NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Trametinib (GSK1120212) + Dabrafenib (GSK2118436)

Trial Indication(s)

Unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma

Protocol Number

115306/CDRB436B2301

Protocol Title

A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy 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: May 2012 (Actual)
Primary Completion Date: August 2013 (Actual)
Study Completion Date: February 2019 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a two-arm, double-blinded, randomized, Phase III study comparing dabrafenib and trametinib combination therapy to dabrafenib administered with a placebo (dabrafenib monotherapy). Subjects with histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E/K mutation positive were screened for eligibility. Subjects who had prior systemic anti-cancer treatment in the advanced or metastatic setting were not eligible although prior systemic treatment in the adjuvant setting was allowed. Subjects were stratified according to the baseline lactate dehydrogenase level and BRAF genotype.

Dabrafenib and trametinib was administered orally at their recommended monotherapy doses of 150 mg b.i.d and 2 mg q.d., respectively. Subjects in the combination therapy arm received both agents; subjects in the dabrafenib monotherapy arm received dabrafenib and placebo. Treatment was continued in both arms until disease progression, death, unacceptable toxicity, or withdrawal of consent. After treatment discontinuation, subjects were followed for survival and disease progression as applicable to collect data for the secondary objective of OS. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.

Centers

121 centers in 14 countries: Germany(31), Spain(7), Australia(6), Canada(6), Argentina(3), Sweden(4), Italy(8), Greece(3), United Kingdom(11), United States(19), Ukraine(7), Russian Federation(4), France(9), Netherlands(3)

Objectives:

Objectives	Endpoints
Primary	
To establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib placebo (dabrafenib monotherapy) with respect to progression free survival (PFS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.	**PFS**: defined as the time from randomization until the earliest date of disease progression or death due to any cause
Secondary	
To compare dabrafenib and trametinib combination therapy with dabrafenib monotherapy for overall survival (OS) (key secondary), objective response rate (ORR), and duration of response (DOR).	**OS**: defined as the time from randomization until death due to any cause
	ORR: defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR)
	DOR: defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve an overall response.
To characterize the safety of dabrafenib and trametinib combination therapy, including incidences of squamous cell carcinoma (SCC) and other proliferative cutaneous lesions; and	Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiogram (ECG), echocardiogram (ECHO), chemistry and hematology laboratory values, incidence of SCC, and adverse events (AEs).
To characterize the concentrations of trametinib and of dabrafenib and its metabolites in the combination arm, dabrafenib and its metabolites in the dabrafenib monotherapy arm.	Concentrations of trametinib and of dabrafenib and its metabolites (GSK2285403, GSK2298683, and GSK2167542) in the combination arm and dabrafenib and its metabolites in the dabrafenib monotherapy arm.

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

Study treatments were administered orally as follows:

- Dabrafenib 150 mg, b.i.d orally plus trametinib 2 mg q.d. orally (Test drug)
- Dabrafenib 150 mg b.i.d plus placebo 2 mg (Reference)

Statistical Methods

Efficacy: The intent-to-treat (ITT) population was used for analysis of primary and secondary efficacy endpoints.

PFS and OS were summarized using Kaplan-Meier curves and a table was produced including the estimates and the 95% confidence intervals for medians and quartiles in each treatment arm. The hazard ratio was estimated using the Pike estimator. The confidence intervals for quantiles used the Brookmeyer-Crowley method. Disease progression was based on assessments by the investigator using radiologic evidence. The best response by investigator assessment was summarized for each treatment arm. Duration of response was calculated only for subjects who achieved a best response of CR or PR, and was summarized using Kaplan-Meier estimates of median and quartiles with corresponding 95% confidence intervals.

Safety: The safety population was used for all analyses of safety data, except for summaries of data in the crossover phase, which used the crossover population.

AEs were coded using MedDRA version 19.0 and CTCAE version 4.0 was used for toxicity grades. Summaries of all AEs, SAEs, drug-related AEs and AEs leading to permanent discontinuation of study treatment, dose reductions or dose interruptions were presented by preferred term. AESI were determined using the categories agreed by the safety management team at the time of data base lock.

