Editorial Commentary

Osimertinib-chemotherapy synergy in *EGFR*-mutant NSCLC: advancing central nervous system control amidst toxicity considerations

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FLAURA2 was a randomized phase III trial that evaluated the efficacy of osimertinib with or without chemotherapy in patients with epidermal growth factor receptor (*EGFR*)-mutated advanced non-small cell lung cancer (NSCLC) (1). Patients with brain metastases (BMs) with no recent progression or active symptoms related to central nervous system (CNS)-related disease following CNS-directed therapy were eligible for the study. Planchard *et al.* (1), reported that the addition of chemotherapy to osimertinib significantly improved progression-free survival (PFS) [hazard ratio (HR) 0.62, 95% confidence interval (CI): 0.49–0.79], with the benefit of combination therapy being most significant among patients with baseline BMs (HR 0.47, 95% CI: 0.33–0.66). Notably, there were higher rates of grades 3–5 adverse events with the addition of chemotherapy (64%) versus monotherapy (27%). In a second interim analysis of data presented at the European Lung Cancer Congress (ELCC) 2024, a trend towards overall survival (OS) benefit was observed at 30-months follow-up (HR 0.75, 95% CI: 0.57–0.97; P=0.02), though it did not meet the prespecified level of statistical significance threshold (P<0.001). A subsequent report of CNS outcomes was later published by Jänne *et al.* (2).

BM commonly occurs in patients with NSCLC, resulting in decreased quality of life (QOL) and overall prognosis. Compared to their wild-type counterparts, patients with *EGFR*-mutant NSCLC have higher rates of CNS involvement, which is a significant cause of morbidity and mortality. There can be significant heterogeneity in clinical presentation and burden of disease, ranging from individuals with single, asymptomatic BMs to large, bulky metastases located in eloquent brain regions (3,4), which can be detrimental to patient QOL. Historically, whole brain radiotherapy (WBRT) was the standard of care for all patients with BMs (5). Furthermore, BMs in non-oncogene driven NSCLC are often treated with radiosurgical approaches. In patients with oncogene-driven NSCLC, highly focal stereotactic radiosurgery (SRS), which spares off-target brain tissues, has become the standard of care for patients with fewer than 15 lesions (6,7). With the introduction of newer generation CNS-penetrant tyrosine kinase inhibitors (TKIs) such as osimertinib, there is a renewed interest in re-evaluating the management of BM in patients with *EGFR* mutations (8). Accordingly, providers are increasingly deferring upfront SRS in the management of asymptomatic BM for patients eligible to receive TKI therapy, with the goal of mitigating long-term CNS toxicities (9-14). With emerging systemic therapies, the treatment landscape for *EGFR*-mutant NSCLC BMs is rapidly evolving.

In their analysis of CNS outcomes from FLAURA2, Jänne *et al.* (2) showed favorable outcomes for patients receiving osimertinib with chemotherapy over osimertinib alone. The median CNS PFS was not reached versus 17.3 months in patients with measurable (>1 cm) BMs (P=0.01) and 30.2 versus 27.6 months in the full cohort (P=0.054) for combination therapy and monotherapy, respectively, suggesting a CNS control benefit from the addition of chemotherapy. In the measurable cohort, the CNS objective response rates showed a trend towards more complete responses, suggesting that the addition of chemotherapy may improve the depth of response over monotherapy (48% *vs.* 16%, P=0.93).

However, the benefit of chemotherapy came at the cost of higher toxicity (grade ≥3 adverse events: 64% *vs.* 27%). While FLAURA2 demonstrated encouraging improvements in CNS PFS with the addition of combination chemotherapy to osimertinib, it also resulted in a substantial increase in grade 3 toxicities. Further studies are needed to identify subgroups who are at high risk or will experience rapid disease progression, as these patients may benefit from treatment intensification with a combination approach over osimertinib monotherapy. It is hypothesized that the presence of CNS metastases disrupts the blood-brain barrier, thereby improving CNS penetration of chemotherapy (15,16). Therefore, we argue for an individualized approach when considering treatment intensification with chemotherapy, incorporating clinical factors and patient preferences.

There is a paucity of prospective studies evaluating the integration of local therapies such as SRS with systemic approaches for *EGFR*-mutant NSCLC. The recently published TURBO-NSCLC study was a multi-institutional cohort study evaluating the use of CNS-penetrant TKIs with or without upfront SRS in treatment-naive *EGFR*- or *ALK*-driven NSCLC (14). The addition of upfront SRS with CNS penetrant TKI improved time to CNS progression (HR 0.63, 95% CI: 0.42–0.96; P=0.03) compared to TKI alone. For patients with metastases ≥1 cm, the cumulative incidence of CNS progression at 12 months was 41% for TKI alone versus 20% for TKI plus SRS (P=0.01), suggesting enhanced CNS control with combined treatment.

Further prospective studies that compare the efficacy of novel systemic treatments with or without upfront local brain-directed treatments are needed to delineate the optimal sequencing of these therapies. There are several trials underway, including the recently activated ICON-RT trial at Memorial Sloan Kettering Cancer Center, which is a randomized phase II study that aims to evaluate a consolidative approach with SRS to large BM (≥1 cm), allowing for deferral of upfront radiation therapy in patients receiving first-line CNS-active therapies.

The analysis of CNS outcomes from FLAURA2 implies that combination therapy may improve disease control over osimertinib alone (1). Combination therapy may provide synergistic effects in the CNS by eradicating drug-resistant microscopic disease, but comes at the expense of increased systemic toxicities and potential neurocognitive effects from chemotherapy (17). FLAURA2 demonstrated that adding chemotherapy to osimertinib significantly improves CNS outcomes (median CNS PFS: 24.9 *vs.* 13.8 months), but at the cost of increased toxicity. Hematologic adverse events, including neutropenia (25%), thrombocytopenia (18%), and anemia (46%), were notably more frequent in the combination arm, largely due to chemotherapy-induced bone marrow suppression. Patients with concurrent active hematologic malignancies or requiring chronic anticoagulation may be at heightened risk of complications. Grade ≥3 adverse events were higher with combination therapy (64% *vs.* 27%), including gastrointestinal events such as nausea (43% *vs.* 10%) and vomiting (26% *vs.* 6%). These toxicities may pose significant impacts to patient QOL, particularly those with poor performance status or significant co-morbidities. For patients with minimal CNS disease burden, osimertinib monotherapy may offer sufficient CNS control while minimizing treatment toxicities.

However, the lack of patient-reported outcomes in the study limits the generalizability of how these treatments may affect a patient's long-term QOL. Furthermore, the addition of chemotherapy resulted in a doubling of grade 3+ toxicities, underscoring the need for refined biomarkers to aid the selection of patients for treatment intensification with chemotherapy or early intervention with SRS. Future trials should incorporate patient-reported QOL surveys, such as the European Organization for Research and Treatment of Cancer (EORTC), QLQ-BN20, EORTC QLQ-C30, and Non-small cell lung cancer Symptom Assessment Questionnaire (NSCLC-SAQ), which evaluates neurocognitive and symptom burden, alongside performance status (18-20). By doing so, future prospective studies can provide insight as to how treatment intensification impacts disease control while incorporating patients' functional outcomes and well-being.

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Footnote

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