Editorial Commentary

Advancing leptomeningeal metastases treatment in *EGFR*-mutated non-small cell lung cancer: lessons from the BLOSSOM trial

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Leptomeningeal metastases (LM), characterized by the spread of cancer cells to the meninges or cerebrospinal fluid (CSF), occur in approximately 3% of patients with non-small cell lung cancer (NSCLC) (1). Patients with NSCLC harboring an epidermal growth factor receptor (*EGFR*) mutation have a significantly higher risk of developing LM compared to those with wild-type *EGFR* (9% *vs.* 2% incidence) (1). There is a high variance in presentation patterns of NSCLC, with LM representing one of the less common but clinically significant complications. Historically, patients with LM have poor outcomes [median overall survival (OS) ~3 months] (2) and a high symptom burden that negatively impacts clinical functioning (3). Currently, limited data is available on the optimal management of patients with NSCLC and LM, as this population is typically excluded from clinical trials (4,5).

Tyrosine kinase inhibitors (TKIs) significantly changed the treatment and prognosis of patients with advanced NSCLC and an *EGFR* mutation, improving survival and quality of life (QoL) (6). However, less benefit was seen in the subgroup of patients with LM, attributed to the poor central nervous system (CNS) penetration of earlier-generation TKIs (7,8). Osimertinib, a third-generation TKI, demonstrated improved CNS activity, including in LM, compared to previous TKIs. In the FLAURA trial, four of five patients with suspected LM receiving osimertinib achieved complete radiographic response of the LM, and one had radiographic stable disease (SD) (9). This encouraging efficacy in LM was also found in other, small studies (10-12).

Current guidelines recommend osimertinib as first-line treatment for advanced *EGFR*-mutated NSCLC or after progression on earlier-generation TKIs in case of T790M resistance mutation (13,14).

The recently published phase II BLOSSOM trial investigated the efficacy of standard dose osimertinib [80 mg once daily (QD)] in 73 Korean patients with NSCLC and an *EGFR* mutation (exon 19 deletion or L858R), who had developed LM after treatment with earlier-generation TKIs, regardless

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of T790M status (15). A promising survival (median OS 15.6 months) was reported in the full-analysis set (n=72). In the group with LM evaluable for response (n=64), the objective response rate (ORR), complete response (CR) rate, disease control rate (DCR), and duration of response (DoR) of LM were determined by neuroradiological blinded independent central review (BICR) using response assessment in neuro-oncology (RANO)-LM criteria. ORR was 51.6%, CR rate 15.6 %, DCR 81.3%, and DoR 12.6 months. ORR of LM as assessed by the investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was 6.3%. Similar median intracranial progression-free survival (PFS) was seen between BICR using RANO-LM (11.2 months) and investigator assessment using RECIST (12.5 months). QoL also improved, and osimertinib treatment was well-tolerated, with only 5% requiring a dose reduction because of side effects.

These results confirm the role of osimertinib in this setting but also raise several questions, such as the optimal dose of osimertinib, its use in T790M negative disease, the optimal LM response evaluation, potential CNS resistance mechanisms to EGFR-TKIs, and the best combination and timing of systemic and local treatment for LM.

Osimertinib optimal dose

Retrospective analyses from the AURA program corroborate the efficacy of osimertinib 80 mg (LM ORR 55%, median PFS and OS up to 11.1 and 18.8 months, respectively) in patients with *EGFR* T790M mutated NSCLC and LM (11).

Based on earlier preclinical data suggesting that a higher exposure may increase CNS tumor shrinkage (16), in the phase I BLOOM trial (n=41) a double dose of osimertinib (160 mg QD) was administered to patients with CSF cytology-confirmed leptomeningeal progression on previous EGFR-TKIs (10). Median OS was 11.0 months, LM ORR and DoR by neuroradiological BICR were 62% and 15.2 months, respectively (10). Similarly, in the LM cohort of a phase II study (n=40), a DCR of 92.5% (12.5% CR) and a median OS of 13.3 months were achieved with osimertinib 160 mg QD (17).

This suggests that standard and double doses of osimertinib provide comparable CNS efficacy. However, given the different study inclusion criteria (performance status, T790M status, previous treatments, extracranial progression), further prospective trials are needed.

