For Investigational Targeted Drugs, Combination Trials Pose Challenges

Second in a two-part series.

In principle, combining old-line cytotoxic chemotherapies made sense. Those combinations went on to prove their worth in extensive clinical trials and are now enshrined in standard practice. Combining the new, targeted therapies often makes sense, too. But many of them have not been approved yet by the U.S. Food and Drug Administration. For clinical investigators, initiating trials of two experimental agents can be tough sledding.

“Getting access to multiple targeted drugs is not easy if they’re still experimental,” said Dave Johnson, M.D., director of the Division of Hematology and Oncology at Vanderbilt University Medical Center in Nashville. “There was a day, years ago, when the only drugs worth testing were coming from CTEP [NCI’s Cancer Therapy Evaluation Program],” said Johnson. But these days, most drugs come from companies, whose corporate cultures—and in particular, their legal departments—render them reluctant to collaborations with potential competitors.

“Pharmaceutical company A may not be so terribly interested in collaborating with pharmaceutical company B when both of their drugs are experimental,” Johnson said. “So there haven’t been a lot of human studies where more than one targeted therapy have been combined.”

One-Stop Shop

However, Johnson and his colleagues are successfully carrying out a trial of two investigational agents that are owned by the same company: Genentech. The phase II trial combines Avastin (bevacizumab), a monoclonal antibody directed at a receptor for vascular endothelial growth factor (VEGF), with Tarceva (erlotinib), a small molecule that targets the epidermal growth factor (EGF) receptor (Genentech calls it HER1), in non–small-cell lung cancer (NSCLC) patients.

Earlier this year, after less than spectacular clinical trial results on its own, Avastin in combination with chemotherapy was shown to improve colon cancer survival more than either therapy alone. Based on those results, Genentech filed for FDA approval. Avastin has since shown antitumor activity in renal cancer.

Tarceva was initially developed by OSI Pharmaceuticals. Genentech obtained access to the OSI compound after taking a major ownership position in the small biotechnology company. Although Tarceva recently failed as a first-line agent in a phase III trial in lung cancer, it is in ongoing trials with refractory patients.

A small phase I trial of Avastin and Tarceva in 12 multiply relapsed NSCLC patients resulted in tumor shrinkage—considerably better than with either agent alone. Three subjects had partial responses, and five others had stabilized tumors.

“That is not something one sees every day of the week in recurrent lung cancer, let’s put it that way,” observed Johnson, who has spent about 25 years in lung cancer research. “Some of these patients are still responding well over a year later.”

Enrollment in the 50-patient phase II trial, which like the phase I study is being conducted at Vanderbilt and the University of Texas M. D. Anderson Cancer Center, Houston, is restricted to patients with adenocarcinoma. Johnson said that is because during a trial of Avastin conducted some years ago, some patients suffered from severe bleeding in the lung near the tumor site. Analysis suggested that the bleeding was confined to patients with squamous-cell carcinoma.

Genentech has several additional targeted therapies, including two of the oldest commercially available monoclonal antibodies: Rituxan (originally developed by IDEC Pharmaceuticals), directed at a surface antigen on B cells, for lymphoma; and Herceptin, which
binds to the growth-factor receptor HER2, for breast cancer. An investigational monoclonal antibody, 2C4, also binds to HER2 in a way that manages to impair the function of the entire HER family. The company has been moving combinations forward into clinical trials whenever there is a good rationale to do so, said Gwen Fyfe, M.D., vice president for clinical oncology development.

“Given the unbelievable crosstalk in the HER family—at least three related receptors that dimerize with HER2, and about 10 known ligands—you’d be surprised that any single intervention would downregulate signaling,” Fyfe said. “We have preclinical data on Avastin and Tarceva, Avastin and Herceptin, and 2C4 and Herceptin, showing at least additive activity”—the sum is better than either part alone. Genentech has initiated early-stage trials of Avastin plus Herceptin and also of Herceptin and Tarceva, both in breast cancer; a phase II Avastin-Tarceva combination trial in renal cell cancer is rapidly accruing patients.

The Broker

Such combination trials are relatively easy when the compounds are all owned or licensed by one company, but what about combining an investigational drug with another investigational drug from a different company? Companies developing one or both compounds have real concerns—not the least of which is the fear of fortuitous bad reactions.

