ALK Inhibitors in NSCLCs

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Contributor: Viviana Bazan

The discovery of the EML4-ALK fusion gene in a limited subset of patients affected by NSCLC and the subsequent clinical development of crizotinib in 2011 has been an impressive milestone in lung cancer research. Unfortunately, acquired resistances regularly develop, hence disease progression occurs. Afterward, modern tyrosine kinase inhibitors (TKIs), such as ceritinib, alectinib, brigatinib, and lorlatinib, have been approved by the Food and Drug Administration (FDA) for the management of anaplastic lymphoma kinase (ALK)-positive NSCLCs. Several compounds are currently under investigation to achieve the optimal strategy of therapy.

Keywords: non-small cell lung cancer (NSCLC),tyrosine kinase inhibitors (TKIs),ALK inhibitors,crizotinib

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide in both men and women, with <20% 5-year Overall Survival (OS) for newly diagnosed patients[1]. Based on histopathological features, lung cancers are classified into two main groups: non–small cell lung cancer (NSCLC; 80–85%) and small cell lung cancer (15–20%) [2]. NSCLCs are further subcategorized into three main types: adenocarcinoma (50%), squamous-cell carcinoma (30%), and large-cell carcinoma (15%). However, recent evidence suggests that lung cancer represents a group of molecularly heterogeneous diseases even within the same histological subcategory[3]. About 3–5% of patients affected by NSCLC harbor chromosomal rearrangements in the anaplastic lymphoma kinase (ALK) gene[4]. Cancers harboring rearrangements in the ALK gene are susceptible to treatment with tyrosine kinase inhibitors (TKIs), which inhibit downstream signaling pathways, binding to receptor tyrosine kinases.

Anaplastic lymphoma kinase is a member of the insulin receptor protein−tyrosine kinase superfamily, originally described as a nucleophosmin (NPM)-ALK fusion form in an anaplastic large cell lymphoma (ALCL) cell line. The physiological role of ALK has not been thoroughly clarified, yet some evidence has confirmed the regulatory activity of ALK in the development and function of the central and peripheral nervous systems[5]. In 2007, ALK fusion was reported in NSCLC for the first time in a small cohort (7%) of Asian patients[6]. The most common rearrangement results were from an inter-chromosomal inversion in the short arm of chromosome 2, which creates a fusion between the 5′ portion of the echinoderm microtubule-associated protein like-4 (EML4) gene and the 3′ portion of the ALK gene Inv(2)-(p21p23). As a consequence of the activation of the ALK signaling pathway, the fusion gene EML4-ALK with tyrosine kinase function promotes cell proliferation and survival [7].

Notably, more than seven ALK rearrangements have been identified involving various EML4-ALK breakpoints or, exceptionally, other non-EML4 fusion partners. ALK gene aberrations are more common in the adenocarcinoma histological subtype, in never or light smoker young women and are considered to be largely mutually exclusive with genetic mutations in the epidermal growth factor receptor (EGFR) and KRAS.

Remarkably, central nervous system (CNS) metastases are common in this subset of patients. ALK rearrangements might be promptly detected in tumor tissue using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription-polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS)[8].

2. Intracranial Efficacy

Approximately 40% of NSCLC patients present CNS involvement during the disease course along with worsening prognosis and quality of life[9]. A total of 20–30% of ALK-positive patients present with CNS metastases at the time of diagnosis but the risk increases up to 50% throughout the disease (reaching 58% at 3 years)[9]. The common treatments include local therapy such as surgery, stereotactic radiosurgery, and whole-brain radiotherapy[10]. However, the development of new targeted agents is changing the treatment approach and may represent an important turning point in the management of brain metastases (BM). The effectiveness of ALK inhibitors on the CNS depends on several factors

