Zelboraf®

Vemurafenib

Information as set forth in this label only applies to Zelboraf

Category

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Vemurafenib is a small molecule that selectively inhibits oncogenic BRAF serine-threonine kinases.
ATC code: L01XE15.

1.2 Type of Dosage Form

Film-coated tablets.
Pinkish white to orange white, oval, biconvex film-coated tablets of approximately 19 mm, with 'VEM' engraved on one side.

1.3 Route of Administration

Oral

1.4 Sterile / Radioactive Statement

Not applicable

1.5 Qualitative and Quantitative Composition

Active ingredient: vemurafenib
Film-coated tablet 240 mg of vemurafenib (as a co-precipitate of vemurafenib and hypromellose acetate succinate)
Excipients: Croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and hydroxypropylcellulose.
The film-coating contains polyvinyl alcohol, titanium dioxide CI77891, marcogol 3350, talc (purified), and iron oxide red CI77491.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Zelboraf® is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (see section 3.1).

2.2 Dosage and Administration

General
Treatment with Zelboraf should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
Patients treated with Zelboraf must have a previously confirmed BRAF V600 mutation-positive tumor status by a validated test. (see section 2.4 and 3.1)

Standard Dosage
The recommended dose of Zelboraf is 960 mg (four 240 mg tablets) twice daily. Zelboraf may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided (see Section 3.2.1 Absorption).
Zelboraf tablets should be swallowed whole with a glass of water. Zelboraf tablets should not be chewed or crushed.

Duration of Treatment
It is recommended that treatment with Zelboraf continue until disease progression or the development of unacceptable toxicity (see Tables 1 and 2).

Missed Doses
If a planned dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice-daily regimen. Both doses should not be taken at the same time.

Vomiting
In case of vomiting after Zelboraf administration the patient should not take an additional dose of the medicinal product but the treatment should be continued as usual.

Dose Modifications (see sections 2.4.1 General, Warnings and Precautions and section 2.6.1 Clinical Trials, Undesirable Effects)
Management of symptomatic adverse events or prolongation of QTc may require dose reduction, temporary interruption or treatment discontinuation of Zelboraf. Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC). Dose reductions resulting in a dose below 480 mg twice daily are not recommended.

Table 1 Dose Modifications

Grade (CTC-AE)*	Recommended Zelboraf Dose Modification
Grade 1 or Grade 2 (tolerable)	Maintain Zelboraf at a dose of 960 mg twice daily
Grade 2 (intolerable) or Grade 3	
1st Appearance^	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered)
2nd Appearance^	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)
3rd Appearance^	Discontinue permanently
Grade 4	
1st Appearance^	Discontinue permanently or interrupt Zelboraf treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)
2nd Appearance^	Discontinue permanently

*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)
^ Any AE where treatment interruption and dose reduction are clinically indicated and undertaken

Table 2 Dose Modification Schedule Based On Prolongation of the QT Interval

Dose modification schedule based on prolongation of the QT interval - QTc value	Recommended dose modification
QTc>500 ms at baseline	Treatment not recommended
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	Discontinue permanently
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains ≤60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms See monitoring measures in section 2.4.1 Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains ≤60ms	Temporarily interrupt treatment until QTc decreases below 500 ms See monitoring measures in section 2.4.1 Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains ≤60ms	Discontinue permanently

2.2.1 Special Dosage Instructions

Pediatric use: The safety and efficacy of Zelboraf in patients under the age of 18 have not been established. Zelboraf is not approved for use in patients under the age of 18 years (see section 3.2.5 Pharmacokinetics in Special Populations).

Geriatric use: No special dose adjustment of Zelboraf is required in patients aged > 65 years.

Renal impairment: There have been no specific renal impairment studies; based on retrospective analyses of data from clinical trials, no starting dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment: There have been no specific hepatic impairment studies; based on retrospective analyses of data from clinical trials, no starting dose adjustment is required in patients with mild or moderate hepatic impairment.

2.3 Contraindications

Zelboraf is contraindicated in patients with known hypersensitivity to vemurafenib or to any of its excipients (*see section 2.4.1 General, Warnings and Precautions)*.

2.4 Warnings and Precautions

2.4.1 General

Before taking Zelboraf, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. The efficacy and safety of Zelboraf in patients with tumours expressing BRAF V600 non-E mutations have not been convincingly established (see section 3.1). Zelboraf should not be used in patients with wild type BRAF malignant melanoma.

Malignancies

Cutaneous Squamous Cell Carcinoma (cuSCC)
Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with Zelboraf (*see section 2.6.1 Undesirable Effects*). CuSCC usually occurred early in the course of treatment. Potential risk factors associated with cuSCC in vemurafenib clinical trials included age (≥ 65 years), prior skin cancer, and chronic sun exposure. Cases of cuSCC were typically managed with simple excision, and patients were able to continue treatment without dose adjustment.
It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. Monitoring should continue for 6 months following discontinuation of Zelboraf or until initiation of another anti-neoplastic therapy.
Patients should be instructed to inform their physicians with the occurrence of any skin changes.

Non-Cutaneous Squamous Cell Carcinoma (non-cu SCC)
In clinical studies two cases of squamous cell carcinoma of the head and neck (tongue and tonsils) have been reported. Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment. Pelvic (for women) and anal examinations are recommended before and at the end of treatment or when considered clinically indicated. In addition, patients should undergo a chest CT scan prior to initiation of treatment and every 6 months during treatment. Following discontinuation of Zelboraf, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be evaluated as clinically indicated.

Other Malignancies
Based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations (*see section 2.6.2 Post Marketing Experience, Undesirable Effects*). Zelboraf should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Zelboraf (see sections 2.3 Contraindications and 2.6.1 Clinical Trials, Undesirable Effects). Severe hypersensitivity reactions may include Stevens-Johnson syndrome, generalized rash, erythema or hypotension. In patients who experience severe hypersensitivity reactions, Zelboraf treatment should be permanently discontinued.

Dermatologic Reactions
Severe dermatologic reactions have been reported in patients receiving Zelboraf, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Zelboraf (*see section 2.6.2 Post Marketing Experience, Undesirable Effects).* In patients who experience a severe dermatologic reaction, Zelboraf treatment should be permanently discontinued.

Potentiation of Radiation Toxicity
Cases of radiation recall and radiation sensitization have been reported in patients treated with radiation either prior, during, or subsequent to Zelboraf treatment (*see sections 2.8 Interactions with other Medicinal Products and other Forms of Interaction and 2.6.2 Post Marketing Experience, Undesirable Effects)*. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes.
Zelboraf should be used with caution when given concomitantly or sequentially with radiation treatment.

Ophthalmologic reactions
Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Patients should be monitored routinely for ophthalmologic reactions (see section 2.6.1 Clinical Trials, Undesirable Effects).

