Sponsor

Novartis, formerly sponsored by Chiron Corporation

Generic Drug Name

None

Trial Indication

Locally advanced or Metastatic melanoma

Protocol Number

CRAF265A2101

Protocol Title

A Phase I/II, open-label, dose escalation trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of RAF265 (CHIR-265) administered orally to patients with locally advanced or metastatic melanoma

Clinical Trial Phase

I/II

Clinical Development Phase

I

Study Start/End Dates

05-Apr-2006 to 30-Nov-2013

Reason for Termination

Since comparable drug exposure was observed between the Arm 5 intermittent dosing schedule (94 mg) and the Arm 2 continuous dosing schedule (48 mg), it was decided not to explore the intermittent dosing schedule any further.

Overall, the level of efficacy was not high enough to warrant further clinical development in the chosen patient population and indication with the identified schedule and doses, and thus the Sponsor decided to initiate procedures to close the study.

Study Design/Methodology

This study was designed primarily to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RPTD), dose-limiting toxicities (DLTs), and safety of oral dosing of RAF265 in patients with locally advanced or metastatic melanoma using different dosing schedules. Pharmacokinetic (PK), pharmacodynamic (PD), and potential antitumor effects of the drug were also examined in order to allow for a more complete assessment of the RPTD, i.e. the dose with the optimal combination of target inhibition, tolerability, and tumor response. No control groups were used. Patients were enrolled in Arm 1, 2, 3 and 5. Arm 4 was never opened.

For Arm 1, run-in phase, raw PK concentrations were listed for 2 patients by dose level. No parameters were derived, and no summary, figures or analyses were produced. The PK results led to the modification of the study design. This arm was terminated; study design was modified to include arm 2 and arm 3.

An interim CSR dated 19-Mar-2013 with a data cutoff of 07-Feb-2012 was based on 104 enrolled patients. At the time of data cut off (07-Feb-2012), 7 patients were ongoing in the study (4 patients in Arm 2, 3 patients in Arm 5). Since comparable drug exposure was observed between the Arm 5 intermittent dosing schedule (94 mg) and the Arm 2 continuous dosing schedule (48 mg), the Sponsor decided not to explore the intermittent dosing schedule any further and initiated procedures to close the study.

Reported herein are efficacy data pertaining to the Phase 1 dose escalation arms (data cutoff = 07-Feb-2012) and safety for the entire duration of the study (data cutoff = 24-Sep-2014).

Centers

Eleven centers in two countries: Switzerland (1) and USA (10)

Publications

None

Objectives:

Primary objectives

- Determine the MTD and/or the RPTD
- Determine DLTs and the safety profile of RAF265 when administered orally to patients with locally advanced or metastatic melanoma.
- Determine the plasma PK of orally administered RAF265
- Evaluate the potential PD effects of RAF265 using tumor/nevus biopsies, peripheral blood samples, and imaging:
    - Tumor/nevi biopsies: signaling molecules, apoptosis, proliferation, microvessel density
    - Peripheral blood: levels of soluble growth factors and melanoma-related markers

- Tumor imaging: Tumor metabolic activity relative to baseline as measured by FDG-PET (dose escalation and dose expansion).

Secondary objectives

- Evaluate the effect of somatic BRAF (B-Raf gene) and NRAS mutations on modulation of PD markers and with clinical response.
- Determine the response rate for BRAF mutant patients at the MTD or RPTD
- Determine the RPTD, based on safety, PK, and PD data, and clinical tumor response

Test Product (s), Dose(s), and Mode(s) of Administration

Oral solution (50 mg/mL) and film-coated tablets (10 mg and 50 mg). The dose was based on the tablet equivalent to the patient's current liquid solution dose rounded to the nearest 10 mg.

Statistical Methods

Data from all centers that participated in this protocol were combined and summarized with respect to demographic and baseline characteristics, safety observations and measurements, efficacy observations and measurements, and PK measurements. No formal interim analysis planned.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Confirmed diagnosis of melanoma, locally advanced AJCC Stage IIIB to metastatic Stage IV
- Measurable disease - at least one lesion measured in at least one dimension as ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral computed tomography (CT) scan
- ECOG performance status of 0 or 1
- No concurrent anticancer or investigational therapy for at least 4 weeks prior to enrollment
- No major surgery for at least 4 weeks prior to enrollment

Exclusion criteria

- Significant cardiac disease or other significant medical/psychiatric disease
- History of primary central nervous system tumor or brain metastases
- History of melena, hematemesis, or hemoptysis within the last 3 months
- Previous therapy with certain molecularly targeted agents

Participant Flow Table

Patient disposition by treatment arm (FAS)

	Arm 1 N=2 n (%)	Arm 2 N=77 n (%)	Arm 3 N=16 n (%)	Arm 5 N=9 n (%)	All patients N=104 n (%)
Patients enrolled	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
untreated	0	0	0	0	0
treated	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
Patients treated	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
Treatment discontinued	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
Treatment ongoing	0	0	0	0	0
Primary reason for end of treatment	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
Adverse event(s)	0	19 (24.7)	0	1 (11.1)	20 (19.2)
Patient withdrew consent	0	2 (2.6)	0	0	2 (1.9)
Administrative problem	0	2 (2.6)	0	0	2 (1.9)
Disease progression	2 (100)	54 (70.1)	16 (100)	8 (88.9)	80 (76.9)
Primary reason for study evaluation completion	2 (100)	77 (100)	16 (100)	9 (100)	104 (100)
Adverse event(s)	0	9 (11.7)	0	0	9 (8.7)
Protocol violation	0	2 (2.6)	0	0	2 (1.9)
Patient withdrew consent	0	2 (2.6)	0	2 (22.2)	4 (3.8)
Lost to followup	0	1 (1.3)	0	1 (11.1)	2 (1.9)
Administrative problems	0	1 (1.3)	0	0	1 (1.0)
Death[1]	0	6 (7.8)	2 (12.5)	0	8 (7.7)
Disease progression	2 (100)	56 (72.7)	14 (87.5)	3 (33.3)	75 (72.1)
F/u phase compl as per prot	0	0	0	3 (33.3)	3 (2.9)

[1] In Arm 2, 1 death occurred 74 days post last dose. In Arm 3, 2 deaths occurred > 28 days post last dose. In Arm 5, 1 death occurred 23 days post last dose. A total of 6 deaths occurred ≤ 28 days post last dose

Demographic and Baseline Characteristics

Demographic summary by treatment arm (Enrolled set)

Demographic variable	Arm 1 N=2	Arm 2 N=77	Arm 3 N=16	Arm 5 N=9
	n (%)	n (%)	n (%)	n (%)
Age (Years)				
Mean (SD)		59.2 (13.02)	57.5 (11.14)	48.3 (15.55)

Demographic variable	Arm 1 N=2	Arm 2 N=77	Arm 3 N=16	Arm 5 N=9
	n (%)	n (%)	n (%)	n (%)
Median		60.0	55.0	43.0
Min-Max	70 - 81	26 - 83	42 - 82	30 - 69
Age category (Years) n (%)				
<65		50 (64.9)	13 (81.3)	7 (77.8)
>=65	2 (100)	27 (35.1)	3 (18.8)	2 (22.2)
Sex n (%)				
Male		43 (55.8)	10 (62.5)	7 (77.8)
Female	2 (100)	34 (44.2)	6 (37.5)	2 (22.2)
Race n (%)				
Caucasian	2 (100)	76 (98.7)	15 (93.8)	9 (100)
Asian		1 (1.3)	1 (6.3)	
Ethnicity n (%)				
Other	2 (100)	76 (98.7)	16 (100)	9 (100)
Missing		1 (1.3)		
Weight (Kg)				
Mean (SD)		79.82 (19.328)	81.57 (15.866)	89.60 (16.563)
Median		78.00	87.95	91.10
Min-Max	120.3 - 54.5	48.3 - 137.5	50.6 - 109.5	64.5 - 107.3
Height (cm)				
Mean (SD)		170.1 (9.60)	175.0 (11.04)	177.1 (6.64)
Median		168.0	173.5	179.0
Min-Max	183 - 162	154 - 194	160 - 194	163 - 185
Body Surface Area (m2)				
Mean (SD)		1.944 (0.2564)	1.997 (0.2432)	2.105 (0.2011)
Median		1.931	2.085	2.147
Min-Max	2.49 - 1.58	1.47 - 2.70	1.56 - 2.40	1.82 - 2.33
ECOG performance status n (%)				
Grade 0-1	2 (100)	77 (100)	16 (100)	9 (100)

