Getting Across the Phase III Finish Line

Targeted drugs and companion diagnostics are increasing success rates in clinical studies

Only one third of all phase III oncology trials succeed. That statistic, contained in an analysis of clinical trial data spanning 2003–2010 and presented at a subsequent Biotechnology Industry Organization CEO & Investor Conference, left researchers, physicians, and patients feeling discouraged. “Study designs and endpoints for early stage trials have substantial limitations, and because of their imperfection, the ‘go/no go’ decisions for phase III trials are compromised, leading to a high rate of failure,” says Anastassios Retzios, PhD, president of Bay Clinical R&D Services, a clinical development consulting firm in San Francisco, CA.

Researchers, pharmaceutical companies, and the U.S. Food and Drug Administration (FDA) have been building new and better tools to increase a drug’s chances at success in phase III, saving money and time. The shift from general cytotoxic drugs to targeted therapies in phase I and II trials has also begun to improve phase III success rates.

TARGETING SUCCESS

A decade ago, an investigator with a new chemotherapy drug would spin the “roulette wheel of phase II testing,” looking for glimmers of activity in different types of cancer with strong market potential, such as lung, breast, and prostate cancers, says Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research. Unfortunately, this approach set up many drugs for failure in phase III, he says.

With targeted therapies, companies are honing in on specific cancers in phase I and II, and some drugs have even been approved after phase II testing due to promising results. A large part of that success is thanks to the use of companion diagnostics, genetic tests that are used in phase II and III clinical trials and typically approved and marketed alongside the drug. Companion diagnostics help identify the patients most likely to benefit from a drug in phase II, and then a phase III trial can focus on a smaller subset of patients for whom the treatment has the greatest effect. A smaller trial with a larger treatment effect is a win for everyone—patients, doctors, companies, and payers.

“This is where the successes are coming from,” says Richard Simon, DSc, chief of the Biometric Research Branch at the National Cancer Institute. “The path is clear.”

Still, such biomarker tests require that investigators obtain tumor specimens and develop analytically validated tests during phase II, additional expenses that can be off-putting to some pharmaceutical and biotech companies. In addition, many clinical trial centers are still working out how to obtain clinical-grade genomics data as well as analyze, store, and use it in a productive way.

THE WHOLE INDUSTRY IS GRAPPLING WITH THE CHANGES

“The whole industry is grappling with the changes,” adds Rafael Amado, MD, senior vice president of oncology at GlaxoSmithKline. Once the field is more experienced with molecular profiling technology, phase III success rates could shoot as high as 80%, he predicts.

ADAPT TO SURVIVE

Another evolution in clinical trials is the use of adaptive designs, in which trials morph and change over time in response to accumulated data at interim analyses. “Adaptive designs are very good at saving time and money” and may increase success rates, says Retzios.

At Canada’s NCIC Clinical Trials Group, for example, these trial designs include randomized phase II-III trials where interim analyses inform decisions to proceed and to make beneficial changes, says Ralph Meyer, MD, director of the group. “These include futility analyses so we can halt what is destined to be a negative trial at an earlier stage,” he says.

The FDA supports adaptive trial design and is working more closely with companies and investigators during trials, says Pazdur. Casting aside the old paradigm of scheduled meetings at set endpoints, 4 initiatives—Fast Track, Accelerated Approval, Priority Review, and the new Breakthrough Therapies program—put the FDA in regular contact with investigators throughout the clinical trial process.

“The drug development process is changing to a flexible, fluid interaction,” says Pazdur.

Improvements in drug development and the tremendous growth in scientific knowledge over the past decade have paid off in oncology: In 2010, only 1% (2 of 21) of all FDA drug approvals were in oncology, but in 2012 that number rose to an impressive 36% (14 of 39). —Megan Scudellari

WHEN TARGETED TRIALS MISS

“Just because something is a targeted therapy doesn’t guarantee it is going to work,” points out Stewart Lyman, PhD, owner and manager of Lyman Biopharma Consulting LLC in Seattle, WA.

One reason such therapies fail is because of an unclear understanding of cancer biology. Sometimes a target is not as critical to the growth or survival of a tumor as believed. In other cases, even when a target is knocked out, cancer cells may survive via redundant pathways or because they lack the target mutation that most other cells have.

Of course, targeted therapies may fail for other reasons, including insufficient exploration of the dose response. Additionally, not all companies use adaptive trial designs. “Adaptive designs in clinical trials are mostly utilized by major pharma companies,” says Anastassios Retzios, PhD, president of Bay Clinical R&D Services in San Francisco, CA. “Small biotech companies simply don’t have the organization, resources, and capabilities to run them.”

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