Differences in the Epidemiology of Rare *EGFR* Mutations in Different Populations

In Response:

We thank Elghissassi et al. for their comment on our study.[1] This is a great opportunity to further discuss the differences in the epidemiology of rare epidermal growth factor receptor gene (*EGFR*) mutations in different patient populations.

The complete coverage of exons 18 to 21 and the *EGFR* analysis in patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations—as we all agree—could very well be one reason for the increased rate of rare *EGFR* mutations. Importantly, it seems that smoking status can also have a great—and indeed patient population–dependent—impact on the rate of rare *EGFR* mutations. Unfortunately, in Hungary as well as in our patient cohort, the number of current smokers is very high, which could lead to enrichment for rare *EGFR* mutations. Interestingly, unlike in white cohorts, the rare *EGFR* mutations in Asian populations do not seem to be associated with smoking. Notably, the findings of Errihani et al. suggest that the epidemiology of such mutations in Morocco has greater resemblance to that in the Asian population than to that in white study cohorts.[2]

We cannot emphasize enough that the lack of identical methods makes side-by-side comparison of the different studies very difficult. A number of commercial mutation analysis methods provide very high sensitivity, but only for a preselected set of molecular alterations that might enrich for classical *EGFR* mutations.[3] In contrast, direct (Sanger) sequencing has a lower sensitivity but can identify novel mutations. Indeed, a number of rare mutations described in our study were reported in lung adenocarcinoma for the first time. Of note, we cannot rule out that some of the mutations might have been artefacts because this possibility has been discussed in a previous exchange of comments.[4,5]

One of the major findings of our study is that the absolute number of rare EGFR mutations in certain patient populations can be rather high, and thus, their clinical relevance needs to be studied further. Moreover, the term *rare EGFR mutation* describes a very heterogeneous group of molecular alterations, and as a result, the clinical relevance of each individual mutation needs to be evaluated separately. Therefore, reporting the clinical relevance and epidemiology of all *EGFR* mutations for different patient populations will lead to more accurate and evidence-based therapy decisions in the future.

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