Vemurafenib (Zelboraf)

National Drug Monograph

November 2012

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Vemurafenib is a selective inhibitor of BRAF with the V600E mutation but does not inhibit BRAF wild-type.
- BRAF mutations occur in 40-60% of melanomas. The most common mutation is the V600E mutation, accounting for approximately 80% of the BRAF mutations in melanoma.
- The FDA indication is for the treatment of patients with unresectable, metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- Dose: 960 mg (4 x 240 mg film coated tablets) orally twice a day.
- Efficacy was shown in the phase III BRIM-3 trial comparing vemurafenib to dacarbazine in patients with the BRAF V600E mutation with previously untreated and unresectable disease..
- The co-primary endpoints were rate of overall survival and progression free survival. The study was stopped at the planned interim analysis as it met its pre-specified criteria for statistical significance for overall survival and progression free survival.
- 6 month overall survival: 84% in the vemurafenib group versus 64% in the dacarbazine group for a hazard ratio for survival of 0.37 (95%CI 0.26-0.55).
- The median progression free survival was 5.3 months in the vemurafenib group versus 1.6 months in the dacarbazine group for a hazard ratio for progression of 0.26 (95%CI 0.2-0.33)
- The median time to response in the vemurafenib group was 1.45 months
- In the phase 2 trial in patients who had previously received treatment, the overall response rate was 53% and included complete and partial responses.
- The median progression free survival was 6.8 months (95%CI 5.6-8.1) and the median overall survival was 15.9 months (05%CI 11.6-18.3) and 6 month overall survival rate was 77% and the 12 month overall survival rate was 58%.
- Although fairly well tolerated, the most common adverse events are arthralgia, rash, alopecia, fatigue, photosensitivity reactions, nausea, pruritus, and skin papilloma.
- Warnings and precautions include hypersensitivity reactions including anaphylaxis, dermatologic reactions including one case each of Stevens Johnsons syndrome and toxic epidermal necrolysis, QT prolongation (without Torsades) that requires ECG and electrolyte monitoring, photosensitivity requiring the use of broad spectrum UVA/UVB blockers and lip balm, liver laboratory abnormalities, ophthalmic reactions including 5 cases of uveitis, and new primary malignant melanoma.
- The most serious warning is for cutaneous squamous cell carcinoma, including keratoacanthamos which occur primarily due to a paradoxical activation of the MEK-ERK pathway and require excision but should not interrupt therapy.

Summary

Vemurafenib is a BRAF inhibitor approved for use in patients with metastatic melanoma with a BRAF V600E mutation. In clinical trials patients with untreated brain metastases or who required corticosteroid treatment of brain metastases were excluded from trials. In the definitive phase III trial in patients who were not previously treated, vemurafenib met its pre-specified criteria for the co-primary endpoints of overall survival and progression free survival and the study was stopped at the planned interim analysis. Although responses are rapid, the development of progressive disease can occur quickly. The median progression free survival was statistically and clinically longer than in the comparator dacarbazine arm. Patients must be monitored for potential QT prolongation. Secondary cutaneous squamous cell carcinomas and keratoacanthomas require monitoring and excision, but should not stop vemurafenib therapy. The ideal sequencing of vemurafenib and ipilimumab has not been determined.

Outcome in clinically significant area	6 month overall survival 84% versus 64% Median progression free survival 5.3 months vs 1.6 months
Effect Size	HR 0.37 (95%CI 0.26-0.55; p<0.001) for OS HR 0.26 (95%CI 0.2-0.33; p <0.001) for PFS
Potential Harms	Grade 3 toxicities: rash 8% vs 0%, arthralgia 4% vs <1%, cutaneous squamous cell carcinoma 22% vs <1%
Net Clinical Benefit	Moderate

Introduction

Metastatic melanoma has a poor prognosis. One year survival rates are dependent on categories of M1 disease: one year rates for M1a are 62%, for M1b 53%, and for M1c 33%.[1] In phase 3 trials, dacarbazine (an alkylating agent) demonstrates response rates of 7-12% and a median overall survival of 5.6-7.8 months, while ipilimumab (a monoclonal antibody against CTLA-4) trials report a median overall survival of 10.1 months compared to peptide vaccine in previously treated patients, and a median overall survival of 11.2 months in treatment naïve patients in combination with dacarbazine.

BRAF is a protein encoded by the BRAF gene and a member of the RAF kinase family of serine/threonine kinases. RAF is normally activated by RAS and in turn regulates the mitogen-activated protein (MAP)/ERK kinase (MEK) signaling pathway that activates extracellular signal-regulated kinase (ERK).[2] Activated ERK pathway drives important cellular processes including cell proliferation and survival.[3]

BRAF mutations occur in up to 40-60% of melanomas. The most common mutation is V600E, accounting for more than 80% of BRAF mutations, followed by the V600K mutation.[4,5,6]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating vemurafenib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Vemurafenib is a potent and selective inhibitor of BRAF with the V600E mutation but does not inhibit $BRAF^{WT}$. It was developed through a scaffold and structure discovery model that identified productive binding interactions of multiple kinases. In pre-clinical cell lines and animal models, vemurafenib produced tumor regression in cells/tumors harboring the BRAF V600E mutation.

Table #1 Pharmacokinetic parameters

Parameter	Drug
Metabolism	Metabolites account for 5% of plasma components
Elimination	94% recovered in feces and 1% in urine
Elimination Half-life	57 hours
Bioavailability	Has not been determined
Pharmacokinetics in Special Populations	
Hepatic Impairment	Pharmacokinetics examined in patients with baseline normal hepatic function (N-=158, total bilirubin ≤ULN), moderate hepatic impairment (N=58 total bilirubin 1.0-1.5 x ULN), and severe hepatic impairment (N=3 total bilirubin >3 x ULN). The apparent clearance in patients with baseline mild and moderate hepatic impairment was similar to that in patients with normal baseline hepatic function. The need for dose adjustment in patients with severe baseline hepatic impairment has not been determined due to data being available in only 3 patients.
Renal Impairment	Pharmacokinetics examined in patients with baseline normal renal function (CLcr≥90 mL/min). mild renal impairment (N=94 CLcr >60 to 89 mL/min), moderate renal impairment (N=11 CLcr 30 to 59 mL/min) and severe renal impairment (N=1 CLcr < 29 mL/min). The apparent clearance in patients with mild or moderate baseline renal impairment was similar to patients with normal baseline renal function. The need for dose adjustment in patients with severe baseline renal impairment has not been determined due to data being available in only 1 patient.
Age	Age has no significant effect on pharmacokinetics.
Body Weight and Gender	There is no clinically relevant effect of body weight or gender on pharmacokinetics.
Race	Insufficient data to evaluate potential differences in pharmacokinetics due to race.

QT prolongation
No large changes in mean QTc interval (i.e. >20ms) from baseline were detected in a multicenter, open-label, single-arm study in 132 patients. The largest change from baseline seen in the 1st month of treatment was 12.8 ms, and in the first 6 months of treatment 15.1 ms.

Nonclinical toxicology
There are no formal studies that assessed the carcinogenic potential of vemurafenib although it did increase the development of cutaneous squamous cell carcinomas. Vemurafenib did not cause mutagenic changes in in vitro assays or genetic damage in the rat bone marrow micronucleus assay.

