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REVIEW

MODERN TREATMENT OF ALK-POSITIVE NON-SMALL CELL LUNG CANCER

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ABSTRACT

Lung cancer (LC) takes the first place in the structure of overall oncology in males. More than 1.8 million of new cases of lung cancer (LC) are registered each year worldwide. LC is the leading cause of cancer death in both developing and developed countries, and the 5-years survival rate is as low as 19 %. Many factors explain such unsatisfactory outcomes, including the LC diagnosis at an advanced stage, when the currently available treatments can rarely provide cure. Non-small cell lung cancer (NSCLC) with chromosomal rearrangement of anaplastic lymphoma kinase (ALK) is sensitive to targeted therapy with tyrosine kinase inhibitors (TKIs). Tumor cells containing ALK fusion are sensitive to TKIs – targeted drugs that have significantly improved the results of treatment of patients with ALK-positive NSCLC, half of whom survive more than 6.8 years after diagnosis. The number of patients with ALK-positive NSCLC varies, so ALK rearrangements are detected in about 3–7 % of lung adenocarcinomas, which accounts for up to 60.000 new cases of the disease annually worldwide. ALK-positive NSCLC is observed almost exclusively in adenocarcinomas associated with persons of younger age, male and never smoked or smoked a little. Patients with ALK-positive stage I–III NSCLC are shown treatment similar to patients with wild-type NSCLC, including surgery, radiation therapy, chemotherapy or multimodal treatment, depending on the stage of the tumor process. Numerous ALK TKIs have been developed in recent years, including alectinib, which is the current preferred first-line agent for patients who haven't received therapy. The study of the mechanisms of resistance has led to the development of next-generation ALK inhibitors that better penetrate the central nervous system, actively affecting brain metastases. This review highlights the current state and prospects for the development of ALK-positive NSCLC therapy.

Keywords:
non-small cell lung cancer, anaplastic lymphoma kinase (ALK), alectinib, brigatinib, crizotinib, lorlatinib, ceritinib

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ОБЗОР

СОВРЕМЕННОЕ ЛЕЧЕНИЕ ALK-ПОЗИТИВНОГО НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО

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РЕЗЮМЕ

Рак легкого (РЛ) занимает первое место в структуре общей онкологической заболеваемости мужского населения. Ежегодно в мире РЛ диагностируется более чем у 1,8 миллиона человек и остается основной причиной смертности от злокачественных новообразований как в развивающихся, так и в развитых странах, а 5-летняя выживаемость, достигающая 19 % вызывает разочарование. Подобные неудовлетворительные исходы объясняются многими факторами, включая диагностику РЛ на поздней стадии, когда излечение остается редким при доступных на сегодняшний день методах лечения. Немелкоклеточный рак легкого (НМРЛ) с хромосомной перестройкой киназы анапластической лимфомы (ALK) чувствителен к таргетной терапии ингибиторами тирозинкиназы (ТКИ). Опухолевые клетки, содержащие слияние ALK, чувствительны к ингибиторам ТКИ – таргетным препаратам, которые существенно улучшили результаты лечения больных ALK-позитивным НМРЛ, половина из которых выживают более 6,8 года после установления диагноза. Количество пациентов с ALK-позитивным НМРЛ варьируется, так ALK реаранжировки обнаруживаются примерно в 3–7 % аденокарцином легкого, что составляет до 60 000 новых случаев заболевания ежегодно во всем мире. ALK-позитивный НМРЛ наблюдается почти исключительно при аденокарциномах, ассоциированных с лицами более молодого возраста, мужского пола и никогда не курившими или курившими мало. Больным ALK-позитивным НМРЛ I–III стадии показано лечение аналогичное пациентам с НМРЛ дикого типа, включая хирургическое вмешательство, лучевую терапию, химиотерапию или мультимодальное лечение в зависимости от стадии опухолевого процесса. В последние десятилетие разработано несколько ALK ТКИ и среди них алектиниб, который в настоящее время является препаратом выбора первой линии терапии больных, не получавших лечения. Изучение механизмов резистентности привело к разработке ингибиторов ALK следующего поколения, которые лучше проникают в центральную нервную систему, активно воздействуя на метастазы в головном мозге. Данный обзор освещает современное состояние и перспективы развития терапии ALK-позитивного НМРЛ.

