NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Dabrafenib and Trametinib

Trial Indication(s)

Melanoma

Protocol Number

116513/CDRB436B2302

Protocol Title

A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: June 2012 (Actual)
Primary Completion Date: April 2014 (Actual)
Study Completion Date: April 2019 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a two-arm, open-label, randomized, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib. A total of 704 subjects were randomized in a ratio of 1:1 to receive combination therapy (352 subjects) or vemurafenib treatment (352 subjects). Subjects were stratified by LDH level (> the ULN versus ≤ ULN) and BRAF mutation (V600E versus V600K). Subjects in both the arms continued treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. An interim analysis for OS, performed as planned in the protocol with a cut-off date of 17-Apr-2014, demonstrated a statistically significant and clinically meaningful OS benefit in favor of the dabrafenib and trametinib combination compared to vemurafenib. Thus, the primary objective of the study was met. As a result, the IDMC recommended that no further IDMC review was required and IDMC review should be stopped. The protocol was amended on 07-Aug-2014 which allowed subjects who were still receiving vemurafenib to cross over to the dabrafenib and trametinib combination arm, including those subjects who were still receiving vemurafenib monotherapy treatment after disease progression. A washout period of a minimum of 7 days was considered prior to initiating dabrafenib in combination with trametinib. Subjects who experienced disease progression on the vemurafenib monotherapy arm, discontinued vemurafenib monotherapy, and subsequently received another anticancer therapy were ineligible for cross over to the dabrafenib and trametinib combination arm. After study treatment discontinuation, subjects were followed for survival and disease progression as applicable. This study completed once all the subjects had at least the 5-years of follow-up

Centers

207 centers in 28 countries: Germany(25), Canada(12), Netherlands(6), Spain(10), Brazil(3), United Kingdom(7), United States(36), New Zealand(2), Sweden(2), Hungary(7), Belgium(8), Argentina(6), France(11), Italy(8), Ireland(6), Ukraine(7), Czech Republic(5), Russian Federation(7), Finland(4), Norway(3), Taiwan(3), Denmark(3), Austria(5), Australia(9), Korea, Republic of(3), Poland(4), Switzerland(3), Israel(2)

Objectives:

Primary objective: to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib monotherapy with respect to OS for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

Secondary objectives: to compare dabrafenib and trametinib combination therapy with vemurafenib monotherapy for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma with respect to PFS, ORR, and DoR.

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

- Dabrafenib, 150 mg, b.i.d orally plus trametinib, 2.0 mg, once daily orally (combination therapy)
- Vemurafenib 960 mg b.i.d orally (monotherapy)

Statistical Methods

OS and PFS were summarized using Kaplan-Meier curves and a table was produced for both, including the estimates and 95% CIs for medians and quartiles in each treatment arm. The landmark Kaplan-Meier estimates at 24, 36, 48 and 60 months were also included in the summary. The hazard ratio was estimated using the Pike estimator. The CIs for median and quartiles used the Brookmeyer-Crowley method. Best overall response (CR and PR) and a 95% CI was calculated for each arm. Duration of response was calculated only for subjects who achieved a best response of CR or PR, and censoring rules were the same as for PFS. Disease progression was based on assessments by the investigator using radiologic evidence. Duration of response were summarized using Kaplan-Meier estimates of median and quartiles with corresponding 95% CIs.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- >= 18 years of age
- Stage IIIc or Stage IV BRAF V600E/K cutaneous melanoma
- Measurable disease according to RECIST 1.1
- Women of childbearing potential with negative serum pregnancy test prior to randomisation
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Adequate baseline organ function

Key Exclusion Criteria:
- Any prior use of a BRAF or MEK inhibitor
- Prior systemic anti-cancer treatment in the advanced or metastatic setting; prior systemic treatment in the adjuvant setting is allowed
- History of another malignancy (except subjects who have been disease free for 3 years or with a history of completely resected non-melanoma skin cancer)

- Known HIV, HBV, HCV infection (except chronic or cleared HBV and HCV infection which will be allowed)
- Brain metastases (except if all known lesions were previously treated with surgery or stereotactic radiosurgery and lesions, if still present, are confirmed stable for >= 12 weeks prior to randomisation or if no longer present are confirmed no evidence of disease for >= 12 weeks, and are asymptomatic with no corticosteroid requirements for >= 4 weeks prior to randomisation, and no enzyme inducing anticonvulsants for >= 4 weeks prior to randomisation
- History or evidence of cardiovascular risk (LVEF < LLN; QTcB >= 480 msec; blood pressure or systolic >=140 mmHg or diastolic >= 90 mmHg which cannot be controlled by anti-hypertensive therapy)
- History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)