Although there have been no studies to assess the effect of vemurafenib on fertility in animals, no histopathologic changes in reproductive organs were noted in males and females in toxicology studies in rats and dogs.

FDA Approved Indication(s)

Vemurafenib is a kinase inhibitor indicated in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Limitation of use: vemurafenib is not recommended in patients with wild-type BRAF melanoma.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Papillary Thyroid Microcarcinomas with BRAF V600E mutation.[7]
Biological plausibility of using a BRAF inhibitor in a subset of patients with papillary thyroid microcarcinoma that harbors the BRAF V600E mutation as this signals a more aggressive behavior in this tumor type.

Refractory Hairy-Cell Leukemia.[8] Most patients with hairy cell leukemia harbor the BRAF V600E mutation. This case report of a patient with refractory disease that did not respond well to standard purine analogue therapy (pentostatin, cladribine, and cladribine plus rituximab) and who had a BRAF V600E mutation who was given vemurafenib demonstrates a complete response to BRAF inhibition therapy.

Non-small cell lung cancer with a BRAF V600E mutation.[9] This is a case report of an elderly patient with newly diagnosed non-small cell lung cancer with a BRAF V600E mutation with a performance status of 4 and not eligible for chemotherapy or clinical trial receiving off-label vemurafenib. Patient showed some evidence of response on 2 week follow-up PET scan but died shortly after due to pleural effusions and dilated heart disease. Autopsy results confirmed response to vemurafenib.

Colorectal carcinoma (CRC) with the BRAF V600E mutation:[10,11] Approximately 10% of patients with CRC harbor a BRAF V600E mutation. In a phase 1 trial of 21 patients with CRC and the mutation, treatment with PLX4032 resulted in a partial response in 1 patient (5%). In vivo studies suggest inhibition of CRC cells with a BRAF inhibitor allows for activation of the epidermal growth factor receptor and cell proliferation. Further studies are needed to test the combination of a BRAF inhibitor with a EGFR inhibitor.

Current VA National Formulary Alternatives

None.

Dosage and Administration

The recommended dose is vemurafenib 960 mg (four film coated 240 mg tablets) twice daily. Doses should be taken approximately 12 hours apart. Doses can be taken without regards to meals. Vemurafenib tablets should be swallowed whole with a glass of water, and not chewed or crushed.

Duration of therapy: Patients should be treated with vemurafenib until disease progression or unacceptable toxicity occurs.

Missed doses: If a dose is missed, it may be taken up to 4 hours prior to the next dose to maintain a twice daily schedule. Do not give both doses at the same time.

Dose Modification

Patients experiencing symptomatic adverse reactions or prolongation of QTc may need dose reductions, dose interruption, or treatment discontinuation. Dose modifications or interruptions are not recommended for patients who develop a cutaneous squamous cell carcinoma adverse reaction. Dose reductions below 480 mg twice daily are not recommended.

Table #2 Dose Modifications

Adverse Event Grade (CTC-AE)	Recommended vemurafenib modification
Grade 1 or Grade 2 (tolerable)	Maintain dose at 960 mg twice daily
Grade 2 (Intolerable) or Grade 3 1st appearance 2nd appearance 3rd appearance	 Interrupt treatment until Grade 0-1. Resume at 720 mg twice daily. Interrupt treatment until Grade 0-1. Resume at 480 mg twice daily. Discontinue permanently.

Grade 4 1st appearance 2nd appearance	 Discontinue permanently or interrupt until Grade 0-1. Resume at 480mg twice daily. Discontinue permanently.

CTC-AE: Common Terminology Criteria for Adverse Events

Efficacy

A. Previously Untreated

Chapman, et al. BRIM-3 Study Group[12]

Efficacy Measures (see Appendix 1: Approval Endpoints)
Original Primary Endpoint:
Rate of Overall Survival

Revised Co-Primary Endpoints:
Rates of Overall Survival and Progression-Free Survival

Secondary Endpoints:
Confirmed Response Rate
Duration of Response
Time to Response

Exploratory
Quality of Life using FACT-M and physical symptom improvement outcome

Summary of efficacy findings

Study Design
Randomized, multicenter, open-label, active control, international trial comparing oral vemurafenib 960 mg twice daily to dacarbazine 1000mg/m^2 intravenous infusion every 3 weeks in patients with unresectable, untreated metastatic melanoma with a BRAF V600E mutation.
- BRAF testing performed at 5 centralized sites
- Randomization numbers provided by Roche

Inclusion Criteria
- Unresectable, previously untreated Stage IIIC or Stage IV melanoma (Stage IIIc=melanoma has spread to at least three lymph nodes which are enlarged due to cancer; Stage IV is divided into 3 subtypes: M1a=metastasis to the skin, subcutaneous tissues, or distant lymph nodes with normal lactate dehydrogenase levels; M1b=metastasis to the lung with a normal lactate dehydrogenase level; M1c=metastasis to any other visceral site or to any site with an elevated lactate dehydrogenase level)
- Positive for BRAF V600E mutation on real time polymerase chain reaction
- Life expectancy of 3 months or longer
- ECOG PS 0-1
- Adequate hematologic, hepatic, and renal function

Exclusion Criteria
- History of cancer within the last 5 years (except basal or squamous cell carcinoma of the skin or cervical carcinoma)

- Metastases to the CNS (unless definitively treated more than 3 months ago with no progression or requirement for corticosteroid treatment)
- Any of the following within 6 months of drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebral vascular disease or transient ischemic attack, or symptomatic pulmonary embolism

Table #3 BRIM-3 Demographics

Characteristic	Vemurafenib (N=337)	Dacarbazine (N=338)
Median Age- yrs	56	52
Male %	59	54
White %	99	100
Geographic region %		
Australia or New Zealand	12	11
North America	26	25
Western Europe	61	60
Other	2	3
ECOG performance status %		
0	68	68
1	32	32
Extent of metastatic disease %		
M1c	66	65
M1b	18	19
M1a	10	12
IIIC	6	4
Lactate dehydrogenase %		
≤ Upper limit of normal	42	42
> Upper limit of normal	58	58

Table #4 BRIM-3 Results

Outcome	Vemurafenib (N=337)	Dacarbazine (N=338)
Co-Primary Endpoints		
6 month Overall Survival % 95%CI	84 (78 – 89)	64 (56 – 73)
Hazard Ratio for death 95%CI P	0.37 (0.26 – 0.55) <0.001	
Progression-Free Survival mos Hazard Ratio for progression 95%CI P	5.3 0.26 (0.2 – 0.33) <0.001	1.6
Secondary Endpoints		
Best Overall Objective Response Rate % (by investigator) P by chi-square	48 (2 Complete +104 Partial) <0.001	5 (12 Partial)
Best Overall Objective Response Rate % In patients with V600K mutation (N=10)	40 (partial response)	
Median time to response- mos	1.45	2.7

The data safety and monitoring board determined the study met its pre-specified criteria for statistical significance for both overall survival and progression free survival at the interim analysis. The interim analysis was performed when 50% of the projected deaths had occurred. They recommended allowing patients in the dacarbazine group be allowed to crossover to vemurafenib and the study protocol was amended. The median follow-up for vemurafenib patients was 3.8 months and for dacarbazine patients 2.3 months.

