Reply to M. Horiguchi et al

We thank Horiguchi et al[1] for their thoughtful correspondence regarding our article[2] and their observation that the profile of the Kaplan-Meier curves is suggestive of nonproportional hazards. This is indeed the case, but the statistical evidence for this is not conclusive. In our prespecified statistical analysis plan for the study, we did test the assumption of proportional hazards by fitting a time-varying covariable. We omitted this detail from the methods described in the article; however, this test for lack of proportional hazards was not statistically significant (two-sided $P = .13$) and, therefore, was not sufficient to indicate that we should not proceed with our plan to analyze the results under the proportional hazards assumption.

The authors are correct to state that deviation of the study data from the assumption of proportional hazards will affect the statistical power to detect treatment differences, and we did conduct a sensitivity analysis using a restricted mean survival time (RMST) approach.[3] After adjusting for stratification factors, the RMST was 1.5 months lower in the pazopanib arm compared with paclitaxel arm (80% CI, −2.7 to −0.3 months; unadjusted one-sided $P = .96$, on the basis of a truncation time of 17.9 months). This is stronger evidence for the superiority of paclitaxel than using the proportional hazards approach, which had a P value of .89. We note in passing that we used 80% CIs to be consistent with the stated significance level for the study (10% one-sided).

We disagree with the statement that "it is puzzling that for almost all cancer studies…there were no formal comparisons performed between two median OS [overall survival] times." The median overall survival is a useful summary statistic for the individual Kaplan-Meier curves, but for the vast majority of studies, the primary analysis is based on the comparison of event rates over the whole follow-up period, with the corresponding summary statistic being the hazard ratio. The suitability of this approach depends, as previously noted, on the assumption of proportional hazards, but if this assumption is not fulfilled, we would rather fall back on the RMST approach rather than a comparison of medians, because this makes greater use of all the data available. In this particular situation, the comparison of the medians corresponds to the point where the difference between the curves is greatest and could be criticized as data prompted and therefore biased.

We do agree that it can be difficult to represent the difference between survival curves in a single summary measure when proportional hazards do not apply. In these situations, we do think that RMST is a useful alternative (although not ideal because it depends on follow-up time) and provides a better approach than, say, a landmark analysis or a comparison of medians because it makes greater use of the information available. However, we finally note that none of the points mentioned affect the fundamental finding of the study that, regrettably, pazopanib conclusively had no greater efficacy than paclitaxel in this setting.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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