



Clinical trial results:

A Multi-Center, Randomized, Double-Blind, Two-Arm, Phase III Study in Patients with Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg of Ipilimumab (MDX-010) vs. Dacarbazine With Placebo.

Summary

EudraCT number	2005-006082-14
Trial protocol	NO IE BE HU ES PT DE GB CZ AT IT NL
Global end of trial date	14 November 2013

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	CA184024
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00324155
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Bristol-Myers Squibb International Corporation, Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, Clinical.Trials@bms.com

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	01 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare Overall Survival in subjects with previously untreated Stage IIIC, N3 (unresectable) or Stage IV melanoma receiving dacarbazine plus 10mg/kg ipilimumab vs. dacarbazine with placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 90
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 65
Country: Number of subjects enrolled	Argentina: 16
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 25

Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	South Africa: 24
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	681
EEA total number of subjects	381

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)	460
From 65 to 84 years	215
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was initiated on August 8, 2006. Primary endpoint (Survival) was evaluated on February 7, 2011 and again at completion of follow-up period, October 13, 2013. Subjects with a histologic diagnosis of untreated, measurable, and unresectable Stage III or Stage IV malignant melanoma were eligible.

Pre-assignment

Screening details:

Of the 681 subjects enrolled, 502 were randomised, and 498 received treatment. Reasons for not starting treatment: 147 no longer met study criteria (including 3 who were randomised but did not receive treatment), 25 withdrew consent, 3 died, 2 had adverse events, 2 lost to follow-up, 2 poor compliance or noncompliance, 1 not reported, and 1 other.

Period 1

Period 1 title	Randomised
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and Dacarbazine

Arm description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-734016
Other name	MDX-010
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Induction Phase: Subjects were administered with ipilimumab intravenous solution, 10 mg/kg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Maintenance Phase: Ipilimumab intravenous solution: 10 mg/kg, every 12 weeks was continued until PD.

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

Dosage and administration details:

Dacarbazine intravenous solution 850-mg/m² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.

Arm title	Placebo and Dacarbazine
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Arm description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or

withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Placebo matched to ipilimumab intravenous solution was administered every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression, unacceptable toxicity, or withdrawal of consent.

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

Dosage and administration details:

Dacarbazine intravenous solution 850-mg/m² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.

Number of subjects in period 1^[1]	Ipilimumab and Dacarbazine	Placebo and Dacarbazine
Started	250	252
Completed	247	251
Not completed	3	1
Subject no longer meet study criteria	3	-
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 681 subjects who were enrolled, only 502 were randomised.

Period 2

Period 2 title	Received Treatment in Induction Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ipilimumab and Dacarbazine
Arm description:	
Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m ² ; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.	
Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-734016
Other name	MDX-010
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
Induction Phase: Subjects were administered with ipilimumab intravenous solution, 10 mg/kg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Maintenance Phase: Ipilimumab intravenous solution: 10 mg/kg, every 12 weeks was continued until PD.	
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
Dacarbazine intravenous solution 850-mg/m ² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.	
Arm title	Placebo and Dacarbazine

Arm description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
Placebo matched to ipilimumab intravenous solution was administered every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression, unacceptable toxicity, or withdrawal of consent.	
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
Dacarbazine intravenous solution 850-mg/m ² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.	

Number of subjects in period 2	Ipilimumab and Dacarbazine	Placebo and Dacarbazine
Started	247	251
Completed	45	54
Not completed	202	197
Consent withdrawn by subject	6	5
Physician decision	2	-
Adverse event, non-fatal	6	7
Death	8	15
Deterioration/Undocumented Progression	9	8
Study Drug Toxicity	83	10
Disease Progression	88	152

Period 3

Period 3 title	Received Treatment in Maintenance Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and Dacarbazine

Arm description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-734016
Other name	MDX-010
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Induction Phase: Subjects were administered with ipilimumab intravenous solution, 10 mg/kg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Maintenance Phase: Ipilimumab intravenous solution: 10 mg/kg, every 12 weeks was continued until PD.