Participant Flow Table

Randomized Phase

	Dabrafenib plus Trametinib	Vemurafenib	Crossover Dabrafenib plus Trametinib	Total
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.	
Started	352	352	0	704
Safety Set	350	349	0	699
Completed	1	0	0	1
Not Completed	351	352	0	703
Death	217	238	0	455
Sponsor Decision	93	39	0	132
Lost to Follow-up	9	16	0	25
Physician Decision	6	3	0	9
Withdrawal by Subject	26	22	0	48
Crossover to Dabrafenib&Trametinib	0	34	0	34

Crossover Phase

	Dabrafenib plus Trametinib	Vemurafenib	Crossover Dabrafenib plus Trametinib	Total
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.	
Started	0	0	34	34
Completed	0	0	0	0
Not Completed	0	0	34	34
Death	0	0	11	11
Withdrawal by Subject	0	0	3	3
Sponsor Decision	0	0	20	20

Baseline Characteristics

	Dabrafenib plus Trametinib	Vemurafenib	Total
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	
Number of Participants [units: participants]	352	352	704
Age Continuous (units: Years) Mean ± Standard Deviation			
	54.1±13.83	54.3±14.06	54.2±13.94

GenderNIH (units:) Count of Participants (Not Applicable)			
Female	144	172	316
Male	208	180	388
Race/Ethnicity, Customized (units: Participants)			
Asian - East Asian Heritage	8	8	16
White - Arabic/North African Heritage	4	2	6
White - White/Caucasian/European Heritage	339	339	678
White - Mixed Race	1	0	1
Mixed Race	0	1	1
African American/African Heritage	0	1	1
American Indian or Alaskan Native	0	1	1

Summary of Efficacy

Primary Outcome Result(s)

Overall Survival (OS)

(Time Frame: From the date of randomization until date of death due to any cause (up to approximately 6 years))

	Dabrafenib plus Trametinib	Vemurafenib
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.
Number of Participants Analyzed [units: participants]	352	352
Overall Survival (OS) (units: Months) Median (95% Confidence Interval)		
	26.0 (22.1 to 33.8)	17.8 (15.6 to 20.7)

Statistical Analysis

Groups	Dabrafenib plus Trametinib, Vemurafenib	
Hazard Ratio (HR)	0.70	Hazard ratios are estimated using a Pike estimator.
95 % Confidence Interval 2-Sided	0.58 to 0.83	

Secondary Outcome Result(s)

Progression-Free Survival (PFS), as assessed by the Investigator

(Time Frame: From randomization until the earliest date of disease progression (PD) or death due to any cause (up to approximately 6 years))

	Dabrafenib plus Trametinib	Vemurafenib
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.
Number of Participants Analyzed [units: participants]	352	352
Progression-Free Survival (PFS), as assessed by the Investigator (units: Months) Median (95% Confidence Interval)		
	12.1 (9.7 to 14.7)	7.3 (6.0 to 8.1)

Statistical Analysis

Groups	Dabrafenib plus Trametinib, Vemurafenib	
Hazard Ratio (HR)	0.62	Hazard ratios are estimated using a Pike estimator.
95 % Confidence Interval 2-Sided	0.52 to 0.73	

Overall Response Rate (ORR) during randomized phase, as assessed by the Investigator

(Time Frame: From randomization until the first documented complete response or partial response (up to approximately 6 years))

	Dabrafenib plus Trametinib	Vemurafenib
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.

Number of Participants Analyzed [units: participants]	351	350
Overall Response Rate (ORR) during randomized phase, as assessed by the Investigator (units: Percentage of Participants) Number (95% Confidence Interval)		
	68 (62.3 to 72.4)	53 (47.2 to 57.9)

Duration of Response (DOR), as assessed by the Investigator

(Time Frame: From the time of the first documented response (CR or PR) until disease progression (up to approximately 6 years))

	Dabrafenib plus Trametinib	**Vemurafenib**
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.
Number of Participants Analyzed [units: participants]	237	185
Duration of Response (DOR), as assessed by the Investigator (units: Months) Median (95% Confidence Interval)		
	13.8 (11.3 to 18.6)	8.5 (7.4 to 9.3)

Statistical Analysis

Groups	Dabrafenib plus Trametinib, Vemurafenib
Hazard Ratio (HR)	0.64
95 % Confidence Interval 2-Sided	0.51 to 0.81