and it seems to be related to both the tumor molecular characteristics and the drug pharmacokinetic features. Indeed, according to a retrospective analysis of the PROFILE 1005 and 1007 trials, 70% of the patients who progressed to crizotinib presented with CNS metastasis, thus representing the most common site of progression disease (PD)[11][12]. Since crizotinib is a substrate of p-glycoprotein, it is characterized by a poor BBB penetration with low cerebrospinal fluid (CSF) concentrations and a low CSF-to-plasma ratio, which hamper the achievement of a therapeutic concentration into the brain, leading to a pharmacological resistance[2]. Despite the aforementioned issues, a pooled analysis demonstrated crizotinib CNS efficacy with an intracranial response of 18% in patients who had previously received radiotherapy and 33% in patients who had not received prior radiotherapy [11][12]. Likewise, it demonstrated a prolongation of the median time to intracranial progression (13.2 vs. 7.0 months) and a similar intracranial disease control rate (DCR) at 12 weeks in these two groups (62% and 56%, respectively) [11][12]. The effectiveness of crizotinib on BM was further supported by the PROFILE 1014 trial where 23% of patients with treated BM at baseline showed longer PFS (9.0 vs. 4.0 months; HR 0.40, 95% CI 0.23–0.69) and a better RR (77% vs. 28%) with crizotinib[13]. Ceritinib is 20 times as potent as crizotinib and it has significant activity on CNS metastasis both in patients who progressed on crizotinib and in naïve patients. As well as crizotinib, ceritinib is a substrate of pump efflux transporters; however, in vivo ceritinib showed a higher efficacy against ALK-rearranged cells and a higher lipophilicity that may allow for the molecule to diffuse through the BBB at a significant rate[14]. Clinical trials from the ASCEND program (ASCEND-1 to 5) reported intracranial responses in patients with measurable baseline brain lesions. Particularly, the phase II ASCEND-2 and -3 trials evaluated ceritinib in both crizotinib-pretreated (ASCEND-2) and crizotinib-naive (ASCEND-3) chemo-pretreated patients demonstrating a remarkable intracranial DCR of 80% [15]. Of note, a recent analysis of the ASCEND-3 confirmed the activity of ceritinib on BM with a median OS of 36.2 months (95% CI 17.7 to not evaluable) in patients with BMs at the baseline, and 55.3 months (95% CI 50.1–55.3) in patients without baseline BMs[16]. Interestingly, the phase II ASCEND-7 study evaluated the activity of ceritinib in patients with ALK and NSCLC metastatic to the brain or leptomeninges, demonstrating a durable intracranial response across all study arms regardless of prior treatments[17]. Unlike crizotinib and ceritinib, alectinib is not a substrate of p-glycoprotein[18]. As demonstrated in preclinical studies, it achieves a high CNS penetration in intracranial metastases, with a high brain-to-plasma concentration ratio[19][20]. In vivo data were confirmed in the phase I/II studies. In particular, the results from the American part of the AF-002JP study showed a remarkable CNS ORR of 75% with a CNS DCR of 100%[21][22][23]. Interestingly, a pooled analysis of CNS response to alectinib showed an outstanding intracranial ORR of 64% (95% CI 49.2–77.1)[24]. Further, patients without CNS involvement at baseline presented low incidence of progression in the CNS, underlying the impressive activity of alectinib and suggesting a preventing role[23]. Finally, alectinib efficacy against CNS metastases was supported by data from phase III studies, which demonstrated the efficacy of alectinib on CNS metastases in comparison with chemotherapy and with crizotinib[25][26][27]. In the ALUR trial, the intracranial ORR was 54.2% vs. 0% for alectinib and chemotherapy, respectively. Data from the specific analysis of alectinib CNS efficacy in the J-ALEX study suggested the ability of alectinib to reduce the risk of CNS progression in comparison with crizotinib, both in patients with baseline CNS metastases (HR 0.51; 95% CI 0.16–1.64) and in patients who did not have baseline CNS metastases (HR 0.19; 95% CI 0.07–0.53)[28]. The results strongly suggest that alectinib in patients with asymptomatic BM may delay or reduce the use of local treatments[25].

However, the intracranial efficacy of brigatinib compares favorably with other second-generation ALK TKIs[22]. Brigatinib demonstrated a superior intracranial efficacy in comparison to crizotinib in the phase 3 ALTA study, which reported an intracranial response among patients with measurable lesions of 78% and 29% for brigatinib and crizotinib, respectively[29][30].

