EDITORIAL

First-line alectinib for ALK-positive lung cancer: is there room for further improvement?

Alfredo Addeo MD, Giulio Metro MD

1Oncology Department, University Hospital Geneva, Geneva, Switzerland; 2Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy

Abstract

In the present editorial we describe the therapeutic achievements in the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). We focus on the major breakthroughs we have been witnessing in this context, from the introduction of crizotinib as the first approved targeted drug, to the meaningful improvement in terms of clinical benefit that alectinib, a second generation ALK-inhibitor, has recently provided over crizotinib. Finally, we address major trends of clinical research in this setting, and whether this might translate into further clinical improvement in the near future.

Keywords: alectinib, ALK, brain metastases, brigatinib, ceritinib, crizotinib, non-small cell lung cancer.

Citation

Addeo A, Metro G. First-line alectinib for ALK-positive lung cancer: is there room for further improvement? Drugs in Context 2018; 7: 212537. DOI: 10.7573/dic.212537

The discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in non-small cell lung cancer (NSCLC) has unveiled a crucial signaling pathway for lung tumorigenesis [1]. In fact, ALK rearrangements, which are present in roughly 5% of NSCLCs, encode a deregulated fusion oncoprotein that promotes ALK dependency by constitutive activation of ALK tyrosine kinase through autophosphorylation. Importantly, they more commonly consist of a chromosome arm of chromosome 2, which results in the formation of the echinoderm microtubule-associated protein-like 4 (EML4)–ALK fusion oncogene [2]. Various EML4–ALK fusion variants have been identified so far, based on the truncated site of EML4, which undergoes chromosomal inversion, with variant 1 (exon 13 of EML4 fused to exon 20 of ALK [E13;A20]) and variant 3a/b (exon 6a/b of EML4 fused to exon 20 of ALK [E6a/b;A20]) representing 60 to 80% of all variants [3]. From a clinical standpoint, the detection of an ALK gene rearrangement in a newly diagnosed advanced NSCLC patient is of utmost importance, as it associates with a response to treatment with an ALK-inhibitor in approximately three quarters of cases [4–9]. Consistently, available clinical data strongly suggest that the most optimal up-front therapy for these patients is an ALK-inhibitor, with crizotinib being the first ALK-targeted drug approved for use in this setting [4]. Of note, long-term outcomes of ALK-positive patients initially treated with crizotinib within the randomized phase 3 PROFILE 1014 trial of crizotinib versus platinum/pemetrexed chemotherapy are becoming available, and they indicate an exceptional 4-year survival rate of 56.6% [10]. Unfortunately, resistance to crizotinib is virtually inevitable, usually occurring after a median of approximately 11 months [4,5]. The mechanisms that underlie acquired resistance to crizotinib have been divided into biological and pharmacokinetic ones. In the first case, on-target (ALK gene amplification, ALK gene secondary mutations) and off-target (bypass tracks, histological transformation) mechanisms have been identified [11]. In the second, resistance is the result of disease progression in the central nervous system (CNS), which reflects the poor CNS penetration of crizotinib [12,13].

Against this background, second-generation ALK-inhibitors have been developed, namely alectinib, ceritinib, and brigatinib, with the aim of overcoming resistance to crizotinib [14]. Common features of these drugs are higher potency than crizotinib against ALK, activity against some, but not all, ALK secondary mutations that are responsible for acquired resistance to crizotinib, and superior clinical efficacy in the CNS compared to crizotinib. Such characteristics have justified the clinical development of this new generation of ALK-inhibitors as up-front treatment instead of crizotinib. Alectinib was among the first agents to be tested in this setting, and AF-001JP was a
**EDITORIAL – First-line alectinib for lung cancer**

Addeo A, Metro G. Drugs in Context 2018; 7: 212537.

