Newer Phase II Trial Designs Gaining Ground

By Steve Benowitz

The onrush of newer targeted therapies aimed at halting cancer growth rather than shrinking tumors has altered the oncology drug landscape. This change has also helped usher in a new view of cancer drug testing and development. Because these drugs work differently from standard chemotherapy agents, clinical trial designs often have had to evolve to reflect such differences, as well as take into account new drug combinations.

Add another impetus for change: Only about 5% of all new cancer drugs make it through to U.S. Food and Drug Administration approval, and traditional clinical trial strategies are coming under increasing scrutiny.

Take, for example, the phase II cancer drug clinical trial—the crucial “go” or “no go” midpoint of drug development designed to test an agent’s effectiveness against cancer. Many people involved in trial design see it as one place that cancer drug development could make some substantial changes for the better.

It’s here, they say, that the door is open to newer, innovative trial designs.

“Oncology drug development is destined to fail if oncologists continue to develop drugs the way they have been,” said Mark Ratain, M.D., a professor of medicine at the University of Chicago. “That’s reflected in the poor success rate in oncology. Failing in phase III means we made the wrong decision to go that far with an agent, and that reflects poor phase II design. The basic premise of how to do drug development in oncology has to change.”

At April’s annual meeting of the American Association for Cancer Research in Los Angeles, Ratain cited several reasons why oncology drug development usually fails: inadequate and nonpredictive preclinical models, overreliance on historical controls, and biomarkers that had not been validated.

There is also too much emphasis put on the speed of drug development, he said. Too often, small, quickly done studies with too few patients yield marginal results—just enough to prevent a company from killing a drug. “Society has accepted this high failure rate, and companies have to charge high prices because of it.”

What is often needed, Ratain and others say, are larger, randomized phase II trials with control groups, less reliance on historical controls, and better surrogate biomarkers of a drug’s effectiveness. Also, trial endpoints that focus on disease progression, for example, may save time, save effort, and better reflect how today’s targeted therapies and drug combinations work.

“In the past, we depended on responses as the ‘gold standard’ for continuing to study an agent,” said Bruce Chabner, clinical director of the Massachusetts General Hospital Cancer Center in Boston. “We’re beginning to understand that the newer cancer drugs can be very effective in combination but show little in terms of individual response rates.”

“New Drugs, New Paradigm
The poor track record in drug development and the changing nature of today’s targeted cancer drugs under development have opened the door for different trial designs.

“It gets difficult to apply our traditional trial designs invented 50 years ago for phase I, phase II, and phase III studies to today’s molecularly targeted drugs, especially in combinations with chemotherapy agents,” said Michael Bookman, M.D., vice president of clinical research and ambulatory care at Fox Chase Cancer Center in Philadelphia.

“The traditional phase II–III paradigm doesn’t give us a good process for developing combinations because it’s been toxicity focused—toxicity in terms of traditional chemotherapy,” he noted. “It hasn’t been efficacy focused. We learn what gives us a better response rate and what dose we can safely give of a drug. That’s not going to apply for a lot of these newer agents, where we want to make sure we are giving enough to have a desired biological effect. That paradigm falls apart.”

“Those are potentially very valuable effects, but we may not see them if we depend on traditional measures, if we don’t have biological measures [biomarkers], or if we don’t have control groups involved in some manner as a barometer,” Chabner said. “We’ve had to rethink the way we conduct these trials because we don’t want to throw out effective agents because we aren’t seeing responses.” Monoclonal antibodies, he noted, “were underappreciated and regarded as a failure for nearly 15 years until they were tried in conjunction with chemotherapy.”
Bookman suggested a design in which a phase II trial of a new drug can, in essence, be embedded within a phase III trial. That is, rather than comparing a new drug against the standard in a typically small phase II trial, conduct a randomized study comparing the effectiveness of several agents at once. Such a trial could use surrogate endpoints other than overall survival to determine which drug is most effective and should be tested in a phase III trial.

A team led by Ratain and statistician Theodore Karrison, Ph.D., a research associate in the department of health studies at the University of Chicago, recently proposed a trial design showing the potential advantages of measuring tumor size as a continuous endpoint in a randomized phase II trial (see p. 1455). The study would compare the combination therapy sorafenib and erlotinib with erlotinib alone in non-small-cell lung cancer by using two different dosage arms and a placebo group. While this study should provide stronger evidence for the effect of the treatments by using certain biomarkers, Karrison said, it would also require more patients than a typical single-arm phase II trial. Whether or not a greater average change in tumor size would translate into benefits for survival or progression-free survival couldn’t be answered until a phase III study, he noted.

