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LETTER TO THE EDITOR

WILEY

Response to: Successful afatinib rechallenge in a patient with non-small cell lung cancer harboring EGFR G719C and S768I mutations

The genetic landscape of nonsquamous non-small cell lung cancer (NSCLC) includes specific mutations involving primarily epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and the proto-oncogene ROS1. With regard to *EGFR*, exon 19 deletion and exon 21 (L858R) mutations are most frequently detected and correlate with a prolonged and significant response in patients to first-line osimertinib.[1]

"Uncommon" *EGFR* mutations have been previously reported to represent 18% of all *EGFR* mutations[2] and large retrospective[3] and perspective studies[4] have confirmed their major sensitivity to first-line treatment with afatinib. They include single or complex punctiform mutations of the exons 18, 19, 20 and 21 and amino acidic insertions of exon 20.

We read with interest the paper by Masuda and colleagues reporting the case of a substantial response to afatinib rechallenge in a patient affected by metastatic lung adenocarcinoma harboring *EGFR* complex uncommon mutations.

We report the case of an 81-year-old patient who was referred to our center after a diagnosis of lung adenocarcinoma with brain metastases. Disease stage was clinical T4N2M1 according to the eighth edition of the International Association for the Study of Lung Cancer (IASLC). *EGFR* mutational analysis revealed concomitant G719S exon 18 and S768I exon 20 mutations.

The patient who was a previous smoker of 40 pack/years started first-line afatinib at a full dose of 40 mg in July 2020.

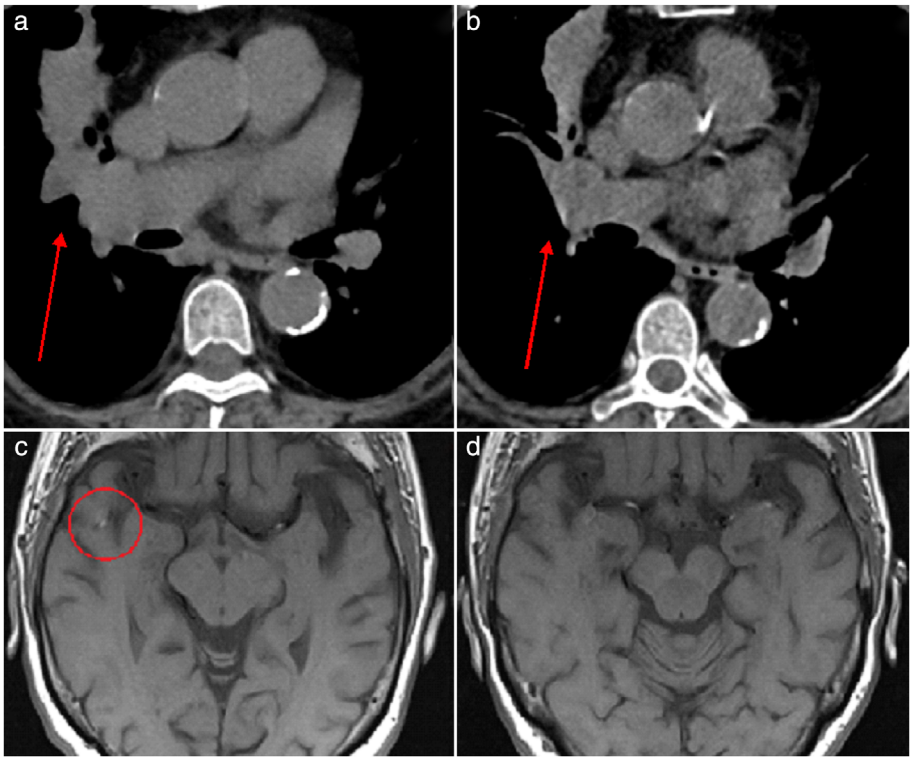

FIGURE 1 Mediastinal and brain radiological response upon treatment with afatinib. Comparison between CT scans of (a) June 2020 and (b) October 2020 and between (c) brain MRI of July 2020 and (d) February 2021

Due to disabling and refractory skin toxicity in the patient, the afatinib dose was reduced to 30 mg in September. The first radiological restaging in October showed a partial pulmonary and nodal disease response, while stable mediastinal disease was reported following a thoracic scan in February 2021. In the same month, the recurrence of severe skin toxicity necessitated a further afatinib dose reduction to 20 mg per day. The brain nuclear magnetic resonance imaging (MRI) of February 2021 revealed a complete intracranial response. Figure 1 shows the pulmonary and intracranial response over time upon treatment with afatinib.

Despite some clinical and pathological differences between the two cases, such as ethnicity, smoking habits, disease stage, and temporal occurrence of concomitant G719S and S768I mutations, we consider that the persistent and significant response to first-line afatinib in such a complex scenario is worthy of being underlined. Despite severe and relapsing skin toxicity, the patient is currently receiving the TKI at a 20 mg dose per day with satisfying tolerability.

The main limitation of our report was the relatively short period of follow-up compared to the case by Masuda et al., but our patient did not progress precociously after commencing afatinib.

Both the cases testify a significant response to the TKI for a double uncommon *EGFR* mutated lung adenocarcinoma, providing a rationale for afatinib treatment not only for single uncommon mutations but in even more complex scenarios.

Given that *EGFR* exon 20 mutations are associated with worse outcomes compared to 18 exon and 21 exon mutations during treatment with afatinib,[4] identifying the main driver becomes challenging when they occur concomitantly.

ACKNOWLEDGMENTS

We thank the patient that provided their informed consent for the submission of the manuscript. The presentation and description of the case conforms to the standards of the Helsinki Declaration.

CONFLICT OF INTEREST

M. Russano received speakers' and consultants' fee from Boehringer Ingelheim. D. Santini received honoraria from advisory board by Boeringher. The other authors declare no conflict of interest.

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