Post-Hoc Outcome Result(s):

All collected deaths

(Time Frame: up to 28 days before Day 1 (Screening), up to 81.1 months (on-treatment), up to approximately 6 years (study duration))

	Dabrafenib plus Trametinib	Vemurafenib	Crossover Dabrafenib + Trametinib
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.
Number of Participants Analyzed [units: participants]	351	349	34
All collected deaths (units: Participants) Count of Participants (Not Applicable)			
Pre-treatment deaths	1 (.28%)	0 (%)	0 (%)
On-treatment deaths	44 (12.54%)	47 (13.47%)	2 (5.88%)
Post-treatment deaths	172 (49%)	191 (54.73%)	9 (26.47%)
All deaths	216 (61.54%)	238 (68.19%)	11 (32.35%)

Summary of Safety

Safety Results

All-Cause Mortality

	Dabrafenib plus Trametinib N = 350	Vemurafenib N = 349	Crossover Dabrafenib plus Trametinib N = 34	All Patients N = 699
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or withdrawal of consent.	With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.	All randomized patients who received at least one dose of study treatment.
Total participants affected	216 (61.71%)	238 (68.19%)	11 (32.35%)	465 (66.52%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from First Patient First Treatment (FPFT) up to 30 days after study drug discontinuation, for a maximum duration of 81.1 months (treatment duration ranged from 0.1 to 80.1 months). In addition, new malignancies and AEs possibly related to study treatment were collected up to approximately 6 years
Additional Description	Any clinically significant sign or symptom that occurs during the study treatment and 30 days post treatment follow up. In addition, new malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	Dabrafenib plus Trametinib N = 350	Vemurafenib N = 349	Crossover Dabrafenib plus Trametinib N = 34	All Patients N = 699
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and	Vemurafenib 960 mg orally BID until disease progression,	With Protocol Amendment 7, patients still receiving study treatment on the	All randomized

	Trametinib 2 mg orally once daily until disease progression, death, unacceptable toxicity, or withdrawal of consent.	death, unacceptable toxicity, or withdrawal of consent.	Vemurafenib monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.	patients who received at least one dose of study treatment.
Total participants affected	172 (49.14%)	139 (39.83%)	15 (44.12%)	319 (45.64%)
Blood and lymphatic system disorders				
Anaemia	4 (1.14%)	2 (0.57%)	1 (2.94%)	7 (1.00%)
Febrile neutropenia	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Leukopenia	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Neutropenia	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Thrombocytopenia	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Cardiac disorders				
Acute coronary syndrome	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Acute myocardial infarction	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Angina unstable	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Arrhythmia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Arteriosclerosis coronary artery	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Atrial fibrillation	3 (0.86%)	4 (1.15%)	0 (0.00%)	7 (1.00%)
Left ventricular dysfunction	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Myocardial infarction	2 (0.57%)	2 (0.57%)	0 (0.00%)	4 (0.57%)
Pericardial effusion	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pericarditis	0 (0.00%)	5 (1.43%)	0 (0.00%)	5 (0.72%)
Sinus tachycardia	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)

Supraventricular tachycardia	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Tachyarrhythmia	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Tachycardia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Ear and labyrinth disorders				
Vertigo	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Eye disorders				
Cataract	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Chorioretinopathy	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Eye haemorrhage	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Glaucoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Retinal degeneration	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Retinal tear	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Retinal vein occlusion	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Uveitis	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Vision blurred	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Vitreous detachment	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	1 (0.29%)	1 (2.94%)	2 (0.29%)
Abdominal pain upper	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Constipation	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Diarrhoea	3 (0.86%)	0 (0.00%)	0 (0.00%)	3 (0.43%)
Diverticulum intestinal haemorrhagic	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Duodenal perforation	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Duodenal ulcer	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Duodenal ulcer haemorrhage	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Gastric ulcer haemorrhage	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Gastrointestinal pain	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Haemorrhoidal haemorrhage	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Ileus	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Inguinal hernia	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Intestinal pseudo-obstruction	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Large intestine perforation	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Leukoplakia oral	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Nausea	5 (1.43%)	1 (0.29%)	0 (0.00%)	6 (0.86%)
Pancreatitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Rectal polyp	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Umbilical hernia	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Vomiting	8 (2.29%)	1 (0.29%)	0 (0.00%)	9 (1.29%)
General disorders and administration site conditions				
Asthenia	3 (0.86%)	0 (0.00%)	0 (0.00%)	3 (0.43%)
Chest pain	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Chills	14 (4.00%)	0 (0.00%)	0 (0.00%)	14 (2.00%)
Fatigue	2 (0.57%)	1 (0.29%)	1 (2.94%)	4 (0.57%)