All AEs and drug-related AEs were also presented by maximum toxicity grade.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV (metastatic), and determined to be BRAF V600E/K mutation-positive using the bioMerieux (bMx) investigational use only (IUO) THxID BRAF Assay (IDE: G120011). The assay will be conducted by a central reference laboratory. Subjects with ocular or mucosal melanoma are not eligible.
- The subject must have a radiologically measurable tumor
- The subject is able to carry out daily life activities without significant difficulty (ECOG performance status score of 0 or 1).
- Able to swallow and retain oral medication
- Sexually active subjects must use acceptable methods of contraception during the course of the study
- Adequate organ system function and blood counts

Exclusion Criteria:
- Prior treatment with a BRAF or a MEK inhibitor
- Prior systemic anti-cancer treatment for Stage IIIC (unresectable) or Stage IV (metastatic) melanoma. Prior systemic treatment in

the adjuvant setting is allowed. (Note: Ipilimumab treatment must end at least 8 weeks prior to randomization.)
- The subject has received major surgery or certain tyes of cancer therapy with 21 days of starting treatment
- Current use of prohibited medication listed in the protocol
- Left ventricular ejection fraction less than the lower limit of normal
- Uncontrolled blood pressurl
- History or current evidence of retinal vein occlusion or central serous retinopathy
- Brain metastases unless previously treated with surgery or stereotactic radiosurgery and the disease has been stable for at least 12 weeks
- The subject is pregnant or nursing

Participant Flow Table

Overall Study

	Dabrafenib + Trametinib	Dabrafenib + Placebo	Total
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	
Started	211	212	423
Safety Set	209	211	420
Crossover Population	0	28	28
Completed	0	0	0
Not Completed	211	212	423
Death	136	146	282
Lost to Follow-up	9	9	18
Investigator discretion	3	2	5

Withdrew consent	13	4	17
Study closed/terminated	50	23	73
Crossover to Dabrafenib + Trametinib	0	28	28

Baseline Characteristics

	Dabrafenib + Trametinib	Dabrafenib + Placebo	Total
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	
Number of Participants [units: participants]	211	212	423
AgeContinuous (units: Years) Mean ± Standard Deviation			
	55.1±13.33	55.3±13.75	55.2±13.52
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	100	98	198
Male	111	114	225

Race/Ethnicity, Customized
(units: Participants)

African American/African Heritage	0	1	1
White - White/Caucasian/European Heritage	211	211	422

Summary of Efficacy

Primary 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 + Trametinib	Dabrafenib + Placebo
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	211	212
Progression-Free Survival (PFS) as assessed by the investigator (units: Months) Median (95% Confidence Interval)		
	10.2 (8.1 to 12.8)	8.8 (5.9 to 9.3)

Statistical Analysis

Groups	Dabrafenib + Trametinib, Dabrafenib + Placebo	
Hazard Ratio (HR)	0.73	Hazard ratios (HRs) were estimated using a Pike estimator.

95 % Confidence Interval 2-Sided	0.59 to 0.91

Secondary 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 + Trametinib	Dabrafenib + Placebo
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	211	212
Overall Survival (OS) (units: Months) Median (95% Confidence Interval)		
	25.8 (19.2 to 38.2)	18.7 (15.2 to 23.1)

Statistical Analysis

Groups	Dabrafenib + Trametinib, Dabrafenib + Placebo	
Hazard Ratio (HR)	0.81	Hazard ratios (HRs) were estimated using a Pike estimator.

95 % Confidence Interval 2-Sided	0.64 to 1.02

Objective Response Rate (ORR) as assessed by the investigator

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

	Dabrafenib + Trametinib	Dabrafenib + Placebo
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	210	210
Objective Response Rate (ORR) as assessed by the investigator (units: Participants) Count of Participants (Not Applicable)		
	146 (69.52%)	113 (53.81%)

Duration of Response (DoR)

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

	Dabrafenib + Trametinib	Dabrafenib + Placebo
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the

	Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	146	114
Duration of Response (DoR) (units: Months) Median (95% Confidence Interval)		
	12.9 (9.3 to 18.4)	10.2 (8.3 to 13.8)

Trametinib Pharmacokinetic Concentrations

(Time Frame: Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose))