Subgroup analysis for overall survival
Pre-specified subgroups included age, sex, region, ECOG status, disease stage, and lactate dehydrogenase level. Point estimates for overall survival all favored vemurafenib. In some subgroups with smaller numbers of patients (age ≤ 40 years old, age ≥ 75 years old, patients in Australia or New Zealand, Disease stages IIIC, M1a, M1b, and the combination IIIC, M1a or M1b) the upper limit of the 95% confidence interval crossed over 1.0.

Subgroup analysis for progression free survival
Pre-specified subgroups included age, sex, region, ECOG status, disease stage, and lactate dehydrogenase level. Point estimates for progression free survival all favored vemurafenib. In one subgroup with a smaller number of patients (age ≥ 75 years old) the upper limit of the 95% confidence interval crossed over 1.0

Adverse events leading to dose modification or interruption of therapy occurred in 38% of vemurafenib patients and in 16% of dacarbazine patients. Cutaneous squamous cell carcinomas or keratoacanthoma or both developed in 18% of patients in the vemurafenib. All were treated with simple excision.

B. Supporting Data

Phase 2 Data in Previously Treated Patients[13]

BRIM-2

Efficacy Measures (see Appendix 1: Approval Endpoints)
Primary Endpoint:
Overall Response Rate = Patients with Complete or Partial Responses

Secondary Endpoints:
Overall survival
Progression Free Survival
Duration of response

Summary of Efficacy Findings

Study Design
A phase 2, multicenter, open label trial of vemurafenib 960 mg orally twice daily until the development of unacceptable side effects or disease progression. If disease progression occurred, patients were allowed to continue vemurafenib if the investigator thought the patient would benefit clinically. Blinded tumor assessments performed by an independent review committee.

Inclusion Criteria
- Histologically proven Stage IV melanoma
- Progressive disease after at least 1 prior systemic treatment for metastatic disease (including interleukin-2 and standard chemotherapy)
- BRAF V600E mutation by polymerase chain reaction

- ECOG performance status of 0 or 1
- Brain metastasis if controlled for at least 3 months after completion of local therapy
- Adequate hematologic, hepatic, and renal function

Exclusion

- Other invasive cancer within 5 years of enrollment

Table #5 BRIM-2 Demographics

Characteristic	Value
Male %	61
Race	
White %	98
Hispanic %	2
Age	
Median-yr	51.5
<65 years old %	81
≥ 65 years old %	19
Number of prior therapies %	
1	51
2	27
≥ 3	22
Previous interleukin-2 %	
No	61
Yes	39
Previous ipilimumab %	
No	95
Yes	5
ECOG status %	
0	46
1	54
Metastatic stage at diagnosis %	
M1a	25
M1b	14
M1c	61
Serum lactate dehydrogenase %	
Normal	51
Elevated	49

Table #6 BRIM-2 Results

Outcome	Result
Best Overall Response Rate (IRC) %	53
95%CI	44-62
Complete	6
Partial	47
Stable	29
Progressive	14
Best Overall Objective Response Rate %	40
In patients with V600K mutation (N=10)	(partial response)
Investigator Best Overall Response Rate %	57
Complete	5
Partial	52
Median Duration of Response mos	6.7
95%CI	5.6-8.6
Median Progression Free Survival mos	6.8
95% CI	5.6-8.1

6 month Progression Free Survival % 95%CI	56 47-64
Median Overall Survival mos 95%CI	15.9 11.6-18.3
6 month Overall Survival % 95%CI	77 70-85
12 month Overall Survival % 95%CI	58 49-67
Estimated 18 month Overall Survival % 95%CI	43 33-53

The two most common reasons for exclusion from the trial were a negative test for BRAF V600 mutation or the presence of central nervous system metastases. Median follow-up for efficacy was 12.9 months (range 0.6-20.1). Point estimates for response rates exceeded the 30% target rate for the protocol in pre-defined sub-groups, but the lower bound of the 95% confidence interval was less than 30% for the subgroups LDH 1-1.5 x ULN and > 1.5 x ULN.

Most responses were evident at the time of the first scan at 6 weeks, but responses in some patients did not occur until 6 months of therapy. After progression of disease while on vemurafenib, 24% of patients received ipilimumab. An unplanned ad hoc analysis of overall survival after excluding the patients who went on to receive ipilimumab found the median overall survival unchanged at 15.9 months (95%CI 8.0 – not yet reached).

Cutaneous squamous cell carcinomas developed in 26% of patients. The median time to development of the first lesions was 8 weeks (range 2 to 36 weeks). The pathology review revealed 39 of 43 lesions as keratoacanthoma or mixed keratoacanthoma type; 4 were invasive cutaneous squamous cell carcinoma, and 4 were basal-cell carcinoma. No metastases of cutaneous squamous cell carcinoma were observed.

Phase 1 Dose Escalation Data in Patients with metastatic cancer[14]

Inclusion criteria listed patients with solid tumors refractory to standard therapy or for which standard or curative therapy does not exist, ECOG Performance Status 0 or 1, and absence of known progressing or unstable brain metastases. The dose escalation portion was open to patients with any tumor type with patients with melanoma with a BRAF V600E mutation overrepresented (89%) due to pre-clinical activity. The extension cohort was limited to patients with melanoma and a BRAF V600E mutation.

Dose cohorts using a microprecipitated version of the study drug were studied at the following dose levels: 160 mg twice a day was the lowest dose, with dose escalations to 240mg, 320 or 260 mg, 720 mg, and 1120 mg twice a day.

Due to toxicities at the 1120 mg twice a day dose level, the dose chosen for the extension cohort and for phase 2 trials was 960 mg twice a day. At that dose level in the extension trial, 41% of patients required a dose reduction.

Cutaneous squamous cell carcinomas developed in 15% of the dose escalation cohorts and in 31% of the extension cohort. The median time to appearance was 8 weeks; the majority were resected and did not require discontinuation of therapy.

For further details on the efficacy results of the clinical trials, refer to *Appendix 2: Clinical* Trials (page 24).

Adverse Events (Safety Data)

