ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 12/18/2012

Grantor: CDER IND/IDE Number: 73,620 Serial Number: 0082

A Study of RO5185426 in Comparison With Dacarbazine in Previously Untreated Patients With Metastatic Melanoma (BRIM 3)

This study is ongoing, but not recruiting participants.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01006980

Purpose

This randomized, open-label study will evaluate the efficacy, safety and tolerability of RO5185426 as compared to dacarbazine in previously untreated patients with metastatic melanoma. Patients will be randomized to receive either RO5185426 [RG7204; PLEXXIKON: PLX4032] 960 mg orally twice daily or dacarbazine 1000 mg/m2 intravenously every 3 weeks. Anticipated time on study treatment is until disease progression or unacceptable toxicity occurs. Patients in the dacarbazine arm may cross over to RO5185426 treatment.

Condition	Intervention	Phase
Malignant Melanoma	Drug: RO5185426 Drug: dacarbazine	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Global Study on Progression-free and Overall Survival in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma With V600E BRAF Mutation Receiving RO5185426 or Dacarbazine

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Overall Survival [Time Frame: From randomization (initiated January 2010) to December 30 2010. Median follow-up time in the vemurafenib group was 3.75 months (range 0.3 to 10.8) and in the dacarbazine group was 2.33 months (range <0.1 to 10.3).] [Designated as safety issue: No]
  An Overall survival event was defined as death due to any cause. The number of participants with overall survival events is reported.
- Progression-free Survival [Time Frame: From randomization (initiated January 2010) to December 30 2010.] [Designated as safety issue: No]
  A progression-free survival (PFS) event was defined as disease progression or death due to any cause. Tumor response (progression) was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria using computed tomography (CT) scans or magnetic resonance imaging (MRI).

Secondary Outcome Measures:

- Participants With a Best Overall Response (BOR) of Complete Response or Partial Response [Time Frame: From randomization (initiated January 2010) until December 30, 2010] [Designated as safety issue: No]
  BOR was defined as a complete response (CR) or partial response (PR) confirmed per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Patients who never received study treatment and treated patients without any post-baseline tumor assessments were considered as non-responders. CR: Disappearance of all target lesions, all non-target lesions and no new lesion. Any pathological lymph nodes must have had reduction in the short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion and no new lesion.
- Duration of Response [Time Frame: From randomization (initiated in January 2010) until December 30, 2010.] [Designated as safety issue: No]
  Duration of response was defined as the time between the date of the earliest qualifying response and the date of disease progression or death due to any cause. Duration of response was calculated only for patients who had a best overall response of Complete Response or Partial Response and was estimated using the Kaplan-Meier method.
- Time to Confirmed Response [Time Frame: From randomization (initiated January 2010) until December 30, 2010.] [Designated as safety issue: No]
  Time to response was defined as the time from randomization to confirmed response (complete response or partial response).
- Time to Treatment Failure [Time Frame: approximately 3 years] [Designated as safety issue: No]
  Treatment failure was defined as a secondary endpoint in the protocol, defined as death, disease progression or premature withdrawal of study treatment. This endpoint was not included in the Statistical analysis plan; therefore no analyses of time to treatment failure were performed.
- Number of Participants With Adverse Events (AEs) [Time Frame: From randomization (initiated January 2010) until December 30, 2010.] [Designated as safety issue: No]
  The intensity of AEs was graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (Grade 1 to 5: Mild, Moderate, Severe, Life-threatening and Death). A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution, for example is life-threatening, requires hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires intervention to prevent one or other of the outcomes listed above.
- Pre and Post-dose Plasma Vemurafenib Concentration by Study Day [Time Frame: Plasma samples were collected before the morning dose (troughs) and 2-4 hours after the morning dose at the beginning of each cycle (Days 1, 22, 43, 64, 106, 148 and 190).] [Designated as safety issue: No]
  The pharmacokinetics of vemurafenib were assessed at the beginning of each 21-day cycle using pre-dose and 2-4 hours post-dose sampling.