	Dabrafenib + Trametinib	**Dabrafenib + Placebo**
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	203	194
Trametinib Pharmacokinetic Concentrations (units: Nanogram per Milliliter (ng/mL)) Mean ± Standard Deviation		
Week 8, pre-dose	9.9209 ± 3.86587	0.0000 ± 0.00000
Week 8, 1-3 hours	19.0382 ± 6.86542	0.0261 ± 0.34598
Week 8, 4-6 hours	16.7496 ± 5.64363	0.0000 ± 0.00000

Week 16 pre-dose	11.0385 ± 4.79185	0.0039 ± 0.03548
Week 24 pre-dose	11.5167 ± 5.19171	0.0548 ± 0.62447

Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations

(Time Frame: Week 8 (0, 1-3, 4-6 hours post dose), Weeks 16 and 24 (0 hour pre-dose))

	Dabrafenib + Trametinib	Dabrafenib + Placebo
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.
Number of Participants Analyzed [units: participants]	203	194
Dabrafenib and Dabrafenib Metabolites (Hydroxy-, Carboxy- and Desmethyl-Dabrafenib) Concentrations (units: Nanogram per Milliliter (ng/mL)) Mean ± Standard Deviation		
GSK2118436, Week 8, pre-dose	92.1 ± 204.85	64.4 ± 96.98
GSK2118436, Week 8, 1-3 hours	1309.6 ± 982.25	1362.3 ± 992.97
GSK2118436, Week 8, 4-6 hours	458.9 ± 318.59	539.7 ± 553.09
GSK2118436, Week 16 pre-dose	151.6 ± 261.31	151.02 ± 381.32
GSK2118436, Week 24 pre-dose	167.0 ± 346.97	156.5 ± 357.50
GSK2285403, Week 8, pre-dose	346.6 ± 261.73	308.9 ± 224.56

GSK2285403, Week 8, 1-3 hours	361.7 ± 245.92	341.8 ± 240.96
GSK2285403, Week 8, 4-6 hours	316.9 ± 208.51	328.1 ± 234.95
GSK2285403, Week 16 pre-dose	335.0 ± 228.26	331.0 ± 250.04
GSK2285403, Week 24 pre-dose	306.2 ± 203.77	312.8 ± 250.28
GSK2298683, Week 8, pre-dose	82.0 ± 123.93	76.7 ± 109.09
GSK2298683,Week 8, 1-3 hours	648.5 ± 459.01	672.7 ± 519.45
GSK2298683, Week 8, 4-6 hours	391.3 ± 206.70	502.2 ± 356.72
GSK2298683, Week 16 pre-dose	128.7 ± 174.26	121.1 ± 195.15
GSK2298683,Week 24 pre-dose	126.1 ± 219.82	145.7 ± 265.57
GSK2167542, Week 8, pre-dose	3237.2 ± 1694.66	3469.4 ± 1854.02
GSK2167542, Week 8, 1-3 hours	4286.3 ± 2514.50	4456.6 ± 2687.32
GSK2167542, Week 8, 4-6 hours	6238.3 ± 2716.05	6891.6 ± 2739.07
GSK2167542, Week 16 pre-dose	3842.4 ± 2428.74	4114.1 ± 2432.72
GSK2167542, Week 24 pre-dose	3617.9 ± 2645.51	4193.2 ± 2730.78

Number of Participants with Adverse Events and Serious Adverse Events

(Time Frame: From the time the first dose of study treatment administered until 30 days after discontinuation of study treatment (up to approximately 6 years).)

	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	Crossover Dabrafenib + Trametinib
Number of Participants Analyzed [units: participants]	209	211	28
Number of Participants with Adverse Events and Serious Adverse Events (units: Participants) Count of Participants (Not Applicable)			
Adverse Event (AEs)	203 (97.13%)	205 (97.16%)	24 (85.71%)
Serious Adverse Event (SAEs)	100 (47.85%)	80 (37.91%)	8 (28.57%)

Post-Hoc Outcome Result(s):

All collected deaths

(Time Frame: up to 28 days before Day 1 (Screening), up to 77.4 months (on-treatment), up to approximately 6 years (study duration))

	Dabrafenib + Trametinib	Dabrafenib + Placebo	Crossover Dabrafenib + Trametinib
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment	Crossover Dabrafenib + Trametinib

	trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	
Number of Participants Analyzed [units: participants]	210	211	28
All collected deaths (units: Participants) Count of Participants (Not Applicable)			
Pre-treatment deaths	1 (.48%)	0 (%)	0 (%)
On-treatment deaths	29 (13.88%)	25 (11.85%)	0 (%)
Post-treatment deaths	106 (50.72%)	121 (57.35%)	5 (17.86%)
All deaths	136 (64.76%)	146 (69.19%)	5 (17.86%)