Summary of Efficacy

Primary Outcome Results

PK results - Arms 2, 3 and 5

RAF265 pharmacokinetic parameters in Arm 2 by dose level and study day (PK Analysis Set)

Study day	PK parameter	DL 1 N=3	DL 2 N=3	DL 3 N=4	DL 4 N=10	DL 5 N=15	DL 6 N=23	DL 7 N=9	DL 7.1 N=10
First dose*	Cmax (ug/mL)								
	n	3	3	4	10	15	22	9	0
	Mean (SD)	0.136 (0.0523)	0.149 (0.0554)	0.263 (0.0829)	0.54 (0.177)	1.06 (0.308)	2.31 (0.916)	2.68 (1.04)	-
	Tmax (Hr)								
	n	3	3	4	10	15	22	9	0
	Median	3	2	2.52	2.01	2.15	3	3	-
	(Range)	2-3	2-3	2-3	2-4	1.05-4	1.98-8	2-3.02	-
	Tlast (Hr)								
	n	3	3	4	7	15	20	9	0
	Median	168	168	168	167	167	167	168	-
	(Range)	166-169	168-215	168-168	165-167	165-192	164-216	120-189	-
	AUC(0-tlast) (Hr*ug/mL)								
	n	3	3	4	7	15	19	9	0
	Mean (SD)	6.2 (1.53)	8.77 (4.37)	12.1 (4.01)	22.6 (8.81)	51.8 (14.3)	99.8 (43.2)	137 (53.5)	-
	T1/2 (Hr)								
	n	2	1	2	5	11	13	4	0
	Median	287	209	127	174	182	183	294	-
	(Range)	163-412	209-209	122-133	151-259	73.4-813	22.6-3850	98.3-409	-
Cycle 1 Day 1	Cmax (ug/mL)								
	n	3	3	4	10	15	22	9	10
	Mean (SD)	0.141 (0.0636)	0.168 (0.0201)	0.276 (0.0695)	0.498 (0.135)	1.07 (0.273)	2.25 (1.15)	2.72 (0.694)	1.13 (0.232)
	Tmax (Hr)								
	n	3	3	4	10	15	22	9	10
	Median	4	3	3.53	3	2	2.58	3	22.3
	(Range)	2-4	2-3.08	1.92-6.08	2-6	0-4	1-4	1-4.02	2-25.2
	Tlast (Hr)								
	n	3	3	4	9	14	21	8	10
	Median	25	22.9	23.8	24.4	24	24.1	24	23.8
	(Range)	21.5-27.1	21.5-24.4	23.3-24.3	23.4-26	23-26.3	21.1-24.6	23.1-25.6	21.5-25.2
	AUC(0-tlast) (Hr*ug/mL)								
	n	3	3	4	9	14	21	8	10
	Mean (SD)	2.08 (0.612)	2.65 (0.408)	3.93 (0.678)	7.28 (1.67)	15.7 (4.01)	28.1 (11.6)	39 (10.1)	18.4 (3.7)
Cycle 1 Day 15	Cmax (ug/mL)								
	n	3	3	4	8	15	19	9	9

Study day	PK parameter	DL 1 N=3	DL 2 N=3	DL 3 N=4	DL 4 N=10	DL 5 N=15	DL 6 N=23	DL 7 N=9	DL 7.1 N=10
	Mean	0.133	0.119	0.199	0.423	0.845	1.65	2.65	1.83
	(SD)	(0.0434)	(0.0343)	(0.0233)	(0.157)	(0.23)	(0.625)	(1.1)	(0.652)
	Tmax (Hr)								
	n	3	3	4	8	15	19	9	9
	Median	3	3.07	2.52	5.13	2.75	3.93	4	3
	(Range)	2.58-4	2.12-4	1-4	2-25	0.967-4.5	1-6.08	0-22.1	1-23.3
	Tlast (Hr)								
	n	3	3	4	7	14	16	9	9
	Median	25.3	22.5	24.1	24	24	23.7	23.4	23.8
	(Range)	22.9-28	22.4-23.5	23.4-24.8	22.8-25.4	18.9-28.9	18.3-25.3	19.8-24.1	21.6-24.2
	AUC(0-tlast) (Hr*ug/mL)								
	n	3	3	4	7	14	16	9	9
	Mean	2.67	2.3	4.15	8.59	16.1	28.5	46.8	35.4
	(SD)	(0.591)	(0.777)	(0.342)	(3.4)	(5)	(11.7)	(23)	(13.7)
Steady State**	Cmin (ug/mL)								
	n	3	3	3	6	12	18	6	8
	Mean	1.23	1.51	1.82	4.31	7.31	13.1	21.8	15.5
	(SD)	(0.217)	(0.82)	(0.282)	(1.22)	(1.99)	(5.57)	(3.76)	(7.47)

* First dose is the PK run-in dose in Arm 2.

** Steady state: Cmin is calculated based on the average of trough concentrations from Cycle 2 Day 1 and onwards.

RAF265 pharmacokinetic parameters in Arm 3 by dose level and study day (PK Analysis Set)

Study day	PK parameter	DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1
Cycle 1 Day 1	Cmax (ug/mL)				
	n	3	7	5	1
	Mean (SD)	0.147 (0.0639)	0.234 (0.087)	0.23 (0.0557)	0.33 (-)
	Tmax (Hr)				
	n	3	7	5	1
	Median	2	2.02	4.03	4
	(Range)	2-3	1-4.07	2-6	4-4
	Tlast (Hr)				
	n	2	7	5	1
	Median	166	167	166	169
	(Range)	166-167	164-171	165-191	169-169
	AUC(0-tlast) (Hr*ug/mL)				
	n	2	7	5	1
	Mean (SD)	5.79 (3.24)	9.67 (4.13)	14.3 (3.41)	16.9 (-)
Steady State**	Cmin (ug/mL)				
	n	2	6	4	1
	Mean (SD)	0.49 (0.156)	1.03 (0.372)	0.942 (0.391)	1.92 (-)

** Steady state: Cmin is calculated based on the average of trough concentrations from Cycle 2 Day 1 and onwards.

RAF265 pharmacokinetic parameters in Arm 5 by dose level and study day (PK Analysis Set)

Study day	PK parameter	DL 1 N=3	DL 2 N=6
Cycle 1 Day 1	Cmax (ug/mL)		
	n	3	6
	Mean (SD)	0.56 (0.145)	0.677 (0.185)
	Tmax (Hr)		
	n	3	6
	Median	3	3
	(Range)	2.08-4.07	2.07-21.3
	Tlast (Hr)		
	n	3	5
	Median	24.1	23.8
	(Range)	22.3-24.4	21.3-24.2
	AUC(0-tlast) (Hr*ug/mL)		
	n	3	5
	Mean (SD)	7.44 (1.8)	9.5 (3.46)
Cycle 1 Day 14	Cmax (ug/mL)		
	n	3	5

