Am J Clin Dermatol (2013) 14:65–69
DOI 10.1007/s40257-012-0007-3

ADIS DRUG CLINICAL Q&A

# Vemurafenib

## A Guide to its Use in Unresectable or Metastatic Melanoma

**Gillian M. Keating · Katherine A. Lyseng-Williamson**

Published online: 15 December 2012


**Abstract** Oral vemurafenib (Zelboraf®) is a first-in-class, small molecule $BRAF^{V600E}$ inhibitor indicated for the treatment of unresectable or metastatic melanoma in $BRAF^{V600}$ mutation-positive patients (EU) or $BRAF^{V600E}$ mutation-positive patients (USA). Compared with intravenous dacarbazine, vemurafenib significantly improved overall survival and progression-free survival in patients with unresectable, previously untreated, $BRAF^{V600E}$ mutation-positive, stage IIIC or IV melanoma. Oral vemurafenib was generally well tolerated, with cutaneous adverse events among the most commonly occurring adverse events.

**Adis evaluation of vemurafenib (Zelboraf®) in unresectable or metastatic melanoma**

**What are its key clinical benefits?**

First-in-class, small molecule $BRAF^{V600E}$ inhibitor

Significantly improves overall survival and progression-free survival, compared with intravenous dacarbazine

Generally well tolerated

**What are its key clinical limitations?**

Acquired resistance leads to disease progression

Potential for cutaneous adverse events, including cutaneous squamous cell carcinoma or keratoacanthomas

Potential for corrected QT interval prolongation

**The manuscript was reviewed by**: *K.S.M. Smalley,* The Moffitt Cancer Center, Programs of Molecular Oncology and Cutaneous Oncology, Tampa, FL, USA.

G. M. Keating (✉) · K. A. Lyseng-Williamson
Adis, 41 Centorian Drive Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand
e-mail: der@adis.com

## 1 What is the Rationale for Developing the Drug?

Approximately 10–15 % of patients with melanoma have metastatic disease at the time of presentation [1]. Metastatic melanoma is an aggressive disease and, historically, treatment options have been limited (e.g., dacarbazine, temozolomide, high-dose interleukin-2) and associated with poor outcomes [1–3].

The development of agents targeting the mitogen-activated protein kinase (MAPK) pathway (comprising RAS, RAF kinases [ARAF, BRAF, CRAF], MAPK kinase [MEK], and extracellular signal-regulated kinase [ERK]) represents a major advance in the treatment of metastatic melanoma [1, 3]. Mutations in the gene encoding the serine-threonine protein kinase BRAF are found in ≈40–60 % of melanomas [1, 3]. Approximately 90 % of these *BRAF* mutations involve the substitution of glutamic acid for valine at amino acid position 600 (i.e., the $BRAF^{V600E}$ mutation) [3]. The $BRAF^{V600E}$ mutation constitutively activates BRAF proteins and downstream signal transduction in the MAPK pathway. This results in cellular proliferation in the absence of growth factors that would usually be needed for proliferation to occur [3].

Thus, the $BRAF^{V600E}$ mutation represents a rational target for drug therapy [3]. Vemurafenib (Zelboraf®) is a first-in-class, small molecule $BRAF^{V600E}$ inhibitor [3], and is one of the systemic therapy options recommended by the US National Comprehensive Cancer Network guidelines for the treatment of patients with unresectable or metastatic melanoma [2].

## 2 How Does the Drug Work?

Vemurafenib is orally available, has a low molecular weight, and is a potent and highly selective inhibitor of

several mutant BRAFs, including $BRAF^{V600E}$ [3, 4]. In vitro, vemurafenib inhibited phosphorylation of MEK and ERK and potently inhibited cellular proliferation in $BRAF^{V600E}$-expressing melanoma cell lines, as well as inhibiting cellular proliferation in melanoma cell lines expressing $BRAF^{V600K}$, $BRAF^{V600R}$, and $BRAF^{V600D}$ [3]. Inhibition of the MAPK pathway was also seen following administration of oral vemurafenib 960 mg twice daily to patients with *BRAF*$^{V600E}$ mutation-positive metastatic melanoma [3].

## 3 For Whom is the Drug Indicated?

Table 1 provides a summary of the EU [4] and US [5] prescribing information for vemurafenib in unresectable or metastatic melanoma in *BRAF*$^{V600}$ mutation-positive patients (EU) or *BRAF*$^{V600E}$ mutation-positive patients (USA).