Osimertinib in T790M negative patients

In the discussion about the optimal dose, the half-maximal inhibitory concentration (IC_{50}) of specific *EGFR* mutations should be considered, as EGFR-TKI efficacy for LM depends on whether therapeutic drug concentration for a specific mutation is achieved in the CSF. In *in-vitro* models, the IC_{50} for osimertinib varies: it is lowest for the L858R-T790M combination (0.9 nM), and gradually increases for exon 19 deletion-T790M (3.1 nM), L858R (6.2 nM), and exon 19 deletion (7.9 nM) (18). This is relevant, as only two patients in the BLOSSOM trial had a T790M positive tumor and the geometric mean CSF concentration of osimertinib was 4.58 (0.46–47.70) nM, suggesting that the IC_{50} was not achieved in most patients. Of note, AZ5104—one of osimertinib's active metabolites—reached a geometric mean CSF concentration of 0.30 nM (0.08–5.98), also lower than its IC_{50} (19). This data, combined with the lower plasma-to-CSF ratio of AZ5104 compared to osimertinib (10% *vs.* 22%), suggests that AZ5104 does not significantly contribute to CNS activity. However, as approximately half of the patients in the BLOSSOM trial still had a disease response, more research including other pharmacokinetic parameters is encouraged.

Another explanation could be the testing method for T790M, as testing was mostly in blood or in extracranial tumor tissue; this does not entirely reflect the intracranial disease status, although a previous study also suggested that CSF T790M occurrence after treatment with earlier-generation TKIs is relatively rare (20). Similarly, the *EGFR* T790M mutation was less frequently detected in blood samples of patients with brain-only progression compared to those with systemic progression (21.9% *vs.* 72.3%, P<0.001) after a first-generation TKI treatment (21). A subgroup analysis (n=28) reported comparable results (P=0.0002) (22). In another study, *EGFR* T790M was identified in the plasma of 5/23 patients with LM after progression on TKIs and in CSF circulating tumor DNA (ctDNA) of 7/23 patients (23). Therefore, an exploratory analysis (n=35) using targeted sequencing on CSF samples was conducted in the BLOSSOM trial; all patients except one, with also a T790M positive extracranial tumor, were T790M negative. As all enrolled patients progressed on earlier-generation EGFR-TKIs and had isolated CNS failure, this confirms that most intracranial resistance mechanisms to earlier EGFR-TKIs might result from pharmacokinetic resistance (i.e., failure of drug delivery to the target) rather than biological resistance; no subgroup analyses were performed elucidating the impact of

the different previous TKIs on outcomes.

Almost all patients (97.3%) enrolled in the BLOSSOM trial had a T790M negative tumor, suggesting that osimertinib can overcome CNS failure, regardless of extracranial T790M status. Although a retrospective study (n=40; n=24 T790M-negative) showed the efficacy of osimertinib 80 mg QD in pretreated *EGFR*-mutated NSCLC with LM regardless of T790M status (12), BLOSSOM is the first to prospectively confirm these findings. Of note, another third-generation EGFR-TKI, lazertinib, also showed substantial CNS activity (brain metastases and LM; intracranial ORR 55%, DCR 97%, median OS not reached) at the standard dose, regardless of T790M status, in patients with CNS progression on earlier-generation EGFR-TKIs (24).

Currently, the demonstration of an *EGFR* T790M resistance mutation remains mandatory for using second-line osimertinib (13,14) as ORR and PFS are significantly lower in *EGFR* T790M-negative compared to T790M positive tumors (25,26).

In addition, osimertinib monotherapy is considered the first-line standard of care for all newly diagnosed advanced *EGFR*-mutated NSCLC (13,14), so it remains unclear whether the results of the BLOSSOM trial can also be achieved in the first-line setting.

Osimertinib in combination with other systemic treatments

Several trials are combining osimertinib with other drugs, and the impact of adding other systemic treatments on controlling LM has yet to be established. In the randomized phase III FLAURA 2 trial (n=557), the addition of platinum-pemetrexed chemotherapy to osimertinib improved median PFS (24.9 *vs.* 13.8 months) in patients with CNS metastases at baseline (n=226) compared to osimertinib alone (27). Of the 13 patients with LM included in the experimental arm, five achieved CR, four partial response (PR), and two SD by RECIST 1.1 (28). Moreover, other treatment options without osimertinib are being examined in this setting. The randomized phase III MARIPOSA trial demonstrated superior efficacy of amivantamab-lazertinib over osimertinib, improving PFS even in the subgroup with CNS metastases (18.3 *vs.* 13.0 months) (29). However, patients with LM were excluded, thus preventing a clear understanding of the true benefit of the combination in this specific subgroup.