Study day	PK parameter	DL 1 N=3	DL 2 N=6
	Mean (SD)	1.18 (0.2)	1.33 (0.452)
	Tmax (Hr)		
	n	3	5
	Median	3	3
	(Range)	2.03-8	1.93-30.3
	Tlast (Hr)		
	n	2	4
	Median	192	192
	(Range)	191-194	190-197
	AUC(0-tlast) (Hr*ug/mL)		
	n	2	4
	Mean (SD)	106 (1.88)	180 (40.3)
Cycle 2 Day 14	Cmax (ug/mL)		
	n	3	5
	Mean (SD)	1.55 (0.264)	1.79 (0.7)
	Tmax (Hr)		
	n	3	5
	Median	3	3
	(Range)	1.13-3.07	2-3.05
	Tlast (Hr)		
	n	2	5
	Median	193	192
	(Range)	193-193	167-196
	AUC(0-tlast) (Hr*ug/mL)		
	n	2	5
	Mean (SD)	167 (29.7)	217 (92)
Steady State**	Cmin (ug/mL)		
	n	3	4
	Mean (SD)	6.12 (1.87)	6.58 (2.9)

** Steady state: Cmin is calculated based on the average of trough concentrations from cycle 2 day 1 and onwards.

Pharmacodynamic results

Tumor /Nevi biopsies – Arms 2 and 3 only

Percent change from baseline of tissue biomarker expression (H-score) and RECIST tumor response in Arm 2 at C02D08 by tissue biomarker (Full Analysis Set)

Location: Cytoplasmic

Tissue Biomar-ker**		DLs 1 - 4 N=20	DL 5 N=15	DL 6 N=23	DLs 7 and 7.1 N=19	All patients N=77
pMEK	n	11	2	6	4	23
	Mean (SD)	0.78 (44.403)	0.00 (0.000)	-16.09 (17.341)	-2.63 (5.263)	-4.28 (31.959)
	Median	-11.11	0.00	-15.26	0.00	-9.09
	Min-Max	-38.1 - 122.2	0.0 - 0.0	-40.0 - 4.0	-10.5 - 0.0	-40.0 - 122.2
pERK	n	2	2	5	4	13
	Mean (SD)	52.55 (79.967)	27.08 (55.979)	-27.03 (40.914)	-17.78 (11.466)	-3.62 (48.610)
	Median	52.55	27.08	-50.00	-13.48	-11.76
	Min-Max	-4.0 - 109.1	-12.5 - 66.7	-63.5 - 19.5	-34.6 - -9.5	-63.5 - 109.1
BIM	n	8	1	2	3	14
	Mean (SD)	-17.97 (65.111)	-1000	-7.13 (11.130)	6.67 (5.774)	-17.00 (54.518)
	Median	-14.29	-1000	-7.13	10.00	0.00
	Min-Max	-100 - 100	-100 - -100	-15.0 - 0.7	0 - 10.0	-100 - 100
CKIT	n	4	0	1	3	8
	Mean (SD)	-60.00 (80.000)		0	0	-30.00 (61.412)
	Median	-1000		0	0	0.00
	Min-Max	-100 - 60.0		0 - 0	0 - 0	-100 - 60.0
PAKT473	n	11	1	4	3	19
	Mean (SD)	20.05(132.918)	-4.55	-48.35 (55.894)	0	1.19 (105.359)
	Median	-20.00	-4.55	-46.70	0	-4.55
	Min-Max	-100 - 400.0	-4.5 - -4.5	-100 - 0	0 - 0	-100 - 400.0
PS6	n	8	1	6	4	19
	Mean (SD)	-16.77 (20.858)	255.56	-20.61 (29.141)	33.44 (55.725)	6.92 (70.820)
	Median	-18.92	255.56	-35.81	16.25	-13.04
	Min-Max	-53.3 - 12.5	255.6 - 255.6	-43.6 - 29.6	-13.0 - 114.3	-53.3 - 255.6
PTEN	n	8	2	5	3	18
	Mean (SD)	-4.98 (44.095)	0.00 (0.000)	-9.43 (27.022)	10.00 (17.321)	-3.16 (32.443)
	Median	-7.39	0	0	0	0
	Min-Max	-72.0 - 83.3	0 - 0	-57.1 - 10.0	0 - 30.0	-72.0 - 83.3

Location: Nuclear

Tissue Biomar-ker**		DLs 1 - 4 N=20	DL 5 N=15	DL 6 N=23	DLs 7 and 7.1 N=19	All patients N=77
pERK	n	10	2	5	4	21
	Mean (SD)	21.11 (52.132)	18.17 (35.795)	-41.80 (47.963)	-20.32 (31.333)	-2.04 (51.626)
	Median	0	18.17	-22.22	-7.60	0
	Min-Max	-17.5 - 135.7	-7.1 - 43.5	-93.7 - 0	-66.1 - 0	-93.7 - 135.7
Ki67	n	11	2	6	4	23
	Mean (SD)	0.21 (59.628)	0	-47.93 (40.786)	-6.08 (19.959)	-13.46 (49.923)
	Median	-11.11	0	-51.75	-2.63	-11.11
	Min-Max	-95.7 - 150.0	0 - 0	-95.7 - 20.0	-33.3 - 14.3	-95.7 - 150.0
PARP	n	8	0	3	3	14
	Mean (SD)	65.14 (180.498)		20.00 (121.244)	222.22 (167.774)	89.13 (172.278)
	Median	-20.00		0.00	200.00	33.33
	Min-Max	-100 - 400.0		-90.0 - 150.0	66.7 - 400.0	-100 - 400.0
Cyclin D1	n	10	3	5	5	23
	Mean (SD)	-4.53 (94.955)	56.79 (125.591)	-49.12 (30.716)	25.00 (113.614)	0.19 (93.705)
	Median	-24.04	5.00	-48.94	0.00	-25.00
	Min-Max	-100 - 233.3	-34.6 - 200.0	-77.8 - 0.0	-71.4 - 221.4	-100 - 233.3
MITF	n	9	2	6	4	21
	Mean(SD)	400.58 (1312.529)	11.79 (23.739)	20.13 (111.294)	98.61 (239.700)	197.33 (856.877)
	Median	-27.27	11.79	-6.60	0	-13.21
	Min-Max	-80.0 - 3900.0	-5.0 - 28.6	-75.0 - 240.0	-61.1 - 455.6	-80.0 - 3900.0
P27	n	9	2	5	4	20
	Mean (SD)	-2.15 (44.004)	-40.00 (56.569)	156.35 (312.151)	261.11 (427.309)	86.34 (251.868)
	Median	0	-40.00	30.43	72.22	5.00
	Min-Max	-50.0 - 72.7	-80.0 - 0.0	-73.7 - 700.0	0.0 - 900.0	-80.0 - 900.0
P53	n	10	2	4	4	20
	Mean (SD)	-27.30 (49.484)	82.35 (190.533)	49.32 (123.273)	188.47 (400.618)	42.14 (195.033)
	Median	-29.17	82.35	-3.75	0.00	-3.75
	Min-Max	-100 - 70.0	-52.4 - 217.1	-28.6 - 233.3	-35.0 - 788.9	-100 - 788.9

** Tissue biomarker: pMEK = phosphorylated MAPK/ERK kinase, pERK = phosphorylated extracellar signal-regulated kinase, Ki67 = proliferation-associated antigen Ki-67, BIM= a pro-apoptotic member of the BCL-2 family, PARP = Poly(ADP-ribose)polymerase, Cyclin D1 = cell cycle gene, MITF = microphthalmia-associated transcription factor, CKIT=c-KIT, P53= Tumor Protein 53/TP53, PAKT473= Phospho Akt S 473, PS6=Phosphoserine 240-S6 ribosomal protein, PTEN=Phosphatase and Tensin homolog.

