OncoTargets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Combination of Aumolertinib, Dabrafenib, and Trametinib for a Patient with Advanced Lung Adenocarcinoma with an Osimertinib-Induced BRAF V600E Mutation: A Case Report

Diming Wang[1,*], Wei Ye[2,*], Zihuan Yin[3,*], Ning Xu[3], Jie Ma[3]

[1]Department of Oncology, Anhui Chest Hospital, Hefei, 230022, People's Republic of China; [2]Department of Pathology, Anhui Chest Hospital, Hefei, 230022, People's Republic of China; [3]Department of Thoracic Surgery, Anhui Chest Hospital, Hefei, 230022, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jie Ma; Ning Xu, Department of Thoracic Surgery, Anhui Chest Hospital, Hefei, 230022, People's Republic of China, Email majie1537@126.com; xuning200901@aliyun.com

Abstract: Osimertinib has become the standard of care in the first-line treatment of advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations. Although previous studies reported that the BRAF V600E mutation is a unique resistance mechanism to osimertinib, the treatment of lung adenocarcinoma patients harboring both EGFR and acquired BRAF-V600E comutations remains unclear. Here, we report a case of a 36-year-old woman diagnosed with stage IV lung adenocarcinoma harboring the EGFR L858R mutation. She received osimertinib for 24 months and experienced progressive disease. Rebiopsy pathology revealed that the lung lesion was still adenocarcinoma, and NGS revealed gains of BRAF V600E and TP53 mutations in addition to the EGFR L858R mutation. This patient subsequently received aumolertinib in combination with dabrafenib and trametinib and achieved a complete response for 8 months. In conclusion, acquired BRAF-V600E mutations may contribute to osimertinib resistance. Aumolertinib plus BRAF inhibitors improves outcomes in patients with EGFR-L858R and acquired BRAF-V600E comutant lung adenocarcinoma in whom osimertinib treatment has failed.

Keywords: lung adenocarcinoma, osimertinib, aumolertinib, dabrafenib and trametinib, BRAF V600E

Introduction

Currently, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are routinely used for the treatment of advanced EGFR-mutant non-small cell lung cancer (NSCLC).[1] Notably, the FLAURA study revealed that, compared with gefitinib, osimertinib significantly prolonged progression-free survival (PFS) and overall survival (OS).[2,3] However, patients develop acquired resistance to first-line osimertinib treatment, with a median time to progression of 18.9 months.[2] The mechanisms of osimertinib resistance include the activation of EGFR-dependent or EGFR-independent pathways and histologic transformation.[4] BRAF-V600E mutations occur in approximately 1.5% of lung adenocarcinomas.[5] Planchard et al[6] reported that dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, had good efficacy in the treatment of BRAF-V600E-mutated advanced lung adenocarcinoma. In addition, approximately 1–3% of advanced NSCLC patients treated with EGFR-TKIs develop BRAF mutations or fusions.[7] Ho et al[8] reported that osimertinib-resistant cells dependent on the RAS signaling pathway are relatively sensitive to BRAF inhibitors. The combination of BRAF inhibitors and osimertinib can further inhibit MEK and ERK phosphorylation.[8] Weng et al[9] reported that NSCLC patients with acquired BRAF mutations after failure of prior EGFR-TKIs received BRAF inhibitors in combination with EGFR-TKIs and exhibited objective response and disease control rates of 61.5% and 92.3%, respectively. Additionally, an in vitro trial revealed

Received: 10 January 2025
Accepted: 5 April 2025
Published: 13 April 2025

a 99.36% tumor growth inhibition rate with dabrafenib, trametinib, and osimertinib.[9] TP53 alterations were found to be associated with decreased PFS after first-line therapy and decreased OS in patients with EGFR-mutated NSCLC.[10] Wei et al[11] reported that the frequencies of variants in TP53, PIK3CA, RB1, MET, LRP1B, APC, CDKN2A, MYC, ERBB2, and SMAD4 were greater than 10% in NSCLC patients with EGFR and BRAF comutations. Here, we report a case of a patient with advanced lung adenocarcinoma with EGFR-L858R and TP53 mutations who failed osimertinib treatment and had EGFR-L858R, TP53 and BRAF V600E mutations on rebiopsy. This patient achieved a complete response (CR) with second-line treatment with aumolertinib in combination with dabrafenib and trametinib.

