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Lung cancer — the clinical benefits of treatment with ALK inhibitors in light of economic constraints in Poland

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ABSTRACT

In 2012, approximately 153,000 new cancer cases and almost 95,000 cancer-related deaths were recorded in Poland. Despite an increase in new cancer cases, the number of deaths decreased as compared to the previous year. It is estimated that in Poland in 2012 more than 364,000 people were alive with cancer having been diagnosed during the previous 5 years. Lung cancer remains the leading cause of mortality and the greatest social challenge among all malignancies. In the female population, both morbidity and mortality from lung cancer are increasing, while both of these indicators are steadily decreasing among men. Non-small cell lung cancer (NSCLC) is the most commonly diagnosed group of lung cancers, accounting for more than 80% of histological diagnoses.

Lung cancer is characterized by unfavorable five-year survival rates (in Poland approximately 14%) and relatively little therapeutic progress for decades. A growing number of genetic determinants of the development and progression of lung cancer have been identified recently with impact on new treatments, in particular molecularly targeted agents. In recent years, results of randomized phase II and phase III clinical trials and retrospective analyses have indicated significant improvements in outcomes of overall survival, progression free survival, the objective response rate, as well as the quality of life in groups of patients with certain genetic abnormalities in tumor cells. The wide availability of epidermal growth factor receptor (EGFR) inhibitors in the first or second line treatment of patients with advanced lung cancer allows for prolonged progression-free survival of patients with mutations in the *EGFR* gene by 66% compared to those receiving standard chemotherapy. However, precise selection of patients for ALK inhibitors in second-line treatment of advanced NSCLC patients with ALK gene rearrangement allows for the prolongation of median overall survival to approximately thirty months, a target which has never been obtained in this group of patients. The drug programs currently funded by the National Health Fund do not cover ALK inhibitors, which have to meet challenging pharmacoeconomic requirements. The growing role of economic analyses in the process of updating and implementating oncological drug programs in Poland has a crucial impact on the availability of new treatment options for patients. It seems, therefore that verification of the updated results and the correct interpretation of pharmacoeconomic data is of greatest importance.

Key words: lung cancer, epidemiology, molecularly targeted therapy, ALK inhibitors, healthcare reimbursement, access to targeted therapies, cancer treatment costs, economic burden of cancer, cost effectiveness, National Health Fund

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Introduction

Quality of life and survival are currently the main parameters considered during the interpretation of results of clinical trials with new antineoplastic treatment methods. Direct comparison of clinical trial results with the current standard of care is very difficult, due to the complexity of evaluation and multiplicity of analytical methods, as well as changing requirements for designing clinical trials. As there is lack of head-to-head comparisons of particular therapeutic methods, making adequate decisions according to the availability of the new modalities is especially challenging. Growing contradictions between the general progress of medicine and the financial possibilities of publicly-funded bodies has led to the tightening of criteria of health technology assessment and establishing price levels on which certain technology may be reimbursed. Many clinical trials are conducted in very small subpopulations of patients with particular molecular abnormalities in cancer cells and despite the multinationality of the studies, it is difficult to obtain results with sufficient statistical power. On the other hand, the expectations of patients regarding their access to new treatment methods is still increasing, a factor which is especially important in patients with lung cancer and hematological malignancies.

Lung cancer is the most common cancer worldwide, with approximately 1.6 million patients suffering from this disease annually. Additionally, lung cancer is the leading cause of cancer-related deaths both in the female and male genders (in general there are approx. 1.4 million deaths each year). Non-small cell lung cancer (NSCLC) is the most commonly diagnosed subtype of lung cancer, accounting for more than 80% of histologically diagnosed diseases. At diagnosis, nearly half of patients are in advanced/metastatic stage. The median of survival time in this group of patients currently ranges between 8 and 12 months. In a proportion of patients, there is the possibility of using targeted treatments, which significantly improve progression-free survival, overall survival, as well as quality of life [1].

Recent research efforts led to the identification of driving molecular abnormalities that serve as predictive features for the benefit from novel cancer targeted therapies. It has been shown that treatment with tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) and TKIs for ALK is beneficial in some patients, which justifies a personalized approach in the process of choosing an optimal management strategy. The clinical trials in patients with cancers driving by molecular abnormalities (*KRAS*, *HER2*, *BRAF* genes mutations and *ROS1*, *RET* and *NTRK* gene rearrangement) are currently during phases I, II and III. The discovery of the predictive value of *EGFR* mutation and *ALK* gene rearrangement in NSCLC patients has facilitated further treatment optimization by distinguishing subpopulations obtaining real clinical benefits from certain treatments. Moreover, the results of clinical trials and retrospective analyses have indicated the high effectiveness of ALK inhibitors in patients with advanced NSCLC and *ALK* gene rearrangement, leading to prolongation of median of overall survival to a period ranging between 2–3 years.