Percent change from baseline of tissue biomarker expression (H-score) and RECIST tumor response in Arm 3 at C02D28 by tissue biomarker (Full Analysis Set)

Location: Cytoplasmic

Tissue Biomar-ker**		DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1	All patients N=16
pMEK	n	3	5	6	1	15
	Mean (SD)	-20.73 (15.682)	36.76 (133.079)	125.00 (182.498)	-55.56	54.40 (145.981)
	Median	-20.83	-16.67	83.33	-55.56	-5.00
	Min-Max	-36.4 - -5.0	-58.3 - 266.7	-33.3 - 466.7	-55.6 - -55.6	-58.3 - 466.7
BIM	n	3	5	5	0	13
	Mean (SD)	-33.33 (115.470)	-34.33 (39.409)	22.58 (46.781)		-12.21 (65.490)
	Median	-1000	-28.57	33.33		-20.00
	Min-Max	-100 - 100	-95.6 - 12.5	-45.5 - 75.0		-100 - 100
CKIT	n	1	1	0	0	2
	Mean (SD)	-25.00	-66.67			-45.83 (29.463)
	Median	-25.00	-66.67			-45.83
	Min-Max	-25.0 - -25.0	-66.7 - -66.7			-66.7 - -25.0
PAKT473	n	3	7	5	1	16
	Mean(SD)	29.20 (101.618)	12.66 (35.145)	33.47 (95.211)	-20.00	20.22 (67.063)
	Median	-21.05	0.00	6.25	-20.00	0.00
	Min-Max	-37.5 - 146.2	-40.0 - 69.2	-40.0 - 200.0	-20.0 - -20.0	-40.0 - 200.0
PS6	n	3	6	6	1	16
	Mean (SD)	3.21 (18.526)	-1.32 (32.391)	-6.92 (9.496)	-25.81	-4.10 (21.769)
	Median	13.51	-4.69	-7.80	-25.81	-7.32
	Min-Max	-18.2 - 14.3	-46.7 - 53.6	-15.8 - 10.0	-25.8 - -25.8	-46.7 - 53.6
PTEN	n	0	6	4	1	11
	Mean (SD)		-29.84 (37.677)	-39.12 (45.917)	35.71	-27.26 (42.416)
	Median		-22.67	-31.82	35.71	-18.18
	Min-Max		-100 - 5.9	-100 - 7.1	35.7 - 35.7	-100 - 35.7

Location: Nuclear

Tissue Biomar-ker**		DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1	All patients N=16
pERK	n	3	7	6	1	17
	Mean (SD)	-17.11 (7.977)	-41.11 (28.682)	-0.23 (18.648)	-52.08	-23.09 (28.677)
	Median	-12.50	-39.02	3.13	-52.08	-17.24
	Min-Max	-26.3 - -12.5	-93.1 - -9.1	-33.3 - 23.1	-52.1 - -52.1	-93.1 - 23.1
Ki67	n	3	7	6	1	17
	Mean (SD)	8.33 (7.217)	-7.14 (17.539)	2.55 (27.392)	-25.00	-2.04 (20.707)
	Median	12.50	0.00	3.85	-25.00	0.00
	Min-Max	0.0 - 12.5	-27.8 - 12.5	-40.0 - 33.3	-25.0 - -25.0	-40.0 - 33.3
PARP	n	2	7	5	1	15

Tissue Biomar-ker**		DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1	All patients N=16
	Mean (SD)	637.50 (866.206)	25.88 (94.003)	158.32 (418.183)	166.67	160.97 (385.895)
	Median	637.50	66.67	-22.22	166.67	55.56
	Min-Max	25.0 - 1250.0	-99.2 - 125.0	-95.6 - 900.0	166.7 - 166.7	-99.2 - 1250.0
Cyclin D1	n	3	7	5	1	16
	Mean (SD)	61.27 (88.147)	-25.45 (45.930)	41.46 (91.893)	18.75	14.48 (74.548)
	Median	33.33	-38.10	3.85	18.75	-10.53
	Min-Max	-9.5 - 160.0	-61.1 - 75.0	-25.0 - 200.0	18.8 - 18.8	-61.1 - 200.0
MITF	n	2	5	6	1	14
	Mean (SD)	159.31 (246.101)	-38.63 (18.835)	79.30 (256.125)	-22.22	41.36 (188.614)
	Median	159.31	-47.62	-20.00	-22.22	-29.44
	Min-Max	-14.7 - 333.3	-52.2 - -6.7	-45.5 - 600.0	-22.2 - -22.2	-52.2 - 600.0
P27	n	2	6	5	1	14
	Mean (SD)	3.82 (21.115)	-28.89 (26.555)	-21.47 (28.987)	-50.00	-23.07 (27.344)
	Median	3.82	-23.33	-12.50	-50.00	-12.92
	Min-Max	-11.1 - 18.8	-60.0 - 0.0	-63.6 - 8.3	-50.0 - -50.0	-63.6 - 18.8
P53	n	3	6	4	1	14
	Mean (SD)	207.78 (287.254)	-23.89 (10.864)	-8.41 (29.285)	-50.00	28.31 (150.050)
	Median	1000	-24.50	-6.11	-50.00	-14.09
	Min-Max	-10.0 - 533.3	-35.1 - -6.3	-46.4 - 25.0	-50.0 - -50.0	-50.0 - 533.3

** Tissue biomarker: pMEK = phosphorylated MAPK/ERK kinase, pERK = phosphorylated extracellar signal-regulated kinase, Ki67 = proliferation-associated antigen Ki-67, BIM= a pro-apoptotic member of the BCL-2 family, PARP = Poly(ADP-ribose)polymerase, Cyclin D1 = cell cycle gene, MITF = microphthalmia-associated transcription factor.CKIT=c-KIT, P53= Tumor Protein 53/TP53, PAKT473= Phospho Akt S 473, PS6=Phosphoserine 240-S6 ribosomal protein, PTEN= Phosphatase and Tensin homolog.

Peripheral blood results – Arms 2 and 3 only

Percent change from baseline of soluble marker concentrations in Arm 2 at C01D15 by soluble marker and dose level group (Full Analysis Set)

Soluble Marker*		DLs 1 - 4 N=20	DL 5 N=15	DL 6 N=23	DLs 7 and 7.1 N=19	All patients N=77
VEGF	n	19	13	19	17	68
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-8.41 (32.521)	11.32 (23.161)	47.32 (74.377)	98.17 (52.878)	37.58 (65.009)
	Median	3.66	7.65	17.84	84.53	14.98
	Min-Max	-83.1-53.4	-30.0-45.6	-29.7-245.2	11.1-180.3	-83.1-245.2
	Geometric mean	6.19	12.75	34.91	81.64	25.62
	CV(%) of geometric mean	252.0	172.7	225.4	80.7	298.1
sVEGFR-1	n	19	13	19	17	68
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-4.73 (30.605)	-4.92 (30.085)	-7.27 (16.894)	26.19 (32.026)	2.26 (30.501)
	Median	-4.29	-5.14	-5.65	14.28	-1.20
	Min-Max	-58.7-84.3	-81.9-29.6	-37.8-24.1	-5.3-100.6	-81.9-100.6
	Geometric mean	28.09	16.34	9.97	13.12	14.32
	CV(%) of geometric mean	104.5	67.8	64.8	337.6	182.3
sVEGFR-2	n	19	13	19	17	68
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-5.71 (16.924)	-2.26 (16.527)	-13.72 (12.383)	-21.76 (12.965)	-11.30 (16.166)
	Median	-4.39	-7.42	-15.40	-22.15	-12.74
	Min-Max	-32.0-26.2	-24.0-39.6	-32.0-15.8	-43.4-10.1	-43.4-39.6
	Geometric mean	9.56	2.70	3.96	10.15	5.48
	CV(%) of geometric mean	73.9	3441.7	210.9		361.7
bFGF	n	19	13	19	17	68
	Below LLOQ(%)	3 (15.0)	3 (20.0)	1 (4.3)	1 (5.3)	8 (10.4)
	Mean (SD)	25.74 (164.101)	-14.00 (31.477)	11.62 (95.093)	-11.54 (42.971)	4.88 (102.744)
	Median	-6.40	-15.30	-13.98	-16.27	-13.35
	Min-Max	-94.9-497.8	-61.5-45.0	-86.3-286.9	-66.5-76.8	-94.9-497.8
	Geometric mean	21.21	31.07	72.42	34.90	36.10