Enrollment: 677
Study Start Date: January 2010
Primary Completion Date: December 2010
Estimated Study Completion Date: June 2014

Arms	Assigned Interventions
Experimental: A	Drug: RO5185426 960 mg orally twice daily

Arms	Assigned Interventions
Active Comparator: B	Drug: dacarbazine 1000 mg/m2 iv every 3 weeks

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- adult patients, >/=18 years of age
- metastatic melanoma, stage IIIC or IV (AJCC)
- treatment-naïve (no prior systemic anticancer therapy)
- positive for BRAF V600E mutation
- measurable disease by RECIST criteria
- negative pregnancy test and, for fertile men and women, effective contraception during treatment and for 6 months after completion

Exclusion Criteria:

- active CNS metastases
- history of carcinomatous meningitis
- severe cardiovascular disease within 6 months prior to study drug administration
- previous malignancy within 5 years prior to study, except for basal or squamous cell carcinoma of the skin, melanoma in-situ, or carcinoma in-situ of the cervix

Contacts and Locations

Locations

United States, Alabama
Birmingham, Alabama, United States, 35243
United States, Arizona
Tucson, Arizona, United States, 85724
United States, California
Los Angeles, California, United States, 90095-1752
San Francisco, California, United States, 94117
Santa Monica, California, United States, 90404
United States, Colorado
Aurora, Colorado, United States, 80045
United States, Georgia
Atlanta, Georgia, United States, 30322

United States, Indiana
Indianapolis, Indiana, United States, 46202
United States, Massachusetts
Boston, Massachusetts, United States, 02114
Boston, Massachusetts, United States, 02215
Boston, Massachusetts, United States, 02115
United States, Michigan
Detroit, Michigan, United States, 48201
United States, Missouri
St Louis, Missouri, United States, 63110
United States, New York
New York, New York, United States, 10016
New York, New York, United States, 10065
United States, North Carolina
Chapel Hill, North Carolina, United States, 27514
United States, Oregon
Portland, Oregon, United States, 97213
United States, Pennsylvania
Philadelphia, Pennsylvania, United States, 19104
Pittsburgh, Pennsylvania, United States, 15213-2584
United States, Tennessee
Nashville, Tennessee, United States, 37232
Nashville, Tennessee, United States, 37203
United States, Texas
Dallas, Texas, United States, 75246
United States, Utah
Salt Lake City, Utah, United States, 84112
United States, Washington
Seattle, Washington, United States, 98109
Australia
Brisbane, Australia, 4006
Frankston, Australia, 3199
Malvern, Australia, 3144
Melbourne, Australia, 3128
Melbourne, Australia, 3002
Nedlands, Australia, 6009
Newcastle, Australia, 2310
St Leonards, Australia, 2065
Sydney, Australia, 2060
Westmead, Australia, 2145
Woolloongabba, Australia, 4102
Canada, Alberta
Edmonton, Alberta, Canada, T5J 3N4
Canada, Manitoba
Winnipeg, Manitoba, Canada, R2H 2A6

Canada, Ontario
- Hamilton, Ontario, Canada, L8V 5C2
- Toronto, Ontario, Canada, M4N 3M5
- Toronto, Ontario, Canada, M5G 2M9

Canada, Quebec
- Montreal, Quebec, Canada, H3T 1E2
- Montreal, Quebec, Canada, H3A 1A1
- Quebec City, Quebec, Canada, G1R 2J6

France
- Bordeaux, France, 33075
- Lille, France, 59037
- Marseille, France, 13005
- Montpellier, France, 34298
- Nantes, France, 44093
- Nice, France, 06202
- Paris, France, 75010
- Pierre Benite, France, 69495
- Rouen, France, 76031
- Villejuif, France, 94805

Germany
- Buxtehude, Germany, 21614
- Dresden, Germany, 01307
- Erfurt, Germany, 99089
- Essen, Germany, 45122
- Frankfurt, Germany, 60596
- Hannover, Germany, 30449
- Heidelberg, Germany, 69120
- Jena, Germany, 07743
- Kiel, Germany, 24105
- Koeln, Germany, 50924
- Leipzig, Germany, 04103
- Mainz, Germany, 55131
- Minden, Germany, 32429
- Muenchen, Germany, 81377
- Regensburg, Germany, 93053
- Tuebingen, Germany, 72076
- Wuerzburg, Germany, 80337

Israel
- Jerusalem, Israel, 91200
- Ramat Gan, Israel, 52621
- Tel Aviv, Israel, 64239

