

## NEWS IN BRIEF

DR5 signaling, thereby triggering apoptosis. In an initial PCT assessing melanoma response to TAS266, just 18% of mice appeared susceptible. A retrospective biomarker analysis then revealed that the response rate to TAS266 was actually 80% in the subset of mice with elevated DR5 and caspase-8.

Importantly, the researchers found that therapeutic activity *in vitro* wasn't necessarily seen *in vivo*, and vice versa. "The disconnect was surprising," Gao says. Novartis's investigational IGF1R inhibitor LFW527 appeared to increase the efficacy of the MEK1/2 inhibitor binimetinib (MEK162; Array BioPharma) in colorectal cancer, non-small cell lung carcinoma, and prostate adenocarcinoma cell lines. When this combination was tested in relevant PCTs, no such synergy was observed—the modest response rate achieved with binimetinib in colorectal cancer "actually worsened" when LFW527 was added, Gao notes.

"It turns out that prior to our analysis, this combination was tried in the clinic, with negative results," Sellers says. "IGF1R inhibitors have long been touted and always look terrific *in vitro*, but they have yet to work out *in vivo*." On the other hand, a clinical investigation of Novartis's CDK4/6 inhibitor, LEE011, combined with BRAF inhibition is under way, based on encouraging PCT results that weren't seen in cell line studies.

The researchers will continue expanding the PDXE, and hope to eventually add difficult-to-establish models, such as glioblastoma and prostate cancer, to the collection. They're also exploring ways to address the limitations of PDXs, chiefly that the mice, being immunodeficient, can't be used to assess candidate immunotherapies.

"Every model system is imperfect in its own way," Sellers says. "We'll use the PDXE in ways best suited to its strengths. Take drug combinations, for instance—the number of permutations is well beyond what could be tested in humans. We think our system will prove very useful here; it should also help significantly with biomarker validation." —*Alissa Poh* ■

## First Oncolytic Viral Therapy for Melanoma

The FDA has approved talimogene laherparepvec (Imlygic; Amgen) to treat surgically unresectable skin and lymph node lesions in patients with advanced melanoma. Also called T-VEC, this is the first oncolytic virus to gain regulatory endorsement.

T-VEC, a genetically modified herpes simplex virus type 1, is thought to have two distinct means of antitumor activity: Its selective replication in cancer cells causes them to rupture and die; meanwhile, it also releases the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), which spurs the patient's own immune system into tumor-fighting mode. However, Amgen has stated that T-VEC's "exact mechanism of action is unknown and being further investigated."

T-VEC's approval was based on data from the multicenter phase III OPTiM study, in which 436 patients with surgically unresectable metastatic melanoma were randomized to receive injections of T-VEC directly into their lesions, or GM-CSF given subcutaneously (J Clin Oncol 2015;33:2780-8). Among patients in the T-VEC arm, 16.3% achieved durable responses—tumor shrinkage lasting at least 6 months—compared with 2.1% in the control group. The median overall survival with T-VEC was 23.3 months, versus 18.9 months with GM-CSF, which was not statistically significant, prompting the FDA and Amgen to emphasize that T-VEC "has not been shown to improve overall survival." The therapy also had no effect on melanoma that had spread to other internal organs.

T-VEC was well tolerated by patients, with the most common side effects being fatigue, chills, and fever. Given the live nature of this therapy, cold sores and other herpetic infections were also observed.

According to preliminary data from a small phase I study, T-VEC plus the immune checkpoint inhibitor ipilimumab (Yervoy; Bristol-Myers Squibb) may also show promise in melanoma: Half of the study's 19 patients responded, 22% completely. In addition, T-VEC is being evaluated alongside another checkpoint

inhibitor, pembrolizumab (Keytruda; Merck), which blocks interactions between the ligand PD-L1 and its receptor, PD-1. A recent review noted that "as oncolytic viruses often induce interferon release in the local tumor microenvironment, and interferon is known to upregulate PD-L1 expression on tumor cells, this combination is especially interesting" (Nat Rev Drug Discov 2015;14:642-62).

Marc Ernstoff, MD, director of the melanoma program at Cleveland Clinic's Taussig Cancer Institute in Ohio, notes that T-VEC has only "modest single-agent activity," and "its place in the growing immunotherapy armamentarium is still unclear." He adds, though, that "its unique mechanism of immune stimulation and high therapeutic index provide significant opportunities for multiagent regimens that can further leverage the immune path to durable tumor destruction."

"It's worth noting that we had only three approved agents for melanoma in the 30 years before 2011," says John Kirkwood, MD, director of the melanoma skin and cancer program at the University of Pittsburgh, PA. T-VEC is the 10th new therapy approved for melanoma in the last 5 years, which the Melanoma Research Alliance has hailed as "a truly unprecedented rate of progress." —*Alissa Poh* ■

## Innate Immune Cells May Prevent Metastasis

A specialized type of white blood cell that helps defend the body from infection also appears to control the spread of cancer. Researchers have found that these innate immune cells, called patrolling monocytes (PMo), slow tumor metastasis to the lung in multiple mouse models (Science 2015;350:985-90).

Most of the body's monocytes are the classic variety, which gobble up bacteria, viruses, and dying cells when recruited to sites of infection. Approximately 10% to 25% are PMo—active surveyors that can travel against blood flow to clear pathogens and other unwanted cells. In the context of cancer, the team discovered that PMo can "sense tumor cells, move toward them, help orchestrate their killing,

# CANCER DISCOVERY

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