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

Dosage and administration details:

Dacarbazine intravenous solution 850-mg/m² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.

Arm title	Placebo and Dacarbazine
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Arm description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Placebo matched to ipilimumab intravenous solution was administered every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression, unacceptable toxicity, or withdrawal of consent.

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

Dosage and administration details:

Dacarbazine intravenous solution 850-mg/m² was administered as 30-60 minutes infusion every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent.

Number of subjects in period 3^[2]	Ipilimumab and Dacarbazine	Placebo and Dacarbazine
Started	43	53
Completed	11	6
Not completed	32	47
Consent withdrawn by subject	1	3
Adverse event, non-fatal	-	3
Deterioration/Undocumented Progression	1	-
Study Drug Toxicity	4	-
Disease Progression	26	41

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of 99 subjects who completed induction phase, only 96 subjects entered maintenance phase.

Period 4

Period 4 title	Follow-up Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and Dacarbazine

Arm description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo and Dacarbazine

Arm description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Ipilimumab and Dacarbazine	Placebo and Dacarbazine
Started	11	6
Completed	0	0
Not completed	247	251
Physician decision	2	-
Documented Disease Progression	114	194
Still on Treatment	1	-
Other Reasons	5	3
Death	8	15
Deterioration/Undocumented Progression	10	8
Adverse Event Unrelated to Study Drug	6	10
Study Drug Toxicity	89	10

Subject Request	7	8
Administrative Reason by Sponsor	5	3
Joined	236	245
Re-joined for follow-up	236	245

Baseline characteristics

Reporting groups

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine	Total
Number of subjects	250	252	502
Age categorical Units: Subjects			
<65 years	165	177	342
≥65 years	85	75	160
Age continuous Units: years arithmetic mean standard deviation	57.5 ± 13.51	56.4 ± 13.71	-
Gender categorical Units: Subjects			
Female	98	103	201
Male	152	149	301

End points

End points reporting groups

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or

withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Primary: Overall survival (OS)

End point title	Overall survival (OS)
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End point description:

OS was defined as the time from the date of randomisation until the date of death. Analysis of OS was to be done once 416 deaths had occurred (primary endpoint). However, analysis occurred at 414 deaths (February 7, 2011), due to operational timing of the study. Median number of months of OS and associated confidence interval calculated using the method of Brookmeyer and Crowley. The analysis was performed in all randomised subjects whose survival follow-up was current (defined as having died or last known alive date occurring on or after the data cutoff date, which was when a total of 414 deaths occurred).

End point type	Primary
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End point timeframe:

Date of randomisation to 37 months through 5-year follow-up and up to approximately 76 months

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Months				
median (confidence interval 95%)	11.17 (9.4 to 13.6)	9.07 (7.75 to 10.51)		

Statistical analyses

Statistical analysis title	Overall survival
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Statistical analysis description:

The improvement in OS for ipilimumab plus Dacarbazine versus placebo plus Dacarbazine was analysed using Kaplan-Meier plot.

Comparison groups	Placebo and Dacarbazine v Ipilimumab and Dacarbazine
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Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.716
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.588
upper limit	0.872

Secondary: Survival Rate at 1 Year, 18 Months, 2 Years, and 3 Years

End point title	Survival Rate at 1 Year, 18 Months, 2 Years, and 3 Years
End point description:	The survival rate (percentage of subjects alive) was defined as the probability that a subject is alive at 1 year (or 18 months, 2 years, or 3 years) following randomisation and was estimated via the Kaplan-Meier method. The analysis was performed in all the subjects who were randomised to a treatment group.
End point type	Secondary
End point timeframe:	
Date of randomisation to 3 years following randomisation	

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of subjects				
number (confidence interval 95%)				
At 1 year	47.3 (41 to 53.6)	36.3 (30.4 to 42.4)		
At 18 months	35.6 (29.7 to 41.6)	26.1 (20.7 to 31.6)		
At 2 years	28.5 (22.9 to 34.2)	17.9 (13.3 to 22.8)		
At 3 years	20.8 (15.7 to 26.1)	12.2 (8.2 to 16.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

