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LETTER TO THE EDITOR

Model-Based Estimates of Tumor Growth Inhibition Metrics Are Time-Independent: A Reply to Mistry

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Mistry[1] states that "One of the key forms of bias when using covariates that are time-dependent, which TTG and in fact any model-derived metrics are, is time-dependent (immortal time) bias." The authors contend that model-derived TGI metrics are not time-dependent and not subjected to immortal time bias. Time to growth (TTG) and other TGI metrics are estimated based on TGI profiles with a nonlinear mixed effect model and not observed (latent variables). As soon as a patient enters a clinical trial and has gotten one postbaseline tumor size measurement (sum of the longest diameters of target lesions per RECIST response evaluation criteria), i.e., typically at the end of the second cycle of treatment (6 or 8 weeks, depending on the dosing schedule), this patient is evaluable for TGI[2] and TGI metrics can be univocally calculated from estimated individual TGI model parameters (see, e.g., supplementary data from ref. 2). Estimates of TTG can take any value independent of patient death; TTG can be estimated after death or tumor size observation time span, as previously commented. [3] This is the case when a patient dies, drops out of the clinical trial, or clinical progression due to other reasons than target lesions. In the extreme case where observations are too sparse, estimated TGI metrics are prone to parameter estimate shrinkage, which cannot create spurious correlations with overall survival.[4] Immortal time bias occurs in observational pharmacoepidemiology studies when cohort assignment depends on a time-varying covariate (see figure 1 in ref. 5). In oncology drug development studies, cohorts are clearly assigned at the start of treatment, estimated TGI metrics are not time-varying observed values that are used to perform cohort assignments, hence they are not subject to immortal time bias.

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