New primary melanoma
New primary melanomas have been reported in clinical trials. Cases were managed with excision and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

QT Prolongation
Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase II QT sub-study in previously treated patients with metastatic melanoma (*see section 2.6.1 Clinical Trials, Undesirable Effects*). QT prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Treatment with Zelboraf is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking medicinal products known to prolong the QT interval.
ECG and electrolytes should be monitored before treatment with Zelboraf and after dose modification. Further monitoring should occur monthly during the first 3 months of treatment followed by every 3 months thereafter or more often as clinically indicated. Initiation of treatment with Zelboraf is not recommended in patients with QTc>500 ms. If during treatment the QTc exceeds 500 ms (CTCAE ≥ grade 3), Zelboraf treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should not occur until the QTc decreases below 500 ms and should be re-initiated at a lower dose, as described in Tables 1 and 2. Permanent discontinuation of Zelboraf treatment is recommended if after correction of associated risk factors, the QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values.

Liver Injury
Liver injury, including cases of severe liver injury, has been reported with Zelboraf (*see sections 2.6.2 Post Marketing Experience, and Laboratory Abnormalities, Undesirable Effects)*.
Liver laboratory abnormalities may occur with Zelboraf (*see section 2.6.1. Laboratory Abnormalities, Undesirable Effects*). Liver enzymes (transaminases and alkaline phosphatase) and bilirubin should be measured before initiation of treatment and monitored monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or with treatment discontinuation (*see section 2.2 Dosage and Administration, Dose Modifications*).

Photosensitivity
Mild to severe photosensitivity was reported in patients who were treated with vemurafenib in clinical trials (*see section 2.6.1. Clinical Trials, Undesirable Effects*). All patients should be advised to avoid sun exposure while taking Zelboraf. While taking the drug, patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sun screen and lip balm (SPF ≥ 30) when outdoors to help protect against sunburn.
For photosensitivity, grade 2 (intolerable) or greater adverse events, dose modifications are recommended (*see section 2.2 Dosage and Administration Dose Modifications*).

Dupuytren's contracture and plantar fascial fibromatosis
Dupuytren's contracture and plantar fascial fibromatosis have been reported with Zelboraf. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported (*see section 2.6.2 Post Marketing Experience, Undesirable Effects*).
Events should be managed with dose reduction, treatment interruption, or with treatment discontinuation (*see section 2.2 Dosage and Administration Dose Modifications*).

Concurrent administration with ipilimumab
In a Phase I trial, asymptomatic grade 3 increases in transaminases and bilirubin were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these data, the concurrent administration of ipilimumab and vemurafenib is not recommended.

Pancreatitis
Pancreatitis has been reported in vemurafenib treated subjects. Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when restarting vemurafenib after an episode of pancreatitis.

Effects of vemurafenib on other medicinal products
Vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer. Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolised by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolised by CYP3A4. Concomitant use of vemurafenib with agents metabolized by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).
Exercise caution and consider additional INR (International Normalised Ratio) monitoring when vemurafenib is used concomitantly with warfarin (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).
Vemurafenib is an inhibitor of the efflux transporters P-glycoprotein (P-gp). Vemurafenib may increase the plasma exposure of medicinal products that are P-gp substrates. Caution should be exercised when dosing vemurafenib concurrently with P-gp substrates. Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction).

Effect of other medicinal products on vemurafenib
As vemurafenib is a substrate of CYP3A4, the concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Caution should be used when administering vemurafenib with strong CYP3A4 inhibitors and inducers (see section 2.8 Interactions with other Medicinal Products and other Forms of Interaction). Dose reduction of vemurafenib may be considered during coadministration with a strong CYP3A4 inhibitor, if clinically indicated (see section 2.2 Dosage and Administration, Dose Modifications).

Laboratory Abnormalities
Creatinine
Creatinine increases mostly cases of mild (> 1-1.5 x ULN) to moderate (> 1.5 – 3 x ULN) and mostly reversible in nature have been reported. See sections 2.6.1. and 2.6.2. Laboratory Abnormalities, Undesirable Effects.
Serum creatinine should be measured before initiation of treatment and periodically monitored during treatment as clinically indicated. For recommended dose modifications, see section 2.2 Dosage and Administration, Table 1.

2.4.2 Ability to Drive and Use Machines
No studies on the effects of Zelboraf on the ability to drive or operate machinery have been performed.
Zelboraf may have a minor influence on the ability to drive and use machines. Fatigue, dizziness and eye problems may occur during treatment with Zelboraf (see sections 2.4.1 General, Warnings and Precautions and section 2.6 Undesirable Effects).

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Fertility
No nonclinical fertility studies have been conducted (*see section 3.3.3 Impairment of Fertility*). No histopathological findings were noted in reproductive organs in males and females in repeat-dose toxicology studies (*see section 3.3.4 Reproductive toxicity*). In animal studies, vemurafenib was found to cross the placenta.

Contraception
Women of childbearing potential and men should use effective contraception while receiving Zelboraf therapy and for at least 6 months after discontinuation of Zelboraf. Zelboraf might decrease the efficacy of hormonal contraceptives.

2.5.2 Pregnancy
Zelboraf is not recommended during pregnancy unless the potential benefits for the mother outweigh the potential risk to the fetus.
No clinical studies of Zelboraf in pregnant women have been performed, however, placental transfer of vemurafenib to a fetus has been reported. Based on its mechanism of action, vemurafenib could cause fetal harm when administered to a pregnant woman. Vemurafenib revealed no evidence of teratogenicity in rat embryo/fetuses in animal studies (*see section 3.3.4 Reproductive toxicity*).

Labor and delivery
The safe use of vemurafenib during labor and delivery has not been established.

2.5.3 Lactation
It is not known whether Zelboraf is excreted in human breast milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue Zelboraf after considering the benefits of breast-feeding for the child and the benefits of therapy for the mother.

2.5.4 Pediatric Use
The safety and efficacy of Zelboraf in pediatric patients under the age of 18 have not been established.

2.5.5 Geriatric Use
Ninety-four of 336 patients (28%) with unresectable or metastatic melanoma treated with vemurafenib in the Phase III study were ≥ 65 years. Elderly patients (≥ 65 years) may be more likely to experience adverse events, including cuSCC, decreased appetite, and cardiac disorders. The effects of vemurafenib on overall survival, progression-free survival and best overall response rate were similar in the elderly and younger patients (*see section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.6 Gender
The grade 3 adverse events reported more frequently in females than males were rash, arthralgia and photosensitivity (*see section 3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 Renal Impairment
No adjustment to the starting dose is needed for patients with pre-existing mild and moderate renal impairment. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, pre-existing mild and moderate renal impairment did not influence the apparent clearance of vemurafenib. Clinical and pharmacokinetic data from one patient with pre-existing severe renal impairment are available from clinical trials, and based on the limited data, the potential need for starting dose adjustment cannot be determined. Vemurafenib should be used with caution in patients with pre-existing severe renal impairment.

2.5.8 Hepatic Impairment
No adjustment to the starting dose is needed for patients with pre-existing mild and moderate hepatic impairment. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, pre-existing mild and moderate hepatic impairment did not influence the apparent clearance of vemurafenib. Clinical and pharmacokinetic data from only three patients with pre-existing severe hepatic impairment are available from clinical trials, and based on the limited data, the potential need for starting dose adjustment cannot be determined. Vemurafenib should be used with caution in patients with preexisting severe hepatic impairment.