Epidemiology

In the second half of the 20th century, lung cancer morbidity among men in Poland dramatically increased. In contrast, in the last two decades this trend has constrained and reversed due to a reduction in smoking. Morbidity and mortality due to lung cancer in young men, as well as those middle-aged, has decreased by up to 30%. At the same time, in the last decade, lung cancer mortality and morbidity rates among women have dramatically increased. Indeed, this was the main reason that, since 2007, lung cancer has become the leading cause of cancer-related mortality in women, preceding even breast cancer (Tables 1, 2). A region-based analysis performed by Polish National Cancer Registry (*Krajowy Rejestr Nowotworów*) indicates that lung cancer mortality rates among women are higher in big urban areas than in surrounding regions [2]. In all provinces in Poland, lung cancer is the most prevalent cancer in men, with subsequent malignant neoplasms including prostate, colon, bladder and stomach cancers. Depending on particular provinces, lung cancer is the second or third most prevalent cancer among women. Moreover, lung cancer has become the most common cause of cancer-related deaths among women in up to 11 out of 16 provinces in Poland.

The rearrangement of the *ALK* gene [*ALK* (+)] is observed in 3–5% NSCLC patients, mainly those presenting adenocarcinoma histology and more commonly in non-smokers [3, 4]. In Poland, this produces the absolute number of approximately 240–360 patients with stage IV disease, of whom approximately 60–100 would be qualified for treatment with ALK inhibitors after the failure of previous lines of treatment. Detection of such number of translocations of the *ALK* gene would need 1200–2000 molecular assessments of primary tumor samples from patients after the failure of first line chemotherapy.

The main risk factor in all lung cancer patients is active smoking while the risk of lung cancer development is proportional to the duration of smoking, the number of cigarettes consumed and age of starting to smoke. Other risk factors have definitely a lower significance in the whole population and they are as follows: radiation exposure, asbestos exposure, cancerogenous chemical

Table 1. Lung cancer morbidity in Poland in 2012

Sex	Absolute number	Percent	Crude rate per 100,000	Standardized rate per 100,000
Male	15,177	19.9	81.4	51.2
Female	6,660	8.7	33.5	17.8

Source: National Cancer Registry (*Krajowy Rejestr Nowotworów*)

Table 2. Deaths in patients with lung cancer (C34) in Poland in 2012

Sex	Absolute number	Percent	Crude rate per 100,000	Standardized rate per 100,000
Male	16,182	30.7	86.7	53.5
Female	6,434	15.3	32.4	16.4

Source: National Cancer Registry (*Krajowy Rejestr Nowotworów*)

substances and some heavy metals (cadmium, lead, nickel, arsenic), as well as the long-lasting exposure to the toxic fumes of coal and liquid fuels [5].

Genetic and molecular diagnostics

The diagnostics of lung cancer, together with disease staging and treatment, is currently a very complex process which needs a multi-specialized approach with a team involving a clinical oncologist, a radiotherapist, a cardiothoracic surgeon, a radiologist, a pathologist, a specialist in molecular biology and a palliative care. Reimbursement of targeted treatments for patients with advanced NSCLC has additionally influenced the need to organize multi-specialized teams and to develop guidelines regarding histology sample processing. The availability of oncology molecular tests, including the assessment of biomarkers of treatment response (molecular predictive factors), plays an essential role in the accurate qualifying of lung cancer patients to targeted treatment. The recognition of such factors is of greatest importance in the making of therapeutic decisions, including matching targeted drugs to the cancer's genetic profile (genotyping). Constraints regarding access to molecular testing could impair the effectiveness of treatment, as well as generate additional costs for the healthcare system. *ALK* gene rearrangement is the second molecular test which, together with the *EGFR* mutation test, is performed on NSCLC patients aiming at qualification to molecular-targeted treatments. According to European and Polish recommendations about molecular testing in NSCLC patients, an assessment of *ALK* gene rearrangement is the standard of care in the process of qualifying patients for treatment with ALK inhibitors. *ALK* gene rearrangement assessment should be performed in all patients with adenocarcinoma and in those with lung cancer presenting an adenocarcinoma component. It is recommended to assess the status of *EGFR* gene mutation at first, while *ALK* gene rearrangement should be performed in patients without somatic mutations in the *EGFR* gene. The turn-around time regarding the results of *EGFR* gene mutation and/or *ALK* gene rearrangement tests should not exceed 10 working days from the delivery the histological material to the genetic laboratory. It is recommended to do preliminary assessment of *ALK* gene rearrangement based on an immunohistochemical assay and, in case of positive results, this should be confirmed by FISH. The time of waiting for genetic assessment results should be a maximum of 5 working days [6].

