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Response to comment on "Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour-agnostic indications"

We thank Sullivan and Hatswell[1] for their interest in the analysis from our article published in the April 2021 issue.[2] They raised a number of interesting points that we would like to address.

Firstly, although the point that "When considered as a proxy for current care, prior-line datasets are generally limited in that they exclude both the most- and least-favourable of the target group, with bidirectional implications for bias that cannot be adjusted for and must be assessed carefully case-by-case" is an important consideration, this equally applies in all clinical trial-based analyses of effectiveness, including within randomised controlled trials. As highlighted in our discussion, "Our analysis comprises a small number of clinical trial patients who may not be representative of real-world patients with NTRK fusion-positive cancer". Follow-on, real-world studies are needed to further explore the effectiveness of study drugs in these rare populations. However, these analyses are limited as, by their nature, they will be unable to inform initial decisions of health technology assessment bodies.

Secondly, we fully agree that "A patient's prognostic profile is definitively different across treatment lines - age, number of prior therapies, last therapy received and response to last therapy are a few typical prognostic factors that definitively vary with treatment line", and that this is important to fully comprehend the results of intrapatient analyses. To aid the interested reader in contextualising our interpretation of the data, we provided a complete list of prior systemic therapies received by the patients (Supplementary Table S1) and a description of the evolution of response to prior therapy by line (Supplementary Figure S1). With regard to age and number of prior therapies received, it is clear that these increase with each subsequent line of therapy, so any growth modulation index (GMI) analysis could be assumed to be conservative for these factors.

Additionally, we have shown in Figure 2 that time to discontinuation (TTD) and progression-free survival are reasonably similar, supporting our decision to use TTD as a proxy for time to progression (TTP) in the absence of more comprehensive progression measures in our prior therapy dataset. Moreover, our main recommendation was that for future single-arm trial designs, intrapatient comparisons should be pre-planned and include the "collection of detailed prior therapy data and responses", in order to overcome these limitations and further increase the value of these analyses as timely supporting evidence for informing decision makers.

Finally, the differences that we highlighted between our study and the larotrectinib GMI analysis reported by Italiano et al.[3] primarily related to the study population. Contrary to our cohort, the larotrectinib population included paediatric patients and patients who had not progressed on prior therapy. It is unclear how these differences would affect the results other than, as we noted in our article, potentially artificially shortening TTP on prior therapy if it was not related to progression.

Overall, we believe this transparent analysis clearly shows the feasibility of intrapatient analyses in a tumour-agnostic, single-arm setting even when planned retrospectively. The timely availability of such analyses gives value to this approach in informing decision makers before the generation and assessment of real-world evidence.

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Available online xxx

https://doi.org/10.1016/j.esmoop.2021.100307
DOI of original article: https://doi.org/10.1016/j.esmoop.2021.100072

FUNDING

None declared.

DISCLOSURE

MGK has participated in advisory boards for Bayer, Roche, Janssen, Octimet, Achilles Therapeutics, and Seattle Genetics; undertaken consultancy for Roche and Janssen; received travel grants from AstraZeneca, BerGenBio, and Immutep; and received research grants from BerGenBio and Roche. IB is an employee of Roche and holds shares in Roche.

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