Lorlatinib is a brain-penetrant next-generation ALK TKI, active against most known resistance mutations[22]. In the phase I trial, Shaw et al. demonstrated that lorlatinib has both systemic and intracranial activity even in TKI pre-treated patients. The phase II trial enrolled a similar population in six different expansion cohorts according to previous treatments and the status of molecular drivers[31][32]. The study confirmed a substantial intracranial efficacy ranging from 42% to 75% in patients with advanced ALK-positive disease. Data from the phase III CROWN trial were recently presented at ESMO 2020. Indeed, the numerical best overall response (BOR) of lorlatinib over crizotinib was also demonstrated in the 30 patients who had measurable BM: 14 out of 17 patients (82%) who received lorlatinib had a CR (*n* = 12) or a PR (*n* = 2) compared with 3 out of 13 (23%) patients (1 CR and 2 PR) treated with crizotinib.

Regarding the efficacy on leptomeningeal metastases, case series described the rapid radiological and clinical cerebral response to lorlatinib in patients who had leptomeningeal PD on prior ALK inhibitors[33].

Ensartinib data on CNS metastasis are scarce. The results from a multicenter phase I/II, which enrolled patients with asymptomatic CNS metastases who were ALK TKI-naïve or had received prior treatments (chemotherapy or a second-generation ALK TKI), showed CNS responses in both naïve and pretreated populations. The IRR was good in patients

with baseline target CNS lesions (69%) as well as in the patients with only non-target baseline lesions (1 CR and 8 SD). The median duration of intracranial response in patients who responded was 5.8 months, with the longest duration being 24 months[34]. Table 2 summarizes the intracranial efficacy of different ALK inhibitors.

Table 2. Summary of ALK inhibitors' efficacy for brain metastases in ALK-positive treatment of naive NSCLC.

Clinical Trial	Drugs/Phase	No. of pts w/BM	PFS	OS	IRR	IORR	IDCR	IDOR
PROFILE 1005	Crizotinib, 2	166	8.4 mo.	21.8 mo.	NA	33%	62%	NR
PROFILE 1007	Crizotinib, 3	109	7.7 mo.	12.2 mo.	NA	18%	56%	NR
PROFILE 1014	Crizotinib, 3	39	9.0 mo.	17.4 mo	77%	15%	NA	NR
ASCEND-1	Ceritinib, 1	94	18.4 mo.	NR	NA	72%	79%	NA
ASCEND-2	Ceritinib, 2	100	5.7 mo.	NR	NA	45%	80%	NA
ASCEND-3	Ceritinib, 2	50	10.8 mo.	36.2 mo.	NA	20%	80%	9.1 mo.
ASCEND-4	Ceritinib, 3	54	16.6 mo.	NR	NA	73%	NA	16.6 mo.
ASCEND-5	Ceritinib, 3	66	4.4 mo.	NA	NA	35%	NA	6.9 mo.
ASCEND-6	Ceritinib,1/2	103	5.7 mo.	NA	NA	39.1%	82.6%	NA
ASCEND-7	Ceritinib, 2	138	5.4 mo.	NA	NA	51.5%	75.8%	7.5 mo.
ALUR	Alectinib, 3	72	7.1 mo.	NA	NA	54.2%	NA	NR
ALEX	Alectinib, 3	64	34.8 mo.	48.2 mo	59%	81%	NA	17.3 mo.
ALTA	Brigatinib, 3	41	29.4 mo.	NA	NA	78%	NR	NA
CROWN	Lorlatinib, 3	30	18.3 mo.	NR	NA	76%	NA	NE
NCT01625234	Ensartinib, 1/2	35	9.2 mo.	NA	69%	64.3%	NA	5.8 mo.

Abbreviations: No. of pts w/ BM, number of patients with brain metastases; IORR, intracranial objective response rate; IDOR, intracranial duration of response; NR, not reported; mo., months; NA, not available; PFS, progression-free survival; OS, overall survival; IRR, intracranial response rate; IDCR, intracranial disease control rate.

3. Mechanisms of Resistance

Despite the clinicians' efforts, after a median period of 10.9 months all ALK-positive patients progress due to different mechanisms of resistance, which have been classified as ALK-dependent and ALK-independent. Commonly, ALK-dependent resistances occur as a result of secondary mutations within the target kinase which block the TKI binding to the target kinase. Additionally, the main secondary resistance mutations located in the ALK tyrosine-kinase domain are the gatekeeper L1196M (present in 7% of crizotinib-resistant cases) and the G1269A mutation (4% of cases) [35]. The solvent-front G1202R mutation (2% of cases) grants high-level resistance to crizotinib, as well as to next-generation ALK inhibitors. Notably, upon progression on a second-generation ALK TKI, emerging data from studies of the third-generation lorlatinib have been promising. In fact, lorlatinib demonstrates great efficacy against different ALK-dependent resistance mechanisms including L1196M and G1202R substitutions[35].