2.6 Undesirable Effects
2.6.1 Clinical Trials
Summary of the safety profile
For the clinical development program of vemurafenib as a whole, an estimated total of 6300 patients have received vemurafenib.

Unresectable or Metastic Melanoma
Adverse drug reactions (ADRs) were identified from two clinical trials, a Phase III study (NO25026) in treatment-naive patients (N=675) with BRAF V600 mutation-positive unresectable or metastatic melanoma and a Phase II study (NP22657) in patients with BRAF V600 mutation-positive metastatic melanoma who have failed at least one prior systemic therapy (N=132).
In the Phase III open-label study (NO25026), patients randomized to the vemurafenib arm received a twice-daily oral starting dose of 960 mg; patients randomized to the active control arm received dacarbazine 1000 mg/m^2 administered intravenously every 3 weeks. The median duration of vemurafenib treatment was 6.6 months compared to 0.8 months for dacarbazine. The Phase II study (NP22657) was an open-label, uncontrolled, single-arm study in which patients received vemurafenib 960 mg twice daily. The median treatment duration in this study was 5.7 months.
The most common ADRs of any grade (≥ 30% in either study) were arthralgia, fatigue, rash, photosensitivity reaction, alopecia, nausea, diarrhea, headache, pruritus, vomiting, skin papilloma and hyperkeratosis. The most common (≥ 5%) Grade 3 ADRs were cuSCC, keratoacanthoma, rash, arthralgia and gamma-glutamyltransferase (GGT) increased. The incidence of Grade 4 adverse reactions was ≤ 4% in both studies.
The incidence of adverse events resulting in permanent discontinuation of study medication in NO25026 was 7 %. In NP22657, the incidence of adverse events resulting in permanent discontinuation of study medication was 3%.

Table 3 below summarizes the ADRs occurring in patients with melanoma and the frequency categories given are the highest incidence seen in any of the major clinical trials. Adverse drug reactions are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3 Summary of adverse reactions*occuring in patients with unresectable or metastatic melanoma treated with Zelboraf in clinical trials

ADRs	Treatment-Naive Patients		Patients who Failed at least One Prior Systemic Therapy		Frequency category
	n= 336		n= 132		
	All Grades (%)	Grade 3 (%)	All Grades (%)	Grade 3 (%)	
Skin and subcutaneous tissue disorders					
Rash	43	9	55	8	Very Common
Photosensitivity reaction	40	4	54	4	Very Common
Alopecia	48	<1	40	-	Very Common
Pruritus	26	1	33	2	Very Common
Hyperkeratosis	29	2	31	-	Very Common
Rash maculo-papular	10	3	21	6	Very Common
Actinic keratosis	13	-	20	-	Very Common
Dry skin	24	-	21	-	Very Common
Erythema	18	-	11	-	Very Common
Palmar-plantar erythrodysaesthesia syndrome	10	<1	11	2	Very Common
Keratosis pilaris	10	<1	10	-	Very Common
Rash papular	5	<1	2	-	Common
Panniculitis	<1	-	2	-	Common
Erythema nodosum	2	<1	3	-	Common
Stevens-Johnson syndrome	<1	<1	-	-	Uncommon
Toxic epidermal necrolysis	<1	<1	-	-	Uncommon
Musculoskeletal and connective tissue disorders					
Arthralgia	56	6	70	9	Very Common
Myalgia	15	1	27	2	Very Common
Pain in extremity	23	<1	11	-	Very Common
Musculoskeletal pain	13	<1	12	-	Very Common
Back pain	16	<1	13	<1	Very Common
Arthritis	4	<1	11	2	Very Common
Dupuytren's contracture	<1	<1	<1	-	Uncommon
General disorders and administration site conditions					
Fatigue	47	3	60	4	Very Common
Edema peripheral	15	<1	27	-	Very Common
Pyrexia	22	<1	20	2	Very Common
Asthenia	15	<1	2	-	Very Common
Gastrointestinal disorders					
Nausea	39	2	45	3	Very Common
Diarrhea	37	2	32	<1	Very Common
Vomiting	22	2	33	2	Very Common
Constipation	16	<1	18	-	Very Common
Nervous system disorders					
Headache	34	2	31	<1	Very Common
Dysgeusia	16	-	11	-	Very Common
Neuropathy peripheral	4	-	11	<1	Very Common
Dizziness	12	<1	10	-	Very Common
VIIth nerve paralysis	<1	-	3	<1	Common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Skin papilloma	29	<1	33	-	Very Common
Squamous cell carcinoma of skin[#]	20	20	26	26	Very Common
Keratoacanthoma	11	11	5	5	Very Common
Seborrhoeic keratosis	14	<1	15	-	Very Common
Basal cell carcinoma	3	3	8	8	Common
Cardiac disorders					
Electrocardiogram QT interval prolonged	4	-	3	-	Common
Eye disorders					
Retinal vein occlusion	-	-	<1	<1	Uncommon
Uveitis	3	<1	5	-	Common
Iridocyclitis	<1	-	2	-	Common
Hepatobiliary disorders					
GGT increased[§§]	7	4	17	7	Very Common
Metabolism and nutrition disorders					
Decreased appetite	23	1	23	-	Very Common
Weight decreased	10	1	11	<1	Very Common
Respiratory, thoracic and mediastinal disorders					
Cough	15	-	17	-	Very Common
Vascular disorders					
Vasculitis	1	<1	2	-	Common
Injury, poisoning and procedural complications					
Sunburn	17	<1	17	-	Very Common
Infections and Infestations					
Folliculitis	8	<1	11	<1	Very Common

*Adverse drug reactions, reported using MedDRA and graded using NCI-CTCAE v 4.0 (NCI common toxicity criteria) for assessment of toxicity.
[#] All cases of cutaneous squamous cell carcinoma were to be reported as Grade 3 per instructions to study investigators and no dose modification or interruption was required.
[§§] Grade 4 GGT increase were reported in patients with unresectable or metastatic melanoma (<1% in Treatment-Naïve patients and 4% in patients who failed at least one prior systemic therapy).

Description of selected adverse drug reactions from clinical trials
Cutaneous squamous cell carcinoma (cuSCC) (see section 2.4.1 General, Warnings and Precautions)
In patients with unresectable or metastatic melanoma, the incidence of cuSCC in vemurafenib-treated patients across studies was approximately 20%. The majority of excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-keratoacanthoma subtype or with mixed-keratoacanthoma features (52%), both of which are a more benign, less invasive type of cuSCC. Most lesions classified as "other" (43%) were benign skin lesions (e.g. verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst). CuSCC usually occurred early in the course of treatment. Among patients who developed cuSCC, the median time to onset ranged from 7.1 to 8.1 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. Cases of cuSCC were typically managed with simple excision, and patients generally continued on treatment without dose modification.

Hypersensitivity Reactions (see section 2.4.1 General, Warnings and Precautions)
A case of hypersensitivity reaction with rash, fever, rigors and hypotension 8 days after starting vemurafenib 960 mg twice daily was reported in a clinical trial. Similar symptoms were observed upon re-initiation of treatment with a single dose of 240 mg vemurafenib. The patient discontinued vemurafenib permanently and recovered without sequelae.

QT Prolongation (*see section 2.4.1 General, Warnings & Precautions*):
Analysis of centralized ECG data from an open-label uncontrolled Phase II QT sub-study in 132 patients treated with vemurafenib 960 mg twice daily showed a mean increase from baseline in QTc from Day 1 (3.3 ms; upper 95% CI: 5 ms) to Day 15 (12.8 ms; upper 95% CI: 14.9 ms). An exposure-dependent QTc prolongation was observed

in this study and the mean QTc effect remained stable between 12 and 15 ms beyond the first month of treatment, with the largest mean QTc prolongation (15.1 ms; upper 95% CI: 17.7 ms) observed within the first 6 months of treatment (n=90 patients). Two patients (1.5%) developed treatment-emergent absolute QTc values > 500 ms (CTCAE Grade 3), and only one patient (0.8%) exhibited a QTc change from baseline of > 60 ms.
Modeling and simulation of QT prolongation resulted in the following estimates: for the 960 mg twice-daily dose, the percentage of patients with QTcP prolongation exceeding 60 ms was predicted to be 0.05%. This percentage was predicted to increase to 0.2%, for obese patients with BMI of 45 kg/m^2. Percentage of patients with change from baseline in QTcP greater than 60 ms was predicted to be 0.043% for males and 0.046% for females. Percentage of patients with QTcP values above 500 ms was predicted to be 0.05% for males and 1.1% for females.

Laboratory Abnormalities
Liver laboratory abnormalities in unresectable or metastatic melanoma patients (Phase III clinical study (NO25026)) are summarized in the table below as the proportion of patients who experienced a shift from baseline to grade 3 or 4.

Table 4 Change From Baseline to Grade 3/4 Liver Enzyme Abnormalities*

	Change From Baseline to Grade 3/4
	Unresectable or Metastatic Melanoma patients (NO25026 Study)
Parameter	%
GGT**	11.5
AST	0.9
ALT*	2.8
Alkaline phosphatase*	2.9
Bilirubin*	1.9

*For ALT, alkaline phosphatase and bilirubin there were no patients with a change to Grade 4
**GGT data were not collected in patients with ECD

Table 5 Creatinine change from baseline
Creatinine changes from baseline in studies are summarized in the table below.

	Unresectable or Metastatic Melanoma patients (NO25026 Study)
	%
Change >= 1 grade from baseline (all grade)	27.9
Change >= 1 grade from baseline to grade 3 or higher	1.2
• To grade 3	0.3
• To grade 4	0.9

2.6.2 Postmarketing Experience
The following adverse drug reactions have been identified from postmarketing experience with vemurafenib (Table 6) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and any corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 6 Adverse Drug Reactions reported in the post marketing experience

System Organ Class (SOC)	Zelboraf (%)	Frequency
Hepatobiliary Disorders Liver Injury[1]	<1	Uncommon
Blood and lymphatic systems disorders Neutropenia	<1	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Chronic myelomonocytic leukemia (CMML)[1,2]	N/A	frequency not known
Pancreatic adenocarcinoma[1,3]	N/A	frequency not known
Skin and Subcutaneous Tissue Disorders Drug reaction with eosinophilia and systemic symptoms (DRESS)[1]	N/A	frequency not known
Injury, poisoning and procedural complications Radiation injury[1,4]	N/A	frequency not known
Gastrointestinal Disorders Pancreatitis	<1	Uncommon
Renal and Urinary Disorders Acute kidney Injury	N/A	frequency not known
Musculoskeletal and connective tissue disorders Dupuytren's contracture	N/A	frequency not known
Plantar fascial fibromatosis	N/A	frequency not known

[1] see section 2.4 Warnings and Precautions
[2] Progression of pre-existing chronic myelomonocytic leukemia with n-ras mutation
[3] Progression of pre-existing pancreatic adenocarcinoma with k-ras mutation
[4] Includes recall phenomenon, radiation skin injury, radiation pneumonitis, radiation esophagitis, radiation proctitis, radiation hepatitis, cystitis radiation, and radiation necrosis.

Description of selected adverse reactions from postmarketing experience
Acute kidney injury
A broad spectrum of renal adverse drug reaction cases has been reported with Zelboraf ranging from mild/moderate creatinine elevations to acute interstitial nephritis and acute tubular necrosis, some observed in the setting of dehydration events. In most cases, creatinine elevations appear to be reversible in nature (*see section 2.4.1 General, Warnings and Precautions)*.

Laboratory Abnormalities
Liver laboratory abnormalities including ≥ 5x ULN ALT, ≥ 2x ULN ALP, and ≥ 3x ULN ALT and simultaneous elevation of bilirubin concentration (> 2x ULN) were reported in the post marketing setting (*see section 2.4.1 General, Warnings and Precautions)*.
Creatinine lab abnormalities were reported in the post marketing setting (*see section 2.4.1 General, Warnings and Precautions)*.

2.7 Overdose
There is no specific antidote for overdosage of Zelboraf. Patients who develop adverse reactions should receive appropriate symptomatic treatment. Dose limiting toxicities for Zelboraf include rash with pruritus and fatigue. In case of suspected overdose, Zelboraf should be withheld and supportive care instituted.

2.8 Interactions with other Medicinal Products and other Forms of Interaction
Effects of Vemurafenib on Drug Metabolizing Enzymes
Results from an *in vivo* drug-drug interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.
Concomitant use of vemurafenib with agents metabolized by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. If co-administration cannot be avoided, exercise caution, as vemurafenib may increase plasma exposure of CYP1A2 substrate drugs and decrease plasma exposure of CYP3A4 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated. Co-administration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39% in a clinical trial. In another clinical trial, vemurafenib increased AUC_{last} and AUC_{inf} of a single 2mg dose of tizanidine (CYP1A2 substrate) approximately 4.2 and 4.7 fold, respectively.
The AUC of dextromethorphan (CYP2D6 substrate) and its metabolite dextrorphan were increased by approximately 47% indicating an effect on dextromethorphan kinetics that may not be mediated by inhibition of CYP2D6.
Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate) (*see section 3.2 Pharmacokinetic Properties*). Exercise caution and consider additional INR (international normalized ratio) monitoring when vemurafenib is used concomitantly with warfarin.
Vemurafenib moderately inhibited CYP2C8 *in vitro*. The *in vivo* relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

Drugs that Inhibit or Induce CYP3A4
Vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Coadministration of rifampin, a strong CYP3A4 inducer, decreased the plasma exposure of vemurafenib (AUC) by approximately 40% following a single 960 mg dose of vemurafenib (*see section 3.2.3 Metabolism*). Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40%. Caution should be used when vemurafenib is co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Dose reduction of vemurafenib may be considered during coadministration with a strong CYP3A4 inhibitor, if clinically indicated (see section 2.4 Warnings and Precautions).

