Successful Study Design in Precision Medicine

Highlights:

- Precision medicine and targeted therapies in oncology are growing rapidly
- Optimal trial design goes beyond 3+3
- Biomarkers and companion diagnostics play an important role in developing targeted therapies
- Feasibility assessments can help define study success

Introduction

The field of oncology has changed dramatically, with rapid change in the past 10 years in particular. Radiation began in the early 1900s, advancing to chemotherapy and hormone treatment in the 1950s. Recently, immunotherapy and targeted medicines have quickly stepped up to take on the challenge; the precision medicine market is anticipated to reach $85.5 billion by 2025 according to researchers from Grand View Research.

Growth of Targeted Therapies

Targeted therapies were conceived as scientists learned more about the basic mechanisms of cancer cells. Examining the molecular changes that allow normal cells to become cancerous, grow, and spread in the body has led to new ways of disrupting this process. Targeted therapies block the specific genes and proteins that drive the growth of cancer.

Personalization extends beyond therapy selection. It's also about drug discovery and how consumers engage with companies seeking to improve health. There are multiple factors that drive precision medicine. Accelerated scientific discovery in genomics and immunology contribute to the evolution, as do increased availability of patient data and the ability to collect, analyze, and preserve data and records.

According to the Personalized Medicine Coalition (PMC), more than one in every four medicines approved by the FDA over the past four years has been a personalized treatment. That's an increase from 10 years ago, when personalized medicines

accounted for less than 10 percent of new targeted therapies. The PMC reported that since 2014, personalized medicines have accounted for more than 20 percent of all new molecular entity approvals each year.

While there are factors outside study control that impact targeted therapy development — such as unclear or conflicting regulatory requirements between regions — there are controllable elements that can improve success, such as designing well-conceived trials, understanding the need for early development of biomarker and companion diagnostic strategies, taking a data-driven approach to feasibility assessments, and starting the process earlier.

Critical Success Factors for Targeted Therapy Development

Many factors contribute to the success of targeted therapy clinical trials. Low success rates may be related to factors that are difficult to control, such as unclear, conflicting, or burdensome regulatory environments or the lack of agreement among clinicians, investigators, and regulators as to what constitutes clinical benefit. Placing focus on factors that can be controlled can improve success.

Understanding patient populations and biomarkers will help identify patients most likely to benefit from specific treatments and the ability to develop analytically and clinically validated biomarker tests that will guide therapy. All of these things can and should be assessed prior to study design in order to select countries and sites, and on an ongoing basis to ensure a protocol can be adopted.

Phase I Trial Design

In Phase I cancer clinical trials involving cytotoxic agents, the conventional primary endpoint has been toxicity, which is assumed to increase with the drug dose (maximum tolerated dose). The benefit of molecularly targeted agents is their ability to modulate specific abnormal cancer cells while sparing normal tissue; the toxicity and efficacy may not be dose dependent. As a result, alternative endpoints to evaluate targeted therapy besides toxicity may be applicable for Phase I trials — including inhibition in tumors.

However, assessing target inhibition may be one of the most challenging aspects of clinical trial design. Standard 3+3 designs, where at least three patients are treated at each dose level, can sometimes result in many patients being treated at a suboptimal dose. Also, tumor tissue must be readily available, there must be a reliable assay to measure the drug's effect, and optimal extent of target inhibition (for example, target inhibition that equates to a meaningful clinical benefit) must be established.

To mitigate the chance that a recommended dose based solely on target inhibition in a Phase I trial is suboptimal, alternative study designs specifically for molecularly targeted agents may be considered, such as a continual reassessment method (CRM), modified toxicity probability interval design (mTPI-2), or Bayesian optimal interval design. Further, as toxicity and efficacy of targeted agents may not be dose-dependent, alternate endpoints should be proposed and considered, such as detection of biologically relevant pharmacokinetics.

Integrated Biomarker Strategy: From Biomarker to Companion Diagnostic

Biomarkers are a measurable response within a body's molecules to the presence of disease or infection, typically referring to an altered expression of gene products or abnormal DNA configurations. Changes to cellular processes can also be considered biomarkers, such as changes in energy metabolism or DNA damage response.

For cancer intervention, biomarkers are used for diagnosis, risk and prognosis assessment. They are also used when evaluating and monitoring the effectiveness of treatment in progress. Notably, biomarkers can be a focus when developing some, but not all, therapeutic targets. Biomarkers are also used to identify subpopulations for patients.

A companion diagnostic test is a biomarker test that enables better decision-making regarding the use of a therapy because it is specifically linked to a therapeutic drug. The goal is to identify predictive biomarkers that may be able to predict effectiveness and safety of a particular targeted therapy for the specified tumor. A companion diagnostic for the biomarker combined with targeted therapy is the "formula" for precision medicine.

Several areas of expertise need to come together when considering classifying biomarkers, such as regulatory affairs and analytical and clinical validation. Once all areas are aligned, a biomarker-based companion diagnostic can successfully be integrated into the clinical process.

Feasibility Assessments

In order to manage expectations and ultimately deliver studies on time and on budget, robust feasibility analysis should be performed, considering all stakeholders — patients, sponsors and CROs, and sites. Using a data-driven approach can provide a high degree of confidence when identifying patient enrollment. Data sources to consider include electronic medical record (EMR) data, next-generation sequencing (NGS) testing data, and natural language processing (NLP) technology and data science.

Feasibility, when evaluated appropriately, provides more than just lists of interested investigators. It can illuminate the path to operational excellence for the trial, foster collaboration with key stakeholders in the community, and help set realistic and achievable recruitment and budgeting goals.

Considering precision medicine from study design through feasibility will result in benefits that can increase the likelihood of delivering timely trials and results with quality data, which is of paramount importance — because patients and their families are waiting.