Italy
- Bari, Italy, 70124
- Genova, Italy, 16132
- Milano, Italy, 20133

Milano, Italy, 20141
Milano, Italy, 20162
Napoli, Italy, 80131
Roma, Italy, 00158
Siena, Italy, 53100

Netherlands

Amsterdam, Netherlands, 1081 HV
Amsterdam, Netherlands, 1066 CX
Groningen, Netherlands, 9713 GZ

New Zealand

Auckland, New Zealand
Dunedin, New Zealand, 9001
Hamilton, New Zealand, 2001
Palmerston North, New Zealand
Wellington, New Zealand, 6021

Sweden

Linkoeping, Sweden, 58185
Lund, Sweden, 22185
Stockholm, Sweden, 17176
Umeå, Sweden
Uppsala, Sweden, 75185

Switzerland

Lausanne, Switzerland, 1011
Zürich, Switzerland, 8091

United Kingdom

Cambridge, United Kingdom, CB2 2QH
Edinburgh, United Kingdom, EH4 2XU
Glasgow, United Kingdom, G12 0YN
London, United Kingdom, NW3 2QG
London, United Kingdom, SE1 9RT
London, United Kingdom, SW3 3JJ
London, United Kingdom, E1 1BB
Manchester, United Kingdom, M20 4BX
Newcastle Upon Tyne, United Kingdom, NE7 7DN
Northwood, United Kingdom, HA6 2RN
Nottingham, United Kingdom, NG5 1PB
Oxford, United Kingdom, OX3 7LJ
Southampton, United Kingdom, SO16 6YD
Sutton, United Kingdom, SM2 5PT
Swansea, United Kingdom, SA2 8QA

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	NO25026
	2009-012293-12
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Pre-Assignment Details	675 patients were randomized, 337 to vemurafenib and 338 to dacarbazine. One patient randomized to dacarbazine was treated in error with vemurafenib throughout the study and is included in the Vemurafenib arm in the table below and for exposure and safety analyses but was included in the dacarbazine arm for efficacy analyses.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Overall Study

	Vemurafenib	Dacarbazine
Started	338 [1]	337
(Randomized)	337	338
Treated	336 [1]	289
Completed	223 [2]	83
Not Completed	115	254
Progression	89	174
Adverse Event	12	9

	Vemurafenib	Dacarbazine
Death	6	11
Refused treatment	4	20
Withdrawal by Subject	2	25
Protocol Violation	0	2
Patient/Investigator/medical decisions	0	6
Randomization error	1	0
Disqualified prior to treatment	1	7

[1] Includes one patient who was randomized to dacarbazine but received vemurafenib in error.
[2] Completed indicates patients still receiving treatment at the time of the clinical cutoff date.

Baseline Characteristics

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Baseline Measures

	Vemurafenib	Dacarbazine	Total
Number of Participants	337	338	675
Age, Customized [units: participants]			
< 65 years	244	270	514
>=65 years	93	68	161
Gender, Male/Female [units: participants]			
Female	137	157	294
Male	200	181	381

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival
Measure Description	An Overall survival event was defined as death due to any cause. The number of participants with overall survival events is reported.
Time Frame	From randomization (initiated January 2010) to December 30 2010. Median follow-up time in the vemurafenib group was 3.75 months (range 0.3 to 10.8) and in the dacarbazine group was 2.33 months (range <0.1 to 10.3).
Safety Issue?	No

Analysis Population Description

The intent-to-treat (ITT) population was defined as all randomized patients, whether or not study treatment was received. The ITT population was analyzed according to the treatment assigned at randomization. Overall survival was assessed on patients randomized at least 15 days prior to the clinical cutoff date of December 30, 2010.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	336	336
Overall Survival [units: participants]		
Patients with events	43	75
Patients without events	293	261

Statistical Analysis 1 for Overall Survival

Statistical Analysis Overview	Comparison Groups	Vemurafenib, Dacarbazine

	Comments	The trial had a power of 80% to detect a hazard ratio of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months for dacarbazine to 12.3 months for vemurafenib), one interim analysis for OS at 50% information.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.37
	Confidence Interval	(2-Sided) 95% 0.26 to 0.55
	Estimation Comments	The hazard ratio for death for vemurafenib relative to dacarbazine and the associated 95% CI were computed using an unstratified Cox regression model.