## 4 Does it Improve Survival Versus Dacarbazine?

Compared with intravenous dacarbazine, oral vemurafenib 960 mg twice daily improved overall survival (OS; co-primary endpoint) in adults with unresectable, previously untreated, *BRAF*$^{V600E}$ mutation-positive, stage IIIC or IV melanoma, according to the results of the pivotal BRAF Inhibitor in Melanoma (BRIM)-3 trial [6–8]. This was a randomized, open-label, multicenter, phase III trial in which 337 and 338 patients were randomized to receive vemurafenib and dacarbazine, respectively. The risk of death was significantly reduced with vemurafenib versus dacarbazine by 63 % at the interim OS analysis [6], by 56 % [7], 38 % [8], and 30 % [8] at subsequent, updated OS analyses (Table 2). The median OS duration was 13.6 months in vemurafenib recipients and 9.7 months in dacarbazine recipients in the most recent analysis (Table 2) [8].

Progression-free survival (PFS; co-primary endpoint) was also significantly improved in vemurafenib versus dacarbazine recipients, with a 74 % relative reduction in the risk of death or disease progression in the final PFS analysis (Table 2) [6].

A confirmed objective response occurred in significantly more vemurafenib recipients than dacarbazine recipients (48 % vs. 5 %; $p < 0.001$), with a median time to response of 1.45 and 2.7 months in the corresponding treatment groups [6]. Of the 219 evaluable vemurafenib recipients, two patients had complete responses and 104 patients had partial responses. All of the 12 responses occurring in the 220 evaluable dacarbazine recipients were partial responses. Only patients who had undergone randomization ≥14 weeks prior to the 30 December 2010 cut-off date were evaluable for tumor response [6].

### 4.1 What was its Efficacy in Other Trials?

Vemurafenib 960 mg twice daily was associated with a high overall response rate in 132 previously treated patients with *BRAF*$^{V600}$ mutation-positive, stage IV metastatic melanoma, according to the results of a noncomparative, multicenter, phase II study (122 patients had *BRAF*$^{V600E}$ mutations and ten had *BRAF*$^{V600K}$ mutations) [9]. The overall response rate (ORR) as assessed by an independent review committee (primary endpoint) was 53 %, with a complete response rate of 6 % and a partial response rate of 47 %. A rapid response (i.e., evident on the first scans at week 6) was seen in most patients, although the time to first response was >6 months in some patients. The median duration of response was 6.7 months [9].

In the phase II study, vemurafenib recipients had a median duration of an independent review committee-assessed PFS of 6.8 months, with a 6-month PFS rate of 56 % [9]. The median duration of OS among vemurafenib recipients was 15.9 months, with OS rates at 6 and 12 months of 77 % and 58 %, and an estimated OS rate at 18 months of 43 % [9].

Vemurafenib recipients had an unconfirmed ORR of 52 %, with a median time to response of 1.8 month, in a US expanded access study that made vemurafenib available to appropriate patients prior to its approval [10]. This multicenter study enrolled 374 patients with *BRAF*$^{V600E}$ mutation-positive metastatic melanoma. Tumor assessment was conducted in 243 patients, who had received vemurafenib for a median of 2 months at the time of analysis [10].

### 4.2 What are the Mechanisms of Resistance?

Both primary and acquired resistance to vemurafenib may occur, with acquired resistance leading to disease progression [3]. Additional secondary mutations in *BRAF* do not seem to be responsible for acquired resistance to vemurafenib. Rather, upstream (e.g., in *NRAS*) and downstream (e.g., in *MEK1*) activating mutations have been implicated in acquired vemurafenib resistance, as has BRAF truncation. Bypass mechanisms that reactivate MAPK signaling or activate MAPK-independent pathways may also lead to acquired vemurafenib resistance. Combining vemurafenib with other appropriately targeted agents (e.g., MEK inhibitors) has the potential to enhance activity and prevent the emergence of, or overcome, resistance [3, 11]. For example, combination therapy with another BRAF inhibitor (dabrafenib) and a MEK 1/2 inhibitor (trametinib) significantly improved PFS relative to dabrafenib monotherapy in an open-label phase I/II study in patients with *BRAF*$^{V600E}$ mutation-positive metastatic melanoma [11].

