Preface on "Emerging treatment options for brain metastases from non-small cell lung cancer"

Significant progress in the treatment of advanced non-small cell lung cancer (NSCLC) became first evident with the recognition that certain molecular subtypes (e.g., *EGFR*-mutant or *ALK*-rearranged tumors) could tremendously benefit from sequential treatment with small molecules tyrosine-kinase inhibitors (TKIs). In fact, an unprecedented median survival of more than 24 months has been reported in patients with oncogene-addicted disease when appropriate targeted therapies are used (1,2). More recently, the introduction of immunotherapy for use after failure of platinum-based chemotherapy has significantly improved the survival of some patients with no identifiable driver mutations (3), and future treatment landscape is rapidly evolving in order to incorporate immunotherapy in the front-line setting (4,5). Having made this preliminary remark, the downside of the improved survival experienced by patients has led to a significant increase in the spread of the disease to the brain, a phenomenon which already affects nearly one third of advanced NSCLCs at diagnosis. On the other hand, frequent use of serial CT scan or MRI of the brain for tumor (re-) staging has significantly contributed to the increased detection of brain metastases (BMs), especially when asymptomatic. Once developed, BMs predictably represent an important cause of morbidity and mortality in NSCLC patients, and counteracting strategies against BMs are crucial in this context.

Historically, local approaches with one or the combination of surgical resection (usually for single brain lesions), whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and stereotactic brain radiotherapy (SBRT) have to be considered standard approach for BMs (6). Nevertheless, concerns exist on the potential side effects of RT in good prognosis patients, which mainly include neurocognitive decline as long-term complication of WBRT or radionecrosis secondary to SRS. On the other hand, TKIs have consistently shown to induce regression of BMs from oncogene-addicted NSCLC, at a rate that is similar to that observed at extra-cranial sites. As a consequence, some oncologists may postpone WBRT for multiple BMs after one or more systemic treatments given sequentially (7,8), and clinical trials are ongoing in order to look specifically at the activity of TKIs in patients with asymptomatic or minimally symptomatic BMs (9). With regard to chemotherapy, antiangiogenic treatment and immunotherapy, all of these approaches have shown some activity against BMs as suggested by small phase II studies/case series/retrospective evaluations, but the evidence is much less compelling as compared with TKIs. That is mainly because NSCLC patients with BMs have been poorly represented so far in clinical trials with these agents.

In this special issue of *Translational Lung Cancer Research (TLCR)*, we touch on new developments of pharmacotherapeutic strategies for advanced NSCLC, specifically focusing on the present and future evolution of systemic treatments for BMs. Included manuscripts cover the following areas: TKIs (with or without RT), chemotherapy, antiangiogenic treatment and immunotherapy. In addition, one paper focuses on less invasive radiation techniques such as hippocampal sparing WBRT. Finally, another review reports on whether criteria exist for defining the response of BMs to treatment, with the final intent of providing comparative measurement of effectiveness across multiple trials with different drugs. We really thank the authors for their vital contribution to this special issue, and hope that all readers involved in the treatment of NSCLC will find this issue of valuable interest and keep it as valid reference for their work.

References

- Lin JJ, Cardarella S, Lydon CA, et al. Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. J Thorac Oncol 2016;11:556-65.
- 2. Chiari R, Metro G, Iacono D, et al. Clinical impact of sequential treatment with ALK-TKIs in patients with advanced ALK-positive non-small cell lung cancer: results of a multicenter analysis. Lung Cancer 2015;90:255-60.
- Gridelli C, Besse B, Brahmer JR, et al. The Evolving Role of Nivolumab in Non-Small-Cell Lung Cancer for Second-Line Treatment: A New Cornerstone for Our Treatment Algorithms. Results From an International Experts Panel Meeting of the Italian Association of Thoracic Oncology. Clin Lung Cancer 2016;17:161-8.
- 4. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell

Lung Cancer. N Engl J Med 2016. [Epub ahead of print].

- Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, nonsquamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
- 6. Metro G, Chiari R, Ricciuti B, et al. Pharmacotherapeutic options for treating brain metastases in non-small cell lung cancer. Expert Opin Pharmacother 2015;16:2601-13.
- 7. Ricciuti B, Chiari R, Chiarini P, et al. Osimertinib (AZD9291) and CNS Response in Two Radiotherapy-Naïve Patients with EGFR-Mutant and T790M-Positive Advanced Non-Small Cell Lung Cancer. Clin Drug Investig 2016;36:683-6.
- 8. Metro G, Lunardi G, Bennati C, et al. Alectinib's activity against CNS metastases from ALK-positive non-small cell lung cancer: a single institution case series. J Neurooncol 2016;129:355-61.
- A Phase II Study to Evaluate the Efficacy and Safety of Oral Ceritinib in Patients With ALK-positive NSCLC Metastatic to the Brain and/or to Leptomeninges (Ascend-7). Available online: https://clinicaltrials.gov/ct2/show/NCT02336451 (Last accessed 15 September 2016).



Giulio Metro, MD



Rita Chiari, MD

Giulio Metro, MD Rita Chiari, MD

Division of Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, 06156 Perugia, Italy. (Email: giulio.metro@ospedale.perugia.it; rita.chiari@ospedale.perugia.it) doi: 10.21037/tlcr.2016.12.04 Conflicts of Interest: The authors have no conflicts of interest to declare. View this article at: http://dx.doi.org/10.21037/tlcr.2016.12.04

Cite this article as: Metro G, Chiari R. Preface on "Emerging treatment options for brain metastases from non-small cell lung cancer". Transl Lung Cancer Res 2016;5(6):561-562. doi: 10.21037/tlcr.2016.12.04

© Translational lung cancer research. All rights reserved.

562