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## Featured Article

# Clinical Trials of Targeted Cancer Drugs: Getting the Right Combinations to the Right Patients

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With the first wave of targeted cancer drugs already on the market, a key dilemma facing researchers is how to create optimal combinations of targeted agents, and how to identify the appropriate patients to receive those combinations.

A key goal of clinical oncology research, which may be achievable in the foreseeable future, is to turn cancer into a chronic rather than fatal disease, much as the advent of anti-retroviral drugs has done for HIV in the developed world. And as with HIV, it is expected that the ability to prevent a neoplasm from progressing will require "cocktails" of targeted agents.

Yet the heterogeneity of cancer makes cocktails difficult to create. Many targeted agents are designed not just to discriminate between cancerous cells and healthy cells, but to hone in on a specific type of tumor, with not only a specific histological subtype, but also specific mutations or over-expression of a specific receptor.

Experience has started to reveal where certain combinations may be additive or synergistic: targeting the PI3K-mTOR and RAS-ERK pathways, for example, or combining IGF-1R inhibitors with EGFR inhibitors. Such combinations may in fact be essential in reducing the development of resistance when treating certain cancers. But evaluating multiple targeted agents in a single clinical trial is uniquely complex – particularly when neither agent is yet approved.

### Investigative Combinations

While animal models are an essential starting place to evaluate combinations of targeted cancer drugs, they are imperfect predictors of activity and side effects in humans. Certain targeted agents have been known to elicit unpredicted toxicities, so the first step to combining two investigational cancer drugs is to study each agent individually in Phase I. And although the combination will likely be developed as an addition to standard-of-care, early Phase I studies should evaluate each drug as a monotherapy to generate uncluttered safety data and early evidence of activity.

Trial sponsors then need to identify the recommended Phase II dose of each drug when used together in combination. Initial combinations should include appropriately low doses of each drug to ensure they are safe when used together. Dose escalation can then continue until dose-limiting toxicities are identified or until target inhibition can be documented.

Ideally, the Phase I portion of the trial should roll seamlessly into a Phase II study, with the Phase II sites ready to enroll patients as soon as doses are fixed. Yet such expansion studies involve a delicate balance, because bringing the Phase II sites online too soon could mean a long gap before enrollment can begin, during which the interest of the investigators might wane. The momentum from the Phase II studies should similarly be leveraged into Phase III.

  
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Clinical design and enrollment are only a small part of the complexity surrounding the evaluation of two unapproved targeted cancer drugs. There are regulatory considerations involved with such trials, as well as business development considerations if the two compounds are being developed by different sponsors. While some companies will seek to license or acquire the asset they need for a combination study, there is increasing interest in the formation of pre-competitive partnerships around such trials.

### Improving Standards

Although combining two unapproved agents is still relatively rare, most targeted cancer drugs are developed for administration in combination with the standard of care, and that standard increasingly includes an approved targeted agent. Such clinical trials bring their own unique challenges.

For example, establishing activity in early trials can be challenging because many targeted agents don't cause tumor shrinkage, rendering response rates ineffective. With cytotoxic drugs, early clinical development was relatively straightforward: the sponsor would evaluate response rates with increasing doses until the maximum tolerated dose was established. But with targeted agents, more is not necessarily better, which makes dose-finding studies a challenge. And in addition to response rates, the sponsor must often evaluate biomarker data, which may be affected by the targeted standard of care agent as well as the investigational agent.

As targeted combination trials expand internationally, additional complications arise. For example, the standard-of-care and the availability of FDA-approved targeted agents may differ from country to country. Additionally, in many countries outside the United States, the sponsor is responsible not only for the cost of the investigational agent, but for the cost of the standard of care as well. If a sponsor wants to test a targeted cancer drug with an approved targeted agent – many of which run upwards of \$50,000 per year – the study can become prohibitively expensive.

Enrollment can also be a challenge, as it is in all oncology trials. There are massive numbers of competing trials underway, but less than 10 percent of cancer patients participate in them. And beyond the patients, certain investigators are highly sought-after for cancer clinical trials. As always, a sponsor's greatest advantage in getting them excited about a study is compelling science.

### Getting Personal

Creating the right combinations of targeted cancer drugs is only half the battle: the other half lies in determining which patients will benefit from which combinations.

Oncology has become somewhat of a proving ground for personalized medicine, since cancer researchers have already realized that the mutations underlying a tumor are far more relevant than the tissue of origin. Some cancer drugs, like Roche's Herceptin (trastuzumab) for breast cancer, are already prescribed according to biomarker-based genetic tests. Other drugs, like AstraZeneca's Iressa (gefitinib), initially demonstrated a low level of activity until patients with the appropriate mutational targets could be identified.