2. Primary Outcome Measure:

Measure Title	Progression-free Survival
Measure Description	A progression-free survival (PFS) event was defined as disease progression or death due to any cause. Tumor response (progression) was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria using computed tomography (CT) scans or magnetic resonance imaging (MRI).
Time Frame	From randomization (initiated January 2010) to December 30 2010.
Safety Issue?	No

Analysis Population Description

The analysis population for PFS consisted of all ITT patients randomized by October 27, 2010 (at least 9 weeks prior to the clinical cutoff date of December 30, 2010). The 9-week interval was chosen to allow time for patients to have had their first scheduled post baseline tumor assessment CT scan.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	275	274
Progression-free Survival [units: participants]		
Patients with events	104	182
Patients without events	171	92

Statistical Analysis 1 for Progression-free Survival

Statistical Analysis Overview	Comparison Groups	Vemurafenib, Dacarbazine
	Comments	The trial had a power of 90% to detect a hazard ratio of 0.55 for progression-free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for dacarbazine to 4.5 months for vemurafenib).
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<.0001
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.26
	Confidence Interval	(2-Sided) 95%

		0.20 to 0.33
	Estimation Comments	Hazard ratios for treatment with vemurafenib, as compared with dacarbazine, were estimated with the use of unstratified Cox regression.

3. Secondary Outcome Measure:

Measure Title	Participants With a Best Overall Response (BOR) of Complete Response or Partial Response
Measure Description	BOR was defined as a complete response (CR) or partial response (PR) confirmed per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Patients who never received study treatment and treated patients without any post-baseline tumor assessments were considered as non-responders. CR: Disappearance of all target lesions, all non-target lesions and no new lesion. Any pathological lymph nodes must have had reduction in the short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion and no new lesion.
Time Frame	From randomization (initiated January 2010) until December 30, 2010
Safety Issue?	No

Analysis Population Description

The analysis population consisted of all ITT patients randomized by September 22, 2010 (at least 14 weeks prior to the clinical cutoff date of December 30, 2010). The 14-week interval was chosen as it was the minimum time needed to observe a confirmed overall response according to protocol-specified schedule for the first two tumor assessments.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	219	220
Participants With a Best Overall Response (BOR) of Complete Response or Partial Response [units: participants]		
Responders	106	12
Non-responders	113	208

4. Secondary Outcome Measure:

Measure Title	Duration of Response
Measure Description	Duration of response was defined as the time between the date of the earliest qualifying response and the date of disease progression or death due to any cause. Duration of response was calculated only for patients who had a best overall response of Complete Response or Partial Response and was estimated using the Kaplan–Meier method.
Time Frame	From randomization (initiated in January 2010) until December 30, 2010.
Safety Issue?	No

Analysis Population Description

Analysis population included all patients randomized by September 22, 2010 and with a best overall confirmed response of complete response or partial response.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	106	12
Duration of Response [units: months] Median (95% Confidence Interval)	5.49 (3.98 to 5.72)	NA (4.60 to NA) [1]

[1] Median duration of response was not reached as only 2 of the 12 patients with a qualifying response had subsequent disease progression or death due to any cause at the time of the analysis.

5. Secondary Outcome Measure:

Measure Title	Time to Confirmed Response
Measure Description	Time to response was defined as the time from randomization to confirmed response (complete response or partial response).

Time Frame	From randomization (initiated January 2010) until December 30, 2010.
Safety Issue?	No

Analysis Population Description

Analysis population included all patients randomized by September 22, 2010 and with a best overall confirmed response of complete response or partial response.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	106	12
Time to Confirmed Response [units: months] Median (Full Range)	1.45 (1.0 to 5.5)	2.72 (1.6 to 5.8)

6. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure
Measure Description	Treatment failure was defined as a secondary endpoint in the protocol, defined as death, disease progression or premature withdrawal of study treatment. This endpoint was not included in the Statistical analysis plan; therefore no analyses of time to treatment failure were performed.
Time Frame	approximately 3 years
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Secondary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AEs)
Measure Description	The intensity of AEs was graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (Grade 1 to 5: Mild, Moderate, Severe, Life-threatening and Death). A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution, for example is life-threatening, requires hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or requires intervention to prevent one or other of the outcomes listed above.
Time Frame	From randomization (initiated January 2010) until December 30, 2010.
Safety Issue?	No