Ratain and Rachel Humphrey, M.D., a vice president at Bristol Myers Squibb in Wallingford, N.J., have also championed the use of a type of adaptive trial called a randomized discontinuation trial in phase II. In these trials, researchers identify patients who may be benefiting from a drug and then randomize those individuals to either stay on or come off the agent. “If the drug is really working, you see a big difference between a key endpoint in the two randomized arms,” explained Humphrey, who was involved in a randomized discontinuation trial for the development of sorafenib (Nexavar) for renal cell cancer at Bayer.

The trial also has a “run in” period in which all participants are taking a drug, which allows investigators time to look for tumor shrinkage and potentially test biomarkers. They also examine the number of patients who appear to benefit and are eligible to be randomized to stay on the drug or come off. This measure, called the randomization rate, may be an early marker of activity, according to Humphrey.

“Currently, all drug studies in cancer biology are associated with trying to understand the biology and mechanism of action of an agent and the patient and tumor characteristics that would select for patient benefit,” Humphrey said. “The randomized discontinuation trial attempts to do that by enriching the patient population based on their drug responses, not cancer characteristics. If they seem to benefit, and all those patients who are rapidly progressing on the agent are not randomized, then theoretically, the clinical benefits in the randomized population will be amplified.”

“There is a great deal of appeal” to adapting in a trial, said Donald Berry, Ph.D., chairman of biostatistics at the University of Texas M. D. Anderson Cancer Center in Houston, which has pioneered the development of several adaptive trials. One of the benefits of such trials, he noted, was to reduce the number of patients exposed to ineffective drugs. “Companies don’t like to spend much money developing a drug without some indication of effect,” noted Berry, a strong advocate for the use of Bayesian statistical methods, which uses information gained during a trial to affect what happens later (see J Natl Cancer Inst 2006;98:1512–3). “Adaptive designs make good, intuitive sense in many cases, and industry has bought into this,” agrees George Demetri, M.D., of Dana-Farber Cancer Institute and Harvard Medical School in Boston.

**Critics and Downsides**

While pharmaceutical companies appear to be adopting many of the new designs, there is still some resistance and skepticism, Humphrey noted.

A randomized discontinuation design—which puts everyone on the drug, then randomizes those who benefit to stay on the drug or stop taking it—has downsides. “Enriching the patient population for those who benefit from the drug doesn’t help guide the doctor when a patient comes in because the randomized discontinuation design doesn’t model clinical behavior,” Humphrey said. “It may tell you the drug is active but doesn’t guarantee success when you randomize all comers to receive the drug or not. It can potentially mislead.”

Dana-Farber’s Demetri worries about bias in patient referrals. “Adaptive designs don’t always take into account that patients and doctors—and referral patterns—differ,” he said. “As a drug looks more promising, you’re probably going to refer that type of patient into a trial,” thereby skewing the results.

Bookman is concerned about a “growing tendency to place phase III trial endpoints such as overall survival within underpowered phase II trials,” or even put phase II trial endpoints in small phase I studies. “The mix of patients in these trials can be very different, and understanding success or failure may be problematic,” he said.

With sorafenib, the randomized discontinuation trial was a good choice, Humphrey said, though it’s not for every agent. For example, a drug whose effect lasts long after the drug is stopped is not a good candidate. The design assumes that once the drug is stopped, the cancer begins to grow again. Randomizing patients to come on and off with an agent that has long-lasting effects might not have a near-term effect that can be measured, she said, and patients all appear to be the same.

“I think that everyone is looking at such trials, but they are difficult and labor intensive because they require real-time pharmacokinetics on every patient,” Humphrey said. “Theoretically it’s another way to get a quick answer and limit your patients’ exposure to inactive doses of drug.

“Nearly everyone in industry and academia agrees that there’s a need for new study designs, and everyone agrees that as new mechanisms of action emerge in drug development, the winning team needs to be innovative and flexible,” Humphrey said. “I suspect that in the coming years, we’ll see more of these creative phase II designs emerging and setting a standard for quality drug development.”

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