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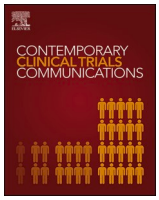

A promising biomarker adaptive Phase 2/3 design – Explained and expanded

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A B S T R A C T

This short communication concerns a biomarker adaptive Phase 2/3 design for new oncology drugs with an uncertain biomarker effect. Depending on the outcome of an interim analysis for adaptive decision, a Phase 2 study that starts in a biomarker enriched subpopulation may continue to the end without expansion to Phase 3, expand to Phase 3 in the same population or expand to Phase 3 in a broader population. Each path can enjoy full alpha for hypothesis testing without inflating the overall Type I error.

Predictive biomarkers play a pivotal role in developing targeted therapies for cancer treatment (e.g., PD-L1 expression for *anti*-PD-(L)1 immune checkpoint inhibitors, TROP2 expression for TROP2 directed antibody-drug conjugates). Barring safety and tolerability concerns, the treatment effect of a new drug is expected to increase with the biomarker level. However, it is unclear whether population enrichment with a biomarker cut-off is needed for the drug to succeed in clinical trials. A preliminary decision often must be made based on limited clinical data from efficacy signal detection post dose-finding. While the ensuing step of development strategy may follow [1] for general guidance, uncertainty about the biomarker hypothesis complicates the decision-making. In terms of population selection for the next step, be it a Phase 2 study or a Phase 3 study, when biomarker enrichment is deemed optional, one may conduct a study in a broader population and stratify it by a biomarker cut-off. In the last decade of the immunotherapy revolution, trials of PD-(L)1 drugs routinely stratify patients by PD-L1 expression levels and they have ended with mixed results [2,3]. This strategy is inefficient if the drug only works in the biomarker positive population, especially when the biomarker prevalence is low. Otherwise, conduct a study in a biomarker enriched subpopulation first. If the drug is more active than expected, implying that the cut-off might have been set too high, follow with a separate study in a broader population by either lowering the biomarker cut-off or relaxing biomarker requirement (i.e., all-comer population). This strategy delays the testing in biomarker negative population when the drug has a broader activity. Alternatively, one may start with a Phase 2 study in a biomarker enriched subpopulation and adaptively expand it to Phase 3 in the same population or in a broader population depending on the strength of data at an interim analysis [4]. In case of weak data, the study will not expand to Phase 3 and a final analysis of Phase 2 will be conducted after adequate follow-up. To mitigate the risk of a false No-Go decision, the final analysis is pre-specified to allow the declaring of a positive outcome, following the 2-in-1 design [5]. This alternative design allows a study to choose the optimal path moving forward based on emerging trial data and provides more flexibility than the fixed designs. In this short communication, we show that trial outcome for each path can be tested at the full alpha level without inflating the overall Type I error of the study (in case of expansion to broader population a co-primary hypothesis on the two populations will be tested) (see Fig. 1).

Let X be the standardized test statistic based on an early efficacy endpoint (e.g., overall response rate based on tumor size reduction in oncology) at the interim analysis of a Phase 2 study for adaptation decision. A positive X favors the experimental arm. Let C_1 and C_2 be the efficacy bars for adaptation ($0< C_1 <C_2$). If $X< C_1$ ("underwhelming"), the study will continue to the end without expansion to Phase 3 and the null hypothesis on the Phase 2 primary endpoint (e.g., overall response rate or progression-free survival in oncology) will be tested at the α level. Let Y be the corresponding standardized test statistic. If $C_1 \leq X< C_2$ ("base case"), the study will expand to Phase 3 in the same population and the null hypothesis on the Phase 3 primary endpoint (e.g., progression-free survival or overall survival in oncology) will be tested at the α level. Let Z_1 be the corresponding standardized test statistic. If $X\geq C_2$ ("overwhelming"), suggesting that the biomarker cut-off was set too high, the study will expand to Phase 3 in a broader population. The Phase 2 patients will be included in the Phase 3 analysis of biomarker enriched population, but they will be excluded from the Phase 3 analysis

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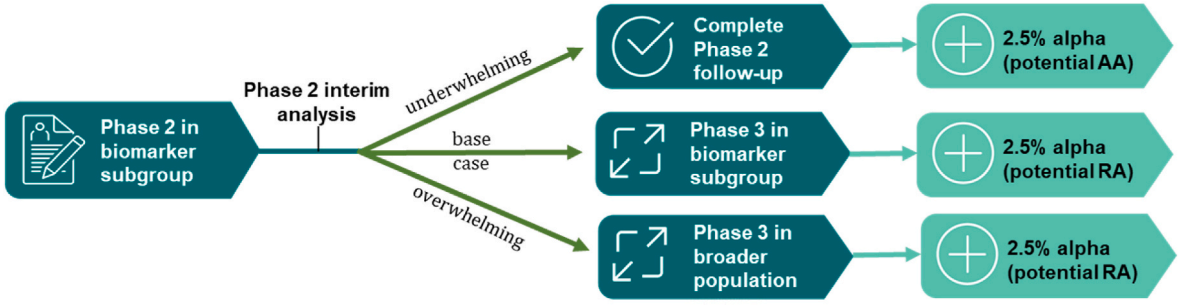