Analysis Population Description

The safety population was defined as all treated patients who had at least one on-study assessment. The safety population was analyzed according to the treatment received.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Measured Values

	Vemurafenib	Dacarbazine
Number of Participants Analyzed	336	282
Number of Participants With Adverse Events (AEs) [units: participants]		
Any adverse event	326	253
Serious adverse event	110	45

8. Secondary Outcome Measure:

Measure Title	Pre and Post-dose Plasma Vemurafenib Concentration by Study Day
Measure Description	The pharmacokinetics of vemurafenib were assessed at the beginning of each 21-day cycle using pre-dose and 2-4 hours post-dose sampling.
Time Frame	Plasma samples were collected before the morning dose (troughs) and 2-4 hours after the morning dose at the beginning of each cycle (Days 1, 22, 43, 64, 106, 148 and 190).
Safety Issue?	No

Analysis Population Description

The pharmacokinetic (PK) analysis population included all patients who received vemurafenib and provided valid PK assessments. The PK population at specific time points varied depending on the availability of confirmed dosing and PK assessment times. "n" indicates the number of participants with available PK data at each time point.

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).

Measured Values

	Vemurafenib
Number of Participants Analyzed	260
Pre and Post-dose Plasma Vemurafenib Concentration by Study Day [units: µg/mL] Mean (Standard Deviation)	

	Vemurafenib
Pre-Dose Day 1 (n = 260)	0 (0)
Post-Dose Day 1 (n = 255)	4.3 (4.35)
Pre-Dose Day 22 (n = 204)	53.0 (26.66)
Post-Dose Day 22 (n = 221)	54.0 (25.67)
Pre-Dose Day 43 (n = 166)	54.4 (24.13)
Post-Dose Day 43 (n = 170)	54.4 (23.28)
Pre-Dose Day 64 (n = 141)	57.4 (23.79)
Post-Dose Day 64 (n = 138)	57.7 (22.29)
Pre-Dose Day 106 (n = 77)	55.0 (17.62)
Post-Dose Day 106 (n = 75)	56.3 (20.36)
Pre-Dose Day 148 (n = 38)	51.8 (24.13)
Post-Dose Day 148 (n = 39)	53.3 (21.55)
Pre-Dose Day 190 (n = 9)	53.6 (12.6)
Pre-Dose Day 190 (n = 9)	50.5 (20.16)

Reported Adverse Events

Time Frame	Onset between Time of Very First Drug Intake and Study Day 9999
Additional Description	[Not specified]

Reporting Groups

	Description
Vemurafenib	Participants received continuous oral doses of Vemurafenib (RO5185426) 960 mg twice a day. Patients took four 240 mg tablets in the morning and four 240 mg tablets in the evening (960 mg twice a day for a total daily dose of 1920 mg).
Dacarbazine	Dacarbazine was administered intravenously 1000 mg/m^2 up to 60 minutes on Day 1 of every 3 weeks (3 weeks was one cycle length).