Case Presentation

In March 2022, a 36-year-old woman presented to Anhui Chest Hospital with cough and chest pain for 2 months. The patient had no history of smoking. On 21 March 2022, a thoracoscopic left pleural biopsy was performed after a chest computed tomography (CT) revealed left pleural thickening and pleural effusion (Figure 1A and B). She was diagnosed with stage IV lung adenocarcinoma. An EGFR exon L858R (p.Leu858Arg) mutation was identified in plasma DNA via next-generation sequencing (NGS) using an amplicon-based Illumina platform. The patient received osimertinib as the first-line treatment. After approximately 2 months, a chest CT (22 May 2022) revealed a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors v1.1 (Figure 1C and D). However, after approximately 24 months, a chest CT (4 April 2024) revealed progressive disease (PD) (Figure 1E and F). We performed a rebiopsy of the lung lesion, and NGS revealed the originally identified EGFR L858R mutation and new BRAF V600E and TP53 mutations (Figure 2). After clinical discussion, the patient started treatment with dabrafenib and trametinib plus aumolertinib concurrently. After 2 months, comparison of a chest CT scan (3 June 2024) (Figure 3A and B) with a previous CT scan (4 April 2024) revealed a CR. During treatment with dabrafenib and trametinib plus aumolertinib, the patient experienced a transient fever with a maximum temperature of 38.5 °C. After a series of tests, fever was determined to be an adverse reaction to drug therapy. After 8 months, a chest CT (6 Dec 2024) revealed that patient still exhibited a CR (Figure 3C and D).

