Q&A: Geoffrey Shapiro on Phase I Drug Trials

Drug development is becoming more complex—and informative—in the era of genomic medicine

Given the ever-expanding pool of potential anticancer agents, the desire to test them individually and in combination, and the ability to molecularly characterize tumors to find likely responders, "doctors who do early-phase drug development won't be put out of business any time soon," says Geoffrey Shapiro, MD, PhD, director of the Early Drug Development Center at Dana-Farber Cancer Institute in Boston, MA. He spoke with *Cancer Discovery's* Suzanne Rose about how phase I trials have evolved over the last decade and the challenges of drug discovery in the era of genomic medicine.

How has genomics changed early-phase drug trials?

The major goals of phase I studies have always been to do careful dose escalation, assess safety, determine the maximum dose, and understand an agent's pharmacokinetics. Over the last several years, we've started thinking early on about which patients are most likely to benefit from a drug. Additionally, many phase I studies now incorporate not only traditional safety endpoints and pharmacokinetic work, but also pharmacodynamic work to provide evidence that the target is engaged before the drug moves on to a larger phase II experience.

This question speaks to the fact that phase I trials must be readily adaptable. For example, crizotinib was originally developed to be a potent inhibitor of the MET kinase. The phase I trial was broadly based to evaluate several tumor types that might have MET dependence. However, two early responses in the study were in patients whose tumors harbored *ALK* rearrangement. The trial adapted quickly from a broad-based study to a study that focused on patients with ALK-positive non–small cell lung cancer. This shift provided an early efficacy signal and greatly accelerated the drug's development.

Similarly, we've been working on a drug combination for solid tumors involving a novel nucleoside analog and a kinase inhibitor. After it was reported that the repair process for this nucleoside analog required the homologous recombination pathway, we thought that the best responders might be those with BRCA-deficient cancers. We began to enroll *BRCA* carriers whose tumors were likely BRCA-deficient, and we saw our first responses. Now we're enrolling only *BRCA* patients. These examples show how adaptable a phase I trial needs to be. You can't continue enrolling everyone if a signal develops in a specific population.

When do you sequence tumors? Do you need to do multiple biopsies?

The majority of cancer centers profile tumors up front. The types of analyses vary, but they may help us choose one trial over another for a patient.

For the "pretrial" biopsy, there's a lot of angst over what is adequate. We tend to use an archival biopsy, one that was taken when the patient was first diagnosed, but the patient may have had five or six treatments between that biopsy and starting on a trial. There's a push to do a fresh biopsy so that we have the most accurate snapshot of the tumor before the patient receives the study drug.

Sam Ogden, Dana-Farber Cancer Institute

Phase I trials need to be readily adaptable, says Geoffrey Shapiro, MD, PhD. "You can't continue enrolling everyone if a signal develops in a specific population."

Now we often obtain another biopsy when the patient responds or has stable disease—and the goals of these biopsies are changing. Previously, we focused on immunohistochemical tests to see if the drug target was hit. Now posttreatment biopsies are also subjected to genomic analyses to find signatures of response. We're also doing biopsies at the time of resistance to understand the mechanisms by which the tumor may have become resistant.

What's the best way to evaluate combination therapies?

Having predictive preclinical models to make sure the effects of two agents are additive or synergistic is critical. There's also an element of practicality to consider. Schedules of agents that need to be specifically sequenced in preclinical models may be difficult to translate to the clinic. The easiest combinations to develop are those in which the drugs can be given simultaneously or relatively close together without developing antagonism.

The next challenge is to decide how to conduct the dose-finding portion of the clinical trial. One popular method is a 2×2 dose-escalation scheme. If the low starting doses are safe, two subsequent groups can be enrolled. In one, the dose of drug A would be escalated and drug B would be left the same. In the other group, drug B would be increased and drug A would be left the same. If both of those are safe, the higher doses of each drug are evaluated together, and escalation of each agent is repeated in a step-wise fashion.

A similar method is to set a fixed dose of one drug, such as the maximum tolerated dose, and escalate the second. The advantage of this approach is that we are giving the maximum dose of at least one of the drugs. Alternatively, if there's a lot of experience with both drugs, we can consider a dose–de-escalation trial, with the first dose level being the maximum dose of both drugs. If there's toxicity, we reduce the dose of one drug or the other.

Do you adjust the approach if the combination includes an immunotherapy?

We're still working that out. The first such trial combined vemurafenib [Zelboraf; Genentech] with ipilimumab [Yervoy; Bristol-Myers Squibb] in melanoma, but unexpected hepatic toxicity led researchers to halt the trial earlier this year. Nonetheless, there will be continued efforts to combine targeted therapies with immune checkpoint blockade. This work will need to proceed carefully because new toxicities might emerge when we unleash the immune system. ■