Summary of Safety

Safety Results

All-Cause Mortality

	Dabrafenib + Trametinib N = 209	Dabrafenib + Placebo N = 211	Crossover Dabrafenib + Trametinib N = 28	All Patients N = 420
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	Crossover Dabrafenib + Trametinib	All Patients
Total participants affected	135 (64.59%)	146 (69.19%)	5 (17.86%)	286 (68.10%)

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 77.4 months (treatment duration ranged from 0.1 to 76.4 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 + Trametinib N = 209	Dabrafenib + Placebo N = 211	Crossover Dabrafenib + Trametinib N = 28	All Patients N = 420
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	Crossover Dabrafenib + Trametinib	All Patients
Total participants affected	100 (47.85%)	80 (37.91%)	8 (28.57%)	183 (43.57%)
Blood and lymphatic system disorders				
Anaemia	5 (2.39%)	3 (1.42%)	0 (0.00%)	8 (1.90%)
Febrile neutropenia	0 (0.00%)	2 (0.95%)	0 (0.00%)	2 (0.48%)
Haemolytic uraemic syndrome	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hypochromic anaemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Neutropenia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pancytopenia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Thrombocytopenia	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Cardiac disorders				
Acute coronary syndrome	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)

Atrial fibrillation	3 (1.44%)	2 (0.95%)	0 (0.00%)	5 (1.19%)
Cardiac failure	0 (0.00%)	2 (0.95%)	1 (3.57%)	3 (0.71%)
Cardiovascular insufficiency	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Myocardial infarction	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Supraventricular tachycardia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Tachycardia	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Eye disorders				
Chorioretinopathy	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Iridocyclitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Uveitis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Visual impairment	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Gastrointestinal disorders				
Abdominal pain	4 (1.91%)	2 (0.95%)	0 (0.00%)	6 (1.43%)
Abdominal pain upper	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Acute abdomen	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Colitis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Constipation	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Diarrhoea	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Gastrointestinal disorder	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Intestinal perforation	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Jejunal perforation	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Melaena	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)

Nausea	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Pancreatitis acute	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Peritoneal haemorrhage	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Rectal haemorrhage	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Small intestinal obstruction	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Upper gastrointestinal haemorrhage	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Vomiting	3 (1.44%)	0 (0.00%)	0 (0.00%)	3 (0.71%)
General disorders and administration site conditions				
Chest pain	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Chills	10 (4.78%)	3 (1.42%)	0 (0.00%)	13 (3.10%)
Drowning	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Fatigue	3 (1.44%)	1 (0.47%)	0 (0.00%)	4 (0.95%)
General physical health deterioration	3 (1.44%)	0 (0.00%)	0 (0.00%)	3 (0.71%)
Influenza like illness	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Malaise	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Pyrexia	36 (17.22%)	15 (7.11%)	2 (7.14%)	51 (12.14%)
Hepatobiliary disorders				
Cholecystitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Cholelithiasis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Hepatic haematoma	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Immune system disorders				
Contrast media allergy	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)

Infections and infestations				
Bacteraemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Cellulitis	2 (0.96%)	1 (0.47%)	0 (0.00%)	3 (0.71%)
Clostridium difficile colitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Cystitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Diverticulitis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Febrile infection	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Herpes zoster	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Kidney infection	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Laryngitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Neutropenic sepsis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Peritonitis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Pneumonia	6 (2.87%)	2 (0.95%)	0 (0.00%)	8 (1.90%)
Pseudomonas infection	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pyelonephritis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Sepsis	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Septic shock	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Staphylococcal sepsis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Superinfection	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Urinary tract infection	2 (0.96%)	1 (0.47%)	0 (0.00%)	3 (0.71%)
Urosepsis	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Injury, poisoning and procedural complications				

