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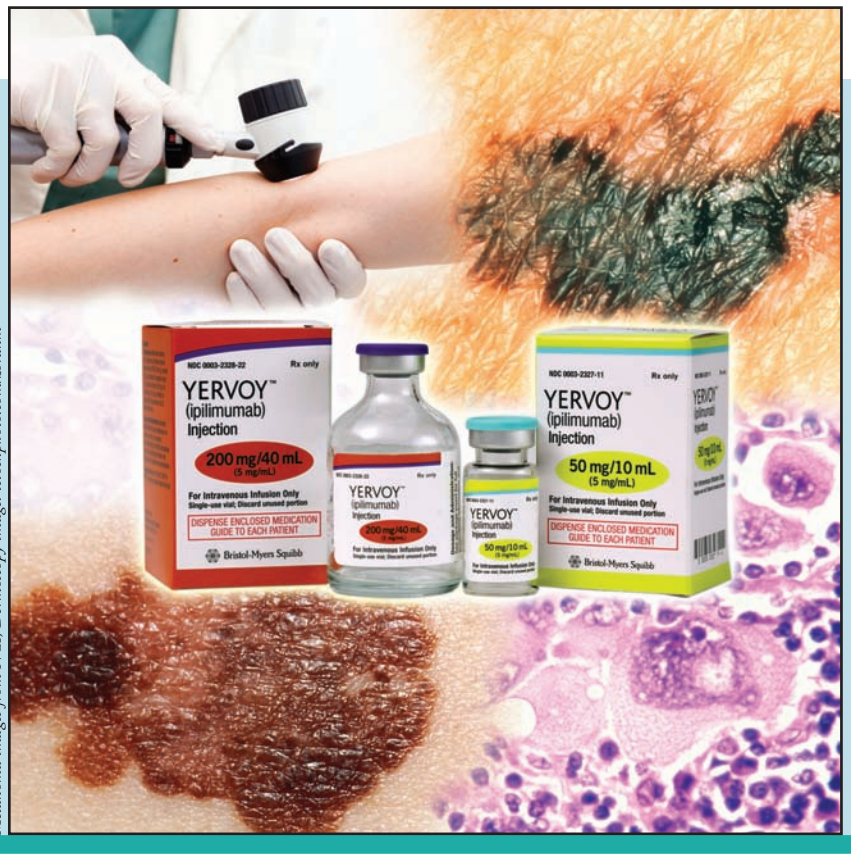

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Melanoma Care Notes from Ipilimumab Trialists

BY RABIYA S. TUMA, PHD

Ipilimumab is the first drug to prolong overall survival in patients with metastatic melanoma, and its recent FDA approval made headlines worldwide. Yet, ipilimumab (Yervoy) is not straightforward to use. A substantial proportion of patients who eventually respond initially develop tumor growth or new lesions, and side effects must be carefully managed to avoid serious problems. We asked physicians who participated in the clinical trials to share their thoughts on how best to use the drug.

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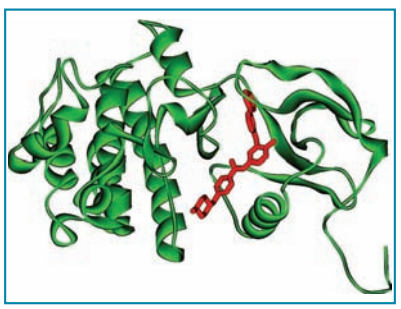

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PERIODICALS

Melanoma Care Enters New Phase with FDA Approval of Ipilimumab: Clinical Care Suggestions from Trialists

BY RABIYA S. TUMA, PHD

Ipilimumab is the first drug to prolong overall survival in patients with metastatic melanoma and its approval by the US Food and Drug Administration on March 25 made headlines worldwide. Yet, the drug is not straightforward to use. A substantial proportion of patients who eventually respond to the drug initially show tumor growth or new lesions, and side effects must be carefully managed to avoid serious problems. We asked two physicians who participated in ipilimumab clinical trials to share their thoughts on how best to use the drug.

Monitoring Response

Unlike conventional cytotoxic chemotherapy, anti-cancer agents that work through the immune system, like ipilimumab, may take time to work. "I think the most important thing for practitioners to understand now, as ipilimumab becomes a commercially available drug that anybody can use, is they shouldn't react to a first disappointing scan the way they would for a patient treated with chemotherapy," said Jedd Wolchok, MD, PhD, Associate Attending Physician at Memorial Sloan-Kettering Cancer Center and a lead investigator on the ipilimumab trials.

He notes that 10 to 25 percent of patients who ultimately benefited from the drug in Phase II trials initially experienced tumor growth or new lesions.

KIM MARGOLIN, MD, notes that contrary to the situation with cytototxic agents, immunotherapies do not work fast. Physicians who haven't used them before will realize pretty quickly that they have to think of immunotherapies differently and that whereas tumor growth over a certain amount during cytotoxic chemotherapy treatment means the agent isn't going to work, that is not always the case with immunotherapies.

Therefore, patience and clinical judgment are needed. "If a patient is not clinically deteriorating and just the scan is worse, then the suggestion is to repeat the scan in four to six weeks," Dr. Wolchok said. "If on that second scan you see no evidence of things turning around or stabilizing, then you move the patient on to some other therapy."

Dr. Wolchok said he starts preparing his patients emotionally for the possibility of a disappointing first scan right from the start. "Before they even get the IV put it in, I start talking to them about how they will get scans at 12 weeks and that there is a potential that those will look worse but then get better. We just keep reinforcing that."

Immunotherapies do not work fast, agrees Kim Margolin, MD, Professor of Medicine at the University of Washington and Member of the Fred Hutchinson Cancer Research Center. Physicians who haven't used them before will realize pretty quickly, she says, that they have to think of immunotherapies differently than they do cytotoxic agents. Whereas tumor growth over a certain amount during cytotoxic chemotherapy treatment means the agent isn't going to work, that is not always the case with immunotherapies.

So how does a physician know if a particular patient is a delayed responder or a non-responder? "You don't. You absolutely don't," she said. But the period of not knowing still leaves the glimmer of hope, and isn't so bad considering that the alternative is to offer the patient something really toxic, like IL-2, or an unproven experimental agent.

Like Dr. Wolchok, she typically re-images patients after four to six weeks and waits to make a decision until then. If, on the other hand, a patient not only shows signs of tumor progression on scans but is also deteriorating clinically, with a dramatically decreased performance status or labs that are considerably worse than before, then it's probably safe to assume that ipilimumab isn't working and the patient should be treated with something else.

Dr. Margolin, however, notes that because ipilimumab was approved as a short-course therapy, the decision about response will typically be made after the patient has already completed a course of therapy.

"Generally you see imaging results after you have already finished the four treatments at three-week intervals," she said. "That means that most of these decisions are going to come after the patient has completed induction, so you are not talking about continuing the therapy and withholding the next therapy. You are only talking about withholding the next therapy."

JEDD WOLCHOK, MD, PHD: "The most important thing for practitioners to understand is that they shouldn't react to a first disappointing scan the way they would for a patient treated with chemotherapy."

Re-induction therapy was not included in the FDA approval and has not been formally tested with the drug, Dr. Margolin noted. During the compassionate use trial, the company, however, provided four additional doses for patients who responded to their initial course but then relapsed. (She likens the re-treatment approach to the intermittent anti-androgen therapy used in prostate cancer patients.) Re-responses were seen with the agent in the compassionate use setting.

As for the question of how or if maintenance therapy should be used with ipilimumab, Dr. Margolin said she expects the question will be addressed in numerous permutations in trial settings since neither re-induction nor maintenance dosing is included in the FDA-approved label. In the clinic, off-protocol, there is no reason to assume patients would do better with maintenance.

"I am a very evidence-based person and until I see the data, I can't say they are missing out on something when we don't give them maintenance," she said.

Managing Toxicity

The other aspect of ipilimumab (Yervoy) care that can be challenging is managing potential adverse events, which are serious enough that the FDA approval came with a boxed warning. The manufacturer (Bristol-Myers Squibb) also released on April 6 a risk evaluation and

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→IPILIMUMAB

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mitigation strategy (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm249770.htm) for severe immune-mediated adverse reactions that are sometimes triggered by ipilimumab.

The document reads in part: "the product can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of Yervoy."

Given these serious side effects, both Drs. Wolchok and Margolin emphasize that regular and early communication between patients and physicians is critical.

"It is all about early communication and not letting things get out of hand," said Dr. Wolchok. "For most of these toxicities, the answer is to give people immunosuppressive medications, such as prednisone. That is not a difficult thing to do."

Dr. Wolchok, however, emphasizes to his patients that if things change, he wants to know about it right away. For example, if a patient starts having three more bowel movements a day than normal, the patient needs to tell him. "I don't care if it is the middle of the night, I want to know about it," he said.

If a patient's bowel movements are just more frequent, then Dr. Wolchok will have his nurse call the patient daily to see how he or she is doing. "If they say it's 15 times a day, watery diarrhea, with crampy pain, then I might do a scan or colonoscopy right away to see how bad the inflammation is, because that is a classic symptom of colitis."

> A substantial proportion of patients who eventually respond to the drug initially show tumor growth or new lesions, and side effects must be carefully managed to avoid serious problems.

"Usually this doesn't just sneak up on you," Dr. Wolchok said. "The people who present with fulminant symptoms are folks who maybe haven't been telling you about the subtle symptoms for the past week or so."

The other side effects Dr. Wolchok watches out for are liver function abnormalities and pituitary inflammation. He runs tests for liver function before each dose, and may recheck the labs if they are elevated but not high enough to warrant steroid use. For pituitary problems, he wants to know if a patient is more tired than usual, has a drop in appetite, or headaches. In that situation, he is likely to request a brain MRI and thyroid function tests to see how pituitary access is.

Dr. Margolin's strategy is similar. "I give them a very stern sermon about how important it is to let me know what is going on—kind of like after bone marrow transplant," she said. "You need to let me know if you are having diarrhea. You need to let me know if you have a skin rash that is more than a little itching. You need to let me know if you are profoundly fatigued and you can't get out of bed, if you start vomiting, or having other GI symptoms.

"I tell them that," she continued. "I make sure they have all the phone numbers. And I tell them again, because that is the key. Early perception and diagnosis of the complications, and intervention with immunomodulatory agents is how we are going to keep patients out of trouble."

Despite the severity of the warnings—and the real need to be vigilant—neither physician is overly worried about the side effects. Dr. Margolin, for example, notes that oncologists are used to dealing with tough situations and with a little practice, they will know how to use the drug safely. In the meantime, she said that physicians with more experience are ready to help with phone consultations and there is literature (http://www.yervoy.com/hcp/rems.aspx) available for physicians, nurses, and patients from the company, including a wallet card for patients.

> Patience and clinical judgment are needed.

Dr. Wolchok is a paid consultant for Bristol-Myers Squibb, which makes ipilimumab. Dr. Margolin does not have any conflicts to report.