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REVIEW ARTICLE

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The role of diagnostics and treatment — lung cancer with *ALK* rearrangement

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ABSTRACT

Lung cancer is the most common cause of cancer-related deaths both in Poland and worldwide. Recently, the incidence of lung adenocarcinoma has been increasing and currently it accounts for about 45% of all diagnosed lung cancers. Patients diagnosed with non-squamous non-small cell lung cancer (NSCLC), especially with adenocarcinoma, cancer containing adenocarcinoma component, large cell carcinoma, as well as patients with not otherwise specified (NOS) cancer may benefit from targeted therapy if molecular tests confirm the presence of activating *EGFR* gene mutations, *ALK*, *ROS1* or *NTRK* rearrangement, or *BRAF* gene mutations. The *ALK* gene rearrangement is a positive predictive marker of tyrosine kinase inhibitors (TKIs) effectiveness, which are more effective than standard chemotherapy in this population, are associated with improving the quality of life and also indicate a different, more tolerable toxicity profile. This study presents the diagnostic sequence and registered treatment options for patients with ALK-positive NSCLC.

Key words: non-small cell lung cancer, *ALK*-rearrangement, ALK-TKI, crizotinib, alectinib, brigatinib, ceritinib

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Introduction

Over the past decade, the approach to the diagnosis and treatment of lung cancer has changed significantly. For many years, the division into a small cell (SCLC) and non-small cell lung cancer (NSCLC) was the most important factor in choosing the treatment option, especially in advanced stages. The subtype of non-small cell lung cancer was not significant as it did not affect the chemotherapy (ChT) or radiochemotherapy (RT) regimen used.

The development of molecular biology, identification of activating mutations and major signalling pathways involved in tumorigenesis and progression of NSCLC and the introduction of targeted therapy using tyrosine kinase inhibitors (TKIs) have resulted in radical changes in the principles of lung cancer diagnosis and choice of treatment method [1, 2]. The *ALK* gene rearrangement is found in approximately 3–7% of patients with non-small cell lung cancer. This aberration almost exclusively affects patients with lung adenocarcinoma and more often non-smokers. Patients with *ALK* rearrangement are clinically characterized by involvement of the mediastinal and supraclavicular lymph nodes, the presence of pleural as well as pericardial or peritoneal effusion and a high percentage of central nervous system (CNS) involvement [3].These patients require an individual therapeutic approach and planning of the treatment strategy from the very beginning. At present, several small-molecule ALK-TKIs are registered by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for systemic treatment in the first and subsequent lines, some of which are also available in Poland as part of the drug program. The sequence of use of individual inhibitors and their activity within the central nervous system is

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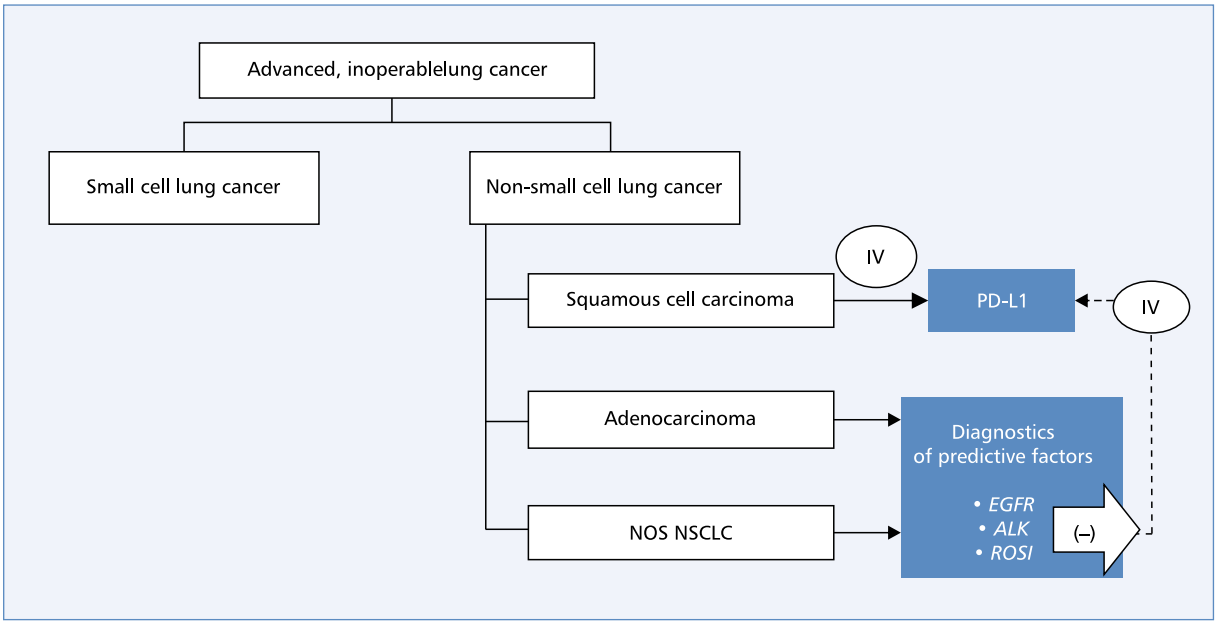

Figure 1. Diagnostic algorithm in advanced, inoperable lung cancer

also important, and the toxicity profile of individual ALK-TKIs should be taken into account.

