EGFR Tyrosine Kinase Inhibitor Sequencing Revisited: From the Revival of Old Tools to the Integration of New Agents

Nicolas Girard, MD, PhD[a,b,*]

In this issue of the *Journal of Thoracic Oncology*, Piccirillo et al.[1] report the results of the BEVERLY trial, a randomized phase 3 study that reveals the progression-free survival (PFS) benefit of bevacizumab to erlotinib as first-line treatment for Italian patients with metastatic NSCLC with common *EGFR* mutations. In this large study, after a median follow-up of 36.3 months, median investigator-assessed PFS was 15.4 months with erlotinib plus bevacizumab and 9.6 months with erlotinib alone (hazard ratio = 0.66, 95% confidence interval: 0.47–0.92). These results add further evidence to that provided by previously reported randomized studies, mostly conducted in Asian patients, that investigated combinations of first-generation *EGFR* TKIs and antiangiogenic agents, including JO25567, NEJ026, CTONG-1509, and other trials with erlotinib and bevacizumab,[2–5] and the RELAY trial with erlotinib and ramucirumab.[6] Taken together, these studies reported on median PFS ranging from 16.4 to 19.4 months.

This brings back to the fore the historical so-called sequencing strategy consisting of the use of first- or second-generation tyrosine kinase inhibitor (TKI) upfront, keeping a chance to use osimertinib as a subsequent therapy in the setting of *EGFR* T790M-related acquired resistance.[7] First, these studies, including BEVERLY, reveal the opportunity to improve the efficacy of first- or second-generation TKIs in the first-line setting to reach the median PFS reported with first-line osimertinib—18.9 months in the FLAURA trial[8]—considered as the current standard of care wherever available. Second, recent improvements in technologies and access to tissue- and blood-based genomic profiling may allow a higher proportion of patients to be identified with *EGFR* T790M at the time of disease progression, a challenge at the time the AURA-3 trial, revealing the benefit of osimertinib after the failure of first- or second-generation TKIs, was reported.[9] In this study, median PFS was 10.1 months on osimertinib, which may provide additional survival to patients in a sequencing approach. In historical real-world evidence studies, the rate of patients eligible to osimertinib ranged from 25% to 40%,[10] whereas this was 47% in the control arm of FLAURA.[8] Indeed, in BEVERLY, 57% and 49% of patients in the control and experimental arm, respectively, did receive second-line osimertinib. Third, the use of antiangiogenic agents may provide protection against central nervous system disease progression, a major challenge for patients with *EGFR*-mutant NSCLC as previously reported in RELAY, although the follow-up of this study remains limited so far.[6] This could actually not be explored in BEVERLY, given the exclusion of patients with brain metastases. Ultimately, the sequencing strategy may offer a prolonged chemotherapy-free time to the patients and more chance of deriving prolonged disease control along with first- and second-line treatments, which may lead to longer median overall survival (OS) as compared with that reported with frontline osimertinib of 38.6 months.[8] From real-world cohorts of patients who received a sequence of first- or second-generation *EGFR* TKI followed by osimertinib, median OS may be similar or even higher: in the GioTag trial, median OS was 37.6 months, rising up to 41.6 and 44.8 months in patients with *EGFR* exon 19 deletion and Asian patients, respectively.[11] Other studies are in line with such finding.[12] The promise of BEVERLY and other trials is

*Corresponding author.

[a]Thoracic Oncology Service, Institut Curie, Institut du Thorax Curie Montsouris, Paris, France, and [b]UFR Simone Veil, Paris Saclay University, Université de Versailles Saint-Quentin-en-Yvelines (UVSQ), Versailles, France.

Disclosures: Dr. Girard reports receiving support from AstraZeneca, United Kingdom, Roche, Switzerland, Pfizer, United States, and Janssen, outside of the current work.

Address for correspondence: Nicolas Girard, MD, PhD, Institut Curie, Institut du Thorax Curie Montsouris, 26 rue d'Ulm, 75248 Paris Cedex 05, France. E-mail: nicolas.girard2@curie.fr

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.07.005

that OS could be even higher with the optimization of first-line through the combination with antiangiogenic agents. Still in BEVERLY, median OS in the combination arm was 33.3 months, despite the exclusion of patients with brain metastases.

Beyond first- and second-line sequencing, several new options are emerging for patients developing refractory disease, which add subsequent options in a sequencing strategy. Most current developments rely on the targeting of the most frequent molecular mechanisms of resistance to *EGFR* TKIs and/or on a deeper targeting of the *EGFR* signaling pathway. MET targeting is a major ongoing focus of clinical research after the failure of first- or second-line osimertinib and is based on *MET* TKIs, such as tepotinib or savolitinib, including on antibodies, such as the dual-specific *EGFR*/*MET* agent, amivantamab. Amivantamab, when combined with lazertinib, a third-generation *EGFR* TKI, was recently reported to produce response rates as high as 39% in heavily pretreated patients associated with PFS higher than 6 months.[13] Although *MET*- or *EGFR*-expressing tumors may have a better response to amivantamab, the combination is being developed without biomarker-driven selection. Another approach at the time of osimertinib resistance relies on the targeting of *EGFR*-mutant tumor cells with the HER3-specific antibody-drug conjugate patritumab-deruxtecan,[14] providing response rates and PFS in the same range. Interestingly, one striking point was that responses were observed across all the diverse mechanisms of *EGFR* TKI resistance, including those not directly related to HER3, such as *EGFR* C797S, *MET* or *HER2* amplification, and *BRAF* fusion. Meanwhile, new strategies that are currently developed in NSCLC overall are also being tested in *EGFR*-mutant NSCLC after the failure of *EGFR* TKIs, such as anti-TROP2 drugs; response rate to datopotamab deruxtecan in this setting is again in the 30% range, with a median duration on treatment of 13 months.[15] How these new options should be integrated in the treatment sequence remains a major question in the clinic; ultimately, adding new sequences in the patient management strategies is expected to increase the overall outcome. This remains a major concept to keep in mind as (1) those agents are now tested concurrently as first-line treatment, in comparison with osimertinib, and (2) *EGFR* inhibitors are also integrated in the adjuvant, neoadjuvant, or consolidation setting after the curative-intent treatment of nonmetastatic disease.

The BEVERLY study also stresses the question of positioning in the treatment sequence of antiangiogenic agents along with the disease evolution in *EGFR*-mutant NSCLC. Bevacizumab has mostly been used after the failure of TKIs, in combination with chemotherapy. The IMpower150 trial revealed, in a prespecified limited subset of 50 patients, the potential benefit of a quadruplet with carboplatin, paclitaxel, atezolizumab, and bevacizumab in this setting.[16] Whether and how the early exposure to antiangiogenic agent modifies the natural history of the disease remain unclear. In BEVERLY, no further follow-up is planned, owing to severe acute respiratory syndrome coronavirus 2 pandemic, and sites of recurrence, including OS, will remain unknown. Of note, combination of osimertinib with bevacizumab was disappointing so far.[17] Similarly, the actual sequencing of chemotherapy in the treatment strategy for *EGFR*-mutant NSCLC is a matter of debate. Although it is currently being used in the refractory setting, several trials recently suggested a room for chemotherapy upfront in combination with *EGFR* TKIs.[18,19] FLAURA2 is an ongoing phase 3, randomized trial to evaluate efficacy and safety of first-line osimertinib with platinum-pemetrexed chemotherapy versus osimertinib monotherapy. MARIPOSA2 is a study of amivantamab and lazertinib in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with acquired resistance to osimertinib.

To conclude, whether combination strategies will ultimately provide more prolonged OS to patients, as compared with sequential approaches, is a major question in the clinic. A challenge is that clinical trials, such as BEVERLY, always focus on one line of treatment and may have limited follow-up; even if providing some information on subsequent therapies, these do not address the full sequencing of therapies. The publication of BEVERLY represents another pledge for prospective, adaptative, real-world studies that integrate historical and new options as soon as these become available and analyze treatment sequences along with clinical and molecular evolution of the disease.

CRediT Authorship Contribution Statement

Nicolas Girard: Conceptualization, Validation, Formal analysis, Writing—original draft, Writing—review and editing, Project administration.

References

1. Piccirillo MC, Bonanno L, Garassino MC, et al. Addition of bevacizumab to erlotinib as first-line treatment of patients with EGFR-mutated advanced nonsquamous NSCLC: the BEVERLY multicenter randomized phase 3 trial. *J Thorac Oncol*. 2022;17:1086–1097.
2. Yamamoto N, Seto T, Nishio M, et al. Erlotinib plus bevacizumab vs erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive nonsquamous non-small-cell lung cancer: survival follow-up results of the randomized JO25567 study. *Lung Cancer*. 2021;151:20–24.

3. Kawashima Y, Fukuhara T, Saito H, et al. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Respir Med*. 2022;10:72–82.
4. Zhou Q, Xu CR, Cheng Y, et al. Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study. *Cancer Cell*. 2021;39:1279–1291.
5. Stinchcombe TE, Jänne PA, Wang X, et al. Effect of erlotinib plus bevacizumab vs erlotinib alone on progression-free survival in patients with advanced EGFR-mutant non-small cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5:1448–1455.
6. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1655–1669.
7. Girard N. Optimizing outcomes and treatment sequences in EGFR mutation-positive non-small-cell lung cancer: recent updates. *Future Oncol*. 2019;15:2983–2997.
8. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
9. Papadimitrakopoulou VA, Mok TS, Han JY, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann Oncol*. 2020;31:1536–1544.
10. Shah R, Girard N, Nagar SP, et al. European and US real-world treatment patterns in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer: a retrospective medical record review. *Drugs Real World Outcomes*. 2021;8:537–545.
11. Hochmair MJ, Morabito A, Hao D, et al. Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: final analysis of the GioTag study. *Future Oncol*. 2020;16:2799–2808.
12. Girard N, Moro-Sibilot D, Bouée S, et al. Treatment sequence of first and second generation tyrosine kinase inhibitor followed by osimertinib in EGFR-mutated non-small-cell lung cancer: a real life study. *Future Oncol*. 2020;16:1115–1124.
13. Shu CA, Goto K, Ohe Y, et al. Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: updated results from CHRYSALIS-2. *J Clin Oncol*. 2022;40(suppl 16):9006–9006.
14. Jänne PA, Baik C, Su WC, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated non-small cell lung cancer. *Cancer Discov*. 2022;12:74–89.
15. Garon E, Johnson ML, Lisberg AE, et al. Efficacy of datopotamab deruxtecan (Dato-DXd) in patients (pts) with advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC) and actionable genomic alterations (AGAs): TROPION-PanTumor01 Preliminary results from the phase I study. *Ann Oncol*. 2021;32(suppl 5):S1283–S1346.
16. Reck M, Mok TSK, Nishio M, et al. IMpower150 study group. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387–401.
17. Kenmotsu H, Wakuda K, Mori K, et al. Randomized phase 2 study of osimertinib plus bevacizumab versus osimertinib for untreated patients with nonsquamous NSCLC harboring EGFR mutations: WJOG9717L study. *J Thorac Oncol*. 2022;17:1098–1108.
18. Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. *J Clin Oncol*. 2020;38:115–123.
19. Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. *J Clin Oncol*. 2020;38:124–136.