cetuximab	√	√		√			√	
bevacizumab	√	√		√			√	
panitumumab	√	√		√			√	
aflibercept	√	√			√			√
regorafenib	√	√			√			√
ramucirumab	√	√			√			√
trifluridine / tipiracil hydrochloride	√	√			√			√
7	7	7	0	3	4	0	3	4

Stomach cancer

Since 2004, 2 new drugs have been registered in Europe which, according to registered indications, can be used in stomach cancer therapy. One of them, ramucirumab, was included in the standard. It is not reimbursed in Poland.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
tegafur / gimeracil / oteracil								
ramucirumab	√	√			√			√
2	1	1	0	0	1	0	0	1

Renal cancer

Ten drugs were registered in Europe with indications to be used for kidney cancer. All are included in NCCN guidelines, and 9 out of 10 are included in ESMO guidelines. In Poland, 4 out of 10 drugs are not reimbursed for the analysed indication, and only two of them are available in accordance with ESMO guidelines (when compared to NCCN guidelines, none of the drugs is available in accordance with the standard).

The remaining 6 drugs can be used; however, their use is limited versus the standards. Provisions of the treatment programme limit a possibility to administer available drugs only to those patients in whom 60% or more kidney cancer tissue contain a clear-cell component (excluding temsirolimus). The standards accept the use of these drugs also for kidney cancers other than clear-cell carcinoma.

For temsirolimus, a difference in approach to a patient performance status according to Karnofsky scale is noticeable. According to the programme provisions, the drug can be administered to patients whose performance status is equal to or exceeding 60, while the NCCN standard specifies as group of patients for this drug those in whom this score is below or equal to 70.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
bevacizumab	√	√			√			√
sorafenib	√	√		√			√	
sunitinib	√	√		√			√	
temsirolimus	√	√		√		√		
everolimus	√	√		√			√	
pazopanib	√	√		√			√	
axitinib	√	√		√		√		
nivolumab	√	√			√			√
lenvatinib	√				√			
cabozantinib	√	√			√			√
10	10	9	0	6	4	2	4	3

Ovarian cancer

Among new drugs registered since 2004 in Europe, there are 3 drugs whose registered indications include the use for ovarian cancer.

Trabectedin is not included in NCCN and ESMO algorithms, where it should be noted that ESMO documents include information about clinical studies in progress, whose results will allow evaluation of the role this formulation may play in the therapy of this cancer.

Requirements of the treatment programme for bevacizumab and olaparib to a larger extent correspond to European therapeutic guidelines. American guidelines accept the use of bevacizumab at earlier stages of that cancer, and this is not included in European guidelines.

In the treatment programme, a criterion is noticeable according to which a patient qualified for bevacizumab or olaparib treatment should have blood haemoglobin levels exceeding or equal to 10.0 g/dL, while a standard for a healthy woman is 11.5–16.0 g/dL. Therefore, potentially, this criterion may be difficult to be met by a large group of ovarian cancer patients.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
bevacizumab	√	√		√		√		
trabectedin								
olaparib	√	√	√			√		
3	2	2	1	1	0	2	0	0

Bladder cancer

Vinflunine was registered by EMA in 2009 for the indication advanced or metastatic transitional cell carcinoma of the urinary tract. Recommendations for vinflunine treatment are included only in ESMO guidelines. This substance is not reimbursed in Poland.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
vinflunina		√						√
1	0	1	0	0	0	0	0	1

Chronic myeloid leukaemia (CML)

Since 2004, 3 drugs have been registered in Europe which registered indications include chronic myeloid leukaemia. All are included in guidelines developed by NCCN, and one, ponatinib, is not included in ESMO guidelines (which may result from the fact that ESMO guidelines for CML identified during the study were from 2012). None of the drugs is available in accordance with both ESMO and NCCN guidelines.

Dasatinib is available to patients qualified into the treatment programme. Programme provisions exclude its use in the first line therapy. This line of the therapy is available in NCCN and ESMO therapeutic guidelines.

The reimbursement situation and guidelines for nilotinib are analogous as for dasatinib.

Bosutinib is only included in NCCN guidelines. It is not reimbursed in Poland.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
dasatinib	√	√		√			√	
nilotynib	√	√		√			√	
ponatinib	√				√			
bosutynib	√				√			
4	4	2	0	2	2	0	2	0

Acute myeloid leukaemia (AML)

Of three drugs registered in Europe with indications to be used for acute myeloid leukaemia, two are included in current NCCN and ESMO guidelines.

In Poland, the azacitidine molecule is available under the chemotherapy catalogue. A disease for which the drug can be used is acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organisation (WHO) classification, in adult patients not qualifying for transplant of hematopoietic stem cells.

The decitabine molecule is not reimbursed for the analysed indication.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
histamine dihydrochloride								
azacitidine	√	√	√			√		
decitabine	√	√			√			√
3	2	2	1	0	1	1	0	1

Myeloproliferative neoplasms (polycythaemia vera, essential thrombocytosis, primary myelofibrosis)

Azacitidine is available under the chemotherapy catalogue; however, indications for its use do not correspond to the analysed therapeutic area.

Ruxolitinib has been available since 1 January 2017, under a treatment programme "treatment of primary myelofibrosis and secondary myelofibrosis in the course of polycythaemia vera and essential thrombocytosis".

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
ruxolitinib	√	√	√			√		
azacitidine	√				√			
2	2	1	1	0	1	1	0	0

Chronic lymphocytic leukaemia (CLL)

From among 5 products registered in Europe with indications for chronic lymphocytic leukaemia, all are included in NCCN guidelines, and 4 out of 5 are included in ESMO guidelines.

In Poland, no drug is available in accordance with the standard, and one drug, obinutuzumab, is reimbursed with limitations for the discussed indication. According to provisions of the treatment programme, treatment with obinutuzumab is possible when a patient was not treated previously for chronic lymphocytic leukaemia, and this represents a limitation versus NCCN and ESMO guidelines, as those guidelines specify that this drug can be used both as the first line therapy, as well as for treatment of disease recurrence.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
ofatumumab	√	√			√			√
obinutuzumab	√	√		√			√	
idelalisib	√	√			√			√
ibrutinib	√	√			√			√
venetoclax	√				√			
5	5	4	0	1	4	0	1	3

Diffuse large B-cell lymphomas

Currently, none of drugs registered specifically for treatment of diffuse large B-cell lymphomas is reimbursed in Poland.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
pixantrone dimaleate								
ibritumomab tiuxetan	√				√			√
2	1	0	0	0	1	0	0	1

Plasma cell myeloma/Multiple myeloma (MM)

Of 10 active substances registered for treatment of multiple myeloma, 7 are not reimbursed in Poland. However, a considerable difference in the number of active substances available for myeloma treatment according to NCCN and ESMO guidelines should also be noted. When compared to the ESMO standard, 3 out of 4 substances are reimbursed in Poland (only thalidomid is not reimbursed). The reimbursement scope for these substances allows their use according to ESMO standards.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
bortezomib	√	√	√			√		
daratumumab	√				√			
elotuzumab	√				√			
panobinostat	√				√			
pomalidomide	√				√			
carfilzomib	√				√			
dexamethasone	√	√	√			√		
ixazomib	√				√			
lenalidomide	√	√		√		√		
thalidomide	√	√			√			√
10	10	4	2	1	7	3	0	1

Hodgkin lymphoma (HL)

Provisions of the treatment programme for brentuximab treatment in patients with recurrent or treatment resistant Hodgkin lymphoma correspond to provisions in the guidelines.

Inclusion of nivolumab in NCCN guidelines for treatment of Hodgkin lymphoma reflect efforts for including valuable therapeutic options in guidelines of this organisation, as nivolumab was registered for this indication in May 2016.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
brentuximab vedotin	√	√	√			√		
nivolumab	√				√			
2	2	1	1	0	1	1	0	0

Non-Hodgkin lymphomas (NHL)

Since 2004, 3 drugs have been registered in Europe with indications to be used for non-Hodgkin lymphomas, where 2 of them are included in NCCN guidelines, and one is included in ESMO guidelines.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
pixantrone dimaleate								
brentuximab vedotin	√	√	√			√		
idelalisib	√				√			
3	2	1	1	0	1	1	0	0

Acute lymphoblastic leukaemia (ALL)

Eight molecules have been found in the EMA database which have been registered since 2004, and which reimbursement indications concern acute lymphoblastic leukaemia.

