FEATURE

Improving Clinical Trials in the Era of Targeted Therapies

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Daniel J. Sargent, PhD, Mayo Clinic, Rochester, Minnesota, USA, discussed end points and novel clinical trial design in the era of targeted therapies, and the need to accelerate the drug development process so that the right therapies can quickly be delivered to the right patients with gastrointestinal cancers.

The increasing number of novel targeted therapies available for testing for cancers, including those of the gastrointestinal tract, requires new approaches to clinical trials to identify promising agents for Phase 3 testing—particularly with respect to end points and trial designs.

END POINTS

When choosing an end point for a trial, it should fit the intended purpose. In the Phase 2 setting, for example, the goal is to make a go or no-go decision to progress to Phase 3. Historically, end points such as response rate that correlate well with clinical benefit outcomes have been used in Phase 2. However, although response rate tends to correlate well with clinical benefit at the individual patient level, this has not translated into a trial-level association, because therapies that produce responses in individual patients do not necessarily extend survival. Using end points like this is therefore inappropriate if the aim is to increase Phase 3 success probability, because they result in many failed Phase 3 trials. Consequently, in Phase 2 studies, there has been a movement toward using end points such as progression-free survival, as well as using randomized trials.

In the Phase 3 setting, the goal is approval of the agent under evaluation, and either a clinical benefit or validated surrogate end point is required. The regulatory standard of the US Food and Drug Administration (FDA) is that treatment needs to be safe and effective. But, although "effective" is demonstrated by patients living either longer or better, living better can be particularly difficult to show, in part because many factors influence survival in addition to the treatment. Nevertheless, the FDA and the European Medicines Agency consider this to be a good end point.

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BIOMARKERS

With the emergence of targeted cancer therapies, biomarkers provide increasing promise for individualizing treatment. A prognostic biomarker is a single trait or signature of traits that identifies individuals with differing risks of a specific outcome, such as progression or death. It cannot, however, guide the choice of a particular therapy. Predictive biomarkers, in contrast, can identify subpopulations of patients who are most likely to respond to a given targeted therapy, and these in particular represent the key to moving forward in drug development.

CLINICAL TRIAL DESIGN

Dr. Sargent discussed some of the design options that have been proposed for predictive marker validation:

UNSELECTED DESIGN

All patients of a specific disease type and stage are eligible for trials of this design, regardless of their marker status. At least 2 distinct randomized controlled trial (RCT) designs exist: The marker-based strategy design randomizes patients to treatment either based on or independent of the marker status, whereas the marker-by-treatment-interaction design uses the marker status as a stratification factor when randomizing patients to treatment.

ENRICHMENT DESIGN

Designs in which eligibility is restricted to subjects considered most likely to benefit from the experimental agent are called "targeted designs" or "enrichment designs."

Table 1. Effect of Marker Prevalence and Relative Efficacy on Efficacy Gain

Prevalence	Relative Efficacy	Efficacy Gain
25%	0%	16×
25%	50%	2.5×
50%	0%	4×
50%	50%	1.8×
75%	0%	1.8×
75%	50%	1.3×

In enrichment trials, patients are screened for the presence (or absence) of a specific marker, and they are included in the clinical trial only if they have (or lack) that marker. These are appropriate in cases in which

- the mechanism of action of the targeted agent is known;
- a reliable assay exists that can be used to allow patients to be enrolled; or
- preliminary evidence suggests that patients with or without the specific marker profile do not benefit from the treatment in question.

This trial design is more efficient than the unselected design, requiring fewer overall randomized patients in comparison (Table 1). For example, when considering a biomarker with 25% prevalence and zero relative efficacy (meaning it performs well in marker-positive patients but has no effect in marker-negative patients), for the same power, a 16-fold smaller trial is needed to perform the trial in the targeted population compared with the general population. This is because including patients who do not benefit from the agent would bring the survival curves together and attenuate the hazard ratio. And if a treatment works half as well in marker-negative patients, there is still a 2.5-fold efficiency gain. In addition, as the prevalence of a marker increases, the efficiency gain decreases; however, even for a marker with 50% prevalence, an enriched-type trial design produces substantial efficiency gains.

UMBRELLA DESIGN

Large-scale sequencing of many cancers has improved treatment by allowing therapies to be selected according to the molecular characteristics of the tumor. Umbrella trials represent another approach that is being exploring as a possible way to improve the efficiency of clinical trials. They are designed to test the impact of different drugs in the development of histology- or mutation-specific therapies directed against oncogenic driver pathways in a single type or multiple types of cancer. In these trials, all patients complete the umbrella screening trial to determine which mutations they have, and they are subsequently assigned to one of several parallel subtype-specific subprotocols to receive a particular drug expected to target their mutations.

ADAPTIVE DESIGN

The adaptive design involves randomization between at least 2 arms within biomarker-defined strata, and it allows modifications to be made to the trial and/or statistical procedures of ongoing clinical trials. For example, as an adaptive design trial progresses, study arms can be added or removed, the randomization ratio can be altered, poor performers can be dropped from the trial, and good performers can be graduated to subsequent Phase 3 testing.

Dr. Sargent emphasized that clinical trials are now becoming smaller, in part because, as understanding of the molecular pathogenesis of tumors continues to improve, the proportion of patients that can be enrolled on any specific trial is decreasing. In contrast, if biomarkers allow therapies to be used on only patients with a high likelihood of benefit, the size of the treatment effect increases and smaller sample sizes are appropriate. This creates challenges for clinical trialists in optimizing the design of clinical studies. In the era of biomarkers and targeted therapies, novel trial designs and end points are needed to take forward the development of new treatments in rare tumors. Fundamental principles should not be overlooked in this venture, however. Randomization therefore remains essential to determine true causal effects and separate prognostic from predictive factors, and rigorous trial design with prespecification is also important, he concluded.