Clinical trial results:
A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.

Summary

EudraCT number	2009-015298-11
Trial protocol	DE NL IE HU ES IT
Global end of trial date	16 September 2016

Results information

Result version number	v1 (current)
This version publication date	22 September 2017
First version publication date	22 September 2017

Trial information

Trial identification

Sponsor protocol code	113683

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, +(1) 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, +(1) 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to establish the superiority of GSK2118436 over DTIC with respect to progression-free survival for subjects with BRAF mutation positive metastatic melanoma

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	250
EEA total number of subjects	167

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	197
From 65 to 84 years	52
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a Phase III randomized, open-label study to compare GSK2118436 to Dacarbazine (DTIC) in previously untreated participants (par.) with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. This study was conducted at 70 centers in 12 countries.

Pre-assignment

Screening details:

The study has 2 phases: Randomized and Crossover Phase. In Randomized Phase, a total of 250 par. were randomized in 3:1 to receive either oral dabrafenib 150 mg twice daily (BID) or intravenous DTIC 1000 milligram/meter square. Par. in DTIC arm with disease progression were considered for crossover to dabrafenib arm in Crossover Phase

Period 1

Period 1 title	Randomized Phase (RP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK2118436 150 mg BID

Arm description:

Participants (par.) were randomly assigned to receive oral GSK2118436 150 milligrams (mg) twice a day (BID). Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until disease progression (DP), death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Participants who experienced investigator-reported DP but were benefitting from study treatment were permitted to continue GSK2118436 treatment upon approval of the GlaxoSmithKline Medical Monitor.

Arm type	Experimental
Investigational medicinal product name	GSK2118436
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Debrafenib 150 milligram (mg) (50 mg x 3 capsules or 75 mg x 2 capsules) was administered twice daily under fasting conditions, either 1 hour before or 2 hours after a meal with approximately 200 milliliter (mL) of water.

Arm title	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase

Arm description:

In the RP, par. received intravenous (IV) Dacarbazine (DTIC) 1000 mg per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Par. continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Par. who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Par. who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover par. continued on GSK2118436 until further DP was noted. After DP on GSK2118436, par. were followed for response, progression, survival, and further anti-cancer therapy.

Arm type	Active comparator

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine 1000mg/m^2 was infused intravenously every 3 weeks.

Number of subjects in period 1	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase
Started	187	63
Completed	0	0
Not completed	187	63
Adverse event, serious fatal	4	-
Physician decision	13	5
Consent withdrawn by subject	15	3
Adverse event, non-fatal	9	-
Study Terminated By Sponsor	10	-
Progressive Disease	135	52
Missing	1	3

Period 2

Period 2 title	Crossover Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase

Arm description:

In the RP, par. received intravenous (IV) Dacarbazine (DTIC) 1000 mg per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Par. continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Par. who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Par. who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover par. continued on GSK2118436 until further DP was noted. After DP on GSK2118436, par. were followed for response, progression, survival, and further anti-cancer therapy.

Arm type	Active comparator

Investigational medicinal product name	GSK2118436
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Debrafenib 150 milligram (mg) (50 mg x 3 capsules or 75 mg x 2 capsules) was administered twice daily under fasting conditions, either 1 hour before or 2 hours after a meal with approximately 200 milliliter (mL) of water.

Number of subjects in period 2	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase
Started	37
Completed	0
Not completed	37
Adverse event, serious fatal	1
Physician decision	3
Consent withdrawn by subject	1
Study Terminated By Sponsor	1
Progressive Disease	31

Baseline characteristics

Reporting groups

Reporting group title	GSK2118436 150 mg BID

Reporting group description:

Participants (par.) were randomly assigned to receive oral GSK2118436 150 milligrams (mg) twice a day (BID). Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until disease progression (DP), death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Participants who experienced investigator-reported DP but were benefitting from study treatment were permitted to continue GSK2118436 treatment upon approval of the GlaxoSmithKline Medical Monitor.