Soluble Marker*		DLs 1 - 4 N=20	DL 5 N=15	DL 6 N=23	DLs 7 and 7.1 N=19	All patients N=77
	CV(%) of geometric mean	1197.9	33.0	132.3	86.5	288.1
PLGF	n	19	13	19	17	68
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	4.01 (22.871)	13.52 (26.976)	33.24 (37.622)	88.80 (46.939)	35.19 (47.693)
	Median	5.20	16.47	32.21	92.46	26.65
	Min-Max	-42.9-53.5	-33.3-61.7	-30.9-127.2	20.7-197.3	-42.9-197.3
	Geometric mean	9.26	16.03	31.61	75.62	27.44
	CV(%) of geometric mean	147.5	174.1	110.6	69.4	182.7
MIA	n	2	12	18	18	50
	Below LLOQ(%)	1 (5.0)	10 (66.7)	10 (43.5)	15 (78.9)	36 (46.8)
	Mean (SD)	2.53 (1.967)	-4.32 (20.111)	-7.74 (28.643)	-16.81 (15.297)	-9.77 (22.133)
	Median	2.53	-2.47	-13.77	-17.24	-13.04
	Min-Max	1.1-3.9	-54.1-28.1	-60.9-61.7	-45.8-21.4	-60.9-61.7
	Geometric mean	2.11	4.07	24.94	4.20	6.86
	CV(%) of geometric mean	107.2	1210.8	64.5	252.3	394.9
cKIT	n	19	13	19	17	68
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-0.86 (15.471)	2.85 (10.522)	6.52 (19.458)	9.00 (17.227)	4.38 (16.483)
	Median	2.33	-0.77	3.95	4.75	3.44
	Min-Max	-25.8-26.3	-11.4-25.9	-24.2-41.4	-14.5-44.6	-25.8-44.6
	Geometric mean	10.05	11.83	13.55	10.89	11.50
	CV(%) of geometric mean	73.9	75.8	118.8	141.3	103.0

*Soluble marker: VEGF = vascular endothelial growth factor, sVEGFR-1 = soluble VEGF receptor type 1, sVEGFR-2 = soluble VEGF receptor type 2, bFGF = basic fibroblast growth factor, PLGF = placental growth factor, MIA = melanoma inhibitory activity protein.

All concentrations are expressed in pg/mL except MIA are expressed in ng/mL.

Percent change from baseline of soluble marker concentrations in Arm 3 at C01D15 by soluble marker and dose level group (Full Analysis Set)

Soluble Marker*		DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1	All patients N=16
VEGF	n	3	6	5	1	15
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-24.51 (68.006)	82.65 (77.753)	-21.57 (33.798)	19.28 (-)	22.26 (76.580)
	Median	-41.22	92.98	-17.54	19.28	3.23
	Min-Max	-82.6-50.3	-7.4-201.1	-58.9-26.5	19.3-19.3	-82.6-201.1
	Geometric mean	50.30	57.16	26.49	19.28	44.61
	CV(%) of geometric mean		373.5			215.5
sVEGFR-1	n	3	6	5	1	15
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-44.92 (87.439)	-0.35 (36.439)	-11.89 (10.735)	10.32 (-)	-12.40 (43.877)
	Median	-93.61	3.01	-11.55	10.32	-6.20
	Min-Max	-97.2-56.0	-66.8-32.8	-21.7-4.6	10.3-10.3	-97.2-56.0
	Geometric mean	56.02	6.93	4.63	10.32	9.33
	CV(%) of geometric mean		882.4			406.1
sVEGFR-2	n	3	6	5	1	15
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	5.64 (14.023)	9.54 (13.702)	-3.79 (9.816)	-1.01 (-)	3.62 (12.638)
	Median	7.23	11.96	-5.93	-1.01	0.06
	Min-Max	-9.1-18.8	-8.7-29.1	-15.7-10.6	-1.0--1.0	-15.7-29.1
	Geometric mean	11.66	15.75	0.78		6.89
	CV(%) of geometric mean	76.1	51.5	89864.4		707.8
bFGF	n	3	6	5	1	15
	Below LLOQ(%)	1 (33.3)	0	1 (20.0)	0	2 (12.5)
	Mean (SD)	271.04 (316.226)	133.11 (201.438)	-10.18 (63.444)	145.98 (-)	113.79 (202.359)
	Median	417.32	64.43	-13.34	145.98	7.10
	Min-Max	-91.8-487.6	-31.7-470.6	-67.5-87.5	146.0-146.0	-91.8-487.6
	Geometric mean	451.11	259.96	24.92	145.98	154.46

Soluble Marker*		DL 1 N=3	DL 2 N=7	DL 3 N=5	DL 4 N=1	All patients N=16
	CV(%) of geometric mean	11.0	63.3	473.8		244.8
PLGF	n	3	6	5	1	15
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-11.29 (24.747)	7.74 (24.123)	-2.39 (8.225)	-14.79 (-)	-0.94 (19.605)
	Median	-8.43	5.90	1.25	-14.79	1.25
	Min-Max	-37.3-11.9	-25.5-49.4	-16.2-4.9	-14.8--14.8	-37.3-49.4
	Geometric mean	11.90	6.24	2.02		4.60
	CV(%) of geometric mean		346.9	90.0		232.7
MIA	n	0	1	0	1	2
	Below LLOQ(%)	0	1 (14.3)	0	1 (100)	2 (12.5)
	Mean (SD)		-8.02 (-)		-12.80 (-)	-10.41 (3.384)
	Median		-8.02		-12.80	-10.41
	Min-Max		-8.0--8.0		-12.8--12.8	-12.8--8.0
	Geometric mean					
	CV(%) of geometric mean					
cKIT	n	3	6	5	1	15
	Below LLOQ(%)	0	0	0	0	0
	Mean (SD)	-2.83 (8.978)	13.39 (11.255)	3.22 (5.652)	-4.30 (-)	5.57 (10.776)
	Median	-5.81	9.83	6.69	-4.30	6.69
	Min-Max	-9.9-7.3	1.4-32.2	-4.8-8.0	-4.3--4.3	-9.9-32.2
	Geometric mean	7.25	9.02	7.16		8.23
	CV(%) of geometric mean		154.3	9.9		100

*Soluble marker: VEGF = vascular endothelial growth factor, sVEGFR-1 = soluble VEGF receptor type 1, sVEGFR-2 = soluble VEGF receptor type 2, bFGF = basic fibroblast growth factor, PLGF = placental growth factor, MIA = melanoma inhibitory activity protein.

All concentrations are expressed in pg/mL except MIA are expressed in ng/mL.