However, ALK-independent mechanisms of resistance are amplifications of the ALK fusion gene, or alternative signaling pathways such as the amplification of epidermal growth factor receptor (EGFR) or of insulin-like growth factor (IGF-1R) or c-kit mutations; epithelial to mesenchymal transition (EMT) or change in tumor histology. Particularly, the transformation from adenocarcinoma to small-cell lung cancer has rarely been described as a mechanism of resistance. Understanding these ALK-independent mechanisms of resistance is a clinical challenge and future studies to investigate combination treatments in this subset are mandatory. In order to overtake acquired resistance to first-line ALK TKIs, several second- and third-generation ALK inhibitors have been developed in the last few years. Table 4 displays the main mechanisms of resistance to ALK-TKIs.

Table 4. Principal mechanisms of resistance to ALK inhibitors.

	ALK-Independent Resistance Mechanism	ALK-Dependent Resistance Mechanism
Crizotinib	**EGFR overexpression and IGF-1R activation**	**Amplification of the ALK fusion gene; L1196M, G1269A/S, I1151Tins, L1152P/R, C1156Y/T, I1171T/N/S, F1174C/L/V, V1180L, G1202R, S1206C/Y, E1210K mutation acquisition**
Ceritinib	**c-Met gene amplification; activating mutation of MEK and PIK3CA mutations**	**G1202R, F1174C/L/V, G1202del, I1151Tins, L1152P/R, C1156Y/T**
Alectinib	**c-Met gene amplification and PIK3CA mutations**	**G1202R, I1171T/N/S, V1180L, L1196M**
Brigatinib	**Not reported**	**E1210K + S1206C, E1210K + D1203N, G1202Ra**
Lorlatinib	**NF2 loss of function mutations**	**L1198F + C1156Yc, L1196M/D1203N, F1174L/G1202R, C1156Y/G1269A [36]**

Abbreviations: ALK, anaplastic lymphoma kinase; IGF-1R, insulin growth factor-1 receptor; EGFR, epidermal growth factor receptor.

References

1. Siegel, R.; Naishadham, D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30.
2. Russo, A.; Franchina, T.; Ricciardi, G.R.; Ferraro, G.; Scimone, A.; Bronte, G.; Russo, A.; Rolfo, C.; Adamo, V. Central nervous system involvement in ALK-rearranged NSCLC: Promising strategies to overcome crizotinib resistance. Expert Rev. Anticancer Ther. 2016, 16, 615–623.
3. Awad, M.M.; Shaw, A.T. ALK inhibitors in non-small cell lung cancer: Crizotinib and beyond. Clin. Adv. Hematol. Oncol. 2014, 12, 429–439.
4. Chia, P.L.; Mitchell, P.; Dobrovic, A.; John, T. Prevalence and natural history ofALK positive non-small-cell lung cancer and the clinical impact oftargeted therapy with ALK inhibitors. Clin. Epidemiol. 2014, 6, 423–432.
5. Hallberg, B.; Palmer, R.H. The role of the ALK receptor in cancer biology. Ann. Oncol. 2016, 27, iii4–iii15.
6. Khan, M.; Lin, J.; Liao, G.; Tian, Y.; Liang, Y.; Li, R.; Liu, M.; Yuan, Y. ALK Inhibitors in the treatment of ALK positive NSCLC. Front. Oncol. 2019, 9, 557.
7. McCusker, M.G.; Russo, A.; Scilla, K.A.; Mehra, R.; Rolfo, C. How I treat ALK-positive non-small cell lung cancer. ESMO Open 2019, 4, e000524.
8. Wynes, M.W.; Sholl, L.M.; Dietel, M.; Schuuring, E.; Tsao, M.S.; Yatabe, Y.; Tubbs, R.R.; Hirsch, F.R. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. J. Thorac. Oncol. 2014, 9, 631–638.
9. Rangachari, D.; Yamaguchi, N.; VanderLaan, P.A.; Folch, E.; Mahadevan, A.; Floyd, S.R.; Uhlmann, E.J.; Wong, E.T.; Dahlberg, S.E.; Huberman, H.; et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015, 88, 108–111.
10. Wang, W.; Sun, X.; Hui, Z. Treatment optimization for brain metastasis from anaplastic lymphoma kinase rearrangement non-small-cell lung cancer. Oncol. Res. Treat. 2019, 42, 599–606.
11. Alexander, M.; Lin, E.; Cheng, H. Leptomeningeal metastases in non-small cell lung cancer: Optimal systemic management in NSCLC with and without driver mutations. Curr. Treat. Options Oncol. 2020, 21, 72.
12. Costa, D.B.; Shaw, A.T.; Ou, S.H.; Solomon, B.J.; Riely, G.J.; Ahn, M.J.; Zhou, C.; Shreeve, S.M.; Selaru, P.; Polli, A.; et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J. Clin. Oncol. 2015, 33, 1881–1888.
13. Solomon, B.J.; Cappuzzo, F.; Felip, E.; Blackhall, F.H.; Costa, D.B.; Kim, D.W.; Nakagawa, K.; Wu, Y.L.; Mekhail, T.; Paolini, J.; et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced alk-positive non-small-cell lung cancer: Results from PROFILE 1014. J. Clin. Oncol. 2016, 34, 2858–2865.
14. Kort, A.; Sparidans, R.W.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. Brain accumulation of the EML4-ALK inhibitor ceritinib is restricted by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2). Pharmacol. Res. 2015, 102, 200–207.