General physical health deterioration	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Inflammation	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Influenza like illness	3 (0.86%)	0 (0.00%)	0 (0.00%)	3 (0.43%)
Malaise	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Non-cardiac chest pain	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pyrexia	55 (15.71%)	6 (1.72%)	0 (0.00%)	61 (8.73%)
Hepatobiliary disorders				
Bile duct obstruction	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Cholecystitis	4 (1.14%)	2 (0.57%)	0 (0.00%)	6 (0.86%)
Cholelithiasis	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Gallbladder polyp	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Hepatitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Hepatocellular injury	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Hepatotoxicity	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Hypertransaminasaemia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Immune system disorders				
Drug hypersensitivity	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Hypersensitivity	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Infections and infestations				
Abdominal sepsis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Abscess soft tissue	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Appendicitis	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Bacteraemia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Biliary sepsis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Bronchitis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Cellulitis	5 (1.43%)	1 (0.29%)	0 (0.00%)	6 (0.86%)
Clostridium difficile colitis	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Corneal abscess	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Diverticulitis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Enterocolitis infectious	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Erysipelas	4 (1.14%)	0 (0.00%)	0 (0.00%)	4 (0.57%)
Escherichia sepsis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Gastroenteritis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Gastroenteritis viral	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Gastrointestinal infection	3 (0.86%)	2 (0.57%)	0 (0.00%)	5 (0.72%)
Haematoma infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Helicobacter infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Infection	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Influenza	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Kidney infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Lower respiratory tract infection	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Lung infection	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Meningitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Oesophageal candidiasis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Peritonitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pleural infection	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pneumonia	4 (1.14%)	6 (1.72%)	1 (2.94%)	10 (1.43%)
Post procedural infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Pyelonephritis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pyelonephritis acute	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Respiratory tract infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Sepsis	3 (0.86%)	0 (0.00%)	1 (2.94%)	4 (0.57%)
Sinusitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Skin infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Streptococcal sepsis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Tonsillitis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Urinary tract infection	10 (2.86%)	1 (0.29%)	1 (2.94%)	12 (1.72%)
Urosepsis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Viral infection	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Injury, poisoning and procedural complications				
Clavicle fracture	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Fall	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Femur fracture	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Pelvic fracture	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Post procedural complication	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Radiation necrosis	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Radius fracture	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Subdural haematoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Thoracic vertebral fracture	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Toxicity to various agents	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)

Vascular pseudoaneurysm	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Wound dehiscence	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Investigations				
Alanine aminotransferase increased	6 (1.71%)	9 (2.58%)	0 (0.00%)	15 (2.15%)
Aspartate aminotransferase increased	3 (0.86%)	5 (1.43%)	0 (0.00%)	8 (1.14%)
Blood alkaline phosphatase increased	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Blood bilirubin increased	2 (0.57%)	6 (1.72%)	0 (0.00%)	8 (1.14%)
Blood creatine phosphokinase increased	3 (0.86%)	0 (0.00%)	0 (0.00%)	3 (0.43%)
Blood creatinine increased	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Ejection fraction decreased	31 (8.86%)	1 (0.29%)	2 (5.88%)	34 (4.86%)
Hepatic enzyme increased	4 (1.14%)	6 (1.72%)	0 (0.00%)	10 (1.43%)
International normalised ratio increased	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Transaminases increased	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Troponin I increased	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Metabolism and nutrition disorders				
Dehydration	8 (2.29%)	2 (0.57%)	0 (0.00%)	10 (1.43%)
Hypercalcaemia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Hyperglycaemia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Hyponatraemia	5 (1.43%)	0 (0.00%)	0 (0.00%)	5 (0.72%)
Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Arthritis	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Chest wall haematoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Intervertebral disc protrusion	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Muscular weakness	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Musculoskeletal pain	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Osteoarthritis	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Pain in extremity	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Rhabdomyolysis	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Acute myeloid leukaemia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Astrocytoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Basal cell carcinoma	13 (3.71%)	5 (1.43%)	2 (5.88%)	20 (2.86%)
Benign neoplasm of adrenal gland	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Bowen's disease	2 (0.57%)	3 (0.86%)	0 (0.00%)	5 (0.72%)
Carcinoma in situ	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Carcinoma in situ of skin	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Colon adenoma	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)

Intracranial tumour haemorrhage	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Keratoacanthoma	3 (0.86%)	23 (6.59%)	1 (2.94%)	26 (3.72%)
Lentigo maligna	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Lip squamous cell carcinoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Lung adenocarcinoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Lung neoplasm malignant	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Lymphoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Malignant melanoma	2 (0.57%)	7 (2.01%)	0 (0.00%)	9 (1.29%)
Malignant melanoma in situ	0 (0.00%)	2 (0.57%)	0 (0.00%)	2 (0.29%)
Meningioma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Metastases to central nervous system	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Metastatic malignant melanoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Neoplasm	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Neoplasm malignant	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Prostatic adenoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Rectal adenocarcinoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Renal cell carcinoma	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Skin papilloma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Squamous cell carcinoma	3 (0.86%)	27 (7.74%)	0 (0.00%)	30 (4.29%)
Squamous cell carcinoma of skin	3 (0.86%)	30 (8.60%)	0 (0.00%)	33 (4.72%)

Superficial spreading melanoma stage unspecified	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Transitional cell carcinoma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Nervous system disorders				
Ataxia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Brain stem haemorrhage	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Cerebral haemorrhage	3 (0.86%)	1 (0.29%)	0 (0.00%)	4 (0.57%)
Cerebral ischaemia	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Cerebrovascular accident	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Dizziness	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Epilepsy	1 (0.29%)	1 (0.29%)	1 (2.94%)	2 (0.29%)
Generalised tonic-clonic seizure	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Haemorrhage intracranial	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Haemorrhagic stroke	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Headache	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Hepatic encephalopathy	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Hypoaesthesia	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Loss of consciousness	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Lumbar radiculopathy	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Migraine	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Partial seizures	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Seizure	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Syncope	1 (0.29%)	0 (0.00%)	1 (2.94%)	2 (0.29%)

Transient ischaemic attack	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Tremor	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Psychiatric disorders				
Confusional state	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Mental status changes	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Renal and urinary disorders				
Acute kidney injury	2 (0.57%)	1 (0.29%)	0 (0.00%)	3 (0.43%)
Calculus urinary	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Nephrolithiasis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Nephropathy toxic	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Prerenal failure	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Renal failure	4 (1.14%)	0 (0.00%)	0 (0.00%)	4 (0.57%)
Urethral stenosis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Reproductive system and breast disorders				
Ovarian cyst	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Uterine haemorrhage	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Respiratory, thoracic and mediastinal disorders				
Asthma	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Cough	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Dyspnoea	2 (0.57%)	2 (0.57%)	0 (0.00%)	4 (0.57%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Haemoptysis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Haemothorax	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Interstitial lung disease	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Pleural effusion	0 (0.00%)	3 (0.86%)	0 (0.00%)	3 (0.43%)
Pneumonia aspiration	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Pneumonitis	2 (0.57%)	0 (0.00%)	1 (2.94%)	3 (0.43%)
Pulmonary embolism	6 (1.71%)	0 (0.00%)	1 (2.94%)	7 (1.00%)
Pulmonary oedema	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Skin and subcutaneous tissue disorders				
Actinic keratosis	0 (0.00%)	2 (0.57%)	1 (2.94%)	3 (0.43%)
Chronic cutaneous lupus erythematosus	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Dermatitis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Dermatitis bullous	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Erythema	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Erythema nodosum	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Purpura	2 (0.57%)	0 (0.00%)	0 (0.00%)	2 (0.29%)
Rash	3 (0.86%)	3 (0.86%)	0 (0.00%)	6 (0.86%)
Rash erythematous	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Rash maculo-papular	1 (0.29%)	2 (0.57%)	0 (0.00%)	3 (0.43%)
Skin lesion	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Vascular disorders				
Aortic aneurysm	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Deep vein thrombosis	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)
Embolism	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Haemorrhage	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Hypertension	1 (0.29%)	1 (0.29%)	0 (0.00%)	2 (0.29%)
Hypotension	5 (1.43%)	0 (0.00%)	0 (0.00%)	5 (0.72%)
Lymphocele	0 (0.00%)	1 (0.29%)	0 (0.00%)	1 (0.14%)
Lymphoedema	0 (0.00%)	0 (0.00%)	1 (2.94%)	1 (0.14%)
Varicose vein	1 (0.29%)	0 (0.00%)	0 (0.00%)	1 (0.14%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from First Patient First Treatment (FPFT) up to 30 days after study drug discontinuation, for a maximum duration of 81.1 months (treatment duration ranged from 0.1 to 80.1 months). In addition, new malignancies and AEs possibly related to study treatment were collected up to approximately 6 years
Additional Description	Any clinically significant sign or symptom that occurs during the study treatment and 30 days post treatment follow up. In addition, new malignancies and AEs possibly related to study treatment were collected even if they occurred more than 30 days post-treatment.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Dabrafenib plus Trametinib N = 350	**Vemurafenib N = 349**	**Crossover Dabrafenib plus Trametinib N = 34**	**All Patients N = 699**
Arm/Group Description	Dabrafenib 150 milligrams (mg) orally twice daily (BID) and Trametinib 2 mg orally once daily	Vemurafenib 960 mg orally BID until disease progression, death, unacceptable toxicity, or	With Protocol Amendment 7, patients still receiving study treatment on the Vemurafenib	All randomized patients who received at least one dose of study treatment.

	until disease progression, death, unacceptable toxicity, or withdrawal of consent.	withdrawal of consent.	monotherapy arm were allowed to cross over to the Dabrafenib and Trametinib combination arm.	
Total participants affected	338 (96.57%)	341 (97.71%)	32 (94.12%)	679 (97.14%)
Blood and lymphatic system disorders				
Anaemia	29 (8.29%)	20 (5.73%)	3 (8.82%)	52 (7.44%)
Leukopenia	17 (4.86%)	7 (2.01%)	6 (17.65%)	29 (4.15%)
Lymphopenia	9 (2.57%)	9 (2.58%)	2 (5.88%)	20 (2.86%)
Neutropenia	37 (10.57%)	6 (1.72%)	9 (26.47%)	51 (7.30%)
Thrombocytopenia	11 (3.14%)	2 (0.57%)	3 (8.82%)	16 (2.29%)
Ear and labyrinth disorders				
Tinnitus	5 (1.43%)	3 (0.86%)	2 (5.88%)	10 (1.43%)
Eye disorders				
Vision blurred	23 (6.57%)	18 (5.16%)	1 (2.94%)	42 (6.01%)
Gastrointestinal disorders				
Abdominal pain	41 (11.71%)	33 (9.46%)	3 (8.82%)	75 (10.73%)
Abdominal pain upper	38 (10.86%)	36 (10.32%)	4 (11.76%)	78 (11.16%)
Constipation	58 (16.57%)	25 (7.16%)	7 (20.59%)	89 (12.73%)
Diarrhoea	131 (37.43%)	137 (39.26%)	5 (14.71%)	268 (38.34%)
Dry mouth	27 (7.71%)	8 (2.29%)	1 (2.94%)	36 (5.15%)

Dyspepsia	20 (5.71%)	15 (4.30%)	3 (8.82%)	37 (5.29%)
Haemorrhoids	4 (1.14%)	7 (2.01%)	3 (8.82%)	14 (2.00%)
Nausea	125 (35.71%)	131 (37.54%)	8 (23.53%)	261 (37.34%)
Vomiting	111 (31.71%)	57 (16.33%)	4 (11.76%)	172 (24.61%)
General disorders and administration site conditions				
Asthenia	65 (18.57%)	62 (17.77%)	8 (23.53%)	131 (18.74%)
Chills	113 (32.29%)	28 (8.02%)	6 (17.65%)	147 (21.03%)
Fatigue	116 (33.14%)	116 (33.24%)	1 (2.94%)	232 (33.19%)
Hypothermia	2 (0.57%)	1 (0.29%)	2 (5.88%)	4 (0.57%)
Influenza like illness	36 (10.29%)	13 (3.72%)	2 (5.88%)	51 (7.30%)
Malaise	16 (4.57%)	8 (2.29%)	2 (5.88%)	24 (3.43%)
Oedema peripheral	61 (17.43%)	45 (12.89%)	3 (8.82%)	108 (15.45%)
Pain	18 (5.14%)	15 (4.30%)	2 (5.88%)	35 (5.01%)
Peripheral swelling	25 (7.14%)	12 (3.44%)	3 (8.82%)	40 (5.72%)
Pyrexia	184 (52.57%)	72 (20.63%)	16 (47.06%)	267 (38.20%)
Infections and infestations				
Angular cheilitis	3 (0.86%)	0 (0.00%)	2 (5.88%)	5 (0.72%)
Conjunctivitis	14 (4.00%)	37 (10.60%)	1 (2.94%)	52 (7.44%)
Folliculitis	18 (5.14%)	25 (7.16%)	1 (2.94%)	43 (6.15%)
Influenza	31 (8.86%)	9 (2.58%)	2 (5.88%)	41 (5.87%)
Nasopharyngitis	64 (18.29%)	32 (9.17%)	6 (17.65%)	100 (14.31%)
Onychomycosis	4 (1.14%)	1 (0.29%)	2 (5.88%)	7 (1.00%)
Pharyngitis	19 (5.43%)	7 (2.01%)	1 (2.94%)	27 (3.86%)
Pneumonia	4 (1.14%)	1 (0.29%)	4 (11.76%)	9 (1.29%)

Rhinitis	14 (4.00%)	8 (2.29%)	2 (5.88%)	24 (3.43%)
Upper respiratory tract infection	23 (6.57%)	14 (4.01%)	3 (8.82%)	40 (5.72%)
Urinary tract infection	31 (8.86%)	7 (2.01%)	3 (8.82%)	41 (5.87%)
Injury, poisoning and procedural complications				
Fall	6 (1.71%)	5 (1.43%)	2 (5.88%)	12 (1.72%)
Sunburn	5 (1.43%)	47 (13.47%)	0 (0.00%)	52 (7.44%)
Investigations				
Alanine aminotransferase increased	54 (15.43%)	54 (15.47%)	2 (5.88%)	110 (15.74%)
Aspartate aminotransferase increased	47 (13.43%)	42 (12.03%)	3 (8.82%)	92 (13.16%)
Blood alkaline phosphatase increased	30 (8.57%)	29 (8.31%)	0 (0.00%)	59 (8.44%)
Blood creatine phosphokinase increased	12 (3.43%)	4 (1.15%)	5 (14.71%)	20 (2.86%)
Blood creatinine increased	16 (4.57%)	36 (10.32%)	2 (5.88%)	53 (7.58%)
Blood lactate dehydrogenase increased	23 (6.57%)	9 (2.58%)	1 (2.94%)	33 (4.72%)
C-reactive protein increased	12 (3.43%)	1 (0.29%)	2 (5.88%)	15 (2.15%)
Gamma-glutamyltransferase increased	45 (12.86%)	35 (10.03%)	1 (2.94%)	81 (11.59%)

Neutrophil count decreased	15 (4.29%)	1 (0.29%)	2 (5.88%)	18 (2.58%)
Weight decreased	21 (6.00%)	42 (12.03%)	1 (2.94%)	64 (9.16%)
White blood cell count decreased	13 (3.71%)	3 (0.86%)	2 (5.88%)	18 (2.58%)
Metabolism and nutrition disorders				
Decreased appetite	47 (13.43%)	72 (20.63%)	6 (17.65%)	123 (17.60%)
Hyperglycaemia	20 (5.71%)	12 (3.44%)	3 (8.82%)	35 (5.01%)
Increased appetite	2 (0.57%)	1 (0.29%)	3 (8.82%)	6 (0.86%)
Musculoskeletal and connective tissue disorders				
Arthralgia	104 (29.71%)	182 (52.15%)	9 (26.47%)	288 (41.20%)
Back pain	43 (12.29%)	29 (8.31%)	5 (14.71%)	77 (11.02%)
Muscle spasms	47 (13.43%)	13 (3.72%)	4 (11.76%)	63 (9.01%)
Musculoskeletal chest pain	19 (5.43%)	10 (2.87%)	0 (0.00%)	29 (4.15%)
Musculoskeletal pain	24 (6.86%)	27 (7.74%)	4 (11.76%)	54 (7.73%)
Myalgia	76 (21.71%)	56 (16.05%)	8 (23.53%)	134 (19.17%)
Pain in extremity	50 (14.29%)	42 (12.03%)	2 (5.88%)	94 (13.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Melanocytic naevus	2 (0.57%)	21 (6.02%)	0 (0.00%)	23 (3.29%)
Skin papilloma	9 (2.57%)	85 (24.36%)	1 (2.94%)	95 (13.59%)
Nervous system disorders				
Balance disorder	4 (1.14%)	1 (0.29%)	2 (5.88%)	7 (1.00%)

Dizziness	46 (13.14%)	24 (6.88%)	3 (8.82%)	73 (10.44%)
Dysgeusia	23 (6.57%)	48 (13.75%)	2 (5.88%)	73 (10.44%)
Headache	123 (35.14%)	86 (24.64%)	8 (23.53%)	214 (30.62%)
Hypoaesthesia	9 (2.57%)	11 (3.15%)	2 (5.88%)	21 (3.00%)
Paraesthesia	17 (4.86%)	18 (5.16%)	0 (0.00%)	35 (5.01%)
Syncope	13 (3.71%)	4 (1.15%)	3 (8.82%)	19 (2.72%)
Psychiatric disorders				
Insomnia	22 (6.29%)	33 (9.46%)	0 (0.00%)	55 (7.87%)
Respiratory, thoracic and mediastinal disorders				
Cough	88 (25.14%)	40 (11.46%)	6 (17.65%)	132 (18.88%)
Dyspnoea	34 (9.71%)	29 (8.31%)	1 (2.94%)	64 (9.16%)
Epistaxis	32 (9.14%)	6 (1.72%)	4 (11.76%)	41 (5.87%)
Nasal dryness	3 (0.86%)	2 (0.57%)	2 (5.88%)	7 (1.00%)
Oropharyngeal pain	27 (7.71%)	19 (5.44%)	1 (2.94%)	47 (6.72%)
Skin and subcutaneous tissue disorders				
Actinic keratosis	10 (2.86%)	24 (6.88%)	2 (5.88%)	36 (5.15%)
Alopecia	26 (7.43%)	138 (39.54%)	0 (0.00%)	164 (23.46%)
Dermatitis acneiform	25 (7.14%)	20 (5.73%)	1 (2.94%)	46 (6.58%)
Dry skin	34 (9.71%)	70 (20.06%)	5 (14.71%)	106 (15.16%)
Eczema	28 (8.00%)	13 (3.72%)	4 (11.76%)	45 (6.44%)
Erythema	41 (11.71%)	44 (12.61%)	2 (5.88%)	86 (12.30%)
Hyperhidrosis	18 (5.14%)	4 (1.15%)	3 (8.82%)	25 (3.58%)
Hyperkeratosis	26 (7.43%)	103 (29.51%)	0 (0.00%)	129 (18.45%)
Keratosis pilaris	5 (1.43%)	44 (12.61%)	1 (2.94%)	50 (7.15%)

Night sweats	24 (6.86%)	8 (2.29%)	2 (5.88%)	33 (4.72%)
Palmar-plantar erythrodysaesthesia syndrome	10 (2.86%)	54 (15.47%)	1 (2.94%)	64 (9.16%)
Palmoplantar keratoderma	9 (2.57%)	21 (6.02%)	1 (2.94%)	31 (4.43%)
Photosensitivity reaction	17 (4.86%)	88 (25.21%)	0 (0.00%)	105 (15.02%)
Pruritus	40 (11.43%)	80 (22.92%)	0 (0.00%)	120 (17.17%)
Rash	95 (27.14%)	153 (43.84%)	4 (11.76%)	248 (35.48%)
Rash maculo-papular	12 (3.43%)	27 (7.74%)	1 (2.94%)	39 (5.58%)
Skin exfoliation	6 (1.71%)	11 (3.15%)	2 (5.88%)	19 (2.72%)
Skin lesion	13 (3.71%)	9 (2.58%)	2 (5.88%)	23 (3.29%)
Skin mass	5 (1.43%)	4 (1.15%)	2 (5.88%)	11 (1.57%)
Vascular disorders				
Hypertension	109 (31.14%)	83 (23.78%)	4 (11.76%)	195 (27.90%)
Lymphoedema	25 (7.14%)	6 (1.72%)	2 (5.88%)	33 (4.72%)

Other Relevant Findings

None

Conclusion:

- The results of the final descriptive analysis were consistent with the primary study results from the interim analysis.
- The data demonstrate a consistent and greater benefit of the combination therapy of dabrafenib (150 mg, b.i.d orally) plus trametinib (2.0 mg, once daily orally) than vemurafenib monotherapy (960 mg b.i.d orally) for subjects with unresectable or metastatic BRAF V600E or V600K mutation positive cutaneous melanoma.
- There was no new safety signal with longer follow-up.

- The combination regimen of dabrafenib and trametinib had an acceptable safety profile in subjects with unresectable or metastatic BRAF V600E or V600K mutation positive cutaneous melanoma, with AEs that are manageable with appropriate intervention.

Date of Clinical Trial Report

Final Clinical Study Report	???
Primary CSR	15-Jan-2015, contained the efficacy and safety results with a data cut-off date of 17 April 2014.