Letter to the Editor

Cancer Research

Quantifying Preexisting Resistant and Persister Populations–Response

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We thank Mistry and colleagues for their careful study and critique of our article (1). We are convinced that the slightly differing conclusions of the two articles are based on differences in model design and our focus on biological interpretation. Specifically, we agree that a model of only preexisting resistance does fit the data well, but results in unrealistic model parameters.

The study by Mistry and colleagues (2) in which time-series data from trial cohorts are analyzed differs from our current study in that it considers only sensitive and resistant tumor cells types. In our study a third, drug-tolerant persister cell population is introduced that grows slowly in the presence of tyrosine kinase inhibitor (TKI) and can mutate into fully resistant cells, which is consistent with *in vitro* studies analyzing clonogenic evolution of human tumor biopsies (3, 4).

Modeling the observed recurrence trajectories using only acquired resistance, we do show that this model can fit the data, but this requires unrealistically high mutation induction rates. It would be interesting to put the *c* variable in Mistry and colleagues' study in a biological context to assess the transition rate between sensitive and resistant compartments.

Regarding the model of only preexisting resistance, the results of Mistry and colleagues' work and ours both show that this model fits the data well, but leads to very high estimates of preexisting resistance (20%–30% on average in Mistry and colleagues). This result is contradicted by clinical data, in which the vast majority of pretreatment biopsies do not contain high (or any) fractions of preexisting resistance (5, 6).

In the light of these two facts, we combined both mechanisms of resistance through a carefully constrained model fit, leading to clinically reasonable and robust parameters.

Note that in our model, the drug-tolerant persister compartment, while slow growing, will still proliferate while exposed to the drug and would therefore be designated as resistant if a two compartment model was forced upon our data. Consequently, our results for the combined model are in fact consistent with the preexisting model by Mistry and colleagues, as their single resistance compartment encapsulates what we distinguish as drug resistance and persistence.

Mistry and colleagues state the two compartment model is necessary for model identifiability. We agree, which is why we initially used the two restricted models (only acquired or preexisting resistance). However, given the contradictions with clinical observations outlined above, we conclude that a combined model is necessary to describe clinical observations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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