

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Clinical Trial Design for Phase 1 Studies of Drug Combinations



Channing Paller, MD
 Assistant Professor of Oncology
 Johns Hopkins University
 Baltimore, Maryland
 Member, Clinical Trial Design Task Force
 Investigational Drug Steering Committee
 National Cancer Institute
 Bethesda, Maryland

H&O What are the reasons for studying multiple drugs in a single phase 1 clinical trial?

CP Experience has shown us that a single drug is often not sufficient for treatment. Even among the most effective single-drug treatments that improve overall survival, resistance develops over time. For example, the BRAF inhibitor vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) achieves a response rate of approximately 80% among melanoma patients who carry a BRAF V600E mutation. However, the median duration of that response is approximately 7 months before the cancer begins progressing. By combining other drugs that target the same BRAF pathway or that inhibit other pathways in malignant cells, it may be possible to avoid resistance.

Many new drugs are available and in development, and we need to start thinking about new ways to use them together. Some drugs are individually active against a tumor. Others may enhance the effect of another drug. One drug alone may be ineffective, but its effectiveness may be enhanced when the drug is administered in combination with another drug.

The safety of the combination is evaluated, and the recommended phase 2 dosing and schedule are determined in the phase 1 combination trial.

H&O Could you give an example of an unexpected drug combination that benefits patients?

CP Imatinib (Gleevec, Novartis), dasatinib (Sprycel, Bristol-Myers Squibb), and nilotinib (Tasigna, Novartis)

are all tyrosine kinase inhibitors (TKIs) used in the treatment of chronic myeloid leukemia. Ketoconazole is an antifungal medication. When any of these TKIs are given in combination with ketoconazole, TKI exposure in the body is increased because the TKI and ketoconazole both inhibit cytochrome P450 3A4 (CYP3A4), an enzyme involved in metabolism in the liver.

H&O Why do drug combinations need to be tested at the phase 1 stage of clinical development?

CP We need to test their safety, optimal dosing levels, pharmacokinetic interactions, and pharmacodynamic interactions.

H&O What is the first consideration when designing a phase 1 trial of a drug combination?

CP It is essential to start with an explicit or implicit hypothesis justifying the combination based on preclinical work or a pharmacologic or biological rationale. The hypothesis should consider the next step in drug development, and should consider the specific patient population. Will this combination be applicable for a subtype of patients harboring a particular mutation, or is the aim to use it for all patients with a particular type of cancer? Could the hypothesis be applicable to more than one type of cancer? It is essential to consider the direction in which the phase 1 combination study is headed.

H&O How does the interest in combination phase 1 studies connect with the increasing amount of data coming from next-generation sequencing efforts?

CP Next-generation sequencing helps researchers identify potentially actionable driver mutations for which a drug may be available or developed to target those mutations. For example, patients with V600 mutations, found in next-generation sequencing, are good candidates for the use of a combination of MEK and BRAF inhibitors, as preclinical data have demonstrated that MEK inhibitors delay resistance to BRAF inhibitors in these patients.

H&O What barriers are there to drug companies working together to test combinations of drugs in phase 1 trials?

CP When more than 1 pharmaceutical company is involved, companies may disagree about intellectual property ownership, and about how to divide the expenses of trials and profits that may develop from the combination.

H&O What regulatory issues need to be addressed in creating phase 1 combination studies?

CP With regard to national regulatory bodies like the US Food and Drug Administration (FDA), the primary concern is safety. The FDA wants to ensure that the public is safe, first and foremost, in addition to helping companies develop new cancer therapies. To that end, regulators focus on limiting toxicities and determining what pharmacokinetic interactions might be expected with a given combination. Because phase 1 combination studies have become increasingly popular, the FDA released new guidance in June 2013 on codevelopment of 2 or more new investigational drugs for use in combination. The guidance document explains how to answer specific scientific and regulatory questions, such as: How will the drugs get developed? What steps are needed to bring a combination through clinical trial development? Is the combination safe? Will there be more toxicities than there would be with a single-agent? Combination therapies are held to a high standard in that not only do they need to improve patient outcomes, they also need to have greater efficacy than the single agent.