Ключевые слова:
немелкоклеточный рак легкого, киназа анапластической лимфомы (ALK) алектиниб, бригатиниб, кризотиниб, лорлатиниб, церитиниб

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INTRODUCTION

The fusion of the EML4 gene (echinoderm microtubule associated protein-like 4) with the ALK gene (anaplastic lymphoma kinase), first described in 2007, represents chromosomal inversions leading to constitutive oncogenic activation. It was found that a small percentage of NSCLC tumors (3–7 %) have EML4-ALK translocation [1]. Tumor cells containing ALK fusion are sensitive to tyrosine kinase inhibitors (TKI), targeted drugs that have significantly improved the results of treatment of patients with ALK-positive non-small cell lung cancer (NSCLC), half of whom survive more than 6.8 years after diagnosis [2].

The number of patients with ALK-positive NSCLC varies [3], so ALK rearrangements are detected in about 3–7 % of lung adenocarcinomas, which accounts for up to 60,000 new cases of the disease annually worldwide [4]. This indicator is the same among the population of the West (3.4 %), and the East. ALK-positive NSCLC is observed almost exclusively in adenocarcinomas associated with younger people (average age 52), male and never smoked or smoked a little [3].

Patients with ALK-positive stage I–III NSCLC are shown treatment similar to patients with wild-type NSCLC, including surgery, radiation therapy, chemotherapy or multimodal treatment, depending on the stage of the tumor process. What role tyrosine kinase inhibitors (TKI) will play in patients in the early stages of the disease has yet to be established. A variety of TKI are available for patients with previously untreated metastatic ALK-mutant NSCLC (Table 1). Over time, drug resistance inevitably arises, which led to the development of more potent ALK TKI of the next generation (Table 2).

Diagnostics of ALK fusion

All patients with metastatic lung adenocarcinoma should be tested for the presence of ALK fusion [5] using in situ fluorescent hybridization (FISH), immunohistochemical assay (IHCA) or next-generation sequencing (NGS) [6]. FISH is the gold standard for detecting ALK rearrangement and uses red and green probes for hybridization on either side of the ALK translocation breakpoint. These probes are either superimposed on each other, forming a yellow signal for wild-type samples, or appear as independent red and green signals if a fusion mutation is present [6].

An alternative to FISH is IHCA, which uses monoclonal antibodies to the ALK fusion oncogene. NGS is performed by extracting genomic DNA from tumor cells using probes targeting tumor–specific genes using either plasma or tumor tissue [7]. Comparing the three methods with each other, it should be noted that IHCA has the highest positive indicator – 94.5 %, NGS – 92.7 %, followed by FISH – 82.4 % [6].

Tyrosine kinase inhibitors. Krizotinib

Krizotinib is the first developed TKI ALK fusion. The PROFILE 1007 protocol is a Phase 3 clinical trial involving 347 patients with ALK-mutant NSCLC, which compared krizotinib with chemotherapy in patients who had previously received chemotherapy (Table 1). Krizotinib demonstrated an improvement in the level of objective response rate (ORR): 65 % vs. 20 % ($p < 0.001$), survival progression-free (PFS): 7.7 months vs. 3 months ($p < 0.001$) and quality of life [4]. In a Phase 3 PROFILE 1014 study comparing crizotinib with first-line chemotherapy in 343 patients, crizotinib demonstrated an improvement in ORR to 74 % vs. 45 % ($p < 0.001$) and PFS to 10.9 months vs. 7.0 months ($p < 0.001$) [8]. There was no difference in overall survival(s) in both studies [4; 8]. These studies have determined the role of crizotinib as the standard of first-line therapy.

Gastrointestinal toxicity is the most common adverse adverse reaction to crizotinib with diarrhea of any degree in 61 % of cases, and 3 or 4 degrees in 22 %; vomiting in 46 % and constipation in 43 % of patients. Liver dysfunction of grade 3 or 4, monitored every 2 weeks for the first 2 months and then periodically observed in 14 % of patients. Cardiotoxicity was manifested by bradycardia and prolongation of the QT interval. Visual impairment was observed in 71 % of patients, but only 1 % had grade 3 or higher [9].