Humerus fracture	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Joint dislocation	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Ligament rupture	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Ligament sprain	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Meniscus injury	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Post procedural persistent drain fluid	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Radius fracture	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Subarachnoid haemorrhage	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Upper limb fracture	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Investigations				
Alanine aminotransferase increased	3 (1.44%)	0 (0.00%)	1 (3.57%)	4 (0.95%)
Aspartate aminotransferase increased	1 (0.48%)	0 (0.00%)	1 (3.57%)	2 (0.48%)
Blood alkaline phosphatase increased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Ejection fraction decreased	13 (6.22%)	5 (2.37%)	1 (3.57%)	19 (4.52%)
Forced expiratory volume decreased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Haemoglobin decreased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hepatic enzyme increased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Neutrophil count decreased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)

Oxygen saturation decreased	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Renal function test abnormal	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Transaminases increased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
White blood cell count decreased	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Metabolism and nutrition disorders				
Dehydration	1 (0.48%)	2 (0.95%)	1 (3.57%)	4 (0.95%)
Hypercalcaemia	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Hyperglycaemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hypoglycaemia	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Hypokalaemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hyponatraemia	0 (0.00%)	1 (0.47%)	1 (3.57%)	2 (0.48%)
Hypophosphataemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Type 2 diabetes mellitus	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Musculoskeletal and connective tissue disorders				
Back pain	0 (0.00%)	2 (0.95%)	0 (0.00%)	2 (0.48%)
Compartment syndrome	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Haemarthrosis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hypercreatinaemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Immunoglobulin G4 related disease	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Intervertebral disc degeneration	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Muscle haemorrhage	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Adenocarcinoma gastric	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Basal cell carcinoma	8 (3.83%)	14 (6.64%)	0 (0.00%)	22 (5.24%)
Bile duct adenocarcinoma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Bowen's disease	2 (0.96%)	2 (0.95%)	1 (3.57%)	5 (1.19%)
Breast cancer	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Hodgkin's disease	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Invasive ductal breast carcinoma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Keratoacanthoma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Lipofibroma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Malignant melanoma	1 (0.48%)	2 (0.95%)	0 (0.00%)	3 (0.71%)
Osteosarcoma	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Papillary thyroid cancer	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Phaeochromocytoma	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Prostate cancer	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Schwannoma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Squamous cell carcinoma	3 (1.44%)	7 (3.32%)	1 (3.57%)	11 (2.62%)
Squamous cell carcinoma of skin	2 (0.96%)	15 (7.11%)	1 (3.57%)	18 (4.29%)
Superficial spreading melanoma stage unspecified	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Transitional cell carcinoma	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)

Tumour haemorrhage	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Nervous system disorders				
Aphasia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Brain oedema	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Central nervous system lesion	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Cerebral haemorrhage	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Cerebral infarction	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Cerebrovascular accident	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Dizziness	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Epilepsy	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Facial paralysis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hemiplegia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Nervous system disorder	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Paraesthesia	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Presyncope	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Sciatica	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Seizure	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Syncope	4 (1.91%)	1 (0.47%)	0 (0.00%)	5 (1.19%)
Tremor	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Psychiatric disorders				
Confusional state	3 (1.44%)	1 (0.47%)	0 (0.00%)	4 (0.95%)
Delirium	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Mania	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)

Organic brain syndrome	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Renal and urinary disorders				
Acute kidney injury	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Azotaemia	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Haematuria	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Hydronephrosis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Nephritis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pelvi-ureteric obstruction	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Renal colic	2 (0.96%)	0 (0.00%)	0 (0.00%)	2 (0.48%)
Renal failure	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Urinary retention	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Reproductive system and breast disorders				
Uterine prolapse	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (0.24%)
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Dyspnoea	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Nasal polyps	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pleural effusion	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pneumonitis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Pulmonary embolism	3 (1.44%)	1 (0.47%)	0 (0.00%)	4 (0.95%)
Respiratory depression	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Skin and subcutaneous tissue disorders				

Dermatitis allergic	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Dermatosis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hyperhidrosis	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hyperkeratosis	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Skin lesion	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Skin ulcer	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Vascular disorders				
Deep vein thrombosis	1 (0.48%)	1 (0.47%)	0 (0.00%)	2 (0.48%)
Hypertension	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.24%)
Hypotension	6 (2.87%)	2 (0.95%)	1 (3.57%)	9 (2.14%)
Hypovolaemic shock	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Peripheral ischaemia	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)
Thrombophlebitis superficial	0 (0.00%)	1 (0.47%)	0 (0.00%)	1 (0.24%)

