RE: Meta-analysis of the Relationship Between Dose and Benefit in Phase I Targeted Agent Trials

I read with interest the article by Gupta et al. describing the relationship between dose and outcome in phase I targeted agent trials (1). I am concerned, however, about the validity of the survival experience portrayed in Figure 1. According to the figure, patients in the cohort that Gupta et al. studied had estimated survival probabilities of 80%–90% at one year after trial entry. This contrasts sharply with estimates from other published meta-analyses of phase I trials, which generally suggest median survivals of six to nine months (2–7).

Inspection of the figure suggests that extensive and differential loss to follow-up may have led to biased estimates of survival probabilities. By four months, approximately 75% of the cohort was no longer at risk, in most cases due to censoring rather than to the occurrence of events. Presumably, most trial participants whose data were censored had come off study due to disease progression or toxicity. Because survival among this censored group was undoubtedly much worse than that among patients with longer follow-up, the survival experience reflected in Figure 1 is likely unrepresentative of that of the cohort as a whole.

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References


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Response

We thank Dr Joffe for his interest in, and careful review of, our article and appreciate the opportunity to respond to his comments regarding the validity of the presented survival experience. We acknowledge, as well, the survival difference between our study and several others that Dr Joffe cites in his commentary. It is important to point out that the primary intent of our study was to determine if clinical benefit increases, in terms of response and overall survival, as dose increases in phase I oncology clinical trials of targeted agents. It may be true that the survival probabilities of the particular patient population examined in our meta-analysis differs from those reported in other meta-analyses, due to any number of reasons (this will be discussed further); however, the dose comparison should be valid. A concern expressed by Dr Joffe was the amount of censoring and the potential effect of the censoring on the results. The meta-analyses cited by Joffe were compiled from smaller studies performed at a single institution, thus allowing for more extensive follow-up and less censoring. In our meta-analysis, the studies were drawn from multiple institutions, thus providing a larger data set and more varied patient populations but also resulting in less intensive follow-up. Although a majority of the patients in our study were censored before death occurred, there is no indication that the censoring was different by dose level, thus supporting our results. In fact, sensitivity analyses, where all patients were censored at 6 months, resulted in Kaplan–Meier curves similar to those of Figure 1, for the comparison of dose levels by tumor type (data not presented).

The difference in survival experience for our patient population and those of other meta-analyses is intriguing, and there are several possible explanations. First, it is quite likely that the specific patient populations differ in important factors such as performance status, number of prior therapies, variety of tumor types, and whether or not they were drawn from a single institution. For example, patients with advanced sarcomas and head and neck tumors often have a poorer prognosis at this point in their disease, compared to other tumor types such as breast, gastric, and hematologic (which composed 70% of the population in our analysis). Additionally, several of the agents investigated in our study had already had preliminary monotherapy experience in other tumor types or with other agencies. As a result, even though dose escalation occurred in several of these trials, many of the lowest doses required for first-in-human testing were not replicated in the context of the trials in our meta-analysis. This may have resulted in more benefit to patients. Typically, eligibility criteria for first-in-human studies require more advanced disease; this will bring down survival rates. Because the studies in our analysis were not first-in-human studies, the populations may have had less advanced disease. Finally, the trials studied in our meta-analysis were investigator-initiated trials. It is typical that these trials are driven by preliminary preclinical data, looking at an agent in the context of a significant tumor profile or signature. This factor could potentially increase agent benefit to patients as was observed in our study, resulting in higher survival rates.

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