In this issue of the *Journal of Thoracic Oncology*, Piccirillo et al. 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 anti-angiogenic agents, including JO25567, NEJ026, CTONG-1509, and other trials with erlotinib and bevacizumab, and the RELAY trial with erlotinib and ramucirumab. 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. 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—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. 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%, whereas this was 47% in the control arm of FLAURA. Indeed, in BEVERLY, 57% and 49% of patients in the control and experimental arm, respectively, did receive second-line osimertinib. Third, the use of anti-angiogenic 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. 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. 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. Other studies are in line with such finding. The promise of BEVERLY and other trials is...
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. MARIPOS2A 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, adaptive, 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