Reporting group title	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase

Reporting group description:

In the RP, par. received intravenous (IV) Dacarbazine (DTIC) 1000 mg per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Par. continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Par. who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Par. who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover par. continued on GSK2118436 until further DP was noted. After DP on GSK2118436, par. were followed for response, progression, survival, and further anti-cancer therapy.

Reporting group values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase	Total
Number of subjects	187	63	250
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 53.5 ± 13.76	 51.6 ± 14.22	 -
Gender categorical Units: Subjects			
Female	75	26	101
Male	112	37	149
Race/Ethnicity, Customized Units: Subjects			
White	186	63	249
Missing	1	0	1

Subject analysis sets

Subject analysis set title	DTIC 1000 mg/m^2 in RP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In the RP, participants received intravenous (IV) Dacarbazine (DTIC) 1000 milligrams per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of

reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study.

Subject analysis set title	GSK25118436 in crossover phase
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Participants who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover participants continued on GSK2118436 until further DP was noted. After DP on GSK2118436, participants were followed for response, progression, survival, and further anti-cancer therapy.

Subject analysis set title	All Screened Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Specimens were tested for V600E mutations to determine trial eligibility with the CTA were retested with the THxID BRAF test. The analytical agreement between the THxID BRAF and the CTA was evaluated for both mutation positive and mutation negative specimens from all sites.

Reporting group values	DTIC 1000 mg/m^2 in RP	GSK25118436 in crossover phase	All Screened Participants
Number of subjects	63	37	250
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender categorical Units: Subjects			
Female	0	0	0
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	0	0	0
Missing	0	0	0

End points

End points reporting groups

Reporting group title	GSK2118436 150 mg BID

Reporting group description:

Participants (par.) were randomly assigned to receive oral GSK2118436 150 milligrams (mg) twice a day (BID). Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until disease progression (DP), death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Participants who experienced investigator-reported DP but were benefitting from study treatment were permitted to continue GSK2118436 treatment upon approval of the GlaxoSmithKline Medical Monitor.

Reporting group title	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase

Reporting group description:

In the RP, par. received intravenous (IV) Dacarbazine (DTIC) 1000 mg per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Par. continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Par. who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Par. who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover par. continued on GSK2118436 until further DP was noted. After DP on GSK2118436, par. were followed for response, progression, survival, and further anti-cancer therapy.

Reporting group title	DTIC 1000 mg/m^2 in RP; GSK2118436 in Crossover Phase

Reporting group description:

In the RP, par. received intravenous (IV) Dacarbazine (DTIC) 1000 mg per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Par. continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Par. who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Par. who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover par. continued on GSK2118436 until further DP was noted. After DP on GSK2118436, par. were followed for response, progression, survival, and further anti-cancer therapy.

Subject analysis set title	DTIC 1000 mg/m^2 in RP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In the RP, participants received intravenous (IV) Dacarbazine (DTIC) 1000 milligrams per meters squared (mg/m^2) every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study.

Subject analysis set title	GSK25118436 in crossover phase
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Participants who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover participants continued on GSK2118436 until further DP was noted. After DP on GSK2118436, participants were followed for response, progression, survival, and further anti-cancer therapy.

Subject analysis set title	All Screened Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Specimens were tested for V600E mutations to determine trial eligibility with the CTA were retested with the THxID BRAF test. The analytical agreement between the THxID BRAF and the CTA was evaluated for both mutation positive and mutation negative specimens from all sites.

Primary: Progression-free Survival (PFS) as assessed by the Investigator

End point title	Progression-free Survival (PFS) as assessed by the

End point description:

PFS is defined as the interval of time between the date of randomization and the earlier of the date of disease progression or the date of death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments were made by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). For participants who did not progress or die,PFS was censored at the date of last contact. Data are presented as median and 96% confidence interval.Intent-to-Treat (ITT) Population: all randomized participants whether or not treatment was

End point type	Primary

End point timeframe:

Time interval between the date of randomization and the earlier of the date of disease progression or the date of death due to any cause (up to 9.9 months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[2]	63		
Units: Months				
median (confidence interval 95%)				
Months	6.9 (5.5 to 9)	2.7 (1.4 to 3.2)		

Notes:

[2] - Intent-to-Treat (ITT) Population: all randomized participants regardless of whether or not treatment

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HRs were estimated using a Pike estimator. HR from a stratified log-rank test was adjusted for disease stage at screening.