Serious Adverse Events

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	110/336 (32.74%)	45/282 (15.96%)
Blood and lymphatic system disorders		
Febrile Bone Marrow Aplasia [A] †	0/336 (0%)	1/282 (0.35%)
Neutropenia [A] †	1/336 (0.3%)	1/282 (0.35%)
Cardiac disorders		
Atrial Fibrillation [A] †	2/336 (0.6%)	0/282 (0%)
Cardiac Failure [A] †	1/336 (0.3%)	0/282 (0%)
Cardiac Tamponade [A] †	0/336 (0%)	1/282 (0.35%)
Cardiopulmonary Failure [A] †	0/336 (0%)	2/282 (0.71%)
Myocardial Infarction [A] †	1/336 (0.3%)	0/282 (0%)
Pericardial Effusion [A] †	1/336 (0.3%)	0/282 (0%)
Pericarditis [A] †	1/336 (0.3%)	0/282 (0%)
Endocrine disorders		
Hypercalcaemia of Malignancy [A] †	0/336 (0%)	1/282 (0.35%)
Eye disorders		
Diplopia [A] †	1/336 (0.3%)	0/282 (0%)
Orbital Oedema [A] †	1/336 (0.3%)	0/282 (0%)
Uveitis [A] †	2/336 (0.6%)	0/282 (0%)
Gastrointestinal disorders		
Abdominal Pain [A] †	2/336 (0.6%)	1/282 (0.35%)
Abdominal Pain Upper [A] †	2/336 (0.6%)	0/282 (0%)
Gastrointestinal Haemorrhage [A] †	1/336 (0.3%)	1/282 (0.35%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal Ulcer [A] †	1/336 (0.3%)	0/282 (0%)
Gastrointestinal Ulcer Haemorrhage [A] †	1/336 (0.3%)	0/282 (0%)
Illeus [A] †	1/336 (0.3%)	0/282 (0%)
Nausea [A] †	0/336 (0%)	1/282 (0.35%)
Small Intestinal Obstruction [A] †	0/336 (0%)	1/282 (0.35%)
Upper Gastrointestinal Haemorrhage [A] †	0/336 (0%)	1/282 (0.35%)
Vomiting [A] †	1/336 (0.3%)	1/282 (0.35%)
General disorders		
Asthenia [A] †	1/336 (0.3%)	0/282 (0%)
Chest Pain [A] †	1/336 (0.3%)	0/282 (0%)
Fatigue [A] †	3/336 (0.89%)	1/282 (0.35%)
Gait Disturbance [A] †	1/336 (0.3%)	0/282 (0%)
General Physical Health Deterioration [A] †	1/336 (0.3%)	0/282 (0%)
Ill-Defined Disorder [A] †	1/336 (0.3%)	0/282 (0%)
Oedema Peripheral [A] †	1/336 (0.3%)	0/282 (0%)
Pain [A] †	2/336 (0.6%)	0/282 (0%)
Pyrexia [A] †	4/336 (1.19%)	4/282 (1.42%)
Hepatobiliary disorders		
Cholecystitis [A] †	1/336 (0.3%)	0/282 (0%)
Hepatitis Acute [A] †	1/336 (0.3%)	0/282 (0%)
Immune system disorders		
Hypersensitivity [A] †	0/336 (0%)	1/282 (0.35%)
Infections and infestations		

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Bronchitis [A] †	0/336 (0%)	1/282 (0.35%)
Cellulitis [A] †	0/336 (0%)	1/282 (0.35%)
Erysipelas [A] †	1/336 (0.3%)	1/282 (0.35%)
Pneumonia [A] †	3/336 (0.89%)	2/282 (0.71%)
Soft Tissue Infection [A] †	0/336 (0%)	1/282 (0.35%)
Wound Infection Staphylococcal [A] †	1/336 (0.3%)	0/282 (0%)
Injury, poisoning and procedural complications		
Femur Fracture [A] †	0/336 (0%)	1/282 (0.35%)
Fracture [A] †	0/336 (0%)	1/282 (0.35%)
Investigations		
Alanine Aminotransferase Increased [A] †	0/336 (0%)	1/282 (0.35%)
Blood Alkaline Phosphatase Increased [A] †	1/336 (0.3%)	0/282 (0%)
Blood Bilirubin Increased [A] †	1/336 (0.3%)	0/282 (0%)
Blood Creatinine Increased [A] †	1/336 (0.3%)	0/282 (0%)
Heart Rate Increased [A] †	1/336 (0.3%)	0/282 (0%)
Hepatic Enzyme Increased [A] †	0/336 (0%)	1/282 (0.35%)
Neutrophil Count Decreased [A] †	0/336 (0%)	1/282 (0.35%)
Pancreatic Enzymes Increased [A] †	0/336 (0%)	1/282 (0.35%)
Transaminases Increased [A] †	1/336 (0.3%)	0/282 (0%)
Metabolism and nutrition disorders		
Dehydration [A] †	2/336 (0.6%)	1/282 (0.35%)
Failure to Thrive [A] †	1/336 (0.3%)	0/282 (0%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Hypercalcaemia [A] †	0/336 (0%)	1/282 (0.35%)
Hyperkalaemia [A] †	2/336 (0.6%)	0/282 (0%)
Hyperuricaemia [A] †	0/336 (0%)	1/282 (0.35%)
Hyponatraemia [A] †	0/336 (0%)	1/282 (0.35%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	2/336 (0.6%)	1/282 (0.35%)
Back Pain [A] †	1/336 (0.3%)	0/282 (0%)
Bone Pain [A] †	1/336 (0.3%)	1/282 (0.35%)
Hypercreatinaemia [A] †	1/336 (0.3%)	0/282 (0%)
Joint Effusion [A] †	1/336 (0.3%)	0/282 (0%)
Musculoskeletal Pain [A] †	0/336 (0%)	1/282 (0.35%)
Neck Pain [A] †	1/336 (0.3%)	0/282 (0%)
Pathological Fracture [A] †	0/336 (0%)	1/282 (0.35%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bowen's Disease [A] †	1/336 (0.3%)	0/282 (0%)
Cutaneous Squamous Cell Carcinoma Right Upper Leg [A] †	1/336 (0.3%)	0/282 (0%)
Intracranial Tumour Haemorrhage [A] †	1/336 (0.3%)	0/282 (0%)
Keratoacanthoma [A] †	23/336 (6.85%)	0/282 (0%)
Lymphoma [A] †	0/336 (0%)	1/282 (0.35%)
Malignant Melanoma [A] †	3/336 (0.89%)	0/282 (0%)
Metastases to Central Nervous System [A] †	0/336 (0%)	1/282 (0.35%)
Seborrhoeic Keratosis [A] †	1/336 (0.3%)	0/282 (0%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Skin Papilloma [A] †	1/336 (0.3%)	0/282 (0%)
Squamous Cell Carcinoma [A] †	2/336 (0.6%)	0/282 (0%)
Squamous Cell Carcinoma of Skin [A] †	38/336 (11.31%)	1/282 (0.35%)
Treatment Related Secondary Malignancy [A] †	1/336 (0.3%)	0/282 (0%)
Nervous system disorders		
Ageusia [A] †	1/336 (0.3%)	0/282 (0%)
Aphasia [A] †	0/336 (0%)	1/282 (0.35%)
Cerebrovascular Accident [A] †	1/336 (0.3%)	1/282 (0.35%)
Convulsion [A] †	0/336 (0%)	1/282 (0.35%)
Headache [A] †	2/336 (0.6%)	0/282 (0%)
Intraventricular Haemorrhage [A] †	1/336 (0.3%)	0/282 (0%)
Loss of Consciousness [A] †	1/336 (0.3%)	1/282 (0.35%)
Peripheral Sensorimotor Neuropathy [A] †	1/336 (0.3%)	0/282 (0%)
Sciatica [A] †	1/336 (0.3%)	0/282 (0%)
Sensorimotor Disorder [A] †	1/336 (0.3%)	0/282 (0%)
Syncope [A] †	1/336 (0.3%)	0/282 (0%)
Renal and urinary disorders		
Acute Prerenal Failure [A] †	1/336 (0.3%)	0/282 (0%)
Haematuria [A] †	0/336 (0%)	1/282 (0.35%)
Renal Failure Acute [A] †	1/336 (0.3%)	1/282 (0.35%)
Reproductive system and breast disorders		
Cervical Dysplasia [A] †	1/336 (0.3%)	0/282 (0%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea [A] †	1/336 (0.3%)	3/282 (1.06%)
Haemoptysis [A] †	1/336 (0.3%)	0/282 (0%)
Pleural Effusion [A] †	1/336 (0.3%)	2/282 (0.71%)
Pleuritic Pain [A] †	0/336 (0%)	1/282 (0.35%)
Pneumothorax [A] †	1/336 (0.3%)	0/282 (0%)
Pulmonary Embolism [A] †	2/336 (0.6%)	1/282 (0.35%)
Skin and subcutaneous tissue disorders		
Pruritus [A] †	1/336 (0.3%)	0/282 (0%)
Rash [A] †	3/336 (0.89%)	0/282 (0%)
Skin Lesion [A] †	1/336 (0.3%)	0/282 (0%)
Stevens-Johnson Syndrome [A] †	1/336 (0.3%)	0/282 (0%)
Vascular disorders		
Deep Vein Thrombosis [A] †	0/336 (0%)	1/282 (0.35%)
Shock [A] †	0/336 (0%)	1/282 (0.35%)
Thrombosis [A] †	0/336 (0%)	3/282 (1.06%)
Vasculitis [A] †	1/336 (0.3%)	0/282 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	324/336 (96.43%)	230/282 (81.56%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Blood and lymphatic system disorders		
Anaemia [A] †	17/336 (5.06%)	15/282 (5.32%)
Neutropenia [A] †	1/336 (0.3%)	31/282 (10.99%)
Gastrointestinal disorders		
Abdominal Pain [A] †	17/336 (5.06%)	11/282 (3.9%)
Abdominal Pain Upper [A] †	21/336 (6.25%)	5/282 (1.77%)
Constipation [A] †	32/336 (9.52%)	65/282 (23.05%)
Diarrhoea [A] †	84/336 (25%)	34/282 (12.06%)
Nausea [A] †	101/336 (30.06%)	114/282 (40.43%)
Vomiting [A] †	49/336 (14.58%)	66/282 (23.4%)
General disorders		
Asthenia [A] †	27/336 (8.04%)	22/282 (7.8%)
Chills [A] †	17/336 (5.06%)	3/282 (1.06%)
Fatique [A] †	109/336 (32.44%)	86/282 (30.5%)
Odema Peripheral [A] †	49/336 (14.58%)	13/282 (4.61%)
Pain [A] †	20/336 (5.95%)	14/282 (4.96%)
Pyrexia [A] †	55/336 (16.37%)	21/282 (7.45%)
Infections and infestations		
Nasopharyngitis [A] †	17/336 (5.06%)	9/282 (3.19%)
Injury, poisoning and procedural complications		
Sunburn [A] †	31/336 (9.23%)	0/282 (0%)
Investigations		
Alanine Aminotransferase Increased [A] †	18/336 (5.36%)	2/282 (0.71%)