DCR=number whose best overall response (BOR) was partial response (PR), complete response (CR) or stable disease (SD), divided by all randomised subjects (unevaluable subjects included). BOR=date of first dose to last tumor assessment prior to subsequent cancer therapy (including tumor resection, excluding palliative local radiotherapy). Modified World Health Organization criteria: CR=disappearance of all lesions; no evidence of progressive disease (PD); PR=50% or more decrease in the sum of products of the longest diameter and greatest perpendicular diameter of all index lesions compared with baseline; SD=neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD; PD=at least 25% increase in sum of products of all index lesions and/or appearance of any new lesions; nonindex lesions: appearance of any new lesions and/or unequivocal progression of nonindex lesions. The analysis was performed in all the subjects who were randomised to a treatment group.

End point type	Secondary
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End point timeframe:

First dose to last tumor assessment prior to subsequent therapy at data cutoff for Primary Endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of subjects				
number (confidence interval 95%)	33.2 (27.4 to 39.4)	30.2 (24.6 to 36.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Number of Months of Progression-free Survival (PFS)

End point title	Median Number of Months of Progression-free Survival (PFS)
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End point description:

PFS=time between randomisation and date of progression or death, whichever occurs first. Subjects who died without reported prior progression were considered to have progressed on date of death. For those alive and not progressed, PFS was censored on date of last evaluable tumor assessment (TA). Those who have not died and have no recorded postbaseline TA were censored at randomisation. Those who died without any recorded postbaseline TA were considered to have progressed on date of death. Progressive disease defined using modified criteria of the World Health Organization: demonstration of at least a 25% increase in the sum of products of all index lesions or the appearance of any new lesions. For nonindex lesions: appearance of any new lesions or unequivocal progression of nonindex lesions. The analysis was performed in all the subjects who were randomised to a treatment group.

End point type	Secondary
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End point timeframe:

Randomisation to date of progression or death to approximately 5 years

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Month				
median (confidence interval 95%)				
PFS per IRC	2.76 (2.63 to 3.29)	2.6 (2.56 to 2.66)		
PFS per investigator	2.73 (2.63 to 3.48)	2.63 (2.6 to 2.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Rate Truncated at Week 12

End point title	Progression-free Survival (PFS) Rate Truncated at Week 12
End point description:	
PFS rate=probability subject was progression-free at Day 78, calculated as total subjects receiving treatment and with an overall response of stable disease (SD), partial response (PR), or complete response (CR) at Week 12, divided by total subjects. For those alive and not progressed at or before Week 12, PFS censored on date of last evaluable tumor assessment (TA) at or before Week 12. Those with an assessment of PD prior to Week 12 and subsequent assessment of SD, PR, or CR at Week 12 were called progression-free at Week 12. Those with no recorded postbaseline TA dated on or before Day 109, and who had not died on or before Day 109, were censored at randomisation. PD=at least 25% increase in sum of products of all index lesions or appearance of any new lesions. Investigator and independent review committee (IRC) assessed radiologic imaging studies, photographs of skin lesions, and clinical data. The analysis was performed in all subjects who were randomised to a treatment group.	
End point type	Secondary
End point timeframe:	
Day 78	

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of subjects				
number (confidence interval 95%)				
PFS rate at Week 12 by IRC	55.4 (48.6 to 62.1)	50.7 (44.2 to 57.3)		
PFS rate at Week 12 by Investigator	58.5 (51.9 to 65)	54 (47.5 to 60.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate (BORR)