Radiation Treatment
Potentiation of radiation treatment toxicity has been reported in patients receiving vemurafenib (*see sections 2.4 Warnings and Precautions and 2.6.2 Post Marketing Experience, Undesirable Effects)*. In the majority of cases, patients received radiotherapy regimens greater than or equal to 2 Gy/day (hypofractionated regimens).

Interaction of Vemurafenib with Drug Transport Systems
In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
Clinical drug interaction study GO28394 using a P-gp substrate drug (Digoxin) demonstrated that multiple oral doses of vemurafenib (960 mg twice daily) increased the exposure of a single oral dose of digoxin, with an approximately 1.8 and 1.5 fold increase in digoxin AUC_{last} and C_{max}, respectively. Caution should be exercised when dosing vemurafenib concurrently with P-gp substrates. Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.
The effects of vemurafenib on drugs that are substrates of BCRP, and the effects of P-gp or BCRP inducers and inhibitors on vemurafenib exposure are unknown.
In vitro studies have also demonstrated that vemurafenib is an inhibitor of bile salt export pump. The *in vivo* relevance of this finding is unknown.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 Pharmacodynamic Properties
3.1.1 Mechanism of Action
Vemurafenib is an inhibitor of BRAF serine-threonine kinase. Mutations in the BRAF gene result in constitutive activation of BRAF proteins, which can cause cell proliferation without associated growth factors.
Nonclinical data generated in biochemical assays demonstrated that vemurafenib can potently inhibit BRAF kinases with activating codon 600 mutations (*see table below*).

Table 7 Kinase inhibitory activity of vemurafenib against different BRAF kinases

Kinase	Anticipated frequency in V600 mutation-positive melanoma (f)	Inhibitory Concentration 50 (nM)
$BRAF^{V600E}$	87.3%	10
$BRAF^{V600K}$	7.9%	7
$BRAF^{V600R}$	1%	9
$BRAF^{V600D}$	<0.2%	7
$BRAF^{V600G}$	<0.1%	8
$BRAF^{V600M}$	0.1%	7
$BRAF^{V600A}$	<0.1%	14
$BRAF^{WT}$	NA	39

(f) Estimated from 16403 melanomas with annotated BRAF codon 600 mutations in the public COSMIC database, release 71 (Nov 2014).

This inhibitory effect was confirmed in the ERK phosphorylation and cellular anti-proliferation assays in available melanoma cell lines expressing V600-mutant BRAF. In cellular anti-proliferation assays the IC50 against V600 mutated cell lines (V600E, V600R, V600D and V600K mutated cell lines) ranged from 0.016 to 1.131 µM whereas the inhibitory concentration 50 against BRAF wild type cell lines were 12.06 and 14.32 µM, respectively.

Determination of BRAF mutation status
Before taking vemurafernib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the phase II and phase III clinical trials, eligible patients were identified using a real-time polymerase chain reaction assay (the cobas 4800 BRAF V600 Mutation Test). This test has CE marking and is used to assess the BRAF mutation status of DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour issue. It was designed to detect the predominant BRAF V600E mutation with high sensitivity (down to 5% V600E sequence in a background of wild-type sequence from FFPE-derived DNA). Non-clinical and clinical studies with retrospective sequencing analyses have shown that the test also detects the less common BRAF V600D mutations and V600K mutations with lower sensitivity. Of the specimens available from the non-clinical and clinical studies (n=920), that were mutation-positive by the cobas test and additionally analyzed by sequencing, no specimen was identified as being wild type by both Sanger and 454 sequencing.

3.1.2 Clinical / Efficacy Studies
The efficacy of vemurafenib has been evaluated in 336 patients from a phase III clinical trial and 278 patients from two phase II clinical trials. Prior to study enrollment, tumor specimens from all patients were tested for the presence of a BRAF V600 mutation by the cobas 4800 BRAF V600 Mutation Test.

Unresectable or Metastatic Melanoma
Treatment-Naive Patients
An open-label, multicenter, international, randomized phase III study supports the use of vemurafenib in previously untreated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Patients were randomized to treatment with vemurafenib (960 mg twice daily) or dacarbazine (1000 mg/m^2 on day 1 every 3 weeks).
A total of 675 patients were randomized to vemurafenib (n=337) or dacarbazine (n=338).
Randomization was stratified according to disease stage, LDH, ECOG performance status and geographic region. Baseline characteristics were well balanced between treatment groups. For patients randomized to vemurafenib, most patients were male (59%) and Caucasian (99%), the median age was 56 years (28% were ≥ 65 years), all patients had ECOG performance status of 0 or 1, and the majority of patients had stage M1c disease (66%). The co-primary efficacy endpoints of the study were overall survival (OS) and progression-free survival (PFS). Key secondary endpoints included confirmed best overall response rate (BORR) and response duration.
At the pre-specified interim analysis (December 30, 2010 data cut-off), statistically significant and clinically meaningful improvements were observed in the co-primary endpoints of overall survival (OS) ($p<0.0001$) and progression-free survival (PFS) ($p<0.0001$) (unstratified log-rank test). At the time of the three month update (March 31, 2011 data cut-off), a total of 200 patients had died (78 on the vemurafenib arm and 122 on the dacarbazine arm). The median follow-up time for OS in the vemurafenib group was 6.2 months (range 0.4 to 13.9 months) and in the dacarbazine group was 4.5 months (range <0.1 to 11.7 months).
Overall survival was longer with vemurafenib compared to dacarbazine with a hazard ratio of 0.44 (95% CI: 0.33, 0.59) which represents a 56% decrease in the hazard of death with vemurafenib compared to dacarbazine. Kaplan-Meier (K-M) estimates of the 6-month survival rates were 83% (95% CI: 79%, 87%) for vemurafenib and 63% (95% CI: 57%, 69%) for dacarbazine. At the time of analysis, K-M estimates of median OS for vemurafenib was not reached (95% CI: 9.6, not reached) and for dacarbazine was 7.9 months (95% CI: 7.3, 9.6).
An updated post-hoc analysis of OS was performed 24 months after the last patient was randomized (December 20, 2012 data cut-off date). At the time of this analysis, 478 patients had died (242 on the vemurafenib arm and 236 on the dacarbazine arm). Median follow-up time in the vemurafenib arm was 13.4 months (range 0.4 to 33.3 months). The K-M estimate of median OS for vemurafenib was 13.6 months (95% CI: 12.0, 15.3).
PFS by investigator assessment was longer with vemurafenib compared to dacarbazine with a hazard ratio for progression or death (PFS) of 0.26 (95% CI: 0.20, 0.33) which represents a 74% decrease in the hazard of progression or death for vemurafenib compared to dacarbazine. The Kaplan-Meier estimate of the 6-month PFS rates were 47% (95% CI: 38%, 55%) for vemurafenib and 12% (95% CI: 7%, 18%) for dacarbazine. Median PFS for vemurafenib was 5.32 months (95% Cl: 4.86, 6.57) and for dacarbazine was 1.61 months (95% Cl: 1.58, 1.74).
The secondary endpoint of confirmed best overall response rate (CR + PR), as assessed by the investigator, was

significantly improved (p<0.0001) in the vemurafenib arm (48.4%) (95% CI: 41.6%, 55.2%) compared to the dacarbazine arm (5.5%) (95% CI: 2.8%, 9.3%). Stable disease assessed according to RECIST 1.1 was observed in 37% of vemurafenib-treated patients and 24% of dacarbazine-treated patients.
Improvement in OS, PFS and confirmed best overall response in favor of vemurafenib treatment were generally observed across subgroups (age, sex, baseline LDH, ECOG performance status, metastatic disease stage) and geographic regions.
Table 8 shows the treatment effect for all pre-specified stratification variables which are established as prognostic factors.

