

Kinga Winiarczyk, Aleksandra Piórek, Maciej Krzakowski

Department of Lung and Thoracic Cancers, Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland

ALK, ROS1 and EGFR next-generation tyrosine kinase inhibitors in advanced non-small-cell lung cancer

Address for correspondence:

Lek. Kinga Winiarczyk
Klinika Nowotworów Płuca
i Klatki Piersiowej,
Centrum Onkologii
— Instytut im. M. Skłodowskiej-Curie
ul. Roentgena 5, 02-871 Warszawa
e-mail: kwiniarczyk@coi.pl

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ABSTRACT

Non-small-cell lung cancer (NSCLC) is the most common cancer in men and the second most common in females. In previous years the significance of some molecular disorders in pathogenesis NSCLC was proven and the value of targeted therapies in the treatment of patients was documented. In subjects with abnormalities of *EGFR*, *ALK* and *ROS1* genes, appropriate tyrosine kinase inhibitors (TKIs) may be used. The use of these drugs in the first and second treatment lines has affected a significant improvement in the prognosis in this subgroup of patients. The article presents mechanisms of action and data on the clinical value of lorlatinib, brigatinib and dacomitinib in the treatment of patients with advanced lung of lung cancer.

Key words: non-small-cell lung cancer, kinase inhibitors, lorlatinib, brigatinib, dacomitinib

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Introduction

Lung cancer is the most commonly diagnosed cancer in men and the second, after breast cancer, most common cancer in women. At the same time, it is the main cause of cancer deaths among both men and women (about 1.7 million per year) [1]. In about 80–85% of patients, non-small cell lung cancer (NSCLC) is diagnosed [2]. The generalised stage of the disease is initially found in more than 40% of patients [2]. Histological type and other pathomorphological factors are now routinely taken into account when choosing the type of treatment. In recent years, the importance of some molecular disorders in the pathogenesis of NSCLC has been demonstrated and the value of targeted therapies in the treatment of patients with this diagnosis has been shown. Currently, the standard is an individual approach in choosing the optimal procedure. In patients with abnormalities of epidermal growth factor receptor (*EGFR*) gene, anaplastic lymphoma kinase (*ALK*) gene, and *ROS1* gene it is possible to use appropriate tyrosine kinase inhibitors.

The use of these drugs in the first and second line of treatment has resulted in significant improvement of prognosis in this subgroup of patients. The observed results of treatment confirmed the validity of searching for new, even more effective molecular target drugs, also effective in patients with developed resistance to earlier therapies or in the group of patients with metastases to the central nervous system (CNS). The article presents the current state of knowledge and potential uses of lorlatinib, brigatinib, and dacomitinib — next generation EGFR ALK/ROS1 tyrosine kinase inhibitor (TKI).

Lorlatinib

Pharmacological characteristics of lorlatinib

Lorlatinib (PF-06463922) is a third-generation low-molecular-weight inhibitor of ALK and ROS1 TKI. It is characterised by high affinity and strong inhibition of kinase. It also shows inhibitory action in the case

of G1202R mutation — the most common secondary mutation responsible for the development of resistance to ALK TKI of previous generations. Lorlatinib has a macrocyclic structure, which distinguishes it from other ALK inhibitors. Thanks to its structure, it has greater metabolic stability and the ability to pass through the blood-brain barrier. Lorlatinib is an orally bioavailable drug. After a single dose (10–200 mg), it is absorbed, reaching its maximum plasma concentration within 1–2 hours. The elimination phase half-life of lorlatinib ranges from 19.0 to 28.8 hours at doses of 10, 50, 75, 100, and 200 mg [3]. Results of *in vitro* and *in vivo* studies indicate that lorlatinib may change the pharmacokinetics of other drugs that are metabolised by P450 cytochrome isoenzymes and are administered at the same time. Therefore, according to the Phase II study, concomitant use of CYP3A inhibitors is not allowed for at least 12 days before the first dose of lorlatinib [3].