End point title	Best Overall Response Rate (BORR)
End point description:	
BORR=number with Best Overall Response (BOR) of complete response (CR) or partial response (PR), divided by total number of randomised subjects. BOR=date of first dose to the last tumor assessment prior to subsequent cancer therapy. Independent review committee (IRC) assessment using modified criteria of the World Health Organization (mWHO): CR=disappearance of all lesions; no evidence of progressive disease; PR=50% or greater decrease in the sum of products of the longest diameter and greatest perpendicular diameter of all index lesions compared with baseline. Immune-related (ir) response criteria assess tumor response in subjects on immunotherapy: irCR=disappearance of all lesions in 2 consecutive observations at least 4 weeks apart; irPR=50% or greater decrease in total measurable tumor burden compared with peak in 2 observations at least 4 weeks apart. Analysis was performed in all subjects who were randomised.	
End point type	Secondary
End point timeframe:	
First dose to last tumor assessment at data cutoff for primary endpoint (approximately 5 years)	

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of subjects				
number (confidence interval 95%)				
IRC BORR	15.2 (11 to 20.3)	10.3 (6.9 to 14.8)		
irBORR	16.8 (12.4 to 22)	11.1 (7.5 to 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Randomised Subjects With Response of Complete Response (CR) or Partial Response (PR)

End point title	Duration of Response (DOR): Randomised Subjects With Response of Complete Response (CR) or Partial Response (PR)
End point description:	
DOR was defined as time between first date of CR or PR, and the date of no progressive disease or death (whichever occurred first) in subjects with best overall response as CR or PR. Subjects who remained alive, DOR was last evaluable Tumor Assessment. IRC assessment using mWHO criteria : CR as disappearance of all lesions within 4 weeks, PR as $\geq 50\%$ decrease in index lesions from baseline, 25% increase compared to nadir or 50% decrease in SPD from baseline for PD and SD respectively. Immune-related (ir) response criteria defined CR as disappearance of all lesions within 4 weeks, PR as $\geq 50\%$ decrease in Total Measurable Tumor Burden (TMTB) from baseline, 25% increase compared to nadir or 50% decrease in TMTB from baseline for PD and SD respectively. Analysis was performed in subjects who were randomised and responded to CR, PR, irCR, or irPR. Here, 'n' signifies subjects who responded by mWHO and irRC criteria.	
End point type	Secondary
End point timeframe:	
Day of CR or PR to day of PD or death up to data cutoff for primary endpoint (approximately 5 years)	

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Months				
median (confidence interval 95%)				
IRC DOR (n=38, 26)	19.3 (12.1 to 26.1)	8.1 (5.2 to 19.8)		
ir-DOR (n=42, 28)	21.1 (16.5 to 26.1)	10.2 (5.6 to 24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response: All Randomised Subjects With Response to Treatment

End point title	Time to Response: All Randomised Subjects With Response to Treatment
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End point description:

Time to response was defined as the time between the first dose of study therapy and the date when measurement criteria were met for Best Overall Response (BOR) of partial response (PR) or complete response (CR), whichever occurred first, per independent review committee. Note that if an overall response of PR occurred before confirmation of CR, the time to response endpoint was not determined by the time that the BOR of CR was shown but rather by the earlier time point showing PR. Modified criteria of the World Health Organization: CR=disappearance of all lesions; no evidence of progressive disease (PD); PR=50% or more decrease in the sum of products of the longest and greatest perpendicular diameters (SPD) of all index lesions compared with baseline; PD=an increase of 25% or greater in the SPD of index lesions compared with the smallest recorded sum, or the appearance of 1 or more new lesions. The analysis was performed in all the subjects who were randomised to a treatment group.

