Editorial Commentary

Brain metastases in EGFR-positive non-small cell lung cancer: the way to the *sanctuary* becomes less winding

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In every day clinical practice, we find ourselves having to face the age-old problem of brain metastases (BM) in non-small cell lung cancer (NSCLC) patients. Despite the high incidence of cerebral metastasis, either at diagnosis or at relapse/progression, not many treatment options were available beyond radiotherapy for the management of these patients, regardless of EGFR mutational status. Furthermore, NSCLC patients with BM were historically excluded from clinical trials due to their poor prognosis, also related to the reduced intra cerebral drug availability caused by the mechanism of efflux pumps in the blood-brain-barrier (BBB) that contribute to create a pharmacological sanctuary (1,2).

It is well known how the therapeutic landscape and the clinical options in patients with advanced or metastatic NSCLC harbouring sensitive EGFR mutations deeply changed during the last 15 years, with a significant improvement of survival, reaching about 30 months (3).

Unfortunately, in these patients, the central nervous system (CNS) involvement still plays an important role with regards to survival and quality of life (QoL) (4,5).

The presence of BM is a crucial issue for patients with EGFR-positive NSCLC, considering a baseline incidence of about 25/30% (1,6-8), and a further risk of CNS progression of about 15–20% during EGFR TKIs treatment (1,9,10). Among patients with baseline pre-existing CNS involvements, the development of further BM is significantly more common and related with a significant worse outcome, compared with those with no prior BM (2-tears cumulative incidence: 47% *vs.* 11%; P=0.003) (1).

These data appear as critical due to the limited capability of first- and second-generation EGFR TKIs to penetrate the BBB, in fact the encephalon represents the first site of progression in approximately 20% of patients with advanced EGFR mutant NSCLC treated with erlotinib or gefitinib (9). Furthermore, during treatment with first generation EGFR TKIs, the rate of acquired T790M mutation in intracranial and extracranial metastases seems to be discordant (17% *vs.* 41%), suggesting a lower selection pressure in the CNS and therefore alternative mechanisms of resistance (11).

To date, a limited number of clinical trials evaluated the activity of EGFR TKIs in patients with BM. Available data from phase I/II or retrospective studies, show that first and second-generation EGFR TKIs present a limited BBB penetration, and consequently little activity towards present or de-novo formation of BM. Indeed, these agents are detected in the CSF only at low concentrations, differing from osimertinib that achieved a greater intracerebral concentration (12).

Interesting data about the activity of osimertinib in EGFR-positive NSCLC came out from the pooled analysis

of two-phase II trials (AURA extension and AURA 2) and from the AURA-3 phase III trial. In the pooled analysis based on 128 patients with CNS metastases, disease control rate (DCR) and overall response rate (ORR) were 92% and 54% respectively, regardless of prior radiotherapy to the brain (13). Following, the results of the phase III AURA-3 randomized clinical trials, confirmed the high activity of osimertinib in patients with T790M-positive NSCLC who progressed after a first-line with first or second-generation EGFR-TKIs, compared with a standard chemotherapy. In this randomized controlled trial (RCT), 116 patients were evaluated, showing a CNS ORR of 70% with a median CNS duration of response (DoR) of 8.9 months (14).

Recently, the results of the FLAURA trial, a randomized double-blind trial comparing osimertinib, a third generation EGFR TKs, with standard EGFR TKIs (gefitinib or erlotinib) switched on a new light for the treatment of EGFR-positive NSCLC with or without BM, suggesting a treatment strategy shift. In this trial, median progression-free survival (PFS) was significantly longer for patients receiving osimertinib versus standard EGFR TKI (18.9 *vs.* 10.2 months; HR =0.46; 95% CI, 0.37–0.57; P=0.001) (15).

Reungwetwattana *et al.* reported in *Journal of Clinical Oncology*, the results of a FLAURA preplanned subgroup analysis evaluating CNS response to osimertinib versus standard EGFR TKIs with CNS PFS as primary objective, conducted in patients with measurable and/or non-measurable CNS lesions on baseline brain scan. In the FLAURA CNS analysis, 128 patients (osimertinib, n=61; standard EGFR-TKIs, n=67) were evaluated. At the time of this analysis, median CNS-PFS resulted not reached in the osimertinib arm compared with 13.9 months with the standard of care (HR, 0.48, 95% CI, 0.26–0.86; P=0.014). CNS ORR in patients with ≥ one measurable CNS lesion, was 91% *vs.* 68% in favor of osimertinib, and 66% and 43% in patients with measurable and/or non-measurable CNS lesions, always in favor of osimertinib compared to first- or second-generation EGFR TKIs. CNS progression was 20% in the osimertinib arm versus 39% of patients in the standard EGFR-TKI arm, indicating a likely protective effect of osimertinib against CNS metastases (16). These data are very important; inasmuch the development of CNS metastases often has an important adverse impact on QOL, considering cancer-related symptoms and immediate or delayed toxicity of treatments. These results, confirming the high activity of osimertinib in first-line are destined to profoundly change our clinical practice, in particular for patients with BM, for several reasons. First of all, osimertinib is the first EGFR TKIs that shows a significant activity in improving response and survival in patients with CNS metastases, pretreated (T790M-positive) or naive to EGFR TKIs. In the pre-osimertinib era, whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) were the only ways to manage with momentary success CNS involvement due to NSCLC. Unfortunately, these different radiotherapic approaches are both associated with side effects and may not improve survival or QoL. Indeed, the issue of neurocognitive sequelae, although reduced in SRS compared to WBRT, is always to be considered particularly for patients with a life expectation greater than 20 months. In addition, the incidence of radionecrosis, steroid dependence and cognitive decline showed us the important drawbacks of these methods especially when compared to the activity and long-term safety of osimertinib in the same setting. The results of the CNS analysis of the FLAURA trial, suggests an upfront systemic therapy with osimertinib in patients with metastatic NSCLC harboring sensitive EGFR mutations and BM. This approach seems to be able to improve QoL, delaying radiotherapy that could be used at a later stage.

Of note, available trials with osimertinib have not been stratified for BM's presence and this element could be considered when further studies will be planned. Although osimertinib showed an important activity on BM, further improvements are needed in terms of response and survival for patients with leptomeningeal metastases (LM). In this setting, the BLOOM trial is ongoing to investigate if osimertinib at the double dosage of 160 mg daily, is able to improve outcomes in patients with positive cerebrospinal fluid (CSF) cytology and LM (17).

Thanks to these interesting findings, showing a very highly activity of osimertinib in EGFR-positive NSCLC, we are moving forward from the idea of the CNS as an unattainable sanctuary crossroads of many therapeutic valleys, to the treatment of lung cancer with brain metastasis as a challenge with great opportunity of success.

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Footnote

Conflicts of Interest: A Passaro served as consultant/advisory role for Astra Zeneca, Agilent/Dako, Bristol-Myers Squibb,

Merck Sharp & Dohme, Roche Genentech. F de Marinis served as consultant/advisory role for Astra Zeneca, Bristol-Myers Squibb, Merck Sharp & Dohme Roche Genentech, Pfizer and Takeda. The other authors have no conflicts of interest to declare.

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