Table 8 Overall survival in previously untreated patients with BRAF V600 mutation positive melanoma by LDH, tumour stage and ECOG status (post hoc analysis, December 20, 2012 cut-off, censored results at time of cross over)

Stratification variable	N	Hazard Ratio	95% Confidence Interval
LDH normal	391	0.88	0.67; 1.16
LDH > ULN	284	0.57	0.44; 0.76
Stage IIIc/M1A/M1B	234	1.05	0.73; 1.52
Stage M1C	441	0.64	0.51; 0.81
ECOG PS=0	459	0.86	0.67; 1.10
ECOG PS=1	216	0.58	0.42; 0.9

LDH: Lactate Dehyrogenase, ECOG PS: Eastern Cooperative Oncology Group Performance Status

Efficacy results are summarized in the table below and Figures 1 (updated OS) and 2 (PFS).

Figure 1 Updated Kaplan-Meier curves of overall survival – previously untreated patients (December 20, 2012 cut-off)

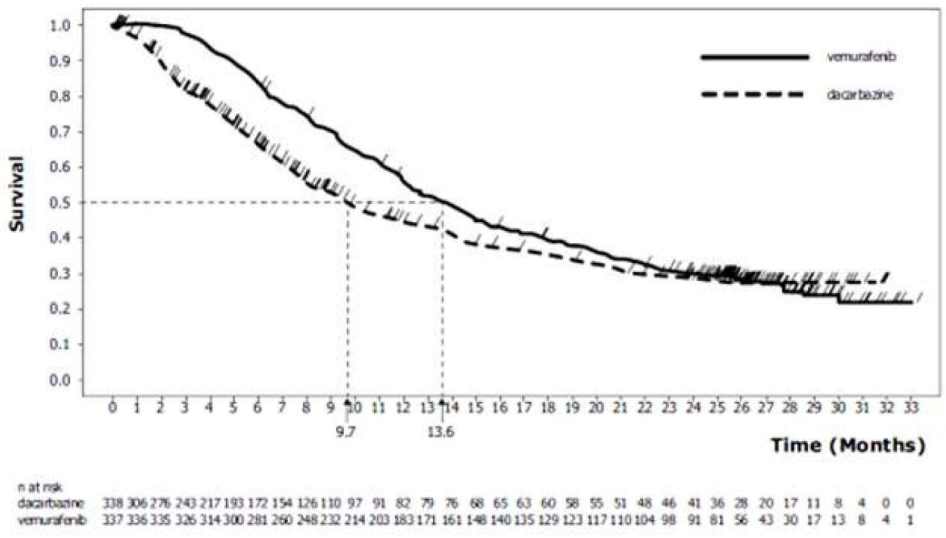
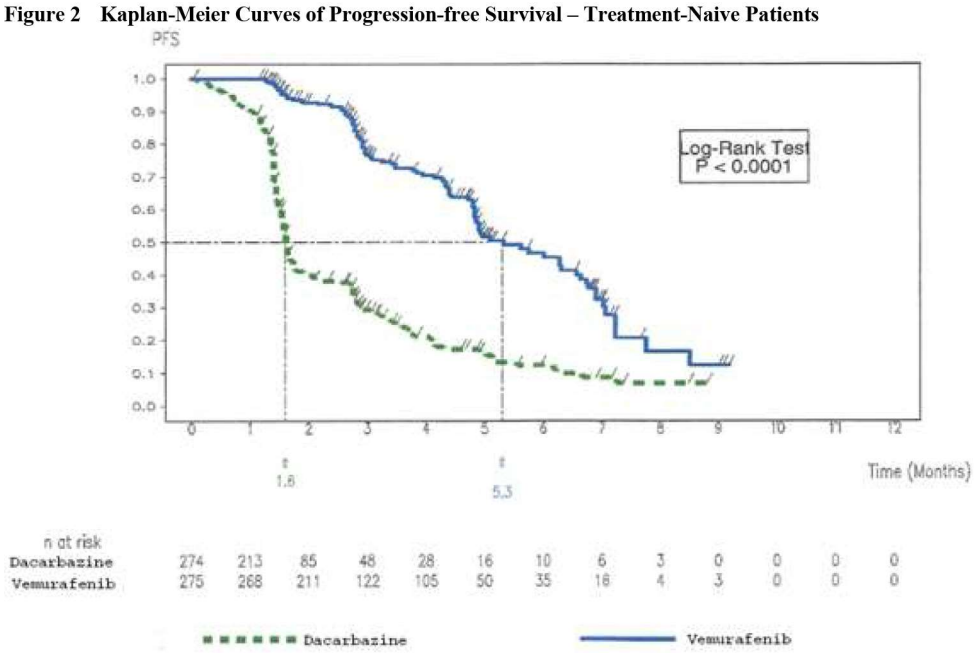


Figure 2 Kaplan-Meier Curves of Progression-free Survival – Treatment-Naive Patients



The proportion of patients with improvement in the physician's assessment of performance status was higher in the vemurafenib group (63.4%) (95% CI: 57%, 69%) than in the dacarbazine group (20.2%) (95% CI: 15%, 26%).
Table 9 shows the overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma.

Table 9 Overall response rate and progression-free survival in previously untreated patients with BRAF V600 mutation positive melanoma

	Vemurafenib (N=337)	Dacarbazine (N=338)	p-value [(d)]
Overall survival Hazard Ratio (95% CI)[a]	0.44 (0.33, 0.59)		<0.0001
Median OS (months) (95% CI)[b]	Not reached (9.6, Not reached)	7.9 (7.3, 9.6)	-
6-month survival rate (95% CI)[b]	83% (79%, 87%)	63% (57%, 69%)	-
Updated OS Median OS (months) (95% CI)[b,c]	13.6 (12.0, 15.3)	9.7 (7.9, 12.8)	-
December 30, 2010 data cut-off date [e]			
Overall Response Rate (95% CI)	**48.4 % (41.6 %, 55.2%)**	**5.5% (2.8%, 9.3%)**	**<0.0001**
Progression-free survival Hazard Ratio (95% CI)	0.26 **(0.20,0.33)**		<0.0001
Number of events (%)	104 (38%)	182 (66%)	
Median PFS (months) (95% CI)	5.32 (4.86, 6.57)	1.61 **(1.58, 1.74)**	-
February 01, 2012 data cut-off date [f]			
Progression-free survival Hazard Ratio (95% CI)	0.38 **(0.32, 0.46)**		<0.0001
Number of events (%)	277 (82%)	273 (81%)	
Median PFS (months) (95% CI)	6.87 (6.14, 6.97)	**1.64** (1.58, 2.07)	

[a] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors vemurafenib
[b] Kaplan-Meier estimate
[c] Updated results (24 months after last patient randomized)
[d] Unstratified log-rank test for OS, PFS and Chi-squared test for Overall Response Rate.
[e] As of December 30, 2010, a total of 549 patients were evaluable for PFS and 439 patients were evaluable for overall response rate.
[f] As of February 01, 2012, a total of 675 patients were evaluable for the post-hoc analysis update of PFS.