End point type	Secondary
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End point timeframe:

First dose to date of BOR up to data cutoff for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Month				
median (full range (min-max))	2.6 (2.3 to 3.9)	2.7 (2.5 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease (SD): Randomised Subjects With Stable Disease

End point title	Duration of Stable Disease (SD): Randomised Subjects With Stable Disease
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End point description:

Duration of SD was defined as the time between Week 12 and date of progressive disease (PD) or death, whichever occurs first in subjects whose Best Overall Response (BOR) was SD. Subjects who underwent tumor resection following Week 12 but prior to PD, duration of SD was censored on date of last evaluable tumor assessment (TA) prior to resection. For those with BOR of SD at Week 12, date of PD was used in analysis of duration of SD. For those with BOR=SD who have not subsequently progressed and who remain alive, duration of SD censored on date of last evaluable TA. Independent review committee (IRC) assessment using mWHO criteria: SD=insufficient decrease to qualify for partial response or sufficient increase to qualify for PD; PD=an increase of 25% or more in sum of products of longest diameter and greatest perpendicular diameter of index lesions compared with smallest recorded sum, or appearance of 1 or more new lesions. Analysis was performed in all the subjects who were randomised.

End point type	Secondary
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End point timeframe:

Week 12 to date of disease progression or death up to data cutoff for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Months				
median (confidence interval 95%)				
IRC (n=45, 50)	4.7 (1.9 to 9.2)	4.6 (3.2 to 6.9)		
Immune-related (n=45, 57)	4.8 (2.8 to 7.7)	3.4 (2.5 to 5.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Brain Metastasis-Free Survival at Time of Data Cutoff

End point title	Percentage of Subjects With Brain Metastasis-Free Survival at Time of Data Cutoff
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End point description:

Brain metastasis-free survival was defined as the time from randomisation to the date of progression with a new lesion located in the brain. New brain lesions prior to Week 12 constituted a progression event (unlike main progression-free survival analysis). A subject who dies without documentation of a brain lesion was considered to have progressed with brain metastasis on the date of death. Subjects who are free of brain metastasis were censored on the date of their last tumor assessment. An independent review committee evaluated images of subjects with clinical symptoms to determine the number of those free of brain metastasis. The brain metastasis-free status was reported as a percent of subjects (n/N), where n= subjects with metastasis-free brains at data cutoff for the Primary Endpoint and N= randomised subjects. A 2-sided Clopper and Pearson confidence interval was performed. Analysis was performed in all the subjects who were randomised.

End point type	Secondary
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End point timeframe:

Date of randomisation up to data cutoff for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of subjects				
number (confidence interval 95%)	93.6 (89.8 to 96.3)	90.9 (86.6 to 94.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Drug-related AEs, AEs Leading to Discontinuation, Serious Adverse Events (SAEs), Drug-related SAEs, Drug-related Hypersensitivity, Immune-related AEs/SAEs, and Inflammatory AEs/SAEs

End point title	Number of Subjects With Adverse Events (AEs), Drug-related AEs, AEs Leading to Discontinuation, Serious Adverse Events (SAEs), Drug-related SAEs, Drug-related Hypersensitivity, Immune-related AEs/SAEs, and Inflammatory AEs/SAEs
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End point description:

AE=any new undesirable symptom, sign, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event was not considered to be drug-related. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling. Randomisation=Day 1; start of treatment (first dose) =Week 1. Summarization time frame is from first dose to 70 days after last dose of study at time of 414 deaths. The analysis was performed in all the subjects who received at least 1 dose of the study drug.

End point type	Secondary
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End point timeframe:

Week 1 (First Dose) to 70 days after last dose of study up to data cutoff for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: Subjects				
AEs	244	236		
Drug-related AEs	221	192		
Discontinuations due to AEs	114	46		
SAEs	170	121		
Drug-related SAEs	116	17		
Drug-related hypersensitivity	15	6		
Immune-related AEs	187	77		
Immune-related SAEs	91	3		
Inflammatory AEs	201	117		
Inflammatory SAEs	101	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects With Grade 2-4 and Grade 3-4 Immune-related Adverse Events (irAEs) With Resolution Resolved

End point title	Number of subjects With Grade 2-4 and Grade 3-4 Immune-related Adverse Events (irAEs) With Resolution Resolved
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End point description:

IrAEs included the categories: gastrointestinal (GI), diarrhea, liver, endocrine, and skin. Grade 2=moderate adverse events (AEs); minimal, local, or noninvasive intervention indicated. Grade 3=severe AEs, medically significant but not immediately life-threatening. Grade 4=life-threatening consequences; urgent intervention indicated. Resolution is defined as improvement to Grade 1 or less or to the Grade at baseline (prior to treatment). The analysis was performed in all the subjects who received at least 1 dose of the study drug and had this specific event. Here 'n' signifies number of subjects evaluable for this outcome measure in both treatment arm respectively.

