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Response to: Correspondence on "Early dynamics of clinical and laboratory parameters predict primary refractory disease in patients with metastatic urothelial carcinoma receiving atezolizumab" by Gao *et al*

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Gao *et al*[1] raised concerns about our recently published article[2], which we respond to in this letter. Note that we developed our model to be a "proof of principle" (as mentioned on page 1 of our article) not ready for clinical implementation, but developed for research purposes—also given the fact that atezolizumab is no longer used for the treatment of metastatic urothelial carcinoma. As stated in the manuscript, "Validation in larger independent cohorts […] is required" (page 1) and our model's "suggestions require validation in a better controlled setting" (page 9).

First, Gao *et al* remark that the inclusion of programmed cell death ligand 1 (PD-L1) "overlooks the dynamic changes in PD-L1 expression during treatment" and state that "baseline measurements alone may not accurately predict treatment outcomes". The dataset of the IMvigor211 trial did not include dynamic data of PD-L1 expression, which we discussed in the manuscript while noting that "granular longitudinal PD-L1 measurements" would be desirable (page 9). We also did not claim that static PD-L1 measurements alone accurately predict treatment outcomes: PD-L1 expression is only one component in a large model. Indeed, we explicitly discuss that the dynamic nature of PD-L1 expression is known to limit its predictive power (page 9).

Next, Gao *et al* remark that using least absolute shrinkage and selection operator (LASSO) may lead to overfitting and suggest employing "more advanced regularization methods […] to improve variable selection stability" and suggest further that "external validation in independent cohorts" is needed. The aim of our study was to explore how multivariable models which explicitly consider early-on-treatment (EOT) dynamics can be used for predicting treatment failure and to identify promising candidates among those variables for future exploration in such predictive models. Our choice of LASSO was motivated by the desire for a sparse model and a focus on variable selection, and we thus did not opt for more stringent regularization. We see no reason why the sample size of this study, 902 patients in the baseline model and 483 in the EOT model, would be considered too small for the feature set with LASSO and lead to overfitting, which LASSO is meant to help avoid. To support their claim, Gao *et al* note that our model has a "variable-to-sample ratio exceeding 1:14". While Gao *et al* do not cite any criteria supporting a threshold of 14, there are pertinent studies which suggest that arguments for such thresholds are weak[3] and that other recommendations of between 10 and 20 samples per variable serve mainly as a "rule of thumb". We thus disagree that our model is significantly at risk of overfitting merely due to the variable-to-sample ratio. Gao *et al* cite a single study[4] regarding the stability in high-dimensional settings which contains its own share of statistical issues. For instance, that study[4] applies backward elimination after using LASSO—despite LASSO already being designed to select relevant features through regularization. Regardless, the key message of the study that Gao *et al* cite is that validation on an independent dataset is needed—a point that we made several times in our paper (see passages referenced above).

Gao *et al* further state that our approach "fails to account for significant differences in post-progression treatments". However, in the supplement, we discuss landmark models which we show to be largely congruent with the models discussed in the main text. In these landmark models, outcomes manifest sufficiently early so that our results cannot be confounded by changes in the treatment regimen. As outlined in the paper, progression assessments were scheduled in "9-week intervals" (page 3), while the landmark models have a cut-off date of 120 days. The landmark analyses hence capture only one progression assessment and are therefore not confounded by effects of treatment switches that would only be recorded after a switch, at later assessment times. More generally, even when considering longer-term outcomes, such investigations still constitute a valid intention-to-treat analysis, as is a common approach in the analysis of clinical studies.

Lastly, Gao *et al* discuss patient consent requirements for use of clinical trial data in secondary analyses. The IMvigor211 trial, which was employed for access to data for this study, was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The consent allowed the collection and post-hoc analyses of clinical data as well as tissue and blood specimens to facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. Thus, the language of the consent allowed the study of the association of clinical data and biomarkers with efficacy, toxicities and progression to increase knowledge and understanding of disease biology. The sponsor of the IMvigor211 trial, Roche, provided the data to the Vivli data repository platform (https://vivli.org), which permitted our analysis to occur in their secure research environment using de-identified patient data.

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