**Table 1** Prescribing summary of vemurafenib (Zelboraf®) in patients with unresectable or metastatic melanoma in the EU [4] and USA [5]. Consult local prescribing information for further details

| | |
|---|---|
| What is its approved indication? | |
| EU | Monotherapy in adult pts with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma |
| USA | Treatment of pts with unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation as detected by a US FDA-approved test[a] |
| How should it be administered? | |
| Recommended dosage | 960 mg twice daily |
| Duration of therapy | Continue treatment until disease progression or the development of unacceptable toxicity |
| Dosage adjustment | Dose reduction, treatment interruption, or treatment discontinuation may be necessary to manage adverse drug reactions or QTc interval prolongation |
| | A dosage of <480 mg twice daily is not recommended |
| How is it available? | |
| 240-mg film-coated tablets | |
| What is its pharmacokinetic profile? | |
| Absorption and distribution | Mean $C_{max}$ of 62 μg/mL reached in a median of ≈3 h; steady state achieved in ≈15–22 days |
| | Highly plasma protein bound (>99 %), with estimated apparent volume of distribution of 106 L |
| Metabolism and elimination | Primarily metabolized by CYP3A4, with conjugation metabolites also identified |
| | ≈94 % of radiolabeled VEM recovered in the feces and <1 % recovered in the urine |
| | Estimated apparent clearance of 29.3 L/day and estimated elimination half-life of 51.6 h |
| How should it be used in special populations? | |
| Pts with hepatic or renal impairment | Mild or moderate: no dosage adjustment needed (USA) |
| | Severe: closely monitor pts as VEM exposure may be increased (EU); use with caution (USA) |
| Are there any monitoring requirements and precautions? | |
| Use is not recommended in pts with long QT syndrome or uncorrectable electrolyte abnormalities, or in pts receiving medications known to prolong the QT interval (EU, USA) | |
| ECG monitoring recommended prior to treatment, after 1 month of treatment, and after dosage modification (EU); ECG monitoring recommended prior to treatment, after dosage modification, and periodically thereafter (USA) | |
| Monitor liver enzymes and bilirubin prior to treatment and monthly during treatment or as clinically indicated (EU, USA) | |
| Pts should avoid sun exposure and wear protective clothing and use a broad-spectrum sunscreen when outdoors (EU, USA) | |
| All pts should undergo a thorough skin examination prior to treatment and should be monitored regularly during treatment; new skin lesions should be examined by a dermatologist and treated according to current standards of care, with excision of cutaneous SCC recommended (EU, USA) | |
| What are its potential drug interactions? | |
| CYP1A2, CYP2D6, and CYP3A4 substrates | Consider adjusting dose of concomitant CYP1A2 substrates or CYP3A4 substrates with a narrow therapeutic window (EU) |
| | Concomitant use of VEM with CYP1A2, CYP2D6, or CYP3A4 substrates with a narrow therapeutic window not recommended; consider reducing the dose of CYP1A2 and CYP2D6 substrates if coadministration cannot be avoided (USA) |
| Warfarin | Exercise caution and consider additional INR monitoring when VEM administered concomitantly (EU, USA) |
| Strong CYP3A4 inducers or inhibitors | Avoid concomitant administration of VEM and strong inducers/inhibitors of CYP3A4, glucuronidation or P-glycoprotein (EU) |
| | Use strong CYP3A4 inducers/inhibitors with caution when coadministered with VEM (USA) |

*$C_{max}$* maximum plasma concentration, *CYP* cytochrome P450, *INR* international normalized ratio, *PCR* polymerase chain reaction, *pts* patients, *QTc* corrected QT, *SCC* squamous cell carcinoma, *VEM* vemurafenib

[a] The cobas® 4800 BRAF V600 Mutation Test is a real-time PCR assay validated to detect the presence of the $BRAF^{V600E}$ mutation

## 5 What is its Tolerability Profile?

Oral vemurafenib was generally well tolerated in patients with metastatic melanoma [6, 12]. In BRIM-3, the most commonly reported adverse events (all grades) included arthralgia (49 % of vemurafenib recipients vs. 3 % of dacarbazine recipients), rash (36 % vs. 1 %), alopecia (35 % vs. 2 %), fatigue (33 % vs. 31 %), nausea (30 % vs. 41 %), and photosensitivity reactions (30 % vs. 4 %) [6].

In a noncomparative, multicenter, safety study in 834 patients with untreated or previously treated, unresectable, $BRAF^{V600}$ mutation-positive, stage IIIC or IV melanoma