Clinical trials with lorlatinib

Phase I study

The phase I multi-centre study was designed to determine the pharmacokinetics and maximum tolerable dose, and to assess the adverse effects of lorlatinib in patients with advanced NSCLC with current *ALK* (77%) or *ROS1* (23%) gene rearrangement [4]. Other eligibility criteria included performance status according to the Eastern Cooperative Oncology Group (ECOG 0–1) and proper function of organs. In the 54 patients enrolled in the study, two or more TKI therapies were previously used in 28 patients and 39 (72%) had metastases to the CNS. Lorlatinib was administered orally at doses from 10 to 200 mg once daily or 35 to 100 mg twice daily. A well-tolerated dose — recommended for further studies — was set at 100 mg once daily. Among 41 *ALK*-positive patients the objective response rate (ORR) was found in 19 patients [46%; 95% confidence interval (CI) 31–63], including 11 out of 26 who previously used TKI (42%; 95% CI 23–63). In *ROS1*-positive patients, including seven patients previously treated with crizotinib, ORR was obtained in six patients (50%; 95%

CI 21–79). Out of 24 patients with measurable target lesions in the CNS (46%; 95% CI 26–67) 11 had an intracranial objective response to the treatment.

Phase II study

In 2017, during the 18th World Conference on Lung Cancer, the results of the Phase II study were presented, in which 275 patients were included. The participants were divided into six cohorts depending on the previously applied therapy (Table 1) [5]. For five cohorts of 197 patients who previously received ALK inhibitors in different configurations, the percentage of ORR ranged from 33% (first line of treatment for ALK TKI other than crizotinib ± chemotherapy) to 74% (patients previously receiving only crizotinib). Objective intracranial responses in patients with CNS metastases ranged from 39% (three treatment lines ALK TKI ± chemotherapy) to 75% (crizotinib ± chemotherapy). The percentage of ORR was 90% in patients receiving lorlatinib as the first-line of treatment [5].

The American Food and Drug Administration (FDA) recognised lorlatinib as a breakthrough therapy in patients with advanced ALK-positive NSCLC [3, 6]. The definition of “breakthrough therapies” aims at accelerating the development and review of a potential new drug if it is intended to treat a serious or life-threatening disease, and initial clinical evidence suggests that the drug can be significantly effective compared to existing therapies [6].

Phase III study

A phase III study (CROWN) is currently underway, in which lorlatinib and crizotinib efficacy is compared in the first line of treatment of NSCLC with *ALK* rearrangement [7]. Patients are randomly assigned to arm A (lorlatinib 100 mg, 1 × daily) or arm B (crizotinib 250 mg, 2 × daily). The primary endpoint of the study is the evaluation of the influence of these therapies on the progression-free duration. Among the secondary endpoints, the percentage of objective intracranial responses in patients with measurable metastases to the CNS will also be assessed.

Table 1. Phase II study results with lorlatinib [5]

Earlier therapy	n	ORR — n (%)	N (metastases to CNS)	ORR (metastases to CNS) — n (%)
Without treatment	30	27 (90)	8	6 (75)
Crizotinib	27	20 (74)	17	10 (59)
Crizotinib + CHTH	32	21 (66)	20	15 (75)
Different ALK TKI ± CHTH	27	9 (33)	12	5 (42)
2 lines ALK TKI ± CHTH	65	27 (42)	45	25 (56)
3 lines ALK TKI ± CHTH	46	16 (35)	38	15 (39)

CHTH — chemotherapy; ORR — objective response rate; ALK — anaplastic lymphoma kinase; TKI — tyrosine kinase inhibitor; CNS — central nervous system

