Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-23-680

Reviewer A

The brief commentary about the role of EGFR mutations in prediction of clinical response for TKIs administration represents a technically correct and timely relevant manuscript suitable to be accepted on this journal after minor considerations.

Comment 1: In the text, I would recommend modifying the "main EGFR deletion" suggesting that these ones are more frequent EGFR deletions.

Reply 1: According to the reviewer's suggestion, we described E746-A750 as a main deletion.

Changes in the text: P4, line 5, 12 and 18.

Comment 2: In the text, I would also encourage the authors to discuss about main technological approaches available to test EGFR deletions.

Reply 2: The EGFR deletions were detected by next-generation genome sequencing in a multicenter, retrospective cohort study based on an international cancer registry conducted by AACR. No further description was found in the report by Grant et al (Ref 13).

Comment 3: In the text, please, could the authors report amino acids change following standardized nomenclature system (p.L858R)

Reply 3: According to the reviewer's suggestion, we changed the description of T790M, L858R, G719X, L861Q, and S768I mutation as p.T790M, p.L858R p.G719X, p.L861Q, and p.S768I, respectively.

Changes in the text: P2, Lines 11, 13, and 17.

Reviewer B

The Editorial Commentary by N. Fujimoto is very well written and properly highlights and elaborates further on the main conclusions of the article by Grant et al. in CCR 2023;29:2123-30.

I only have two suggestions (not at all criticisms) to the Author aimed at increasing even more the nice impact of the Editorial on the TLCR's readership:

Comment 1: To consider changing the title to something that explains more what the terms "major" and "minor" indicate. Indeed, the two adjectives are in the commentary referred to both the frequency (i.e., common EGFR mutations = "major" and uncommon EGFR mutations = "minor") and the response of the different EGFR mutations to EGFR-TKIs. In this respect, Fujimoto rightfully cites data from previous studies and those presented now in the article by Grant et al. indicating that uncommon "minor" mutants have a more variable and lower/shorter response to these drugs. There is a risk that by reading the title "Major or minor? Subtypes of EGFR exon 19 deletion mutations" one does not capture the whole focus of the Commentary by the Author and may become even uncertain as to whether major and minor are referred to the different sizes of the EGFR ex19dels rather than the fact that they are common/uncommon and TKI-responsive/less TKI-responsive.
Reply 1: We agree that the term "major" and "minor" could cause confusion. I deleted those terms throughout the manuscript. Instead of 'major' and 'minor', I used 'common' and 'uncommon' to describe 19Dels.
Changes in the text: P2, Line 12 and 15, P5, lines 7 and 14, and P7, line 14.

Comment 2: To briefly comment on possible genomic co-alterations that may accompany EGFR mutations in NSCLC and may affect the response to treatment with EGFR-TKIs. Indeed, these co-alterations do not seem to be taken into account in the discussed article by Grant et al. in CCR, nor in the Commentary by Fujimoto. Yet, while the most common EGFR mutations p.L858R and ex19del p. E746-A750 mostly occur in non-smokers, the uncommon ("minor") EGFR mutations can be detected in a significant fraction of smokers and they may not infrequently be accompanied by co-alterations in other genes (for ex. TP53 mutations) that may have an impact on the sensitivity to EGFR-TKIs.
Reply 2: According to the reviewer's suggestion, I added description of concomitant alterations. A paper by Hong S et al. was cited as reference 25.
Changes in the text: P7, lines 7-11.