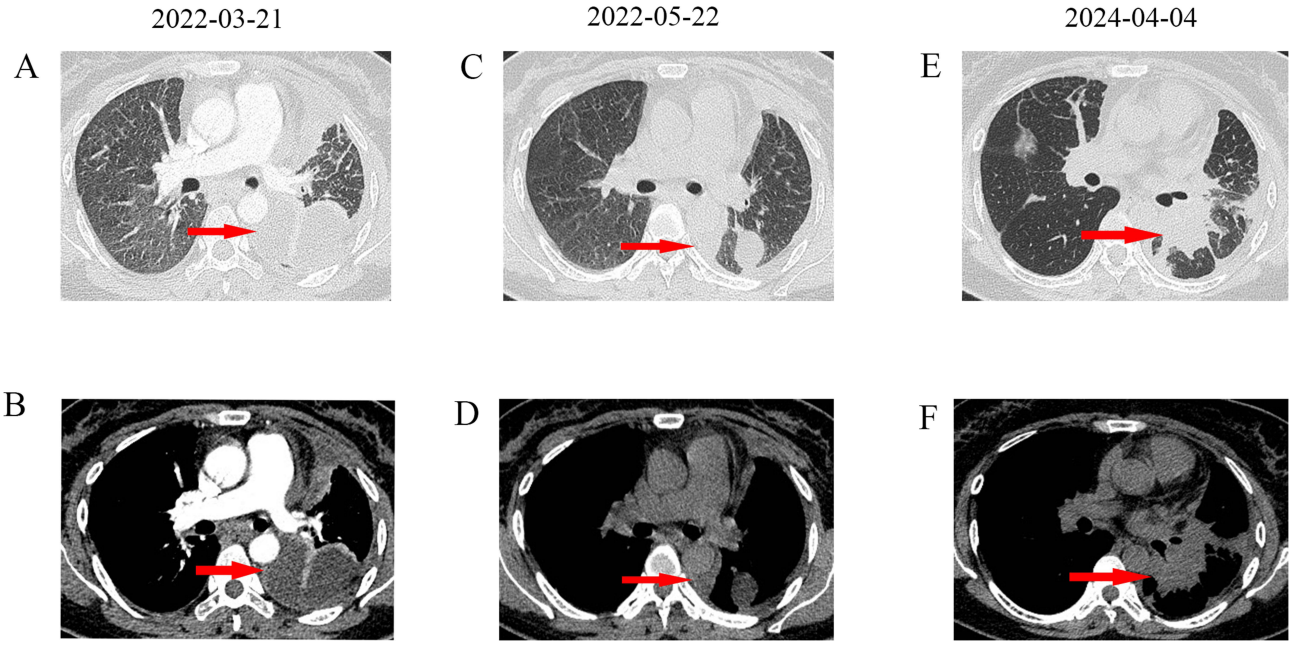

Figure 1 (**A** and **B**) Baseline CT images. (**C** and **D**) Evaluation of the lung mass indicated a partial response (PR) after 2 months of osimertinib. (**E** and **F**) Evaluation of the lung mass indicated PD after 24 months of osimertinib. The red arrow indicates lung lesion.
Abbreviations: PR, partial response; PD, progressive disease; CT, computed tomography.

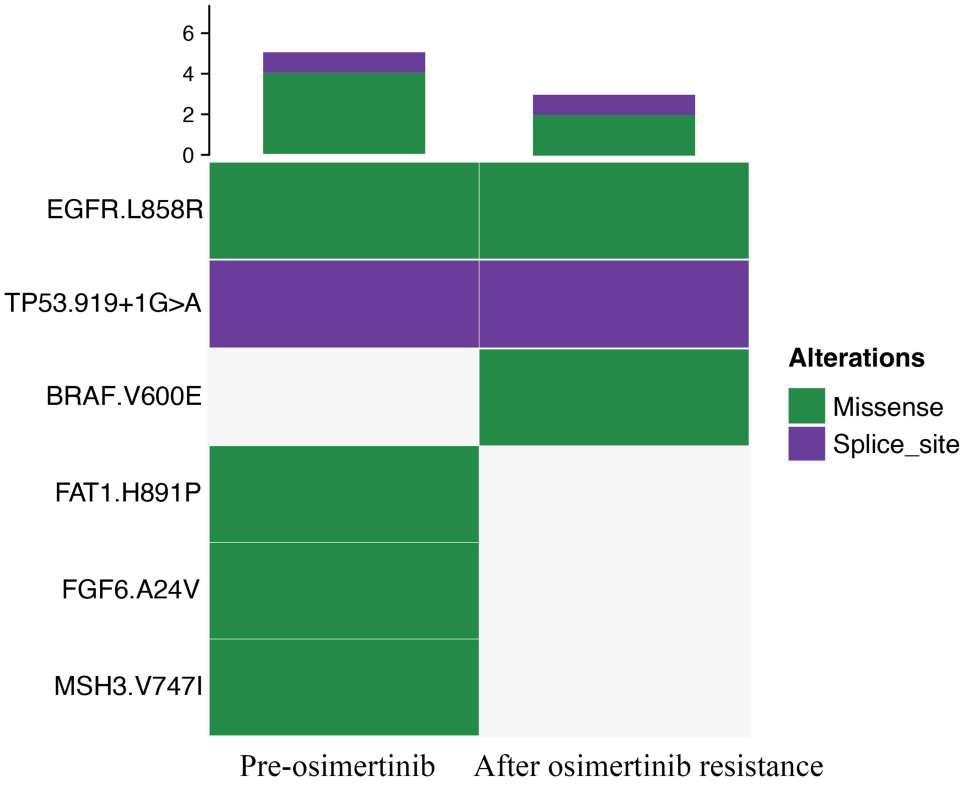

Figure 2 The landscape of molecular alterations detected in this patient before and after treatment with osimertinib.

