Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-21-888

Reviewer A

Authors described two cases of EGFR-RAD51 gene fusion NSCLC with a mini-review.
The fusion gene was detected by FoundationOne DX1 assay. Thus, authors advocated a broader molecular profiling in young or never smoker NSCLC patients without detectable molecular aberration using standard NGS panels. I agree with the opinion. Their case series as a mini-review are educational and beneficial for pulmonary oncologists.

Reply: Thank you for taking time to revise our work.

Reviewer B

This is an interesting and well-written report of two cases with oncogenic EGFR fusions successfuly targeted by available EGFR TKI. I have a couple of minor only comment:
1. since this is the first published case of successful osimertinib treatment for a NSCLC patient with EGFR fusion, the authors could also make the point that osimertinib could be the preferable option, especially if there is brain involvement, like in the 1st reported patient. Tolerability is also better than with earlier EGFR TKI.
2. The FoundationOne panel also reports the TMB. Could you please add the TMB values for both tumors to your manuscript? One would expect a low TMB here, maybe even lower than 4.5 mut/Mb (=the mean value for EGFR+ NSCLC, compared to 9.5 mut/Mb for WT NSCLC), because fusion-driven NSCLC, like ALK+ and RET+ have the lowest TMB among all NSCLC (<3mut/Mb), and lower than EGFR-driven tumors. On the other hand, TP53-mutated tumors, like the 2nd case, have a higher TMB than TP53-wild type tumors and worse outcome (i.e. shorter duration or response to TKI).

Reply 1: Thanks for pointing this out. We added a sentence in the discussion (see page 6, lines 163-164).
Reply 2: We added TMB values of both cases (see Page 4, line 102 for case #1 and Page 4, lines 118-119 for case #2).

Reviewer C

The authors describe 2 novel cases of NSCLC patients presenting an EGFR-RAD51 gene fusion.
The cases are well described, and the previously reported cases are collected in a Table.
Minor comments:
-The number of the exons (EGFR and RAD51) that are fused must be indicated.

-Only one of these patients has been treated with osimertinib. The abstract must be clarified (lanes 32-33).
-Table 1. Patient 8 should be characterized as Caucasian
-The legend to figures (1 & 2) must be completed with the case number

Reply 1: thanks for the comments. We indicated the number of exons in the introduction (page 3, line 77-78)
Reply 2: we clarified that point in the abstract (see page 2, lines 41-43)
Reply 3: we corrected case 8 in table 1.
Reply 4: we completed the legends adding the case number they refer to.

Reviewer D

Federico and colleagues report a case series of the patients with EGFR-RAD51 gene fusion NSCLC responsiveness to different generations EGFR-TKIs. This manuscript is generally well-written. I have a few comments.

In line 24:
“Most NGS panels cannot detect these alterations" seems to be an exaggeration, since many of the NGS panels in use today can detect unknown fusion genes.

In Table 1:
The coexisting genetic mutations other than EGFR-RAD51 are very interesting. I think what the reader is interested in is the association between the presence or absence and the amount of this coexisting genetic mutation and the effect of EGFR-TKIs. If possible, data on PFS would be even better.

Reply 1: thanks for your comments. We modified that sentence in the abstract (see page 2, line 35).
Reply 2: we agree that PFS data would be even more interesting than objective response ones; however, we decided not to report them since they were not available in many cases.