“Suppose we did a combination trial,” Johnson mused, “and had some catastrophic result—like the first three patients just up and died within 2 hours of being treated. That would put a cold chill on both drugs. That’s the conundrum that companies face.”

NCI’s CTEP has been the broker of many combination trials of investigational drugs. CTEP has experimental access to a large number of drugs, including many that are still investigational, said Jon Wright, M.D., Ph.D., a CTEP senior investigator who deals exclusively with targeted therapies, most of them small molecules. More than a dozen CTEP-sponsored combination trials of targeted therapies are under way. CTEP investigators meet informally with a broad cross-section of FDA representatives once a month to discuss any possible concerns about combination trials and the best options for moving those trials forward, according to Wright. If two single agents each have decent safety profiles, the FDA does not ordinarily require lengthy toxicologic studies of the combination. However, just as was the case with the old cytotoxics, investigators must proceed with care when they combine the new drugs.

Millennium Pharmaceuticals, maker of the small-molecule drug Velcade (bortezomib), has been supportive of CTEP-sponsored combination studies of its drugs with other companies’ investigational agents. “The hope is that these novel therapies will not have—and they should not have—overlapping toxicities,” said David Schenkein, M.D., Millennium’s vice president for clinical oncology development. Velcade, recently approved for multiple myeloma, targets the proteasome, an intercellular garbage can that digests proteins tagged by molecular labels for destruction.

One CTEP study now being contemplated would combine Velcade with 17-allylamino-geldanamycin, or 17-AAG, which originated with CTEP but is now being developed by Kosan Biosciences. Velcade’s inhibition of proteasome function renders cancer cells more susceptible to apoptosis (programmed cell suicide), whereas 17-AAG triggers apoptosis by interfering with the chaperone function of heat-shock proteins (HSPs), intercellular molecules that among other things assist nascent proteins to assume their correct shapes.
Preclinical investigations suggest potential synergy between these two mechanisms. Both drugs appear to be well tolerated as single agents. However, because 17-AAG's parent molecule is quite toxic, CTEP investigators are doing additional toxicology studies of the combination to come up with safe dosing levels.

Also working closely with CTEP is Genentech. CTEP is sponsoring a phase II study of Avastin plus Celgene's Thalomid (thalidomide) in multiple myeloma (Thalomid is approved, but not for that indication) and another in prostate cancer of Avastin plus Dendreon's Provenge (a vaccine prepared from dendritic cells pulsed with an antigen often found on prostate cancer cells).

Genentech wants the NCI to coordinate the possible pairing of Avastin with Erbitux (cetuximab), co-developed by ImClone Systems and Bristol-Myers Squibb, in colon cancer trials, Fyfe said: “Both will potentially be on the market sometime early next year, so it becomes very important for the companies to work together to provide safety, if not efficacy, data on how to combine them. Because, as we know, physicians will experiment. Better for us to do a well-controlled, well-conducted trial than to have it unfold in an uncontrolled, patient-by-patient fashion.”

CTEP does not necessarily wait for companies to come calling. When CTEP investigators become aware of preclinical data that justifies trying a combination, they try to facilitate it by approaching the various entities and asking them to work together, said Sherry Ansher, Ph.D., who coordinates research and development agreements for CTEP. CTEP may have found a remedy for companies' second major concern (the first is side effects) regarding collaborating with one another: intellectual property. All CTEP-sponsored collaborations now commence with an agreement in which the collaborating companies accept a non-exclusive, royalty-free license to the drug when used in combinations, if an application is filed. Thus, if a combination of the two agents is approved for a new indication, neither company can block the other one from using that combination in the indication tested, nor can it charge the other one for using it. Each can use it, sell more of its own product, and make money. And if the other company sells more of its products as a result, so be it.

“The only way to test experimental combinations is to get companies to play together,” said James Zwiebel, M.D., CTEP’s associate branch chief for biologics evaluation, which covers everything from monoclonals to antisense to oncolytic viruses and vaccines composed of living cells. “The alternative—to wait for each drug to be approved, and then mix and match—would take years. And that means many patients who will not be able to benefit as a result.”

—Bruce Goldman