EBioMedicine 41 (2019) 9–10

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Refining precision cancer therapy in ALK-positive NSCLC

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The treatment approach to advanced anaplastic lymphoma kinase fusion-positive (ALK-positive) non-small cell lung cancer (NSCLC) serves as a paradigm for precision oncology. To date, five ALK-tyrosine kinase inhibitors (TKIs)—crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib—have been approved by the US Food and Drug Administration [1,2]. Although each TKI has significant efficacy in ALK-positive NSCLC, the duration of benefit is invariably limited by the development of acquired resistance.

Alectinib, a second-generation ALK-TKI, is the current standard initial therapy for advanced ALK-positive NSCLC [3,4]. Once patients develop alectinib resistance, second-line options include lorlatinib, chemotherapy, or a clinical trial. Lorlatinib is a potent, brain-penetrant, third-generation ALK/ROS1-TKI with efficacy against most known *ALK* resistance mutations including G1202R [2,5], the most common alectinib-resistant mutation [6]. Based on phase II results demonstrating its activity in patients who progressed on second-generation ALK-TKIs [2], lorlatinib recently received FDA approval for second- or third-line treatment of ALK-positive NSCLC. Sequential therapy with alectinib followed by lorlatinib is therefore anticipated to be a common treatment approach. Yet, resistance to lorlatinib invariably develops, and thus, elucidating mechanisms of resistance to lorlatinib is critical to developing effective next-line treatments.

In this issue of *EBioMedicine*, Okada and colleagues report the identification of 14 lorlatinib-resistant compound *ALK* mutations [7]. Using an ENU mutagenesis screen of Ba/F3 cells expressing EML4-ALK-I1171N or -G1202R—the most common alectinib-resistant mutations [6]—the authors identified nine I1171N-based and four G1202R-based double mutants. A G1202R/G1269A double mutant was additionally identified in an EML4-ALK-G1202R mouse model made lorlatinib-resistant. Indeed, three of these compound mutations (G1202R/G1269A, G1202R/L1196 M, and I1171N/L1198F) had previously been reported based on lorlatinib-resistant tumour biopsies [8]. The *ALK* mutations identified herein expand upon those reported in an independent mutagenesis study [7,8], suggesting lorlatinib resistance may emerge from a diverse array of compound *ALK* mutations as patients receive sequential alectinib then lorlatinib.

Importantly, the authors evaluated the *in vitro* sensitivity of several compound *ALK* mutants to approved ALK inhibitors. Interestingly, certain I1171N-based double mutants could be overcome by earlier-generation ALK-TKIs [7]. For example, I1171N/L1256F was sensitive to alectinib; I1171N/L1196M and I1171N/G1269A were sensitive to brigatinib or ceritinib. These findings are reminiscent of a prior report on a lorlatinib-resistant *ALK* C1156Y/L1198F compound mutation, which re-sensitised tumour cells to crizotinib [9]. Okada et al. similarly found double *ALK* mutants containing L1198F (G1202R/L1198F and I1171N/L1198F) to be sensitive to crizotinib. Collectively, these results highlight that structurally distinct, even earlier-generation, ALK-TKIs may be useful at different time points during the disease course as patients receive sequential ALK targeted therapies.

It should be noted that a significant fraction of lorlatinib-resistant compound *ALK* mutations are not sensitive to earlier-generation ALK-TKIs. In this study, G1202R-based double mutants G1202R/L1196 M, G1202R/F1174C, and G1202R/F1174L were refractory to all approved ALK inhibitors [7]. While G1202R/G1269A was moderately sensitive to brigatinib *in vitro*, the IC_{50} was modestly higher than that for G1202R. As *ALK* G1202R has been detected in brigatinib-resistant biopsies [6], it is unclear to what degree brigatinib will prove clinically effective against G1202R/G1269A. For these refractory compound *ALK* mutations, novel rationally designed inhibitors are urgently needed.

Overall, the current study contributes to the growing understanding of lorlatinib-resistant compound *ALK* mutations. The observation that specific compound mutations are sensitive *versus* refractory to earlier-generation ALK inhibitors *in vitro* could help inform practice, and underscores the importance of repeat biopsies in identifying resistance mutations, some of which may predict sensitivity to alternative TKIs. However, this study raises several important questions. First, can these compound *ALK* mutations be reliably identified in the clinic by tumour or liquid biopsies? While the individual mutations themselves may be readily detected, determining the allelic context of the *ALK* mutations (*i.e.*, whether the *ALK* mutations reside on the same or different alleles) can be much more challenging and will often not be feasible using the standard next-generation sequencing assays on genomic DNA. Second, will earlier-generation ALK inhibitors induce meaningful clinical benefit in lorlatinib-resistant patients harbouring sensitive compound *ALK* mutations? In patients relapsing after multiple sequential therapies, tumours may harbour a greater degree of genomic complexity and heterogeneity that tempers the efficacy of any single ALK-TKI and effectively dampens the ALK-dependent phenotype. CNS disease status will further influence the extent of clinical benefit from earlier-generation TKIs which are generally less active in the CNS than

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.01.019.
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https://doi.org/10.1016/j.ebiom.2019.01.059

lorlatinib. Third, will upfront treatment with lorlatinib result in more durable benefit than a sequential approach which fosters the accumulation of genetic changes including *ALK* resistance mutations? Lorlatinib is potent against most known single *ALK* resistance mutations; hence, upfront lorlatinib may delay or suppress the emergence of refractory compound *ALK* mutations [8]. A phase III trial (ClinicalTrials.gov identifier NCT03052608) is evaluating the first-line efficacy of lorlatinib compared to crizotinib.

Finally, although not addressed in this study, ALK-independent mechanisms of resistance such as bypass signaling or lineage changes remain a major therapeutic hurdle in ALK-positive NSCLC. In an analysis of 20 lorlatinib-resistant tumour biopsies, 65% did not harbour compound *ALK* resistance mutations [8], implicating ALK-independent resistance. The prevalence of ALK-independent resistance mechanisms will likely rise as strategies to overcome *ALK* mutations continue to improve. Thus, effective combinatorial approaches that address both ALK-dependent and ALK-independent resistance are needed. Together, these endeavours will help fine-tune our treatment approach to ALK-positive NSCLC to more precisely match the biology of the tumour.

Disclosures

JJL has served as a compensated consultant or received honorarium from Chugai Pharma and Boehringer-Ingelheim. ATS has served as a compensated consultant or received honoraria from Pfizer, Novartis, Genentech/Roche, Ariad/Takeda, Ignyta, LOXO, Blueprint Medicines, KSQ Therapeutics, Daiichi Sankyo, EMD Serono, Taiho Pharmaceutical, TP Therapeutics, Bayer, Chugai, Foundation Medicine, Natera, and Guardant, and has received research funding from Pfizer, Novartis, Genentech/Roche, Ignyta, and TP Therapeutics.

References

[1] Lin JJ, Riely GJ, Shaw AT. Targeting ALK: precision medicine takes on drug resistance. Cancer Discov 2017;7(2):137–55.
[2] Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19(12):1654–67.
[3] 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(10089):29–39.
[4] Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377(9):829–38.
[5] Shaw AT, Martini J-F, Besse B, et al. Abstract CT044: efficacy of lorlatinib in patients (pts) with advanced ALK-positive non-small cell lung cancer (NSCLC) and ALK kinase domain mutations. Cancer Res 2018;**78**(13 Supplement):CT044-CT.
[6] Gainor JF, Dardaei 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(10):1118–33.
[7] Okada K, Araki M, Sakashita T, et al. Prediction of ALK mutations mediating ALK-TKIs resistance and drug re-purposing to overcome resistance. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.01.019.
[8] Yoda S, Lin JJ, Lawrence MS, et al. Sequential ALK inhibitors can select for lorlatinib-resistant compound ALK mutations in ALK-positive lung cancer. Cancer Discov 2018;8(6):714–29.
[9] Shaw AT, Friboulet L, Leshchiner I, et al. Resensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. N Engl J Med 2016;374(1):54–61.