Table #7 Adverse Events in ≥10% of patients receiving vemurafenib

Adverse Event	Treatment Naive						Failure of at least 1 prior therapy		
	Vemurafenib N=336			Dacarbazine N=287			Vemurafenib N=132		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Skin and subcutaneous tissue			-						-
Rash	37	8	-	2	-	-	52	7	-
Photosensitivity	33	3	-	4	-	-	49	3	-
Alopecia	45	<1	-	2	-	-	36	-	-
Pruritus	23	1	-	1	-	-	30	2	-
Hyperkeratosis	24	1	-	<1	-	-	28	-	-
Rash maculopapular	9	2	-	<1	-	-	21	6	-
Actinic keratosis	8	-	-	3	-	-	17	-	-
Dry skin	19	-	-	1	-	-	16	-	-
Rash popular	5	<1	-	-	-	-	13	-	-
Erythema	14	-	-	2	-	-	8	-	-
Musculoskeletal and connective tissue									
Arthralgia	53	4	-	3	<1	-	67	8	-
Myalgia	13	<1	-	1	-	-	24	<1	-
Pain in extremity	18	<1	-	6	2	-	9	-	-
Musculoskeletal pain	8	-	-	5	<1	-	11	-	-
Back pain	8	<1	-	4	<1	-	11	<1	-
General and administration site						-			
Fatigue	38	2	-	33	2	-	54	4	-
Edema peripheral	17	<1	-	5	-	-	23	-	-
Pyrexia	19	<1	-	9	<1	-	17	2	-
Asthenia	11	<1	-	9	<1	-	2	-	-
Gastrointestinal									
Nausea	35	2	-	43	2	-	37	2	-
Diarrhea	28	<1	-	13	<1	-	29	<1	-
Vomiting	18	1	-	26	1	-	26	2	-
Constipation	12	<1	-	24	-	-	16	-	-
Nervous System									
Headache	23	<1	-	10	-	-	27	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
Neoplasms, benign and malignant									
Skin papilloma	21	<1	-	-	-	-	30	-	-
Cutaneous SCC	24	22	-	<1	<1	-	24	24	-
Seborrheic keratosis	10	<1	-	1	-	-	14	-	-
Investigations Gamma-glutamyltransferase increased	5	3	<1	1	-	-	15	6	4
Metabolism/nutrition Decreased appetite	18	-	-	8	<1	-	21	-	-
Respiratory, thoracic Cough	8	-	-	7	-	-	12	-	-
Injury, poisoning and procedural complications									

Sunburn	10	-	-	-	-	-	14	-	-

Deaths and Other Serious Adverse Events
Serious, non-fatal adverse events: squamous cell carcinomas of the skin, keratoacanthomas, and pyrexia.

More total deaths occurred in the dacarbazine arm than the vemurafenib arm. Deaths within 30 days of the start of treatment occurred in nine patients on dacarbazine and none on vemurafenib. Deaths within 28 days of the last drug dose occurred in 8.3% of vemurafenib arm and 5.9% of the dacarbazine arm. Death due to a treatment emergent adverse event occurred in 1.2% of vemurafenib patients and 1% of dacarbazine patients.

Common Adverse Events
Arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.

Other Adverse Events
Atrial fibrillation (all grades) occurred in 9 patients on vemurafenib. One patient discontinued therapy due to atrial fibrillation, but there were no deaths.

Torsade de Pointes/QT prolongation: due to pre-clinical and early clinical safety signals, this was of special interest. While there were cases of QT prolongation (see Warnings and Precautions) there were no cases of Torsade de Pointes.

Uveitis: Five patients develop uveitis in the vemurafenib arm (none on dacarbazine). The uveitis responded to steroid eye drops although one patient had scarring.

Tolerability
The most common reason for discontinuation was disease progression. Discontinuation due to adverse events occurred in 7.1% on vemurafenib versus 4.2% on dacarbazine. The three most common adverse events leading to discontinuation were Arthralgia, dysphagia, and pneumonia.

For further details on the safety results of the clinical trials, refer to *Appendix 2: Clinical* Trials (page 2422).

Contraindications

None

Warnings and Precautions

Cutaneous Squamous Cell Carcinoma (cuSCC)
The incidence of cutaneous squamous cell carcinomas, which includes squamous cell carcinoma and keratoacanthoma, in treatment naïve patients was reported in 24%. cuSCC generally occurred early in therapy with a median time to first appearance of 7-8 weeks. Thirty-three percent of patient experienced >1 cuSCC, with a median time between occurrences of 6 weeks. Potential risk factors from the trial included age (≥65 years old), prior skin cancer, and chronic sun exposure. Cases were managed with excision and patients continued therapy without dose adjustment. It is recommended that all patients receive a dermatologic evaluation prior to the start of therapy and every 2 months while on therapy. Suspicious lesions should be excised and sent for dermatopathologic examination. Continue dermatologic monitoring for 6 months after

discontinuing therapy. Development of cuSCC is thought to be due to MEK pathway activation by vemurafenib. This paradoxical effect of vemurafenib, the ability to block one oncogenic pathway in tumor cells but activate that same pathway in wild-type melanoma cells and normal cells is argued to be the cause of both the occurrence of these secondary cutaneous carcinomas and also the development of resistance to BRAF inhibition.[15,16,17,18,19,20]

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been reported with initial therapy and upon re-initiation of therapy. Serious reactions include generalized rash and erythema or hypotension. Permanently discontinue therapy in patients who experience a severe hypersensitivity reaction.

Dermatologic Reactions
Reports of severe dermatologic reactions including one case of Stevens-Johnson syndrome and one case of toxic epidermal necrolysis occurred in the trial of treatment naïve patients. Permanently discontinue therapy in patients who experience a severe dermatologic reaction.

QT Prolongation
QT prolongation can lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Dose dependent QT prolongation was reported in patients receiving vemurafenib in an uncontrolled phase 2 QT substudy in previously treated patients with BRAF V600E mutated metastatic melanoma.
Monitoring during therapy should include: ECG and electrolytes (including potassium, magnesium, and calcium) prior to initiation of therapy and after each dose modification. ECGs should be monitored 15 days after starting therapy, and then monthly during the first 3 months, then every 3 months as clinically indicated.

Liver Laboratory Abnormalities
Monitor liver enzymes (transaminases and alkaline phosphatase) and bilirubin prior to start of therapy and then monthly during therapy or as clinically indicated a liver laboratory abnormalities have been reported during treatment. Manage laboratory abnormalities with dose reduction, dose interruption, or treatment discontinuation.

Photosensitivity
Mild to severe photosensitivity was reported in clinical trials. While on therapy, advise all patients to avoid sun exposure, wear protective clothing, and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥30) when outdoors.

Dose modification are recommended for intolerable grade 2 (tender erythema covering 10-30% of BSA) or greater photosensitivity.

Ophthalmologic Reactions
In the clinical trial for treatment naïve patients, 5 cases of uveitis were reported. Uveitis may require treatment with mydriatic ophthalmic drops. Routinely monitor patients for signs and symptoms of uveitis. There were an additional 5 patients with complaints of blurry vision, 5 patients with iritis, and 6 patients with photophobia. In the second-line trial there was one report of retinal vein occlusion.

New Primary Malignant Melanoma

In the first line trial there were 8 new skin lesions in seven patients reported as a new primary malignant melanoma. All cases were managed with excision. Patients continued vemurafenib without a dose adjustment. Monitor patients for skin lesions as outlined in the cuSCC above.

Pregnancy Category D
See Special Populations below.

BRAFV600e Testing
Confirmation of BRAF V600E mutated melanoma detected by and FDA-approved test is required for treatment with vemurafenib as these are the only patients studied and for whom there is benefit of treatment. Tumor tissue was assessed with the cobas® 4800 BRAF V600 Mutation Test designed to detect BRAFV600E mutations in DNA isolated from formalin-fixed, paraffin-embedded human melanoma tissue. Safety and efficacy of vemurafenib has not been established in patients whose melanoma tested negative by the cobas® 4800 BRAF V600 Mutation Test.

Special Populations

Pregnancy
Based on its mechanism of action, vemurafenib may cause fetal harm if administered to a pregnant woman. Women of child-bearing potential and men should be advised to use appropriate contraception during therapy and for at least 2 months after discontinuation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while on therapy advise the patient of the potential hazards to the fetus.

