Vemurafenib in melanoma with the BRAF V600E mutation

See related Commentary on page 83

Vemurafenib, an oral inhibitor of some mutated forms of the BRAF serine threonine kinase, was recently approved for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation as detected by an FDA-approved test.[1,2] It is not recommended for use in patients with wild-type BRAF melanoma. The clinical trial supporting approval of vemurafenib (PLX4032) was performed in treatment-naïve patients with the V600E mutation as detected by the Cobas 4800 BRAF V600 Mutation Test. About 40%-60% of cutaneous melanomas have BRAF mutations that result in constitutive activation of downstream signaling through the MAPK pathway; about 90% of those carry the V600E mutation.

In a phase III trial, 675 patients with unresectable previously untreated stage IIIC or IV melanoma positive for the BRAF V600E mutation were randomized to receive vemurafenib 960 mg orally twice daily (337 patients) or dacarbazine 1,000 mg/m^2 (338 patients) via IV infusion every 3 weeks.[1] Patients were excluded if they had a history of cancer within the previous 5 years (except for basal or squamous cell carcinoma of the skin or carcinoma of the cervix) or metastases to the central nervous system, unless such metastases had been definitively treated more than 3 months previously with no progression and no requirement for continued glucocorticoid therapy. Concomitant treatment with any other cancer therapy was not permitted. For the vemurafenib and dacarbazine groups, respectively, median ages were 56 and 52 years, 59% and 52% of patients were men, 99% and 100% were white, 68% and 68% had ECOG performance status of 0, 66% and 65% had M1c extent of metastatic disease and 6% and 4% had unresectable stage IIIC disease, and 58% and 58% had lactate dehydrogenase above the upper limit of normal. Coprimary endpoints of the trial were overall survival (OS) and progression-free survival (PFS).

At interim analysis, both OS and PFS were significantly improved with vemurafenib, and patients in the dacarbazine arm were subsequently permitted to cross over to receive vemurafenib. At that time, median follow-up durations were 3.8 months in the vemurafenib group and 2.3 months in the dacarbazine group. Among 672 patients evaluated for OS, vemurafenib treatment was associated with a 63% reduction in risk for death (hazard ratio [HR], 0.37; $P < .001$), with a survival benefit being observed in all prespecified subgroups according to age,

What's new, what's important

The treatment of refractory metastatic melanoma is one of the most frustrating challenges oncologists face in the clinic. But over the past 12 months, two new FDA-approved drugs, ipilimumab, an anti-CTLA4 blocking antibody, and more recently, vemurafenib, for patients with the BRAF V600E mutation, have boosted our treatment possibilities and present promising options for these patients.

In August last year, the FDA approved vemurafenib for patients with the BRAF mutation as detected by the accompanying FDA-approved Cobas 4800 BRAF V600 Mutation Test. An interim analysis in the pivotal trial, comparing vermurafenib and dacarbazine, showed that both overall survival (OS) and progression-free survival (PFS) were significantly improved with vemurafenib, and patients in the dacarbazine arm were permitted to cross over to receive vemurafenib. Follow-up at 2 months showed that OS was 84% in the vemurafenib group and 64% in the dacarbazine group. The estimated median progression-free survival durations were 5.3 months and 1.6 months, respectively. Superior PFS was observed for vemurafenib in all subgroups.

The FDA-approved dose of vemurafenib is 960 mg, orally twice daily administered every 12 hours. Common side effects are joint pain, alopecia, fatigue, photosensitivity reaction, rash, and nausea. It is important to note that about 24% of the patients who were treated with vermurafenib developed cutaneous squamous cell carcinomas. Patients who develop these lesions can have them excised and continue to be treated with vemurafenib.

Long-term benefit from this drug is still limited due to the emergence of resistance. Better understanding of the mechanism of resistance and development of novel drugs to overcome the resistance will be looked at future trials.

— Jame Abraham, MD

Report prepared by Matt Stenger, MS

Commun Oncol 2012;9:85-86
doi:10.1016/j.cmonc.2012.02.013

TABLE 1 Adverse events of grade 2 or higher in patients receiving vemurafenib or dacarbazine

	% of patients	
	Vemurafenib (n = 336)	Dacarbazine (n = 282)
Arthralgia		
Grade 2	18	<1
Grade 3	3	<1
Rash		
Grade 2	10	0
Grade 3	8	0
Fatigue		
Grade 2	11	12
Grade 3	2	2
Cutaneous squamous cell carcinoma		
Grade 3	12	<1
Keratoacanthoma		
Grade 2	2	0
Grade 3	6	0
Nausea		
Grade 2	7	11
Grade 3	1	2
Alopecia		
Grade 2	8	0
Pruritus		
Grade 2	6	0
Grade 3	1	0
Hyperkeratosis		
Grade 2	5	0
Grade 3	1	0
Diarrhea		
Grade 2	5	1
Grade 3	<1	<1
Headache		
Grade 2	4	2
Grade 3	<1	0
Vomiting		
Grade 2	3	5
Grade 3	1	1
Neutropenia		
Grade 2	<1	1
Grade 3	0	5
Grade 4	<1	3
Grade 5	0	<1

From Chapman et al [Chapman 2011].

sex, ECOG performance status, tumor stage, lactate dehydrogenase level, and geographic region. At the time of interim analysis, the number of patients with follow-up greater than 7 months was inadequate to provide reliable estimates for Kaplan-Meier survival curves. At 6 months, OS was 84% in the vemurafenib group and 64% in the dacarbazine group. Follow-up for OS is ongoing. In 549 patients who were evaluated for PFS, vemurafenib was associated with a 74% reduction in risk for tumor progression (HR, 0.26; $P < .001$). Estimated median PFS durations were 5.3 months for vermurafenib, compared with 1.6 months for dacarbazine, and superior PFS was observed for vemurafenib in all subgroups examined. Among 439 patients evaluated for tumor response, response rates were 48% in the vemurafenib group (104 partial and 2 complete responses), compared with 5% (all partial responses) in the dacarbazine group ($P < .001$). Most patients in the vemurafenib group had a detectable decrease in tumor size.

Adverse events of grade 2 or higher among 618 patients included in the safety analysis are shown in the Table 1. The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue. Photosensitivity reactions of grade 2 or 3 were observed in 12% of vemurafenib patients; grade 3 reactions were characterized by blistering that could be prevented with sun block. Cutaneous squamous cell carcinoma or keratoacanthoma or both developed in 61 vemurafenib patients (18%), with all lesions being treated by simple excision. Pathological analysis of skin biopsies from these patients is under way. The most common adverse events in dacarbazine patients were fatigue, nausea, vomiting, and neutropenia. Adverse events required dose modification or interruption in 38% of vemurafenib patients, compared with 16% of dacarbazine patients.

The safety and efficacy of vemurafenib have not been investigated in melanoma with wild-type BRAF. The labeling for vemurafenib carries warnings and precautions for cutaneous squamous cell carcinomas, serious hypersensitivity reactions (including anaphylaxis), severe dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), QT interval prolongation, liver function abnormalities, photosensitivity, serious ophthalmologic reactions (including uveitis, iritis, and retinal vein occlusion), new primary malignant melanomas, and use in pregnancy.

References

1. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507-2516.

2. Zelboraf (vemurafenib) [package insert]. San Francisco, CA: Genentech USA Inc; 2011.