scenarios; however, these do not overcome the inherent limitations of single-arm studies with vastly different patient characteristics. The authors’ conclusion that “larotrectinib provided improved life-year and quality-adjusted life-years outcomes compared to entrectinib” is an inappropriate extrapolation using a limited dataset and does not provide robust information to the readers.

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DISCLOSURES

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THE AUTHORS RESPOND

We thank Ogale et al. from Roche/Genentech for their interest in our recent publication “The Potential Long-Term Comparative Effectiveness of Larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer.”¹ They note many valid limitations of preliminary simulation modeling to understanding the potential comparative effectiveness of emerging therapies, most of which were discussed in our original publication. The new issues raised by Ogale et al. can be grouped into 2 main points, which are addressed as follows.

First, Ogale et al. suggest that it is problematic to publish preliminary simulation-based comparative

effectiveness assessments that extrapolate data from small samples. It is important to note that our publication in JMCP was categorized as a “Brief Report”—a category of manuscript that “is reserved for small or pilot studies that have limited generalizability or descriptive studies that may not test a hypothesis or have comparative study groups.”² We believe that our publication is well aligned with the scope of that category.

Furthermore, Ogale et al. note alternative approaches to assess comparative effectiveness but do not critically review their feasibility. One approach that was suggested is network meta-analysis, but it is unclear to us how such an analysis would be conducted when larotrectinib and entrectinib have only been evaluated in single-arm phase 1/2 trials. Additionally, the authors suggest matching adjusted indirect comparison as an alternative analytic approach, but such matching would yield limited benefit in larotrectinib and entrectinib non-small cell lung cancer (NSCLC) samples of 12 and 10, respectively.¹

Exploring the shortcomings of these alternative study designs help to highlight the rationale and need for the preliminary comparative effectiveness modeling study that we conducted. Nonetheless, there are many limitations to this approach, which we discuss in our publication. Our study is intended to provide initial insights into the potential comparative effectiveness of larotrectinib versus entrectinib until higher levels of evidence can be developed.

Second, Ogale et al. characterize the interpretation of our study results as “strong,” present an inaccurate quote to support this assertion (the underlined text in the following excerpt is omitted), and omit qualifying language before and after the quote that does not support the

assertion. We urge readers to critically evaluate the diction of our conclusion in the publication and assess whether it is accurately represented in Ogale et al.'s letter. The text in question is as follows:

Among TRK inhibitors for treatment of metastatic NSCLC, larotrectinib is estimated to provide improved life-year and QALY outcomes compared with entrectinib based on parametric extrapolations of in-trial survival data. Our analysis is limited by a paucity of NSCLC-specific data on entrectinib OS; the small sample size of patients with NSCLC in source trials; and a naive, direct (cross-trial) comparison. Future studies should re-evaluate the comparative effectiveness of larotrectinib and entrectinib as greater numbers of patients are treated and as long-term survival data mature.¹

As stated in the original publication, the objective of our study was to “use available evidence to extrapolate and compare expected life-years and QALYs for both TRK inhibitors in metastatic NSCLC to inform initial stakeholder considerations about potential comparative effectiveness.”¹ Our conclusions about potential comparative effectiveness are consistent with the short-term in-trial survival outcomes for larotrectinib

and entrectinib in NSCLC, as well as survival outcomes in pooled tumor types included in the respective clinical trials. We stand by our approach and conclusions and urge Ogale et al. to carefully consider the role of simulation modeling to provide timely insights about potential comparative effectiveness in cases where alternative comparativeness effectiveness study designs are not currently feasible.

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