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The International Drug Development Institute (IDDI) provides statistical services to biopharmaceutical companies and academic organizations dedicated to the development of drugs, biologics, and medical devices. We have a special focus on oncology, and a particular interest in improving and proposing methods that can make clinical development more efficient and reliable. We commend the Food and Drug Administration for the recent Draft Guidance for Industry regarding the use of expansion cohorts in first-in-human (FIH) clinical trials. The document is well crafted and quite comprehensive with regard to issues that may arise when designing or conducting such studies.

The purpose of our comments is to emphasize the need to consider randomization whenever feasible in expansion cohorts, even though randomization has rarely been used until now in this setting. Our view is that the use of a randomized control group should be considered when designing any clinical trial, including an expansion cohort, in order to produce an unbiased assessment of a drug's efficacy. Randomization is mentioned in the Draft Guidance with respect to dosing regimens, and indeed it can help when the choice of dose requires more information than is typically available after the dose-finding phase I trials that precede expansion cohorts. However, randomization can be more generally useful than to merely choose between two or more doses of an experimental agent (see, e.g., Saad et al., Nature Reviews Clinical Oncology 2017; 14:317-323). Below we present a brief summary of the arguments in favor of randomization that are relevant for the expansion cohorts considered in the Guidance, followed by pre-emptive statements to counter arguments against randomization.

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Arguments in favor of randomization in expansion cohorts

1. The main purpose of a control group is to provide grounds for assessing the amount of selection bias that might affect the results of expansion cohorts. In particular, a randomized control can help in evaluating whether historical data are suitable for arguing in favor of the "promising" status of the new drug (i.e., a level of efficacy incompatible with the available historical data, which are often unreliable or unavailable in the specific subset of interest in the expansion cohort).
2. For "promising" drugs, a formal statistical comparison with the control group might have enough statistical power to actually provide pivotal evidence towards full registration of the new drug. With such "promising" drugs, there may be a "window of opportunity" after the dose escalation phase I trial for performing a randomized comparison of the new drug with a control group. If a non-randomized expansion cohort is carried out and "promising" results are reported, such a window of opportunity may disappear, and the chance to obtain unbiased evidence regarding the drug's efficacy may be lost for good. Yet, the initial results may be due to selection bias or to the play of chance, and discovering this fact might require additional cohorts and studies, which is ineffective. Thus, randomization of early (i.e., immediately following the dose escalation phase I trial) cohort(s) should be generally recommended and might, in fact, be more efficient. Of note, while it is true that tumor shrinkage in a large enough number of patients is sufficient evidence of a drug's activity, the converse is not true and absence of tumor shrinkage in a large number of patients is by no means proof of a drug's lack of efficacy.
3. For drugs that do not show as high an efficacy as initially expected after the dose-escalation phase I trial, a randomized comparison with a control may be instrumental in deciding whether it is nevertheless worthwhile to develop the drug further or to stop the development.

Pre-emption of arguments against randomization in expansion cohorts

1. It may be argued that the use of expansion-cohort designs may be limited to FIH trials in serious diseases for which no adequate treatment options are available. Hence, the choice of a "control" treatment might not be trivial. There are, however, several options that could be considered, including "treatment of physician's choice" (excluding the experimental drug) or "best supportive

care", a delayed administration of the experimental drug after cross-over from another established therapy, or single drug versus combination.

2. If patient availability for enrollment is an issue, randomization to the control group may not need to be conducted using the 1:1 ratio. A 2:1, or even larger, ratio can be considered, depending on patient availability and the nature of the control treatment. Imbalanced randomization is attractive because it maximizes the number of patients treated with the experimental agent, and therefore maximizes information on the efficacy and safety of this agent, while keeping a concurrent control group to help in the interpretation of patient outcomes. The small size of expansion cohorts may seem to argue in favor of treating every patient with the experimental agent, but the limitations of uncontrolled data must be carefully considered before deciding against randomization.

3. Finally, we wish to emphasize that it does not make logical sense to argue that expansion cohorts should not be randomized because the drug might have outstanding efficacy; indeed, this will only be known after treating patients in the expansion cohort, rather than before reliable information is available. It may well be that the drug's true efficacy, assessed in a properly controlled way, falls far short of expectations in some patient subsets (or even in all patients). Moreover, it may also be that the toxicities of the drug, at doses that have efficacy, are so serious as to make the drug unusable in clinical practice. Randomization should be used when uncertainty is high, which is precisely the situation of expansion cohorts in FIH trials.

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