15. Crinò, L.; Ahn, M.J.; De Marinis, F.; Groen, H.J.; Wakelee, H.; Hida, T.; Mok, T.; Spigel, D.; Felip, E.; Nishio, M.; et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J. Clin. Oncol. 2016, 34, 2866–2873.

16. Nishio, M.; Felip, E.; Orlov, S.; Park, K.; Yu, C.J.; Tsai, C.M.; Cobo, M.; McKeage, M.; Su, W.C.; Mok, T.; et al. Final overall survival and other efficacy and safety results from ASCEND-3: Phase II study of ceritinib in ALKi-naive patients with ALK-rearranged NSCLC. J. Thorac. Oncol. 2020, 15, 609–617.

17. Cho, B.C.; Obermannova, R.; Bearz, A.; McKeage, M.; Kim, D.W.; Batra, U.; Borra, G.; Orlov, S.; Kim, S.W.; Geater, S.L.; et al. Efficacy and safety of ceritinib (450 mg/d or 600 mg/d) with food versus 750-mg/d fasted in patients with ALK receptor tyrosine kinase (ALK)-positive NSCLC: Primary efficacy results from the ASCEND-8 study. J. Thorac. Oncol. 2019, 14, 1255–1265.

18. Hirota, T.; Muraki, S.; Ieiri, I. Clinical pharmacokinetics of anaplastic lymphoma kinase inhibitors in non-small-cell lung cancer. Clin. Pharmacokinet 2019, 58, 403–420.

19. Kodama, T.; Hasegawa, M.; Takanashi, K.; Sakurai, Y.; Kondoh, O.; Sakamoto, H. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. Cancer Chemother. Pharmacol. 2014, 74, 1023–1028.

20. Kodama, T.; Tsukaguchi, T.; Satoh, Y.; Yoshida, M.; Watanabe, Y.; Kondoh, O.; Sakamoto, H. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. Mol. Cancer Ther. 2014, 13, 2910–2918.

21. Shaw, A.T.; Gandhi, L.; Gadgeel, S.; Riely, G.J.; Cetnar, J.; West, H.; Camidge, D.R.; Socinski, M.A.; Chiappori, A.; Mekhail, T.; et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, Phase 2 trial. Lancet Oncol. 2016, 17, 234–242.

22. Remon, J.; Besse, B. Brain metastases in oncogene-addicted non-small cell lung cancer patients: Incidence and treatment. Front. Oncol. 2018, 8, 88.

23. Gadgeel, S.M.; Shaw, A.T.; Govindan, R.; Gandhi, L.; Socinski, M.A.; Camidge, D.R.; De Petris, L.; Kim, D.W.; Chiappori, A.; Moro-Sibilot, D.L.; et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. J. Clin. Oncol. 2016, 34, 4079–4085.