All these drugs are included in NCCN guidelines. ESMO guidelines for blinatumomab include information that this drug is currently being evaluated.

Out of these 8 drugs, 3 are not reimbursed in Poland. The great majority of the remaining ones (4 out of 5) are reimbursed under the chemotherapy catalogue without limitations to their use in a patient.

For dasatinib, standards provide for a more extensive use of this drug than provided for in the treatment programme.

A list of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard (U.S.) (Sept 2016)	ESMO standard (Europe) (Sept 2016 NSCLC, July 2011 SCLC)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)		
			Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland according to the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)
clofarabine	√	√	√			√		
dasatinib	√	√		√			√	
nelarabine	√	√	√			√		
6-mercaptopurine monohydrate	√	√	√			√		
blinatumomab	√				√			
ponatinib	√	√			√			√
pegaspargase	√	√	√			√		
asparaginase	√	√			√			√
8	8	7	4	1	3	4	1	2

The above analysis indicates that patients in Poland have limited access to therapeutic options, when compared to NCCN or ESMO standards. This situation results from:

- no reimbursement of many active substances included and considered in treatment algorithms specified in the guidelines;
- limitations introduced at the level of detailed provisions of treatment programmes, resulting in:
  - excluding a possibility to administer drugs at earlier treatment lines;
  - excluding a possibility to administer drugs at successive treatment lines in the event of failure in a therapeutic regimen under which a specific drug was previously administered.

Also, one's attention is drawn to the detailed descriptions of patients' condition and diagnostic and laboratory test results that should be met to qualify patients for treatment under a treatment programme. Usually, the standards do not contain provisions at that level of detail, therefore, it is not possible to evaluate to what extent the adopted parameters are consistent with current medical know-how and thus useful in patient qualification, and to what extent they are used as a factor limiting a population of patients in which that treatment can be used.

> Of all examined therapeutic areas (10 solid tumors and 10 haematooncologic diseases with the highest mortality rates according to the National Cancer Register), only in one case patients are treated in accordance with the current guidelines of international scientific society.

When a therapeutic standard available under the public reimbursement system is compared, it should be noted that:

- versus the NCCN standard:
  - less than a half (37/82) of therapeutic options are available to Polish patients;
  - less than one in five (14/82) of therapeutic options are available in accordance with the current standard;
  - other are available with limitations (23/82).
- versus the ESMO standard:
  - slightly more than a half (37/68) of therapeutic options are available to Polish patients;
  - less than one in three (18/68) of therapeutic options are available in accordance with the current standard;
  - other are available with limitations (19/68).

	The number of active substances registered in the EMA with indication for treatment within a therapeutic area	NCCN standard	ESMO standard (Europe)	Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the NCCN standard (U.S.)			Availability of therapeutic options in Poland according to the reimbursement announcement (Jan 2017) versus the ESMO standard (Europe)			Is the treatment available in Poland compliant with the latest standard?
				Active substance available in Poland compliant with the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	Active substance available in Poland compliant with the standard	Active substance available in Poland with limitations in relation to the standard	Unavailable active substance (not reimbursed in Poland)	
Bronchial and lung (NSCLC and SCLC) cancer	14	12	13	2	3	7	2	3	8	NO
Breast cancer	8	8	7	1	2	5	1	2	4	NO
Prostate cancer	5	5	5	1	1	3	1	1	3	NO
Colon cancer Rectal cancer	7	7	7	0	3	4	0	3	4	NO
Stomach cancer	2	1	1	0	0	1	0	0	1	NO
Renal cancer	10	10	9	0	6	4	2	4	3	NO
Ovarian cancer	3	2	2	1	1	0	2	0	0	YES
Bladder cancer	1	0	1	0	0	0	0	0	1	NO
Chronic myeloid leukaemia (CML)	4	4	3	0	2	2	0	2	0	NO
Acute myeloid leukaemia (AML)	3	3	2	0	2	1	0	2	0	NO
Myeloproliferative neoplasms	2	2	1	1	0	1	1	0	0	NO
Chronic lymphocytic leukaemia (CLL)	5	5	4	0	1	4	0	1	3	NO
Diffuse large B-cell lymphomas	2	1	0	0	0	1	0	0	1	NO
Plasma cell myeloma (MM)	10	10	4	2	1	7	3	0	1	NO
Hodgkin lymphoma	2	2	1	1	0	1	1	0	0	NO
Non-Hodgkin lymphoma	3	2	1	1	0	1	1	0	0	NO
Acute lymphoblastic leukaemia (ALL)	8	8	7	4	1	3	4	1	2	NO
Summary of access to therapeutic options	89	82	68	14	23	45	18	19	31	

Less current standard – figures are in grey. For standards with the same validity status, the ESMO standard was taken into consideration in the comparison.

Legal comments

Legal comments

Introduction

Cancer patients' access to an effective therapy based on current medical knowledge is of particular importance. In most cases, cancer represents a direct and real hazard to life. Lack of necessary treatment, involving modern diagnostic methods and access to required medicinal products, makes effective fight with a disease impossible, thus limiting the constitutional right to protection of health guaranteeing an equal treatment for all patients with different diseases.

What is important, individual cancers are divided into numerous subtypes resulting from different genetic mutations; therefore, cancer patients require an individualised approach, detailed diagnosis and access to safe and effective therapy.

Furthermore, cancer treatment is characterised by a high level of ailments related to chemo- or radiotherapy, therefore, the products used should be as effective as possible for a given type of the disease to ensure an effective fight with the disease.

Increasingly effective cancer therapies are being developed, frequently associated with high costs, in particular, when a given type of cancer is rare and does not affect a large population of patients.

It should be emphasised here, that a right to protection of life expressed in the Constitution should be understood as equal access to services regardless of the type of the disease affecting a patient. Therefore, access to a relevant treatment should be ensured both for common diseases, and for rare or ultra-rare diseases. At the same time, the issue of a small population of patients or high costs of a therapy should not lead to unjustified limitations in access to necessary

The right to health protection specified in more detail in other documents, including the Act concerning Patients' Rights or the Medical and Dental Practitioners Act, indicates that the applied treatment should correspond to the current medical knowledge. Therefore, it is a duty of a doctor to select the best treatment from all available therapies, using their knowledge and experience. At the same time, it is unacceptable to use methods and means that are outdated or ineffective, when they are generally replaced with other treatment methods.

A patient has a right to expect that the applied therapy will be appropriate for their condition and adapted to their needs. At the same time, they should be informed by a doctor about alternate treatment methods, whenever available, and be able to make an informed decision about the type of therapy used.

To ensure appropriate therapy for cancer patients, an approach ensuring access to effective therapies should be considered together with introduction of system mechanisms ensuring monitoring of provided services and evaluating their effectiveness. In particular, areas should be indicated in which current regulations do not ensure full rights to health protection, including treatment of rare and ultra-rare diseases, delay in access to relevant services, or providing individual access to unregistered or non-reimbursed drugs in special cases.

Introduction of relevant legal regulations aims at creating tools to provide required treatment in the best way possible, and to implement the patient's right to required care and equal treatment.

The most important legal acts governing patients' access to therapies.

The Polish legal system includes acts relating to health protection. Regulations cover both patients' rights and obligations, particularly, in terms of services to which they are entitled, as well as principles underlying

organisation of the health care system. The most important legal acts governing patients' access to therapies include:

- The Constitution of the Republic of Poland of 2 April 1997 (Journal of Laws No. 78, item 483 as amended; http://isap.sejm.gov.pl/DetailsServlet?id=WDU19970780483);
- The Medical and Dental Practitioners Act of 5 December 1996 (Journal of Laws of 2017, item 125; http://isap.sejm.gov.pl/DetailsServlet?id=WDU19970280152);
- Pharmaceutical Law of 6 September 2001 (Journal of Laws of 2016, item 2142, as amended; http://isap.sejm.gov.pl/DetailsServlet?id=WDU20011261381);
- The Act concerning health care services financed from public resources of 27 August 2004 (Journal of Laws of 2016, item 1793, as amended; http://isap.sejm.gov.pl/DetailsServlet?id=WDU20042102135);
- The Act concerning Patients Rights and a Commissioner for Patients' Rights of 6 November 2008 (Journal of Laws of 2016, item 186, as amended; http://isap.sejm.gov.pl/DetailsServlet?id =WDU20090520417);
- The Act on Reimbursement of Medicines, Foodstuffs for Particular Nutritional Purposes and Medical Devices of 12 May 2011 (Journal of Laws of 2016, item 1536, as amended; http://isap.sejm.gov.pl/DetailsServlet?id=WDU20111220696).