Osimertinib resistance in LM

Another main issue is the optimal management of patients with leptomeningeal progression on osimertinib as resistance inevitably occurs, encompassing *EGFR*-dependent as well as *EGFR*-independent mechanisms (30). After systemic disease progression, a resistance mechanism (plasma and/or tissue based) can be identified in about 50% of patients (30); but data on intracranial resistance mechanisms are limited. The ORA-LM study investigated osimertinib-induced DNA resistance mutations in CSF of *EGFR*-mutated NSCLC patients with newly diagnosed or progressive LM; a resistance mutation was found in CSF ctDNA in 27% of patients, none of which were targetable (31). This underlies the urgency to develop new strategies and drugs to overcome these pathways. Notably, the ORA-LM study showed that doubling the osimertinib dose to 160 mg QD in these patients led to a 20% clinical response rate (RR) and a 16% radiological RR.

Another prospective, single-arm, phase II study evaluated the efficacy and safety of intrathecal pemetrexed in patients with confirmed *EGFR*-mutated NSCLC and LM who progressed during EGFR-TKIs (n=132), showing promising results (median OS 12.0 months, RANO-assessed ORR 80.3%) also in those who developed LM during third-generation EGFR-TKI treatment (84%) (32). Lazertinib combined with amivantamab also seems an option, as LM ORR (RANO-LM) was 44% (4/9) and 25% (2/8) in the subgroup of patients with an L858R or exon 19 deletion, respectively (33). In the overall LM cohort (n=22) the median PFS and OS were 8.3 and 14.4 months, respectively (33). No patients with LM were included in the phase III MARIPOSA-2 trial (34). Ongoing trials are assessing new treatment strategies in patients with LM after osimertinib failure, such as intrathecal pemetrexed + EGFR-TKIs (NCT05805631), double dose furmonertinib + intrathecal chemotherapy (not specified) (NCT06339242), almonertinib + bevacizumab (NCT04944069).

Osimertinib in combination with local treatment

Due to osimertinib's promising results, it is also important to understand how to combine it with local approaches used in the current therapeutic landscape (whole brain radiotherapy (WBRT)/stereotactic radiotherapy (SRT) or intrathecal chemotherapy) (35). In the BLOSSOM trial previous radiotherapy, including WBRT, or intrathecal

chemotherapy were allowed following a 2-week washout period. LM ORR was consistent across patients with prior cranial radiotherapy (n=10) or intrathecal chemotherapy (n=8). OS was similar regardless of prior intrathecal methotrexate therapy (15.0 *vs.* 18.3 months, P=0.513) while median OS appeared longer in patients who had not received WBRT compared to those who had (18.3 *vs.* 9.6 months, P=0.022). These findings indicate no significant impact of prior CNS local therapies on the efficacy of osimertinib. However, detailed information regarding the timing of previous treatment is lacking, which could potentially bias the outcomes. Overall, in patients with LM a systemic approach with a third-generation TKI should be considered over locoregional therapies, which are often associated with significant toxicity and complications that can negatively impact survival. An ongoing Chinese trial (NCT06304441) aims to assess whether combining osimertinib (160 mg QD) with intrathecal pemetrexed can further increase the clinical RR.

