Melanoma Treatment’s Changing Landscape

By Susan Jenks

As treatment options for late-stage melanoma change rapidly, a new strategy that combines two immune-checkpoint inhibitors to render invading cancer cells more vulnerable looks particularly promising.

The combination of ipilimumab and nivolumab holds promise as a treatment advance not only for metastatic melanoma but also for head and neck, renal, and even some small-cell lung cancers, said John Thompson, M.D. Thompson is codirector of the Seattle Cancer Care Alliance and professor of medical oncology at the University of Washington School of Medicine.

“There’s tremendous excitement because of a 50% response rate” in patients with advanced disease—considerably higher than that achieved with any other therapies so far, he said.

Now in phase III clinical trials, the ipilimumab–nivolumab regimen signals a new phase in developing immune-checkpoint antibodies. Such antibodies target proteins in the immune system that are ordinarily involved in restraining or turning off an immune response. According to Thompson, early data on durability of patients’ responses in melanoma could be available by midyear, when the American Society of Clinical Oncology convenes in Chicago, May 30–June 3, for its annual meeting.

Although the drugs target different molecular pathways, he said, the pathways they use to bolster T-cell antitumor activity against these deadly cancers are closely related. Ipilimumab, often referred to simply as “ipi,” blocks the cytotoxic T-lymphocyte antigen 4 (CTLA-4) protein, which slows T-cell activation. Nivolumab interacts directly with cancer cells, blocking the interaction between the programmed death 1 (PD-1) protein on T cells and PD-L1, a ligand that binds to PD-1 and sits on the surface of some cancer cells when they’re under attack.

At the National Comprehensive Cancer Network’s 19th annual conference in Hollywood, Fla., themed “Advancing the Standard of Cancer Care,” Thompson addressed new agents and opportunities for treating melanoma while offering a guideline update (he serves on the organization’s clinical guidelines committee). With the changing landscape for treating these late-stage cancers, he said afterward, revising guidelines can be challenging. But the committee reviews them often, he said, adding new treatment options whenever possible.

One example where reviewers moved quickly to place a new therapy on the “preferred list,” Thompson said, occurred earlier this year. The U.S. Food and Drug Administration granted accelerated approval to the first molecularly targeted combination for inoperable, metastatic melanoma in patients carrying a genetic mutation, known as BRAF. BRAF-mutated melanoma occurs in roughly 38% of patients, Thompson said, although “a large part of the molecular pie is still unknown.”

The combination therapy, targeting both the BRAF mutation and MEK further downstream (N. Engl. J. Med. 2012;367:1694–703), had positive results, Thompson said. Patients had a least 9.5 months of progression-free survival while circumventing the resistance common with a single agent. Moreover, despite common side effects of chills and fever, sometimes requiring patients to stop therapy, he said, far fewer secondary skin

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cancers occurred in patients on the dual treatments.

Surprisingly, perhaps, older patients often carry a different type of BRAF mutation from that seen in younger patients, for reasons not yet clearly understood.

“But this doesn’t mean you don’t use a BRAF–targeted therapy—just that the duration of response may be less,” Thompson said. “It’s important for treating doctors to understand this.”

### Immunotherapy Plus Targeted Therapy?

As scientists unravel the molecular drivers of melanoma and develop monoclonal antibodies that disarm the immune system’s checkpoint inhibitors, interest in combining these approaches has grown. Early attempts, however, didn’t go well, Thompson conceded, notably an attempt to combine vemurafenib, which targets the BRAF mutation, with ipilimumab. Patients in the first phase I study experienced unexpected toxic effects on the liver (N. Engl. J. Med. 2013;368:1365–6), so investigators shut the trial down. Nevertheless, interest is still there, Thompson said.

“Instead of giving these drugs at the same time, it might be better to give one first, then the other,” adding that “we could be surprised at the outcome.”

Some data suggest that targeted drugs enhance the immune response at the tumor site, Thompson said, preparing for follow-up with immunotherapy.

Investigators also are looking to combine immune-checkpoint inhibitors, such as anti–PD-1s, with adoptive T-cell therapy, an approach that the National Cancer Institute’s Stephen A. Rosenberg, M.D., Ph.D., pioneered with striking results in mice (Science 2013;340:928–31). In the first human phase I study involving 85 patients. Nearly half of patients with inoperable and widely disseminated melanoma showed an antitumor response at 12 weeks, including eight who experienced a complete response. And although seven patients had serious immune-related complications, side effects were minor overall.

FDA’s breakthrough designation underscores that some treatments offer such obvious benefits to patients early in development that traditional large-scale clinical trials might not be necessary before a drug can come to market. FDA, however, reserves the designation for drugs that treat patients whose diseases either lack adequate treatment or have none at all.

“It’s a good drug,” Weber said of MK-3475, describing FDA’s action as guaranteeing more attention and intense guidance in the months ahead.

### “Quite Hopeful”

In the community, physicians such as Terrence Cronin Jr., M.D., past president of the Florida Society of Dermatologic Surgeons, see melanoma far too often, especially in a state where residents face constant UV radiation.

Fortunately, he said, most patients in his Melbourne practice are diagnosed with melanoma in situ, caught early and easily treatable. So even though the diagnosis is bad news, Cronin said, “it makes us want to dance; the prognosis is excellent.”

Cronin monitors research developments. He said he considers progress on the molecular front quite hopeful, especially in the last few years, as scientists find checkpoints that prevent T cells from doing their job and identify molecular pathways that enable melanoma to grow.

“Eventually, I think we’re going to find melanoma is not all one disease, but different diseases with different patterns and different risks.”

### Awaiting Approval

Nivolumab is one of two new immune-checkpoint inhibitors poised for FDA approval by the end of the year, according to Weber. His research group found, in a six-cohort study involving 90 late-stage melanoma patients, that the drug is well tolerated and works either in combination with ipilimumab or sequentially after treatment with ipilimumab alone fails. The Journal of Clinical Oncology published the study were published last October (J. Clin. Oncol. 2013;31:4311–8). The other drug, lambrolizumab, now called MK-3475, garnered “breakthrough therapy” status from FDA last April after drug company researchers documented dramatic clinical benefits in an open-label phase I study involving 85 patients. Nearly half of patients with inoperable and widely disseminated melanoma showed an antitumor response at 12 weeks, including eight who experienced a complete response. And although seven patients had serious immune-related complications, side effects were minor overall.

For describing any of these strategies, however—including immune-checkpoint inhibitors—he considers the term breakthrough a bad word, he said.

“But are they an advance? Absolutely.” Compared with chemotherapy, where you might see a response rate of 10%–20%, Weber said, response rates with immune-checkpoint inhibitors are 30% or better and last much longer—sometimes 2 years.

For cancers such as melanoma, where advanced stages often carry a grim prognosis, Weber added, “that’s pretty good.”

The American Cancer Society estimates that doctors will diagnose 76,100 melanoma cases in 2014 and that 9,710 men and women will die of their disease. Five-year survival for stage IV melanoma is 15%–20%, compared with 92%–97% with early detection.

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