End point type	Secondary
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End point timeframe:

Week 1 (first dose) to 70 days after last dose up to data cutoff for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: Subjects				
GI AE Grade 2-4 (n=39, 7)	36	7		
GI AE Grade 3-4 (n=14, 0)	13	0		
Liver AE Grade 2-4 (n=89, 8)	81	4		
Liver AE Grade 3-4 (n=69, 5)	63	2		
Skin AE Grade 2-4 (n=46, 2)	42	2		
Skin AE Grade 3-4 (n=8, 0)	6	0		
Diarrhea AE Grade 2-4 (n=31, 7)	29	7		
Diarrhea AE Grade 3-4 (n=10, 0)	9	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Grade 2-4, Grade 3-4 Immune-related Adverse Events (IrAEs)

End point title	Time to Resolution of Grade 2-4, Grade 3-4 Immune-related Adverse Events (IrAEs)
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End point description:

IrAEs included the categories: gastrointestinal (GI), diarrhea, liver, endocrine, and skin. Grade 2=Moderate adverse events (AEs); minimal, local or noninvasive intervention indicated. Grade 3=severe AEs, medically significant but not immediately life-threatening. Grade 4=life-threatening consequences; urgent intervention indicated. Time to resolution is defined as improvement to Grade 1 or less or to the Grade at baseline (prior to treatment). The analysis was performed in all the subjects who received at least 1 dose of the study drug and had this specific event that resolved. Here "99999" represents that median time to resolution could not be computed due to low/no occurrence of either the resolution of the AE or low/no occurrence the AE in this arm. Here 'n' signifies number of subjects evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Week 1 (first dose) to 70 days after last dose up to database lock for primary endpoint (approximately 5 years)

End point values	Ipilimumab and Dacarbazine	Placebo and Dacarbazine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	251		
Units: Weeks				
median (confidence interval 95%)				
GI AE Grade 2-4 (n=36, 7)	2 (1.14 to 2.71)	0.14 (0.14 to 0.29)		
GI Grade 3-4 (n=13, 0)	2.14 (2 to 4.57)	99999 (99999 to 99999)		
Liver AE Grade 2-4 (n=81, 4)	3.43 (3.14 to 4.43)	99999 (99999 to 99999)		
Liver AE Grade 3-4 (n=63, 2)	3.43 (3 to 4.43)	99999 (99999 to 99999)		
Skin AE Grade 2-4 (n=42, 2)	4.71 (3.14 to 7)	0.93 (0.57 to 1.29)		
Skin AE Grade 3-4 (n=6, 0)	4.71 (3.14 to 5.29)	99999 (99999 to 99999)		
Diarrhea AE Grade 2-4 (n=29, 7)	1.43 (0.71 to 2.57)	0.14 (0.14 to 0.29)		
Diarrhea AE Grade 3-4 (n=9, 0)	2 (0.71 to 2.57)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 1 (First Dose) to 70 days after last dose of study drug up to last subject, last visit (LPLV) of follow up period; approximately 7 years.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ipilimumab and Dacarbazine
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Reporting group description:

Ipilimumab: Intravenous solution; intravenous; 10 mg/kg; 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24, until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution; intravenous; 850 mg/m²; 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. In Maintenance Phase: Only Ipilimumab: 10 mg/kg, every 12 weeks was continued until PD. Dacarbazine was given up to Week 22 and was not given in the Maintenance Phase. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Reporting group title	Placebo and Dacarbazine
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Reporting group description:

Placebo: Intravenous solution, intravenous, 0 mg, 1 dose every 3 weeks for 12 weeks, then 1 dose every 12 weeks starting at Week 24; until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Dacarbazine: Intravenous solution, intravenous, 850 mg/m², 1 dose every 3 weeks for 22 weeks, until PD, unacceptable toxicity, or withdrawal of consent. Subjects who experienced PD or who did not wish to continue study assessments in the Induction or Maintenance Phases entered the Follow-up Phase.