Legislation works considering access of cancer patients to therapies

At the time this comment is being written (February 2017), legislation works are in progress aiming at increasing the availability and quality of health care services. Changes important from the cancer patients' point of view include changes concerning the Reimbursement Act and changes to the organisation of care for cancer patients.

The list below provides the most important legal amendments influencing access to therapy for cancer patients:

- A draft of the act amending the Act on Reimbursement of Medicines, Foodstuffs for Particular Nutritional Purposes and Medical Devices and some other acts (a number in the list: UD125; http:y/legislacja.rcl.gov.pl/projekt/12290204) – so-called large amendment of the Reimbursement Act.

  The most important changes included in the draft:
  - introduction of a budget for a reimbursement development mode, representing additional funds in form of a targeted subvention used to cover part of costs of drugs previously not reimbursed;
  - introduction of a definition for an ultra-rare indication and separate rules for reimbursement of drugs used for ultra-rare indications. The ultra-rare indication was defined as a clinical condition occurring not more often than in one person per 50 thousand inhabitants in the RP or the European Union territory. In the reimbursement proceedings concerning drugs used for ultra-rare indications, which do not have a reimbursed equivalent, separate requirements will apply – an obligation to present an economic analysis will not apply, instead, grounds justifying a specific price should be attached. Additionally, in this case the cost-effectiveness criterion will not apply;
  - new rules for determining contents of treatment programmes, increasing flexibility in expanding a treatment programme with new products. A treatment programme description will not form an appendix to individual decisions, instead, the programme title and conditions for use of a given drug under that programme will be specified in a decision. The description of a treatment programme will be provided in the reimbursement announcement on the basis of information specified in individual decisions.
- A draft of the act amending the act on health care services financed from public funds and some other Acts (a number in the list: UA18; http://legislacja.rcl.gov.pl/projekt/12283610) – so-called small amendment of the Reimbursement Act.

  The most important changes included in the draft: introduction of emergency access to drug technologies in the form of financing of drugs that have a marketing authorisation and are available on the market, but are not financed from public resources in a given indication, in the case of justified current medical knowledge, and resulting from guidelines, need to use that drug when all reimbursed medical technologies possible to use for a given indication are exhausted, when it is necessary for saving the life or maintaining the health of patients.
- A draft of assumptions for a draft of the act on quality in health care and patient safety (number in the list: ZD7; http:/ylegislacja.rcl.gov.pl/projekt/12294407).

  The draft includes assumptions for future solutions concerning:
  - an authorisation for entities conducting treatment operations (an authorisation system);
  - a systemic monitoring of side effects (a system for monitoring of side effects);
  - internal quality and safety monitoring systems maintained at hospitals;
  - monitoring of clinical quality indicators;
  - maintaining medical registers for purposes of quality evaluation;
  - increasing importance of the accreditation system in health care.
- A draft of the act amending the act on an information system in health care and some other acts (a number in the list: UD82, http://legislacja.rcl.gov.pl/projekt/12288551)

  The most important change included in the draft is the improvement in maintaining medical registers.
- A cabinet draft of the act amending the act on health care services financed from public funds (the form number: 1098; http://sejm.gov.pl/Sejm8.nsf/PrzebiegProc.xsp?nr=1098).

  The most important changes included in the draft:
  - changes in the Cancer Diagnostic and Treatment Form (DiLO), including implementation of a new template for the DiLO Form and integration of data from

the DiLO Form with the NFZ IT system for DiLO Form processing;
- removal of a significant number of reporting obligations;
- obliging the Minister of Health to publish, in the form of an announcement, guidelines (standards) for cancer diagnostics and treatment procedures and development of measures for evaluation of cancer diagnostics and treatment procedures;
- removal of a need to establish a multidisciplinary therapeutic team, planning and coordinating the treatment process.

Patients' problems with access to therapy

When analysing a problem concerning patients' access to therapy, legal limitations should also be considered, which in the current reimbursement system may negatively influence the availability of modern drugs to patients. Due to the comprehensive nature of this situation and a number of acts currently being developed, we have focused on issues most important in our opinion, including:
- the cost-effectiveness criterion and its influence on the process of making cancer therapies available to patients;
- treatment programmes and the Minister of Health's rights to make reimbursement decisions;
- progress in introduction of medical registers monitoring treatment effectiveness;
- a time from a reimbursement decision to actual availability of the therapy;
- providing access to modern drugs before their registration (so-called *Compassionate Use*);
- providing emergency access to drugs.

Cost-effectiveness criterion and its influence on the process of making cancer therapies available to patients

One of the criteria for including a given product in the reimbursement system is the level of the threshold for the cost to gain a quality-adjusted year of life, provided for in Article 12(13) of the Reimbursement Act, and amounting to three times the Gross Domestic Product per capita. It represents a certain measure used to evaluate a therapy, by estimating the cost of therapy ensuring patient survival for another year at a specified level of quality of life. This means that the correctly calculated therapy effectiveness threshold amounts to PLN 125,955, so when the costs of treatment exceed the specified threshold, this criterion is not met.

This criterion is also considered during negotiations with the Economic Commission. At the same time, the Reimbursement Act leaves certain freedom to the Minister of Health in making reimbursement decisions – it only indicates criteria that should be considered, without specifying the consequences of not meeting each of them.

The threshold specified in the Reimbursement act aims at securing the public payer expenditures. This solution does not distinguish evaluation of therapies used for common diseases (e.g. diabetes) from those used for rare and ultra-rare diseases. In the case of these last ones, treatment costs are usually very high. It mainly results from a small population of patients, and thus, limited demand for a given medicinal product. In this situation, a manufacturer establishes a high market price of the drug based on costs of developing its technology, conducting clinical studies, and manufacturing.

At the same time, regulations at the level of the Constitution of the RP and Acts guarantee fair and equal access to health care services financed from public funds. Furthermore, the act concerning Patients' Rights ensures the right to health care services corresponding to the requirements of the current medical knowledge to every patient.

High costs of therapy frequently limit access of many patients. They may not have an option for treatment, particularly, when no alternate forms of therapy are available and their disease poses a direct risk to their life. This also concerns therapies used to treat cancer, which, with a progress in medical knowledge, concern small groups of patients.

The Polish legal system does not include a definition of a rare and ultra-rare disease. The currently considered large amendment of the Reimbursement Act includes a proposal for defining an ultra-rare indication as a clinical condition occurring not more often than in one person per 50 thousand inhabitants in the RP or the European Union territory. Furthermore, the large amendment provides for including separate components of the reimbursement proceedings in case of drugs used for ultra-rare indications. As authors of that draft indicate, the issue of specific drugs is to be governed according to the equality principle and ensure access to therapy even when its cost-effectiveness is lower. Proposed solutions include limiting required grounds for the application concerning the economic analysis when a reimbursed equivalent is not available, and replacing that obligation only with presenting grounds underlying a price. At the same time, in this case the cost-effectiveness criterion will not apply. Thus, the therapy cost will not form a direct criterion to refuse the inclusion of a given drug in the reimbursement system. Furthermore, drugs without reimbursed equivalents, apart from financing under a standard reimbursement budget can receive subventions from a budget for a reimbursement development mode.

Treatment programmes and the Minister of Health's rights to make reimbursement decisions

Currently, when any new drug appears, adding it to an already existing treatment programme may pose certain problems. For this reason, a solution is considered to facilitate patients' access to therapy by increasing the flexibility of determining contents of treatment programmes.

Therefore, a proposition indicated in the large amendment should be perceived as a positive, as it introduced significant changes to how treatment programme contents are specified.

Currently, the treatment programme content forms an appendix to reimbursement decisions for products qualified into a given programme. This means that any change in the contents of the treatment programme requires changes in individual decisions, with the consent of their recipients. Therefore, when even one recipient does not give its consent, the treatment programme cannot be changed.

