**CCR Translations**

Commentary on Shimizu, T. et.al.

**Double Down for a Double Win**

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The rationale for using multiple inhibitors between and within the PI3K/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.
In this issue of *Clinical Cancer Research*, Shimizu, et al (1), report the results of an early stage clinical study measuring the effects of dual inhibition of the PI3K/AKT/mTOR and RAS/MEK/ERK pathways. Their data, interpreted within a retrospective analysis of over 1500 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 demonstrated patient benefit in the mono-therapy setting. The growing armamentarium of new targeted therapies give 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 FDA late last year (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 mono-therapy 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 et al. demonstrates 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 are 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 NMEs 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 demonstrated activity in a preclinical model that is impressive enough to warrant a clinical study, but the overall 90-95% failure rate in progression from Phase I anti-cancer assets to registration and marketing, proves the point.

One explanation for this troublesome situation is that preclinical scientists tend to optimize their studies to demonstrate 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. Where scientists and clinicians have been able to bridge these two very different approaches is where recent success have occurred- 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 has allowed for the selection of appropriate pre-clinical biological models, and of equal importance, the generation of clinical biomarker tools that can inform dose selection and identify a responsive patient population. While it is early to be conclusive, the expectation that new combination therapies will have broad clinical activity appears not to be the case. Combination therapy, like successful mono-therapy 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 PI3KC 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 anti-tumor effect. (e.g., (6), see Figure 1a). Cancer types where these pathway activating mutations are found, whether alone or in concert, represent attractive candidate sub-populations for the clinical testing of this specific combination. Indeed, while the number of genetically characterized patients is small in the study presented by Shimizu et al., 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, pharmacological 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. While considering pharmacological 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 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 de-repression 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 RTKi alone (8). An ongoing clinical study that exploits this concept in ER positive breast cancer patients is described in Fig 2b (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 (10), Fig 1c). 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 re-activation 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, e.g. squamous cell carcinoma (12). The dual combination, which does not directly modulate the PI3K/AKT/mTOR axis, could have the potential to both enhance the anti-cancer properties of mutant BRAF in this specific patient subset, while blunting the disorders that may arise due to 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 in Shimizu et al and the other studies described here, are a welcome beginning to the creation of development paths that will rapidly deliver effective combination therapies for patient response.

Acknowledgments

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References:


Dead BRAF and Oncogenic RAS Cooperate to Drive Tumor Progression through CRAF”. 2010. Cell140(2): 209–221.

Caption for Fig 1:

A: Cross pathway combinations studied in Shimura, et al. AKT and MEK pathways converge to regulate apoptosis and proliferation.  B: IGF1R 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 derived from (11).
# Clinical Cancer Research

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