Advanced Melanoma & BRAF Inhibitors—What Oncology Nurses Need to Know

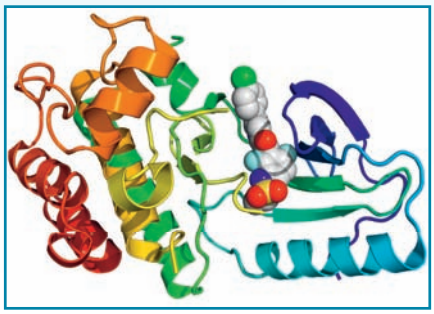
BY SARAH DIGIULIO

NEW ORLEANS—Since last year's strikingly successful Phase I clinical trial results for the BRAF inhibitor vemurafenib in advanced melanoma patients, the new drug has garnered much attention. Phase II and III clinical trials promptly followed, and the FDA expedited the drug's review. "This has been tremendous in the world of melanoma and very exciting," said Krista Rubin, MS, RN, FNP, BC, a nurse practitioner at Massachusetts General Hospital, speaking here on the topic during a special lecture at the Oncology Nursing Society Annual Congress. "You can get these patients responding very quickly."

> Approximately 40 to 60 percent of advanced melanoma patients carry the BRAF V600E mutation.

Phase III trial results compared use of vemurafenib in advanced melanoma patients who had the BRAF V600E mutation with use of dacarbazine (the only FDA-approved chemotheapeutic agent for metastatic melanoma at that time), and found that the BRAF inhibitor was associated with a 63% relative reduction in risk of death, and 74% relative reduction in risk of tumor progression, as compared with use of chemotherapy (***NEJM 2011;364:2507-2516***).

Approximately 40 to 60 percent of advanced melanoma patients carry the BRAF V600E mutation, which helps explain the excitement about the drug's success, since it can potentially help so many patients, Rubin said. The FDA expedited vemurafenib's approval, along with a companion diagnostic test, last summer for patients with the mutation (***OT, 9/10/11***). ASCO named it one of the top five advances of



2011—"a new standard treatment for patients with melanoma and this gene mutation," according to the organization's annual progress report, "Clinical Cancer Advances 2011: ASCO's Annual Report on Progress Against Cancer" (***OT, 1/10/12***).

Unfortunately, though, despite the excellent response rates among patients with the BRAF mutation taking vemurafenib, resistance often starts to build at about six months, and many patients stop responding within seven to nine months, Rubin explained during the session.

The drug blocks BRAF activity, which stops tumor progression. But, because the agent targets tumor growth pathways, it does not actually kill the tumor cells, which in many cases, then find other pathways and eventually progress. "After a while, the signaling takes another route, so the patient becomes resistant."

The drug is highly effective for most patients, especially those with rapidly progressing early symptoms of advanced melanoma, for at least a limited duration—but the overall survival benefits of the drug have not been proven. Slower-acting, first-line treatments, such as the also recently approved ipilimumab (an immunotherapy agent), should be considered (***OT, 1/10/12***).

Bottom line, Rubin noted in an interview after the meeting: Patients need to be educated about expected outcomes before starting a treatment regimen—and that is where the oncology nurse can play an important role.

Nurses as Educators

"Understanding the basics of these inhibitors—why there's resistance, what the next step is—is absolutely crucial for oncology nurses to be able to communicate with their patients, to explain the next steps and what can be anticipated for the next course of action," she said.

Providing realistic information is key, she emphasized: "Patients get excited about reports of high success rates and quick results seen with the drug. They hear the word 'response' and may interpret that as cure or remission…. It's an extreme disappointment to hear that they're really only going to get about seven to nine months from this drug."

> "Understanding this signaling pathway gives us an understanding of how melanoma works and grows."

Uncertain long-term results, though, should not deter hopefulness, Rubin added: For patients with aggressive and rapidly progressing disease with adverse symptoms (intense pain, inability to eat, or disfiguring skin metastases), the drug has meaningful results.

"For patients who feel very sick or have a lot of pain or just don't have any energy, this drug can rapidly make them feel better," she said. "If the patient is very symptomatic—having a lot of pain, weakness, fatigue, is not able to function—and needs some sort of therapy quickly, and if they do have an identified BRAF mutation, then the likely first-line recommended treatment would be a BRAF inhibitor."

Vemurafenib can be the bridge to get these patients on other, slower-acting

continued on page 6

Pharmacology Spotlight at ONS Congress

BY SARAH DIGIULIO

NEW ORLEANS—The first day of the Oncology Nursing Society's 37th Annual Congress wrapped up with a session highlighting noteworthy newly approved pharmacologic agents, recently expanded indications for pharma agents already available, and the FDA's response to critical drug shortages seen in the past year.

The following 11 agents have been recently approved by the FDA, noted Natalie Christine Mandolfo, MSN, APRN-NP, AOCN, a nurse practitioner at Nebraska Cancer Specialists, who also provided information on how to dose the treatments and possible side effects.

- **Crizotinib** is approved for treatment of patients with locally advanced or non-small cell lung cancer that is anaplastic lymphoma kinase-positive.
- **Peginterferon alfa-2b** is approved as an adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including completion lymphadenectomy.

continued on page 7

→B-RAF INHIBITORS

continued from page 5

immunotherapies with improved long-term survival outcomes, she said. After being on vemurafenib, some patients have success with ipilimumab.

Clinical trials are ongoing to test the effectiveness of a combination of BRAF and MEK inhibitors, or a combination of PD1 antibodies and a BRAF inhibitor (***OT, 6/10/12***). The theory is to eliminate the next pathway, to try to completely eliminate any pathway the tumor cells could grow along, Rubin said.

Understanding Side Effects

Oncology nurses should also be able to educate patients about the side effects profile of BRAF inhibitors, which can be unique. "The molecularly targeted therapies have associated 'off-target' or ancillary effects on surrounding cell-signaling pathways."

One of the more common side effects, for example, can be squamous cell carcinoma, she noted. Patients should be advised to look for new skin lesions (any wart-like spot, or skin change that doesn't seem to heal—often bumpy or scaly), and schedule an evaluation by a dermatologist if noticed. The lesions can develop on any skin surface, so even non-sun-exposed areas, such as the vulva, the cervix, and the genitals should be examined, Rubin said.

KRISTA RUBIN, MS, RN, FNP, BC: "Understanding the basics of these inhibitors—why there's resistance, what the next step is—is absolutely crucial for oncology nurses to be able to communicate with their patients."

Another side effect is extreme sun-sensitivity, so patients should be advised to be extra vigilant about using sunscreen and to stay in the shade whenever possible. And, since vemurafenib is associated with prolongation of the QTC interval, EKG testing is recommended for patients on other medications that also prolong the QTC.

"It's also important to educate patients that they must report any medications they are using, both prescription and non-prescription, and any kind of alternative therapies—vitamins, minerals, herbals—so that risks of toxicity will be minimalized," Rubin said.

She concluded the ONS session by emphasizing the role of the oncology nurse in helping patients understand how the drug works—the role it can play, and also the limitations of the drug. "We as nurses need to understand what's happening so we can bring the information down to a patient level."

Despite the drug's shortcomings, the excitement among the melanoma community is not unwarranted, she said. "Even though we're seeing maybe not durable responses, we are seeing something that at least is understandable. Understanding this signaling pathway really gives us an understanding of how melanoma works and grows."

Hyperlinks!

Access the hyperlinks (shown in grey) in this article and throughout the issue by reading it on *OT*'s free iPad app: ***http://bit.ly/OT-iPadApp***