**Table 2** Efficacy of vemurafenib in patients with unresectable, previously untreated, *BRAF*$^{V600E}$ mutation-positive stage IIIC or IV melanoma

| Analysis (cut-off date) | Treatment (median follow-up in months) | OS [% of pts] (timepoint in months) | Median OS duration (months) | HR (95 % CI) for death | Median PFS duration (months) | HR (95 % CI) for death or disease progression |
|---|---|---|---|---|---|---|
| Interim OS analysis [6][a] | VEM (3.8) | 84 (6) | | 0.37 (0.26–0.55)* | 5.3 | 0.26 (0.20–0.33)* |
| (30 December 2010) | DAC (2.3) | 64 (6) | | | 1.6 | |
| Updated OS analysis [7][b, c] | VEM (6.2) | 83 (6) | NR | 0.44 (0.33–0.59)* | | |
| (31 March 2011) | DAC (4.5) | 63 (6) | 7.9 | | | |
| Updated OS analysis [8][b, c] | VEM (10.5) | 55 (12) | 13.2 | 0.62 (0.49–0.77) | | |
| (3 October 2011) | DAC (8.4) | 43 (12) | 9.6 | | | |
| Updated OS analysis [8][b, c] | VEM (12.5) | | 13.6 | 0.70 (0.57–0.87)* | | |
| (1 February 2012) | DAC (9.5) | | 9.7 | | | |

Results of a randomized, open-label, multicenter, phase III trial comparing oral vemurafenib with intravenous dacarbazine [6–8]. Patients could cross over from dacarbazine to vemurafenib after release of the interim survival analysis, with survival data censored at the time of crossover

*DAC* dacarbazine, *HR* hazard ratio, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *VEM* vemurafenib

* $p < 0.001$ vs. DAC

[a] 336 VEM recipients and 336 DAC recipients were evaluable for OS and 275 VEM recipients and 274 DAC recipients were evaluable for PFS. Although this was the interim analysis for OS, it was the final analysis for PFS

[b] Available as an abstract and/or oral presentation

[c] 50, 81, and 83 pts had crossed over from DAC to VEM at the time of the 31 March 2011, 3 October 2011, and 1 February 2012 analyses, respectively

who received vemurafenib 960 mg twice daily (median treatment duration of 68 days), adverse events were reported in 66 % of vemurafenib recipients, with 88 % of these adverse events considered related to treatment [12]. The majority of adverse events were of grade 1 or 2 severity, with grade 3 and 4 adverse events reported in 33 % and 2 % of vemurafenib recipients, respectively. The most commonly occurring adverse events (all grades) included arthralgia (31 % of patients), rash (29 %), fatigue (22 %), photosensitivity (21 %), and nausea (15 %) [12].

Adverse events resulting in dose modification or dose interruption occurred in 129 of 336 vemurafenib recipients (38 %) and in 44 of 282 dacarbazine recipients (16 %) in the BRIM-3 trial [6]. In the safety study, treatment interruption because of adverse events occurred in 141 of 834 vemurafenib recipients (17 %), with 6 % of patients discontinuing vemurafenib treatment because of adverse events [12].

Vemurafenib was associated with exposure-dependent prolongation of the corrected QT (QTc) interval [4, 5], according to the results of a noncomparative, multicenter study [9] in 132 patients with *BRAF*$^{V600}$ mutation-positive, metastatic melanoma. Beyond the first month of vemurafenib treatment, the effect on the mean QTc interval remained stable (mean prolongation of 12–15 msec). Treatment-emergent absolute QTc intervals of >500 msec were seen in two patients, and an increase from baseline in the QTc interval of >60 msec was seen in one patient [4] (see also Table 1).

### 5.1 Is it Associated with Cutaneous Adverse Events?

Cutaneous adverse events (all grades) reported in vemurafenib recipients in the BRIM-3 trial included rash (36 % of patients), photosensitivity reactions (30 %), pruritus (22 %), hyperkeratosis (20 %), skin papilloma (18 %), dry skin (16 %), cutaneous squamous cell carcinoma (SCC) [12 %], erythema (11 %), sunburn (9 %), maculo-papular rash (9 %), keratoacanthoma (8 %), seborrhoeic keratosis (7 %), palmar-plantar erythrodysesthesia (7 %), and actinic keratosis (6 %) [6].

Mild to severe photosensitivity skin reactions have been reported in vemurafenib recipients [5]. Grade 3 photosensitivity reactions were characterized by blistering that could usually be prevented by the use of sunscreen [6]. Severe dermatologic reactions have been reported in vemurafenib recipients, with Stevens-Johnson syndrome and toxic epidermal necrolysis each reported in one vemurafenib recipient in the BRIM-3 trial [5].

Cutaneous SCC and/or keratoacanthoma were reported in 61 vemurafenib recipients (18 %) in the BRIM-3 trial (all cases were treated by simple skin excision) [6], and in 4.3 % of vemurafenib recipients in the safety study [12]. Cutaneous SCC usually occurs early in the course of vemurafenib treatment, with a median time to first appearance of 7–8 weeks [5].

The development of cutaneous SCC or keratoacanthomas in vemurafenib recipients is attributed to paradoxical activation of MAPK signaling [3]. Specifically, vemurafenib recipients who have pre-existing mutations in

the oncogene *RAS* appear predisposed to develop these cutaneous adverse events [3]. Of note, the incidence of SCC was lower in patients who received combination therapy with the BRAF inhibitor dabrafenib plus the MEK 1/2 inhibitor trametinib than in those who received dabrafentib monotherapy in the open-label trial in patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma [11].

### 5.2 How Should Cutaneous Events be Managed?

All patients should undergo a thorough skin examination before starting treatment with vemurafenib and should be monitored regularly during treatment [1] (see also Table 1). Any new skin lesions should be examined by a dermatologist and treated according to current standards of care, with excision of cutaneous SCCs recommended [1].

Regular use of an alcohol-free emollient cream and a broad-spectrum sunscreen is recommended to help prevent skin rash [1, 13]. In terms of photosensitivity reactions, patients should avoid sun exposure and wear protective clothing and use a broad-spectrum sunscreen when outdoors [5]. Modification of the vemurafenib dosage is recommended to manage photosensitivity of intolerable grade 2 or greater severity [5].

## 6 What is its Current Positioning?

Vemurafenib is approved in the USA for the treatment of patients with unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation as detected by a US FDA-approved test, and in the EU as monotherapy in adult patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

Compared with intravenous dacarbazine, oral vemurafenib significantly improves both OS and PFS in patients with unresectable, previously untreated, $BRAF^{V600E}$ mutation-positive, stage IIIC or IV melanoma. Oral vemurafenib is generally well tolerated, with cutaneous adverse events among the most commonly occurring adverse events.

Trials examining the use of vemurafenib in metastatic melanoma are ongoing, including studies examining its efficacy in combination with other agents (e.g., ipilimumab or the PI3K inhibitor BKM-120). The efficacy of vemurafenib in patients with metastatic melanoma and brain metastases is also under investigation, with preliminary evidence of activity in this patient population [14].

**Disclosure** This article was adapted from *BioDrugs* 2012;26(5); 325–34 [3]. The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on the articles. Changes results from comments received were made by the authors on the basis of scientific and editorial merit.

## References

1. Lemech C, Arkenau H-T. Novel treatments for metastatic cutaneous melanoma and the management of emergent toxicities. Clin Med Insights Oncol. 2012;6:53–66.
2. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology (NCCN guidelines®): melanoma. Version 1.2013. Fort Washington: National Comprehensive Cancer Network; 2012.
3. Keating GM. Vemurafenib in unresectable or metastatic melanoma. Biodrugs. 2012;26(5):325–34.
4. Zelboraf (vemurafenib) 240 mg film-coated tablets: EU summary of product characteristics. London: European Medicines Agency; 2012.
5. Zelboraf® (vemurafenib) tablet, oral: US prescribing information. San Francisco: Genentech USA, Inc.; 2011.
6. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16.
7. McArthur G, Hauschild A, Robert C, et al. Vemurafenib improves overall survival compared to dacarbazine in advanced BRAFV600E-mutated melanoma: updated survival results from a phase III randomized, open-label, multicentre trial [abstract]. Stockholm: European Multidisciplinary Cancer Congress; 2011.
8. Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma [abstract no. 8502 plus oral presentation]. 48th Annual Meeting of the American Society of Clinical Oncology. Chicago (IL); 2012.
9. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012;366(8):707–14.
10. Schucter LM, Flaherty LE, Hamid O, et al. A single-arm, open-label, U.S. expanded access study of vemurafenib in patients with metastatic melanoma [abstract no. 8567]. 48th Annual Meeting of the American Society of Clinical Oncology. Chicago (IL); 2012.
11. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(18):1694–703.
12. Larkin JMG, Queirolo P, Arance AM, et al. An open-label, multicenter safety study of vemurafenib (PLX4032, RO5185426) in patients with metastatic melanoma [abstract no. 8517]. 48th Annual Meeting of the American Society of Clinical Oncology. Chicago (IL); 2012.
13. Manousaridis I, Mavridou S, Goerdt S, et al. Cutaneous side effects of inhibitors of the RAS/RAF/MEK/ERK signalling pathway and their management. J Eur Acad Dermatol Venereol. 2012. doi:10.1111/j.1468-3083.2012.04546.x. (Epub ahead of print).
14. Dummer R, Rinderknecht J, Goldinger SM, et al. An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases [abstract no. 8548]. 47th Annual Meeting of the American Society of Clinical Oncology. Chicago (IL); 2012.