Tumor imaging results – Arms 2, 3 and 5

Arm 2

Metabolic response from FDG-PET data in Arm 2 by FDG-PET scan time and dose level group (Full Analysis Set)

FDG-PET scan time	Metabolic response**	DLs 1 to 4 N=20 n (%)	DL 5 N=15 n (%)	DL 6 N=23 n (%)	DLs 7 and 7.1 N=19 n (%)	All patients N=77 n (%)
C01D08	CMR	0	0	0	0	0
	PMR	1 (5.0)	0	0	0	1 (1.3)
	SMD	2 (10.0)	0	0	0	2 (2.6)
	PMD	1 (5.0)	0	0	0	1 (1.3)
	NA	1 (5.0)	0	0	0	1 (1.3)
	Missing/Not done	15 (75.0)	15 (100)	23 (100)	19 (100)	72 (93.5)
C01D15	CMR	0	0	0	0	0
	PMR	2 (10.0)	1 (6.7)	3 (13.0)	5 (26.3)	11 (14.3)
	SMD	8 (40.0)	11 (73.3)	14 (60.9)	12 (63.2)	45 (58.4)
	PMD	2 (10.0)	3 (20.0)	2 (8.7)	2 (10.5)	9 (11.7)
	Missing/Not done	8 (40.0)	0	4 (17.4)	0	12 (15.6)
C01D28	CMR	0	0	0	0	0
	PMR	2 (10.0)	2 (13.3)	4 (17.4)	4 (21.1)	12 (15.6)
	SMD	5 (25.0)	9 (60.0)	12 (52.2)	10 (52.6)	36 (46.8)
	PMD	5 (25.0)	3 (20.0)	1 (4.3)	1 (5.3)	10 (13.0)
	Missing/Not done	8 (40.0)	1 (6.7)	6 (26.1)	4 (21.1)	19 (24.7)
End of Trt.	CMR	0	0	0	0	0
	PMR	0	0	0	0	0
	SMD	0	0	1 (4.3)	0	1 (1.3)
	PMD	0	0	0	0	0
	Missing/Not done	20 (100)	15 (100)	22 (95.7)	19 (100)	76 (98.7)

** Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25% from the baseline scan.

Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of >=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Metabolic response from FDG-PET data at C01D28 and tumor response from RECIST data (CT or MRI) at C02D28 in Arm 2 (Full Analysis Set)

	RECIST tumor reponse				
FDG-PET tumor response*	**CR n (%)**	**PR n (%)**	**SD n (%)**	**PD n (%)**	**Missing/ Not done n (%)**
CMR	0	0	0	0	0
PMR	1 (1.3)	1 (1.3)	6 (7.8)	0	4 (5.2)
SMD	0	1 (1.3)	13 (16.9)	5 (6.5)	16 (20.8)
PMD	0	0	1 (1.3)	3 (3.9)	6 (7.8)
Missing/Not done	0	1 (1.3)	5 (6.5)	3 (3.9)	11 (14.3)

* Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25% from the baseline scan. Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of >=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Arm 3

Metabolic response from FDG-PET data in Arm 3 by FDG-PET scan time and dose level group (Full Analysis Set)

		DL 1	**DL 2**	**DL 3**	**DL 4**	**All patients**
FDG-PET scan time	**Metabolic response****	**N=3 n (%)**	**N=7 n (%)**	**N=5 n (%)**	**N=1 n (%)**	**N=16 n (%)**
C01D08	CMR	0	0	0	0	0
	PMR	1 (33.3)	1 (14.3)	1 (20.0)	0	3 (18.8)
	SMD	1 (33.3)	2 (28.6)	2 (40.0)	1 (100)	6 (37.5)
	PMD	0	1 (14.3)	1 (20.0)	0	2 (12.5)
	NA	1 (33.3)	0	1 (20.0)	0	2 (12.5)
	Missing/Not done	0	1 (14.3)	0	0	1 (6.3)
	Unknown	0	2 (28.6)	0	0	2 (12.5)
End of Trt.	CMR	0	0	0	0	0
	PMR	0	0	0	0	0
	SMD	0	1 (14.3)	0	0	1 (6.3)
	PMD	0	0	0	0	0
	Missing/Not done	3 (100)	6 (85.7)	5 (100)	1 (100)	15 (93.8)

FDG-PET scan time	Metabolic response**	DL 1 N=3 n (%)	DL 2 N=7 n (%)	DL 3 N=5 n (%)	DL 4 N=1 n (%)	All patients N=16 n (%)

** Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25% from the baseline scan. Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of >=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Metabolic response from FDG-PET data at C01D08 and tumor response from RECIST data (CT or MRI) at C02D28 in Arm 3 (Full Analysis Set)

	RECIST tumor reponse				
FDG-PET tumor response*	CR n (%)	PR n (%)	SD n (%)	PD n (%)	Missing/ Not done n (%)
CMR	0	0	0	0	0
PMR	0	0	1 (6.3)	2 (12.5)	0
SMD	0	0	1 (6.3)	3 (18.8)	2 (12.5)
PMD	0	0	0	2 (12.5)	0
Missing/Not done	0	0	1 (6.3)	2 (12.5)	2 (12.5)

* Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is

the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25%

from the baseline scan. Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of

>=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Arm 5

Metabolic response from FDG-PET data in Arm 5 by FDG-PET scan time and dose level group (Full Analysis Set)

FDG-PET scan time	Metabolic response**	DL 1 N=3 n (%)	DL 2 N=6 n (%)	All patients N=9 n (%)
C01D14	CMR	0	0	0
	PMR	0	0	0
	SMD	2 (66.7)	4 (66.7)	6 (66.7)
	PMD	1 (33.3)	1 (16.7)	2 (22.2)
	NA	0	1 (16.7)	1 (11.1)
C02D14	CMR	0	0	0
	PMR	0	2 (33.3)	2 (22.2)
	SMD	1 (33.3)	1 (16.7)	2 (22.2)
	PMD	2 (66.7)	0	2 (22.2)
	Missing/Not done	0	3 (50.0)	3 (33.3)
End of Trt.	CMR	0	0	0
	PMR	0	0	0
	SMD	1 (33.3)	0	1 (11.1)
	PMD	0	0	0
	Missing/Not done	2 (66.7)	6 (100)	8 (88.9)

** Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25% from the baseline scan. Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of >=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Metabolic response from FDG-PET data at C01D14 and tumor response from RECIST data (CT or MRI) at C03D01 in Arm 5 (Full Analysis Set)

	RECIST tumor reponse				
FDG-PET tumor response*	CR n (%)	PR n (%)	SD n (%)	PD n (%)	Missing/ Not done n (%)
CMR	0	0	0	0	0
PMR	0	0	0	0	0
SMD	0	0	2 (22.2)	0	2 (22.2)

	RECIST tumor reponse				
FDG-PET tumor response*	**CR n (%)**	**PR n (%)**	**SD n (%)**	**PD n (%)**	**Missing/ Not done n (%)**
PMD	0	0	0	0	0
Missing/Not done	0	0	4 (44.4)	0	1 (11.1)

* Complete metabolic response (CMR) - complete resolution of tumor FDG-PET uptake so SUVmax is the same as background, Partial metabolic response (PMR) - a decrease in tumor sSUVmax of >=25% from the baseline scan. Progressive metabolic disease (PMD) - an increase in tumor sSUVmax of >=25% from the baseline scan, or the appearance of new FDG-PET uptake in metastatic lesions,

Stable metabolic disease (SMD) - a change in tumor sSUVmax between the PMR and PMD criteria,

Missing/Not done data only pertains to imaging data (technical failure and missed visit),

NA = Not assessable.

Secondary Outcome Results

Somatic mutation and clinical response – Arms 2, 3 and 5

Arm 2

Best overall response (central radiological assessment) by BRAF mutation status and dose level group - Arm 2 (Full Analysis Set)

	DLs 1 to 4 N=20 n (%)	**DL 5 N=15 n (%)**	**DL 6 N=23 n (%)**	**DLs 7 and 7.1 N=19 n (%)**	**All patients N=77 n (%)**
Best overall response					
BRAF mutation					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	2 (10.0)	0	0	0	2 (2.6)
Stable disease (SD)	1 (5.0)	7 (46.7)	6 (26.1)	4 (21.1)	18 (23.4)
Progressive disease (PD)	3 (15.0)	1 (6.7)	1 (4.3)	2 (10.5)	7 (9.1)
Unknown	0	0	0	0	0
Not assessed	3 (15.0)	1 (6.7)	4 (17.4)	4 (21.1)	12 (15.6)
BRAF wild-type					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	1 (4.3)	0	1 (1.3)
Stable disease (SD)	2 (10.0)	2 (13.3)	3 (13.0)	6 (31.6)	13 (16.9)
Progressive disease (PD)	5 (25.0)	1 (6.7)	3 (13.0)	0	9 (11.7)
Unknown	0	0	0	0	0
Not assessed	3 (15.0)	3 (20.0)	3 (13.0)	1 (5.3)	10 (13.0)
BRAF unspecified / unknown					
Complete response (CR)	0	0	0	1 (5.3)	1 (1.3)

	DLs 1 to 4 N=20 n (%)	DL 5 N=15 n (%)	DL 6 N=23 n (%)	DLs 7 and 7.1 N=19 n (%)	All patients N=77 n (%)
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	1 (5.0)	0	0	0	1 (1.3)
Progressive disease (PD)	0	0	1 (4.3)	1 (5.3)	2 (2.6)
Unknown	0	0	0	0	0
Not assessed	0	0	1 (4.3)	0	1 (1.3)
Total					
Complete response (CR)	0	0	0	1 (5.3)	1 (1.3)
Partial response (PR)	2 (10.0)	0	1 (4.3)	0	3 (3.9)
Stable disease (SD)	4 (20.0)	9 (60.0)	9 (39.1)	10 (52.6)	32 (41.6)
Progressive disease (PD)	8 (40.0)	2 (13.3)	5 (21.7)	3 (15.8)	18 (23.4)
Unknown	0	0	0	0	0
Not assessed	6 (30.0)	4 (26.7)	8 (34.8)	5 (26.3)	23 (29.9)
Best response					
CR or PR	2 (10.0)	0	1 (4.3)	1 (5.3)	4 (5.2)
CR, PR or SD	6 (30.0)	9 (60.0)	10 (43.5)	11 (57.9)	36 (46.8)
SD or better after 12 months	3 (15.0)	0	2 (8.7)	0	5 (6.5)
95% CI for the proportion CR, PR or SD	(9.9, 50.1)	(35.2, 84.8)	(23.2, 63.7)	(35.7, 80.1)	(35.6, 57.9)
95% CI for SD or better after 12 months	(0.0, 30.6)	(0.0, 0.0)	(0.0, 20.2)	(0.0, 0.0)	(1.0, 12.0)

Arm 3

Best overall response (central radiological assessment) by BRAF mutation status and dose level group - Arm 3 (Full Analysis Set)

	DL 1 N=3 n (%)	DL 2 N=7 n (%)	DL 3 N=5 n (%)	DL 4 N=1 n (%)	All patients N=16 n (%)
Best overall response					
BRAF mutation					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	0	0	1 (20.0)	0	1 (6.3)
Progressive disease (PD)	1 (33.3)	0	0	0	1 (6.3)
Unknown	0	0	0	0	0
Not assessed	1 (33.3)	1 (14.3)	0	0	2 (12.5)
BRAF wild-type					
Complete response (CR)	0	0	0	0	0

	DL 1 N=3 n (%)	DL 2 N=7 n (%)	DL 3 N=5 n (%)	DL 4 N=1 n (%)	All patients N=16 n (%)
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	0	1 (14.3)	1 (20.0)	0	2 (12.5)
Progressive disease (PD)	1 (33.3)	5 (71.4)	3 (60.0)	1 (100)	10 (62.5)
Unknown	0	0	0	0	0
Not assessed	0	0	0	0	0
BRAF unspecified / unknown					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	0	0	0	0	0
Progressive disease (PD)	0	0	0	0	0
Unknown	0	0	0	0	0
Not assessed	0	0	0	0	0
Total					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	0	0	0
Stable disease (SD)	0	1 (14.3)	2 (40.0)	0	3 (18.8)
Progressive disease (PD)	2 (66.7)	5 (71.4)	3 (60.0)	1 (100)	11 (68.8)
Unknown	0	0	0	0	0
Not assessed	1 (33.3)	1 (14.3)	0	0	2 (12.5)
Best response					
CR or PR	0	0	0	0	0
CR, PR or SD	0	1 (14.3)	2 (40.0)	0	3 (18.8)
SD or better after 12 months	0	0	0	0	0
95% CI for the proportion CR, PR or SD	(0, 0)	(0, 40.2)	(0, 82.9)	(0, 0)	(0, 37.9)
95% CI for SD or better after 12 months	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)

The BRAF mutation status data for arm 3 is not validated.

Arm 5

Best overall response (central radiological assessment) by BRAF mutation status and dose level group - Arm 5 (Full Analysis Set)

	DL 1 N=3 n (%)	DL 2 N=6 n (%)	All patients N=9 n (%)
Best overall response			
BRAF mutation			
Complete response (CR)	0	0	0
Partial response (PR)	0	0	0

	DL 1 N=3 n (%)	DL 2 N=6 n (%)	All patients N=9 n (%)
Stable disease (SD)	2 (66.7)	3 (50.0)	5 (55.6)
Progressive disease (PD)	0	0	0
Unknown	0	0	0
Not assessed	1 (33.3)	0	1 (11.1)
BRAF wild-type			
Complete response (CR)	0	0	0
Partial response (PR)	0	0	0
Stable disease (SD)	0	1 (16.7)	1 (11.1)
Progressive disease (PD)	0	0	0
Unknown	0	0	0
Not assessed	0	0	0
BRAF unspecified / unknown			
Complete response (CR)	0	0	0
Partial response (PR)	0	0	0
Stable disease (SD)	0	1 (16.7)	1 (11.1)
Progressive disease (PD)	0	0	0
Unknown	0	0	0
Not assessed	0	1 (16.7)	1 (11.1)
Total			
Complete response (CR)	0	0	0
Partial response (PR)	0	0	0
Stable disease (SD)	2 (66.7)	5 (83.3)	7 (77.8)
Progressive disease (PD)	0	0	0
Unknown	0	0	0
Not assessed	1 (33.3)	1 (16.7)	2 (22.2)
Best response			
CR or PR	0	0	0
CR, PR or SD	2 (66.7)	5 (83.3)	7 (77.8)
SD or better after 12 months	0	0	0
95% CI for the proportion CR, PR or SD	(13.3, 100)	(53.5, 100)	(50.6, 100)
95% CI for SD or better after 12 months	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)

The BRAF mutation status data for arm 5 is not validated.

Summary of Safety

Safety Results - Arms 2, 3 and 5

Dose limiting toxicities

Dose limiting toxicities occurring during the first 28 days of treatment by dose level in Arm 2 (Dose determining set 1)

Abnormality Type	DL 1 N=3 n (%)	DL 2 N=3 n (%)	DL 3 N=4 n (%)	DL 4 N=8 n (%)	DL 5 N=15 n (%)	DL 6 N=20 n (%)	DL 7 N=7 n (%)	DL 7.1 N=10 n (%)
No. patients with DLT	0	0	0	0	0	2 (10.0)	2 (28.6)	2 (20.0)
DLT Event:								
ATAXIA GRADE 1	0	0	0	0	0	0	1 (14.3)	0
DIARRHEA GRD 3	0	0	0	0	0	0	1 (14.3)	0
LIPASE ELEVATED (GRADE 3)	0	0	0	0	0	1 (5.0)	0	0
PULMONARY EMBOLISM GRADE 4	0	0	0	0	0	0	0	2 (20.0)
TOXIC RETINOPATHY GRADE 2	0	0	0	0	0	1 (5.0)	0	0
VISION-FLOATERS GRADE 3	0	0	0	0	0	0	1 (14.3)	0

* Note that the type of dose limiting toxicities may not add up to the total if there are patients that experience multiple DLTs

Dose limiting toxicities occurring during the first 28 days of treatment by dose level in Arm 3 (Dose determining set 1)

Abnormality Type	DL 1 N=3 n (%)	DL 2 N=6 n (%)	DL 3 N=5 n (%)	DL 4 N=1 n (%)

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**********************************************
**   No records match the selection criteria   **
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* Note that the type of dose limiting toxicities may not add up to the total if there are patients that experience multiple DLTs

Dose limiting toxicities occurring during the first 28 days of treatment by dose level in Arm 5 (Dose determining set 1)