There are no adequate and well controlled trials in pregnant women. There was no evidence of teratogenicity in rat embryo/fetuses at doses approximately 1.3 times the human clinical exposure based on AUC nor in rat embryo/fetuses at doses up to 0.6 times the human clinical exposure. Vemurafenib has the potential to be transmitted from mother to developing fetus based on fetal drug levels that were 3-5% of maternal levels in animal models.

Nursing Mothers
Although it is unknown if vemurafenib is excreted in breast milk, we know that many drugs are excreted in breast milk and may cause serious adverse reactions in nursing infants. If a nursing mother is taking vemurafenib, a decision should be made whether to discontinue breastfeeding or discontinue vemurafenib therapy, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and efficacy in patients under the age of 18 year old has not been established.

Geriatric Use
Twenty-eight percent of patients in the treatment naïve trial were ≥65 years old. Elderly patients may be more likely to experience the following adverse events: cutaneous squamous cell carcinoma, nausea, decreased appetite, peripheral edema, keratoacanthoma, and atrial fibrillation. Overall survival, progression free survival, and best overall response rates were similar in elderly patients as compared to younger patients. (see Appendix 1 for definitions of outcomes)

Gender
The following Grade 3 adverse events were reported more frequently in females: rash, arthralgia, photosensitivity, and increased creatinine.
The following Grade 3 adverse events were reported more frequently in males: keratoacanthoma, increased alkaline phosphatase, and increase total bilirubin.

Hepatic Impairment
No dose adjustment is needed for patients with baseline mild or moderate hepatic impairment based on pharmacokinetic analysis of the clinical trials. Vemurafenib should be used with caution in patients with baseline severe hepatic impairment; the need for a starting dose adjustment in these patients is unknown as there is pharmacokinetic data from only 3 patients with severe hepatic impairment in the clinical trials.

Renal Impairment
No dose adjustment is needed for patients with baseline mild or moderate renal impairment based on pharmacokinetic analysis of the clinical trials. Vemurafenib should be used with caution in patients with baseline severe renal impairment; the need for a starting dose adjustment in these patients is unknown as there is pharmacokinetic data from only 1 patient with severe renal impairment in the clinical trials.

Postmarketing Safety Experience

Dermatologic
- Exacerbation of pre-existing acantholytic dyskeratosis with subsequent complication of Kaposi varicelliform eruption.[21]
- Predominantly lobular neutrophilic paniculitis with arthralgia reported in 2 women on BRAF inhibitors for metastatic melanoma. Treatment with non-steroidal anti-inflammatory drugs was initiated early in the development of this adverse event.[22]
- A pruritic, grade 3 rash developed within 6-8 days of starting vemurafenib in 4 of 13 patients who had recently progressed on ipilimumab therapy. The rash did not respond to glucocorticoid therapy but did respond to discontinuation of vemurafenib. All 4 patients were successfully retreated with vemurafenib at a lower dose.
- Changes in nevi in a patient with melanoma during vermurafenib therapy, including involution and a decrease in pigmentation in nevi with a BRAF V600E mutation and the development of new nevi which were BRAF wild type.[23]
- An oral retinoid, acetretin, was used to treat multiple cutaneous squamous cell carncinomas in a male patient on vemurafenib for metastatic melanoma.[24]

Hematologic
There is a case report of progression of a previously unsuspected RAS-mutant chronic myelomonocytic leukemia in a patient with melanoma receiving vemurafenib. The patient's white count responded to discontinuation of vemurafenib therapy but worsened when vemurafenib was restarted at a lower dose. Patient currently receiving intermittent vemurafenib as his melanoma did respond to therapy.[25]

Central Nervous System Metastases
- Case report of the use of vemurafenib in a 16 year old girl with melanoma that metastasized to her brain. She was originally treated with high dose IL-2 and then by ipilimumab. Vemurafenib decreased the size and metabolism of melanoma in the brain, decreased edema in brain, and caused symptomatic relief. Patient continues on therapy for 6 months.[26]
- Case report of an adult male with brain metastases from melanoma who survived for three years using the sequential therapy whole brain radiotherapy, chemotherapy, ipilimumab, stereotactic radiosurgery, and vemurafenib.[27]

Sentinel Events

No data.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three ~~four~~ data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name Vemurafenib: Sorafenib, Vandetanib, Verapamil
LA/SA for trade name Zelboraf: None

Drug Interactions

Drug-Drug Interactions

Vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor, and a CYP3A4 inducer and a substrate for CYP3A4 based on in vivo data. Co-administration with drugs with narrow therapeutic windows metabolized by CYP1A2, CYP2D6, or CYP3A4 is not recommended. If co-administration is required, use caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 drugs.

Table #8 Effects of vemurafenib on co-administration

Co-administered Drug	Enzyme	Effect
Caffeine	CYP1A2 substrate	Increased AUC 2.6 fold
Dextromethorphan	CYP2D6 substrate	Increased AUC 47%
Midazolam	CYP3A4 substrate	Decreased AUC 39%

Vemurafenib is a substrate for CYP3A4, therefore co-administration with CYP3A4 inhibitors or inducers may alter vemurafenib serum concentrations. Strong CYP3A4 inhibitors or inducers should be used with caution if co-administered with vemurafenib.

Table #9 Drugs inhibiting or inducing CYP3A4

Inhibitor or Inducer	Drug names
Strong CYP3A4 Inhibitors	Ketoconazole Intraconazole Clarithromycin Atazanavir Nefazodone Saquinavir Telithromycin Ritonavir Indinavir Nelfinavir Voriconazole
Strong CYP3A4 Inducers	Phenytoin Carbamazepine Rifampin Rifabutin Rifapentine Phenobarbital

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

No data available.

Conclusions

Clinical Efficacy

Pre-clinical data showed the inhibitory effects of a BRAF inhibitor on melanoma cell lines harboring the BRAF V600E mutation. Following a phase I dose finding trial, vemurafenib was first tested in a phase II trial of patients with metastatic melanoma harboring the BRAF V600E mutation who had previously received at least 1 prior therapy which could have included chemotherapy or high-dose IL-2. The overall response rate of 53% included complete and partial responses. The median duration of response was 6.7 months and the median progression free survival was 6.8 months. At 6 months the overall survival rate was 77%, and at 12 months the overall survival rate was 58%. The estimated overall survival rate at 18 months was 43%. Most responses occurred by the first scan at 6 weeks, but some patients did not respond until 6 months of therapy.

The phase III BRIM-3 trial compared vemurafenib to dacarbazine in patients with metastatic melanoma with the BRAF V600E mutation who were previously untreated. The co-primary endpoints were rate of overall survival and progression free survival. The study was stopped at the interim analysis by the independent data review committee as it has met its pre-specified criteria for statistical significance for both overall survival and progression-free survival. The 6 months overall survival rate was 84% in the vemurafenib group and 64% in the dacarbazine group; the hazard ratio for death of 0.37 (95%CI 0.26-0.55). The median progression free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group; the hazard ratio for progression was 0.26 (95%CI 0.2-0.33). The median time to response in the vemurafenib group was 1.45 months, similar to the phase II results. In a pre-specified subgroup analysis, the point estimates for overall survival for all subgroups favored vemurafenib although the upper bound of the 95% confidence interval crossed one for some smaller subgroups. The point estimates for the pre-specified subgroups for progression free survival all favored vemurafenib.