Efficacy in patients with metastases to the central nervous system

Metastases to the brain are a common complication of cancer, and the effectiveness of drugs is significantly reduced in this area. Retrospective analysis showed that 20–30% of all NSCLC patients with *ALK* rearrangement had metastases in the CNS at the time of diagnosis (compared to 10–20% of patients with NSCLC regardless of *ALK* status) [8]. This number increases to 45–75% during the disease in patients using *ALK* inhibitors, which indicates that the disease in the CNS is a major problem in patients with *ALK* rearrangement. This is due to the presence of the blood-brain barrier. It is a semi-permeable barrier separating blood from extracellular CNS fluid. It consists of closely connected endothelial cells. It prevents the penetration of harmful substances into the brain, at the same time blocking the supply of many medicinal substances to it. The blood-brain barrier is not only a physical barrier to most substances, but thanks to P-glycoprotein and multidrug resistance proteins it also actively removes drugs [9]. The limitation for the first-generation *ALK* inhibitor crizotinib were frequent recurrences of the disease in the CNS. Next-generation inhibitors are characterised by better penetration to the CNS. Lorlatinib was designed to penetrate through the blood-brain barrier. This was confirmed by the pre-clinical studies of Collier et al. in which the penetration of lorlatinib was evaluated by positron emission tomography (PET) using carbon and fluorine marking [10]. In phase I clinical trials 46% of patients with measurable CNS metastases received an objective intracranial response to treatment [4]. The Phase II study showed high systemic and intracranial ORR (Table 1) in patients treated with the first line of treatment as well as in those receiving TKI *ALK* [5].

Efficacy in patients with drug resistance

Regardless of the type of TKI *ALK* used, disease progression occurs in patients treated with these drugs about 12 months after the onset of therapy [8]. However, the mechanisms of molecular progression vary. In about 50–60% of patients with acquired resistance to first-generation *ALK* TKI (crizotinib) activation of other cellular transmission pathways starting with EGFR or IGF1-R, mutation in the *KRAS* gene, or amplification of *ALK* and *KIT* genes occurs [11]. However, in 30–40% they depend on the selection of a clone cell with a point mutation in the *ALK* gene [8, 11]. Lorlatinib in pre-clinical studies showed activity against most known resistance mutations. Phase I and II studies confirmed its high efficacy in patients with advanced *ALK*-positive NSCLC, most of whom had previously been treated. Shaw et al. evaluated circulating DNA and tumour tissue samples from patients previously treated with *ALK* TKI, who

took part in the phase II study [12]. samples were analysed from patients in five cohorts (Table 1): previously just crizotinib, previously crizotinib + chemotherapy or any other *ALK* TKI ± chemotherapy, two previous *ALK* TKI ± chemotherapy, and three previous *ALK* TKI ± chemotherapy. Samples were evaluated for the presence of mutations. A total of 75 mutations were detected, with G1202R being the most frequent (25%), followed by F1174 (15%), L1196M (15%), G1269A (11%), and I1171 mutations (8%). Responses were observed in 64% of patients whose samples contained more than one mutation in the *ALK* kinase domain. Also, 42% of patients without detectable mutation responded to lorlatinib. Mutation of G1202R was often observed in patients who earlier received 2 or 3 *ALK* TKI treatment lines [12].

Lorlatinib has been designed to overcome resistance to earlier therapy, but resistance may also occur when using this drug. Shaw et al. also demonstrated a new mechanism of resistance to this drug. In patients resistant to lorlatinib, they detected a double mutation (*ALK* C1156Y-L1198F), which if present, surprisingly, restores sensitivity to crizotinib [13].

Adverse effects

Hypercholesterolaemia (72%), hypertriglyceridaemia (39%), peripheral oedema (39%), and peripheral neuropathy (39%) were the most common side effects of lorlatinib [4]. In the Phase I study, level 2 CNS toxicity was found in the form of slowed speech and mental activity but also difficulty in finding words. It appeared in patients receiving 200 mg of lorlatinib once a day — dose-limiting toxicity (DLT) [4]. In the phase II study, third- and fourth-degree adverse effects related to treatment were found, which included hypercholesterolaemia (16%) and hypertriglyceridaemia (16%) [5]. No treatment-related deaths were reported. The toxicity of lorlatinib differs from that reported for other *ALK* TKIs. Hepatotoxicity (increased activity of aspartate transaminase or alanine transaminase) and gastrointestinal disorders (nausea, vomiting, diarrhoea) are mainly associated with other inhibitors and occur much less frequently with lorlatinib [3]. The side effects of lorlatinib do not affect the quality of life of patients. About 43% of treated patients report improved quality of life [5].