Crizotinib is practically ineffective in lung adenocarcinoma metastases to the central nervous system (CNS), with a response rate barely reaching 7 % [10]. The brain is the most common site of disease progression in patients receiving crizotinib. Krizotinib is a well-known substrate of the p-glycoprotein pump of drug outflow, limiting its accumulation in the central nervous system [11]. The lack of effective exposure to CNS damage stimulated the development of a new generation of inhibitors.

Ceritinib

Ceritinib is a second-generation ALK inhibitor with activity against IGF-R1, IR and ROS-1. The drug has activity against crizotinib-resistant NSCLC, as it targets resistance mutations such as L119M and G1269A, as well as I1171T and S1206Y. Ceritinib penetrates the blood-brain barrier better [12].

Ceritinib is approved for both untreated and crizotinib-resistant patients. The ASCEND-5 protocol study demonstrated the advantage of prescribing ceritinib compared to third-line chemotherapy in 231 patients who previously received platinum-based chemotherapy and crizotinib [13]. The ASCEND-4 protocol compared ceritinib with chemotherapy in 376 untreated patients, including those with asymptomatic brain metastases. Median PFS in the ceritinib group was 16.6 months versus 8.1 months in the chemotherapy group ($p < 0.00001$) (Table. 1) [14]. Neither the ASCEND-4 protocol nor ASCEND-5 showed an improvement in the indicators of S. The poor tolerability of ceritinib and the higher efficacy of alectinib prevented its widespread use [15].

What is the role of ceritinib in the treatment of ALK-positive NSCLC resistant to alectinib remains to be seen. The ASCEND-9 clinical study examining the efficacy of prescribing ceritinib to patients who progressed on alectinib demonstrates an ORR of 25 % and a disease control level (DCR) of –70 % [16].

Ceritinib has excellent activity against CNS metastases with a response rate to therapy reaching 72 % [17]. Despite the high activity, the median PFS of patients with brain metastases treated with ceritinib was shorter than patients who did not receive this drug: 10.7 months versus 26.3 months, respectively [14]. Nevertheless, the study of the efficacy and safety of ceritinib in patients with brain metastases continues within the framework of the ASCEND-7 Phase 2 study [NCT01828112] [18].

When treated with ceritinib, toxicity of the 3rd or 4th degree is observed in 78 % of patients [14]. Gastrointestinal toxicity of varying severity is noted most often, namely: diarrhea in 85 %, nausea in 69 %, vomiting in 66 % and abdominal pain in 25 % of cases. More than 70 % of patients have a violation of the functional parameters of the liver of the

Table 1. ALK TKI in targeted first-line therapy of ALK-mutant NSCLC

Protocol.	Drug.	Groups.	*N*	ORR, %	*p*	PFS month	*p*	OS month	*p*
PROFILE 1014 [9]	Crizotinib	Crizotinib	172	74	< 0.001	10.9	< 0.001	-	0.097
		CT	171	45		7.0		47.5	
ASCEND-4 [14]	Peritinib	Ceritinib	189	72.5	< 0.01	16.6	< 0.00001	-	0.056
		CT	187	26.7		8.1		26.2	
J-ALEX [22]	Alectinib	Alectinib	103	92	0.072	34.1	< 0.0001	НД	-
		Crizotinib	104	79		10.2		НД	
ALEX [20]	Alectinib	Alectinib	152	83	0.0936	34.8	< 0.001	-	-
		Crizotinib	151	75.5		10.9		-	
ALESIA [23]	Alectinib	Alectinib	125	91	< 0.01	НД	< 0.0001	-	-
		Crizotinib	62	77		11.1		-	
ALTA-1L [25]	Brigatinib	Brigatinib	137	71	-	НД	-	-	-
		Crizotinib	138	60		9.8		-	

Note: *N* – number of patients enrolled in the study; ORR – objective response rate; PFS – progression-free survival; OS – overall survival; NA – not achieved.

3rd or higher degree, clinically manifested by severe anorexia, asthenia and fatigue [14]. Poor tolerability of the recommended dose of ceritinib 750 mg once a day on an empty stomach prevented its intake [15]. A new lower dose approved by the FDA, equal to 450 mg taken with meals, improved the tolerability of this adverse reaction [19].

Alectinib

Alectinib is a second-generation ALK inhibitor, which, due to its high efficacy and excellent safety profile, has become the drug of choice for the first-line targeted therapy of metastatic ALK-positive NSCLC. Not being a substrate of the outflow transporter of p-glycoprotein, alectinib is able to penetrate into the central nervous system [20].

In a worldwide phase 3 clinical trial of ALEX, 303 untreated patients were randomized for targeted first-line therapy with alectinib or crizotinib [20]. Median PFS in the alectinib group reached 35 months versus 11 months in the crizotinib group (HR = 0.43, $p < 0.001$) [21]. Similar results were obtained in 207 Japanese patients included in the J-ALEX protocol [22], as well as in the third later phase 3 study of ALESIA [23], which compared the effectiveness of alectinib with crizotinib in patients from Asian countries. These studies have made alectinib the drug of choice for targeted first-line therapy (Table 1).

In addition, alectinib plays an important role in the treatment of patients whose disease has progressed while taking crizotinib or intolerance to the latter drug has been noted. In the ALUR Phase 3 study, 107 patients who had previously received chemotherapy and crizotinib were assigned to groups for alectinib therapy or chemotherapy. Median PFS in the targeted therapy group was 7.1 months. compared with 1.6 months in the chemotherapy group (HR = 0.32, $p < 0.01$) [24].

The excellent activity of alectinib in CNS metastases has been consistently demonstrated in all studies. In the ALEX protocol, the time to progression of metastases in the central nervous system was significantly longer in the alectinib group compared to the crizotinib group (HR = 0.16, $p < 0.001$) [20]. In 16 patients with initial metastatic CNS lesion treated with alectinib, responses to targeted therapy were

Table 2. ALK TKI in subsequent lines of targeted therapy of previously treated ALK-positive NSCLC

Protocol.	Drug.	Previous treatment.	Groups.	*N*	ORR, %	*p*	PFS Mec.	*p*
PROFILE 1007 [4]	Crizotinib	CT	Crizotinib	173	65	< 0.001	7.7	< 0.001
			CT	174	20		3.0	
ASCEND 5 [38]	Ceritinib	Crizotinib or/and CT	Ceritinib	115	39	< 0.01	5.4	< 0.01
			CT	116	7		1.6	
ALUR [24]	Alectinib	CT and Crizotinib	Alectinib	72	37.5	< 0.01	7.1	< 0.001
			CT	35	3		1.6	
ALTA [26]	Brigatinib	Crizotinib	H Dose	112	48	-	9.2	-
			B Dose	110	53		16.7	
Solomon et al. 2018 [31]	Lorlatinib	Crizotinib 2 TKI ALK 3 TKI ALK	Lorlatinib	59	НД	-	-	-
			Lorlatinib	198	7.3		-	
ASCEND 9 [16]	Ceritinib	Alectinib ± Crizotinib	Lorlatinib	111	6.9	-	-	-
			Ceritinib	20	25		3.7	

Note: *N* – the number of patients included in the study; ORR (objective response rate) – the level of objective response; PFS (progression-free survival) – progression-free survival; NA – not achieved.

achieved in 75 % of cases. Consequently, many patients with brain metastases can only be treated with TKI without local exposure: surgery and/or radiation therapy.

As noted above, alectinib is much better tolerated than krizotinib, with a toxicity of 3–5 degrees in about 40 % of patients [20; 24]. The profile of adverse side effects includes: anemia in 20 %, nausea in 14 %, diarrhea in 12 %, vomiting in 7 % and elevated bilirubin levels in 15 %. Alectinib causes myalgia in 16 % of cases, and therefore creatine kinase (CK) levels are monitored every 2 weeks during the first month of therapy. Photosensitization is less frequent in 5 % [20].

Brigatinib

Brigatinib is a second-generation oral TKI that is able to overcome several mutations of resistance to crizotinib. Brigatinib is indicated for targeted therapy of ALK-positive NSCLC in patients with disease progression while taking crizotinib, in addition, studies on its first-line appointment are continuing

In the ALTA-1L study, 275 untreated patients were divided into groups for therapy with brigatinib or krizotinib. After 12 months of follow-up, PFS in the brigatinib group was 67 % versus 43 % in the crizotinib group (HR = 0.49, $p < 0.001$) [25]. OV in the protocols of targeted first-line therapy has not yet been studied. There are no studies comparing the effectiveness of brigatinib with alectinib in untreated patients. At the same time, the use of brigatinib is considered promising in patients refractory to crizotinib with a median PFS of 16.7 months in a recent phase 2 study [26]. There is evidence that the use of brigatinib during progression on alectinib improves the median PFS from 4.4 to 6.6 months [27; 28].

Brigatinib showed excellent activity in 78 % of patients with measurable brain metastases with targeted first-line therapy. Updated results of the phase 2 study showed that patients refractory to crizotinib with measurable CNS lesions achieved an objective response rate of 67 % with a median PFS of 18.4 months [29].

In the ALTA-1L protocol, adverse side effects of the 3rd and higher degree occurred in 61 % of observations of 136 patients receiving brigatinib [25]. Like other ALK inhibitors, brigatinib is characterized by the most frequent gastrointestinal adverse side effects of any severity in 49 %, increased creatinine kinase in 39 % and alanine aminotransferase (ALT) in 19 % [25]. There is also an increase in the level of amylase in 19 % and lipase in 14 % of observations, and cardiotoxicity in the form of bradycardia [25]. Blood pressure should be monitored before taking brigatinib and then monthly, since arterial hypertension is observed in 23 % of patients [30].

A distinctive feature of brigatinib is the possibility of acute development of severe pulmonary toxicity. An undesirable side effect, as a rule, occurs within 24–48 hours after the start of therapy, clinically manifests itself by shortness of breath, decreased oxygen saturation, and radiologically manifests itself by turbidity in the form of "frosted glass" and interstitial darkening [12]. The described reaction develops in 3–6 % of patients and is probably more common in patients previously treated with crizotinib, and depends on the dose [12; 25; 26]. In patients with newly emerging or worsening respiratory symptoms, urgent diagnosis should be carried out to exclude pneumonitis, and if it is confirmed, brigatinib should be discontinued [30].

Lorlatinib

Lorlatinib is a selective inhibitor of ALK and ROS1 of the third generation [1], which demonstrates ORR in 57 % in patients with the G1202R mutation, usually detected after the use of second-generation ALK inhibitors.

A modern phase 2 study was conducted in a group of 228 patients with ALK-positive NSCLC who had previously undergone multicomponent treatment. The clinical status varied depending on the previous therapy of TCI. Patients receiving only crizotinib demonstrated an ORR of 69 %. The median PFS was not reached. Patients who received targeted therapy with two or more ALK TKI had an ORR equal to 39 % with a median PFS of 6.9 months [31].

An ongoing phase 3 trial using the CROWN protocol [NCT03052608] randomizes patients with untreated ALK-positive NSCLC either to the lorlatinib therapy group or to the first-line crizotinib therapy group [32]. The French study LORLATU [NCT 02327477] studies the sequence of therapy in patients receiving lorlatinib [33]. Studies comparing lorlatinib with chemotherapy for alectinib-resistant NSCLC have not yet been conducted.

The ratio of lorlatinib concentration in cerebrospinal fluid and blood plasma in early studies was 0.75, which confirms the significant penetration of the drug into the central nervous system. In patients

with initial brain metastases who had previously taken at least one ALK TKI, the objective response rate was 63 %, and the median duration of response to treatment was 14.5 months [33].

Severe hyperlipidemia of 3–4 degrees is observed in 31 % of patients, in which 81 % of patients need hypolipidemic therapy [34]. Peripheral edema was observed in 43 % of patients in combination with peripheral neuropathy in 30 %. Neurological disorders occur in 39 % of patients, including changes in cognitive functions in 23 %, mood in 22 % and speech in 8 %. Most cognitive disorders were moderate and easily reversible with dose reduction [34].

Ensartinib (X-396) is a novel TCI with activity against ALK and ROS1 mutations of resistance to crizotinib, such as L1196M and C1156Y [35]. In a recent study, the ORR was 60 % with a median PFS of 26.2 months [35]. The drug is active in patients who previously received second-generation ALK TKI with ORR = 23 %, as well as in patients who previously received from 2 to 5 different targeted ALK TKI therapy regimens. The level of response of brain metastases reaching 64 % and the level of disease control equal to 92.9 % should be recognized as particularly promising [35]. A phase 3 clinical trial using the eXalt3 protocol [NCT02767804], currently compares ensartinib with crizotinib [36].

Entrectinib is another new ALK inhibitor. A modern phase 1 study has shown that entrectinib is highly effective in patients with NSCLC carrying NTRK, ROS1 and ALK rearrangements. However, in patients previously treated with ALK inhibitors, the drug did not cause any reactions [37].

Repotrectinib – ROS, a next-generation TRK-A and ALK inhibitor, demonstrates significant preliminary results in the Trident-1 clinical trial [NCT03093116], which is still ongoing [38].

Mechanisms of resistance

Mutations in the ALK kinase domain are the most well-described mechanism of resistance to TKI, occurring in 20–36 % of patients treated with crizotinib and 50 % of patients receiving second-generation ALK TKI [39]. Each TCI is associated with an individual spectrum of mutations. Genetic analysis of 103 biopsies of ALK-positive tumors from patients treated with various ALK inhibitors revealed that L1196M is the most common mutation found in resistance to crizotinib [39]. G1202R resistance mutation is often found after the use of second-generation drugs, including: ceritinib in 21 %, alectinib in 29 % and brigatinib in 43 % [24,30]. Despite the fact that the G1202R mutation creates high resistance, it is overcome by lorlatinib [39]. Little is known about resistance to lorlatinib.

Resistance mechanisms also arise outside the domain of ALK kinase. Amplification of ALK occurs in approximately 10 % of samples resistant to crizotinib, either in isolation or with other mutations. Activation of the bypass signaling pathway is another mechanism of resistance with activation of the EGFR receptor [40].

After the possibilities of targeted therapy are exhausted, chemotherapy is used with or without immunotherapy. The use of combined chemoimmunotherapy is confirmed by the study of a subgroup of 111 patients with NSCLC carrying EGFR and ALK mutations from the IMpower150 study. The combination of carboplatin, paclitaxel, bevacizumab and atezolizumab demonstrated an improvement in PFS up to 9.7 months. compared only with chemotherapy for 6.1 months [41].

In addition to the IMpower150 study, data confirming the effectiveness of immunotherapy in patients with ALK-mutant NSCLC are clearly insufficient. In studies on immuno- and chemoimmunotherapy in patients with ALK-mutant NSCLC, unsatisfactory results are observed [42; 43]. In addition, extrapolation of EGFR data [44] leads to safety problems of either TCI or immunotherapy [45]. Testing for ALK should be performed before starting chemoimmunotherapy to avoid an increased risk of toxicity.

Summing up, it should be emphasized that alectinib is currently the drug of choice for targeted first-line therapy of ALK-positive metastatic NSCLC [5]. This preference is based on high efficacy, acceptable profile of adverse toxic events and activity against metastases in the central nervous system compared with krizotinib [20]. Brigatinib, ceritinib and crizotinib remain first-line targeted therapy options and are considered in the context of specific clinical circumstances. Lorlatinib should be prescribed to patients with disease progression during treatment with alectinib.

The excellent activity of alectinib and brigatinib is able to treat metastases in the central nervous system with targeted therapy, thereby allowing to delay or even avoid the use of radiation therapy or surgery [17; 20; 26; 29]. In patients with progression of brain metastases during treatment with alectinib, the appointment of lorlatinib is rational [33].

The results of targeted therapy with brigatinib require continued monitoring for a reliable assessment. Ensartinib, entrectinib and repotrectinib continue to be studied in clinical trials, their role in targeted therapy of ALK-mutant NSCLC has also yet to be determined. Additional data are needed regarding the optimal treatment after ALK TC therapy, whether it is chemotherapy or chemoimmunotherapy.

Currently, the possibilities of perioperative use of TKI ALK are being investigated. Krizotinib is being studied in neoadjuvant [NCT03088930] [46], as well as in adjuvant mode as part of a large, multicenter ALCHEMIST study (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) [NCT02201992] [NCT02201992] [47; 48].

The ongoing phase 3 study of ALINA is studying the efficacy and safety of the administration of alectinib compared with platinum-based chemotherapy in radically operated patients with stage IB-IIIA ALK-positive NSCLC as adjuvant therapy [49].

CONCLUSION

The progress made in the treatment of ALK-positive NSCLC over the past decade is obvious. Four ALK inhibitors have been developed, which are currently approved both for first-line targeted therapy and as additional options available during disease progression. ALK inhibitors of the new generation demonstrate excellent activity against metastatic damage to the central nervous system. Current research areas include the development of next-generation ALK inhibitors, the study of their role in neo- and/or adjuvant therapy and optimal drug treatment tactics when the available options for targeted therapy have already been exhausted.

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