Recently published evidence suggests an increasing significance of the analysis of plasma free-circulating DNA and cancer cells in peripheral blood. This could be especially useful in prophylactic testing, noninvasive diagnostics, prognosis of the course of the disease and the monitoring of molecular therapy effectiveness.

At the beginning of 2015, an additional procedure of oncology diagnostic reimbursement (e.g. an oncology package), was implemented in Poland making a healthcare providers able to finance preliminary diagnostics tests and in-depth diagnostics based on lump sums dedicated to particular cancers, providing that the timing outlined for diagnostic procedures is kept. Lump sums for deep diagnostics of lung cancer patient also include an amount for pathological tests. According to the new regulations, molecular and genetic tests should be performed in outpatient care, within so-called in-depth diagnostics. Moreover, the healthcare provider is expected to abide by the rules of medical management presented in the standards of care, published as rules and regulations, as well as the guidelines and recommendations issued by scientific societies of specialists from particular disciplines [7]. Since treatment with

ALK inhibitors is not available within National Health Fund (NHF) reimbursement, *ALK* gene rearrangement testing is commonly done on a commercial basis (cost of FISH assay — approx. 700–900 PLN) [8, 9].

Possibilities of targeted treatment in patients with *ALK* (+) NSCLC

The possibility of using subsequent therapeutic strategies is based on toxicity and the effectiveness of the first line treatment. Evidence published during last decade has revealed a number of molecular aberrations in NSCLC patients which has contributed to the development of new tyrosine kinase inhibitors, blocking *ALK*, *MET*, *ROS1* and *HER2* related pathways, currently playing an increasing role in the targeted treatment of lung cancer. After the accelerated registration of crizotinib in the United States, the American Food and Drug Administration (FDA) designated this drug as a breakthrough treatment, enabling the a reduction in the time of the registration process for two additional drugs from this group: ceritinib (LDK378) and alectinib (RO5424802).

Crizotinib is the first orally available, small-molecule TKI registered by the European Medicine Agency (EMA), inhibiting *ALK*, *MET* and *ROS1* kinases. Results of *in vitro* and *in vivo* studies have shown that crizotinib inhibits the phosphorylation of *ALK* and signal transduction, which leads to the shutting down of the cell cycle and apoptosis induction [10]. In a multicenter, open-label, single arm phase II clinical trial (PROFILE 1005), aimed at assessing the effectiveness of crizotinib treatment in patients with advanced *ALK* (+) NSCLC after failure of at least 2 chemotherapy lines, the median progression-free survival (PFS) was 8.1 months and the objective response rate (ORR) was 60% (the median of response duration was 10.5 months). This trial also confirmed the favorable safety profile of crizotinib [11]. It was very important for clinical practice to assess quality of life and cancer-related symptoms, using EORTC (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) QLQ-C30 and QLQ-LC13 questionnaires. After 2 treatment cycles, a significant improvement in dyspnea, cough control, pain and asthenia was observed.

In 2013 the results of the phase III randomized clinical trial PROFILE 1007 were published, which evaluated the efficacy of crizotinib in second line treatment in comparison with pemetrexed or docetaxel [12]. PROFILE 1007 was the first phase III clinical trial comparing directly efficacy of crizotinib with standard chemotherapy in patients presenting advanced NSCLC with *ALK* gene rearrangement. Among 347 eligible patients, 173 were treated with crizotinib resulting in a progression-free survival which was significantly prolonged (primary endpoint) with a median PFS of 7.7 months in patients treated with crizotinib and 3 months in the group with standard chemotherapy (HR = 0.49; 95% confidence interval [CI] 0.37–0.64; $p < 0.001$). A subsequent subgroups analysis showed clinical benefits regarding the improvement of PFS in patients with brain metastases (HR = 0.67; 95% CI 0.44–1.03), in whom prognosis was especially poor.