Serious adverse events	Ipilimumab and Dacarbazine	Placebo and Dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	170 / 247 (68.83%)	121 / 251 (48.21%)	
number of deaths (all causes)	193	217	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 247 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 6	
Laryngeal neoplasm			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			

subjects affected / exposed	2 / 247 (0.81%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 3	
Malignant pleural effusion			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain neoplasm			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	35 / 247 (14.17%)	58 / 251 (23.11%)	
occurrences causally related to treatment / all	0 / 36	0 / 58	
deaths causally related to treatment / all	0 / 58	0 / 81	
Transitional cell carcinoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 247 (0.40%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to skin			

subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	2 / 247 (0.81%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 247 (1.21%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor venous access			

subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Malaise			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Condition aggravated			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	6 / 247 (2.43%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	3 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	19 / 247 (7.69%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	15 / 19	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperpyrexia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chills			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 247 (0.40%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperthermia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia pain			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 247 (0.81%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 247 (1.21%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 247 (0.00%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 247 (0.81%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	48 / 247 (19.43%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	72 / 73	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased subjects affected / exposed	4 / 247 (1.62%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance increased subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased subjects affected / exposed	49 / 247 (19.84%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	68 / 70	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased subjects affected / exposed	3 / 247 (1.21%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			

subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 247 (0.81%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Speech disorder			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Headache			
subjects affected / exposed	5 / 247 (2.02%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Presyncope			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve disorder			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 247 (1.62%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	4 / 4	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 247 (1.62%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	2 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 247 (2.43%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	7 / 8	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 247 (1.21%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 247 (1.21%)	7 / 251 (2.79%)	
occurrences causally related to treatment / all	3 / 3	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 247 (0.40%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal polyp haemorrhage			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctocolitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 247 (1.21%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	8 / 247 (3.24%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	16 / 247 (6.48%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	23 / 23	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 247 (4.05%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	10 / 10	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 247 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 247 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	3 / 247 (1.21%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	3 / 247 (1.21%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	4 / 247 (1.62%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative rash			

subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 247 (0.81%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			