Morphological diagnostics, assessment of predictive factors in lung cancer

The current diagnostic algorithm strictly depends on disease stage and morphological cancer type. In patients eligible for surgery it is sufficient to determine cancer type (small cell vs non-small cell carcinoma) without specifying the NSCLC subtype. In patients with advanced cancer, accounting for about 80%, it is important not only to determine the NSCLC subtype (squamous cell vs adenocarcinoma) but also to secure the material for predictive factors assessment enabling the selection of patients to appropriate treatment, primarily targeted therapy and immunotherapy [1, 4, 5] (Fig. 1).

The subtype of approximately 70% of NSCLC could be specified based on the morphological features recognized by standard hematoxylin + eosin staining (H+E). In other cases, additional tests are necessary: histochemical (staining for mucin in cancer cells) and immunohistochemical (IHC), which allow the determination of the morphological type of NSCLC [2, 6, 7].

Due to the unique nature of samples, based on which the diagnosis is established (cytological material and/or small, several-millimeter sections), two most sensitive and specific IHC markers are mainly used: thyroid transcription factor-1 (TTF-1) and p40. TTF-1 expression in cancer cells indicates glandular differentiation (GD), whereas p40 is a marker of squamous cell lung cancer. In about 10% of cases, the cancer subtype cannot be determined despite additional tests; this is so-called NOS non-small cell lung cancer [2, 6, 7].

Diagnosis of predictive factors is carried out following a specific algorithm, according to which in patients with locally advanced or generalized adenocarcinoma or NOS, *EGFR* gene mutation is assessed first, then in case of a negative result, *ALK* gene expression and/or rearrangement is assessed, followed by *ROS1* gene rearrangement [1, 3, 4]. In patients with stage IV squamous cell carcinoma or adenocarcinoma and NSCLC-NOS with not confirmed evidence of biomarkers, a predictive IHC test is possible, to assess the expression of PD-L1 protein qualifying for treatment with immune checkpoints inhibitors (so-called immunocompetent drugs) (Fig. 1) [4].

Approximately 10% of patients with adenocarcinoma harbor *EGFR* gene mutation. The presence of *EGFR* mutation in exons 18-21 is an indication for targeted therapy with tyrosine kinase inhibitors already in I line. The basic method used in the diagnosis of *EGFR* gene mutation is the real-time polymerase chain reaction (RT-PCR) technique, characterized by high sensitivity and specificity. It allows detecting genetic aberrations in the hypocellular cell sample containing even ≥ 1% (the minimum number of neoplastic cells required for the diagnosis of EGFR mutation is 100 cells) of cancer cells [1, 4, 5, 8].

In *EGFR*-negative NSCLC the abnormalities in *ALK* gene are assessed in the next step. *ALK* belongs to the insulin receptor tyrosine kinase family, wich is normally expressed in the developing nervous system. In 2007, *ALK* gene rearrangement was found in NSCLC. It results from the fusion of *ALK* and *EML4* genes, which are normally at opposite ends of the same short arm

of chromosome 2p. As a result of intra-chromosomal inversion occurring within the chromosome 2p, both genes fuse and encode fusion protein EML4-ALK, which consequently leads to permanent activation of intracellular signalling pathway, stimulation of tumor cell proliferation and inhibition of apoptosis [4, 9, 10]. In addition to the most common *EML4-ALK* rearrangement in NSCLC, there are also other types of *ALK* gene translocation (*TGF-ALK*, *KIF5B-ALK*, *KLC1-ALK*) that probably do not affect the treatment outcome [9–11].

Aberrations in *ALK* gene are found primarily in patients with adenocarcinoma, often of solid structure or with a signet-ring cell, mucinous or acinar especially cribriform type, less often a papillary component. Patients with confirmed *ALK* gene mutations are usually slightly younger than other NSCLC patients. They are generally non-smokers or light smokers (≤ 10 pack-years) [9, 10].

ALK rearrangement is most commonly considered to be exclusionary for the *EGFR* and *KRAS* mutations, although there is some data indicating possible coexistence of both aberrations.

Until recently, the main validated diagnostic test to detect *ALK* gene rearrangement was the fluorescence in situ hybridization (FISH) method with specially labelled probes. There is a sufficient method, but requiring adequate diagnostic facilities, especially a special fluorescence microscope and qualified staff. In addition, FISH is expensive, difficult to interpret and time-consuming method. Another disadvantage is reaction instability; the signal disappears after some time, precluding reassessment [4, 5, 9, 12].

Currently, the predictive immunohistochemical test with anti-D5F3 antibody is used with very good effects. It is more accessible, cheaper, does not require additional diagnostic facilities, in addition to the standard used in the pathology department [4, 5, 9].

Another, currently required predictive test is the assessment of abnormalities in *ROS1* gene. *ROS1* gene rearrangement is found in about 1–2% of NSCLC patients, non-smokers, mainly with adenocarcinoma. This aberration occurs within the long arm of chromosome 6 (6q22) encoding a protein that functions as a receptor with an intracellular tyrosine kinase domain. Similarly to *ALK* gene, various gene fusions also appear in *ROS1* gene; of these, the *CD74-ROS1* fusion has been reported as the most common [1, 4, 5, 9]. Detection of *ROS1* rearrangement allows the use of crizotinib.

In Poland, the reimbursed method for determining disorders in *ROS1* gene, based on NSCLC treatment program, is FISH method, subjected to the abovementioned limitations.

In the United States and many Western European countries IHC is used as a screening test. Positive results require confirmation by FISH, while negative ones are considered binding [1, 4, 5].

Despite the increasingly widespread next-generation sequencing (NGS) method, which allows the simultaneous detection of many genetic abnormalities, including *EGFR*, *ALK*, and *ROS1* aberrations, monogenic techniques are still widely used worldwide. First of all, this is due to the fact that they are more accessible, faster and less expensive. In addition, NGS results which are questionable or discrepant with clinical data, need to be confirmed by monogenic tests [13].

The first line of systemic treatment with ALK tyrosine kinase inhibitors

Crizotinib was the first small molecule ALK tyrosine kinase inhibitor approved by FDA. It is a first-generation inhibitor, inhibiting not only ALK but also c-MET and ROS1 tyrosine kinase. Its efficacy and safety in the first-line treatment were evaluated in an open-label, multicenter PROFILE 1014 trial [14]. The study enrolled 343 patients with ALK-positive advanced or metastatic non-squamous NSCLC, with no previous systemic treatment. Patients were randomly assigned (1 : 1) to the arm receiving crizotinib 250 mg twice daily until disease progression or unacceptable toxicity (n = 172) or standard first-line chemotherapy (pemetrexed 500 mg/m^2 in combination with a platinum derivative: cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6 mg/mL/min for up to 6 cycles) (n = 171). Patients from chemotherapy arm were permitted to crossover to crizotinib arm at the time of disease progression. Crizotinib has demonstrated superiority over chemotherapy in terms of progression-free survival (PFS). The median PFS was 10.9 months *versus* 7 months, respectively, and the use of crizotinib in first-line treatment reduced 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, a significantly higher response rate (RR) was found in patients receiving crizotinib (74% *vs.* 45%). There was no difference in overall survival (OS), most likely due to the design of the study (crossover): in PROFILE1014, the percentage of patients in chemotherapy arm receiving crizotinib after disease progression was close to 85% [14]. In 2018, the results of the final analysis of crizotinib first-line treatment effect on the overall survival were published. After a median follow-up of 46 months, eliminating the crossover effect using appropriate statistical tools, crizotinib was shown to reduce the risk of death by nearly 65% (mOS 59.8 months for crizotinib versus 19.2 months for chemotherapy, HR 0.346; 95 % CI 0.081–0.718). Therefore, the use of molecularly targeted therapy improves the patients' prognosis from the very beginning of treatment and is more effective than standard first-line chemotherapy [15].

Alectinib is a second-generation ALK-TKI, demonstrating the high intracranial activity, which is very important in ALK-positive lung cancer. The efficacy and safety of this drug in treatment-naive patients with advanced ALK-positive NSCLC was evaluated in ALEX trial and compared directly with the first-generation inhibitor. In total, 303 patients were enrolled to this multicenter, open-label clinical trial, randomly assigned (1: 1) to the arm receiving alectinib 600 mg twice daily (n = 152) or crizotinib 250 mg twice daily (n = 151). After a median follow-up of 17.6 months for crizotinib and 18.6 months for alectinib, disease progression or death was reported in 68% and 41% of patients, respectively. After 12 months, 68.4% of patients in alectinib arm and 48.7% of patients in crizotinib arm were progression-free (HR 0.47; 95% CI 0.34–0.65; P < 0.001). It has been shown statistically and clinically significant prolongation of PFS in patients treated with alectinib by more than 15 months compared to crizotinib. The median PFS was 25.7 months in patients in alectinib arm versus 10.4 months in crizotinib arm (HR 0.50; 95% CI 0.36–0.70; P < 0.001) [16]. The updated PFS results were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. The use of alectinib has been shown to reduce the risk of disease progression or death by 57% compared to crizotinib and extend progression-free survival by more than 2 years (median PFS 34.8 months *vs.* 10.0 months for alectinib and crizotinib, respectively, HR 0.43; 95% CI 0.32–0.58) [17]. Overall survival data has not yet matured. According to ALEX trial protocol crossover was not permitted, but some patients treated with crizotinib received alectinib after disease progression as part of another clinical trial or expanded access program (EAP) [16].

Ceritinib is another second-generation ALK inhibitor registered in the first-line treatment. An open, multicenter, phase III phase ASCEND 4 clinical trial enrolled 376 patients with stage IIIB/IV non-squamous NSCLC. Patients were randomly assigned (1: 1) to arm receiving ceritinib 750 mg/day (n = 189) or chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min in combination with pemetrexed 500 mg/m^2 for 4 cycles with the possibility of pemetrexed maintenance treatment) (n = 187). The study showed the superiority of ceritinib over chemotherapy in terms of PFS (median PFS 16.6 months versus 8.1 months, respectively; HR 0.55, 95% CI 0.42–0.73; P < 0.00001). Overall response rate (ORR) was significantly higher in patients treated with ceritinib (72.5% in ceritinib arm *vs.* 26.7% in the chemotherapy arm) [18].

There are also available the preliminary results of phase III ALTA-1L clinical trial, which directly compared the efficacy and safety of the next second-generation ALK inhibitor, brigatinib and the first-generation ALK inhibitor, crizotinib. The study included 275 treatment-naive ALK-positive NSCLC patients, who were randomly assigned (1: 1) to arm receiving brigatinib 180 mg daily (n = 137) or crizotinib 250 mg twice daily (n = 138). PFS was a primary endpoint of the study. Interim analysis performed after a median follow-up of 11 months for brigatinib and 9.3 months for crizotinib showed a significantly increased percentage of progression-free patients after 12 months in brigatinib arm (67% *vs.* 43% in crizotinib arm); HR 0.49; 95% CI 0.33–0.74; P < 0.001). Brigatinib was also superior in terms of ORR (71% *vs.* 60%) and intracranial response rate (78% *vs.* 29%) [19]. Updated ALTA-1L results after a median follow-up of over 2 years indicate that the use of brigatinib is associated with a 57% reduction in disease progression or death risk (HR 0.43, 95% CI 0.31–0.61) compared to crizotinib [20]. Therefore, brigatinib is the next ALK-TKI being more effective than crizotinib in first-line treatment. In February this year, EMA issued a positive recommendation regarding the use of brigatinib in the first-line treatment; the drug is awaiting FDA registration in this indication.

An open, randomized phase III clinical trial is currently ongoing that directly compares the efficacy and safety of crizotinib and lorlatinib in treatment-naive patients with ALK-positive advanced lung cancer [21]. Lorlatinib is a third-generation ALK-TKI that is effective against the largest number of different resistance mutations resulting from treatment with lower generation ALK-TKIs.

The second and subsequent lines of systemic treatment with ALK tyrosine kinase inhibitors

In patients with *ALK*-rearranged NSCLC the use of ALK-TKI in the first line of treatment is of key importance. Otherwise, when the material for *ALK* gene rearrangement determination is not available or patient needs to immediately initiate the treatment due to the deteriorating general condition, it is necessary to pursue toward tissue specimen collection and testing molecular disorders before qualifying for the next line treatment.

The efficacy and safety of crizotinib in the treatment of patients with advanced or metastatic *ALK*-rearranged NSCLC after the failure of a prior platinum-based therapy was evaluated in a multicenter, open-label phase III PROFILE 1007 study. Patients were randomly assigned (1: 1) to the arm receiving crizotinib 250 mg twice daily or standard second-line chemotherapy (docetaxel 75 mg/m^2 intravenously every 3 weeks or pemetrexed 500 mg/m^2 intravenously every 3 weeks in patients with non-squamous NSCLC). The primary endpoint of the study was PFS. A statistically and clinically significant benefit has been demonstrated with 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 did not show any benefits in terms of OS, probably due to the possibility of crossover of patients from chemotherapy to crizotinib arm at the time of disease progression) [22].

In patients with disease progression during crizotinib treatment, the next-generation ALK-TKIs are more effective than chemotherapy. The effectiveness of alectinib in sequential treatment has already been confirmed in phase II single arm clinical trial with ORR as the primary endpoint (48%) [23]. The superiority of alectinib over chemotherapy in patients with crizotinib resistance was confirmed in a multicenter, open-label, phase III ALUR study involving 107 patients. Prior use of one line of systemic chemotherapy was permitted. Patients were randomly assigned (2 : 1) to the arm receiving alectinib 600 mg twice daily (n = 72) or investigator's choice chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 intravenously every 3 weeks) (n = 35). PFS, the primary endpoint of the study, was statistically prolonged in the alectinib arm compared to chemotherapy arm (mPFS 9.6 versus 1.4 months, respectively; HR 0.15; 95% CI 0.08–0.29; P < 0.001). The response rate in patients receiving alectinib was 37.5%, while in patients treated with chemotherapy only 2.9% [24].

Brigatinib was another inhibitor whose efficacy and safety was assessed in patients with disease progression during treatment with crizotinib. In total, 222 patients after prior chemotherapy (regardless of the number of treatment lines) were included in the multicenter, open-label, phase II ALTA clinical trial/ They were randomly assigned to the arm receiving brigatinib 90 mg daily (arm A, n = 112) or brigatinib 180 mg daily, after an initial 7-day treatment with a loading dose of 90 mg/day (arm B, n = 110). ORR, the primary endpoint of the study, was 45% for 90 mg dose and 54% for 180 mg dose, respectively. PFS was one of the secondary endpoints, with a median of 9.2 months and 12.9 months for lower and higher dose of brigatinib, respectively. The daily dose of 180 mg was determined to be assessed in further clinical studies [24]. In 2020, updated results of the ALTA clinical trial were published after a median follow-up of 19.6 months for Arm A and 24.3 months for Arm B. The median PFS was 9.2 months versus 16.7 months for arms A and B, respectively, while median OS was 29.5 months versus 34.1 months for patients receiving brigatinib 90 mg and 180 mg, respectively [26]. The effectiveness of ceritinib sequential treatment was evaluated in a multicenter, randomized, open-label, phase III ASCEND 5 clinical trial, which included 231 patients with stage IIIB/IV ALK-positive NSCLC. Patients enrolled in the study had to have disease progression during or after treatment with one or two lines of chemotherapy, and progression during crizotinib treatment. Patients were randomly assigned (1 : 1) to the arm receiving ceritinib 750 mg/day on an empty stomach (n = 115) or pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 (n = 116). The primary endpoint of the study was PFS, and secondary endpoints included OS, objective response rate and intracranial response rate. The use of ceritinib was associated with a 51% reduction in the risk of disease progression (median PFS 5.4 months for ceritinib and 1.6 months for chemotherapy, HR 0.49; 95% CI 0.36–0.67; P < 0.0001). There was also a huge difference in terms of response rate: 39.1% and 6.9%, respectively. Despite its high effectiveness, ceritinib is unfortunately characterized by an unfavorable toxicity profile [27].

The efficacy and safety of treatment with third-generation ALK inhibitor lorlatinib was assessed in phase II clinical trial in which patients were assigned to six cohorts: EXP1 — treatment-naive patients, EXP2 — patients with disease progression after treatment with crizotinib only, EXP3A — patients with disease progression after treatment with crizotinib and one or two chemotherapy lines used before or after crizotinib, EXP3B — patients with disease progression after treatment with crizotinib and one other ALK-TKI and any number of chemotherapy lines, EXP4 — patients with disease progression after treatment with two ALK-TKIs, and EXP5 — patients with disease progression after treatment with three ALK-TKIs. Patients who previously received at least one ALK-TKI (EXP2-5) had an ORR of 47% and an intracranial response rate of 63%. In patients who were treated with one ALK-TKI — crizotinib (EXP2-3A), the ORR was 69.5%, while in patients treated with crizotinib and one or two/more other ALK-TKIs, the ORR was 32.1% and 38.7%, respectively (mPFS 6.9 months) [28]. The available ALK TKI and their pivotal trials are summarized in Table 1.

The intracranial activity of small molecule ALK tyrosine kinase inhibitors

About 40% of patients with *ALK*-rearranged NSCLC have metastases in the central nervous system (CNS) at the time of initial diagnosis. ALK-positive lung cancers show some kind of neurotropism, which is probably associated with the role-playing by ALK protein in the development of the nervous system [29].

In more than 30% of patients treated with crizotinib, the disease progresses within 12 months of starting treatment, and the most common location for the progressing or new metastatic lesions are the central nervous system. In the ALEX clinical trial, the high intracranial activity of alectinib was noteworthy. At the time of enrollment, central nervous system metastases occurred in 42% of patients in alectinib arm and 38% of patients in crizotinib arm. It was shown that the time to progression of metastases in the central nervous system was significantly

Table 1. Available ALK TKI and pivotal trials (proszę o podanie odnośnika w tekście)

Drug	Trial	Primary endpoint	Control arm	FDA/EMA registration
First-line treatment				
Crizotinib	PROFILE 1014 [14, 15]	mPFS 10.9 *vs.* 7.0 months Hr 0.45. P < 0.001 95% CI 0.35–0.60 MOS 59.8 *vs.* 19.2 months HR 0.346; 95% CI 0.081–0.718)	Cisplatin/carboplatin + pemetrexed	2011/22.10.2015
Ceritinib	ASCEND 4 [18]	mPFS 16.6 *vs.* 8.1 months HR 0.55. P < 0.00001 95% CI 0.42–0.73	Platinum-based cht	26.05.2017/18.05.2017
Brigatinib	ALTA-1L [19, 20]	12-miesięczny PFS 67% *vs*. 43% HR 0.49. P < 0.001 95% CI 0.33–0.74 *HR dla PFS 0.43 95% CI 0.31–0.61	Crizotinib	
Alectinib	ALEX [17]	mPFS 34.8 *vs*. 10.0 months HR 0.43; 95% CI 0.32–0.58)	Crizotinib	6.11.2017/12.10.2017
Subsequent treatment lines				
Crizotinib	PROFILE 1007 [22]	mPFS 7.7 *vs.* 3.0 months HR 0.49. P < 0.001 95% CI 0.37–0.64	Docetaxel/pemetrexed Second-line treatment after failure of platinum-based CHT	2011/19.07.2012
Ceritinib	ASCEND 5 [27]	mPFS 5.4 *vs.* 1.6 months HR 0.49. P < 0.0001 95% CI 0.36–0.67	Docetaxel/pemetrexed Progression after one or two cht lines and crizotinib	29.04.2014/26.02.2015
Brigatinib	ALTA [26]	ORR 45% *vs.* 54% mPFS 9.2 *vs.* 12.9 months	90 mg/day *vs.* 180 mg/day Progression after any number of cht lines and crizotinib	28.04.2017/20.09.2018
Alectinib	ALUR [24]	mPFS 9.6 *vs*. 1.4 months HR 0.15. P < 0.001 95% CI 0.08–0.29	Docetaxel/pemetrexed Progression after one cht line and crizotinib	11.12.2015/15.12.2016

CI — confidential interval; CHT — chemotherapy; HR — hazard ratio; mPFS — median progression-free survival; ORR — overall response rate

longer in patients receiving alectinib. The cumulative risk of progression or new metastatic lesions in the central nervous system after 12 months of ALK TKI treatment was 41.4% for crizotinib and 9.4% for alectinib and is, therefore, more than four times lower in patients receiving second-generation inhibitor [16]. The median PFS for patients with metastatic lesions in the central nervous system was 27.7 months in alectinib arm and 7.4 months in crizotinib arm (HR 0.35) [17]. Alectinib has a lower molecular weight than crizotinib. The alectinib molecule is more lipophilic, more easily crosses the blood-brain barrier, moreover it is not a substrate for p-glycoprotein (P-gp), which allows achieving a higher concentration in the cerebrospinal fluid (CSF) [29].

The updated results of ALTA-1L clinical trial after a median follow-up of over 2 years also indicate that the use of brigatinib in patients with metastatic lesions in the central nervous system at baseline is associated with a reduction in the risk of disease progression or death by 76% compared to crizotinib (HR 0.24, 95% CI 0.12–0.45) [20]. In patients receiving brigatinib after disease progression during crizotinib treatment, the intracranial response rate was 50% and 67% in patients receiving the lower (90 mg) and higher dose of brigatinib (180 mg), respectively. The median duration of intracranial response in these patients was 9.4 months and 16.6 months, respectively [26]. Patients treated with ceritinib in first-line also had a significantly higher intracranial response rate com-

pared to standard platinum-based chemotherapy (72.7% *vs.* 27.3%) [18]. For lorlatinib, the rates of intracranial responses were 87% and 53.1% for the EXP2-3A and EXP4-5 cohorts, respectively [28].

At present, in patients with asymptomatic metastases in the central nervous system, it is recommended to start treatment with next-generation small-molecule ALK tyrosine kinase inhibitors that penetrate the central nervous system. In patients with isolated asymptomatic progression in the central nervous system treated with crizotinib it is recommended to switch the therapy to an inhibitor with high activity in CNS, thus postponing brain radiotherapy [29]. The intracranial activities of individual ALK inhibitors are described in Table 2.

The sequence of treatment with ALK tyrosine kinase inhibitors

The validity of the concept of sequential treatment with ALK-TKIs was confirmed in the French retrospective IFCT-1302 CLINALK clinical study. The analysis included data from 318 ALK-positive NSCLC patients who received crizotinib as part of the EAP after drug registration. Among others, a multivariable OS analysis was performed in patients treated with crizotinib as the first ALK inhibitor, followed by treatment with next-generation inhibitors after disease progression (n = 84, 32%). It was demonstrated that in patients who received next-generation inhibitors after disease progression, the median OS was 25 months, e.g. up to 89.6 months from diagnosis of metastatic lung cancer and was significantly longer than in patients receiving chemotherapy or only the best supportive care (BSC) after progression during crizotinib treatment. However, researchers point out that among patients with disease progression during crizotinib treatment only 60% received any treatment, while next-generation inhibitors were used only in 32% of patients [30]. This was most often due to the disease-related deterioration of patients performance status (PS) and dynamically progressing lesion(s) within the central nervous system. Therefore, and in view of the latest data from clinical trials, it seems reasonable to start therapy with an inhibitor showing high activity within CNS. The use of alectinib in first-line treatment is associated with PFS improvement by more than 24 months (34.8 months *vs.* 10 months) compared to crizotinib in first-line [16]. Similarly, the use of brigatinib in first-line treatment reduces the risk of disease progression or death by 57% compared to crizotinib with OS prolongation by more than 4 months (mOS 29.5 months *vs.* 34.1 months) [19]. It is extremely important to postpone radiotherapy of the central nervous system in patients who are mostly younger, professionally, family and socially active. In the case of disease progression during the treatment with second-generation ALK-TKI, third-generation ALK-TKI lorlatinib can be used, whose activity covers the largest spectrum of secondary resistance mutations to lower generation ALK-TKIs.

Side effects of ALK tyrosine kinase inhibitors

ALK-TKIs have a different toxicity profile than chemotherapy. The most common adverse reactions

Table 2. ALK TKIs activity in the central nervous system

First-line treatment with ALK TKI		ALK TKIs in second and subsequent treatment lines (after failure of other ALK TKIs)	
CRYZOTINIB			
PROFILE1014 [14]	icORR 50% icDOR 5.5 months		
CERITINIB			
ASCEND-4 [18]	icORR 73% icDOR 16.6 months	ASCEND-5 [27]	icORR 35% icDOR 6.9 months
ALECTINIB			
ALEX [16]	icORR 81% icDOR 17.3 months	ALUR [24]	icORR 54%
BRIGATINIB			
ALTA-1L [20]	icORR 83% icDOR NR HR dla PFS 0.24	ALTA 180 mg [26]	icORR 67% icDOR 16.6 months

ALK TKI — ALK tyrosine kinase inhibitor; icORR — intracranial overall response rate; icDOR — intracranial duration of response; NR — not reached; HR — hazard ratio; PFS — progression-free survival

Table 3. Adverse events of ALK tyrosine kinase inhibitors [32–34]

	CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
Grade G3 adverse events in > 5% of patients	↑ AST/ALT 14% ↓ ANC 11%	↑ ALT 31% ↑ GGT 29% ↑ ALP 29% ↑ AST 17% diarrhea 5% vomitus 5%	↑ ALT 5% ↑ AST 5%	↑ CPK 16% ↑ lipase 13% hypertension 10% ↑ amylase 5%	↑ cholesterol 18% ↑ triglycerides 18% ↑ lipase 10% dyspnea 5,4%
SAE	38%	41%	26%	41%	32%
Respiratory complications	10.5%	14.7%	5.9%	13.5%	7.5%
Characteristic adverse events	visual disturbances (flashes, light columns, blurred vision) NEUTROPENIA	gastrointestinal disorders (diarrhea, abdominal pain, nausea, vomiting)	Anemia	ILD, hypertension	Mental disorders, mood, speech and sleep disorders
The need to reduce the dose	21%	80%	16%	29%	22%
Molecular target	ALK ROS1 MET/HGF	ALK IGF-1	ALK	ALK EGFR	ALK ROS1 MET/HGF

ALK — anaplastic lymphoma kinase; ALP — alkaline phosphatase; ALT — alanine aminotransferase; ANC — absolute neutrophil count; AST — asparaginian aminotransferase; CPK — creatine phosphokinase; EGFR — epidermal growth factor receptor; GGT — gamma-glutamyl transpeptidase; HGF — hepatocyte growth factor; IGF-1 — insulinę growth factor; ILD — intestinal lung disease; SAE — serious adverse even

of crizotinib reported in at least 5% of patients in the PROFILE 1007 clinical trial included visual disturbances, like visual acuity impairment or blurred vision, as well as diarrhea, nausea, vomiting, constipation, elevated liver enzymes, peripheral edema, dysgeusia (taste disturbance), dizziness or upper respiratory tract infection. Most side effects were mild to moderate in severity and transient in nature as well manageable. The most common side effects of chemotherapy were fatigue, alopecia, shortness of breath and rash [22]. In the PROFILE 1014 clinical trial, the most common adverse reactions in the crizotinib arm included, as in the PROFILE 1007 study, visual disturbances, diarrhea and edema, while in the chemotherapy arm fatigue, anemia and neutropenia [14]. The percentage of adverse effects of alectinib and crizotinib in the ALEX clinical study was similar in both arms, while both inhibitors differed significantly in the toxicity profile. Adverse reactions more commonly seen in the alectinib group were anemia (20% *vs.* 5% in crizotinib arm), myalgia (16% *vs.* 1%), elevated bilirubin level (15% *vs.* 1%), weight gain (10% *vs.* 1%), musculoskeletal pain (7% *vs.* 2%) and photosensitivity reactions (5% versus 0%). In contrast, side effects more commonly seen in patients receiving crizotinib included nausea (48% *vs.* 14% in alectinib arm), diarrhea (45% *vs.* 12%), and vomiting (38% *vs.* 7%). Grade 3–5 adverse reactions were more common in the crizotinib arm (41% for alectinib and 50% for crizotinib, respectively) so that alectinib appears to be a safer drug [16]. In the case of brigatinib, the percentage of adverse reactions in the form of interstitial pneumonia in patients using the dose of 180 mg was successfully reduced by introducing 7-days treatment with a loading dose of 90 mg [26]. Ceritinib appears to have the least favorable toxicity profile. The most common side effects of ceritinib reported in ASCEND-4 clinical trial included diarrhea, which occurred in up to 85% of patients, nausea (69%), vomiting (66%), and elevated alanine aminotransferase level (60%). The most common chemotherapy side effects were nausea and vomiting, but they were less common than in patients treated with ceritinib (55% *vs.* 36%, respectively), and anemia (35%) [18]. In the ASCEND-5 clinical trial, adverse events that were significantly more common in ceritinib arm than in chemotherapy arm were diarrhea (up to 72% *vs.* 18%, respectively), nausea (66% *vs.* 24%), vomiting (52% *vs.* 5%), elevated alanine aminotransferase (43% *vs.* 9%) and aspartate aminotransferase level (37% *vs.* 5%). At least one dose reduction due to adverse reactions was required in 61% of patients in ceritinib arm and 18% of patients receiving pemetrexed and 26% of patients receiving docetaxel [27]. The incidence and intensity of gastrointestinal adverse reactions quite significantly hindered the widespread use of ceritinib at a dose of 750 mg daily (ASCEND-4 and ASCEND-5 clinical studies). The phase I ASCEND-8 clinical trial compared the pharmacokinetics and frequency of adverse reactions of ceritinib 450 mg daily and 600 mg daily taken with a low-fat meal and ceritinib 750 mg daily taken fasting. Ceritinib 450 mg daily with a low-fat meal and 750 mg taken fasting has been shown to have similar pharmacokinetics, but 450 mg daily was associated with fewer

side effects. Diarrhea was found in 43% of patients, nausea in nearly 30% of patients and vomiting in over 18% of patients. The gastrointestinal side effects were mild (mainly grade 1), no grade 3 or 4 side effects or no serious side effects were reported. No patient discontinued the treatment due to gastrointestinal adverse reactions [31]. The currently recommended dose of ceritinib is 450 mg daily taken with a low-fat meal.

Although ALK-TKI treatment is better tolerated than chemotherapy, the toxicity profile of individual inhibitors varies. The most characteristic adverse effects of different ALK TKI are summarized in Table 3.

Possibilities of using ALK-TKI in Poland

In Poland, patients are qualified for ALK TKI treatment in accordance with the criteria of Drug Program (Appendix B6 — treatment of non-small cell lung cancer). As part of the first-line treatment of patients who have not received prior systemic therapy, a first-generation inhibitor, crizotinib and two second-generation inhibitors, alectinib and ceritinib are available. Crizotinib can also be used in a patient with *ALK* gene rearrangement and disease progression after one or two lines of chemotherapy. Treatment with alectinib or ceritinib is also possible when other ALK TKI treatment fails (including failure of crizotinib treatment). The basic qualification criterion for ALK TKI treatment is confirmation of *ALK* gene rearrangement (by immunohistochemistry [IHC], which does not require further confirmation by fluorescence in situ hybridization [FISH] or next-generation sequencing [NGS]). This molecular aberration should be sought in patients diagnosed with adenocarcinoma or NSCLC with a predominance of this histological subtype. In the case of alectinib treatment, this group should also include patients with a diagnosis of large cell carcinoma or NOS NSCLC. As part of the drug program, it is possible to use ALK TKIs in patients with metastatic lesions within the central nervous system. The prerequisite for this is no signs of progression after local treatment (neurosurgery or irradiation), no clinically significant neurological symptoms, and no need to increase glucocorticoid doses within a month before starting ALK TKI treatment. Alectinib, which is highly active within the central nervous system, can be used in systemic treatment in patients who have not received prior local treatment. The condition for this is also the absence of clinically significant neurological symptoms resulting from CNS involvement.

Treatment with ALK TKI is continued until disease progression or unacceptable toxicity. The effectiveness of treatment is determined based on imaging tests and according to the RECIST 1.1 criteria every 3 months and treatment toxicity based on laboratory tests performed every 4 weeks. For alectinib, it is important to monitor the phosphocreatine kinase level (every 2 weeks in the first month of treatment, then every 4 weeks or as clinically indicated) [35].

Summary

Introduction of ALK-TKI treatment improved the prognosis of patients with ALK-positive NSCLC. Several medications of this group are currently registered and reimbursed. For first-line treatment, both first-generation (crizotinib) and second-generation inhibitors (alectinib and ceritinib) are available. Another second-generation ALK-TKI, brigatinib is awaiting registration and reimbursement. Due to higher activity in the central nervous system and longer time to disease progression, it is recommended to start therapy with a second-generation inhibitor. In case of disease progression during crizotinib treatment, two second-generation inhibitors are available for sequential treatment (alectinib or ceritinib). To make the use of ALK-TKI possible, molecular diagnostics and confirmation of *ALK* gene rearrangement play a key role, and thus the availability of an adequate amount of good-quality tissue material for these tests.

Conflicts of interest

The authors declare to have no conflict of interest.

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