Many targeted cancer drugs are being developed with a specific mutational subtype in mind. But it is important to understand the drug's mechanism of action before starting clinical trials that focus on that subpopulation. For example, many kinase inhibitors are rather promiscuous, and focusing in on patients with a mutation in one pathway might miss efficacy generated in another pathway.

Once the drug's mechanism has been elucidated, companies may choose to conduct clinical trials that focus on patients with a specific mutation. Trials in which most patients with a particular cancer harbor the mutation of interest are relatively straightforward, but if the mutation only occurs in 25 to 30 percent of patients, enrollment can be more challenging. The benefit of focusing on a narrow patient population is that, theoretically, there should be a higher degree of efficacy. Some sponsors choose instead to conduct a broader trial and to evaluate the mutational subsets retrospectively, and there are pros and cons to both approaches.

Regardless, companies developing cancer drugs that target specific biomarkers must ensure that there are valid, approved diagnostic tests for that biomarker either on the market or in development. ChemGenex Pharmaceuticals recently received a complete response letter from the FDA for Omapro (omacetaxine mepesuccinate) requiring the development of a diagnostic test to identify chronic myeloid leukemia patients with the T315I genetic mutation. The decision and the related advisory panel clearly show that the agency and the physician community expect developers of targeted drugs to provide a means for identifying the targeted patients.

Regardless of whether a sponsor intends to develop a companion diagnostic test internally or with a partner, such development must be planned early in the clinical trials process. Perhaps some day, complete cancer genome sequencing will be a standard of care for all patients – the technology exists and some companies are pushing it forward – but for now, each sponsor must take responsibility for identifying which patients are most likely to benefit from its drugs.

### About INC Research®

*At INC Research, we understand that cancer is not one disease, but a category of widely varying diseases, each with its own specialized scientific complexities, patient populations, and range of treatment options. Our oncology team offers global contract research services with a unique understanding of the challenges facing cancer drug developers. We have conducted more than 350 Phase I through Phase IV oncology trials, dealing with targeted therapies, combinations of investigational agents, immunotherapies, preventative measures and supportive care indications such as cancer pain. As a full-service contract research organization, we have the breadth to run global trials as well as deep connections with oncology thought leaders, investigators (both academic and community based), professional societies, cancer cooperative groups and patient support groups around the world. For more information, contact Nicholas Kenny, Ph.D., Executive Vice President, & General Manager, Oncology INC Research at [nkenny@incresearch.com](mailto:nkenny@incresearch.com) or 919-334-3589.*

### About the Authors

**J. Michael Hamilton, M.D., Senior Medical Director, Oncology** has more than 25 years of experience in clinical oncology and hematology -oncology drug development. During 17 years at the National Cancer Institute, he oversaw clinical strategy in colorectal cancer and CNS tumors in the Cooperative Group system. In this setting he also conducted Phase I clinical trials with new agents, including anti-tumor vaccines, and fulfilled duties as chairman of the NCI Institutional Review Board, director of the Oncology Fellowship Training Program, and supervisor of the hematology-oncology research nurses, outpatient clinic, and in-patient oncology unit at the National Naval Medical Center.

Subsequently, for seven years at GlaxoSmithKline (GSK), he was the medical director for the FDA approval and late phase development of BEXXAR and the early development, leading to the FDA approval of Promacta (eltrombopag) as well as the development of other hematology -oncology compounds and vaccines. After leaving GSK, Dr. Hamilton served as the chief medical officer (CMO) at Avalon Pharmaceuticals where he oversaw all clinical strategic planning and development of discovery and clinical projects, as well as evaluation and ranking of licensing opportunities. Dr. Hamilton continues to teach patient care and clinical oncology to NCI Fellows at the National Naval Medical Center in Bethesda, MD.

**Michael Kurman, M.D., Senior Medical Director, Oncology** has 30 years of oncology drug development experience as both a clinical investigator and pharmaceutical executive. Dr. Kurman started his career in the practice of oncology, during which he was an investigator on several oncology clinical trials. Since joining industry, he has held positions of progressively more responsibility in Janssen, Cytogen and US Bioscience, and was involved in the successful development or launch of four oncology products. Before joining INC Research, Dr. Kurman was Vice President of Clinical Operations for Quintiles' Oncology Division.

His primary interests are in early phase oncology clinical trial design and drug development, and in strategic portfolio management. In addition, he serves on the Scientific Advisory Boards of several companies and is on the Board of Directors of Thallion Pharmaceuticals. Dr. Kurman is board certified in Internal Medicine and Oncology, and did his oncology training at Mt. Sinai Hospital in New York.

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