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Appropriate Analysis of Duration of Response Data in Cancer Trials

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To the Editor

We read with interest the recent Original Investigation by Reardon et al[1] reporting results of the CheckMate 143 randomized clinical trial, which compared nivolumab with bevacizumab among patients with recurrent glioblastoma. For the end points of overall survival, progression-free survival, and objective response rate, nivolumab was either inferior or neutral to bevacizumab. The only signal potentially favoring nivolumab was from the duration of response (DOR),[1] as underscored in the accompanying Editorial.[2] The reported median DORs were 11.1 and 5.3 months for nivolumab and bevacizumab, respectively. However, this comparison might not be appropriate because these 2 medians were based on the DORs among responders only, and the objective response rates of the 2 treatment groups differed substantially: 7.8% for nivolumab vs 23.1% for bevacizumab.[1]

Duration of response is becoming an increasingly important end point for evaluating cancer treatments in all stages of clinical studies. Effective therapies should not only promote a rapid response but also keep patients responding for a long duration. However, the conventional DOR analysis is descriptive and based on responders only. Without including data from nonresponders, this approach can result in biased inferences about the DOR when, as in the present case, the cumulative response rates of the treatment groups are markedly imbalanced. To this end, one could consider an ineffective treatment that only achieves response in patients with low disease burden at baseline and who were less likely to experience progression. For this ineffective treatment, the median DOR among the few responders might misleadingly appear impressive, yet most patients would not benefit. Even if we are interested in the DOR among responders only, the standard approach of estimating the median DOR using Kaplan-Meier curves is not valid owing to the presence of dependent censoring. Dependent censoring arises because the DOR and its censoring time are both measured from the time of initial response and are therefore correlated. These issues have

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been discussed previously, and a simple procedure for estimating the mean DOR while including both responders and nonresponders was presented in a recent Research Letter published in *JAMA Oncology*.[3] For the current study,[1] if we incorporate data from all patients, then the median DORs would be zero for both arms. On the other hand, we can assess the treatment effect using the mean DOR, which may be implemented via R code for estimating the probability of being in response in a given time window (available at https://web.stanford.edu/~lutian/pdf/PBIRcode.R). We encourage investigators to consider applying mean DOR analysis for ongoing and future trials of objective responses in the treatment of this deadly cancer.

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