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A 2-in-1 adaptive phase 2/3 design for expedited oncology drug development☆

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ABSTRACT

We propose an adaptive design that allows us to expand an ongoing Phase 2 trial into a Phase 3 trial to expedite a drug development program with fewer patients. Rather than the usual practice of increasing sample size with a less positive interim outcome, here we propose maintaining sample size with such a result and wait for fully mature data. The final Phase 2 data may be negative, may warrant a larger Phase 3 trial, or, in the extreme, could provide a definitively positive outcome. If the interim outcome is more positive, the trial continues to an originally planned larger sample size for a definitive Phase 3 evaluation. All patients from the study are used for inference regardless of the interim expansion decision. We show that no penalty needs to be paid in order to control the overall Type I error of the study, under a mild assumption that is expected to generally hold in practice.

The proposed design may be considered an alternative approach to sample size adjustment for ongoing trials. As such, the use of an intermediate endpoint for adaptive decision is a unique feature of the design. A hypothetical example is provided for illustration purpose.

1. Introduction

After an experimental oncology drug has demonstrated promising anti-tumor activity in Phase 1 efficacy expansion with small sample size, randomized follow-up trials are often conducted for more definitive testing in the same tumor indications. A follow-up trial can be a confirmatory Phase 3 trial or a Phase 2 proof-of-concept (POC) trial, in the same or a different line of treatment. Phase 2 POC trials, which play a critical role in conventional drug development, are being skipped increasingly as a trade-off for speed in contemporary oncology drug development. This shift in the balance between certainty and speed is especially evident in the immune-oncology space where the tremendous success of immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) pathway, such as pembrolizumb (Keytruda®), nivolumab (Optivo®), atezolizumab (Tecentriq®), and avelumab (Bavencio®) has also brought unprecedented competition in the field. There are close to 1000 ongoing clinical trials involving anti-PD-1/PD-L1 therapies including a flood of the next generation immunotherapies all poised to be tested in clinical trials [1]. A study team may choose to directly initiate a Phase 3 trial (i.e., skip Phase 2) after Phase 1 efficacy expansion purely due to the competitive pressure. The aggressive approach can be very risky. While the expectation is high for new immune-oncology drugs, it is unrealistic to expect all of them to have the same success as the PD-1 immune checkpoint inhibitors. Even if they are indeed as effective as these checkpoint inhibitors, it will be challenging to demonstrate their clinical benefit relative to the improved standard-of-care (SOC). The aggressive approach can be costly, too. A new immunotherapy can be potentially active in a wide range of tumor types, and can be studied in a variety of possible combinations with marketed or investigational therapies. When ubiquitously applied to all promising new drugs for all viable combinations, the aggressive approach could easily exhaust the resources for drug development. It is imperative to improve the efficiency of drug development via innovation.

To mitigate the risk of a failed Phase 3 trial, a futility analysis can be conducted during the course of the trial to potentially stop the trial early for lack of efficacy. However, in practice, an ongoing Phase 3 trial commends substantial upfront investment and there is little incentive to stop it midway for futility. As a result, the futility bar is often set low, rendering the analysis nothing more than a “disaster check”. A low bar Phase 3 futility analysis can hardly replace a bona fide Phase 2 POC trial. In this article, we introduce an alternative adaptive design that is

☆ All authors are stock holders of pharmaceutical companies that can potentially benefit from expedited oncology drug development.

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applicable to situations when clinical data from Phase 1 efficacy expansion suggests that a conventional Phase 2 POC trial is needed before launching a Phase 3 trial. The proposed approach adds an option in the study design that, without changing the inclusion and exclusion criteria for enrollment or randomization scheme, allows the expansion of the Phase 2 trial into Phase 3 (i.e., by adding additional patients and/or extending the follow-up time if needed). An analysis for making the adaptation decision is pre-specified in the study protocol. The criterion for expansion is carefully chosen to give the Phase 3 trial a reasonable chance to succeed while properly balancing the risk and benefit of expansion. If the decision is to not expand, the study is kept as a Phase 2 trial and the primary analysis is conducted at the end of Phase 2. Otherwise, the study is expanded into a Phase 3 trial and the primary analysis of the study is conducted at the end of Phase 3, consisting of all enrolled patients including those already used for the decision making in the ongoing trial. All patients are given equal weight in this analysis. Because the design approach provides an option of switching between Phase 2 and Phase 3, we call it a "2-in-1" adaptive design. The proposed approach is more efficient than the conventional approach that conducts and analyzes Phase 2 and Phase 3 trials sequentially, and is less risky than the contemporary approach of skipping Phase 2.

In practice, the adaptation decision may be made around the time when the Phase 2 trial has completed enrollment in order to expand to Phase 3 seamlessly or later in order to have more confidence about the decision. The primary endpoint is usually objective response rate (ORR) or progression-free survival (PFS) for Phase 2 oncology trials. These endpoints are natural candidates suited for the adaptation decision. Alternative endpoints such as tumor size reduction (%) at the first tumor assessment may also be considered as appropriate. Pros and cons should be well vested in endpoint selection. A general discussion on cost-effectiveness of intermediate endpoints for statistical and clinical decisions can be found in [2]. A real example on the application of an intermediate endpoint for seamless transition of a Phase 2 trial to Phase 3 can be found in [3]. Timing of the analysis and choice of endpoint are driven by various scientific as well as practical considerations, and are considered out of the scope of this article. Note that, while we are considering seamless Phase 2/3 transition here, our propose design is different from the seamless Phase 2/3 designs [4] that involve the treatment selection, population selection, or change of endpoint. But it does share similarity with sample size adjustment (or re-estimation).