Limited possibilities to change programme contents are particularly cumbersome when one of the programme components, e.g. qualification criteria, does not reflect current medical knowledge. Thus, although its contents should be amended, it is extremely difficult. A change in the way of determining contents of treatment programmes is included in the so-called large amendment. The draft assumes that the reimbursement decision will only specify the treatment programme title and conditions for use of a given product under the programme, in the form of an appendix to the decision. The contents of the treatment programme will therefore form a set of appendices to the decision and will be published in a reimbursement announcement.

The state of introduction of medical registers monitoring treatment effectiveness

The national health care system does not contain effective tools for collection and processing of data concerning health services provided. It is necessary to obtain specific information to monitor and evaluate the quality and results of the care provided to patients. Collected data may also be considered when a decision about financing health care is being made, as centres achieving better quality performance, for example, in terms of safety or treatment effectiveness will be preferred. The obtained information could also be available in the public domain, and not only made available to the Minister of Health. Considering the above, a requirement to create open, publicly available registers, e.g. via websites of relevant bodies, seems to be justified.

A problem with the functioning of medical registers was observed by the Minister of Health. Considering the above, an amendment to the Act concerning information system in health protection is currently being considered, to improve maintaining of registers. This draft establishes a data controller at a level of the entity maintaining the register, creates an obligation to outsource technical servicing of teleinformation systems and an obligation to provide data from a register to the Minister of Health free of charge, and determines financing principles.

The indicated changes, technical to a large extent, aim at improving the functioning of the registers, while the issue of the use of the data obtained to create an appropriate health care policy is included in the draft of the act concerning quality in health care and patient safety. According to assumptions, the act is to form a comprehensive regulation implementing solutions deploying priorities of health care policy in the area of quality, and in particular, concerning:

- an authorisation for entities conducting treatment operations;
- systemic monitoring of side effects;
- internal quality and safety monitoring systems maintained at hospitals;
- monitoring of clinical quality indicators;
- maintaining medical registers for the purposes of quality evaluation;
- increasing importance of the accreditation system in health care.

These changes are to result in an improvement in diagnostic and treatment effectiveness, and in improvement in clinical practice due to regular monitoring and evaluation. Furthermore, comparability of centres is to be achieved in terms of their effectiveness and quality, and possibility for introducing a system of financial incentives motivating to improve the quality of provided services. The assumptions also indicate that results concerning effectiveness and quality will be made available in the public domain.

In particular, it is assumed that an Agency for Health Care Quality Issues and Patient Safety will be created, as a part of the Centre for Monitoring Quality in Health Protection. Furthermore, a specific role is to be played by relevant registers established and maintained for quality evaluation purposes, facilitating evaluation of health services quality in actual conditions, including an evaluation of procedures, medical technologies or medicinal products and medical devices used.

Creation of individual registers together with including patients into them will be based on issues including:

- specific diagnosis, disorder (type of disorder, type of diagnostic activities);
- subjecting a specific therapy to a specific procedure (type of care);
- use of a specific medicinal product or medical device.

All patients conforming to given characteristics should be notified to a register, regardless of a source for financing the services.

At the current stage – assumptions to a draft of the Act – proposed changes are relatively general, and it is difficult to say what the final regulation will look like. When a draft is published, it will be possible to evaluate whether the collected data will be published and whether technical solutions will be implemented, ensuring patients' effective access to that data, to select an optimum centre and therapy for a given disease.

Time from a reimbursement decision to actual availability of the therapy

A reimbursement decision made by the Minister of Health is not tantamount to providing cancer patients with access to a necessary therapy. Due to current regulations and practices at various offices, this process may take from several to several dozen weeks.

To initiate a therapy under a treatment programme that is not contracted by individual Voivodeship Branches of the National Health Fund as of a day of including the drug in the reimbursement system, all the following requirements must be met:

- an amendment must be issued to the President of the National Health Fund order establishing conditions for concluding and performance of contracts of a hospital treatment type within heath (treatment) programmes scope;
- an amendment must be issued to the Minister of Health Regulation concerning specific criteria for selection of bids,
- contracting of services by individual NFZ Voivodeship Branches and agreements in that respect,
- conducting of tender proceedings.

Of course, all those components require specific time for their performance. Apart from statutory deadlines, also of importance is how individual stages are performed by bodies responsible for implementation of a treatment programme – mostly, the NFZ President and centres providing care to a patient. The practice itself may either increase the time required for this process, or reduce it considerably.

There are many options for shortening of this time, and this may accelerate the availability of this treatment to patients. According to the first one, relevant solutions can be specified in reimbursement decisions, enabling an applicant to provide free of charge packages of the drug covered by a treatment programme before an agreement for its performance is concluded. This way patients that cannot wait until the whole process is completed are given a chance for an earlier therapy.

Second, tender proceedings can be conducted before an agreement for the performance of a given treatment programme is concluded, and this solution conforms to current regulations. With this solution, several weeks resulting from deadlines specified in regulations governing public procurements[1] may be saved.

Currently, the process of changing an order of the NFZ President takes from several to several dozen weeks. What is important, when a new drug in a new treatment programme is included in the reimbursement system, the contents of the order itself are not changed. In practice, individual appendices are changed in this process. When new drugs are included in the reimbursement system, changes are introduced to these appendices concerning establishing of a scope of a given service, determining costs of providing the drug under a given programme, evaluation of its diagnostics (flat rate catalogue) or precise determination of qualification criteria to a given programme. In consequence, activities aiming at improving a process of implementation of a given programme could focus on:

- accelerating collection and processing of data required by the President of the National Health Fund to establish the above scopes;
- adapting an internal procedure aiming at reducing time necessary for processing of specified changes.

There are many possible solutions that could shorten the time from the reimbursement decision issued by the Minister of Health to the actual availability of a previously not reimbursed therapy. In this respect, necessary activities include relevant changes in legislation, as well as establishing of a necessary practice at institutions participating in this process. Proposed solutions may be established at a level of administrative decisions, publication of reimbursement announcements, contracting of centres and tender proceedings, as well as processing of necessary changes required by current regulations. When these activities are coordinated, it would be possible to shorten the time which the patients have to wait for an effective and safe treatment.

Providing access to modern drugs before their registration (so-called *Compassionate Use*)

Currently, there are still doubts concerning the possibility of providing access to medicinal products before the registration stage, particularly, for therapies promising a significant therapeutic progress. In practice, in the past, the Ministry of Health indicated that Polish legislation did not include relevant regulations which could not be fully replaced by other regulations.

However, this does not undermine the fact that apart from the EU regulations, a detailed mechanism for granting a marketing authorisation to these products is not regulated. Appropriate regulations in this area could result in providing treatment to patients remaining without a therapeutic option, as well as ensure monitoring of therapy effectiveness and safety, to provide information of importance from the public payer's point of view during making a reimbursement decision – early access to medicinal products, apart from clinical studies, is the only source of information about a given product in that case.

An answer to this recommendation is the proposal included in the above-mentioned large amendment of the Reimbursement Act to introduce in the Pharmaceutical Law provisions concerning a programme for individual use of a medicinal product, including an option to use a medicinal product undergoing clinical studies or waiting for a marketing authorisation. Thus, in specific cases, patients

1 See M. Pieklak, K. Kumala, *Czy można rozpisywać przetarg na program lekowy którego jeszcze nie ma?* (*Can a tender be announced for a treatment programme that does not exist yet?*) „Puls Medycyny", 1 02 2016.

will be offered the possibility to use an unregistered product following the consent of the Minister of Health. The programme can be used in groups of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, or when an effective therapy with products holding marketing authorisation is not available.

The applicant can be a marketing authorisation holder or a sponsor of a clinical study, who, by submitting its application undertakes to ensure the availability of a product and indicates a way it will perform that obligation, as well as specifies a way for financing the therapy. Before issuing the decision, the Minister of Health can consult the European Medicines Agency or a consultant specialising in the relevant branch of medicine. When a consent is granted, the applicant is obliged, amongst others, to monitor the safety of the product.

The proposed regulation concerning a programme for individual use of a medicinal product is a positive one, particularly in terms of increasing patients' access to therapy. At the same time, the introduction of strict regulations concerning obtaining of data on products used under programmes, seems to be beneficial, particularly in regard to safety and effectiveness. The draft imposes specific obligations on the applicant, including monitoring of the product's safety; however, it does not provide for establishing of a separate register and collecting specific data in it. It should be emphasised, at the same time, that information concerning the use of drugs under a programme may later be useful during proceedings concerning including them in the first reimbursement decision. Additionally, the creation of these registers will facilitate monitoring of the programme's performance and meeting their obligations by applicants.

Emergency access to drugs

Apart from making available the products which are at the stage preceding their registration, it is also planned to regulate an option for the use of registered products not included in the reimbursement system in specifically justified cases, i.e. for medicinal products that are life-saving or do not have an alternate therapy. The current system does not include such a solution. However, this was proposed as part of the so-called emergency access to drug technologies, included in a so-called small amendment to the Reimbursement Act. According to the proposal included in the draft, the emergency access is to be used in justified cases resulting from indications in current medical knowledge, after all possible reimbursed medical technologies for a given indication are exhausted, when it is necessary to save a patient's life or maintain health.

Products used under emergency access must have a marketing authorisation and be available on the market. The therapy is financed under individual consent of the Minister of Health on an applicant's request. This consent is issued for a period not exceeding a three-month therapy or three treatment cycles, and then another consent can be issued to continue the treatment when a specialist confirms the effectiveness of the therapy applied.

In specific cases, i.e. when costs of the treatment exceed the statutory cost-effectiveness threshold or when a consent has been issued previously for a given product, the Minister of Health request the Agency for Health Technology Assessment and Tariff System to prepare an opinion whether financing of the therapy from public funds for a requested indication is justified. The draft does not provide for the collection of data gained when a drug is administered under emergency access. Analogously to the programme for the individual use of a medicinal product discussed above, an introduction of an institutional solution should be considered, to collect and process information following the establishment of an obligatory register. This data will facilitate monitoring of therapy safety and efficacy, and it can later be used during reimbursement proceedings.

Expert comments

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We have received an exceptionally mature study, containing a great wealth of information not only on the availability of individual cancer drugs in Poland, but also about numerous factors determining oncology care. Unfortunately, it is easily visible that in a country that spends little on health when compared to other countries with similar or larger national income, decisions concerning reimbursement of medicinal products must be negative more frequently than anywhere else. Actual decisions (concerning expenditures on health) are made much higher. At the level of the Ministry of Health and the National Health Fund these scant resources are only allocated. The report, in fact, does not include systemic accusations concerning the role of individual institutions in the process of making reimbursement decisions. The main accusation concerns delays in the decision-making process, and we must agree with it. On the other hand, this situation is rational to some extent, as institutions are waiting until an appropriate body of evidence is collected confirming the efficacy of a given drug technology. Although in recent years the absolute value of money forming the NFZ budget have been increasing, the needs have also been increasing due to ageing of our population. This is also accompanied by a technological progress. Many new therapies are not intended to replace old ones, but represent a treatment offer in situations where no effective treatment has been available so far (however, there also have been no expenditures). Due to all these reasons, we, as society, do not notice a significant improvement with time.

Drugs introduced nowadays are usually intended for a relatively small group of patients, as their "targeted" nature implies. For this reason, their possible implementation will not result in improvement of national cancer treatment indices. However, they can solve or alleviate many individual tragedies. For this reason, my opinion about clinical studies also differs slightly. In majority of international recommendations concerning cancer therapies, patients' participation in clinical studies represents an integral part of the recommended procedure. However, it does not represent an alternate solution to reimbursement of the already registered drugs for individual indications, as here clinical studies have already been conducted and completed. In oncology, clinical studies often concern situations when a patient has already exhausted available and known clinical options, but still feels well and wants to live longer. In many cases these studies are non-commercial, when there are indications that an available and registered drug for one disease may also be effective for another. For example, rituximab mentioned in the report is already registered for several types of B-cell lymphomas, but there are several dozens of these lymphomas, and this drug is also effective for most of them.

In Poland, the entities responsible for organising health care do not seem to understand the role played by clinical studies. A prevailing approach treats medicine as something intellectually complete, while in fact this is a system that changes rapidly, and clinical studies are a driver for these changes. Commercial studies provide patients with access to innovative molecules which are not commercially available, and thus their reimbursement should not be discussed. However, at another level they can solve a relatively similar problem – a need for an additional treatment option for patients who have already exhausted available and reimbursed treatment options. Non-commercial studies play a similar role, but using drugs that are commercially available; however, they are registered and reimbursed for other indications than a disease that a given patient has. Furthermore, in some cases a good concept for a non-commercial study may give more to a patient for much less money than access to an advertised new medicine.

Another problem is a situation, when a drug is registered but not reimbursed. Many hospitals refuse patients

an option to receive that drug when a patient or a foundation representing them are ready to finance it. Apparently, it should be clearly emphasised that such refusal is in breach of the Constitution of Poland.

As human beings we must remember that we are all equal when facing the risk of disease and in many cases, only our good fortune is responsible for the fact that we are still healthy. Therefore, as society, our duties towards patients increase along with the extent to which they have been affected by a disease. We need to ensure that whenever we fall ill, we will be placed in the most favourable environment that our country can afford. The biggest unchanging problem in oncology are patients for whom no treatment options are available.

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The report – prepared by PEX PharmaSequence to the order of the ALIVIA Foundation – evaluates the availability of new cancer drugs in Poland. The authors have analysed the situation relating to drugs used for solid tumours and proliferative diseases of haematopoietic and lymphatic systems, representing the largest hazard in terms of mortality ratios. The main aim of this study was to establish the basis for initiating a discussion about the possibilities of increasing access to effective methods of pharmacological treatment of cancer.

An attempt to reduce limitations and ensure differentiation facilitating the performance of correct – in medical and economic terms – diagnostic and therapeutic processes for cancers in Poland is of particular importance, as recently many drugs have been introduced of different (higher or lower, yet still considerable) clinical value and usually requiring high financial expenditures.

In 2014, in Poland nearly 160 thousand people were diagnosed with cancer, and this incidence will continue to increase. The increasing morbidity ratio is also of importance – currently nearly 400 thousand people living in Poland have been diagnosed with cancer within the last 5 years. Due to the increasing incidence and morbidity rates, ensuring a required diagnostic and therapeutic process becomes increasingly challenging. It is necessary to provide substantial financial resources and use the available options rationally. Financial expenditures on fighting the hazard of cancer available to the health care system in Poland are, when calculated per capita, more than twice as low as the EU average. Insufficient financing opportunities, together with strict rules for establishing a clinical value and deciding about reimbursing new cancer treatment methods with public finances, as well as the insufficient use of risk-sharing mechanisms, result in limited options for the use of many new drugs with scientifically confirmed efficacy. The above-mentioned limitations still exist for drugs used for certain cancers, regardless of the positive reimbursement decision and supplementation of treatment programmes in recent months (e.g. breast cancer, gastrointestinal stromal sarcomas, or Hodgkin lymphoma).

Limited access to new cancer treatment methods is not a problem faced by Poland alone. This problem concerns – to a lesser or greater extent – many European countries. In February 2017, a conference of the European Council was held in Malta, focusing, amongst the others, on challenges related to high costs of new pharmacological treatment methods for cancer faced by all European Union Member States. In May of this year, another meeting of European experts is planned, in which pharmaceutical companies will also participate, aiming at finding solutions for problems related to the issue of high costs.

Due to the importance of that problem, European scientific societies have undertaken initiatives aiming at developing methods for establishing an actual value of new treatment methods (e.g. an algorithm proposed by the European Society of Medical Oncology). It should be mentioned here that also the Polish Society of Clinical Oncology (PTOK) and the Polish Society of Oncology (PTO) have developed and published in 2015 an algorithm for comprehensive evaluation of an added value of new treatment methods, which considers the conditions of the Polish health care financing system. What is important, the modern algorithms used to evaluate the value of new treatment methods consider efficacy, scientific grounds, influence on quality of patients' life and safety of new drugs. It is particularly important to consider in the evaluation the nature of side effects that may be less frequent and severe, when compared to standard methods (e.g. chemotherapy – common reference in evaluation of other pharmacological treatment methods – causes numerous complications, requiring relevant supportive therapy). Unfortunately, so far institutions responsible for reimbursement decisions have not been interested in using the said algorithm developed by PTOK and PTO.

This report indicates that in Poland the access to new cancer drugs is insufficient and should be improved. On the one hand, it is necessary to increase the number of reimbursed drugs with modern mechanism of their anti-cancer effect. On the other, processes of making reimbursement decisions should be accelerated. The authors of this report are right to say that a reduction in delays in making financing decisions (and thus, improving availability) for modern cancer drugs depends on the cooperation of all parties concerned, being: the payer, drug manufacturers, and the scientific community.

A valuable method for improving options for financing new methods for cancer treatment is the use of additional sources of financing. For example, additional resources can be obtained from the CANCER DRUGS FUND, whose structure and principles of operations were presented in 2016. This additional source of financing should use its funds to provide access to modern treatment methods for all cancer patients.

For many procedures currently financed from public resources under the current basket of guaranteed oncology services there are doubts concerning the justification and amount of that financing. Options for reimbursement of new methods for cancer treatment can be expanded by analysing the so-called basket of guaranteed medical services and determine the value of existing methods to limit the scope of application for ineffective methods and obtain resources for more valuable ones.

The authors of this report focused, as assumed, on most common cancers representing the biggest threat to the population. However, one should remember that the fact that in many clinical situations no valuable treatment methods are available should influence the determination of possibilities to reimburse new procedures. It is recommended to verify the so-called cost-effectiveness thresholds used to determine the value of new diagnostic and therapeutic methods, and differentiate their levels

depending, mainly, on the clinical characteristics of the evaluated indication (e.g. incidence rate and assumed treatment with the evaluated method). In many common cancers we should consider the transfer of currently available treatment methods to earlier stages of the process, as this may result in greater health benefits. An example of such situation is the program for the treatment of patients with advanced colorectal cancer, for which monoclonal antibodies can only be used during the third line therapy, while their use in the first line is more justified in terms of scientific evidence and clinical value.

It is a duty of oncology societies to create conditions for a more extensive use of modern diagnostic and treatment methods. An example of such activities includes promoting a more extensive use of molecularly targeted drugs and immunotherapy in patients with advanced non-small-cell lung carcinoma – both these treatment methods are more valuable than traditional chemotherapy, provided patients are correctly qualified on the basis of well-organised genetic and molecular diagnostics.

Concluding, it should be emphasised that the value of the report focusing on the availability of modern methods for cancer treatment in Poland results from a detailed evaluation of the current situation and making references to conditions in other European countries. We can only hope that the conclusions of this report are taken into regard and that they initiate a discussion and actions aiming at expanding the options available for pharmacological treatment of cancer.

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In Poland, the main problem faced by clinical oncology is the difficult access to therapies having a significant influence on the prognosis for patients undergoing systemic palliative treatment. It is a population of patients with an incurable, usually systemic neoplastic process, for whom pharmacotherapy usually represents a sole option for long-term treatment controlling the disease, maintaining good quality of life and significantly increasing its length.

In the case of patients with early stages of solid tumors, a quick, radical and multidisciplinary approach, combining strategies coming from surgical oncology, clinical oncology and radiotherapy, is crucial for effective and successful treatment (curing). For radical treatment, it can be assumed that therapeutic standards in Poland, including access to new drug therapies, do not deviate significantly from European standards. Unfortunately, the issue of access to effective systemic therapies for systemic palliative treatment, representing in fact long-term treatment for a chronic disease, looks completely different. All new drugs used for treatment of cancer are practically first registered for palliative treatment. Considering the above, this is a population of patients for which new options for systemic treatment appear the fastest.

Certainly, costs of new therapies are enormous, and continue to increase. Even for very rich countries, such as the U.S., these costs are sometimes completely unacceptable, and this is reflected in publications analysing the cost effectiveness of new therapies, e.g. in the American insurance system. In our country, in which expenditures on oncology belong to the lowest amongst the developed countries, challenges associated with the financing of new therapies are incomparably higher, and patients, oncology specialists and the payer are all aware of this fact.

By establishing the Agency for Health Technology Assessment and Tariff System, a transparent system for evaluation of innovative oncology therapies was introduced. The factors including the adapted cost-effectiveness threshold used to evaluate new therapies can be questioned, yet certainly the cost of using the majority of innovative therapies is much lower in Poland than in Western Europe. However, from the perspective of the last few years of AOTMiT operations it seems that this institution, previously operating relatively efficiently, has been increasingly slow and inert. A very negative impression caused by the publication of a letter of deputy minister Igor Radziewicz-Winnicki to AOTMiT and the Transparency Board, persists. Some of independent experts evaluating innovative systemic cancer therapies on request of AOTMiT are of the impression that when their opinions do not conform to the Agency's assumptions, they are not considered at all. These doubts result in the deterioration of cooperation between the circles of clinical oncologists and the Agency, and this certainly does not have a favourable effect on the activities of this body concerning the provision of opinions for new cancer therapies.

Another problem associated with access to innovative cancer therapies is the completely untransparent, very long and often ending in failure process for making reimbursement decisions by the Ministry of Health. This long process can be justified for drugs whose reimbursement is considered despite the negative recommendation of the AOTMiT President. But a need to wait frequently for several months before therapies that have been positively evaluated by AOTMiT are included in the reimbursement system is completely unacceptable! From the point of view of patients and their families, who are waiting for access to a new, active therapy with the positive opinion of AOTMiT, this delay at the Ministry is completely unethical.

One of the most important problems in clinical oncology in Poland, which is not extensively discussed in this study, is the issue of limited access to traditional, cheap cancer drugs (chemotherapy drugs). A lot of well-known chemotherapeutic agents were registered for specific indications 20 or 30 years ago, and numerous studies conducted through the decades confirmed the effectiveness of these drugs also against other cancers which were not considered in the primary registration (so-called summary of product characteristics). Unfortunately, due to generic drugs introduced, high costs and complicated procedures for changing provisions in the registration provisions, frequently the new indications are not included in summaries of product characteristics. The fight for the longest and the best survival of patients undergoing systemic palliative treatment, in conditions of limited access to innovative cancer therapies in Poland, forces doctors to seek other pharmacological options. Frequently, such an option is the use of classic chemotherapeutic agents outside their registered indications. This procedure is one of the components of a routine clinical practice in many countries, while in Poland it is practically impossible, as an institution of the so-called non-standard chemotherapy was abolished, and drugs available under the so-called chemotherapy catalogue are strictly assigned to specific diagnoses.

Oncology communities in Poland, including the Polish Society of Clinical Oncology, for many years have been informing the Ministry of Health about the need to modify provisions in the chemotherapy catalogue for specific drugs, on the basis of the latest scientific findings. Unfortunately, although Polish experts have prepared detailed lists of those drugs together with specific indications, the Ministry of Health has not been able to reach a decision for over six months. This decision does not concern drugs that cost PLN 15000–30000, but PLN 300–1000 per one patient per month!

Inertia, resistance and unwillingness of the Ministry of Health to introduce changes in the chemotherapy reimbursement, which for many patients means that their last option for a possibly effective cancer treatment is removed, particularly considering low costs of that therapy, are unacceptable and wrong. The recently published

announcement of the Minister of Health, containing a chemotherapy catalogue in force as of 1 March 2017, which does not contain a single change of those suggested by the community of clinical oncologists, only deepens frustration and bitterness of patients and doctors alike.

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The presented report: "Oncology patients' access to drug therapies in Poland in view of current medical knowledge" focuses on a very important issue. The study presents an analysis of epidemiological data concerning cancers in Poland, against European data. It also describes access to drugs for 10 solid tumors and 10 haematological cancers. A task that the authors set for themselves was very ambitious, and focusing on this important subject should be praised once again. However, it seems that a competent support at a level of designing the analysis, not limited just to expert comments, could enrich this report. The presented epidemiological data referring to Eurostat data does not include detailed methods and a critical discussion of presented analyses. Data concerning incidence rates should always be referred to detection levels and reporting effectiveness, as it may appear that countries with high incidence rates in fact developed effective methods for reporting of cancer incidence rates.

In relation to haematooncology, access to therapeutic resources is a very important component of effective treatment. This concerns both patients in whom the use of effective drugs results in curing, as well as those patients in whom the progression-free survival can be improved. This second component is of paramount importance for patients suffering from incurable and recurrent proliferative haematological diseases, in whom a therapeutic benefit depends on the availability of various therapeutic agents, and the improved total survival is a sum of individual disease-free intervals. Access to drugs should however be analysed in detail. When access to a drug required by 5% of patients is limited, can we say that the whole population does not receive optimum treatment or is not treated according to a standard? The report includes such simplifications, similarly as the table summing up the report which indicates that in general, 95% of cancer patients in Poland are treated in a way not conforming to international standards. This statement is far from the truth. In clinical practice we see certain limitations in access to the latest innovative drugs. In Poland, when a reimbursement decision is made, its effect on the budget is also considered, and with the limited budget this results in a negative decision. With new possibilities for financing emerging, a debate concerning analyses of medical needs should be conducted. The creators of the National Comprehensive Cancer Network (NCCN) are also aware of financial limitations and the inevitable approach of the moment when the financial capabilities of the health care systems of richer countries will be exhausted, and in the latest versions they add the "evidence blocks" analyses, graphically illustrating the relationship between treatment effectiveness, its safety, a level of medical evidence, data coherence and costs. These last ones consider not only the purchase of the drug, but also costs of medical care, monitoring of treatment and toxicity, and supportive treatment. Unfortunately, all innovative drugs in this last category are marked as very expensive for the system. When access to specific drugs is considered, an analysis of countries with a similar gross domestic product seems to be a good tool. Unfortunately, even this analysis shows that amongst countries from the Visegrad Group, Poland allocates small funds to innovative drugs, and access to some important drugs is limited. Apart from recently registered drugs, for which reimbursement processes are currently in progress, the authors of the report notice limitations in access to drugs under treatment programmes. This results both from narrowed registration indications and from geographically diversified access to drugs. It seems that an effective solution, proposed many times before, would be to move drugs to the chemotherapy catalogue with limited indications after 2–3 years, and then after a few more years the drug should be available according to its registration indications.

Concluding, the table of international standards in relation to access to drugs in Poland is insufficient to propose systemic solutions. However, it indicates that a detailed analysis is necessary to determine the most important medical needs that are still unsatisfied, as well as a need for introducing changes to improve the effectiveness of treatment for cancer patients in Poland.

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Cancers are one of the most common causes of death, and epidemiological data for Poland are not optimistic and indicate a foreseeable increase in health and social importance of this group of diseases. In Poland, incidence rates remain at relatively low levels, when compared to Western Europe (and this implies their possible increase in the nearest future); unfortunately, data concerning morbidity are significantly less advantageous; the improvement in these results in recent years has also been lower than in the majority of European countries. The example of the Czech Republic is particularly notable here, as this is a country with similar geographic and socio-economic conditions. In 1990–2013, the cancer mortality rate in that country dropped by over 28 percent, while in Poland it was less than 8%. What is particularly worrying, mortality rates higher than in other countries concern mainly the "economically active" population (below 65 years of age).

When cancer morbidity and mortality rates are analysed, the human factor is mainly considered; however, we should remember that results of cancer treatment translate also into economic indices – it is estimated that during just one year about PLN 900 million is lost in GDP due to cancer mortality. Those values are much higher when the "lost" theoretical expected cancer-free survival is considered, and they reach 8 to 10 billion zloty. This amount is further increased by costs related to sick leaves of cancer patients and their families that provide care to them.

However, moving to the main aim of the prepared analysis: the presented picture of the situation indicates numerous limitations – resulting not only from economic limitations (it should be assumed that Poland, similarly to many other countries, cannot afford financing all new drugs launched onto the market), but also, what is most worrying, from procedural and bureaucratic limitations. The average time for making a reimbursement decision for individual formulations in great majority of cases exceeds the statutory assumptions; additionally, a few more months frequently passes between that decision and the actual availability of the drug, necessary to implement relevant legal regulations at the NFZ level and conducting tender proceedings.

At this level, very worrying differences related to the time for introducing individual programmes and amounts allocated to their reimbursement between individual NFZ branches can be seen. An example of that situation is the treatment of the prostate cancer with abirateron, where the amounts allocated to its reimbursement in neighbourhood voivodeships (of similar demographics) differed by as much as one order of magnitude.

It should, however, be remembered that in some cases benefits associated with the use of a new drug may be small and counterbalanced by its toxicity, and thus its reimbursement is not a priority from a medical point of view. A tool helpful in prioritising reimbursement needs may be scales developed by leading international scientific societies, including Magnitude of Clinical Benefit Scale prepared by the European Society for Medical Oncology or the Value Framework for Anticancer Drugs developed by the American Society of Clinical Oncology. Development of objective criteria for the evaluation of benefits of individual drugs measured as their effect on the total survival and progress-free survival, while considering toxicity and effect on the quality of life, allows to arrange available drugs in terms of priority of their reimbursement. At the moment, the Agency for Health Technology Assessment and Tariff System (AOTMiT) and the Ministry of Health to a large extent use data prepared by a drug producer or an entity authorised by it, without any attempts to objectively refer their value to other formulations that are reimbursed or apply for reimbursement in individual populations of patients. For these reasons, some reimbursement decisions may raise substantial doubts or be considered subjective.

Additionally, it would be recommended to introduce a previously absent mechanism for verification of value of drugs that were included in the reimbursement system in the past, and for which (or other formulations for the same therapeutic indications) new data on their efficacy or toxicity is available.

Another problem associated with Polish treatment programmes is an artificial limiting of the population of patients that may be covered by them. A great majority of them accepts treatment of populations of patients narrower than provided in the drug registration records. This may concern an "artificial", unjustified by evidence exclusion of some patients (for example, due to comorbidity such as another cancer or a need for a surgical treatment for a primary cancer, as it is required by the treatment programme for kidney cancer), or limiting of a possibility to use that treatment only to a specific therapy line. This problem may result, for example, from lack of attention of people developing the programme, who define the rules for treatment under a programme by transferring inclusion criteria from clinical study protocols using a "copy-paste" method. Additionally, existing programmes remain unmodified to a large extent, even when experts indicate errors in their descriptions or when knowledge on a specific drug simply changes. Moreover, this situation may lead to unfair promotion of one manufacturer. For example, trastuzumab in its subcutaneous form was introduced into the treatment programme for breast cancer under more favourable conditions (conforming to current knowledge) than specified for trastuzumab administered intravenously. Its conditions are defined by an "old" provision, on one side referring to a much narrower population of patients, while on the other requiring the use of much more extensive diagnostic procedures. These differences in the possibility of using trastuzumab in its subcutaneous or intravenous form are not justified by the available evidence, and in a situation, when intravenous trastuzumab biosimilar preparations will soon appear on the market, they create clearly advantageous conditions for a manufacturer of that drug in its subcutaneous form.

Apart from all these formal and organisational limitations, the main problem seems to be the lack of political

will to improve Polish peoples' access to innovative drugs. Public expenditures on drugs and other perishable medical goods per capita (with purchase power parity considered) in Poland are the lowest amongst all European OECD countries. Unfortunately, after the Reimbursement Act was implemented in 2012 (which declared an increase in access to innovative drug therapies), NFZ reimbursement expenditures dropped by over 16%. Additionally, in 2015–2016 a share of cancer drugs in NFZ expenditures on innovative drugs also decreased. Also striking is the dramatic drop in the number of positive recommendations of AOTMiT since 2015, and it was correlated with a letter of the deputy minister of health at that time disclosed by newspapers, which recommended focusing more on financial aspects when analysing a reimbursement application. Additionally, AOTMiT recommendations are not biding to the Ministry of Health, and decisions about granting reimbursement are frequently made despite a negative AOTMiT recommendation. Possibly it should be considered here whether Polish society can afford maintenance of an institution which does not follow guidelines specified in the Act in its operations, and whose recommendations are frequently not considered.

Another problem is an inadequate valuation of treatment programmes, so they are unprofitable to service providers, and in some cases even generate losses. For this reason, some institutions are not interested in implementing them, and patients' access to treatment is unnecessarily hindered. Due to extensive formal requirements and high penalties for not meeting requirements that are frequently of secondary importance, doctors are not willing to manage treatment programmes, and when they do this, reporting requirements take a considerable part of their time which should be dedicated to their patients.

With budget limitations, clinical studies could provide an alternate access to innovative therapies for some patients; unfortunately, legal regulations significantly hinder them. Additionally, patients are sometimes even "punished" for their participation in the study (and thus relieving the budget) by limiting to them access to successive lines of the therapy (as they do not meet criteria for the preceding treatment).

For all these reasons, the participation of Polish patients in treatments with innovative drugs, even when they are nominally reimbursed, is not optimal. The estimations indicate that the use of trastuzumab in Polish patients is lower by half than in the richer countries of Western Europe and the U.S. (data up to 2013). Similar reports are presented in the discussed report.

It should also be analysed why certain producers do not even attempt or withdraw from activities aiming at

reimbursement of their drugs in the large, and thus potentially attractive Polish market. According to the discussed report, this situation occurred for 56% of drugs planned to be implemented! The reasons underlying this situation may vary, but formal difficulties, high costs of preparing required analyses, and the very uncertain result of the whole process are definitely of importance.

Another problem is the fact that even when a drug is nominally reimbursed, patients may still have to pay significant amounts. This situation may occur for some drugs available in out-patient health care (pharmacies) covered by one price limit – in some cases, despite different indications and use. And so, because the short- and the long-acting granulocyte colony-stimulating factors were classified in one limit group, a co-payment at a pharmacy for one package of that last drug amounts currently to over 500 zloty (February 2017).

For all these reasons, the access of Polish patients to modern oncology treatment is suboptimal. At the same time, epidemiological data indicate much worse treatment outcomes when compared to other European countries. A direct causal relationship cannot be clearly indicated here, but data from other countries clearly show that treatment expenditures and outcome are correlated, so the conclusions are obvious...

Glossary

non-standard chemotherapy – (non-standard chemotherapy programme) a mechanism allowing NFZ financing a therapy that is not available in standard financing channels/reimbursement system when available drugs proved to be ineffective or could not be administered to a patient due to medical indications. The basis for initiating financing of a therapy under non-standard chemotherapy was the NFZ's consent to finance it issued on request of a doctor in charge of a given patient. In general, non-standard chemotherapy was available in the system until the end of 2014. In subsequent years, only 2 groups of patients had access to non-standard chemotherapy:

- patients continuing therapies initiated before 1 January 2015 under a procedure "Treatment programme for non-standard chemotherapy" for a given drug, a relevant indication in a given patient;
- patients who received an approval for non-standard chemotherapy for applications submitted at a voivodeship NFZ branch by 31 December 2014.

risk-sharing instruments – agreements between the Ministry of Health and pharmaceutical companies applying for adding their products into the reimbursement system, concluded to limit a risk of excessive expenditures charged to the National Health Fund. The risk sharing instruments contain mechanisms of financial nature (e.g. when a number of packages sold specified in the agreement is exceeded, an equivalent of a part of the reimbursement paid by NFZ to finance therapy with "excessive" drug packages is reimbursed to the Ministry of Health) and based on health outcome (e.g. the Ministry of Health agrees to finance costs of therapy with a given drug only for patients in whom this drug resulted in an improvement in their health; for patients that did not benefit from using that drug a pharmaceutical company reimburses costs borne by NFZ in relation to its use in that group of patients).

chemotherapy catalogue – a category of reimbursement availability specified in the Reimbursement Act. The catalogue includes a list of active substances used and reimbursed as a part of chemotherapy for cancers. A characteristic feature of drugs from the chemotherapy catalogue is that they can be freely used by a doctor in charge of a cancer patient whose diagnosed cancer is on a list of diseases allocated to a given active substance. A list of drugs included in the chemotherapy catalogue, together with diseases for which they can be used, forms an appendix to each reimbursement announcement published by the Minister of Health.

ATC class – (anatomical-therapeutic-chemical classification), a system organising drugs, and other agents and products used in medicine. Classification is based on assigning a given drug to a relevant anatomical, therapeutic and chemical group. The ATC Classification is managed by the World Health Organisation (WHO). In the report, drugs from two ATC classes were used: **L01** – Cytostatics and **L02** – Drugs used in endocrine therapy

generic drug – (equivalent of an original drug, equivalent of a reference drug) another drug containing the same active substance, manufactured when patent protection for the first drug containing that substance (original/innovative drug) expires. The companies manufacturing generic drugs do not bear costs associated with the development of a new drug and launching it onto the market (e.g. costs of clinical studies). For this reason, they can offer a drug at a considerably lower price than the price of the original drug. From the point of view of the health care system, generic drugs significantly reduce costs of treatment.

original drug – (innovative, or reference drug) – **the first** drug with a new active substance launched onto the market and granted marketing authorisation due to its therapeutic efficacy, quality and safety documented on the basis of clinical studies, versus other products used for the same indication. From the patients' point of view, original drugs represent a new therapeutic option, thus it is important for them to get quick access to such drugs. From the

point of view of the health care system, innovative drugs are a cost-generating item in the system. In general, financing of original and generic drugs should be associated with each other – savings appearing in the health care system when generic drugs are launched onto the market should be used to finance new original drugs.

LYG – life years gained – a modified mortality measure including in its definition the expected remaining years of life. This measure puts more emphasis on the younger part of the population, as saving a life of a newborn guarantees gaining more years of life than it is possible when a life of an elderly person is saved.

reimbursement announcement – a communication of the Minister of Health published every two months, being a kind of an announcement listing all drugs, foodstuffs for particular nutritional purposes and medical devices that are included in the reimbursement system during the announcement validity (have a valid reimbursement decision). In general, only drugs listed in the announcement are reimbursed (from the reimbursement system, a drug is a single package labelled with a given EAN code, meaning that a package of the same drug, containing the same number of pills, at the same dose, but packed in a different way (for example, pills in a bottle instead of a blister pack), having a different EAN code not included in the announcement cannot be issued to a patient with reimbursement).

treatment programme – a category of reimbursement availability specified in the Reimbursement Act. Treatment programmes allow a regulatory body controlling a population of patients who can be qualified for treatment with a given drug. Thus, a regulatory body can limit reimbursement costs borne by NFZ on treatment with a relevant drug. In general, treatment programmes concern innovative, expensive active substances. A description of a treatment programme contains specific criteria to be met by a patient to be included in the programme and receive a given drug, and criteria which, when present, result in excluding a patient from the programme. Lists of drugs reimbursed under treatment programmes and detailed descriptions of individual programmes form an appendix to the Minister of Health announcement published every 2 months and concerning a list of reimbursed drugs, foods for particular nutritional uses and medical devices.

QALY – quality adjusted life years. This tool is a "positive" measure of health. It determines the length of the further life adjusted for limited activity due to a disease or disability. This measure is commonly used to determine the maximum cost of a new therapy acceptable to a payer; e.g. according to provisions of the current Reimbursement Law, for a new therapy covered by reimbursement in Poland a cost of achieving 1 QALY should not exceed three times the GDP per capita.

logarithmic scale – a type of measuring scale used to present in one chart data characterised by a large range of analysed values.

therapeutic standard – (medical standard, therapeutic guidelines) – a list of recommendations for prevention, diagnostics, treatment and rehabilitation for a given disease developed by experts in a given area of medicine. They can be developed by domestic or international scientific bodies. Standards are not a law. They represent valuable guidelines for doctors in their daily clinical practice.

mortality rate – a measure of disease severity defined as a ratio of the number of deaths of a given disease to all diagnosed cases of that disease within a period of time (usually per year).

drug technology – a medical technology with a drug being its main component.

medical technology – a technology whose main component are not only drugs or devices, but also procedures and algorithms, and methods of caring for a patient in a given disease, in a given health care system.

Reimbursement Act – the Act of 12 May 2011; the main legal act in Poland governing Reimbursement of Medicines, Foodstuffs for Particular Nutritional Purposes and Medical Devices .

standardised ratio – a parameter used in epidemiology determining how many cases of disease (deaths) would occur in a given population, if the age structure of that population were the same as the age structure of the population used as the standard. Usually expressed as calculated for 100 thousand inhabitants. It facilitates analyses of populations differing in their age structure.

incidence – the number of newly diagnosed cases of a given disease in a population within a period of time (usually per year) calculated per 100 thousand people.

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