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 sample size requirements of a confirmatory study. Many rare cancer sub-group studies present some of the greatest patient recruitment challenges.

A new breed of clinical study – the adaptive trial – is proving particularly well suited to oncology studies. Adaptive designs are providing sponsors with considerably more optimal set of conditions to proceed with studies that traditionally would have been too risky to go forward.

Why Adapt?

Adaptive trial designs allow beneficial modifications to the ongoing study based on interim analysis. Pre-determined adaptations can take many forms, including recent phase 3 designs that re-estimate the sample size – the patient population – to increase the probability of a successful study.

FDA and EMEA-approved sample size re-estimation approaches optimize sample sizes without undermining the study's integrity and statistical validity. Re-assessing the required number of subjects following interim analysis enables sponsors to confidently go forward with late stage studies despite the expensive prospect of recruiting large patient populations in severe or rare diseases.

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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

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.

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.

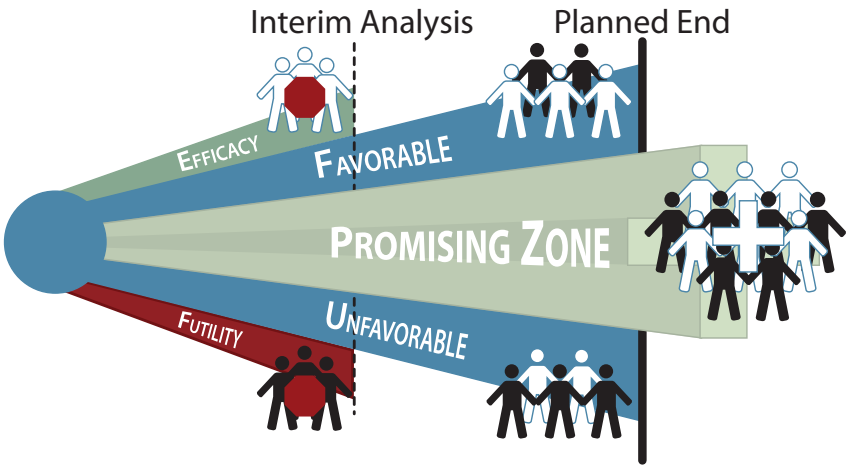
The potential adaptive advantage is all the more important – even potentially life-saving – in cancer and other severe disease therapeutic studies.

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.

Defining the "Promising Zone"



The Cytel Advantage

The statisticians of Cytel pioneered the science and technology of adaptive trial design and have trained thousands of health sciences industry biostatisticians, clinicians, and regulatory staff. Benefiting both sponsors and patients, Cytel experts have designed more validated adaptive trials than anyone else.

The trial design and implementation services of Cytel Pharmaceutical Research Services place our study innovation experience at the disposal of your clinical research and development programs. From trial simulation and process development to independent data assessment and regulatory review, Cytel stands with you every step of the way.

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