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# Molecular targeted therapy of patients with non-small-cell lung cancer

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## ABSTRACT

Lung cancer is the most common cause of cancer-related death both in men and women in Poland and worldwide. Patients diagnosed with non-small-cell lung cancer (NSCLC) of non-squamous and not otherwise specified (NOS) histologies may benefit from targeted therapies, because these types of cancers most often harbor molecular disturbances such as activating *EGFR* gene mutations, rearrangements of *ALK*, *ROS1* or *NTRK* genes and *BRAF* gene mutation. These disorders are a positive predictors of the response to treatment with tyrosine kinase inhibitors. The necessity of molecular tests in patients with advanced NSCLC to be performed prior to qualification for systemic chemotherapy should be emphasized and — in the case of positive results — the use of targeted therapy in the first line treatment.

**Key words:** non-small-cell lung cancer, *EGFR*, *ALK*, *ROS1*, *BRAF*, targeted therapy

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## Introduction

Lung cancer is the most common cause of cancer-related death in men as well as in women in Poland and worldwide. In Poland, there were 14,500 male and 7700 female patients diagnosed with lung cancer in 2016. In the same year there were 16,200 and 7600 deaths from lung cancer among men and women, respectively [1]. Recently, the incidence of adenocarcinoma has increased, and currently it accounts for approximately 45% of all newly diagnosed lung cancers. Patients diagnosed with non-small-cell lung cancer (NSCLC) of non-squamous histology (adenocarcinoma, large cell carcinoma, and mixed cancer, with the predominance of histological subtypes mentioned above), as well as with cancer of undetermined histological subtype (NOS, not-otherwise specified) may benefit from molecular targeted therapy, because this type of cancer is characterized by the most frequent presence of molecular disturbances such as activating *EGFR* gene mutation, *ALK*, *ROS1*, or *NTRK* genes rearrangements, and *BRAF* gene mutation. The presence of specific molecular disorders is a positive predictive marker of the effectiveness of treatment with tyrosine

kinase inhibitors, which in this situation are more effective than classical chemotherapy, are associated with improving the quality of life of patients, and also have a different toxicity profile. There is a need for molecular tests in tissue or cytological material (when tissue is not available) in patients with advanced NSCLC prior to qualification for systemic chemotherapy, and in the case of molecular abnormalities the molecular targeted therapy should be used in first-line treatment.

This review presents the treatment options available in Poland for NSCLC patients with the presence of *EGFR* gene mutations and *ALK/ROS1* gene rearrangements (Table 1, 2).

## EGFR tyrosine kinase inhibitors

In the Caucasian population activating mutations in *EGFR* gene occur in 10–15% of patients with adenocarcinoma or lung cancer with a predominance of this histological type [2]. They are found more often in women, young people, and non-smokers. The most common *EGFR* gene mutations include exon 19. deletion, representing approximately 45% of all

Table 1. Molecular-targeted therapies in non-small-cell lung cancer available within the Drug Program

TKI	Study	Therapeutic ARMS	Results	Comments
<b>EGFR TKIs</b>				
Gefitinib	IPASS Phase 3	Gefitinib vs. carboplatin + paclitaxel	*mPFS 9.5 vs. 6.3 months HR 0.48 (95% CI 0.36–0.64) p < 0.001	Asian race, non-smokers or light smokers Without the need to confirm EGFR-positive status First-line treatment
Gefitinib	IFUM Phase 4	Gefitinib	*mPFS 9.7 months ORR 69%	Caucasian race EGFR+ Single-arm study
Erlotinib	EURTAC Phase 3	Erlotinib vs. carboplatin/cisplatin + docetaxel/gemcitabine	*mPFS 10.4 vs. 5.1 months HR 0.37 (95% CI 0.25–0.54) p < 0.0001	European study First-line treatment
Erlotinib	OPTIMAL Phase 3	Erlotinib vs. carboplatin + gemcitabine	*mPFS 13.1 vs. 4.6 months HR 0.16 (95% CI 0.10–0.26) p < 0.0001	Asian race First-line treatment
Afatinib	LUX-Lung 3 Phase 3	Afatinib vs. cisplatin + pemetrexed	*mPFS 11.1 vs. 6.9 months HR 0.58 (96% CI 0.43–0.78) p = 0.001 COMMON MUTATIONS (del19, L858R ex21) *mPFS 13.6 vs. 6.9 months HR 0.47 (95% CI 0.34–0.65) p = 0.001 mOS del19 33.3 vs. 21.1 months HR 0.54 (95% CI 0.36–0.79) p = 0.0015	Worldwide study First-line treatment
Afatinib	LUX-Lung 6 Phase 3	Afatinib vs. cisplatin + gemcitabine	*mPFS 11 vs. 5.6 months HR 0.28 (95% CI 0.20–0.39) p < 0.0001 mOS 31.4 vs. 18.4 months HR 0.64 (95% CI 0.44–0.94) p = 0.023	Asian race First-line treatment
Osimertinib	AURA 3 Phase 3	Osimertinib vs. cisplatin/carboplatin + pemetrexed	*mPFS 10.1 vs. 4.4 months HR 0.30 (95% CI 0.23–0.41) p < 0.001 ORR 71% vs. 31%	Second-line treatment after failure of first- and second-generation EGFR TKIs
<b>ALK TKIs</b>				
Crizotinib	PROFILE 1007 Phase 3	Crizotinib vs. pemetrexed/docetaxel	*mPFS 7.7 vs. 3.0 months HR 0.49 (95% CI 0.37–0.64) p < 0.001	Further treatment lines
Crizotinib	PROFILE 1014 Phase 3	Crizotinib vs. cisplatin/carboplatin + pemetrexed	*mPFS 10.9 vs. 7.0 months HR 0.45 (95% CI 0.35–0.60) p < 0.001	First-line treatment
Alectinib	ALEX Phase 3	Alectinib vs. crizotinib	*mPFS 34.8 vs. 10.9 months HR 0.43 (95% CI 0.42–0.58) p < 0.001	First-line treatment
Alectinib	ALUR Phase 3	Alectinib vs. pemetrexed/docetaxel	*mPFS 9.6 vs. 1.4 months HR 0.15 (95% CI 0.08–0.29) p < 0.001	Further treatment lines
<b>ROS1 TKI</b>				
Crizotinib	PROFILE 1001 Phase 1	Crizotinib	*ORR 72% mPFS 19.2 months	Single-arm study

mPFS — median progression free survival; HR — hazard ratio; ORR — objective response rate

\*The primary endpoint

Table 2. Application and dosage regimen of TKIs in patients with EGFR+, ALK+, or ROS1+ non-small cell lung cancer

	Drug	Treatment line	Dosage		Dose reduction	Basic criteria for inclusion in the drug program
EGFR+	Gefitinib	First-line treatment Second-line treatment	1 × 250 mg	Regardless of the meal	No dose reduction possible	Adenocarcinoma or large cell carcinoma (EGFR+ only) or non-small cell cancer with a predominance of adenocarcinoma or large cell carcinoma (EGFR+ only) or non-small cell lung cancer NOS (EGFR+ only)  Absence of metastases in the central nervous system or features of progression of metastases in the central nervous system in patients after previous local treatment (surgery or radiotherapy) and absence of clinically significant neurological symptoms and the need to increase the dose of glucocorticoids in the last month before qualification to the program  For alectinib, the absence of symptomatic metastases in central nervous system or features of progression of metastases in central nervous system in patients after previous local treatment (surgery or radiotherapy) and the absence of clinically significant symptoms and absence of clinically significant neurological symptoms and the need to increase glucocorticosteroids dose during the last month before enrollment
	Erlotinib	First-line treatment Second-line treatment	1 × 150 mg	1 hour before or 2 hours after a meal	150 mg → 100 mg → 50 mg	
	Afatinib	First-line treatment	1 × 40 mg	1 hour before or 3 hours after a meal	40 mg → 30 mg → 20 mg Maximally 50 mg	
	Osimertinib	Second-line treatment after failure of first- and second-generation EGFR TKIs	1 × 80 mg	Regardless of the meal	80 mg → 40 mg	
ALK+	Crizotinib	1st, 2nd, 3rd line treatment	2 × 250 mg	Regardless of the meal	2 × 250 mg → 2 × 200 mg → 1 × 250 mg	
ROS1+						
ALK+	Alectinib	1st, 2nd, 3rd line treatment	2 × 600 mg	together with meal	2 × 600 mg → 2 × 450 mg → 2 × 300 mg	

detected mutations, and exon 21. point mutation, consisting of substitution of leucine with arginine in codon 858 (L858R), constituting 40–45% of all mutations in *EGFR* gene. Other *EGFR* gene mutations are much less common and include, but are not limited to, exon 18. substitution or exon 20. insertion. All patients treated with EGFR tyrosine kinase inhibitors (EGFR TKI) will eventually experience disease progression. The most frequent mechanism of resistance to EGFR TKI is the development of secondary mutations, including T790M mutation in exon 20. of *EGFR* gene, which is found in more than 50% of patients with confirmed disease progression during treatment with first- or second-generation EGFR TKI [3]. Treatment with a small-molecule EGFR TKIs is the treatment of choice for patients with metastatic NSCLC with an activating *EGFR* gene mutation and should be first-line systemic treatment; however, in patients receiving classical chemotherapy as a front-line treatment EGFR TKIs should be used in a second line after the disease progression. EGFR TKIs are oral drugs and are divided into three generations: first generation (gefitinib and erlotinib), available within the Therapeutic Drug Program in first- or second-line treatment; second generation (afatinib and dacomitinib), of which in Poland only afatinib in first-line treatment is available; and

third generation (osimertinib), available in Poland for patients with secondary T790M resistance mutation in exon 20. of *EGFR* gene).

#### Gefitinib

Gefitinib is a first-generation EGFR TKI, which reversibly inhibits EGFR receptor (HER1), used once daily in a total daily dose of 250 mg regardless of the food intake [4]. In the phase 3 IPASS study, which included patients with stage IIIB/IV NSCLC from the Asiatic population, the efficacy of the first-line treatment with gefitinib was compared with carboplatin/paclitaxel chemotherapy regimen. Gefitinib was shown to be superior according to the primary endpoint, which was progression-free survival (PFS) in the entire study population, and in the subgroup of patients with *EGFR*-activating mutation (reduction in the risk of disease progression by 52% in favor of gefitinib, mPFS 9.5 vs. 6.3 months, 95% CI 0.36–0.64,  $p < 0.001$ ). The most common adverse events in the gefitinib arm were acne-like rash, dry skin, itching of the skin, stomatitis, paronychia, and diarrhea, while the most common side effects of chemotherapy included nausea, vomiting, constipation, alopecia, peripheral neuropathy, neutropenia, and anemia [5]. In Caucasian NSCLC patients with *EGFR*-activating mutation included in the single-arm

phase IV study IFUM a median PFS after first-line treatment with gefitinib was similar [6].

## Erlotinib

Erlotinib is another first-generation EGFR TKI that can be used in both first- and second-line treatment, after systemic chemotherapy. Erlotinib is used in a single daily dose of 150 mg and should be taken at least one hour before or two hours after a meal [7]. A multicenter, open, randomized, phase 3 OPTIMAL study included 185 adult *EGFR*-positive, locally advanced or metastatic NSCLC patients, randomly assigned to the arm receiving erlotinib or chemotherapy (carboplatin + gemcitabine). The study demonstrated the superiority of erlotinib over platinum-based chemotherapy regarding PFS (mPFS, 13.1 vs. 4.6 months, respectively) with a reduction in the risk of disease progression of 84% in the erlotinib arm [8]. In the EURTAC study, which included Caucasian patients diagnosed with stage IIIB/IV NSCLC with *EGFR* activating mutation, the efficacy of erlotinib and standard platinum-based chemotherapy was compared. Again, in the Caucasian population erlotinib was more effective regarding PFS, with a median of 10.4 vs. 5.1 months in the erlotinib and chemotherapy arm, respectively [9].

## Afatinib

Afatinib is an irreversible pan-HER inhibitor of the second generation, which covalently binds to the receptor and inhibits the formation of all homo- and heterodimers of the HER family receptors. Afatinib is administered in a single daily dose of 40 mg, at least one hour before or three hours after a meal, until disease progression or unacceptable toxicity [10]. The efficacy and safety of afatinib were evaluated in two multicenter clinical trials, LUX-Lung 3 being a global study and LUX-Lung 6, which included only Asian patients. In both studies, afatinib demonstrated superiority over chemotherapy (cisplatin/pemetrexed in the LUX-Lung 3 study and cisplatin/gemcitabine in the LUX-Lung 6 study) regarding PFS. The median PFS in patients treated with afatinib in an intention-to-treat population (ITT) was 11.1 and 11 months in LUX-Lung 3 and 6 studies, respectively, while the median PFS in patients treated with chemotherapy was 6.9 and 5.6 months, respectively [11, 12]. In patients with common mutations, i.e. deletion in exon 19. and substitution of L858R in exon 21., there was an even greater benefit from afatinib use (13.6 vs. 6.9 months in the arm with chemotherapy). In addition, patients with exon 19. deletion who had been treated with afatinib showed an increase in overall survival (OS). As demonstrated in the LUX-Lung 3 study, afatinib reduces the risk of death by 46% compared to chemotherapy (median OS 33.3 vs. 21.1 months for

afatinib and chemotherapy, respectively) [13]. Afatinib is also effective in patients with metastatic lesions in the central nervous system (CNS) existing since the beginning of treatment, extending the median PFS by nearly 3 months compared to chemotherapy [14]. The combined analysis of the results LUX-Lung 2, 3, and 6 studies also showed the effectiveness of afatinib in terms of PFS prolongation in patients with uncommon *EGFR* gene mutations, such as G719X, L861Q, and S768I [15]. Afatinib has also been registered by the American Food and Drug Administration (FDA) in this indication [16].

Another second-generation inhibitor is dacomitinib, which is not yet reimbursed in Poland within the Drug Program. In the ARCHER1050 study dacomitinib was shown to be superior to gefitinib in term of PFS (median PFS 14.7 months for dacomitinib and 9.2 months for gefitinib) [17], and OS (median OS 34.1 months vs. 26.8 months, respectively); however, at the expense of much higher toxicity [18].

Not without significance is the fact that EGFR TKI treatment, in addition to the effectiveness in terms of prolonging the disease progression-free time or overall survival, also improves patients' quality of life (QoL). In the LUX-Lung 3 and 6 studies it was shown that afatinib treatment was associated with a prolongation (in relation to classic chemotherapy) of time to deterioration of three basic lung cancer symptoms: cough, dyspnea, and pain [14]. It should be underlined that EGFR TKIs have a different toxicity profile, so the basic side effects of chemotherapy, such as nausea, vomiting, hair loss, or myelotoxicity, occur very rarely during treatment with inhibitors. The most common adverse events of EGFR TKIs include diarrhea, acne-like rash, which is localized mainly in the skin of the face, chest, or hairy skin of the head, as well as paronychia or increase in transaminase levels [8, 9, 19, 20]. In addition, there are also differences in the toxicity profile between individual inhibitors — afatinib causes diarrhea and rash more often, whereas an increase in aminotransferases is observed more often after gefitinib. Side effects are usually mild or moderate, are reversible, and are easily manageable with symptomatic treatment. In the case of CTCAE (Common Terminology Criteria for Adverse Events) grade 3 toxicity or intolerable or not resolving after symptomatic treatment grade 2 toxicity (diarrhea lasting over 48 hours or rash not resolving during more than seven days), treatment with an inhibitor should be interrupted until the side effect is resolved or its severity reduced to grade 1. At the resumption of treatment, the reduced dosage is mandatory; however, this reduction is possible only with erlotinib (150 mg – 100 mg – 50 mg) and afatinib (40 mg – 30 mg – 20 mg). In the case of afatinib, if the treatment is well tolerated during the first three weeks of therapy, there is a possibility of dose escalation to 50 mg daily.

## Osimertinib

During EGFR TKI therapy patients with primary response can develop a secondary resistance to the treatment leading to disease progression. In 50–60% of cases the secondary T790M mutation in exon 20. of the *EGFR* gene is responsible for secondary resistance to treatment [21]. If the disease progresses during administration of first- or second-generation EGFR TKI, the biological material should be re-sampled for histopathology to look for T790M mutation. If the sampling is not possible or the patient does not consent to this procedure, the molecular test may be carried out from peripheral blood. After confirmation of the presence of the T790M mutation, it is possible to use the third-generation tyrosine kinase inhibitor osimertinib. Osimertinib binds to EGFR covalently and irreversibly, demonstrating activity both in the presence of activating mutations in *EGFR* gene and in the presence of T790M resistance mutation. The efficacy and safety of osimertinib in the second-line treatment was assessed in the international, multicenter AURA-3 study. Patients with T790M mutation were randomly assigned in a ratio of 2:1 to the arm receiving either osimertinib or standard chemotherapy (pemetrexed + cisplatin/carboplatin). The study showed an increase in PFS in patients receiving osimertinib, with a 70% reduction in the risk of disease progression (median PFS 10.1 vs. 4.4 months, HR 0.30, 95% CI 0.23–0.41,  $p < 0.001$ ). The efficacy of osimertinib has also been confirmed in patients with metastases in CNS. For these patients, the median PFS in the osimertinib arm was 8.5 months compared to 4.2 months in the chemotherapy arm (HR 0.32, 95% CI 0.21–0.49) [22]. Osimertinib is administered in a daily dose of 80 mg, at the same time, and regardless of the meal. If dose reduction is required, osimertinib should be used in a daily dose of 40 mg [23].

Based on the results of the FLAURA trial, osimertinib has also been registered in the first-line treatment in patients with NSCLC with *EGFR*-activating mutation. In the FLAURA study patients were randomly assigned in a ratio of 1:1 to the arm receiving either a first-generation EGFR TKI (erlotinib or gefitinib) or osimertinib. The median PFS in the osimertinib arm has been shown to increase in comparison to patients receiving chemotherapy. The median PFS was 18.9 and 10.2 months, respectively (HR 0.46,  $p < 0.001$ ) [24]. OS data are not mature yet.

At present, in Poland, within the framework of the Drug Program, erlotinib, gefitinib, and afatinib in the first-line treatment and erlotinib and gefitinib in the second-line treatment in patients not previously receiving EGFR TKI in the first line, as well as osimertinib in the second line in patients with disease progression while using first- or second-generation EGFR TKI, with the presence of the T790M mutation in exon 20. of the *EGFR* gene, are reimbursed [25].

## ALK tyrosine kinase inhibitors

The proportion of patients with NSCLC with *ALK* gene rearrangement is between 3% and 7%. This molecular disorder is almost exclusively observed in patients with lung adenocarcinoma, more often with the signet ring subtype, and more often in non-smokers. The presence of rearrangement virtually excludes the presence of mutations in *EGFR*, *KRAS*, and *BRAF* genes or rearrangements in *ROS1* and *NTRK* genes. The rearrangement leads to the formation of an oncogenic *EML4-ALK* fusion gene, which has constitutive tyrosine kinase activity, which results in a stimulation of intracellular signaling pathways as well as neoplastic transformation and tumor progression. Patients with ALK-positive NSCLC are often clinically characterized by the presence of metastases in supraclavicular/cervical lymph nodes, the presence of pleural effusion, and a high rate of primary central nervous system involvement. Rearrangement in the *ALK* gene is now routinely assessed in patients with adenocarcinoma of the lung prior to initiation of systemic therapy, and its presence determines the sensitivity of tumor cells to small-molecule inhibitors of ALK tyrosine kinase. Similar to EGFR TKIs, ALK TKIs also includes three generations: first generation (crizotinib), second generation (alectinib, ceritinib, brigatinib) and third generation (lorlatinib).

Currently in Poland two ALK inhibitors are reimbursed as part of the drug program: a first generation inhibitor — crizotinib in the first- and second- as well as third-line treatment in patients with disease progression after or during treatment with platinum-based therapy, and (since July 1, 2019), second generation inhibitor — alectinib — available in the first-line and in subsequent treatment lines in case of ineffectiveness of or intolerance to crizotinib.

### Crizotinib

The efficacy and safety of crizotinib in the treatment of patients with advanced or metastatic NSCLC with *ALK* gene rearrangement after the failure of one prior line of platinum-based therapy was evaluated in a multicenter, open-label, phase 3 PROFILE 1007 study. Patients were randomly assigned in the ratio 1:1 to arm receiving either crizotinib 250 mg twice daily or standard second-line chemotherapy (pemetrexed 500 mg/m<sup>2</sup> intravenously every three weeks in patients with non-squamous NSCLC or docetaxel 75 mg/m<sup>2</sup> intravenously every three weeks). The primary endpoint of the study was PFS. A statistically and clinically significant benefit has been demonstrated for crizotinib compared to second-line chemotherapy. The median PFS was 7.7 months and 3 months, respectively (HR 0.49, 95% CI 0.37–0.64,  $p < 0.001$ ), and the response



rate was 65% and 20%, respectively ( $p < 0.001$ ). The study showed no benefit in OS, probably due to the possibility of using crizotinib in patients in the arm receiving standard second-line chemotherapy after disease progression (crossover). Investigators also pointed to the fact that crizotinib had a beneficial effect on the patients' quality of life. There has been a significant reduction of intensity of symptoms like alopecia, cough, dyspnea, fatigue, chest pain, shoulder or arm pain, and a significant delay of deterioration of the three main lung cancer symptoms: cough, dyspnea, and chest pain (4.5 months in the crizotinib arm *versus* 1.4 months in the chemotherapy arm, HR 0.50, 95% CI 0.37–0.66,  $p < 0.001$ ). The toxicity profile of crizotinib was different from the chemotherapy toxicity profile. The most common adverse reactions reported in at least 5% of patients treated with crizotinib included visual impairment in the form of visual acuity loss or blurred vision, diarrhea, nausea, vomiting, constipation, increased liver enzymes, peripheral edema, dysgeusia, dizziness, or upper respiratory tract infections. The side effects were mostly mild to moderate in severity, transient, and responded well to symptomatic treatment. The most common side effects of chemotherapy were fatigue, alopecia, dyspnea, and rash [26].

The efficacy and favorable safety profile of crizotinib in second-line treatment in patients with ALK-positive NSCLC became the basis for conducting a phase 3 clinical trial assessing the efficacy and safety of first-line treatment with crizotinib. An open-label, multicenter PROFILE 1014 study included 343 patients with ALK-positive advanced or metastatic non-squamous NSCLC, who had not received prior systemic treatment. Patients were randomly assigned in a ratio of 1:1 to the arm receiving either crizotinib 250 mg twice daily until disease progression or unacceptable toxicity ( $n = 172$ ) or standard first-line chemotherapy (pemetrexed 500 mg/m<sup>2</sup> in combination with platinum derivative: cisplatin 75 mg/m<sup>2</sup> or carboplatin AUC 5 or 6 mg/mL/min up to a maximum of six cycles) ( $n = 171$ ). The primary endpoint of the study was PFS, and patients in the chemotherapy arm had the opportunity to change to the crizotinib arm after disease progression. Similarly to the PROFILE 1007 study, in the PROFILE 1014 study the investigators also demonstrated the superiority of crizotinib over chemotherapy in terms of PFS (median 10.9 months *vs.* 7 months, respectively). It has been shown that the use of crizotinib in first-line treatment reduces the risk of disease progression by as much as 55% compared to chemotherapy (HR 0.45; 95% CI 0.35–0.60;  $p < 0.001$ ). In addition, there was a significantly higher response rate in patients receiving crizotinib (74% *vs.* 45%). Similarly to the PROFILE 1007 study, there were no statistically significant differences in OS, which results from the study design,

allowing the majority of patients after disease progression during or after chemotherapy to receive crizotinib in the next treatment line (crossover). The median OS in the crizotinib arm was not reached, whereas in the chemotherapy arm it was 47.5 months (HR 0.76, 95% CI 0.54–1.05,  $p = 0.09$ ). After a median follow-up of 46 months and after adjusting for the crossover effect by means of appropriate statistical tools, OS benefit was demonstrated in patients treated with crizotinib with a risk reduction of 66% (median OS 59.8 *vs.* 19.2 months, respectively; HR 0.34; 95% CI 0.081–0.718) [27]. Typical side effects of ALK TKIs, which occur in patients treated with chemotherapy much less frequently include: visual disturbances in the form of flares or light columns, peripheral edema, diarrhea, constipation, vomiting, and elevation of aminotransferases. However, when using standard chemotherapy, patients are more likely to experience fatigue, anemia, neutropenia, thrombocytopenia, or oral mucositis [28]. In patients with disease progression during treatment with first-generation ALK inhibitor it is possible to use a second-generation inhibitor — brigatinib, ceritinib, or alectinib.

#### Alectinib

Alectinib is second-generation ALK-TKI showing high activity within the central nervous system, which is very important in ALK-positive lung cancer patients. The efficacy and safety of this drug in previously untreated patients with advanced ALK-positive NSCLC were evaluated in the ALEX study. This multicenter, open-label clinical trial involved 303 patients randomly assigned (1:1 ratio) to the arm receiving twice daily either alectinib 600 mg ( $n = 152$ ) or crizotinib 250 mg ( $n = 151$ ). The primary endpoint of the study was investigator-assessed PFS, while the secondary endpoints included IRC-assessed PFS, time to progression in the CNS, ORR and OS. After median follow-up of 17.6 months for crizotinib and 18.6 months for alectinib, disease progression or death occurred in 68% and 41% of patients, respectively. At 12 months, the disease progression was not detected in 68.4% of patients in the alectinib arm and 48.7% of patients in the crizotinib arm (HR 0.47, 95% CI 0.34–0.65,  $p < 0.001$ ). It has been shown statistically and clinically significant prolongation of IRC-assessed PFS in patients treated with alectinib by more than 15 months as compared to crizotinib. The median of PFS, as assessed by ICR, in alectinib arm was 25.7 months *versus* 10.4 months in crizotinib arm (HR 0.50; 95% CI 0.36–0.70;  $p < 0.0001$ ) [30]. According to the investigators, the median PFS was not achieved in the alectinib arm: NE (17.7–NE).

At the American Society of Clinical Oncology annual meeting in 2018, updated PFS results were presented. Treatment with alectinib has been shown to reduce the

risk of disease progression or death by 57% compared to crizotinib and to prolong the progression-free survival by almost 3 years (median PFS 34.8 months vs. 10.9 months for alectinib and crizotinib, respectively; HR 0.43, 95% CI 0.42–0.58) [31]. The study also highlighted high intracranial activity of alectinib. At enrollment, metastases in the CNS occurred in 42% of patients in the alectinib arm and 38% of patients in the crizotinib arm. It was shown that the time to progression of CNS metastases was significantly longer in patients receiving alectinib. The cumulative risk of progression or development of CNS metastases after 12 months of treatment with ALK TKI was 41.4% for crizotinib and 9.4% for alectinib, therefore it is more than four times lower in patients receiving the second generation ALK inhibitor [30]. The median PFS for patients with metastatic CNS lesions was 27.7 months in the alectinib group and 7.4 months in the crizotinib group (HR 0.35) [31]. Data on OS are not yet mature. The ALEX study protocol did not assume the possibility of crossover, however, some crizotinib-treated patients received alectinib after disease progression as part of another clinical trial or expanded access program. The adverse reactions rate was similar in both groups, however the investigators noted that toxicity profile of both inhibitors differed significantly. Side effects occurring more frequently in the alectinib group were anemia (20% vs. 5% in the crizotinib arm), myalgia (16% vs. 1%), blood bilirubin level increased (15% vs. 1%), weight gain (10% vs. 1%), musculoskeletal pain (7% vs. 2%) and photosensitivity reactions (5% vs. 0%). However, adverse events that occurred more frequently in patients receiving crizotinib included nausea (48% vs. 14% in the alectinib arm), diarrhea (45% vs. 12%), and vomiting (38% vs. 7%). Grade 3 to 5 adverse events occurred more frequently in the crizotinib arm (41% for alectinib and 50% for crizotinib, respectively), so that alectinib appears to be a safer drug [30].

The advantage of alectinib over chemotherapy in patients with resistance to crizotinib was confirmed in a multicenter, open-label phase III ALUR, study which included 107 patients. Patients were allowed to use a single line of previous systemic chemotherapy. Patients were randomly assigned at a 2:1 ratio to the arm receiving either alectinib 600 mg twice daily ( $n = 72$ ) or investigator's choice chemotherapy (pemetrexed 500 mg/m<sup>2</sup> or docetaxel 75 mg/m<sup>2</sup> intravenously every three weeks) ( $n = 35$ ). The primary endpoint of the study was PFS, which was prolonged in the alectinib arm compared to chemotherapy (median PFS 9.6 vs. 1.4 months, respectively; HR 0.15, 95% CI 0.08–0.29,  $p < 0.001$ ). The response rate was 37.5% in patients receiving alectinib, compared to 2.9% in patients treated with chemotherapy. To note, alectinib appeared to be very effective against central nervous system metastases. The ORR in CNS was 54.2% for

alectinib and 0% for chemotherapy ( $p < 0.001$ ). The favorable safety profile of alectinib is also significant. The adverse events rate of any grade was comparable in both groups of patients [32].

## ROS1 tyrosine kinase inhibitors

The percentage of patients with NSCLC harbouring *ROS1* gene rearrangement is between 1% and 2% and is higher in the Asian population (2–3%). Rearrangement in the *ROS1* gene occurs more frequently in women (60%), younger patients, non-smokers (75%), those diagnosed with adenocarcinoma, especially with solid subtype, and poorly differentiated NSCLC (G2–G3). About 20% of patients have metastatic lesions in CNS. *ROS1* gene rearrangements are most often mutually exclusive with other leading molecular disorders.

The only drug available in Poland within the Drug Program for *ROS1*-positive non-small-cell lung cancer patients regardless of the treatment line is crizotinib. Its effectiveness and safety in this indication has been demonstrated in the multicenter, single-arm, phase 1 PROFILE 1001 study. This clinical trial included 50 patients, most of whom previously received systemic treatment. The primary endpoint was the response rate, which was 72%, while mPFS was 19.2 months. The proportion of patients who remained alive six and 12 months after starting treatment with crizotinib was 91% and 79%, respectively [33].

## Summary

The outcomes of systemic treatment of NSCLC patients with standard chemotherapy is still unsatisfactory. Molecular targeted therapy makes possible a significant improvement of treatment results, with extension of progression-free survival and overall survival. However, this requires molecular assessment and insight into molecular abnormalities, which have predictive value for response to targeted therapy. Molecular targeted therapies can be used in a small percentage of patients due to the low incidence of molecular abnormalities. However, it is emphasized that it is necessary to search for them before starting standard systemic chemotherapy, which gives the possibility to offer the patients with molecular changes more valuable therapy. It is also important that TKIs can improve patients' quality of life and delay the deterioration of lung cancer symptoms. In addition, the side effects are different from those of chemotherapy, usually mild or moderate, reversible, and easily manageable with symptomatic treatment. Therefore, TKI treatment should be considered in the first place in patients with known molecular targets for which systemic therapies have been developed and registered.

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