Brigatinib

Pharmacological characteristics of brigatinib

Brigatinib (AP26113, Alunbrig) is another oral TKI *ALK*. In preclinical studies with use of *ALK*-positive cell lines brigatinib showed a 12-fold greater potency than crizotinib [14]. It was characterised by a high

degree of selectivity, inhibiting only 11 kinases (from 289 evaluated), including ROS1, FLT3, mutant variants of FLT3 (D835Y), and EGFR (L858R). Whilst brigatinib demonstrated a lower anti-EGFR (including T790M resistance mutation), anti-IGF1R, and anti-INSR activity, it did not show activity against the MET pathway [14]. Compared to crizotinib, brigatinib showed an activity advantage and inhibitory profile against all assessed secondary *ALK* mutations, including G1202R [14]. After administration of a single oral dose (30–240 mg) the median time to maximum drug concentration (T_{max}) is 1–4 hours [16]. The mean elimination half-life in plasma is 25 hours, and hepatic excretion is the main route of drug elimination [15]. In *in vitro* studies, brigatinib has been shown to be metabolised by cytochrome CYP2C8 and CYP3A4, and, to a much lesser extent, by CYP3A5. Brigatinib is eliminated mainly through faeces [16].

Clinical trials with brigatinib

Phase I/II study

The multicentre phase I/II study was designed to determine the pharmacokinetics and the maximum tolerated dose, and to evaluate the side effects of brigatinib. In total 66 patients were enrolled with performance status 0–1 according to ECOG (Eastern Cooperative Oncology Group) scale, with measurable change according to RECIST 1.1 criteria. The study involved patients with asymptomatic CNS metastases.

Brigatinib was given orally at the doses of 30 mg, 60 mg, 90 mg, 120 mg, and 180 mg once daily. In the phase II study the doses of 90 mg, 180 mg, and 180 mg were used preceded by a seven-day initial period in which a dose of 90 mg was administered. In the phase II study patients were divided into five cohorts — patients with NSCLC and *ALK* gene rearrangement previously not treated with ALK TKI (cohort 1), patients with NSCLC and *ALK* gene rearrangement previously treated with crizotinib (cohort 2), patients with NSCLC and with T790M mutation in *EGFR* gene treated with TKI (cohort 3), patients with other cancers with concomitant disorders in *ALK* and *ROS1* gene (cohort 4), and patients with CNS metastases both treated and not treated with crizotinib [17].

The endpoint of the first part of this study was to determine the tolerated dose, and in the second part, the ORR. In the second part of the study a response was achieved by 100% of the patients in cohort 1, 74% of the patients in cohort 2 (31 out of 42 patients), none of the patients in cohort 3, 17% of the patients in cohort 4, and 83% of the patients in cohort 5 [17].

Phase II study

The study involved 222 patients from 71 sites randomly assigned (1:1) to arm A (brigatinib 90 mg once daily) and arm B (brigatinib 180 mg once daily with pre-

vious seven-day initial period in which a dose of 90 mg was used) [18]. Patients were stratified according to the CNS metastases (present or absent) and the type of response to previously used crizotinib (complete or partial response). The primary endpoint was ORR and the secondary endpoint was PFS and overall survival (OS). In arm A the ORR was 45% (97.5%, range from 34% to 56%), including one patient with complete response (CR), and in arm B 54% (97.5%, range from 43% to 65%), including four patients achieving CR. In arm A, PFS was 9.2 months, in arm B it reached 12.9 months [18]. The one-year OS rate was 71% and 80% in A and B arm, respectively.

Phase III study

From April 2016 to August 2017 at total of 275 patients in 124 sites were randomised (1:1) to the arm receiving crizotinib or brigatinib [19].

Patients were stratified according to the CNS metastases (present or absent). Patients in the brigatinib group received a 180-mg dose once daily (with a prior seven-day period with a dose of 90 mg) in 28-day cycles, and the patients in the crizotinib arm received 250 mg of the drug twice daily in 28-day cycles. In both arms the treatment was continued until the disease progressed. Patients in the crizotinib arm were allowed to cross-over to the brigatinib group after disease progression. The primary endpoint of the study was PFS. Secondary endpoints included the overall ORR and, in patients with measurable CNS, metastases.

The first analysis of the study showed the superiority of brigatinib over crizotinib in 12-month PFS (67% vs. 43%). ORR in the brigatinib arm was 71% vs. 60% in the crizotinib arm.

Efficacy in patients with metastases in the central nervous system

In the ALTA study the ORR in the group of patients with baseline measurable CNS metastases assessed by an independent expert committee reached 42% in arm A (11 out of 26 patients) and 67% in arm B (12 out of 18 patients) [18]. Among 39 patients with measurable lesions in CNS participating in a phase III clinical study, intracranial responses were achieved by 78% patients in the brigatinib group compared with 29% patients in the crizotinib group [19].

Adverse events

The most common adverse events reported during brigatinib treatment are summarised in Table 2.

In the ALTA study, 6% of patients experienced pulmonary adverse reactions in general (3% grade ≥ 3 ; including interstitial lung disease [ILD], pneumonia, and dyspnoea). These events were reported during the

Table 2. Adverse events of brigatinib [15, 19]

Study	Patients	AE G1–2	AE G3–4
I/II	71	Nausea (53%) Fatigue (43%) Diarrhoea (41%)	↑ lipase (9%) Dyspnoea (6%) Hypertension (5%)
ALTA	A — 112/B — 110	Nausea (33%/40%) Diarrhoea (19%/38%) Headaches (28%/27%) Cough (18%/34%)	↑ CPK (3%/9%) Hypertension (6%/6%) Pneumonia (3%/5%)
ALTA-1L	137	Diarrhoea (49%) ↑ creatinine (39%) Nausea (26%) Cough (25%) Hypertension (23%)	↑ creatinine (16%) ↑ lipase (13%) Hypertension (10%)

↑ — elevated level; AE — adverse event; CPK — creatine phosphokinase

early treatment period (median time to onset — two days) [16, 18]. Early pulmonary adverse events also occurred in patients recruited to the dose escalation study — including three fatal cases (hypoxia, acute respiratory distress syndrome, and pneumonia). In addition, 2.3% of patients in ALTA study had pneumonia at a later stage of treatment, and in two patients it was grade 3 pneumonitis [16]. Interstitial lung disease or pneumonia was found in 4% of patients treated with brigatinib in the ALTA-1L study (2% in the crizotinib treated group) [19].

In 2017, the FDA approved the accelerated registration of the drug in the treatment of patients who have progressed after crizotinib treatment or with intolerance of this drug (breakthrough therapy).

Dacomitinib

Pharmacological characteristics of dacomitinib

Dacomitinib (PF-299804) is a strong, highly selective, second-generation oral TKI that irreversibly blocks EGFR/HER1, HER2, and HER4. It inhibits the tyrosine kinase activity by binding at the ATP binding site, which results in covalent modification of cysteine in the ATP binding cassette. The irreversible and highly selective properties of dacomitinib cause a persistent suppression of the tyrosine kinase receptor activity. Dacomitinib is absorbed orally with a median time of maximum concentration (T_{max}) in the range of five to 12 hours. The average half-life is 54 to 90 hours [21].

Clinical trials with dacomitinib

Phase I study

The phase I multi-centre study was designed to determine pharmacokinetics and maximum tolerable dose,

and to assess the adverse effects of dacomitinib. It was attended by 57 patients previously treated with erlotinib or gefitinib with advanced NSCLC with ECOG 0–1 efficiency and normal organ function. Patients received dacomitinib at a dose of 0.5 to 60 mg once a day. A well-tolerated dose — recommended for further studies — was set at 45 mg once daily. In 33 patients the presence of *EGFR* gene activation mutation was confirmed, and in four patients T790M resistance mutation was detected. Out of 57 patients, 56% had ORR of whom four had partial response (PR) and 28 had stable disease (SD) [22].

Phase II study

The study involved 89 patients, 85% of whom were patients with confirmed mutation of *EGFR* gene activation (in 25 patients, deletion in 19 exon was detected, and in 20, insertion in exon 21). In 15% of patients, other types of mutations were identified; 15% of the studied population were patients without *EGFR* gene mutations. The average observation period was 24.8 months.

ORR in the whole population was 53.9%. In 47 patients (53%) PR was achieved, and in one CR — complete response — was noted. The percentage of PFS was 11.5 months. In the population of patients with confirmed activating mutation of *EGFR* gene, PFS was 18.2 months with no significant differences between patients with exon 19 deletion (16.6 months) and exon 21 insertion (18.3 months). PR was achieved in 34 out of 45 patients with mutation (76%).

The mean duration of treatment in the whole evaluated population was 9.2 months, and in the population with confirmed activation mutation it was 16.5 months. The most common side effects were diarrhoea (93%) and acne-like rash (78%). A promising improvement in PFS was observed in patients with *EGFR* gene activation mutation treated in the first line [22].

For comparison, in studies with reversible TKI, the first-generation PFS median in the population of patients with *EGFR* mutation was about 9–11 months [23, 24]. In a phase III study for afatinib, the PFS median was about 13 months in patients with mutation of *EGFR* gene activation [25].

Phase III study

From May 2013 to March 2015, in 71 centres, 452 patients were recruited, who were assigned in a ratio of 1:1 to one of two arms: the first arm was dacomitinib and the second was gefitinib (Table 3) [26]. Patients were stratified according to their race (Asian vs. non-Asian) and type of *EGFR* activating mutation (deletion in exon 19 vs. insertion in exon 21). In the first arm patients received dacomitinib 45 mg once a day in 28-day cycles, and in the second arm patients received gefitinib 250 mg once a day in 28-day cycles as well. In both arms the treatment was continued until progression of the disease. Treatment after progression was allowed in case of clinical benefit. The primary end-point was PFS. Secondary end-points included time to treatment failure (TTF) and OS.

In the arm with dacomitinib PFS was 14.7 months, and in the arm with gefitinib — 9.2 months.

In the group of patients with deletion of exon 19, 76% of patients with dacomitinib and 70% of patients with gefitinib received ORR.

In the group of patients with exon-21 mutation, this percentage was 73% in the arm receiving dacomitinib and 74% in the arm that received gefitinib.

The first analysis of the study in July 2016 showed that dacomitinib was superior to gefitinib in the first-line of treatment of patients with advanced NSCLC with activating mutation of *EGFR* gene in terms of PFS. The OS data did not reach maturity [26].

A second analysis in February 2017 showed an improvement in OS in favour of dacomitinib (34.1 months vs. 26.8 months) (Fig. 1).

In the group of patients with deletion in the 19 exon the mean OS was 34.1 months in the arm with dacomitinib; in the arm with gefitinib no OS was achieved.

In the group of patients with exon-21 mutation, the mean OS was 32.5 months in the dacomitinib arm and 23.2 months in the arm with gefitinib. In the analysis of subgroups concerning race, the mean OS in the

Table 3. Characteristics of patients — phase III study ARCHER 150 [26]

Data	Dacomitinib (n = 227)	Gefitinib (n = 225)
Age median (years)	62 (28–87)	61 (33–86)
< 65	133	140
> 65	94	85
Men	81	100
Women	146	125
ECOG		
0	75	62
1	152	163
Smoking status		
Never	147	144
Current	15	19
Prior	65	62
Exon		
19	134	133
21	93	92

ECOG — Eastern Cooperative Oncology Group

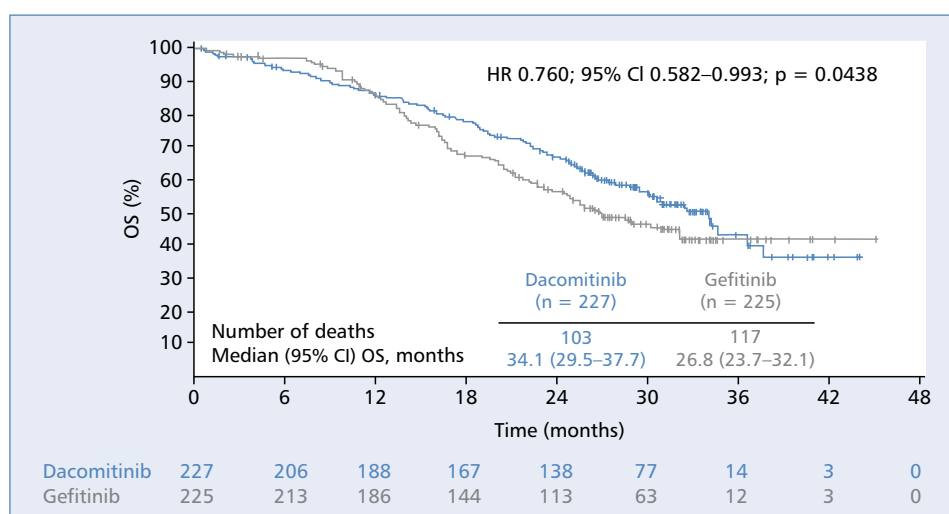


Figure 1. Overall survival time (OS) in the phase III ARCHER 150 study [26]

non-Asian population was 29.5 months in the arm of patients receiving dacomitinib, and 20.6 months in the arm of patients treated with gefitinib. In the Asian population these results were as follows: in the arm with dacomitinib OS was 34.2 months, and in the arm with gefitinib it was 29.1 months. During the 30-month observation period, the percentage of survivors was 56.2% in the arm with dacomitinib and 46.3% in the arm with gefitinib.

Dacomitinib is the first second-generation inhibitor that has significantly improved survival in advanced NSCLC patients with activating mutation of the *EGFR* gene [27].

Conclusions

The treatment of patients with NSCLC is still in progress. It concerns both deepening of knowledge about the cancer itself as well as the development of new therapeutic methods. The progress in basic sciences resulting in better understanding of cancer biology has contributed to the development of molecular target therapies. Their use in the first- and second-line of treatment has enabled us to achieve significant improvement in the prognosis of selected patients. The results confirm the legitimacy of searching for new, even more effective molecular target-oriented therapies, also effective in patients with developed resistance to earlier therapies or in the group of patients with metastases to the CNS and with previously very poor.

Lorlatinib is a third-generation ALK//ROS1 TKI, which showed significant activity in preclinical studies. It is active in patients with resistance to other ALK inhibitors (it showed anticancer effects in various resistance mutations, including the difficult-to-treat ALK G1202R mutation), and it is also characterised by the ability to penetrate the blood-brain barrier. Lorlatinib is a drug currently in clinical trials, so it has not been registered yet in any indication. The breakthrough therapy status granted the by the FDA was based on the efficacy and safety data from the Phase I and Phase II clinical trials. Recruitment for an open, randomised, bi-armed phase III CROWN clinical trial comparing lorlatinib with crizotinib in the first-line of treatment in patients with metastatic NSCLC with the presence of *ALK* gene rearrangement has been started.

Another ALK TKI is brigatinib. In 2017, the FDA approved the accelerated registration of the drug in the treatment of patients who had progression after crizotinib treatment or with intolerance of this drug (breakthrough therapy). Then, during the 19th WCLC and in the full-paper publication, preliminary results of the phase III ALTA-1L study were presented. Brigatinib compared to crizotinib significantly prolonged PFS in

patients with ALK-“positive” NSCLC, previously untreated with ALK inhibitors. Brigatinib was also associated with an improvement of intracranial response rate.

Dacomitinib — a highly selective second-generation TKI that irreversibly blocks *EGFR/HER1*, *HER2*, and *HER4* — is the first kinase inhibitor that has significantly improved survival in advanced NSCLC patients with mutation of *EGFR* gene activation. This review shows that dacomitinib should be considered as one of the standard drugs in the first line of treatment in patients with NSCLC with a confirmed mutation of *EGFR* gene activation.

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