Abnormality Type	DL 1 N=3 n (%)	DL 2 N=6 n (%)
No. patients with DLT	0	1 (16.7)
DLT Event:		
ELEVATED LIPASE	0	1 (16.7)

* Note that the type of dose limiting toxicities may not add up to the total if there are patients that experience multiple DLTs

Incidence of AEs by primary system organ class (Safety set)

Primary system organ class	Arm 1 N = 2 n (%)	Arm 2 N = 77 n (%)	Arm 3 N = 16 n (%)	Arm 5 N = 9 n (%)
Patients with at least one AE	2 (100)	77 (100)	16 (100)	9 (100)
Gastrointestinal disorders	1 (50)	59 (76.6)	12 (75.0)	7 (77.8)
General disorders and administration site conditions	2 (100)	56 (72.7)	9 (56.3)	6 (66.7)
Investigations	1 (50)	47 (61.0)	3 (18.8)	5 (55.6)
Nervous system disorders	1 (50)	44 (57.1)	5 (31.3)	5 (55.6)
Musculoskeletal and connective tissue disorders	2 (100)	43 (55.8)	12 (75.0)	7 (77.8)
Eye disorders	0	39 (50.6)	1 (6.3)	4 (44.4)
Metabolism and nutrition disorders	1 (50)	35 (45.5)	8 (50.0)	3 (33.3)
Respiratory, thoracic and mediastinal disorders	0	34 (44.2)	4 (25.0)	4 (44.4)
Skin and subcutaneous tissue disorders	1 (50)	28 (36.4)	2 (12.5)	6 (66.7)
Blood and lymphatic system disorders	0	27 (35.1)	2 (12.5)	0
Infections and infestations	0	25 (32.5)	4 (25.0)	5 (55.6)
Vascular disorders	1 (50)	21 (27.3)	3 (18.8)	1 (11.1)
Neoplasms benign, malignant and unspecified (incl cysts & polyps)	0	16 (20.8)	1 (6.3)	1 (11.1)
Psychiatric disorders	1 (50)	15 (19.5)	5 (31.3)	1 (11.1)
Injury, poisoning and procedural complications	0	10 (13.0)	2 (12.5)	0
Renal and urinary disorders	0	9 (11.7)	1 (6.3)	0
Cardiac disorders	0	4 (5.2)	2 (12.5)	1 (11.1)
Immune system disorders	0	3 (3.9)	0	0
Ear and labyrinth disorders	0	2 (2.6)	1 (6.3)	0
Hepatobiliary disorders	0	2 (2.6)	1 (6.3)	0
Endocrine disorders	0	1 (1.3)	0	0
Reproductive system and breast disorders	0	1 (1.3)	0	1 (11.1)

Summary tables include AEs which started or worsened after Cycle 1 Day 1 and before last dose + 28 days. Listings include all AEs collected during the study.

AEs by SOC are presented in descending order of frequency in Arm 2.

Incidence of AEs by preferred term (at least 10% incidence in Arms 2 and 3; at least 2 patients in Arm 5) (Safety set)

Preferred term	Arm 2 N=77 n (%)	Arm 3 N=16 n (%)	Arm 5 N = 9 n (%)
Fatigue	48 (62.3)	7 (43.8)	5 (55.6)
Diarrhoea	34 (44.2)	3 (18.8)	5 (55.6)
Weight decreased	32 (41.6)	0	1 (11.1)
Nausea	26 (33.8)	7 (43.8)	4 (44.4)
Decreased appetite	24 (31.2)	5 (31.3)	0
Vomiting	21 (27.3)	4 (25.0)	2 (22.2)
Vitreous floaters	21 (27.3)	0	1 (11.1)
Thrombocytopenia	20 (26.0)	0	0
Dysgeusia	19 (24.7)	0	1 (11.1)
Photopsia	19 (24.7)	0	2 (22.2)
Muscle spasms	17 (22.1)	0	2 (22.2)
Abdominal pain	16 (20.8)	2 (12.5)	2 (22.2)
Cough	14 (18.2)	2 (12.5)	0
Constipation	13 (16.9)	4 (25.0)	2 (22.2)
Headache	13 (16.9)	0	2 (22.2)
Hypertension	13 (16.9)	0	1 (11.1)
Arthralgia	12 (15.6)	2 (12.5)	0
Pain in extremity	12 (15.6)	4 (25.0)	4 (44.4)
Back pain	11 (14.3)	6 (37.5)	3 (33.3)
Dyspnoea	11 (14.3)	2 (12.5)	1 (11.1)
Oedema peripheral	11 (14.3)	0	1 (11.1)
Rash	11 (14.3)	0	1 (11.1)
Musculoskeletal pain	10 (13.0)	0	1 (11.1)
Dehydration	9 (11.7)	3 (18.8)	2 (22.2)
Dizziness	9 (11.7)	0	4 (44.4)
Alanine aminotransferase increased	9 (11.7)	0	0
Lipase increased	9 (11.7)	0	3 (33.3)
Hemoglobin decreased	8 (10.4)	0	1 (11.1)
Myalgia	8 (10.4)	0	0
Insomnia	6 (7.8)	3 (18.8)	1 (11.1)
Pyrexia	6 (7.8)	3 (18.8)	3 (33.3)
Non-cardiac chest pain	4 (5.2)	1 (6.3)	2 (22.2)
Oropharyngeal pain	4 (5.2)	0	2 (22.2)
Abdominal pain upper	4 (5.2)	2 (12.5)	1 (11.1)
Musculoskeletal chest pain	3 (3.9)	2 (12.5)	1 (11.1)

Preferred term	Arm 2 N=77 n (%)	Arm 3 N=16 n (%)	Arm 5 N = 9 n (%)
Upper respiratory tract infection	3 (3.9)	2 (12.5)	1 (11.1)
Chills	3 (3.9)	1 (6.3)	2 (22.2)
Dysphonia	2 (2.6)	0	2 (22.2)
Musculoskeletal stiffness	2 (2.6)	2 (12.5)	0
Increased upper airway secretion	1 (1.3)	2 (12.5)	0
Somnolence	0	2 (12.5)	0
Anxiety	0	2 (12.5)	0

Summary tables include AEs which started or worsened after Cycle 1 Day 1 and before last dose + 28 days. Listings include all AEs collected during the study.
Preferred terms are sorted in descending frequency, as reported in Arm 2 column.

Deaths or other serious or significant adverse events (Safety set)

	Arm 1 N=2 n (%)	Arm 2 N=77 n (%)	Arm 3 N=16 n (%)	Arm 5 N=9 n (%)
Deaths reported within 28 days of last dose of study drug	0	5 (6.5)		1 (11.1)
SAEs	0	30 (39.0)	6 (37.5)	2 (22.2)
Discontinued treatment due to AEs	0	19 (24.7)	0	0
AEs requiring dose adjustment/interruption	0	32 (41. 6)	1 (6.3)	5 (55.6)

Other Relevant Findings

Not applicable

Conclusion:

The primary objective of the study was achieved with the identification of the MTD of RAF265 when given daily, and determination of its safety and PK profile when administered as single-agent therapy in patients with locally advanced or metastatic melanoma. It is important to note that the MTD (48 mg continuous daily dosing schedule) was established based on safety only. A tablet formulation of RAF265 was introduced during the study with acceptable bioavailability.

In general, RAF265 was safe and well tolerated at the recommended doses. No deaths occurred that were suspected to be related to RAF265. Only 7 of 96 (7.3%) patients reported dose-limiting toxicities.

Some evidence of efficacy was observed across all dose levels and regardless of BRAF mutation status, suggesting mechanisms in addition to BRAF inhibition. However, overall the level of efficacy was not high enough to warrant further clinical development in the chosen patient population and indication with the identified schedule and doses.

Date of Clinical Trial Report

Interim CSR: 15-May-2013

Final/Close-out CSR: 22-May-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

28-May-2015

Date of Latest Update

Not applicable

Reason for Update

Not applicable