subjects affected / exposed	2 / 247 (0.81%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 247 (0.40%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck mass			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 247 (1.21%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary mass			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 247 (1.21%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related infection			
subjects affected / exposed	2 / 247 (0.81%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	2 / 247 (0.81%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 247 (2.02%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 247 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 247 (1.21%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab and Dacarbazine	Placebo and Dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 247 (89.07%)	218 / 251 (86.85%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 247 (6.48%)	9 / 251 (3.59%)	
occurrences (all)	24	18	
Weight decreased			
subjects affected / exposed	27 / 247 (10.93%)	13 / 251 (5.18%)	
occurrences (all)	43	23	
Aspartate aminotransferase increased			
subjects affected / exposed	50 / 247 (20.24%)	14 / 251 (5.58%)	
occurrences (all)	117	22	
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 247 (7.69%)	9 / 251 (3.59%)	
occurrences (all)	36	22	
Alanine aminotransferase increased			
subjects affected / exposed	60 / 247 (24.29%)	14 / 251 (5.58%)	
occurrences (all)	164	24	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 247 (6.48%)	10 / 251 (3.98%)	
occurrences (all)	24	12	
Headache			
subjects affected / exposed	38 / 247 (15.38%)	33 / 251 (13.15%)	
occurrences (all)	63	54	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	16 / 247 (6.48%)	14 / 251 (5.58%)	
occurrences (all)	31	24	
Anaemia			
subjects affected / exposed	20 / 247 (8.10%)	12 / 251 (4.78%)	
occurrences (all)	38	28	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	29 / 247 (11.74%)	32 / 251 (12.75%)	
occurrences (all)	57	63	
Fatigue			
subjects affected / exposed	100 / 247 (40.49%)	95 / 251 (37.85%)	
occurrences (all)	265	200	
Pyrexia			
subjects affected / exposed	82 / 247 (33.20%)	20 / 251 (7.97%)	
occurrences (all)	145	35	
Chills			
subjects affected / exposed	27 / 247 (10.93%)	10 / 251 (3.98%)	
occurrences (all)	44	14	
Chest pain			
subjects affected / exposed	13 / 247 (5.26%)	8 / 251 (3.19%)	
occurrences (all)	17	10	
Influenza like illness			
subjects affected / exposed	19 / 247 (7.69%)	11 / 251 (4.38%)	
occurrences (all)	25	16	
Oedema peripheral			
subjects affected / exposed	20 / 247 (8.10%)	12 / 251 (4.78%)	
occurrences (all)	32	19	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	13 / 247 (5.26%)	6 / 251 (2.39%)	
occurrences (all)	16	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	119 / 247 (48.18%)	120 / 251 (47.81%)	
occurrences (all)	305	302	
Abdominal pain			
subjects affected / exposed	28 / 247 (11.34%)	29 / 251 (11.55%)	
occurrences (all)	39	49	
Diarrhoea			
subjects affected / exposed	83 / 247 (33.60%)	61 / 251 (24.30%)	
occurrences (all)	162	103	
Vomiting			

subjects affected / exposed	74 / 247 (29.96%)	69 / 251 (27.49%)	
occurrences (all)	152	124	
Constipation			
subjects affected / exposed	69 / 247 (27.94%)	68 / 251 (27.09%)	
occurrences (all)	127	106	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 247 (10.12%)	25 / 251 (9.96%)	
occurrences (all)	37	33	
Dyspnoea			
subjects affected / exposed	25 / 247 (10.12%)	28 / 251 (11.16%)	
occurrences (all)	42	45	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	73 / 247 (29.55%)	22 / 251 (8.76%)	
occurrences (all)	212	38	
Rash			
subjects affected / exposed	63 / 247 (25.51%)	17 / 251 (6.77%)	
occurrences (all)	186	22	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 247 (3.64%)	13 / 251 (5.18%)	
occurrences (all)	11	17	
Insomnia			
subjects affected / exposed	22 / 247 (8.91%)	16 / 251 (6.37%)	
occurrences (all)	33	22	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	18 / 247 (7.29%)	20 / 251 (7.97%)	
occurrences (all)	34	31	
Arthralgia			
subjects affected / exposed	19 / 247 (7.69%)	18 / 251 (7.17%)	
occurrences (all)	30	36	
Back pain			
subjects affected / exposed	27 / 247 (10.93%)	23 / 251 (9.16%)	
occurrences (all)	42	29	

Pain in extremity subjects affected / exposed occurrences (all)	15 / 247 (6.07%) 31	22 / 251 (8.76%) 29	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	53 / 247 (21.46%) 105	47 / 251 (18.73%) 61	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2006	Provided additional information regarding tumour imaging assessments and disease response assessment criteria.
25 May 2006	Added an interim analysis of overall survival (OS), to be conducted at the same time as the analyses of other efficacy endpoints, i.e., when at least 416 events for progression-free survival (PFS) have been observed in the study and all subjects have been followed for at least 12 weeks; clarified that the comparison of OS between treatment arms was the main secondary analysis and described the testing procedure to be followed in order to maintain the overall significance level.
09 October 2008	Changed the primary objective to a comparison of overall survival and rank secondary objectives; added a Prohibited Therapy during the follow-up phase; clarified analyses of time to response and duration of response; made various administrative updates.
24 March 2009	Modified the dose skipping criteria for ipilimumab/placebo to make the criteria more conservative; changed the contact details for the BMS Study Director.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported