

Longer Follow-Up Data Maintain Lasting Responses With Amivantamab/Lazertinib in *EGFR*-Mutant NSCLC

In a recent *Between the Lines* program, Joshua K. Sabari, MD, and Sandip P. Patel, MD, discussed long-term findings from the phase 3 MARIPOSA trial (NCT04487080), which evaluated first-line treatment with amivantamab-vmjw (Rybrevant) plus lazertinib (Lazcluze) vs osimertinib (Tagrisso) for patients with *EGFR*-mutant advanced non-small cell lung cancer (NSCLC).¹ Sabari is the director of the High Reliability Organization Initiatives at the Perlmutter Cancer Center and an assistant professor of medical oncology at the NYU Grossman School of Medicine in New York, New York. Patel is a medical oncologist at the Precision Immunotherapy Clinic of UC San Diego Health and a professor of medicine at UC San Diego Health in California.

These experts analyzed how efficacy and safety data from MARIPOSA, which investigators presented in a poster session at the 2024 World Conference on Lung Cancer, may help the combination therapy fit in among 2 other FDA-approved regimens for this patient population. After a discussion about applying these trial findings to the treatment of various treatment subgroups, as well as adverse effect (AE) and toxicity management practices, Sabari and Patel spoke about oncologist-patient treatment discussions to best decide optimal dosing regimens.

MARIPOSA Design

The experts began by discussing the study design of the phase 3 MARIPOSA trial, which was composed of 3 arms: amivantamab plus lazertinib, osimertinib monotherapy, and lazertinib monotherapy. According to Patel, the trial was designed well, with multiple interventions investigated that highlight individual agents in combinatorial regimens. Additionally, he highlighted

proper identification of mutations, as a means of more accurately assigning patients for treatment.

“It is increasingly important when we are talking about a patient not to say *EGFR*-positive. You could have exon 20 insertions [that] are targetable now that they are *PAC* mutations, for example, which are a subset of atypical mutations that there are some novel therapeutics for as well,” Patel said. “When we are thinking about the molecular profile of a patient, thinking about not only the street name but the full address, [it] is important to get patients on the right therapy.”

Patel went on to highlight the reasonability of progression-free survival (PFS) as an end point within the trial, noting the prevalence of postprogression therapy following first-line treatment. Sabari concurred but suggested that he would have preferred a 1:1:1 design as opposed to a 2:2:1 design to assess lazertinib as a registrational approach vs a contribution of components. Sabari further reiterated Patel’s emphasis on distinct *EGFR* subtypes before asking how testing is undertaken in Patel’s clinical practice.

Testing for *EGFR* Mutations

Patel began by stressing the importance of molecular testing for patients with *EGFR*-mutated localized or advanced NSCLC. He suggested 2 methods in the metastatic setting: tissue-based or cell-free DNA liquid biopsies. In his clinic, he utilizes both at the same time, with the intent to cancel the tissue test if the liquid biopsy returns sooner, with the tissue test available if the liquid biopsy results do not materialize.

Sabari agreed, stating that he orders the circulating tumor DNA



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liquid biopsy with the tissue next-generation sequencing (NGS). He continued by explaining that identification of *EGFR* alterations, as well as all driver mutations, cannot be made without testing, and treatment could therefore not be considered.

Sabari noted that the amivantamab plus lazertinib regimen received FDA approval in August 2024 in the first-line setting for patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R deletions.² Patel disclosed that prior studies have elicited less durable responses in patients with L858R mutations taking targeted therapies than in patients with exon 19 deletions.

Patel noted that smoking history should not dictate whether to test patients. “The other data point I see here is one-third of these patients smoke. There is nothing protective about smoking from *EGFR*. It changes your relative probability because you get more *KRAS* mutation probability.... We should not use smoking history to decide who we test. Every patient with advanced NSCLC...deserves NGS,” Patel said.