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 77.4 months (treatment duration ranged from 0.1 to 76.4 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 + Trametinib N = 209	Dabrafenib + Placebo N = 211	Crossover Dabrafenib + Trametinib N = 28	All Patients N = 420
Arm/Group Description	Participants received dabrafenib 150 milligram (mg) HPMC capsules orally twice daily (BID), once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib 2 mg once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.	Participants received dabrafenib 150 mg HPMC capsules orally BID, once in the morning and a second dose approximately 12 hours after the morning dose, and trametinib placebo once daily in the morning. Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover to the combination therapy arm was allowed for subjects still receiving study treatment on the dabrafenib monotherapy arm after the positive result for the final OS analysis.	Crossover Dabrafenib + Trametinib	All Patients
Total participants affected	194 (92.82%)	200 (94.79%)	23 (82.14%)	394 (93.81%)
Blood and lymphatic system disorders				
Anaemia	16 (7.66%)	22 (10.43%)	3 (10.71%)	38 (9.05%)
Leukopenia	7 (3.35%)	1 (0.47%)	2 (7.14%)	10 (2.38%)
Neutropenia	20 (9.57%)	5 (2.37%)	3 (10.71%)	28 (6.67%)
Thrombocytopenia	9 (4.31%)	2 (0.95%)	2 (7.14%)	13 (3.10%)
Cardiac disorders				
Atrial fibrillation	2 (0.96%)	2 (0.95%)	2 (7.14%)	6 (1.43%)
Tachycardia	6 (2.87%)	13 (6.16%)	3 (10.71%)	21 (5.00%)
Ear and labyrinth disorders				
Tinnitus	5 (2.39%)	2 (0.95%)	3 (10.71%)	9 (2.14%)
Endocrine disorders				
Hypothyroidism	3 (1.44%)	2 (0.95%)	2 (7.14%)	7 (1.67%)

Eye disorders				
Blepharitis	2 (0.96%)	0 (0.00%)	2 (7.14%)	4 (0.95%)
Cataract	2 (0.96%)	4 (1.90%)	3 (10.71%)	8 (1.90%)
Dry eye	11 (5.26%)	4 (1.90%)	1 (3.57%)	15 (3.57%)
Vision blurred	10 (4.78%)	5 (2.37%)	3 (10.71%)	18 (4.29%)
Gastrointestinal disorders				
Abdominal pain	29 (13.88%)	17 (8.06%)	1 (3.57%)	47 (11.19%)
Abdominal pain upper	20 (9.57%)	12 (5.69%)	3 (10.71%)	35 (8.33%)
Constipation	27 (12.92%)	22 (10.43%)	3 (10.71%)	52 (12.38%)
Diarrhoea	67 (32.06%)	34 (16.11%)	9 (32.14%)	107 (25.48%)
Dry mouth	18 (8.61%)	6 (2.84%)	1 (3.57%)	24 (5.71%)
Nausea	79 (37.80%)	57 (27.01%)	7 (25.00%)	138 (32.86%)
Vomiting	57 (27.27%)	31 (14.69%)	3 (10.71%)	89 (21.19%)
General disorders and administration site conditions				
Asthenia	29 (13.88%)	30 (14.22%)	4 (14.29%)	60 (14.29%)
Chest pain	12 (5.74%)	5 (2.37%)	0 (0.00%)	17 (4.05%)
Chills	63 (30.14%)	34 (16.11%)	3 (10.71%)	98 (23.33%)
Fatigue	79 (37.80%)	79 (37.44%)	7 (25.00%)	161 (38.33%)
Influenza like illness	17 (8.13%)	12 (5.69%)	3 (10.71%)	31 (7.38%)
Oedema peripheral	48 (22.97%)	17 (8.06%)	2 (7.14%)	66 (15.71%)
Pain	14 (6.70%)	9 (4.27%)	1 (3.57%)	23 (5.48%)
Pyrexia	118 (56.46%)	63 (29.86%)	10 (35.71%)	183 (43.57%)
Immune system disorders				

