Q&A: From Approval to Practice -- MEK/BRAF Combos

Keith Flaherty, MD, Director of Developmental Therapeutics at the Cancer Center of Massachusetts General Hospital led clinical trials resulting in the approval of the first-in-class BRAF inhibitor, vemurafenib, as well as the first trial of BRAF/MEK combination therapy (dabrafenib plus trametinib). Here, Dr. Flaherty discusses the latest and forthcoming research with respect to MEK/BRAF combination therapies.

What potential advantages does the BRAF inhibitor LGX818/ MEK inhibitor MEK162 combo have in your current study have over combinations of now-approved agents from previous studies?

A: Adding a MEK inhibitor to a BRAF inhibitor has efficacy advantages but also advantages with respect to reduced toxicity. We have observed that already with the dabrafenib/trametinib combination, but the benefits tend to be even greater with LGX818 plus MEK 162. This combination potentially gives us even greater capacity for using a higher dose of LGX818 than could safely or tolerably be administered on its own when it is coadministered with MEK162. This combination potentially offers us a chance of breaking into new territory that we have not yet reached with any of the other BRAF/MEK combinations.

Q: Another type of combination therapy for BRAF V600 melanoma currently in trials involves combining a CDK4/6 inhibitor, such as LEE011 or palbociclib, with a BRAF inhibitor (LGX818) or a MEK inhibitor (trametinib). Can you comment on the use of CDK4/6 inhibitors in combination therapy for treatment of BRAF V600 melanoma?

There are multiple CDK4/6 inhibitors in clinical development right now, 3 of which look comparable to each other, namely the ones from Pfizer, Eli Lilly, and Novartis. We are very keen to deploy these agents on top of a MAP kinase pathway inhibitor backbone. In BRAF mutant melanoma it would be difficult to embrace anything other than a BRAF/MEK combination as the backbone because it is simply the most efficacious approach to block the pathway. In tumors that do not have a BRAF mutation, those that have other mutations, such as NRAS or NF1, combining a CDK4/6 inhibitor with a MEK inhibitor is the strategy that we think is the most scientifically and clinically relevant.

Q: Based on results you have seen to date, which BRAF and/or MEK inhibitors could you imagine would work well in combination with the CTLA-4 antibody ipilimumab? Would you sequence these agents?

We are quite excited about the notion that BRAF inhibitor-based therapy is potentially a powerful combination strategy with any of the immune therapies, including ipilimumab and the PD-1 antibodies. A lot of questions remain to be answered in terms of how to do that clinically from a safety perspective, but also how to optimize the use of these types of combinations. It may not be the case that simply administering all the drugs starting on the same day and then using them continuously is the way to do it. Better efficacy and safety may instead be achieved by using various interrupted schedules.

It is most easy to interrupt is BRAF inhibitor-based therapy because it is pill-based, and the drugs will be cleared from the body in relatively short order, in a matter of days. So there is the possibility of having patients use an on again/off again inhibitor treatment schedule while they are building up immunologic effects through continuous use of agents such as ipilimumab.
Are there any other combinations of importance you'd like to mention?

Other agents that are drawing a fair amount of attention are combinations with the same MAP kinase pathway backbone, either a BRAF/MEK combination or MEK inhibitor alone in the relevant genetically-defined subsets, combined with MDM2 antagonists. These are drugs that we hope will be useful in at least a subset of tumors where p53 is not mutated. More specifically, some tumors have MDM2 that is responsible for essentially shutting down or silencing p53 function. Blocking MDM2 in the laboratory seems capable of restoring p53 function and therefore restoring some of the damage- and stress-sensing apparatus within cells.

We think that MDM2 blockers could be advantageous in combination with molecular-targeted therapies such as BRAF inhibitor-based therapy. Interesting preclinical data have been produced by our group and others that support this approach. So that is another direction that over the next year or two is going to receive attention, because, thankfully, there are multiple MDM2 inhibitors moving forward in clinical development.

Another topic that has been on the radar for quite some time, but remains an area of interest, is trying to co-target the PI3K pathway, either PI3K itself or Akt, in combination with BRAF, BRAF/MEK, or MEK inhibitor backbones. These targeted therapy combination approaches are front and center in the field right now. The other category, as noted, that is really a major area of focus is the targeted therapy/immunotherapy intersection.

Anything else that you would like to add?

That certainly covers the landscape of what we hope will be the next quantum leap beyond the past couple of quantum leaps we have seen in the field. We are hopeful that the PD-1, PD-L1 antibodies will become approved within a relatively short time. The Merck PD-1 antibody NDA was filed for regulatory consideration in the US a couple of months ago, so we are hoping that this agent might be approved in 2014. As the first of these drugs becomes a standard treatment, we will derive multiple possibilities in terms of next-generation clinical trials to go further into that targeted therapy/immunotherapy intersection.

References