24. Yang, J.C.; Ou, S.I.; De Petris, L.; Gadgeel, S.; Gandhi, L.; Kim, D.W.; Barlesi, F.; Govindan, R.; Dingemans, A.C.; Crino, L.; et al. Pooled systemic efficacy and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small cell lung cancer. J. Thorac. Oncol. 2017, 12, 1552–1560.

25. Peters, S.; Camidge, D.R.; Shaw, A.T.; Gadgeel, S.; Ahn, J.S.; Kim, D.W.; Ou, S.I.; Pérol, M.; Dziadziuszko, R.; Rosell, R.; et al. Alectinib versus Crizotinib in untreated ALK-positive non-small-cell lung. N. Engl. J. Med. 2017, 377, 829–838.

26. Novello, S.; Mazières, J.; Oh, I.J.; de Castro, J.; Migliorino, M.R.; Helland, Å.; Dziadziuszko, R.; Griesinger, F.; Kotb, A.; Zeaiter, A.; et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: Results from the phase III ALUR study. Ann. Oncol. 2018, 29, 1409–1416.

27. Hida, T.; Nokihara, H.; Kondo, M.; Kim, Y.H.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J.-ALEX): An open-label, randomised phase 3 trial. Lancet 2017, 390, 29–39.

28. Nishio, M.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Tanaka, T.; Kuriki, H.; Zeaiter, A.; Tamura, T. Analysis of central nervous system efficacy in the J.-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. Lung Cancer 2018, 121, 37–40.

29. Huber, R.M.; Hansen, K.H.; Paz-Ares Rodríguez, L.; West, H.L.; Reckamp, K.L.; Leighl, N.B.; Tiseo, M.; Smit, E.F.; Kim, D.W.; Gettinger, S.N.; et al. Brigatinib incrizotinib-refractory ALK+ non-small cell lung cancer: 2-year follow-up on systemic and intracranial outcomes in the phase 2 ALTA trial. J. Thorac. Oncol. 2020, 15, 404–415.

30. Camidge, D.R.; Kim, H.R.; Ahn, M.J.; Yang, J.C.H.; Han, J.Y.; Hochmair, M.J.; Lee, K.H.; Delmonte, A.; García Campelo, M.R.; Kim, D.W.; et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N. Engl. J. Med. 2018, 379, 2027–2039.

31. Solomon, B.J.; Besse, B.; Bauer, T.M.; Felip, E.; Soo, R.A.; Camidge, D.R.; Chiari, R.; Bearz, A.; Lin, C.C.; Gadgeel, S.M.; et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. Lancet Oncol. 2018, 19, 1654–1667.

32. Shaw, A.T.; Felip, E.; Bauer, T.M.; Besse, B.; Navarro, A.; Postel-Vinay, S.; Gainor, J.F.; Johnson, M.; Dietrich, J.; James, L.P.; et al. Lorltinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: An international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol. 2017, 18, 1590–1599.

33. Alexander, M.; Lin, E.; Cheng, H. Leptomeningeal metastases in non-small cell lung cancer: Optimal systemic management in NSCLC with and without driver mutations. Curr. Treat. Options Oncol. 2020, 21, 72.

34. Horn, L.; Infante, J.R.; Reckamp, K.L.; Blumenschein, G.R.; Leal, T.A.; Waqar, S.N.; Gitlitz, B.J.; Sanborn, R.E.; Whisenant, J.G.; Du, L.; et al. Ensartinib (X-396) inALK-positive non-small cell lung cancer: Results from a first-inhumanPhaseI/II, multicenter study. Clin. Cancer Res. 2018, 24, 2771–2779.
35. Gainor, J.F.; Dardaei, L.; Yoda, S.; Friboulet, L.; Leshchiner, I.; Katayama, R.; Dagogo-Jack, I.; Gadgeel, S.; Schultz, K.; Singh, M.; et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK rearranged lung cancer. Cancer Discov. 2016, 6, 1118–1133.
36. Recondo, G.; Mezquita, L.; Facchinetti, F.; Planchard, D.; Gazzah, A.; Bigot, L.; Rizvi, A.Z.; Frias, R.L.; Thiery, J.P.; Scoazec, Y.J.; et al. Diverse resistancemechanisms to the third-generation ALK inhibitor lorlatinib inALK-rearranged lung cancer. Clin. Cancer Res. 2020, 26, 242–255.