Comparison groups	GSK2118436 150 mg BID v DTIC 1000 mg/m^2 in RP
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.6

Notes:

[3] - The p value from a stratified log-rank test was adjusted for disease stage at screening.

Primary: Progression-free Survival (PFS) as assessed by an Independent Radiologist: Randomized Phase

End point title	Progression-free Survival (PFS) as assessed by an Independent Radiologist: Randomized Phase[4]

End point description:

PFS is defined as the interval of time between the date of randomization and the earlier of the date of disease progression or the date of death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments were made by an independent radiologist according to RECIST version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm. For participants who did not progress or die, PFS was censored at the date of last contact.

End point type	Primary

End point timeframe:

Time interval between the date of randomization and the earlier of the date of disease progression or the date of death due to any cause (up to 9.9 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[5]	63		
Units: Months				
median (confidence interval 95%)				
Months	6.7 (5 to 6.9)	2.9 (1.7 to 4.9)		

Notes:

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HRs were estimated using a Pike estimator. HR from a stratified log-rank test was adjusted for disease stage at screening.

Comparison groups	GSK2118436 150 mg BID v DTIC 1000 mg/m^2 in RP
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.61

Secondary: Overall survival

End point title	Overall survival[6]

End point description:

Overall survival is defined as the interval of time between the date of randomization and the date of death due to any cause. For participants who did not die, overall survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

Time interval between the date of randomization and the date of death due to any cause (up to 22.1 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[7]	63		
Units: Months				
median (confidence interval 95%)				
Months	20 (16.7 to 24.2)	15.6 (11.9 to 21.2)		

Notes:

[7] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HRs were estimated using a Pike estimator. HR was adjusted for disease stage at screening.

Comparison groups	GSK2118436 150 mg BID v DTIC 1000 mg/m^2 in RP
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.18

Secondary: Number of participants with a best overall response of confirmed complete response (CR) or confirmed partial response (PR) as assessed by the Investigator: Randomized Phase

End point title	Number of participants with a best overall response of

	confirmed complete response (CR) or confirmed partial response (PR) as assessed by the Investigator: Randomized Phase[8]

End point description:

A participant was defined as a responder if he/she achieved either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]). Response was evaluated by an investigator per RECIST, version 1.1. A participant without a post-Baseline assessment of response was considered a non-responder. Confirmation, per RECIST version 1.1, requires a confimatory disease assessment of CR or PR at least 28 days after the initial disease assessment of CR or PR.

End point type	Secondary

End point timeframe:

From randomization until the first documented evidence of a confirmed complete response or partial response (median of 6.6 weeks)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[9]	63		
Units: participants				
CR	26	4		
PR	86	11		

Notes:

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a best overall response of confirmed CR or PR as assessed by an Independent Radiologist: Randomized Phase

End point title	Number of participants with a best overall response of confirmed CR or PR as assessed by an Independent Radiologist: Randomized Phase[10]

End point description:

A participant was defined as a responder if he/she achieved either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]). Response was evaluated by an independent radiologist per RECIST, version 1.1. A participant without a post-Baseline assessment of response was considered a non-responder. Confirmation, per RECIST version 1.1, requires a confimatory disease assessment of CR or PR at least 28 days after the initial disease assessment of CR or PR.

End point type	Secondary

End point timeframe:

From randomization until the first documented evidence of a confirmed complete response or partial response (median of 12.0 weeks)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[11]	63		
Units: participants				
CR	6	1		
PR	87	3		

Notes:

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as assessed by the Investigator: Randomized Phase

End point title	Duration of Response as assessed by the Investigator: Randomized Phase[12]

End point description:

Duration of response for participants with either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) was defined as the time from the first documented evidence of a PR or CR until the first documented sign of PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.

End point type	Secondary

End point timeframe:

Time from the first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause (up to 65.6 weeks)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	112[13]	15		
Units: Months				
median (confidence interval 95%)				
Months	9.2 (7.4 to 11.9)	8.2 (3.5 to 18.3)		

Notes:

[13] - ITT Population. Only participants with a confirmed CR or PR were assessed for duration of response.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as assessed by an Independent Radiologist: Randomized Phase

End point title	Duration of Response as assessed by an Independent Radiologist: Randomized Phase[14]

End point description:

Duration of response for participants with either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) was defined as the time from the first documented evidence of a PR or CR until the first documented sign of PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm. 99999 indicates that data is not available.

End point type	Secondary

End point timeframe:

Time from the first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause (up to 7.4 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	93[15]	4		
Units: Months				
median (confidence interval 95%)				
Months	5.5 (5 to 6.7)	99999 (99999 to 99999)		

Notes:

[15] - ITT Population. Only participants with a confirmed CR or PR were assessed for duration of response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS2) as assessed by the Investigator: Crossover Phase

End point title	Progression-free Survival (PFS2) as assessed by the Investigator: Crossover Phase

End point description:

PFS2 is defined as the time from the first dose of GSK2118436, in participants randomized to DTIC who crossed over to GSK2118436 after initial progression, to the earliest date of radiographic or photographic disease progression or death due to any cause. Disease progression was based on radiographic or photographic evidence, and assessments were made by the investigator according to RECIST version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm. For participants who did not progress or die, PFS was censored at the date of last contact. Crossover Treatment Population: participants who were randomized to DTIC arm, and elected to receive GSK2118436

End point type	Secondary

End point timeframe:

Time from first dose of GSK2118436 in participants who crossover after initial progression to the earliest date of radiographical or photographical PD or death due to any cause (up to 6.4 months)

End point values	GSK25118436 in crossover phase			
Subject group type	Subject analysis set			
Number of subjects analysed	37[16]			
Units: Months				
median (confidence interval 95%)				
Months	4.3 (4.1 to 6.1)			

Notes:

[16] - Crossover Treatment Population: Only participants who received at least one dose of GSK2118436

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a best overall response of confirmed complete response (CR) or confirmed partial response (PR) as assessed by the Investigator: Crossover Phase

End point title	Number of participants with a best overall response of confirmed complete response (CR) or confirmed partial response (PR) as assessed by the Investigator: Crossover Phase

End point description:

A participant was defined as a responder if he/she achieved either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]). Response was evaluated by an investigator per RECIST, version 1.1. A participant without a post-Baseline assessment of response was considered a non-responder. Confirmation, per RECIST version 1.1, requires a confimatory disease assessment of CR or PR at least 28 days after the initial disease assessment of CR or PR.

End point type	Secondary

End point timeframe:

From randomization until the first documented evidence of a confirmed complete response or partial response (up to 6.4 months)

End point values	GSK25118436 in crossover phase			
Subject group type	Subject analysis set			
Number of subjects analysed	37[17]			
Units: participants				
CR	0			
PR	12			

Notes:

[17] - Crossover Treatment Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as assessed by the Investigator: Crossover Phase

End point title	Duration of Response as assessed by the Investigator: Crossover Phase

End point description:

Duration of response for participants with either a CR (the disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) was defined as the time from the first documented evidence of a PR or CR until the first documented sign of PD or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm. Crossover Population: Only participants with a confirmed CR or PR were assessed for duration of response.

End point type	Secondary

End point timeframe:

Time from the first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause (up to 6.4 months)

End point values	GSK25118436 in crossover phase			
Subject group type	Subject analysis set			
Number of subjects analysed	12[18]			
Units: Months				
median (confidence interval 95%)				
Months	4.4 (2.5 to 6.2)			

Notes:

[18] - Crossover Treatment Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with non-melanoma skin lesions: Randomized Phase

End point title	Number of participants with non-melanoma skin lesions: Randomized Phase[19]

End point description:

Dermatological examinations were performed by the investigator, or at the discretion of the investigator, referred to a dermatologist. The number of participants with non-melanoma skin lessions was assessed from the time of Screening until study completion or discontinuation from the study for any reason.

End point type	Secondary

End point timeframe:

From Screening until study completion or discontinuation from the study (up to 9.9 months)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	187[20]	59		
Units: participants				
Number of Subjects with Event	14	0		
Number of Events	24	0		

Notes:

[20] - Safety Population: all randomized participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Agreement rate for V600E mutation validation of the BRAF mutation assay

End point title	Agreement rate for V600E mutation validation of the BRAF mutation assay

End point description:

Analytical and clinical validation of the companion diagnostic (cDx) assay was performed to determine the extent of agreement between the bioMerieux cDx assay (THxID BRAF Assay) and the Clinical Trial Assay (CTA) to detect BRAF mutations to determine participant eligibility into the study. Skin tissue samples collected at the Screening visit were used for this analysis. Multiple specimen per participant were analyzed.

End point type	Secondary

End point timeframe:

Screening

End point values	All Screened Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	734[21]			
Units: Percent agreement				
number (confidence interval 95%)				
Agreement for V600E	96.7 (93.6 to 98.3)			
Agreement for V600K	90 (78.6 to 95.7)			
Agreement for mutation negative	95 (91.6 to 97)			
Agreement for overall	94.9 (92.7 to 96.4)			

Notes:

[21] - V600E positive participants screened for BREAK-3 study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the first dose of investigational product to the end of the study. The total duration of the study including a long-term follow-up phase was up to 5 years.

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all randomized participants who received at least one dose of study drug, based on the actual treatment received, if this differed from that to which the participant was randomized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	GSK2118436 150 mg BID

Reporting group description:

Participants were randomly assigned to receive oral GSK2118436 150 mg BID. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study. Participants who experienced investigator-reported DP but were benefitting from study treatment were permitted to continue GSK2118436 treatment upon approval of the GlaxoSmithKline Medical Monitor.

Reporting group title	DTIC 1000 mg/m^2 in RP

Reporting group description:

In the RP, participants received IV DTIC 1000 mg/m^2 every 3 weeks. Dose reductions were permitted based on the severity of the hematological toxicity. Stopping recommendations for study treatment were also provided for cases of reoccurring skin toxicity, cardiovascular complication or abnormalities, and liver abnormalities. Participants continued on treatment until DP, death, the occurrence of an unacceptable AE, or withdrawal from the study.

Reporting group title	GSK25118436 in the Crossover Phase

Reporting group description:

Participants who received DTIC in the RP and experienced DP had the option, at the discretion of the Investigator, of receiving GSK2118436 150 mg BID in the Crossover Phase. Participants who permanently discontinued DTIC treatment due to an AE, withdrawal of consent, or for any reason other than DP were not eligible for crossover to GSK2118436. Crossover participants continued on GSK2118436 until further DP was noted. After DP on GSK2118436, participants were followed for response, progression, survival, and further anti-cancer therapy.

Serious adverse events	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP	GSK25118436 in the Crossover Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 187 (34.22%)	14 / 59 (23.73%)	9 / 37 (24.32%)
number of deaths (all causes)	5	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of the cervix			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	6 / 187 (3.21%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen’s disease			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal nodular hyperplasia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	3 / 187 (1.60%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			

subjects affected / exposed	3 / 187 (1.60%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma stage I			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue sarcoma			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	7 / 187 (3.74%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	11 / 11	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	8 / 187 (4.28%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	12 / 12	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrous histiocytoma			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 187 (1.07%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 187 (2.14%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Euthanasia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	11 / 13	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 187 (1.07%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychotic disorder			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	3 / 187 (1.60%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 187 (1.60%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 187 (1.07%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Lethargy			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 187 (0.53%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 187 (0.53%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid oedema			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 187 (0.53%)	2 / 59 (3.39%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 187 (0.53%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 187 (0.53%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic necrosis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 187 (1.07%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	2 / 187 (1.07%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 187 (0.53%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperhidrosis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Urinary bladder polyp			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain in extremity			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal abscess			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 187 (1.07%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 59 (1.69%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 187 (1.07%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipasaemia			

subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	GSK2118436 150 mg BID	DTIC 1000 mg/m^2 in RP	GSK25118436 in the Crossover Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 187 (96.79%)	51 / 59 (86.44%)	37 / 37 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	20	0	0
Melanocytic naevus			
subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	18	0	0
Papilloma			
subjects affected / exposed	15 / 187 (8.02%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	23	0	2
Seborrhoeic keratosis			
subjects affected / exposed	23 / 187 (12.30%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	55	0	3
Skin papilloma			
subjects affected / exposed	48 / 187 (25.67%)	0 / 59 (0.00%)	10 / 37 (27.03%)
occurrences (all)	85	0	15
Dysplastic naevus			

subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	4
Fibroma			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Fibrous histiocytoma			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Keratoacanthoma			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	5
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	16	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 187 (19.79%)	9 / 59 (15.25%)	6 / 37 (16.22%)
occurrences (all)	56	11	8
Chills			
subjects affected / exposed	23 / 187 (12.30%)	0 / 59 (0.00%)	4 / 37 (10.81%)
occurrences (all)	40	0	5
Fatigue			
subjects affected / exposed	48 / 187 (25.67%)	14 / 59 (23.73%)	6 / 37 (16.22%)
occurrences (all)	57	21	6
Influenza like illness			
subjects affected / exposed	14 / 187 (7.49%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	16	0	2
Oedema peripheral			
subjects affected / exposed	12 / 187 (6.42%)	5 / 59 (8.47%)	0 / 37 (0.00%)
occurrences (all)	13	5	0
Pyrexia			
subjects affected / exposed	61 / 187 (32.62%)	8 / 59 (13.56%)	9 / 37 (24.32%)
occurrences (all)	102	8	11
Non-cardiac chest pain			

subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Peripheral swelling			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	5
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 187 (18.18%)	4 / 59 (6.78%)	2 / 37 (5.41%)
occurrences (all)	42	6	2
Dyspnoea			
subjects affected / exposed	22 / 187 (11.76%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	28	0	2
Dyspnoea exertional			
subjects affected / exposed	0 / 187 (0.00%)	3 / 59 (5.08%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	12	0	3
Nasal congestion			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 187 (5.35%)	5 / 59 (8.47%)	3 / 37 (8.11%)
occurrences (all)	10	5	3
Insomnia			
subjects affected / exposed	16 / 187 (8.56%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	19	0	0
Depression			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	12 / 187 (6.42%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	13	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	10	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 187 (0.00%)	3 / 59 (5.08%)	2 / 37 (5.41%)
occurrences (all)	0	7	3
Platelet count decreased			
subjects affected / exposed	0 / 187 (0.00%)	4 / 59 (6.78%)	0 / 37 (0.00%)
occurrences (all)	0	5	0
Weight decreased			
subjects affected / exposed	13 / 187 (6.95%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	13	0	2
White blood cell count decreased			
subjects affected / exposed	0 / 187 (0.00%)	3 / 59 (5.08%)	0 / 37 (0.00%)
occurrences (all)	0	7	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 187 (8.02%)	3 / 59 (5.08%)	5 / 37 (13.51%)
occurrences (all)	17	3	5
Headache			
subjects affected / exposed	68 / 187 (36.36%)	5 / 59 (8.47%)	6 / 37 (16.22%)
occurrences (all)	109	6	7
Paraesthesia			
subjects affected / exposed	12 / 187 (6.42%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	13	0	3
Hyperaesthesia			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Sciatica			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	10 / 187 (5.35%)	7 / 59 (11.86%)	3 / 37 (8.11%)
occurrences (all)	14	9	5
Leukopenia			
subjects affected / exposed	0 / 187 (0.00%)	8 / 59 (13.56%)	0 / 37 (0.00%)
occurrences (all)	0	8	0
Neutropenia			
subjects affected / exposed	0 / 187 (0.00%)	10 / 59 (16.95%)	0 / 37 (0.00%)
occurrences (all)	0	18	0
Thrombocytopenia			
subjects affected / exposed	0 / 187 (0.00%)	8 / 59 (13.56%)	0 / 37 (0.00%)
occurrences (all)	0	11	0
Lymphopenia			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 187 (8.02%)	7 / 59 (11.86%)	8 / 37 (21.62%)
occurrences (all)	16	8	10
Abdominal pain upper			
subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	20	0	4
Constipation			
subjects affected / exposed	27 / 187 (14.44%)	8 / 59 (13.56%)	4 / 37 (10.81%)
occurrences (all)	32	9	4
Diarrhoea			
subjects affected / exposed	31 / 187 (16.58%)	7 / 59 (11.86%)	4 / 37 (10.81%)
occurrences (all)	42	8	5
Nausea			
subjects affected / exposed	55 / 187 (29.41%)	29 / 59 (49.15%)	9 / 37 (24.32%)
occurrences (all)	69	49	9
Vomiting			
subjects affected / exposed	42 / 187 (22.46%)	15 / 59 (25.42%)	5 / 37 (13.51%)
occurrences (all)	55	19	5
Abdominal distension			

subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	22 / 187 (11.76%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	51	0	2
Alopecia			
subjects affected / exposed	54 / 187 (28.88%)	0 / 59 (0.00%)	7 / 37 (18.92%)
occurrences (all)	59	0	7
Dry skin			
subjects affected / exposed	28 / 187 (14.97%)	0 / 59 (0.00%)	5 / 37 (13.51%)
occurrences (all)	36	0	5
Eczema			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	10	0	0
Erythema			
subjects affected / exposed	18 / 187 (9.63%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	28	0	0
Hair texture abnormal			
subjects affected / exposed	13 / 187 (6.95%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	14	0	0
Hyperkeratosis			
subjects affected / exposed	71 / 187 (37.97%)	0 / 59 (0.00%)	11 / 37 (29.73%)
occurrences (all)	156	0	20
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	37 / 187 (19.79%)	0 / 59 (0.00%)	5 / 37 (13.51%)
occurrences (all)	44	0	5
Palmoplantar keratoderma			
subjects affected / exposed	17 / 187 (9.09%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	20	0	2
Photosensitivity reaction			
subjects affected / exposed	0 / 187 (0.00%)	4 / 59 (6.78%)	2 / 37 (5.41%)
occurrences (all)	0	4	2
Pruritus			

subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	13	0	3
Rash			
subjects affected / exposed	35 / 187 (18.72%)	0 / 59 (0.00%)	10 / 37 (27.03%)
occurrences (all)	45	0	13
Skin lesion			
subjects affected / exposed	14 / 187 (7.49%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	18	0	3
Hyperhidrosis			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Night sweats			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	4
Skin exfoliation			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	74 / 187 (39.57%)	0 / 59 (0.00%)	16 / 37 (43.24%)
occurrences (all)	111	0	23
Back pain			
subjects affected / exposed	41 / 187 (21.93%)	4 / 59 (6.78%)	8 / 37 (21.62%)
occurrences (all)	48	4	8
Musculoskeletal chest pain			
subjects affected / exposed	10 / 187 (5.35%)	0 / 59 (0.00%)	3 / 37 (8.11%)
occurrences (all)	10	0	3
Musculoskeletal pain			
subjects affected / exposed	18 / 187 (9.63%)	0 / 59 (0.00%)	6 / 37 (16.22%)
occurrences (all)	20	0	9
Myalgia			

subjects affected / exposed	32 / 187 (17.11%)	0 / 59 (0.00%)	7 / 37 (18.92%)
occurrences (all)	41	0	7
Pain in extremity			
subjects affected / exposed	31 / 187 (16.58%)	6 / 59 (10.17%)	6 / 37 (16.22%)
occurrences (all)	40	7	6
Infections and infestations			
Folliculitis			
subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	0 / 37 (0.00%)
occurrences (all)	13	0	0
Nasopharyngitis			
subjects affected / exposed	35 / 187 (18.72%)	4 / 59 (6.78%)	4 / 37 (10.81%)
occurrences (all)	57	6	8
Upper respiratory tract infection			
subjects affected / exposed	12 / 187 (6.42%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	15	0	2
Urinary tract infection			
subjects affected / exposed	0 / 187 (0.00%)	4 / 59 (6.78%)	0 / 37 (0.00%)
occurrences (all)	0	4	0
Sinusitis			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
INFLUENZA			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 187 (13.90%)	6 / 59 (10.17%)	4 / 37 (10.81%)
occurrences (all)	34	7	5
Hyperglycaemia			
subjects affected / exposed	14 / 187 (7.49%)	3 / 59 (5.08%)	3 / 37 (8.11%)
occurrences (all)	19	4	4
Hypophosphataemia			
subjects affected / exposed	11 / 187 (5.88%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	13	0	2
Hypoglycaemia			

subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 187 (0.00%)	0 / 59 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2010	Amendment No. 01: This amendment modified the contraception section based upon additional non-clinical toxicology results; added a computed tomography scan for respiratory symptoms within the dose modification guidelines table corrected typographical errors in the statistics section; added assessment of secondary malignancies to the secondary safety objectives; added evaluation of Health-Related Quality of Life (HRQOL) parameters for participants who crossover to dabrafenib from randomized treatment with DTIC following initial progression; and changed the collection requirements for a Circulating cell-free DNA (cfDNA) sample at progression from optional to mandatory.
04 March 2011	Amendment No. 02: It was a country specific amendment for France to modify the QTc stopping criteria in response to a request from the French regulatory agency, AFSSAPS
23 March 2011	Amendment No. 03: This amendment added the collection of serial pharmacokinetics (PK) samples in a subset of participants to further characterize final dabrafenib formulation; clarified crossover eligibility criteria; included administrative corrections to Time and Events tables and specifically clarified timing of assessments; modified the tumor tissue requirements to allow primary tissue for screening; clarified QOL time points and modified data collection instructions to allow 1 questionnaire to be completed via phone; and added best ORR as a secondary efficacy objective.
03 June 2011	Amendment No. 04: This amendment updated the dose monitoring and management guidelines for neutropenia and fever based on emerging safety data from other ongoing dabrafenib studies; added wording to allow the collection of non-melanoma skin biopsy slides and pathology reports; changed the collection of full body skin photos at baseline from required to recommended; clarified the Safety and QOL endpoints; added wording to recommend PK collection for all serious adverse events; included administrative corrections and added a Day 8 absolute neutrophil count. Dexamethasone was added to the cautionary medications section.
14 November 2011	Amendment No. 05: This amendment added a treatment option that allowed participants with investigator reported disease progression who were still benefitting from study treatment with dabrafenib to continue study drug. Also added new guidelines for the management of renal insufficiency and new criteria for dose modifications related to grade 3 toxicities.
20 April 2012	Amendment No. 06: The results of the planned primary analysis confirmed that the primary endpoint of improved progression free survival in the dabrafenib (dabrafenib arm) was achieved. The data was reviewed with the IDMC and the committee unanimously recommended that participants who were randomized to the DTIC arm of the study be allowed the option to receive dabrafenib prior to disease progression based on the judgment of the investigator. Independent review confirmation of disease progression will no longer be prior to crossover. The crossover rules were updated. Time and Events Table 13 was updated with requirement for re-establishing efficacy and safety baseline measures within 28 days of first dose of dabrafenib and QOL requirement at crossover was clarified. Statistics section updated to reflect the new analyses plans and to address multiple testing issues. Wording was modified in the safety section to clarify intent in the collection of events of pyrexia and basal cell carcinoma.

19 February 2014	Amendment No. 07: Major updates include changes to secondary objectives and study design; study closure at 70% of deaths was removed and updated to follow participants to estimate long-term OS (particularly 5 years in treatment groups). Definition to permanent discontinuation was updated to clarify that all participants were to be followed to death or until lost to follow up. Study completion was changed to collect long-term (5 years), overall survival. The other key changes include updates to Adverse Events of Special Interest (AESIs) and dose modification to reflect latest label language: Dose Modification Guidelines for AESI are updated; Neutropenia was removed from the list; QTc updated to align with French Guidelines for reporting; Liver chemistry monitoring, management and restarting treatment conditions were updated; Secondary analysis updated to reflect long-term OS estimates; Appendix added for French specific skin monitoring guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported