Novel BRAF Inhibitor Receives FDA Approval in Metastatic Melanoma
BRAF targeting reduces mortality by 63%.

By Caroline Helwick

Vemurafenib (Zelboraf) received FDA approval on August 17, 2011, for treatment of metastatic or unresectable melanoma, based on the results of the phase III BRIM3 trial.1 BRIM3 compared vemurafenib to dacarbazine in 675 untreated patients with the BRAF V600E mutation. Vemurafenib targets the mutation, which is present in approximately 50% of patients with advanced melanoma. A companion diagnostic test called the cobas 4800 BRAF V600 Mutation Test was concurrently approved.

Omid Hamid, MD, of The Angeles Clinic and Research Institute (www.theangelesclinic.org), Los Angeles, reviewed data from BRIM3 and BRIM2 at the Best of ASCO meeting in Miami, Florida.1,2 “With vemurafenib we see an initial separation between the arms [vemurafenib vs dacarbazine] that continues. There are durable and ongoing responses. The data in both the first-line [BRIM3] and second-line [BRIM2] settings seem extremely promising,” said Dr. Hamid.

Pivotal BRIM3 Trial
BRIM3 enrolled 675 patients, including 337 patients who were assigned to vemurafenib, 960 mg orally twice daily, and 338 who were assigned to dacarbazine, 1,000 mg/m² intravenously, every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. All patients had an ECOG performance status of 0 or 1, and 95% of patients had metastatic disease. The major endpoints of the trial were overall and progression-free survival.

Survival Data
The first interim analysis found progression-free survival to be 5.3 months with vemurafenib vs 1.6 months with dacarbazine, a 74% reduced risk (P < .0001). Overall survival at 6 months was 84% vs 64%, respectively, a 63% reduction (P < .0001). Overall responses were observed in 48.4% vs only 5.5%, respectively, and all subgroups benefited.

The most common grade 3 adverse reactions were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, and nausea.

Next Steps
Future studies, Dr. Hamid said, should evaluate vemurafenib in combination, and sequentially, with MEK inhibitors, PI3K and mTOR inhibitors, insulin-like growth factor receptor inhibitors, immunomodulators, and cytotoxics. Simultaneous inhibition of BRAF and MEK has been associated with resumption of response in patients who progressed on a prior BRAF inhibitor.

The recommended dose of vemurafenib is 960 mg orally twice daily.

Disclosure: Dr. Hamid reported receiving consulting and speaking fees from Bristol-Myers Squibb and Roche, and research funding from Bristol-Myers Squibb, GlauSmithKline, and Roche.

References

What Will It Cost?
According to Genentech, manufacturer of vemurafenib, cost of the drug will be approximately $9,400 per month with a total cost of approximately $56,400 for 6 months duration of treatment.

Clinical Trials of Protons
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improved local control of prostate cancer at the higher dose. These randomized trials were successful because they were focused on dose, not technology (but only the improved technology could safely deliver the higher dose).

A corollary to this approach comes from tumors that are already fairly well controlled with current treatment (such as head and neck cancer), with the goal of delivering the same tumor dose while using the better technology to decrease dose to the normal organs and, thereby, to preserve normal organ function (eg, parotid and other salivary glands). Here, too, it has been shown that IMRT is superior to older techniques.

The Bottom Line
Thus, the big question is, where is the evidence that protons can be used to safely deliver a higher dose of radiation than photons to, for example, the prostate? Or that the rectum and bladder can be better protected by protons at the same tumor dose? If proton facilities could generate such evidence, it could be useful to support a trial testing whether the increase in tumor dose permitted by protons controls more tumors, or whether the decrease in dose to normal tissue decreases toxicity.

Our field has shown that randomized dose trials can be successfully conducted. In my opinion, proton facilities should not be permitted to continue to produce results that cannot be distinguished—except by the far greater price—from those produced by IMRT photons. Our patients deserve true improvements in outcome, rather than the hype and added expense that currently dominates the field.

Disclosure: Dr. Lawrence reported no potential conflicts of interest.