HHS Public Access

Author manuscript

*JAMA Oncol*. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

*JAMA Oncol*. 2019 August 01; 5(8): 1226. doi:10.1001/jamaoncol.2019.1187.

# Survivorship Bias in Analyses of Immune Checkpoint Inhibitor Trials

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## To the Editor

In a retrospective analysis of 137 patients with advanced non–small cell lung cancer treated with nivolumab or pembrolizumab monotherapy, Toi et al[1] observed larger progression-free survival and overall survival probabilities among 66 patients who developed immune-related adverse events (irAEs) compared with 71 who did not. It is possible that the comparison is biased. The 2 groups are compared with regard to survival from the start of treatment, but the occurrence of irAEs is obviously not determined at baseline but later during follow-up. Patients with irAEs must have survived from treatment initiation to the time of the irAE, but there is no such requirement for patients without irAEs. Toi et al[1] reported a median onset of irAEs of 4.7 weeks. By design, the survival curves will be more favorable to patients with irAEs and less favorable to those without irAEs. This survivorship bias is identical to the time-to-response bias in oncology studies comparing responders and nonresponders.[2–4]

Other statistical methods are needed to conduct an unbiased comparison. For example, the landmark method involves a priori selection of a time point, or landmark time, for the classifying criteria and outcomes.[2–4]In the present case, one could ignore all irAEs after the specified time point and all progressions of disease or death before the specified time point. Kaplan-Meier curves can still be used to display survival conditional on the occurrence of an irAE. Alternative approaches are the Cox proportional hazards model with a time-varying covariate or a marginal structural Cox model.[5] These methods would address the time-varying group membership of patients with and without irAEs. A limitation of the landmark method is the exclusion of patients, although the Cox models would retain all patients.

We would like to know if differences in survival are still apparent when addressing this bias.

## Conflict of Interest Disclosures:

Ms Conner was supported by the National Institute of General Medical Sciences Interdisciplinary Training Grant for Biostatisticians (T32GM74905-14). No other disclosures were reported.

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