CLINICAL INVESTIGATION

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Utilizing interim Phase II results to streamline Phase III development: what does the future hold?

"Routine and systematic utilization of the Phase II interim results would greatly streamline the decision-making, expedite the development process and reduce the overall drug-development cost."

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Jie Huang
Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080, USA
Tel.: +1 650 452 3865
huang.jenny@gene.com

Drug-development cost has been rising continually [1] and now reaching US$5 billion per new medicine [2]. The cost of anticancer drugs is especially high due to the longer development durations [3]. It takes an average of over 8 years for an oncology drug to go through Phase I–III trials [3] and only 5% of them make through to the registration [4].

Clinical trials are at the heart of medical advances and central for drug development. In drug development, clinical trials are commonly classified into four phases, where Phase I trials are the first testing in humans to evaluate if the drug is safe, Phase II trials examine whether the drug has any efficacy and merit further investigation, Phase III trials are used to determine the drug's therapeutic effect and enable regulatory approval for marketing the drug and Phase IV trials are 'post-approval' studies to collect the drug's long-term effect [5,6]. Therefore, Phase II trials are on the critical path of successful drug-development gating the go/no-go decisions to Phase III testing. Only those Phase II trials with very promising final result trigger the Phase III trial with the corresponding commitment in resource and time.

An effective way to reduce the development cost is to shorten the development timeline with a more streamlined decision-making process in terms of the transition from Phase II to III trials. Interim efficacy analysis has been routinely built into the Phase III trials to enable the potential for an earlier registration with positive interim results or cut the loss by stopping the Phase III earlier with negative interim results. Though it is common to see interim safety analysis built in the Phase II trials, interim efficacy analysis has been more *ad hoc*. In principle, the interim efficacy analysis could be built into the Phase II trials similar to those in the Phase III trials.

Phase II trials range from single-arm studies to randomized studies with a control arm. For a single-arm Phase II study, the primary endpoint tends to be a binary outcome variable and a two-stage design can be used to make development decisions at interim (i.e., the end of stage 1), where the stage I efficacy result will decide whether to continue into stage 2 with more enrollment [7].

For a randomized Phase II study with two or more arms, the seamless Phase II/III trial has been used and the development decision (stop early or continue and expand to Phase III) is continually assessed during the Phase II part of the study [8,9]. The Bayesian approach is often applied to assess the updated posterior distribution of the parameter of interest by utilizing the newest data available. The advantage of this type of design is that it not only shortens the trial duration by eliminating the gap time between the end of a Phase II trial and the beginning of the Phase III trial, but also reduces the total sample size by counting the Phase II patients toward the accrual goal for the Phase III trial [8–10].

However, the interim analyses for efficacy are not routinely conducted in Phase II trials due to various concerns surrounding the existing approaches. One reason is that the interim analysis at Phase II may substantially complicate the trial design and conduct. For

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example, for a seamless Phase II/III trial design, the sponsor would not only need extensive discussions with US FDA to address the complicated design issues before the trial start and more strenuous coordination among all study sites during the trial conduct, but also has little opportunity to reflect on the data and incorporate new information thoughtfully into the Phase III part of the trial [8–10]. The subjective model specification in making Bayesian inference may also present a concern for the robustness of the results. The other concern is that the interim Phase II results may be unreliable and depend heavily on the timing of the analysis for oncology trials where progression-free survival (PFS) is the primary end point. In contrast to Phase III trials, the sponsors in general hesitate to terminate a Phase II trial early for either the efficacy or futility because of the large variability intrinsic to the small size of data at Phase II interim. For the most part, it is legitimate to be wary about the Phase II interim analysis. But given that the primary goal for Phase II studies is to provide preliminary rather than the definitive evidence for the efficacy of the drug, phase II studies shall have more flexibility in the conduct and interpretation of interim analysis so long as the interim analysis plan is reasonable and feasible and the corresponding results interpretation is clear and appropriate [11].

> "While we often lack power to estimate the true hazard ratio at the interim analysis due to limited sample size and inadequate follow-up, we could predict the HR at the final analysis reasonably well when over half of the final information is available at the interim analysis."

A recent proposal on the systematic utilization of interim efficacy analyses from comparative Phase II trials provides a practical approach to retain the benefit of interim analysis in Phase II studies without complicating the trial design and compromising the sponsor's ability to identify gaps in knowledge and thoughtfully design the Phase III trial [12].

One key aspect of the proposal is to separate the decision of starting preparing for the Phase III trial from the decision of starting the Phase III trial: the former decision is made after the interim analysis while the latter is made after the final analysis. More specifically, the sponsor would pre-specify the plan of conducting the interim efficacy analyses in Phase II protocols and use the interim results to effectively make further development decisions on whether or not jump start Phase III preparation with a positive interim result or hold off further development decisions till the end of the trial. It differs from the traditional interim analyses in that any decision made at interim will be further gated by the final result, as the Phase II trial will generally continue if there's no safety concern. As a result, this strategy will not only warrant the inclusion of a potentially effective drug for further Phase III testing, but also circumvent the premature exclusion of a potentially effective drug from further test due to false-negative interim result. In addition, continuing the ongoing Phase II trial will also enable the collection of more complete efficacy and safety information, including potentially rare adverse events, which would be crucial for making more informed decision on the further testing in Phase III trials with a higher probability of success.

Another key aspect of this proposal is that in the interim analysis in Phase II trials with PFS as the primary end point, in addition to estimating the true PFS hazard ratio (HR), one may also predict the HR to be observed at the final analysis or the distribution thereof. This useful feature would allow the sponsor to assess the likelihood of obtaining the results within a certain range of interest, e.g., compute the probability of an estimated final PFS HR at or below a target value of interest (e.g., 0.65) given the data observed at interim. While we often lack power to estimate the true HR at the interim analysis due to limited sample size and inadequate follow-up, we could predict the HR at the final analysis reasonably well when over half of the final information is available at the interim analysis. The empirical study using data from 35 historical Roche/Genentech oncology trials with 44 treatment comparisons between an experimental arm and a control arm demonstrated that one may accurately predict the Phase III go/no-go decisions at the final analysis based on the interim data: the positive predictive value is 83.3% and the negative predictive value is 90.6%. For the trials with both positive interim and final results, there's an average of 8 months potential gain in the development timeline if an earlier Phase III preparation carried out based on the Phase II interim results.

There are a few important practical issues to consider when implementing this (or other) strategy of using interim Phase II analysis to streamline the Phase III drug-development decisions. The study protocol should clearly describe the plan for the interim efficacy analysis. Although the timing of the interim analysis would be mostly event driven, it is recommended to conduct the analysis after the end of enrollment and the first scheduled tumor assessment. This will help minimize the impact of interim analysis on patient enrollment while maximize the information at interim. If accrual is slow, the sponsor may need to conduct the interim analysis before the end of recruitment, in which case, the potential impact on future patient enrollment should be duly considered. Nor-

mally, there would be no need to modify the study protocol only based on the go/no-go result from the interim analysis due to the short study duration, limited information and the potential effect on the validity of the final analysis.

In conclusion, the need for randomized Phase II trials is rising with the need for targeted therapeutic agents to facilitate biomarker discovery [13,14]. With the ever growing number of anticancer drugs and limited development resources, more randomized Phase II trials are being conducted to reduce the costly failure in Phase III. Routine and systematic utilization of the Phase II interim results would greatly streamline the decision-making, expedite the development process and reduce the overall drug-development cost. The interim analysis, when carefully conducted and appropriately used in the decision-making, can gain aforementioned merits, while retaining the simplicity of study design, trial conduct, data analysis and result interpretation, as well as offering the opportunity for ample reflection on the Phase II data to enable careful design of a Phase III trial with the updated knowledge.

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