ORR was 65% (95% CI 58–72%) in crizotinib-treated patients and 20% (95% CI 14–26%) in chemotherapy group, respectively ($p < 0.001$). A preliminary analysis showed no significant difference in overall survival, probably due to the use of crizotinib in the second line after disease progression in 62% of patients previously

Table 3. Comparison of standardized rates of 5-years relative survival rates in patients with lung cancer diagnosed between 2000 and 2007. Data are presented as percentage (%) of relative survival (95% confidence interval)

Country	Lung cancer
Germany*	15.6 (15.3–16.0)
Island	13.9 (11.5–16.7)
Belgium*	15.4 (14.9–16.0)
Switzerland*	15.3 (14.4–16.3)
Austria	16.7 (16.1–17.2)
Finland	11.5 (10.8–12.2)
Sweden	14.7 (14.1–15.3)
Italy*	14.3 (14.0–14.6)
France*	13.8 (13.2–14.4)
Norway	12.9 (12.3–13.6)
Portugal*	11.2 (10.6–11.9)
Netherlands	13.4 (13.1–13.7)
Malta	10.3 (7.9–13.0)
Spain*	10.7 (10.2–11.2)
Europe (mean)	13.0 (12.9–13.1)
Slovenia	10.7 (9.9–11.6)
Denmark	10.3 (9.8–10.8)
Czech Republic	11.5 (11.0–11.9)
Great Britain and Ireland	9.0 (8.8–9.1)
Estonia	11.7 (10.5–13.0)
Slovakia	10.3 (9.6–11.0)
Croatia	14.8 (14.2–15.5)
Lithuania	9.1 (8.4–9.9)
Poland*	**14.4 (13.8–15.0)**
Bulgaria	6.2 (5.8–6.7)
Latvia	12.2 (11.2–13.2)

*Countries in which cancers were not registered in whole population. Source: De Angelis R et al. (EUROCARE-5 Working Group). Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5 — a population-based study. Lancet Oncology 2014; 15: 23–34.

treated with chemotherapy (crossover design). In both groups, the overall survival time exceeded 20 months, which is spectacular therapeutic success in a group of patients receiving second line palliative treatment. Furthermore, this trial indicated that crizotinib was well tolerated. Indeed, the majority of adverse events noted in crizotinib-treated patients were of grade 1 or 2, except elevated aminotransferase levels, which were observed at grade 3 and 4 in 16% of patients. In general, adverse events of grade 3 and 4 were noted in 19% of patients in the group treated with standard chemotherapy and 13% of crizotinib treated patients. Of note, the necessity of using an anti-nausea drug in the group with standard chemotherapy was significantly higher than in the crizotinib group (67% vs. 20%). In the PROFILE 1007 study the patients treated with crizotinib reported an improvement in the general quality of life as compared with the patients receiving standard chemotherapy ($p < 0.001$), who had no improvement in the quality of life.

In 2014 Ou et al. published a retrospective analysis of data from PROFILE 1001 and PROFILE 1005 studies, regarding clinical benefits in previously treated *ALK* (+) patients, with continuous treatment with crizotinib, even beyond disease progression [13]. The median survival from initial crizotinib treatment in patients treated beyond progression was 29.6 months as compared with 10.8 months in patients who discontinued therapy upon progression of the disease (HR = 0.30, 95% CI, 0.19–0.46, $p < 0.0001$). A multivariate analysis revealed that treatment beyond progression was significantly associated with improved overall survival. The median survival after disease progression in patients who continued treatment with crizotinib beyond disease progression was more than 4-fold longer than in patients who discontinued crizotinib after disease progression (16.4 months vs. 3.9 months, HR = 0.27, 95% CI 0.17–0.42, $p < 0.0001$). Such long survival time was previously unreachable in this group of patients. These results may be explained mainly by progressions in the central nervous system (crizotinib is characterized by low brain-blood barrier penetration) and further treatment effectiveness, observed in progressive disease limited to intracranial localization after brain radiotherapy.

The results of presented analysis suggest that the progression of disease limited only to intracranial lesions needs a specific approach during crizotinib treatment. Continuation of crizotinib treatment after radiotherapy of brain metastases provides further clinical benefits regarding systemic disease control. Lower drug concentrations in the central nervous system (CNS) are the main reason for the failure of treatment of lesions in this localization. A subgroup of 138 patients with disease progression presenting new metastatic lesions was analyzed. It was indicated that in up to 51% of patients treated with crizotinib beyond progression, this progression was limited only to the central nervous system.

The efficacy analysis of crizotinib treatment in particular subgroups indicates special clinical benefits which may be observed in NSCLC patients with brain metastases. In January 2015 the results of a retrospective analysis of the effectiveness of treatment in 275 patients with brain metastases participating in PROFILE 1005 and 1007 studies were published [14]. The rates of general, as well as intracranial disease control were higher in patients with asymptomatic brain metastases. The median time to progression was 7 months (95% CI 6.7–16.4) in the group of patients who had previously not undergone radiation treatment due to metastases in the CNS and 13.2 months (95% CI 9.9 – not reached) in the group of patients who had undegone previous radiotherapy. At the time of data analysis, the final results of overall survival were not available due to the high number of on-treatment patients. Nevertheless, a preliminary estimated probability of 12-months survival was 59% in the subgroup of patients untreated due to metastases to the CNS, 64% in previously irradiated patients due to metastases in the CNS and 69% in subgroup of patients with no metastases at recruitment.

The efficacy and safety of crizotinib used in the first line treatment in patients with advanced *ALK* (+) NSCLC was evaluated in a randomized, open-label phase III study, PROFILE 1014. Patients (n = 343) were randomly assigned in a ratio 1:1 to the crizotinib-treated group or to the group receiving pemetrexed and platinum derivatives (cisplatin or carboplatin). According to the protocol, it was allowed in both arms to continue or to start treatment with crizotinib after disease progression (crossover design). The primary endpoint was PFS. Secondary endpoints included: ORR, OS, safety and quality of life.

The study results, presented during Annual Meeting of the American Society of Clinical Oncology (ASCO) and published in *The New England Journal of Medicine*, supported the benefits of crizotinib over chemotherapy with pemetrexed and platinum analogue in the improvement of PFS (10.9 months vs. 7.0 months, HR = 0.454, 95% CI 0.346–0.596, $p < 0.0001$). The objective response rate was statistically significantly higher in crizotinib treated patients (74% vs. 45%, $p < 0.0001$). Although at the presentations of results there was no statistically significant improvement in overall survival (HR = 0.821, 95% CI, 0.536–1.255, $p = 0.1804$), finally, 109 patients in the chemotherapy group received crizotinib upon treatment failure, a factor which could have significantly influenced lack of difference between groups regarding overall survival. Adverse event incidences in both groups were consistent with previous trial results in patients with advanced *ALK* (+) NSCLC. The most common reported adverse events (regardless of reason) in the crizotinib-treated group

Table 4. Summary of clinical trial results according to the survival rates and objective response rates in NSCLC patients treated with crizotinib

Study	Patients group	Median of progression-free survival (months)	Objective response rate (ORR)	Median of overall survival (months)
PROFILE 1005	Patients treated with crizotinib in 2 and further lines	**8.1** (95% CI 6.8–9.7)	60%	ND
PROFILE 1007 (comparison with standard chemotherapy)	Patients treated with crizotinib in 2 line	**7.7** (HR = 0.49; 95% CI 0.37–0.64, p < 0.001)	65%	**20.3** (indirect analysis)
	Patients with brain metastases treated with crizotinib in 2 line	HR = 0.67; 95% CI 0.44–1.03	ND	ND
Retrospective analysis of data from PROFILE 1001 and PROFILE 1005 studies (Ou 2014)	Patients after diseae progression treated with crizotinib in 2 and further lines (majority with brain metastases)	ND	ND	**29.6** (HR = 0.30, 95% CI 0.19–0.46, p < 0.0001)
PROFILE 1014 (comparison with standard chemotherapy)	Patients treated with crizotinib in 1 line	**10.9** (HR = 0.454. 95% CI 0.346–0.596, p < 0.0001)	74%	ND

NA — lack of data

were visual disturbances and gastrointestinal disease. To conclude, the PROFILE 1014 study indicated significant improvement in first line treatment results regarding PFS and ORR in patients with advanced *ALK* (+) NSCLC as compared with standard chemotherapy and an acceptable safety profile of treatment with crizotinib (Table 4) [15]. However, the above-presented results should be treated as preliminary due to the continuing nature of the study, planned to end in July 2016 [16].

In 2014, a report was published indicating the clinical benefits of crizotinib treatment also in NSCLC patients with *ROS1* gene rearrangement [17]. These results need to be confirmed in larger, prospective clinical trials, which are very difficult to obtain taking into consideration the relatively rare *ROS1* gene rearrangement among patients with NSCLC (approx. 2%). These results additionally support the increasing need for genetic profiling of tumor samples already at the stage of qualifying for treatment, which, in the near future, will be an efficient way to improve treatment results and optimize treatment costs in lung cancer patients.

Polish experience

Since ALK inhibitors are not systematically available in Poland, only a limited group of patients was treated with crizotinib (ceritinib and alectinib were not used outside clinical trials — personal communication). All data regarding the results from all patients treated in Poland with crizotinib were collected, enabling an analysis of the clinical benefits regarding PFS and OS in this group of patients (Figs. 1, 2).

The median PFS among patients treated with crizotinib was 15.4 months. It is to be noted that after 46 months (maximal observation time) the median of overall survival was not reached. Despite the retrospective nature of the analysis and the small sample size, which limits conclusions, survival times confirms data on crizotinib activity.

Cost-effectiveness of new technologies used in treatment of NSCLC patients

The growing costs of treatment are especially challenging in oncology. As a result, the implementation of innovative therapeutic methods in this area of healthcare is connected with especially restrictive measures, taking into consideration clinical, economic and social aspects. Antineoplastic drugs are a growing part of budgets allotted to the public healthcare system [18]. An increasing number of new discoveries in oncology and accelerated marketing authorization of a growing

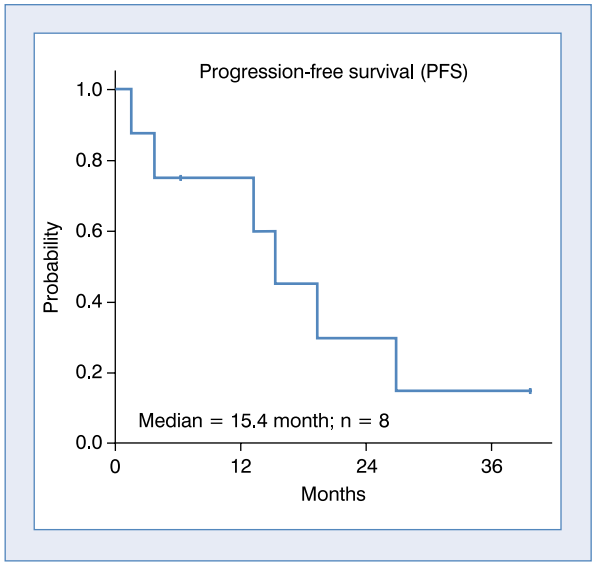

Figure 1. Progression-free survival in NSCLC patients treated in Poland (2 and 3 treatment lines). Source: data from Dept. of Oncology and Radiotherapy, Medical University of Gdansk

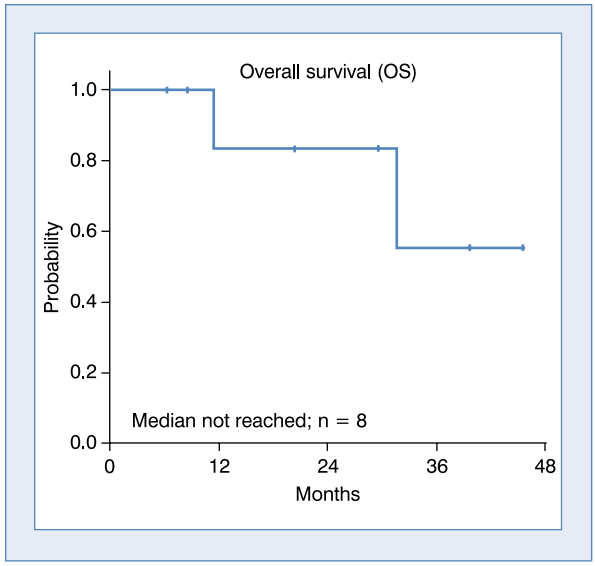

Figure 2. Overall survival in NSCLC patients treated in Poland (2 and 3 treatment lines). Source: data from Dept. of Oncology and Radiotherapy, Medical University of Gdansk

number of promising drugs have increased pressure to improve the cost-effectiveness of new drug-based technologies and decrease the costs of diagnostic molecular and genetic tests. Although this direction is justified, it could lead to wide differences in the cost-effectiveness of the same medical technology not only between different countries, but also within the same country. Additionally, the improved treatment results in NSCLC patients treated by crizotinib shown in very recent publications comparing it with standard chemotherapy, have led to situations where the results of cost-effectiveness analysis with using of incremental cost-effectiveness ratio (ICER), performed in many previous economic analyses are no longer valid.

The long-term benefits, as well as therapeutic-added value, have been extrapolated in economic evaluations using mathematical models, supplemented by data from available short-term analyses of clinical effectiveness. Since the results of such modeling more commonly determine the availability of new technologies in the treatment of potentially fatal diseases, validation of modeling methods and verification of results play a crucial role, with incremental – cost-effectiveness ratio (ICER) being one of the most commonly cited [19]. The ICER ratio is a subtraction of costs between comparing treatment options divided by the subtraction of effects expressed most often as a quality-adjusted life year (QALY). The policy makers correlate ICER values with an assumptive threshold of cost-effectiveness in a particular country (region). New treatment options, for which an ICER value exceeds this threshold are treated as cost-ineffective and are commonly not reimbursed (Poland) or are financed within special, separate budgets (Great Britain).

Another difficulty in the objective evaluation of cost-effectiveness could be the fact that prolonged survival time, indicated in randomized phase III clinical trials is very often influenced by crossing over, e.g. by patients from control group taking the experimental drug due to ethical reasons. Therefore, it should be underlined that although the cost-effectiveness of new technology is a variable relating to survival rates estimated in the mathematical model, it also includes the incremental cost of new technology, the timing landscape of analysis, the legal regulations in force in given country and social values, attributed to the analyzed health states [20]. As already mentioned, the results of the new retrospective clinical trials with criziotinib, indicating possible gains in survivial time that led to median overall survival of nearly 30 months, could significantly change the cost of an additional life year in this group of patients. Moreover, the comparator is an additional factor that significantly influences the ICER value. In the comparison of crizotinib with standard chemotherapy in second line treatment in NSCLC patients, pemetrexed and docetaxel could be considered comparators. Nevertheless, the results of retrospective analyses suggest that *ALK* gene rearrangement presence is connected with a higher susceptibility to pemetrexed, which enforces the use of this drug as a comparator in economic models [21, 22]. It is also worth mentioning that in the majority of clinical trials with EGFR TKIs inhibitors used in NSCLC patients, no survival benefit was noted.

An additional difficulty in economic analysis, especially regarding antineoplastic drugs, is the frequent lack of final results of overall survival, even a long time after marketed authorization. If one estimates the overall survival benefit based on a surrogate like PFS, it should be highlighted that many trials have supported the utility of PFS in NSCLC. As a standard, the additional life years of patient are multiplied during the economic analysis by the value of a statistical life year (VSLY) to convert it into national currency units. VSLY values differ between countries. In a review of articles published in 2015 in *The Journal of the American Medical Association* it was noted that the mean cost of an additional QALY gained by using a new medical technology most often ranged between $40,000 and $400,000. Currently, $200,000 is recognized as optimal [23]. As taxpayer-funded bodies very often demand final results regarding the effect of a new technology on overall survival time, in the presented review it was assessed as the mean time period since the publication of PFS data till the publication of OS data. In case of NSCLC, this time was between 7 and 46 months.

Currently, to optimize the expenditure incurred on new medical technologies many countries use new financial mechanisms improving the access of the patients to high-cost, innovative methods of treatment. The new reimbursement regulations, introduced in Poland in 2012 enabled the improvement of the cost-effectiveness of many medicinal products through the use of risk-sharing schemes (RSS) [24]. Similar solutions were already introduced in practice in last decade in the healthcare systems in many countries. In addition, crizotinib has been approved by publicly funded bodies in the majority of countries using RSS [25–28]. At the same time, Polish reimbursement regulations mentioned above implemented very restrictive requirements regarding pharmacoeconomic indices, identical for all new drugs and regardless of diagnosis. This led to demands for drug manufacturers to show cost-effectiveness also for new, high-cost antineoplastic drugs. It seems that in Polish conditions, the financing of costs of *ALK* gene rearrangement testing by drug manufacturers could be an additional factor, significantly optimizing the cost-effectiveness of treatment with ALK inhibitors.

It should be also underlined that according to the NHF data, in 2011 there were 58,657 procedures (diagnostic and therapeutic) reimbursed in patients with confirmed diagnosis of lung cancer (ICD10–C34). At the same time, aggregated investment of the NHF for lung cancer on the national level amounted to 751.8 million PLN [29]. As NHF analyses have indicated, currently, lung cancer ranks as the third most common oncological disease (after breast and colorectal cancer) in spending for public healthcare system. Furthermore, comparing the costs of services connected with lung cancer per capita in particular countries in European Union (EU) it was shown that Poland is among those countries with the lowest expenditure in this area (Table 5) [30].

Table 5. Expenditures of health services connected to the treatment of cancer per capita in particular European Union (EU) countries in 2009 [30]

Country	Cost per capita (€)	
	All cancers	Lung cancer
Bulgaria	16	1
Lithuania	18	1
Romania	20	1
Latvia	26	2
Malta	39	2
Cyprus	45	2
Portugal	53	3
Hungary	39	4
Estonia	45	4
Poland	**37**	**5**
Czech Republic	57	5
Slovakia	57	5
Spain	90	5
Slovenia	72	6
Great Britain	85	7
France	110	7
Belgium	94	8
In general for EU	102	8
Sweden	105	8
Italy	114	9
Denmark	104	10
Greece	111	10
Finland	151	12
Netherlands	130	13
Ireland	139	13
Austria	144	13
Germany	182	16
Luxemburg	184	21

Summary

The morbidity of lung cancer in Poland is continuously growing. The crucial factors for decreasing of morbidity and mortality in the nearest future in this group of patients will be as follows: development of primary and secondary prophylaxis methods, diagnosis at the very early stage of disease and the access of patients to the new, effective treatment methods. The latter are charac-

terized by very dynamic progress. One of the indicators of this progress could be increasing number of innovative medicinal products registered by FDA and EMA in this setting. ALK inhibitors are one of the most important group of targeted treatment for which genetic predictive factors have been identified, enabling an adequate selection of patients with the highest benefits from this treatment. The very first two ALK inhibitors (crizotinib, ceritinib) were registered in an accelerated procedure due to their high effectiveness shown in clinical trials [31]. The FDA is still proceeding with another ALK inhibitor (alectinib), which has already been authorized in Japan [32]. Currently published evidence indicates the possibility of the prolongation of median survival time in patients with advanced NSCLC with *ALK* gene rearrangement of up to 30 months. It should be noted that significant clinical benefits could also be obtained by patients with brain metastases, who previously had previously very poor prognosis. The mean overall survival in this group of patients after using of standard chemotherapy still ranges between 3 and 10 months (depending on prognosis factors and treatment schedule).

As many reports have shown, Poland is a country with a high cancer mortality which results not only from the magnitude of exposure to risk factors and low population effectiveness of screening programs, but also delays in the marketing authorization of new programs of cancer treatment compared with other EU countries [33]. In the current drug program, through which Poland regulates the financing of second line treatment of NSCLC patients, the usage of ALK inhibitors is not possible. According to the Ministry of Health announcement regarding the list of reimbursed drugs, foods for special medical purposes, and medical products (effective since 1 July 2015) molecular targeted treatment of NSCLC patients within drug programs includes three EGFR TKI inhibitors (erlotinib, gefitinib and afatinib) [34]. These drugs may be used in the first and the second line treatment in patients with some morphological subtypes of NSCLC with an activating mutation of the *EGFR* gene in a locally advanced stage (patients ineligible for radical surgery) or metastatic disease. The treatment with EGFR inhibitors allows for prolonged progression-free survival by 66% in this group of patients compared with those receiving standard chemotherapy. However, most prospective clinical trials failed to show any effect of EGFR on OS [35]. ALK inhibitors (crizotinib, ceritinib) are still outside the reimbursement system. It should be also noted that the recommendations of the Head of Polish HTA agency AOTM (*Agencja Oceny Technologii Medycznych*) issued in 2013 (114/2013) accorded the reimbursement of crizotinib with the following indication: the treatment of *ALK* (+) NSCLC within drug program, needs to be supplemented with currently published evidence [36]. Considering this, it could significantly change the perception of cost-effectiveness, which is a critical issue in the reimbursement process of antineoplastic drugs. As indicated in an IMS Institute report published in 2014, in countries where reimbursement decisions are connected with restrictive assessments of cost of additional QALY gained, the problem with the availability of new drugs is observed mainly in the area of oncology [37].

Observations of molecular targeted drug development in last decade allows one to assume that improvement of access to innovative antineoplastic drugs in the nearest future will be mainly influenced by identifying new predictive factors and widespread use of genetic testing, performed during process of qualification for treatment. However, the main prerequisite will be financing of molecular testing by publicly funded bodies (or drug manufacturers within so-called risk-sharing schemes) at a level corresponding to the real costs incurred by healthcare providers. The adequate selection of patients to undergo high-cost treatments will be a significant determinant of their clinical and cost-effectiveness. New discoveries in pharmacology, pharmacogenetics and molecular biology could change the standards of diagnostic and therapeutic management and, along with them, the expectations and requirements of patients and their families. The next few years will will possibly bring a new information, which will enable further progress in the treatment results in patients with advanced lung cancer.

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