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Blood Alkaline Phosphatase Increased [A] †	24/336 (7.14%)	0/282 (0%)
Weight Decreased [A] †	20/336 (5.95%)	6/282 (2.13%)
Metabolism and nutrition disorders		
Decreased Appetite [A] †	53/336 (15.77%)	20/282 (7.09%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	163/336 (48.51%)	8/282 (2.84%)
Back Pain [A] †	19/336 (5.65%)	13/282 (4.61%)
Musculoskeletal Pain [A] †	21/336 (6.25%)	8/282 (2.84%)
Myalgia [A] †	39/336 (11.61%)	4/282 (1.42%)
Pain in Extremity [A] †	45/336 (13.39%)	17/282 (6.03%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Seborrhoeic Keratosis [A] †	23/336 (6.85%)	3/282 (1.06%)
Skin Papilloma [A] †	61/336 (18.15%)	0/282 (0%)
Nervous system disorders		
Dizziness [A] †	20/336 (5.95%)	10/282 (3.55%)
Dysgeusia [A] †	44/336 (13.1%)	9/282 (3.19%)
Headache [A] †	70/336 (20.83%)	26/282 (9.22%)
Psychiatric disorders		
Insomnia [A] †	19/336 (5.65%)	12/282 (4.26%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	23/336 (6.85%)	16/282 (5.67%)
Dyspnoea [A] †	18/336 (5.36%)	17/282 (6.03%)
Skin and subcutaneous tissue disorders		

	Vemurafenib	Dacarbazine
	Affected/At Risk (%)	Affected/At Risk (%)
Actinic Keratosis [A] †	21/336 (6.25%)	9/282 (3.19%)
Alopecia [A] †	117/336 (34.82%)	6/282 (2.13%)
Dry Skin [A] †	54/336 (16.07%)	3/282 (1.06%)
Erythema [A] †	38/336 (11.31%)	4/282 (1.42%)
Erythrodysaesthesia Syndrome Skin Lesion [A] †	20/336 (5.95%)	1/282 (0.35%)
Hyperkeratosis [A] †	67/336 (19.94%)	0/282 (0%)
Keratosis Pilaris [A] †	17/336 (5.06%)	0/282 (0%)
Palmar-Plantar [A] †	22/336 (6.55%)	1/282 (0.35%)
Photosensitivity Reaction [A] †	101/336 (30.06%)	10/282 (3.55%)
Pruritus [A] †	73/336 (21.73%)	4/282 (1.42%)
Rash [A] †	118/336 (35.12%)	3/282 (1.06%)
Rash Maculo-Papular [A] †	29/336 (8.63%)	1/282 (0.35%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Results Point of Contact:

Name/Official Title: Medical Communications
Organization: Hoffman-LaRoche
Phone: 800-821-8590
Email: