Double Down for a Double Win

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The rationale for using multiple inhibitors between and within the phosphoinositide 3-kinase/AKT/mTOR and RAS/MEK/ERK pathways is scientifically compelling, and a limited number of experimental agents are currently being tested in phase I combinations. Patient subpopulations, whose tumors are defined by genetic lesions, are showing promising responses to this approach. Clin Cancer Res; 18(8): 2124–6. ©2012 AACR.

In this issue of Clinical Cancer Research, Shimizu and colleagues (1) report the results of an early-stage clinical study measuring the effects of dual inhibition of the phosphoinositide 3-kinase (PI3K)/Akt/mTOR and RAS/mitogen-activated protein (MAP)–extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK pathways. Their data, interpreted within a retrospective analysis of more than 1,500 phase I cancer patients from a single study center, support the conclusion that combined pathway inhibition has the potential for activity in the advanced disease population. These preliminary results illustrate both the opportunities and challenges for accelerating development of combined agents that have not rigorously shown patient benefit in the monotherapy setting. The growing armamentarium of new targeted therapies gives cancer patients and their caretakers reasons for optimism, and yet, scientists argue that even greater success can be achieved when these new therapies are combined for treatment. Recognition of this potential was validated in the draft "Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination," released by the U.S. Food and Drug Administration in 2010 (2), placing this problem squarely in the hands of drug developers who must now meet the challenge.

Definitive combination studies are enabled by previous knowledge of compound activity in the monotherapy setting and large studies characterized by high patient enrollment numbers. The conservative approach to initiating combination studies is to accumulate this information via a drug development path that requires demonstration of efficacy as a single therapy, delaying the initiation of combination studies by many years. Alternatively, the study described by Shimizu and colleagues shows a novel and quick approach to addressing the feasibility and potential efficacy for therapeutic combinations of new molecular entities. Like the "double down" risk taken by the blackjack player who has an urgency to win, the risks of failure associated with a combination study in the phase I setting are high. However, the potential for greater benefits is undeniable.

What can scientists and clinicians do to design the most meaningful clinical study in this space? A popular and woeful adage for modern cancer drug discovery and development is the statement that preclinical models fail to predict lack of efficacy when new molecular entities (NME) are tested in the clinical setting. Like all adages, this statement is at least partially correct: Every agent that is tested in the phase I clinical setting has shown activity in a preclinical model that is impressive enough to warrant a clinical study, but the overall 90% to 95% failure rate in progression from phase I anticancer assets to registration and marketing proves the point.

One explanation for this troublesome situation is that preclinical scientists tend to optimize their studies to show the possibility of a drug working in a handful of representative settings. In contrast, clinical decisions are made based on the probability of responses in a mixed patient population. Recent successes have occurred when scientists and clinicians have been able to bridge these 2 very different approaches; the mapping of genomic drivers of cancers and the identification of molecular endpoints to measure pathway state have vastly improved the ability to create new agents with well-understood mechanisms of action. This research has allowed for the selection of appropriate preclinical biologic models and, of equal importance, the generation of clinical biomarker tools that can inform dose selection and identify a responsive patient population. Although it is early to be conclusive, the expectation that new combination therapies will have broad clinical activity seems not to be the case. Combination therapy, like successful monotherapy approaches, will be most successful in genetically defined patient subpopulations.

The notion to combine inhibitors of the PI3K/Akt and MEK/ERK pathways is supported by multiple lines of evidence. Specifically, both pathways are subject to mutational
activation, and these genetic lesions can co-occur, for example, in mutant BRAF/PTEN–null melanoma (3) and mutant BRAF/KRAS and PI3KCA in colorectal cancer (4). Both pathways are also downstream effectors of oncogenic receptor tyrosine kinase signaling and can be inhibited when these receptors are blocked by therapeutic intervention (5). Finally, multiple downstream effectors of the pathways, with roles in cellular proliferation and apoptosis, integrate signaling to mediate an antitumor effect. (Fig. 1A; ref. 6).

Cancer types in which these pathway-activating mutations are found, whether alone or in concert, represent attractive candidate subpopulations for the clinical testing of this specific combination. Indeed, although the number of genetically characterized patients is small in the study presented by Shimizu and colleagues, it is very encouraging to see consistent responses to dual pathway inhibition in a patient subpopulation with complementary-activating mutations.

Are there other combinations using PI3K/AKT/mTOR pathway inhibitors that have the potential to be successful? Even a cursory examination of the parameters for combination study design for these pathways produces a mind-boggling list of options. To date, multiple inhibitors of each pathway with different specificities, pharmacologic properties, and mechanisms of action are ready for study. How can we choose? Combination therapies are used extensively in the treatment of many diseases and are limited by pharmacokinetic properties, overlapping toxicities, and drug–drug interactions, which are important factors to consider in the development of treatment. These issues have been addressed numerous times in the pharmaceutical literature, providing guidelines for NME selection in combination treatments. When considering pharmacologic criteria, however, another critical factor is having an understanding of the interplay between the NMEs that goes beyond the phenomena of growth arrest and tumor shrinkage. This consideration is especially relevant to the PI3K/AKT/mTOR pathway, as it regulates itself and can respond to inhibition by quickly initiating feedback loops, activating expression of upstream signal transduction receptors through multiple mechanisms, a major one being the derepression of the FOXO transcription factor (7). In preclinical studies, combinations of PI3K pathway inhibitors with upstream receptor tyrosine kinase inhibitors can blunt this response, leading to greater efficacy than with the receptor tyrosine kinase inhibitors alone (8). An ongoing clinical study that exploits this concept in estrogen receptor–positive breast cancer patients is described in Fig. 1B (9).

Finally, turning to the RAS/MEK/ERK pathway, an ongoing study worth noting is the combination of BRAF and MEK inhibitors, currently moving to phase III confirmatory studies (Fig. 1C; ref. 10). The remarkable efficacy of the selective BRAF inhibitor vemurafenib has led to quick approval for use in patients with V600E BRAF mutant–driven melanoma. In the preclinical setting, the reactivation of MEK signaling during BRAF repression is a mechanism of acquired resistance in tumor cells (11) and is postulated to induce hyperproliferation in other tissues where RAS signaling is dominant, for example, squamous cell carcinoma.

Figure 1. A, cross-pathway combinations studied by Shimizu and colleagues. AKT and MEK pathways converge to regulate apoptosis and proliferation. B, insulin-like growth factor receptor (IGF)-IR inhibitors blunt the feedback loop induced by mTOR rapalogues. C, MEK inhibitors potentiate BRAF inhibition in tumor cells and block the paradoxical activation of RAF in cells with RAS activation. Figure adapted from Heidorn et al. (11).
The dual combination, which does not directly modulate the PI3K/AKT/mTOR axis, could have the potential to both enhance the anticancer properties of mutant BRAF in this specific patient subset and blunt the disorders that may arise because of BRAF inhibition in tissues with elevated RAS activity.

In summary, the use of combination therapy is not unique, as combination treatments are the rule for many disease areas. Selective, rationally designed inhibitors enable development of combinations with better efficacy outcomes. A necessary component of this approach is proper selection of responder populations. There are many challenges to execution in this space, but the innovative analysis done by Shimizu and colleagues, as well as in the other studies described here, is a welcome beginning to the creation of development paths that will rapidly deliver effective combination therapies for patient response.

Disclosure of Potential Conflicts of Interest
P.S. Huang is the VP of Oncology for Merck and the CSO and founder of Beigene.

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