Since ipilimumab may also be used in patients with a BRAF V600E mutation, consideration should be taken as to sequencing of these drugs. The survival curve for ipilimumab drops quickly at the start of therapy and then levels off, likely due to the delayed immune effects from that drug. Ipilimumab may be better suited for patients with a low disease burden with little symptoms who do not require a quick response. Vemurafenib produces responses fairly quickly although resistance also appears to develop quickly as evidenced by the drop in the survival curve. Vemurafenib may be best suited to patients with a larger disease burden who require a quick response. There is little data on the appropriate sequence for these two drugs. A retrospective analysis of patients at a single institution in Italy evaluated if the sequence of ipilimumab with a BRAF inhibitor affected outcome and identified predictive factors to guide therapy. In this retrospective analysis, 6 patients received a BRAF inhibitor after disease progression on ipilimumab, and 28 patients received ipilimumab after disease progression on a BRAF inhibitor. While the results of this retrospective analysis are not conclusive, their findings that patients with

2 or more baseline risk factors that predict for a more progressive disease may benefit from receiving ipilimumab first followed by a BRAF inhibitor.[28]

Clinical Safety

The paradoxical effects of BRAF inhibition on cells that are BRAF wild type may contribute to some of the unique adverse effects seen with vemurafenib.

In general, therapy is well tolerated, with a single Grade 4 toxicity in clinical trials, and a limited number of grade 3 toxicities. The most common adverse events in clinical trials were arthralgia, rash, alopecia, fatigue, photosensitivity reactions, nausea, pruritus, and skin papilloma. QT prolongation was observed in early clinical trials, but no cases of Torsade de Pointes were seen in late stage clinical trials. Baseline and periodic monitoring, including ECGs and electrolytes should be performed. Patients should be advised to wear broad spectrum UVA/UVB sunscreen and lip balm along with protective clothing to minimize photosensitivity reactions.

The most frequent serious, non-fatal adverse event is the development of cutaneous squamous cell carcinomas and keratoacanthomas. These lesions are thought to be due to the paradoxical activation of the MEK-ERK pathway in cells without a BRAF mutation. Most cases were removed by excision and patients were able to continue on vemurafenib therapy without interruption. Careful, periodic dermatologic exams are recommended throughout therapy. The lesions occurred within the first 6-8 weeks of therapy in most cases and none were metastatic to other sites.

Summary

Vemurafenib is a BRAF inhibitor approved for use in patients with metastatic melanoma with a BRAF V600E mutation. In clinical trials patients with untreated brain metastases or who required corticosteroid treatment of brain metastases were excluded from trials. In the definitive phase III trial in patients who were not previously treated, vemurafenib met its pre-specified criteria for the co-primary endpoints of overall survival and progression free survival and the study was stopped at the planned interim analysis. Although responses are rapid, the development of progressive disease can occur quickly. The median progression free survival was statistically and clinically longer than in the comparator dacarbazine arm. Patients must be monitored for potential QT prolongation. Secondary cutaneous squamous cell carcinomas and keratoacanthomas require monitoring and excision, but should not stop vemurafenib therapy. The ideal sequencing of vemurafenib and ipilimumab has not been determined.

Outcome in clinically significant area	6 month overall survival 84% versus 64% Median progression free survival 5.3 months vs 1.6 months
Effect Size	HR 0.37 (95%CI 0.26-0.55; p<0.001) for OS HR 0.26 (95%CI 0.2-0.33; p <0.001) for PFS
Potential Harms	Grade 3 toxicities: rash 8% vs 0%, arthralgia 4% vs <1%, cutaneous squamous cell carcinoma 22% vs <1%
Net Clinical Benefit	Moderate

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

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Prepared November, 2012 by Mark C. Geraci, Pharm.D., BCOP

Appendix 2: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

Appendix 2: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to October 2012) using the search terms vemurafenib (with a Clinical Query search filter) and PLX4032. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Table Vemurafenib Clinical Trials

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results	Safety
Chapman, et al. (2011) The BRIM-3 Study Group MC, OL, AC, RCT ITT N=672 International Funding: Hoffman-La Roche	Inclusion criteria Unresectable, previously untreated Stage IIIC or Stage IV melanoma that tested positive for the BRAF V600E mutation on RT-PCR Life expectancy of 3 months or longer ECOG PS 0-1 Adequate hematologic, hepatic, and renal function Exclusion criteria History of cancer within the past 5 years (except basal or squamous-cell carcinoma of the skin or cervical carcinoma) Metastases to the CNS (unless definitively treated more than 3 months ago with no progression or requirement for glucocorticoid therapy) Any of the following within 6 months of drug administration: MI, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, serious cardiac arrhythmia requiring medication, uncontrolled	Rx1 Vemurafenib Orally 960mg twice a day Rx2 Dacarbazine Intravenous infusion 100 mg/m^2 Every 3 weeks Endpoints: Co-primary endpoints: OS and PFS	Med Age: Vemurafenib 56; dacarbazine D 52 Sex: M54-59% Race: white 99-100% ECOG PS 0: 68% 1: 32% Extent of disease M1c: 65-66% M1b: 18-19% M1a: 10-12% Unresectable IIIC: 4-6% LDH ≤ULN: 42% >ULN: 58%	<table><tr><th>Outcome</th><th>Vemurafenib N = 337</th><th>Dacarbazine N = 338</th></tr><tr><td colspan="3">Co Primary</td></tr><tr><td>6 month Overall Survival HR for death 95% CI P</td><td>84% 0.37 0.26 to 0.55 <0.001</td><td>64%</td></tr><tr><td>Progression Free Survival HR 95%CI P</td><td>5.3 months 0.26 0.20 to 0.33 <0.001</td><td>1.6 months</td></tr><tr><td colspan="3">Secondary</td></tr><tr><td>Best Overall Response Rate P by chi-square</td><td>48% (2 CR + 104 PR) <0.001 N=10 had BRAF V600K mutation; 40% PR</td><td>5% (All PR)</td></tr><tr><td>Med time to response</td><td>1.45 months</td><td>2.7 months</td></tr></table> Other Secondary Outcomes: duration of response, time to treatment failure Exploratory Objectives: Quality of Life using the FACT-	Withdrawals <table><tr><th></th><th>Vem</th><th>Dacarb</th></tr><tr><td>Randomized</td><td>337</td><td>338</td></tr><tr><td>Treated</td><td>336</td><td>289</td></tr><tr><td>Refused Never received</td><td>0 2</td><td>37 11</td></tr><tr><td>Discontinued</td><td>113</td><td>206</td></tr><tr><td>Progression or death Lost to f/u AE Other</td><td>95 6 12 -</td><td>181 12 10 3</td></tr></table> Adverse Events (All Grades) <table><tr><th>AE</th><th>Vem</th><th>Dacarb</th></tr><tr><td>Skin Rash Photo-sensitive Alopecia Pruritus Hyperkeratosis Rash-MP Actinic keratosis Dry skin Rash- popular Erythema</td><td> 37 33 45 23 24 9 8 19 5 14</td><td> 2 4 2 1 <1 <1 3 1 - 2</td></tr><tr><td>Musculoskeletal Arthralgia Myalgia Pain/extremity MS pain Back pain</td><td> 53 13 18 8 8</td><td> 3 1 6 4 5</td></tr></table>

<table>
<tr>
<td></td>
<td>hypertension, CVA or TIA, or symptomatic pulmonary embolism</td>
<td></td>
<td></td>
<td>Melanoma, physical symptom improvement outcome (PIO)
Median follow-up: Interim analysis: 3.8 months in the vemurafenib group and 2.3 months in the dacarbazine group.

Point estimates for all sub-group analyses for overall survival favored vemurafenib. 95% Confidence Intervals crossed 1.0 in several groups, some of which contained smaller numbers of patients. For the subgroups of Age, Sex, ECOG Status, and initial LDH level, the point estimate and 95% Confidence Intervals favored vemurafenib for each classification within those groups. In the subgroups of Age Group, Region, and Disease State some classifications within each of those groups had Confidence Intervals that crossed 1.0.

Point estimates for all sub-group analyses for Progression Free Survival favored vemurafenib. 95% Confidence Intervals all favored vemurafenib except for the classification of age ≥75 years old in the Age Group subgroup which crossed over 1.0 (n=38).</td>
<td>
<table>
<tr><td>General</td><td></td><td></td></tr>
<tr><td>Fatigue</td><td>38</td><td>33</td></tr>
<tr><td>Edema-peripheral</td><td>17</td><td>5</td></tr>
<tr><td>Pyrexia</td><td>19</td><td>9</td></tr>
<tr><td>Asthenia</td><td>11</td><td>9</td></tr>
<tr><td>Gastrointestinal</td><td></td><td></td></tr>
<tr><td>Nausea</td><td>35</td><td>43</td></tr>
<tr><td>Diarrhea</td><td>28</td><td>13</td></tr>
<tr><td>Vomiting</td><td>18</td><td>26</td></tr>
<tr><td>Constipation</td><td>12</td><td>24</td></tr>
<tr><td>Nervous system</td><td></td><td></td></tr>
<tr><td>Headache</td><td>23</td><td>10</td></tr>
<tr><td>Dysgeusia</td><td>14</td><td>3</td></tr>
<tr><td>Neoplasms,benign</td><td></td><td></td></tr>
<tr><td>Skin papilloma</td><td>21</td><td>-</td></tr>
<tr><td>Cutaneous SCC</td><td>24</td><td><1</td></tr>
<tr><td>Seborrheic keratosis</td><td>10</td><td>1</td></tr>
<tr><td>Nutrition</td><td></td><td></td></tr>
<tr><td>Decreased appetite</td><td>18</td><td>8</td></tr>
<tr><td>Respiratory</td><td></td><td></td></tr>
<tr><td>Cough</td><td>8</td><td>7</td></tr>
<tr><td>Injury</td><td></td><td></td></tr>
<tr><td>Sunburn</td><td>10</td><td>-</td></tr>
</table>

Most Common
Arthralgia, rash, alopecia, fatigue, photosensitivity, nausea, pruritus and skin papilloma.
Serious (Grade 3)
Rash, photosensitivity, pruritus, hyperkeratosis, macula-papular rash, Arthralgia, fatigue, nausea, vomiting, cutaneous squamous cell carcinoma, increased gamma-glytamyltransferase</td>
</tr>
<tr>
<td>Sosman, et al. (2012)
MC, Phase 2, OL
BRIM-2
Independent Review Committee Assessment</td>
<td>Inclusion Criteria
Metastatic melanoma
Completed and failed at least 1 prior standard of care regimen (e.g.</td>
<td>Vemurafenib 960mg orally twice a day until development of progressive disease, unacceptable toxicity,</td>
<td>Med Age: 51.5 years
Age ≥65 years: 19%
Sex: Male 61%
Race: White 98%
No. of prior therapies</td>
<td>Primary
Best Overall Response Rate (IRC): 53% (95%CI 44 to 62)
Complete Response: 6%
Partial Response: 47%
Stable Disease: 29%</td>
<td>Withdrawals
<table>
<tr><td>Withdrawal event</td><td>Further data</td></tr>
<tr><td>Discontinued due to AE</td><td>1 retinal-vein occlusion</td></tr>
</table>
</td>
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N=132 Hoffman-La Roche	dacarbazine, temozolomide, etc.) BRAF V600E positive by Roche CoDx test ECOG 0 or 1 Measurable disease Adequate hematologic, renal, and liver function (ANC >1500/mm^3, platelets ≥100,000/mm^3, hemoglobin ≥9gm/dL, serum creatinine ≤1.5 times the ULN or CrCl >40ml/hr by Cockroft-Gault AST and ALT ≤ 2.5 times the ULN (5 times the ULN for patients with concurrent liver metastases), bilirubin ≤1.5 times the ULN, alkaline phosphatase ≤2.5 times the ULN (5 times the ULN for patients with liver metastases) Exclusion Criteria Active CNS metastases (pts with asymptomatic lesions previously irradiated are eligible if pts are ≥3 months beyond therapy and ≥3 weeks off glucocorticoids) Prior major surgery or traumatic injury not full recovered for at least 2 weeks (or anticipate need for major surgery) History or known carcinomatous meningitis Anticipated or on-going therapy with other anti-	consent withdrawal, or other criteria for withdrawal set in protocol. Primary Endpoint: Best overall response rate (BORR) by independent review committee (IRC) Secondary Endpoints: BORR assessed by investigators Duration of response (IRC) Time to response (IRC) Progression-free survival (IRC) Overall survival (IRC) Physical symptom improvement outcome (PIO)	1: 51% 2: 27% ≥3: 22% Previous ipilimumab: 5% ECOG status 0: 46% 1: 54% Metastatic stage M1a: 25% M1b: 14% M1c: 61% Serum LDH Normal: 51% Elevated: 49%	Progressive Disease: 14% Secondary Investigator BORR: 57% Complete Response: 5% Partial Response: 52% Overall response rates greater than 30% in all pre-specified subgroups comprised of more than 25 patients Patients with a LDH more than 1.5 times the ULN had the lowest subgroup response rate of 33% 10 patients with BRAF V600K mutation: 4 partial response 3 stable disease 2 progressive disease Median duration of response: 6.7 months (95%CI 5.6 to 8.6) (IRC). Most responses seen at 6 weeks but in some, responses not seen until more than 6 months Median Progression Free Survival: 6.8 months (95%CI 5.6 to 8.1) Median Overall Survival: 15.9 months (95%CI 11.6 to 18.3)	<table><tr><td>Death</td><td>Rapid progression of melanoma and acute renal failure possibly related to drug</td></tr></table> Dose Interruptions 45% had dose reductions 64% required dose interruptions Most common AEs leading to dose reduction or interruption: rash, arthalgia, elevated liver enzymes, photosensitivity reactions Median dose received: 1740 mg per day (91% of intended 1920 mg per day dose) Adverse Events (All Grades) <table><tr><th>AE</th><th>Vemurafenib</th></tr><tr><td>Skin</td><td></td></tr><tr><td>Rash</td><td>52</td></tr><tr><td>Photo-sensitive</td><td>49</td></tr><tr><td>Alopecia</td><td>36</td></tr><tr><td>Pruritus</td><td>30</td></tr><tr><td>Hyperkeratosis</td><td>28</td></tr><tr><td>Rash-MP</td><td>21</td></tr><tr><td>Actinic keratosis</td><td>17</td></tr><tr><td>Dry skin</td><td>16</td></tr><tr><td>Rash- popular</td><td>13</td></tr><tr><td>Erythema</td><td>8</td></tr><tr><td>Musculoskeletal</td><td></td></tr><tr><td>Arthralgia</td><td>67</td></tr><tr><td>Myalgia</td><td>24</td></tr><tr><td>Pain/extremity</td><td>9</td></tr><tr><td>MS pain</td><td>11</td></tr><tr><td>Back pain</td><td>11</td></tr><tr><td>General</td><td></td></tr><tr><td>Fatigue</td><td>54</td></tr><tr><td>Edema-peripheral</td><td>23</td></tr><tr><td>Pyrexia</td><td>17</td></tr><tr><td>Asthenia</td><td>2</td></tr><tr><td>Gastrointestinal</td><td></td></tr></table>

	cancer drugs Pregnant or lactating women Refractory nausea or vomiting, malabsorption,, external biliary shunt, significant bowel resection, must be able to swallow pills Mean QTc interval ≥450 msec NCI CTCAE Version 4.0 grade 3 h3emorrhage within 4 weeks of starting therapy Any of the following within 6 months prior: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism Ongoing cardiac dysrhythmias ≥grade 2 (NCI CTCAE Version 4.0) Uncontrolled hypertension (>150/100 mm Hg despite optimal medical therapy) Thyroid function abnormality that can't be maintained in normal range with medication Clinically significant active infection History of allogeneic bone marrow transplant or organ transplant Treatment of drugs with				<table><tr><td>Nausea</td><td>37</td></tr><tr><td>Diarrhea</td><td>29</td></tr><tr><td>Vomiting</td><td>26</td></tr><tr><td>Constipation</td><td>16</td></tr><tr><td>Nervous system</td><td></td></tr><tr><td>Headache</td><td>27</td></tr><tr><td>Dysgeusia</td><td>11</td></tr><tr><td>Neoplasms,benign</td><td></td></tr><tr><td>Skin papilloma</td><td>30</td></tr><tr><td>Cutaneous SCC</td><td>24</td></tr><tr><td>Seborrheic keratosis</td><td>14</td></tr><tr><td>Nutrition</td><td></td></tr><tr><td>Decreased appetite</td><td>21</td></tr><tr><td>Respiratory</td><td></td></tr><tr><td>Cough</td><td>12</td></tr><tr><td>Injury</td><td></td></tr><tr><td>Sunburn</td><td>14</td></tr></table> Most common Arthralgia, rash, photosensitivity reactions, fatigue, and alopecia. Serious (Grade 3) Rash, photosensitivity reactions, pruritus, macula-papular rash, Arthralgia, fatigue, pyrexia, nausea, vomiting, cutaneous squamous cell carcinoma, increased gamma-glutamyltransferase (including 4% Grade 4)

	dysrhythmic potential: terfenadine, quinidine, procainamide, disopyramide,sotalol, probucol, bepridil, haloperidol, risperidone, or indapamide Known infectious disease including HIV positivity or AIDS-related illness, HBV, and HCV Previous malignancy except patients with basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, any curatively treated cancer from which patient is currently disease free, or any malignancy from which patient is disease free for at least 5 years (isolated elevation in PSA in the absence of prostate cancer is allowed)				
Flaherty, et.al. 2010 Phase 1, dose escalation followed by extension phase N=55 (dose escalation) N=32 (Extension cohort) Plexxikon and Roche	Inclusion Solid tumors refractory to standard therapy or for which there is no standard or curative therapy ECOG status 0 or 1 Life expectancy of 3 months or longer Absence of progressing or unstable brain metastases Adequate hematologic, hepatic, and renal function For the Extension cohort, patients were restricted	Initial crystalline formulation: Dose escalation cohorts from 200 mg per day to 1600 mg twice daily Reformulated as microprecipitated powder due to poor oral availability. Dose escalation cohorts from 160 mg twice a day to 1120 mg twice a day. Dose identified for Extension phase: 960 mg twice daily.	Dose Escalation population Med Age: 63 Male: 62% Tumor types: Melanoma 89% Thyroid 5% Other 5% Stage: M1a 14% M1b 12% M1c 73% ECOG: 0 51% 1 49% Previous therapies 0 10% 1 33% 2 10%	The initial crystalline formulation had no side effects at doses ranging from 200 mg per day to 1600 mg twice a day. However, serum levels were lower than predicted from pre-clinical models due to low bioavailability. The reformulated microprecipitated powder had higher bioavailability. The lowest dose was 160 mg twice daily and doses were escalated as scheduled to 240, 320, 360, 720, and 1120 mg twice daily. Dose limiting side effects were first observed at 720 mg twice daily. At the next dose level of 1120 mg twice daily, 4 of 6 patients experienced dose limiting toxicity. A dose of 960 mg twice daily was evaluated in a cohort of six patients, established as the phase 2 dose, and administered to the Extension Cohort. Dose Escalation phase	Dose limiting toxicities at 1120 mg twice daily: Grade 3 rash, fatigue, arthalgia At 960 mg twice daily: 41% required dose reduction Most common grade 2 or 3 adverse events: Arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous squamous-cell carcinoma, pruritus, palmar-plantar dysesthesia. Rash was evenly distributed on face or neck, trunk, and extremities. Median time to appearance of cutaneous squamous-cell carcinoma: 8

	to patients with melanomas with the V600E BRAF mutation by polymerase-chain-reaction.		≥3 47% Extension Cohort Med Age: 52 Male: 59% Tumor types: Melanoma 100% Stage: M1a 19% M1b 6% M1c 75% ECOG: 0 47% 1 53% Previous therapies 0 22% 1 28% 2 12% ≥3 38% LDH>ULN 41%	No tumor responses were seen at 160 mg daily of the microprecipitated formulation or at any dose of the crystalline formulation. At doses of 240mg or more twice daily, the response rate was 69% (11 of 16 patients with BRAF mutated melanoma) with 10 partial responses and 1 complete response. Duration of response: 2-18 months Three patients with papillary thyroid cancer had a partial or complete response lasting 8 months in 1 patient and stable disease lasting 11 and 13 months each of 2 other patients. Extension Phase Response rate: 81% (26/30) with a complete response in 2 and a partial response in 24. Improvement in symptoms occurred within 1-2 weeks (e.g. reduced need for narcotics). Responses seen in lung, lymph nodes, visceral organs and bones. Partial responses observed in patients with elevated LDH and in patients who received more than 1 previous therapy. Estimated PFS is 7 months. Median OS not yet reached.	weeks.

N_R, Number randomized, MC=multicenter, OL=Open label, AC=active control, RCT=randomized clinical trial, RT-PCR=real-time polymerase chain reaction, ECOG=Eastern Cooperative Oncology Group, PS=performance status, MI=myocardial infarction, CHF=congestive heart failure, CVA=cerebrovascular accident, TIA=transient ischemic attack, ULN=upper limit of normal range, HR=hazard ratio, CI=confidence interval, CR=complete response, PR = partial response, f/u= follow up, AE=adverse event, SCC=squamous cell carcinoma, ANC=absolute neutrophil count