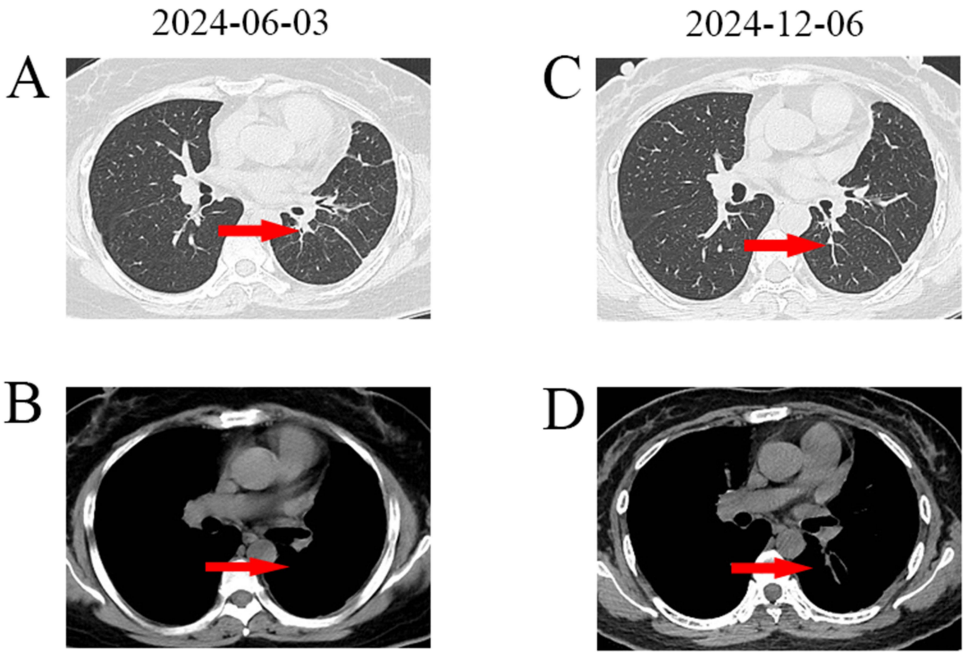

Figure 3 (**A** and **B**) Evaluation of the lung mass indicated a CR after 2 months of aumolertinib in combination with dabrafenib and trametinib compared with the prior CT (4 April 2024). (**C** and **D**) Evaluation of the lung mass indicated a CR after 8 months of aumolertinib in combination with dabrafenib and trametinib. The red arrow indicates lung lesion.

Abbreviations: PD, progressive disease; CR, complete response; CT, computed tomography.

https://doi.org/10.2147/OTT.S512704

Discussion

The non-EGFR-dependent pathways activated by the EGFR-TKI resistance pathway include the RAS-RAF-MEK-ERK signaling pathway, which is a key regulator of cell growth.[12] Notably, BRAF is a member of the RAS/RAF/MEK/ERK signaling pathway that mediates cell growth and malignant transformation.[13] Ho et al[8] reported that osimertinib inhibited EGFR phosphorylation but had no effect on AKT, MEK, or ERK, which could lead to activation of the RAS-RAF-MEK-ERK signaling pathway. Wei et al[11] reported that four patients who failed treatment with first- or second-generation EGFR-TKIs presented with BRAF-V600E and EGFR-T790M mutations, all of whom were treated with osimertinib, did not achieve disease control, with a median PFS of only 3.4 months. Notably, one of the patients who failed osimertinib treatment was retreated with osimertinib in combination with dabrafenib and trametinib and achieved a 10-month PFS.[11] Ribeiro et al[14] described a patient with advanced EGFR-19 deletion lung adenocarcinoma who failed to receive osimertinib, presented with acquired EGFR-T790M and BRAF-V600E mutations and received osimertinib in combination with dabrafenib and trametinib. He achieved an objective response of his primary tumor lesion but developed grade 3 fever, leading to a half-dose reduction in dabrafenib and trametinib. He finally achieved a PFS of 6 months. In our case, the patient initially had an EGFR-L858R mutation with TP53 mutation, and pathological examination of the rebiopsy sample after failure of first-line osimertinib treatment revealed lung adenocarcinoma with EGFR-L858R, TP53 and BRAF-V600E mutations. Therefore, we believe that the BRAF-V600E mutation in this patient might be one of the main reasons for osimertinib resistance. For second-line treatment, we replaced osimertinib with aumolertinib in combination with dabrafenib and trametinib, which induced a CR with tolerable toxicity.

The FLAURA study[3] revealed that osimertinib had an OS of 38.6 months as a first-line treatment for advanced EGFR-mutated lung adenocarcinoma. However, osimertinib did not prolong OS compared with gefitinib in the EGFR-L858R subgroup of patients.[3] In the AENEAS study,[15] aumolertinib, as a first-line treatment for locally advanced or metastatic EGFR-mutated NSCLC, led to a PFS time of 19.3 months, which was marginally greater than the PFS of 18.9 months achieved with osimertinib in the FLAURA study.[2] In addition, the median PFS in the brain metastasis population was 15.3 months (hazard ratio: 0.38) for aumolertinib[15] and 15.2 months (hazard ratio: 0.47) for osimertinib.[2] Notably, Shen et al[16] reported a patient with advanced EGFR exon 19 deletion lung adenocarcinoma harboring EGFR-L861Q and EGFR-790M comutations after osimertinib treatment failure. The patient was then treated with aumolertinib and exhibited a PFS period of 4 months. Ding et al[17] reported on 3 patients with advanced EGFR-mutant lung adenocarcinoma in whom osimertinib treatment failed; these patients subsequently received aumolertinib rechallenge and achieved a PR. Among them, 2 patients with EGFR-L858R-mutated lung adenocarcinoma achieved sustained remission. In this case, we found that a patient harboring the EGFR-L858R mutation who failed osimertinib treatment also harbored BRAF-V600E and TP53 mutations. This patient was rechallenged with aumolertinib in combination with dabrafenib and trametinib and achieved a CR. In addition, this patient has now achieved 8 months+ of deep remission. Thus, osimertinib in combination with dabrafenib and trametinib was efficacious in this patient. However, Meng et al[18] presented 2 patients with advanced EGFR-mutated lung adenocarcinoma who failed treatment with osimertinib and were treated with osimertinib in combination with dabrafenib and trametinib. Among these patients, one experienced progression after 6 weeks, and the other died after 3 weeks due to uncontrolled disease. In our case, the clinical outcome of the patient receiving aumolertinib in combination with dabrafenib and trametinib was significantly better than the outcomes reported by Wei et al.[11] Meng et al[18] and Ribeiro et al.[14] Notably, the structure of aumolertinib was innovatively optimized on the basis of that of osimertinib but with the replacement of a cyclopropyl group on the indole nitrogen. As a result, nonselective metabolites that inhibit wild-type EGFR are not generated during drug metabolism.[19] Therefore, we believe that aumolertinib in combination with dabrafenib and trametinib is a good treatment option for patients with advanced EGFR-L858R/BRAF-V600E-comutated lung adenocarcinoma with osimertinib treatment failure.

There are some limitations to our case report. This report was written after only a short follow-up period for this patient, and we continue to perform chest CT every 8 weeks to assess this patient for long-term benefit. In the future, if

this patient shows disease progression, we will perform genetic testing again to explore the mechanisms of resistance. In addition, we reported only that this patient had fever with aumolertinib in combination with dabrafenib and trametinib and did not report the economic cost and bioavailability of this treatment regimen. In the future, we will enroll more patients to investigate the efficacy of this treatment option.

In conclusion, acquired BRAF-V600E mutations may contribute to osimertinib resistance. Aumolertinib in combination with BRAF inhibitors is effective in patients with EGFR-L858R/BRAF-V600E-comutated lung adenocarcinoma for whom osimertinib treatment has failed. The use of aumolertinib plus BRAF inhibitors for patients with lung adenocarcinoma with osimertinib-induced BRAF-V600E mutations should be further investigated.

Ethical Approval

Written informed consent was provided by the patient to have the case details and accompanying images published. Institutional approval was not required to publish the case details. This study was approved by the Human Research Ethics Committee of Anhui Chest Hospital.

Funding

This work was supported by the Anhui Province Health Research Program (No. AHWJ2023Baa20191).

Disclosure

Diming Wang, Wei Ye and Zihuan Yin are co-first authors for this study. The authors have no conflicts of interest to declare for this work.

References

1. Yu X, Si J, Wei J, et al. The effect of EGFR-TKIs on survival in advanced non-small-cell lung cancer with EGFR mutations: a real-world study. *Cancer Med*. 2023;12(5):5630–5638. doi:10.1002/cam4.5413
2. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *New Engl J Med*. 2018;378(2):113–125. doi:10.1056/NEJMoa1713137
3. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *New Engl J Med*. 2020;382(1):41–50. doi:10.1056/NEJMoa1913662
4. Chhouri H, Alexandre D, Grumolato L. Mechanisms of acquired resistance and tolerance to EGFR targeted therapy in non-small cell lung cancer. *Cancers*. 2023;15(2):504. doi:10.3390/cancers15020504
5. Qu J, Shen Q, Li Y, et al. Clinical characteristics, co-mutations, and treatment outcomes in advanced non-small-cell lung cancer patients with the BRAF-V600E mutation. *Front Oncol*. 2022;12:911303. doi:10.3389/fonc.2022.911303
6. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, Phase 2 trial. *Lancet Oncol*. 2017;18(10):1307–1316. doi:10.1016/S1470-2045(17)30679-4
7. Westover D, Zugazagoitia J, Cho BC, et al. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol*. 2018;29:i10–i19. doi:10.1093/annonc/mdx703
8. Ho CC, Liao WY, Lin CA, et al. Acquired BRAF V600E mutation as resistant mechanism after treatment with osimertinib. *J Thorac Oncol*. 2017;12(3):567–572. doi:10.1016/j.jtho.2016.11.2231
9. Weng CD, Liu KJ, Jin S, et al. Triple-targeted therapy of dabrafenib, trametinib, and osimertinib for the treatment of the acquired BRAF V600E mutation after progression on EGFR-tyrosine kinase inhibitors in advanced EGFR-mutated non-small cell lung cancer patients. *Transl Lung Cancer Res*. 2024;13(10):2538–2548. doi:10.21037/tlcr-24-358
10. Vokes NI, Chambers E, Nguyen T, et al. Concurrent TP53 mutations facilitate resistance evolution in EGFR-mutant lung adenocarcinoma. *J Thorac Oncol*. 2022;17(6):779–792. doi:10.1016/j.jtho.2022.02.011
11. Wei XW, Deng JY, Xu CR, et al. Characteristics of and treatment strategies for advanced EGFR-mutant NSCLC with concomitant BRAF variations. *JTO Clin Res Rep*. 2022;3(7):100348. doi:10.1016/j.jtocrr.2022.100348
12. Yu D, Zhao W, Vallega KA, et al. Managing acquired resistance to third-generation EGFR tyrosine kinase inhibitors through co-targeting MEK/ERK signaling. *Lung Cancer*. 2021;12:1–10. doi:10.2147/LCTT.S293902
13. Aboubakar Nana F, Ocak S. Targeting BRAF activation as acquired resistance mechanism to EGFR tyrosine kinase inhibitors in EGFR-mutant non-small-cell lung cancer. *Pharmaceutics*. 2021;13(9):1478. doi:10.3390/pharmaceutics13091478
14. Ribeiro M, Knebel FH, Bettoni F, et al. Impressive response to dabrafenib, trametinib, and osimertinib in a metastatic EGFR-mutant/BRAF V600E lung adenocarcinoma patient. *NPJ Precision Oncol*. 2021;5(1):5. doi:10.1038/s41698-021-00149-4
15. Lu S, Dong X, Jian H, et al. AENEAS: a randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic non-small-cell lung cancer With EGFR Exon 19 deletion or L858R mutations. *J Clin Oncol*. 2022;40(27):3162–3171. doi:10.1200/JCO.21.02641
16. Shen G, Shi L, Tian X, et al. Case report: response to almonertinib in a patient with metastatic NSCLC resistant to osimertinib due to acquired EGFR L718Q mutation. *Front Pharmacol*. 2021;12:731895. doi:10.3389/fphar.2021.731895

17. Ding X, Ding J, Leng Z, et al. Aumolertinib challenge as an optional treatment in advanced non small-cell lung cancer after osimertinib failure with epidermal growth factor receptor-sensitive mutation: a case series. *Oncol Lett*. 2022;24(5):400. doi:10.3892/ol.2022.13520
18. Meng P, Koopman B, Kok K, et al. Combined osimertinib, dabrafenib and trametinib treatment for advanced non-small-cell lung cancer patients with an osimertinib-induced BRAF V600E mutation. *Lung Cancer*. 2020;146:358–361. doi:10.1016/j.lungcan.2020.05.036
19. Yang JC, Camidge DR, Yang CT, et al. Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: a multicenter, open-label, phase 1 trial. *J Thorac Oncol*. 2020;15(12):1907–1918. doi:10.1016/j.jtho.2020.09.001