The FDA guidance recommends that any proposed combination regimen have a strong biological rationale. There must be a full nonclinical characterization of the activity of both the individual drugs and the combination. In addition, there needs to be a compelling rationale for why the combination may be more effective than monotherapy.

H&O Could you provide an example of a successful phase 1 combination study?

CP The combination of trametinib (Mekinist, Glaxo-SmithKline) and dabrafenib (Tafinlar, GlaxoSmithKline) in the treatment of melanoma provides a useful example. As reported in the *New England Journal of Medicine* by Flaherty and colleagues in 2012, this combination was found to significantly improve overall survival among patients with BRAF V600 mutant metastatic melanoma. At the same time, the combination significantly reduced the incidence of secondary cutaneous squamous cell carcinoma compared with monotherapy: 19% for patients receiving dabrafenib monotherapy vs 2% for patients receiving the combination. In addition, skin rashes were less common with the combination approach than with monotherapy. The 2-drug approach was approved by the FDA for the treatment of metastatic melanoma based on the phase 1/2 results because it improved efficacy and decreased toxicity.

H&O You mentioned earlier that strong preclinical data, a pharmacologic or biological rationale, and a plan for further development are important prerequisites for a phase 1 trial. What are other important considerations?

CP There are 3 important scenarios that determine the design of a phase 1 combination trial. First, if there are known or potential overlapping, dose-limiting toxicities, a formal phase 1 study is required. Second, in the absence of overlapping dose-limiting toxicities and no plausible reason to anticipate pharmacodynamic interactions, but plausible pharmacokinetic interactions, a formal drug-drug interaction design should be employed. Finally, if there is no plausible basis for pharmacokinetic or pharmacodynamic interaction, no formal phase 1 trial is required, although a tolerability run-in phase of a phase 2 trial may be helpful.

H&O How do investigators handle the risk of drug-drug interactions in a phase 1 combination study?

CP If 2 drugs being given to patients at the same time interact, there may be synergistic toxic effects as well as beneficial effects. If there is evidence of increased toxicity, the dosing and scheduling of the combination may be altered.

H&O What other barriers exist in designing and executing phase 1 combination trials?

CP In addition to questions of intellectual property ownership and cost sharing I mentioned earlier, the length of time required for phase studies may be a barrier. Phase

1 studies take a long time because investigators monitor patients for toxicities for several weeks at each dose level before starting the next group of patients at a higher dose level. Another barrier is difficulty in accruing patients to phase 1 trials because patients in early dosing cohorts often receive subtherapeutic doses. Subtherapeutic doses are less common in trials of molecularly targeted agents than in trials of cytotoxic agents.

H&O Is there any way to shorten the time required?

CP One way to shorten the testing time for a combination at phase 1 is by using an accelerated titration design. If we know, based on either other drugs in the same class, preclinical data in animal models, or other studies, that the drugs are safe at certain dose levels, it may be possible to accelerate the titration, using 1 or 2 patients per cohort instead of the usual 3, and escalating the doses faster.

H&O Are phase 1 combination trials becoming more common?

CP Yes, definitely, because of the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) leadership. CTEP works with drug companies and academic investigators who provide preclinical data or data from phase 1 single-agent studies. Investigators may submit a letter of intent demonstrating a strong biological rationale why a combination approach might be superior to a single-agent approach. If CTEP agrees, it will facilitate the partnership and provide funding for the clinical trial.

H&O How do phase 1 investigators navigate finding the right dose levels for 2 different medications?

CP If 2 drugs are being studied in combination, it is necessary to try to determine which is more biologically active. If a drug is approved and known to be active in a particular tumor type, the dose of that drug should be kept constant at its known effective level. If another drug is known to enhance the first drug, it should be added slowly. The dose of the active drug will be fixed, and the dose of the enhancer will be titrated up in a phase 1 trial in order to find the optimal dosing level. If excessive toxicity arises, the dose or doses will be reduced.

H&O How do phase 1 combination studies impact phase 2 studies?

CP The phase 1 trial determines the recommended phase 2 dosing for the combination. In some cases, a phase 1 trial may detect toxicities that prevent investigators from proceeding with a phase 2 trial.

Suggested Reading

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