Fig. 1. Depending on the strength of Phase 2 interim data, the adaptive Phase 2/3 study may finish as a Phase 2 study, a Phase 3 study in the same population, or a Phase 3 study in a broader population. In general, each path can be analyzed at the 2.5 % alpha level while keeping the overall Type I error under 2.5 %. Therefore, a positive outcome at end of the Phase 2 may lead to accelerated approval (AA) and a positive outcome at end of either path of Phase 3 may lead to regular approval (RA).

of the broader population as the inclusion would skew the biomarker distribution [4]. To maintain the power for the biomarker enriched population, the overall sample size of this population will be kept the same as the base case or even increased to compensate for the power loss due to α sharing with the broader population. Let Z_{1+} be the corresponding standardized test statistic to the biomarker enriched population whereas the plus sign in subscript indicates a possibly greater sample size than for Z_1. Let Z_2 be the corresponding standardized test statistic to the broader population. In this case, the study will be declared positive if the outcome on the Phase 3 primary endpoint is either positive in the biomarker enriched population at the α_1 level or in the broader population at the α_2 level, whereas (α_1, α_2) satisfy $Pr(Z_{1+} \geq Z_{1-\alpha_1}$ or$Z_2 \geq Z_{1-\alpha_2}) \leq \alpha$ under the null. Like the alpha-spending function in a group sequential design, once an alpha-sharing function is defined, α_1 and α_2 can be derived based on the information fraction of the biomarker subgroup in the broader population with respect to the primary endpoint [6].

With a slight abuse of notations, let ρ_{XY} be the correlation between the early endpoint used for adaptation decision and the Phase 2 primary endpoint, and ρ_{XZ} be the correlation between the early endpoint and the Phase 3 primary endpoint. We show in the following that the overall Type I error of this design is controlled at α under a mild condition of $\rho_{XY} \geq \rho_{XZ} \geq 0$ that is expected to hold in practice [5].

$$P(X < C_1, Y \geq Z_{1-\alpha}) + P(C_1 < X < C_2, Z_1 \geq Z_{1-\alpha}) + P(X \geq C_2, \{Z_{1+} \geq Z_{1-\alpha_1} \text{ or } Z_2 \geq Z_{1-\alpha_2}\})$$

$$\leq P(X < C_1, Z_1 \geq Z_{1-\alpha}) + P(C_1 < X < C_2, Z_1 \geq Z_{1-\alpha}) + P(X \geq C_2, \{Z_{1+} \geq Z_{1-\alpha_1} \text{ or } Z_2 \geq Z_{1-\alpha_2}\})$$

$$= P(X < C_2, Z_1 \geq Z_{1-\alpha}) + P(X \geq C_2, \{Z_{1+} \geq Z_{1-\alpha_1} \text{ or } Z_2 \geq Z_{1-\alpha_2}\})$$

$$\leq P(X < C_2, Z_{1+} \geq Z_{1-\alpha}) + P(X \geq C_2, \{Z_{1+} \geq Z_{1-\alpha_1} \text{ or } Z_2 \geq Z_{1-\alpha_2}\}) \leq \alpha$$

The first inequality is a consequence of Slepian's lemma [5] based on the assumption $\rho_{XY} \geq \rho_{XZ}$ which implies that X has higher correlation with Y than with Z_1. Because the population for Z_1 is a subset of that for Z_{1+}, the assumption $\rho_{XZ} \geq 0$ implies that X has higher correlation with Z_1 than with Z_2. Therefore, the second inequality also follows. The last inequality generally holds under $Pr(Z_{1+} \geq Z_{1-\alpha_1}$ or$Z_2 \geq Z_{1-\alpha_2}) \leq \alpha$ following the same derivation as in [7]. Apparently, it also holds under a more conservative Bonferroni adjustment (i.e., $\alpha_1 + \alpha_2 = \alpha$) applied in [4] whereas a different proof was used.

Precision medicines are the future of cancer treatment and predictive biomarkers will continue to play a growing role in oncology drug development. However, there is often great uncertainty about the biomarker effect before a registrational study is initiated. In this short communication, we have expanded a promising biomarker adaptive Phase 2/3 design to make it even more powerful. The design framework may be expanded to include multiple interim analyses for adaptation decision based on readouts from multiple early endpoints [8]. Execution of the design, just like for any novel design, requires strong team collaboration across relevant functional areas. Throughout the article, we have only required the relevant correlations to be non-negative to make the design robust. Conceptually, more flexibility may be achieved (e.g., sample size adaptation in Phase 3) if the actual correlations are accounted for and simulation studies may be conducted to assist with the assessment of Type I error control. The early endpoint for adaptation should be sensitive to the intervention so that adaptation can be made timely, while other characteristics should also be considered [9]. In oncology, overall response rate is often the default choice, partly because it is generally correlated with clinical benefit so much so that it has been routinely used for justification of accelerated approval by FDA and partly because of the need to confirm the preliminary tumor response signal that has triggered the Phase 2/3 program. Sponsor has a lot of freedom in deciding how to analyze the data for adaptation decision. For example, in case delayed treatment effect is expected, which has been a concern for immunotherapies and personalized vaccines in oncology, a weighted analysis method may be considered. The choice of efficacy bars for adaptation (i.e., C_1 and C_2) depends not only on the relative effect sizes (and the uncertainties) between the early endpoint and the Phase 2/3 endpoints but also on the cost and benefit of each path [10]. This and various other statistical and practical considerations are beyond the scope of this article.

Declaration of competing interest

The authors are stockholders of biopharmaceutical companies and may benefit from the publication of this work.

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