Hypersensitivity	1 (0.48%)	2 (0.95%)	2 (7.14%)	5 (1.19%)
Infections and infestations				
Bronchitis	12 (5.74%)	8 (3.79%)	1 (3.57%)	21 (5.00%)
Cystitis	11 (5.26%)	2 (0.95%)	0 (0.00%)	13 (3.10%)
Folliculitis	12 (5.74%)	11 (5.21%)	2 (7.14%)	25 (5.95%)
Influenza	17 (8.13%)	7 (3.32%)	5 (17.86%)	28 (6.67%)
Nasopharyngitis	28 (13.40%)	21 (9.95%)	4 (14.29%)	50 (11.90%)
Upper respiratory tract infection	16 (7.66%)	7 (3.32%)	1 (3.57%)	24 (5.71%)
Urinary tract infection	29 (13.88%)	7 (3.32%)	2 (7.14%)	38 (9.05%)
Injury, poisoning and procedural complications				
Fall	6 (2.87%)	2 (0.95%)	2 (7.14%)	10 (2.38%)
Tendon rupture	0 (0.00%)	1 (0.47%)	2 (7.14%)	3 (0.71%)
Investigations				
Alanine aminotransferase increased	25 (11.96%)	12 (5.69%)	1 (3.57%)	38 (9.05%)
Aspartate aminotransferase increased	29 (13.88%)	8 (3.79%)	0 (0.00%)	37 (8.81%)
Blood alkaline phosphatase increased	18 (8.61%)	8 (3.79%)	3 (10.71%)	29 (6.90%)
Blood creatine phosphokinase increased	8 (3.83%)	0 (0.00%)	2 (7.14%)	10 (2.38%)
Blood creatinine increased	8 (3.83%)	2 (0.95%)	2 (7.14%)	12 (2.86%)

Blood lactate dehydrogenase increased	8 (3.83%)	2 (0.95%)	2 (7.14%)	12 (2.86%)
Ejection fraction decreased	7 (3.35%)	2 (0.95%)	3 (10.71%)	12 (2.86%)
Gamma-glutamyltransferase increased	6 (2.87%)	5 (2.37%)	4 (14.29%)	14 (3.33%)
Neutrophil count decreased	7 (3.35%)	0 (0.00%)	2 (7.14%)	9 (2.14%)
Weight decreased	13 (6.22%)	19 (9.00%)	0 (0.00%)	32 (7.62%)
Metabolism and nutrition disorders				
Decreased appetite	30 (14.35%)	28 (13.27%)	5 (17.86%)	60 (14.29%)
Hyponatraemia	5 (2.39%)	1 (0.47%)	2 (7.14%)	8 (1.90%)
Musculoskeletal and connective tissue disorders				
Arthralgia	57 (27.27%)	68 (32.23%)	6 (21.43%)	127 (30.24%)
Back pain	30 (14.35%)	34 (16.11%)	3 (10.71%)	67 (15.95%)
Muscle spasms	19 (9.09%)	7 (3.32%)	3 (10.71%)	29 (6.90%)
Muscular weakness	5 (2.39%)	4 (1.90%)	2 (7.14%)	11 (2.62%)
Musculoskeletal chest pain	14 (6.70%)	11 (5.21%)	0 (0.00%)	25 (5.95%)
Musculoskeletal pain	12 (5.74%)	19 (9.00%)	1 (3.57%)	31 (7.38%)
Myalgia	27 (12.92%)	28 (13.27%)	3 (10.71%)	56 (13.33%)
Pain in extremity	34 (16.27%)	38 (18.01%)	3 (10.71%)	73 (17.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				

Melanocytic naevus	2 (0.96%)	16 (7.58%)	0 (0.00%)	18 (4.29%)
Seborrhoeic keratosis	12 (5.74%)	22 (10.43%)	0 (0.00%)	34 (8.10%)
Skin papilloma	6 (2.87%)	46 (21.80%)	1 (3.57%)	52 (12.38%)
Nervous system disorders				
Dizziness	32 (15.31%)	15 (7.11%)	1 (3.57%)	47 (11.19%)
Dysgeusia	6 (2.87%)	13 (6.16%)	2 (7.14%)	21 (5.00%)
Headache	71 (33.97%)	63 (29.86%)	6 (21.43%)	138 (32.86%)
Paraesthesia	9 (4.31%)	12 (5.69%)	1 (3.57%)	22 (5.24%)
Psychiatric disorders				
Anxiety	12 (5.74%)	6 (2.84%)	3 (10.71%)	21 (5.00%)
Depression	9 (4.31%)	12 (5.69%)	1 (3.57%)	22 (5.24%)
Insomnia	11 (5.26%)	18 (8.53%)	1 (3.57%)	30 (7.14%)
Respiratory, thoracic and mediastinal disorders				
Cough	51 (24.40%)	46 (21.80%)	3 (10.71%)	97 (23.10%)
Dyspnoea	16 (7.66%)	19 (9.00%)	1 (3.57%)	36 (8.57%)
Epistaxis	21 (10.05%)	11 (5.21%)	1 (3.57%)	33 (7.86%)
Oropharyngeal pain	24 (11.48%)	11 (5.21%)	0 (0.00%)	35 (8.33%)
Skin and subcutaneous tissue disorders				
Actinic keratosis	12 (5.74%)	15 (7.11%)	1 (3.57%)	27 (6.43%)
Alopecia	19 (9.09%)	61 (28.91%)	0 (0.00%)	80 (19.05%)
Dermatitis acneiform	21 (10.05%)	8 (3.79%)	0 (0.00%)	29 (6.90%)
Dry skin	30 (14.35%)	33 (15.64%)	3 (10.71%)	65 (15.48%)
Eczema	19 (9.09%)	8 (3.79%)	2 (7.14%)	29 (6.90%)

Erythema	24 (11.48%)	16 (7.58%)	1 (3.57%)	41 (9.76%)
Hair texture abnormal	0 (0.00%)	18 (8.53%)	0 (0.00%)	18 (4.29%)
Hyperhidrosis	14 (6.70%)	9 (4.27%)	1 (3.57%)	23 (5.48%)
Hyperkeratosis	18 (8.61%)	79 (37.44%)	3 (10.71%)	97 (23.10%)
Night sweats	12 (5.74%)	5 (2.37%)	1 (3.57%)	17 (4.05%)
Palmar-plantar erythrodysaesthesia syndrome	11 (5.26%)	39 (18.48%)	2 (7.14%)	50 (11.90%)
Pruritus	28 (13.40%)	30 (14.22%)	2 (7.14%)	59 (14.05%)
Rash	62 (29.67%)	45 (21.33%)	3 (10.71%)	109 (25.95%)
Rash maculo-papular	13 (6.22%)	8 (3.79%)	3 (10.71%)	24 (5.71%)
Skin lesion	13 (6.22%)	10 (4.74%)	0 (0.00%)	23 (5.48%)
Vascular disorders				
Hot flush	8 (3.83%)	5 (2.37%)	2 (7.14%)	15 (3.57%)
Hypertension	51 (24.40%)	33 (15.64%)	2 (7.14%)	85 (20.24%)

Other Relevant Findings

None

Conclusion:

The results of the final analysis further confirmed the clinical efficacy and favorable benefit/risk ratio of dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily reported in the MEK115306 primary CSR and final OS analysis for subjects with BRAF V600E/K mutation-positive, unresectable or metastatic, cutaneous melanoma.

- The combination therapy of dabrafenib and trametinib demonstrated a reduction (27%) in the risk of disease progression or death compared with dabrafenib monotherapy (HR 0.73; 95% CI: 0.59, 0.91).
- All secondary endpoints favored the combination therapy including OS, ORR and DOR. Taken together, these data demonstrate a consistent and greater benefit of the combination therapy compared with dabrafenib.
- The safety profile of the combination of dabrafenib and trametinib generally reflects the safety profiles of the individual agents, with toxicities that are manageable with appropriate intervention and is consistent with the profile previously reported in the MEK115306 Primary CSR. No new safety signals have been identified with the increased exposure since Primary CSR.

Date of Clinical Trial Report

03-Jul-2014	Interim Report (describing the primary endpoint analysis at data cutoff date of 26-Aug-2013)
30-Mar-2015	Interim Report (describing final statistical comparison of OS for the dabrafenib and trametinib combination versus dabrafenib monotherapy, together with a comprehensive report of safety results at data cutoff date of 12-Jan-2015) and an amendment CSR to the latter)
30-Sep-2015	Interim Report (containing revised data listings)
25-Feb-2020	Abbreviated Clinical Study Report (Final report)