A total of 57 patients out of 673 whose tumours were analysed retrospectively by sequencing were reported to have BRAF V600K mutation-positive melanoma in NO25026. Although limited by the low number of patients, efficacy analyses among these patients with V600K-positive tumours suggested similar treatment benefit of vemurafenib in terms of OS, PFS and confirmed best overall response. No data are available in patients with melanoma harboring rare BRAF V600 mutations others than V600E and V600K.

Patients who Failed at least One Prior Systemic Therapy
A Phase II single-arm, multi-center, multinational study was conducted in 132 patients who had BRAF V600E mutation-positive metastatic melanoma according to the cobas 4800 BRAF V600 Mutation Test and had received at least one prior therapy. The median age was 52 years with 19% of patients being older than 65 years. The majority of patients was male (61%), Caucasian (99%), and had stage M1c disease (61%). Forty-nine percent of patients failed ≥ 2 prior therapies.
The median duration of follow-up was 6.87 months (range, 0.6 to 11.3).
The primary endpoint of confirmed best overall response rate (CR + PR) as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%). The median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment. The median duration of response by IRC was 6.5 months (95% CI: 5.6, not reached). Stable disease by RECIST 1.1 was observed in 30% of patients. The median overall survival was 15.9 months (95% CI: 11.2, 19.3), the 6-month survival rate was 0.77 (95% CI: 0.69, 0.84) and at 1 year was 0.58 (95% CI: 0.48, 0.66). The median PFS was 6.1 months (95% CI: 5.5, 6.9), and the 6-month PFS rate was 52% (95% CI: 43%, 61%).
Nine of the 132 patients enrolled into NP22657 had V600K mutation positive tumors according to retrospective Sanger sequencing. Amongst these patients, 3 had a PR, 3 had SD, 2 had PD and one was not evaluable.

Patients with brain metastases
An open-label, single-arm, multicenter, phase II study (N = 146) of vemurafenib was conducted in adult patients with histologically confirmed metastatic melanoma harboring the BRAF V600 mutation and with brain metastases. The study included two simultaneously enrolling cohorts:

- Previously untreated patients (cohort 1: N = 90): Patients who had not received previous treatment for brain metastases; prior systemic therapy for metastatic melanoma was allowed.
- Previously treated patients (cohort 2: N = 56): Patients who had been previously treated for their brain metastases and had progressed following this treatment. For patients treated with stereotactic radiotherapy (SRT) or surgery, a new RECIST-assessable brain lesion must have developed following this prior therapy.

The median age of the patients was 54 years (range 26 to 83 years), and was similar in the two cohorts. The majority of patients were men (61.6%) and similarly distributed between the two cohorts. A total of 135 patients (92.5%) were reported as white, with the race of 11 patients (7.5%) not reported due to local regulations. The median number of brain target lesions at baseline was 2 (range 1 to 5), in both cohorts.
The primary objective of the study was to evaluate the efficacy of vemurafenib using best overall response rate (BORR) in the brain of metastatic melanoma patients with previously untreated brain metastases, as assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).
Secondary objectives included an evaluation of the efficacy of vemurafenib using BORR in the brain of previously treated patients, duration of response (DOR), progression-free survival (PFS) and overall survival (OS) in patients with melanoma metastatic to the brain.

Table 10 Efficacy of Vemurafenib in patients with brain metastases

	Cohort 1 No Previous Treatment	Cohort 2 Previously Treated	Total
BORR[a] in brain (n)	90	56	146
Responders (n[%]) (95% CI)[b]	16 (17.8%) (10.5-27.3)	10 (17.9%) (8.9-30.4)	26 (17.8%) (12.0-25.0)
DOR[c] in brain (n)	16	10	26
Median (months) (95% CI)[d]	4.6 (2.9, 6.2)	6.6 (2.8, 10.7)	5.0 (3.7, 6.6)
PFS - overall (n)	90	56	146
Median (months)[e] (95% CI)[d]	3.7 (3.6, 3.7)	3.7 (3.6, 5.5)	3.7 (3.6, 3.7)
PFS - brain only (n)	90	56	146
Median (months)[e] (95% CI)[d]	3.7 (3.6, 4.0)	4.0 (3.6, 5.5)	3.7 (3.6, 4.2)
OS	90	56	146
Median (months) (95% CI)[d]	8.9 (6.1, 11.5)	9.6 (6.4, 13.9)	9.6 (6.9, 11.5)

[a] Best Overall Response Rate as assessed by independent review committee, number of responders - n (%)
[b] two-sided 95% Clopper-Pearson Confidence Interval (CI)
[c] Duration of response as assessed by an Independent Review Committee
[d] Kaplan-Meier estimate
[e] assessed by investigator

3.2 Pharmacokinetic Properties
The pharmacokinetic parameters for vemurafenib were determined using Non-Compartmental analysis in a Phase I and a Phase III study. Mean C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ were approximately 62 µg/mL, 53 µg/mL and 600 µg*h/mL. Population PK analysis using pooled data from 458 patients estimated the median of the steady-state C_{max}, C_{min} and AUC to be 62 µg/mL, 59 µg/mL and 734 µg*h/mL, respectively. The median accumulation ratio estimate for a twice-daily regimen is 7.36. The PK of vemurafenib is shown to be dose proportional between 240 and 960 mg twice daily, and population PK analysis also confirmed that the PK of vemurafenib is linear.

3.2.1 Absorption
Vemurafenib is absorbed with a median T_{max} of approximately 4 hours following a single 960 mg dose (four 240 mg tablets). Vemurafenib exhibits marked accumulation after repeat dosing at 960 mg twice daily with high inter-patient variability. In the Phase II study mean vemurafenib plasma concentration at 4 hours post dose increases from 3.6 µg/mL on Day 1 to 49.0 µg /mL on Day 15 (range 5.4 to 118 µg/mL).
Food (high fat meal) increases the relative bioavailability of a single 960 mg dose of vemurafenib. The geometric mean ratios between the fed and fasted states for C_{max} and AUC were 2.5 and 4.6 to 5.1 fold, respectively. The median T_{max} was increased from 4 to 7.5 hours when a single vemurafenib dose was taken with food. Safety and efficacy data from pivotal studies were collected from patients taking vemurafenib with or without food.
At steady state (reached by day 15 in 80% of patients) the mean vemurafenib exposure in plasma is stable (concentrations before and 2-4 hours after the morning dose) as indicated by the mean ratio of 1.13. Similar marked inter-patient variability in plasma exposure was observed at steady state independent of dose reduction.
The effect of food on steady state vemurafenib exposure is currently unknown. Consistent intake of vemurafenib on an empty stomach may lead to significantly lower steady state exposure than consistent intake of vemurafenib with or a short time after a meal. Occasional intake of vemurafenib on an empty stomach is expected to have limited influence on steady state exposure due to the high accumulation of vemurafenib at steady state. Safety and efficacy data from pivotal studies were collected from patients taking vemurafenib with or without food.
Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients is estimated to be 0.19 hr^{-1} (with 101% between patient variability).

3.2.2 Distribution
The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be 91 L (with 64.8% inter-patient variability). It is highly bound to human plasma proteins *in vitro* (> 99%).

3.2.3 Metabolism
The relative proportions of vemurafenib and its metabolites were characterized in a human mass balance study with a single dose of ^{14}C-labeled vemurafenib administered orally.
On average, 95% of the dose was recovered within 18 days. The majority (94%) in feces, with <1% recovered in urine. CYP3A4 is the primary enzyme responsible for the metabolism of vemurafenib *in vitro*. Conjugation metabolites (glucuronidation and glycosylation) were also identified in humans. However, the parent compound was the predominant component (95%) in plasma. Although metabolism does not appear to result in a relevant amount of metabolites in plasma, the importance of metabolism for excretion cannot be excluded. Coadministration of rifampin, a strong CYP3A4 inducer, significantly decreased the plasma exposure of vemurafenib (AUC) by approximately 40% following a single 960 mg dose of vemurafenib, suggesting CYP3A4 pathway could be important elimination pathway for vemurafenib. Coadministration of itraconazole, a strong CYP3A4 inhibitor, increased steady state vemurafenib AUC by approximately 40%.

3.2.4 Elimination
The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be 29.3 L/day (with 31.9% inter-patient variability). The median of the individual elimination half-life estimates for vemurafenib is 56.9 hours (the 5th and 95th percentile range is 29.8-119.5 hours).

3.2.5 Pharmacokinetics in Special Populations
Geriatric Population: Based on the population PK analysis, age has no statistically significant effect on vemurafenib pharmacokinetics.

Gender: In the population PK analysis, gender was found to be statistically significant in explaining the inter-patient variability, with a 17% greater apparent clearance (CL/F) and a 48% greater apparent volume of distribution (V/F) in males. However, results from the population analysis have shown that the differences in exposure are relatively small (with an estimated median 12-hour steady-state AUC and C_{max} of 792 µg*h/mL and 67 µg/mL in females and 696 µg*h/mL and 63 µg/mL in males, respectively), indicating that there is no need to dose adjust based on gender.

Pediatric Population: Limited pharmacokinetic data from six adolescent patients aged 15 to 17 suggest that vemurafenib pharmacokinetic characteristics in adolescents are generally similar to those in adults. However, no conclusion can be made due to the limited amount of data (*see section 2.2.1 Special Dosage Instructions*).
Renal impairment: In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, mild and moderate renal impairment did not influence the apparent clearance of vemurafenib (creatinine clearance >30 ml/min). The potential need for dose adjustment in patients with severe renal impairment (creatinine clearance <29 ml/min) cannot be determined as clinical and pharmacokinetic data are insufficient (*See sections 2.2.1 Special Dosage Instructions, and 2.5.7 renal Impairment)*.

Hepatic impairment: Based on preclinical data and the human mass balance study, the major part of vemurafenib is eliminated via the liver. In the population pharmacokinetic analysis using data from clinical trials in patients with metastatic melanoma, increases in AST, ALT, and total bilirubin up to three times the upper limit of normal did not influence the apparent clearance of vemurafenib. The potential need for dose adjustment in patients with severe hepatic impairment cannot be determined as clinical and pharmacokinetic data are insufficient to determine the effect of metabolic or excretory hepatic impairment on vemurafenib pharmacokinetics (*See sections 2.2.1 Special Dosage Instructions and 2.5.8 hepatic impairment)*.

3.3 Nonclinical Safety
3.3.1 Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Zelboraf.
3.3.2 Genotoxicity
Standard genotoxicity studies with vemurafenib were all negative.

3.3.3 Impairment of Fertility
No fertility studies in animals have been performed to evaluate the effect of Zelboraf.
In the repeat-dose toxicology studies, no histopathological findings were noted on reproductive organs in males and females in rats and dogs at doses up to 450 mg/kg/day (at exposures below the anticipated clinical exposure based on AUC comparison).

3.3.4 Reproductive toxicity
Vemurafenib revealed no evidence of teratogenicity in rat embryo/fetuses at doses up to 250 mg/kg/day (approximately 1.7 times the human clinical exposure based on AUC) or rabbit embryo/fetuses at doses up to 450 mg/kg/day (approximately 0.7 times the human clinical exposure based on AUC). However, exposures in the embryofoetal development studies were below the clinical exposure based on AUC comparison, it is therefore difficult to define to what extent these results can be extrapolated to humans. Therefore an effect of vemurafenib on the foetus cannot be excluded. No studies were performed regarding pre- and postnatal development.
Fetal drug levels were 3-5% of maternal levels, indicating that vemurafenib has the potential to be transmitted from the mother to the developing fetus.
No specific studies with vemurafenib have been conducted in animals to evaluate the effect on fertility; nevertheless, no histopathological findings were noted in reproductive organs in males and females in repeat-dose toxicology studies in rate at doses up to 450 mg/kg/day (approximately 0.6 and 1.6 times the human exposure based on AUC in males and females, respectively) and dogs at doses up to 450 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC in both males and females respectively).

3.3.5 Other
Repeat-dose toxicology studies identified the liver and bone marrow as target organs in the dog. Reversible toxic effects (hepatocellular necrosis and degeneration) in the liver at exposures below the clinical exposure (based on AUC comparisons) were noted in a 13-week dog study with twice-daily dosing. Focal bone marrow necrosis was noted in one dog in a prematurely terminated 39-week dog study with twice-daily dosing at exposures within the range of clinical exposures.
Vemurafenib was shown to be phototoxic *in vitro* in cultured murine fibroblasts after UVA irradiation, but not *in vivo* in a rat study.
CYP2C9 inhibition with vemurafenib was observed *in vitro* (i.e., IC_{50} of 5.9 µM).

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
Do not store above 30°C, store in the original package, protect from moisture.
This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Special Instructions for Use, Handling and Disposal

Disposal of Unused/Expired Medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.3 Packs
Film-coated tablets 240 mg — 56 tablets (8 tablets x 7 blister strips)

Medicine: keep out reach of children

Current at Jan 2020

Roche

Product owner: F.Hoffmann-La Roche Ltd,
Grenzacherstrasse 124, CH-4070 Basel, Switzerland