While the focus of this article is on expansion of a Phase 2 trial to Phase 3, the proposed adaptive design approach equally applies to adaptation between a smaller trial and a larger trial in same or different development phases. A critical issue of interest is overall Type I error control of the study. We investigate this issue under the general setting first, followed with an application of the proposed approach to a hypothetical study.

2. Materials and methods

Let X be the primary endpoint for adaptation decision, Y be the primary endpoint for the smaller trial and Z be the primary endpoint for the larger trial. A study that applies the adaptive design will be considered positive if either the smaller trial is positive (in case of no expansion) in Y or the larger trial (in case of expansion) is positive in Z. In practice, X, Y and Z may be the same or different endpoints. For example, X and Y may be both ORR and Z may be OS, or X may be ORR and Y and Z may be both OS.

With a slight abuse of notation, the same capital letters X, Y and Z are also used to denote the corresponding standardized test statistic at the three analyses (adaptive decision, end of smaller trial and end of larger trial). A positive test statistic favors the experimental drug. The two test statistics X and Y are (reasonably) assumed to follow an asymptotic standard bivariate normal distribution with correlation ρ_{XY}, with a similar assumption for the two test statistics X and Z with correlation ρ_{XZ}. We assume that $\rho_{XY} \geq \rho_{XZ}$ throughout this article, which is expected to generally hold in practice. To see this, note that the correlation between the test statistics is driven by the correlation between the two corresponding endpoints as well as by how much the two underlying analysis populations overlap with each other, the more the greater (approximately proportional to square root of the overlap proportion for binary or continuous endpoints and more complicated when a time-to-event event is involved). This means that, given that the underlying patient populations for X, Y, and Z are nested, we always have $\rho_{XY} \geq \rho_{XZ}$ when X and Y are the same endpoint, irrespective of Z. We also have $\rho_{XY} \geq \rho_{XZ}$ when Y and Z are the same endpoint as long as X is not negatively correlated with them. When X and Z are the same endpoint and Y is different, a scenario of little practical relevance, the assumption may not hold even if the sample size has increased a lot after expansion. When X, Y and Z are mutually different endpoints, the assumption still holds as long as X has a higher correlation with Y than with Z, and may not hold otherwise especially if the smaller trial and the larger trial have comparable sample size. Table 1 illustrates correlation assumption $\rho_{XY} \geq \rho_{XZ}$ under different scenarios for the endpoints. Consequence to the violation of the assumption will be discussed at the end of this section.

Table 1
Validity of correlation assumption $\rho_{XY} \geq \rho_{XZ}$ for test statistics under different scenarios for the endpoints.

Scenarios for endpoints	Implication to correlation assumption $\rho_{XY} \geq \rho_{XZ}$
X, Y and Z are same	Holds because of the nested structure
X and Y are same, Z different	Holds because of the nested structure
X and Z are same, Y different	May not hold
Y and Z are same, X different	Holds unless X negatively correlated with Y and Z
X, Y and Z are different	May hold

Let c be the cutpoint of the test statistic X, i.e., the trial will be expanded to a larger trial if $X \geq c$ or be kept as the smaller trial otherwise. In practice, a reasonably large positive value may be chosen for c in order to justify the expansion of a smaller trial to a larger one. However, we do not make any assumption on c in the theoretical development below. The null hypothesis of the study will be tested at an alpha level that corresponds to a cutpoint w for the test statistic (Y or Z). With c serving as a switch, under the above setup, the overall probability of declaring a positive outcome from this study is Prob $(X < c, Y > w)$ + Prob$(X \geq c, Z > w)$. We want to find a proper value for w to keep this probability less than or equal to a target alpha level under the null hypothesis $E\{Y\} = E\{Z\} = 0$. When X is the same endpoint as Y or Z, the null hypothesis implies $E\{X\} = 0$ as well. However, when X is a different endpoint from Y and Z, no assumption is made on $E\{X\}$.

Given that the bivariate normal quadrant Prob$(X \geq c, Z > w)$ increases with the correlation between X and Z irrespective of the sign of the correlation [5,6], under the assumption $\rho_{XY} \geq \rho_{XZ}$, we have that Prob$(X \geq c, Z > w) \leq$ Prob$(X \geq c, Y > w)$. Therefore,

$$\text{Prob}(X < c, Y > w) + \text{Prob}(X \geq c, Z > w)$$

$$\leq \text{Prob}(X < c, Y > w) + \text{Prob}(X \geq c, Y > w)$$

$$= \text{Prob}(Y > w)$$

This means the overall Type I error of the study is controlled at the target alpha level when w is set at the corresponding normal quantile, i.e., no extra penalty needs to be paid for Type I error control. As a straightforward extension, the overall Type I error of the study remains under control when a group sequential design [7] is subsequently applied to control alpha at the same level. Though not of our interest in this article, by the same argument, the overall Type I error will be inflated at the same w if the opposite decision rule is applied (i.e., expand to a larger trial if $X < c$) or if $\rho_{XY} \leq \rho_{XZ}$.