Melanoma Researchers Turn to Targeted Inhibition

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WAIKOLOA, HAWAII — Researchers, frustrated by more than 3 decades of entirely negative clinical trials that were aimed at establishing new treatments for metastatic melanoma, have pinned their hopes on targeted mitogen-activated protein kinase inhibitors.

"In metastatic melanoma, we have no defensible treatment standard. There are a few treatments that are offered to patients with the possibility of some palliative benefit, but little to no possibility of curative benefit," Dr. Keith T. Flaherty said at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

This dismal current state accounts for the hopeful buzz surrounding the investigational targeted mitogen-activated protein (MAP) kinase inhibitors, said Dr. Flaherty, who is on the advisory boards of AstraZeneca Pharmaceuticals LP and Schering-Plough Corp., which are actively pursuing development of targeted inhibitors.

It is unlikely, though, that any of these agents will be effective as single-agent therapy. Multiple concomitant mutations in different signal transduction pathways are a hallmark of metastatic melanoma, so when one pathway is blocked, another is likely to increase compensatory signalling.

"Ultimately, combination targeted therapy is the direction we're going. We think that's what one is going to need to counter the various signal transduction pathways which are simultaneously activated in this disease. It's not a single pathway that drives this disease, and we need to take that complexity into account," said Dr. Flaherty, a medical oncologist who is clinical investigations program leader at the University of Pennsylvania, Philadelphia.

That being said, the field hasn't advanced to the point where definitive clinical trials of combinations of targeted therapies can be done. There simply aren't enough signal transduction inhibitors available.

In the interim, investigators are exploring the therapeutic potential of single-agent MAP kinase pathway inhibitor therapy in combination with conventional chemotherapy. Encouraging preclinical studies suggest that there is a synergistic apoptotic effect, and a few small clinical trials have shown a modest benefit, Dr. Flaherty said.

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For example, when sorafenib (Nexavar), the first BRAF inhibitor, was combined with dacarbazine in a phase II randomized trial involving 101 chemotherapy-naive patients, the objective response rate doubled, compared with the 12% figure for dacarbazine alone. Progression-free survival improved from 2.7 months with chemotherapy alone to 4.9 months with combination therapy.

In another randomized phase-II study, however—this one in chemotherapy-refractory patients—the addition of sorafenib brought no benefit over chemotherapy alone. So if sorafenib does enhance the effects of chemotherapy, it's a benefit that seems to be restricted to chemotherapy-naive patients.

The definitive phase III study of this approach is underway: Accrual is nearly complete in a study randomizing 800 metastatic melanoma patients with no prior chemotherapy to carboplatin/paclitaxel alone or combined with sorafenib. The primary end point is overall survival.

Sorafenib has proved to be unimpressive as single-agent therapy in metastatic melanoma. It is an unselective agent that hits numerous other targets in addition to BRAF, and the impedance of these collateral targets may cause toxicity without contributing to efficacy, thereby limiting the ability to deliver enough of the oral drug to inhibit BRAF, Dr. Flaherty explained.

Newer, more potent, and selective orally administered MAP kinase pathway inhibitors are now entering early dose-finding, proof-of-concept clinical trials. These promising agents include RAF265 and PLX4032, by far the most selective of them all, and animal studies suggest that they will be more efficacious than sorafenib.

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