Adaptive Approaches in Oncology

When a Patient Population Increase is the Best Bet

Trial design: Sample Size Re-Estimation in Phase 3 Confirmatory Studies

Disease area: Abdominal Cancer

The Setting

In the most serious disease areas, clinical trial sponsors are often hard pressed to induct sufficient subjects needed to satisfy confirmatory study sample size requirements. Many of the rarer cancer sub-groups studies present the greatest patient recruitment challenges.

A new breed of clinical study – the adaptive trial – is proving particularly well suited to oncology studies. These adaptive approaches are today providing sponsors with much more favorable circumstances to proceed with studies that would have not have gone forward with traditional methods.

Why Adapt?

Unlike traditional, fixed studies, adaptive trials allow predetermined modifications to an on-going study based on interim analysis. Design adaptations can take many forms, including phase 3 designs that re-estimate the sample size – the patient population – to increase the probability of study success.

FDA and EMEA-approved adaptive sample size re-estimation approaches optimize sample sizes without undermining the study's integrity and statistical validity. Re-assessing patient requirements based on interim analysis can make it reasonable for sponsors to confidently run even late stage studies despite the expensive prospect of treating large patient populations with a severe disease.

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An Adaptive Sample Size Re-Estimation Study

Why Interim Analysis?

What would an interim analysis accomplish? In the absence of overwhelming efficacy, a Promising Zone is defined as conditional power between 30% and 80%.

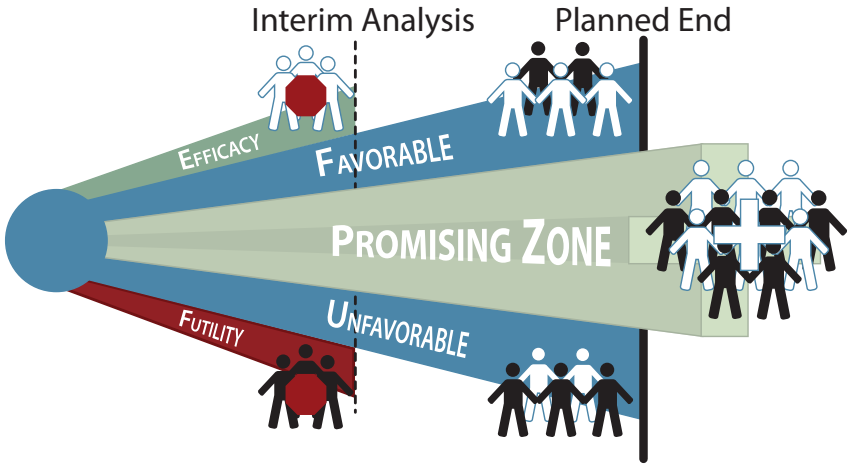
- If results not in the Promising Zone, continue study without sample size increase
- If within Promising Zone, increase sample size so as to achieve 80% conditional power

Ethical Advantages

Compared to traditional, fixed clinical studies, adaptive trials by their very nature offer unique advantages for patients, too. For instance, in a typical adaptive dose finding trial, the typical study patient has a greater probability of receiving a meaningful medicinal dose compared with traditional studies that offer no possibility of "migrating" from an ineffective dose group to a more effective one.

The potential adaptive advantage is all the more important – even potentially life-saving – in cancer and other severe disease therapeutic studies.

Defining the "Promising Zone"



Regulatory Considerations

- The FDA and EMEA have both accepted trials utilizing this concept. Appropriate methods are employed to preserve the statistical validity of the trial despite the sample size increase potential.
- An independent data monitoring committee (DMC) is provided with a detailed charter including pre-specified rules for sample size increase, and the flexibility to override same in case of unusual circumstances such as unforeseen safety issues.
- Only the DMC has interim result access: the sponsor remains blinded. Thereby the integrity of the trial is not compromised by premature study data disclosure.

Conclusion

Should interim analysis results enter the Promising Zone, the chances of success dramatically improve by engaging the sample size increase. If the interim results do not enter the Promising Zone, the sponsor is no better off nor worse off than with a conventional study design (without a sample size reassessment option).

The sponsor need not commit to the larger sample size up front; but instead can wait until the study demonstrates sufficient evidence that the cost of more patients is justifiable given the high probability of a successful outcome.

The Cytel Advantage

Sponsors choose Cytel to both design and help implement new trial approaches that increase the probability of success despite challenging circumstances. They also choose Cytel for qualified independent statisticians to serve on Data Monitoring Committees (DMCs) and to appear with sponsor representatives at trial design regulatory review meetings.

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