Response evaluation of LM

The difference in CNS ORR between RANO-LM and RECIST criteria highlighted in the BLOSSOM trial emphasizes the complexities in evaluating LM response. Although the RANO-LM working group developed a tool for assessing neurologic response in patients with LM (36), a standardized and universally recognized assessment of LM response is lacking. Neurological examination, CNS imaging, and CSF cytology are commonly considered in the evaluation of LM response. However, importantly, LM-related neurological deficits may be irreversible, and therefore, a lack of improvement should not necessarily be interpreted as treatment failure. Additionally, neurological function changes may result from coexisting brain metastases, systemic disease progression, concurrent medications, or treatment-related toxicity, complicating the clinical interpretation of the response. Moreover, neuroimaging evaluation poses challenges. Although contrast-enhanced magnetic resonance imaging (MRI) of the brain and entire spine is the recommended imaging modality, it may appear normal in 30–40% (37) and does not permit a proper quantitative assessment due to the typically small volume and complex geometry of LM. Furthermore, the RECIST criteria, still commonly used in many trials, apply a 10-mm size threshold, which may not adequately capture LM responses. In contrast, the proposed RANO-LM criteria, with a smaller 5-mm size threshold and consideration of six specific radiographic features, is likely more suitable for LM evaluation. Both neurologic examinations and interpretation of radiographic findings in LM can vary among evaluators, as well as imaging instruments. The development of new more precise tools, which can be easily and universally applied, is essential to deliver the most accurate and objective response assessment. Radiomics models and AI-derived algorithms could represent a promising field of research to address this issue.

As previously stated, CSF evaluation is crucial in patients with LM. Currently, CSF cytology (presence or absence of malignant cells) is considered the standard approach, although its sensitivity is suboptimal (estimated 44–67%) and depends upon different factors (i.e., CSF volume, collection site, time of analysis) (38).

Also, CSF cytology predominantly consists of qualitative analysis and no quantitative data is provided (38). Response based on CSF cytology is considered when CSF converts from positive to negative but clearance of CSF cytology is challenging to achieve. In the BLOSSOM trial, baseline CSF cytology was positive in 84.7% of patients available for CSF testing and increased to 89.2% after cycle three of osimertinib despite radiological and clinical improvements, underscoring the limitations of this tool in assessing LM response. Detection and enumeration of circulating tumor cells (CTCs) in CSF has recently been used to overcome these limitations. In particular, the detection of epithelial-cell adhesion molecule (EpCAM), a transmembrane glycoprotein expressed in epithelial cancer cells, has been studied for diagnosing LM in CSF. Currently, two major EpCAM-based techniques (the CELLSEARCH® technology and flow cytometry assays) have reported highly promising sensitivities, between 76% and 100%, and a specificity of up to 100% (39). In a retrospective study (n=101), CSF-CTC quantification using the CellSearch® platform predicted survival in patients with newly diagnosed LM in various solid tumors, provided a quantitative assessment of disease burden in the CNS compartment, and outperformed neuroimaging, appearing as a new promising tool in this setting (40). A limitation of this technique is that CTCs deteriorate rapidly after CSF collection. Standardization, with special attention given to the speed of processing and adequate use of centrifugation, is needed. Although a RANO review on liquid biopsies states that CTCs quantification shows a substantially higher sensitivity to detect malignant cells in CSF than cytology (38), its definite role and optimal use have yet to be defined.

ctDNA detection represents another promising

diagnostic tool in CSF, as CSF typically has low cellularity and background cell-free DNA. ctDNA was successfully isolated and sequenced in 92% of patients with LM and *EGFR*-mutated NSCLC (n=28) (23). In the ORA-LM trial, CSF ctDNA was detected in 26/28 of LM patients in whom CSF samples were analyzed, whereas the *EGFR* driver mutation was identified in all samples (31). This suggests that ctDNA could help track tumor genomic profiles in CSF over time, monitor the development of resistance mechanisms, and understand differences in responses between intracranial and extracranial sites. A small ongoing prospective trial is comparing plasma and CSF ctDNA in *EGFR*-mutated NSCLC with LM (NCT05257967). However, larger trials are necessary before these new CSF assays can be adopted into routine clinical practice and the identification of new soluble CSF biomarkers to detect and monitor LM is essential.

In conclusion, the BLOSSOM study is the largest prospective trial to date showing promising outcomes for patients with *EGFR*-mutated NSCLC and LM treated with standard dose osimertinib following progression on earlier-generation TKIs. Based on these findings, we believe that osimertinib standard dose should be preferred over the frequently used double dose in this population, as it demonstrated comparable efficacy with a lower incidence of treatment-related adverse events and reduced costs. However, the optimal management of LM in *EGFR*-mutated NSCLC remains challenging. Further prospective studies focusing on the ongoing questions discussed in this commentary are urgently needed to provide clinicians with more robust evidence to select the most effective treatment.

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Footnote

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