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Response to Sarayani et al Regarding Article, "Association Between Immune Checkpoint Inhibitors with Cardiovascular Events and Atherosclerotic Plaque"

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In response:

We thank Sarayani and colleagues for their interest in our recent publication [1] as they raise important issues related to the difficulty in studying a population with predominately late-stage cancer on a relatively novel cancer therapy.

Within the limitations of a retrospective design, we believe we adequately captured outcomes in the control group or prior to immune checkpoint inhibitor (ICI) start. Relevant events were captured by individual chart review and the median number of visits per patient in both cohorts was >40. We think it unlikely that a major cardiac event such as bypass surgery, a stent, myocardial infarction, or a stroke would not be referenced in any of those encounters. Additionally, the event rate among the control group is similar to the event rates noted in a large cohort of contemporary cancer patients.[2] The competing risk of death is an important one. Patients were censored at the first event or last date of follow-up. We originally presented expanded data in subgroups restricted to those who survived 6 months and one year with similar findings. In additional steps, we repeated our analysis including only patients that survived during follow-up. The hazard ratio of having an event after ICI treatment remained increased (6.61, 95% CI: 4.31–10.16). Moreover, we calculated cause-specific hazards using a cause-specific Cox proportional-hazard model and a flexible parametric survival model (Royston-Parmar model). We also calculated sub-distribution hazards by using a competing-risks regression model (Fine and Gray method) and a flexible parametric competing-risks regression model in which death was included as a competing risk.[3] The hazards remained increased using all 4 approaches. For example, the sub-distribution hazard in the competing risks analyses were 2.53 (95% CI: 1.94–3.29) and 2.96 (95% CI: 2.24–3.92). Dr. Sarayani and colleagues also ask whether a comparison of time to

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event before and after ICI initiation produces bias and whether natural history may be a contributing factor. However, our approach included not only a Cox proportional-hazard approach but also a Poisson regression. We believe it unlikely that natural history explains the increase in events with an ICI as large cohort studies among traditionally higher risk patients have not noted such a change in atherosclerotic events over such a relatively short period.[4] The findings of an increase in clinical events are also supported by our mechanistic study which showed a marked increase in the rate of plaque progression.[1]

We again thank Sarayani and colleagues and acknowledge many of their concerns with the challenges of finding an optimal control group as we noted in our limitations. The ideal design is where patients would be randomized to an ICI or equivalent-efficacy cancer therapy, where the equivalent cancer therapy does not lead to accelerated atherosclerosis or related events, but has a similar cancer efficacy. However, in the absence of such a study, we believe our results remain robust and we think that our study should be considered as a starting point for such further investigations. Related, we are currently planning a prospective mechanistic study among a sub-group with melanoma who meet many of these criteria. Until then, our understanding of the potential cardiac toxicities of ICIs and their treatment remained limited but needs to improve.[5]

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