**Table 1. Cross comparison of clinical activity in alectinib and ceritinib phase 3 trials for ALK-inhibitor-naive ALK-positive advanced NSCLC patients.**

| Trial | J-ALEX [7,17] | ALEX [8,9] | J-ALEX [7,17] | ALEX [8,9] | ASCEND-4 [6] |
|-------|---------------|------------|---------------|------------|--------------|
| Drug  | Crizotinib    | Crizotinib | Alectinib     | Alectinib  | Ceritinib    |
| Number of patients | 104 | 151 | 103 | 152 | 189 |
| Median PFS | 10.2 months | 10.9 months | NR (>21 months) | 34.8 months | 16.5 months |
| PFS HR (95% CI) | - | - | 0.34* (0.17–0.71) | 0.43* (0.32–0.58) | 0.55** (0.42–0.73) |
| ORR (%) | 79 | 75.5% | 92 | 82.9 | 73 |
| Median PFS with BM | 10.2 months | 7.4 months | NR (>21 months) | 27.7 months | 10.7 months |
| Median PFS without BM | 10.0 months | 14.7 months | 20.3 months | 34.8 months | 26.3 months |

BM, brain metastases; HR, hazard ratio; NR, Not reported; ORR, overall response rate; PFS, progression-free survival.

*Versus crizotinib.

**Table 1. Cross comparison of clinical activity in alectinib and ceritinib phase 3 trials for ALK-inhibitor-naive ALK-positive advanced NSCLC patients.**

phase 1/2 trial that evaluated alectinib as the first ALK-inhibitor treatment in ALK-positive advanced NSCLC patients from Japan [15]. The results of the phase 2 part of this study showed that alectinib at a dose of 300 mg twice daily provides an outstanding overall response rate (ORR) of 93.5% with a median progression-free survival (PFS) that has not been reached after a median follow-up of 3 years (3-year PFS rate=62%) [16].

On this basis, alectinib was subsequently tested in a phase 3 study, the Japanese-ALEX (J-ALEX) trial, in which ALK-inhibitor-naive ALK-positive advanced NSCLC patients were randomized to standard crizotinib at a dose of 250 mg twice daily or alectinib 300 mg twice daily, the primary endpoint being PFS as assessed by an independent review facility (IRF) (Table 1) [7]. Under an assumption of expected hazard ratio (HR) of 0.643, 164 events were required to have 80% power for a superiority hypothesis at a two-sided alpha of 0.05. Three interim analyses for early stopping due to efficacy were planned after 33, 50, and 75% of required PFS events had occurred. Overall survival, ORR, time to progression in the brain, and safety were among key secondary endpoints. Initially presented at the American Society of Clinical Oncology (ASCO) 2016 meeting, the results of this study have been recently published by Hida and colleagues in Lancet. Overall, 207 patients were allocated to either alectinib (n=103) or crizotinib (n=104). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), treatment line (first versus second), and disease stage (IIIB or IV versus postoperative recurrence), but not for brain metastases, which resulted in a disproportionate prevalence of brain metastases in the crizotinib arm (28% for crizotinib versus 14% for alectinib). Remarkably, the study met its primary endpoint, as at the second planned interim analysis, the HR for IRF-assessed PFS was 0.34 (99.7% CI: 0.17–0.71) in favor of alectinib (median not estimable [NE], 95% CI: 20.3-NE, versus 10.2 months, 95% CI: 8.2–12.0; p<0.0001). A multiple stratified Cox regression analysis, adjusting for the potential of imbalance in the distribution of prognostic factors between treatment groups on IRF-assessed PFS, showed a similar HR as the primary analysis (HR=0.34). Therefore, it can be concluded that the superior efficacy observed with alectinib was independent of the different distribution of patients with baseline brain metastases between the two arms of the study. Benefits in terms of IRF-assessed PFS were seen across different subsets, including patients with brain metastases (HR=0.08) as well as those who had received prior chemotherapy (HR=0.39). Notably, the total number of patients with at least one grade 3 or 4 adverse event was higher in the crizotinib arm (52 versus 26%). Also, significant more patients interrupted crizotinib due to an adverse event (29 versus 20%), and drug discontinuation rate was higher with crizotinib (20 versus 9%). Therefore, the results of J-ALEX suggested for the first time a superior efficacy and tolerability of alectinib compared to crizotinib, although it should be noted that previous data have shown that the rate of crizotinib-associated toxicities might be higher in the Japanese population, accounting for a higher rate of discontinuation with crizotinib [18].

To put the results of J-ALEX in context, we should compare them with those of the global phase 3 ALEX trial, which similarly randomized a larger population of ALK-inhibitor-naive ALK-positive advanced NSCLC patients (n=303) to either crizotinib (n=152) or alectinib (n=151) (Table 1) [8]. However, unlike J-ALEX, the ALEX trial had a doubled dose of alectinib (600 mg twice daily), which was based on a previous dose finding study conducted in a Northern American population, while in Japan dose escalation beyond 300 mg twice daily was not possible due to restrictions on the quantity of an additive present in alectinib capsules [15,19]. Second, the ALEX trial only allowed patients who were treatment-naive as opposed to J-ALEX, which could include also patients who had received one prior chemotherapy regimen. Thirdly, the eligibility for ALEX was based on ALK-positivity by immunohistochemistry (IHC) as assessed through VENTANA ALK (DSF3) assay, while in
J-ALEX ALK positivity was assessed by IHC and confirmed by fluorescence in situ hybridization or by reverse transcription polymerase chain reaction (RT-PCR). Finally, although both trials shared the same primary PFS endpoint, this was investigator-assessed in ALEX and not based on an IRF as it was for J-ALEX. However, despite these few differences, alectinib was consistently found to be more active than crizotinib also in ALEX, with a recently updated analysis showing a huge HR for PFS of 0.43 (95% CI: 0.32–0.58) (median 34.8 months, 95% CI: 17.7-NE, versus 10.9 months, 95% CI: 9.1–12.9) in favour of alectinib [9]. Table 1 shows the superiority of up-front alectinib over crizotinib in terms of ORR and PFS in the overall population as well as in patients with or without brain metastases, with an indirect comparison with another second-generation ALK-inhibitor, namely ceritinib. Apparently, the superior efficacy of alectinib over ceritinib seems to be mainly driven by the higher activity exerted by alectinib in the group of patients with brain metastases at baseline, which represent approximately 20 to 30% of newly diagnosed ALK-positive advanced NSCLC patients who are seen in daily clinical practice [14].

Based on these results, it can be reasonably stated that alectinib has replaced crizotinib as standard of care in ALK-positive advanced NSCLC. Particularly attractive features that favor the up-front use of alectinib are the clinically meaningful PFS benefit over crizotinib, the higher activity against brain metastases as well as the lower rate of progression in the CNS [7–9,17,20]. Also, alectinib is associated with a more favorable toxicity profile compared to crizotinib, despite the fact that treatment duration with alectinib is more than tripled [8–9]. In addition, a recent meta-analysis of studies evaluating crizotinib, alectinib, ceritinib, and brigatinib for the treatment of ALK-positive advanced NSCLCs has suggested a relevant difference in terms of select toxicities among these ALK-inhibitors. Importantly, with regard to second-generation ALK-inhibitors, toxicity significantly favored alectinib over ceritinib for grade 3/4 gastrointestinal adverse events (diarrhea, nausea, vomiting), fatigue, and alanine transaminase (ALT)/aspartate transaminase (AST) elevation [21]. On the downside, the use of up-front alectinib leaves no established treatment options at progression, mainly due to the lack of characterization of the resistance mechanisms to alectinib when this drug is used as first-line. In fact, we could only assume that they resemble those that have been observed in patients who have received alectinib as subsequent line of therapy after crizotinib. If this is the case, it can be anticipated that G1202R secondary mutation is among the most common on-target resistance mechanism [22]. In fact, G1202R, which affects the solvent-exposed region of ALK, resulting in steric hindrance of most ALK-inhibitors, has been found in approximately 30% of patients who progress on alectinib when this drug is used in a post-crizotinib setting. Of note, alectinib-resistant tumors bearing a G1202R mutation may respond to lorlatinib, a third-generation ALK-inhibitor with proven preclinical and clinical activity against this form of ALK-mutant disease [22,23]. Therefore, in the near future it can be hypothesized a sequence of treatment in which patients progressing on first-line alectinib could be switched to lorlatinib, especially in cases with biopsy-proven G1202R resistance mechanism.