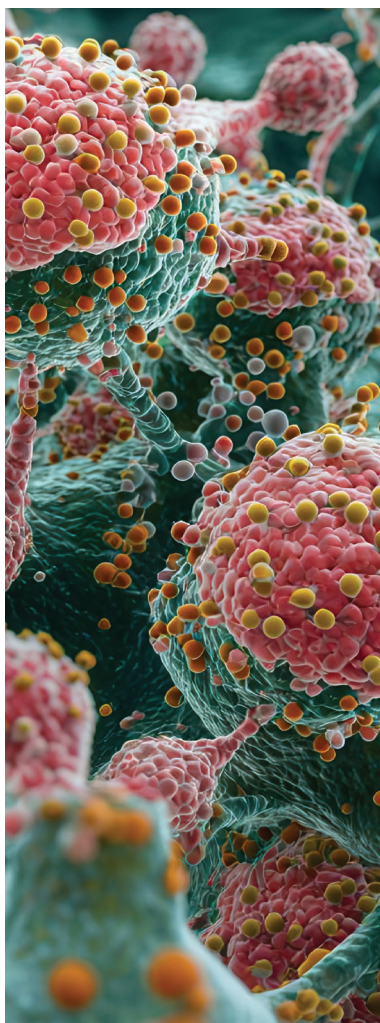
Patel explained that his clinic orders staging MRIs with stereotactic radiosurgery (SRS) sequencing, so radiation is administered if systemic therapy is delayed. Furthermore, he explained that standard procedure at his clinic is to administer systemic therapy prior to receiving an SRS MRI later to lesions growing or not responding.

Evaluating Phase 3 MARIPOSA Efficacy Data

Sabari highlighted an improvement in PFS with the investigational combination therapy over standard of care osimertinib. “At a median follow-up of 22 months, amivantamab plus lazertinib significantly improved PFS.... The HR was 0.70, and early interim overall survival [(OS) was] trending positive with an HR of 0.08,” Sabari said.

Patel regarded the combination therapy as provocative and attractive, citing its use as a treatment for *EGFR* both as a protein and a small molecule, and for metastases. He followed up by considering whether the relatively short dosing period makes up for greater incidence of AEs and second-line treatment options.

Sabari then contrasted the updated OS between the combination and osimertinib arms: not reached vs 37.3 months, respectively. He then asked Patel how the findings compared



with those from the phase 3 FLAURA2 trial (NCT04035486), which assessed osimertinib with platinum-based chemotherapy in the same patient population.³ The regimen assessed was approved in February 2024.⁴ Patel highlighted intracranial PFS data that displayed efficacy with amivantamab, and central nervous system (CNS) responses based on amivantamab responses vs osimertinib.

Sabari then expressed that intracranial PFS and OS are important when considering systemic therapy for patients, before highlighting the positive OS results within the phase 3 MARIPOSA study.⁵ Patel expressed that OS was the “gold standard” as an end point but further iterated that postprogression therapies have to be considered.

“There are multiple reasonable [treatment] paths. For example, in the frontline space, one can still use osimertinib alone up front, and you are giving [amivantamab] second line as part of MARIPOSA with chemotherapy. You could also decide if you want to do chemotherapy plus osimertinib in the front line.... Finally, if one uses [amivantamab plus lazertinib] up front, what are you doing in the second line?” Patel asked.

Patel further contrasted academic clinics, which may have access to a next-generation agent, with practices that

may not have access to clinical trials and whose options may be limited for treatment. He followed up by considering how the MARIPOSA data change thinking regarding intracranial activity. “Initially we did not think amivantamab had much CNS penetration, but here we are seeing profound activity in the CNS over osimertinib, a third-generation *EGFR* inhibitor,” Sabari said.

Patel asked whether the intracranial PFS was worth the greater infusion rate and related toxicities. He additionally pondered what the optimal sequence regimen was before suggesting that molecular features, persistent shedding, and higher-risk organ sites impact treatment decisions.

Patel then highlighted a need for a biomarker in combinatorial treatment selection for amivantamab, asserting that subset analysis was required to assess which treatment would benefit patients the most. He stated that the presence of options complicates selecting optimal treatment regimens in light of treatment developments. “It used to be easy. If I had a patient with *EGFR*

mutation, there was one therapy—one approval is the best therapy, and 10 out of 10...oncologists agreed.⁴ Now it has changed a bit, but it is good to have options for our patients. I am not sure we know the best sequence,” Patel said.

Safety Profile of the MARIPOSA trial

Sabari introduced the safety data of the trial by highlighting grade 3 or greater AE incidence in the combination therapy over osimertinib; 75% vs 43%, respectively. Patel responded by highlighting an understanding of patients’ perception of how the combination will impact their health goals, particularly pertaining to quality of life and OS, was necessary in discussing treatment with patients.

Patel outlined the toxicity profile of the combination therapy, touching upon increased toxicity with the presence of a second agent, as well as vigilant monitoring of treatment-related AEs (TRAEs) and infusion site reactions. “In my experience, the stomatitis, the paronychia, and [gastrointestinal toxicities] can be something we have to be cognizant of. This is not a drug where you see the patient every month; you have to see them more often. In the first month, you will be present for the infusion cycle. In the current form, which is intravenous, not subcutaneous, the infusion-related reactions and the amount of time they spend in the infusion center can be a barrier,” Patel said.

Patel then iterated identical treatment-related discontinuation incidences in both agents in the combination therapy, highlighting a greater need for lazertinib, calling it “the main dish.” Sabari then expressed that infusion-related reactions were concerns at his practice but were manageable. Highlighting findings from the phase 2 SKIPPirr trial (NCT05663866), Sabari explained that prophylactic use of steroids or antipyretics and patient education may help in managing toxicities.⁵ Furthermore, Sabari indicated that separating doses across consecutive days and moving toward subcutaneous formulation may help to reduce the incidence and severity of infusion reactions.

Sabari continued by explaining that a greater need to aggressively and proactively manage skin toxicities is present. He further highlighted another clinical trial, the phase 2 COCOON trial (NCT06120140), which seeks to prevent skin toxicities prophylactically.⁶ He then emphasized adhering to dose reduction or interruption practices as toxicities arise to help mitigate the discontinuation rate in longer-term follow-up with the combination therapy.

Patel further expressed a desire to involve caregivers to help ease cancer-associated burdens for patients, with an emphasis on caregiver education. He further extended this to infusion center nurses, who have large patient-facing roles and can assist in evaluating whether patients are experiencing toxicities. Sabari concurred, emphasizing ongoing patient education and early toxicity intervention to best optimize outcomes.

Deciding Between Treatment Options in EGFR-mutant NSCLC

Sabari then introduced National Comprehensive Cancer Network guidelines showcasing 3 regimens—osimertinib, amivantamab plus lazertinib, and osimertinib plus pemetrexed—in the frontline setting for *EGFR*-mutant lung cancer.⁷ Patel expressed that selecting among the 3 regimens is largely a patient-oncologist discussion, underscoring that varying treatments may align with different health goals or treatment needs.

Sabari highlighted that the oncologist-to-oncologist discussion can be informative in terms of treatment delivery and assisting patients with managing TRAEs, but that an oncologist cannot take the place of a patient in deciding which regimen may be the most impactful for their treatment goals. He expressed that age, frailty, and distance from the cancer center may primarily impact treatment decisions.

Key Takeaways From the MARIPOSA Trial

Highlighting the multiplicity of treatment options, Sandip stated benefits can be attained with all 3 treatment regimens. He further iterated that clarity regarding an optimal treatment strategy may not be attained soon and that treatment intensity may vary based on higher risk features, such as mutational status and brain metastases.

Sabari expressed a previous need to build upon the success with osimertinib, which he suggested may have been achieved with amivantamab plus lazertinib. He contextualized this achievement by comparing OS results in the MARIPOSA trial with similar ones in the phase 3 FLAURA trial (NCT02296125): 37.3 months vs 38.6 months.^{8,9} He further highlighted a 3-month improvement in intracranial PFS with MARIPOSA, which was similar to that in the osimertinib-pemetrexed arm in the FLAURA2 trial but with greater OS benefit.

Patel emphasized a greater focus on the risks affiliated with treatment options when faced with similar efficacy across regimens while maintaining that an optimal regimen was ultimately up to patient priorities.

Sabari concluded by suggesting that oncologists may not be able to predict patient desires in how treatment is administered or whether they may want more aggressive therapies. “The one fault would be if you did not discuss all 3 of these regimens with your patients, because we cannot predict what our patients want in the sense of their therapies, and you might have a patient who wants to be more aggressive. We owe that to them, to give them the options that are currently available,” Sabari said. ■

 FOR REFERENCES VISIT
cancernetwork.com/12.24_NSCLCBTL