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Letter re: 'Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour-agnostic indications'

We read with interest the article by Krebs et al.[1] To convey the clinical value of entrectinib across its tumour-agnostic licensed indication, the authors report and interpret within-patient and within-cohort comparisons with prior line of therapy using their pivotal phase II trial (clinicaltrials.gov identifier: NCT02568267) in lieu of randomised, controlled trial data.

We commend the extent of data reported in an open-access forum and see strength in this application in the level of prior therapy data available, although quality issues with prior-line data collection in NCT02568267 is a limitation, as recognised by the authors. However, we would like to draw attention to further issues which we feel are vital for interpretation of the results, but only partly captured in the authors' Discussion.

Although useful in the absence of more robust comparator data, any comparison with previous line of therapy is intractably confounded by sample selection, an essential consideration for interpretation. As we covered in our general exploration of comparisons with previous line of treatment,[2] those patients who have prior line of therapy data available upon entry into NCT02568267 were both prognostically favourable enough to survive with sufficient health to meet clinical trial entry requirements, and simultaneously prognostically unfavourable enough to be candidates for as-yet-unlicensed treatment. 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.

Further, there is issue in the authors' assertion that 'by using patients as their own control, intrapatient analyses also eliminate between-patient variability'. 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. In tumour-agnostic medicine, the implications of the biases highlighted here are complicated further, as they are influenced by the natural history of each disease in question.

We briefly note two additional issues with the approach and interpretation that we feel are important for inference, without the space to explicitly critique each issue here: the comparison of current progression-free survival with prior time to discontinuation (TTD), when current TTD versus prior TTD has clear internal consistency advantages; the authors' interpretation of the likely bias in their censoring points, and between their entrectinib intrapatient comparison and the elsewhere published intrapatient comparison for larotrectinib.[3]

Again, we are grateful for the contribution of Krebs et al.; however, in lieu of a 'like for like' comparison of endpoints, and a more balanced and comprehensive assessment of potential biases, we do not share the authors' conviction that results presented 'show the value and feasibility of using an intrapatient analysis to assess comparative effectiveness of tumour-agnostic MTAs in a heterogeneous patient population.' To achieve this we feel further analyses and information are required.

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