Nevertheless, a crucial point for the time being is whether we can further improve in the future the outcome of ALK-positive NSCLC patients treated with first-line alectinib. Currently, three phase 3 randomized trials are investigating novel, more potent ALK-inhibitors as up-front treatment of ALK-positive advanced NSCLC patients (Table 2). However, based on their design, which includes crizotinib in the comparator arm, these trials will likely yield positive results in favor of the experimental treatment. This, in turn, will produce a crowded environment in terms of newly approved ALK-inhibitors besides alectinib, without providing direct evidence on the superiority of any of these novel ALK-inhibitors over alectinib.

Against this scenario, the outcome of ALK-positive patients can only be improved by selecting the most appropriate ALK-inhibitor based on the predicted resistance mechanism that may develop according to the type of EML4–ALK fusion variant. Recent evidence suggests that resistance of ALK fusion variant 3 NSCLC patients is more often mediated by the G1202R mutation compared to other variants [3]. This finding, coupled with the notion that G1202R is commonly observed in alectinib-resistant patients, may support the fact that ALK-positive variant 3 NSCLC patients could benefit from the use of up-front lorlatinib (in order to prevent the onset of G1202R). Similarly, the up-front use of an ALK-inhibitor with a high CNS penetration rate could prevent/delay the onset of pharmacokinetic failure of treatment, and again, lorlatinib is a good candidate based on both preclinical and clinical findings [24,25].

### Table 2. Ongoing phase 3 randomized trials of ALK-inhibitors first-line treatment of ALK-positive advanced NSCLC.

| Comparator          | ClinicalTrials.gov identifier | Acronym | Expected data availability |
|---------------------|-------------------------------|---------|---------------------------|
| Brigatinib          | NCT02737501                   | ALTA-1L | April 2019                |
| Lorlatinib          | NCT03052608                   | CROWN   | February 2020             |
| Ensartinib          | NCT02767804                   | eXalt3  | April 2020                |
Table 3. Selected overview of ALK-inhibitor combinatorial trials that are ongoing in ALK-positive advanced NSCLC patients.

| Drugs                                             | ClinicalTrials.gov identifier            |
|---------------------------------------------------|------------------------------------------|
| Immunotherapy combination                         |                                          |
| Crizotinib + nivolumab or ipilimumab              | NCT01998126 (completed)                  |
| Crizotinib + pembrolizumab                        | NCT02511184 (terminated, slow accrual)   |
| Alectinib + atezolizumab                          | NCT02013219 (active, not recruiting)     |
| Lorlatinib or crizotinib + avelumab               | NCT02584634 (recruiting, Javelin Lung 101) |
| Alectinib + durvalumab                            | NCT02898116 (active, not recruiting)     |
| Targeted treatment combination                    |                                          |
| Ceritinib + trametinib                            | NCT03087448 (recruiting)                 |
| Alectinib + cobimetinib                           | NCT03202940 (recruiting)                 |
| Ceritinib + ribuciclib                            | NCT02292550 (active, not recruiting)     |
| Ceritinib + everolimus                            | NCT02321501 (recruiting)                 |
| Antiangiogenic combination                        |                                          |
| Alectinib + bevacizumab                           | NCT03202940 (recruiting)                 |

On the other hand, ALK-inhibitor combination strategies represent an appealing treatment approach in this context (Table 3). A strategy could be that of combining an ALK-inhibitor with immune checkpoint inhibitor(s), termed immunotherapy, although there are still limited preclinical data to support this combination [26]. In addition, recent data on the combination of crizotinib with the anti-programmed death-1 (PD-1) agent nivolumab have produced a poor ORR of 38%, with safety concerns because of a high rate of hepatic toxicity [27]. Therefore, combinations of an ALK-inhibitor with immunotherapy need to be more extensively studied and schedules optimized, before being utilized in clinical practice.

At the same time, combinations of an ALK-inhibitor with the antiangiogenic agent, bevacizumab, are also under clinical evaluation.

In conclusion, with the current knowledge of the complex and heterogeneous mechanisms behind ALK resistance, multiple next-generation ALK-inhibitors and combinatorial treatment approaches can be envisioned beyond alectinib. These new therapeutic strategies have the potential to improve further the results of treatment for an increasing portion of patients with ALK-positive advanced NSCLC.

Contributions: Giulio Metro wrote the first draft of the editorial and both authors reviewed it for important intellectual content.

Disclosure and potential conflicts of interest: The authors declare that there is no conflict of interest regarding the publication. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/06/dic.212537-COI.pdf

Funding declaration: There was no funding for this manuscript.

Copyright: Copyright © 2018 Addeo A, Metro G. Published by Drugs in Context under Creative Commons License Deed CC BY NC ND 4.0 which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

Correct attribution: Copyright © 2018 Addeo A, Metro G. https://doi.org/10.7573/dic.212537. Published by Drugs in Context under Creative Commons License Deed CC BY NC ND 4.0.

Article URL: http://www.drugsincontext.com/first-line-alectinib-for-alk-positive-lung-cancer-is-there-room-for-further-improvement?

Correspondence: Giulio Metro, MD, Staff Physician, Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, via Dottori, 1, 06156, Perugia, Italy. giulio.metro@yahoo.com

Provenance: invited; externally peer reviewed.

Submitted: 10 May 2018; Peer review comments to author: 6 June 2018; Revised manuscript received: 9 June 2018; Accepted: 11 June 2018; Publication date: 10 July 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 SPT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

For all manuscript and submissions enquiries, contact the Editorial office dic.editorial@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com
References

1. Iacono D, Chiari R, Metro G, et al. Future options for ALK-positive non-small cell lung cancer. *Lung Cancer*. 2015;87:211–219. http://doi.org/10.1016/j.lungcan.2014.12.017

2. Ou SH, Bartlett CH, Mino-Kenudson M, Cui J, Iafrate AJ. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. *Oncologist*. 2012;17:1351–1375. http://doi.org/10.1634/theoncologist.2012-0311

3. Lin JJ, Zhu VW, Yoda S, et al. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. *J Clin Oncol*. 2018;36:1199–1206. http://doi.org/10.1200/JCO.2017.76.2294

4. Solomon BJ, Mok T, Kim DW, et al. PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167–2177. http://doi.org/10.1056/NEJMoa1408440

5. Lu S, Mok T, Lu Y, et al. Phase 3 study of first-line crizotinib vs pemetrexed-cisplatin/carboplatin (PCC) in East Asian patients (pts) with ALK+ advanced nonsquamous nonsmall cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34(Suppl 15):9058(abSTRACT).

6. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389:917–929. http://doi.org/10.1016/S0140-6736(17)30123-X

7. Hida T, Nokihara H, Kondo M, 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. http://doi.org/10.1016/S0140-6736(17)30565-2

8. Peters S, Camidge DR, Shaw AT, et al. ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829–838. http://doi.org/10.1056/NEJMoa1704795

9. Camidge DR, Peters S, Mok T, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. *J Clin Oncol*. 2018;36(Suppl);9043(abtract).

10. Solomon BJ, Kim DW, Wu YL, et al. Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive non-small-cell lung cancer. *J Clin Oncol*. May 16, 2018. http://doi.org/10.1200/JCO.2017.77.4794

11. Rotow J, Bivona TG. Understanding and targeting resistance mechanisms in NSCLC. *Nat Rev Cancer*. 2017;17:637–658. https://doi.org/10.1038/nrc.2017.84

12. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29(15):e443–445. http://doi.org/10.1200/JCO.2010.34.1313

13. Metro G, Tazza M, Matocci R, Chiari R, Crinò L. Optimal management of ALK-positive NSCLC progressing on crizotinib. *Lung Cancer*. 2016;106:58–66. http://doi.org/10.1016/j.lungcan.2017.02.003

14. Seto T, Nishio M, Kondo M, et al. Alectinib versus crizotinib in patients with ALK+ NSCLC with CNS metastases deriving clinical benefit from treatment. *J Thorac Oncol*. 2015;10:e26–e27. http://doi.org/10.1097/JTO.0000000000000468

15. Metro G, Tazza M, Matocci R, Chiari R, Crinò L. Optimal management of ALK-positive NSCLC progressing on crizotinib. *Lung Cancer*. 2016;106:58–66. http://doi.org/10.1016/j.lungcan.2017.02.003

16. Tamura T, Kiura K, Seto T, et al. Three-year follow-up of an alectinib phase I/II study in ALK-positive non-small-cell lung cancer: primary results from phase III study (J-ALEX). *Lancet Oncol*. 2015;16(Suppl):S378–379(abtract).

17. Fujiwara Y, Hamada A, Mizugaki H, et al. Pharmacokinetic profiles of significant adverse events with crizotinib in Japanese patients with ABCB1 polymorphism. *Cancer Sci*. 2016;107:1117–1123. http://doi.org/10.1111/cas.12983

18. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK+ advanced non-small cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol*. 2017;35:1515–1521. http://doi.org/10.1200/JCO.2016.70.5749

19. Kim Y, Hida T, Nokihara H, et al. Alectinib (ALC) versus crizotinib (CRZ) in ALK-positive non-small cell lung cancer (ALK+ NSCLC): primary results from phase III study (J-ALEX). *J Thorac Oncol*. 2017;12(Suppl):S378–379(abtract).

20. Nishio M, Nakagawa K, Mitsudomi T, et al. 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. http://doi.org/10.1016/j.jtho.2016.11.427

21. Costa DB, Costa RL, Talamantes SM, et al. Systematic review and meta-analysis of selected toxicities of approved ALK inhibitors in metastatic non-small cell lung cancer. *Oncotarget*. 2018;9:22137–22146. http://doi.org/10.18632/oncotarget.25154

22. Gainor JF, Dardei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov*. 2016;6:1118–1133. http://doi.org/10.1158/2159-8290.CD-16-0596
23. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib 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.  
http://doi.org/10.1016/S1470-2045(17)30680-0

24. Johnson, TW, Richardson PF, Bailey S, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclopentadecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J Med Chem*. 2014;57:4720–4744.  
http://doi.org/10.1021/jm500261q

25. Collier TL, Normandin MD, Stephenson NA, et al. Synthesis and preliminary PET imaging of $^{11}$C and $^{18}$F isotopologues of the ROS1/ALK inhibitor lorlatinib. *Nat Commun*. 2017;8:15761.  
http://doi.org/10.1038/ncomms15761

26. Hong S, Chen N, Fang W, et al. Upregulation of PD-L1 by EML4-ALK fusion protein mediates the immune escape in ALK positive NSCLC: implication for optional anti-PD-1/PD-L1 immune therapy for ALK-TKIs sensitive and resistant NSCLC patients. *Oncoimmunology*. 2015;5:e1094598.  
https://10.1080/2162402X.2015.1094598

27. Spigel DR, Reynolds C, Waterhouse D, et al. Phase 1/2 study of the safety and tolerability of nivolumab plus crizotinib for the first-line treatment of ALK translocation-positive advanced non-small cell lung cancer (CheckMate 370). *J Thorac Oncol*. 2018;13:682–688.  
http://doi.org/10.1016/j.jtho.2018.02.022