Clinical trial results:
A randomized, open-label, two-arm phase II trial comparing the efficacy of sequential Ipilimumab versus best supportive care following first-line chemotherapy in subjects with unresectable locally advanced/metastatic gastric or gastro-esophageal junction cancer

Summary

EudraCT number	2011-000853-22
Trial protocol	ES DE IT
Global end of trial date	02 April 2015

Results information

Result version number	v1 (current)
This version publication date	22 May 2016
First version publication date	22 May 2016

Trial information

Trial identification

Sponsor protocol code	CA184-162

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01585987
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee 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	02 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to compare the efficacy of Ipilimumab and standard of care as sequential or maintenance treatment immediately after first-line chemotherapy in the treatment of unresectable or metastatic gastric and gastro-esophageal cancer.

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	11 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Korea, Republic of: 53
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	143
EEA total number of subjects	52

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)	79
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 31 centres in 12 countries.

Pre-assignment

Screening details:

A total of 143 subjects were enrolled in the study, out of which 114 were randomized. 29 subjects were not randomised due to: 26 no longer met study criteria; 2 withdrew consent, 1 other reason.

Period 1

Period 1 title	Randomised
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab

Arm description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab 10 mg/kg of body weight was administered intravenously, over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression.

Arm title	All Best Supportive care (BSC)

Arm description:

All BSC includes both active and non-active BSC. Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation to this study), but no other active systemic anti-cancer treatment. In non-active BSC, the fluoropyrimidine used during lead-in chemotherapy was not continued on study and no other chemotherapy or active treatment was used

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuation of Capecitabine dose used during the lead-in chemotherapy, administered orally as per standard of care until disease progression or toxicity.

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

Continuation of 5-FU dose used during the lead-in chemotherapy, administered intravenously as per standard of care until disease progression or toxicity.

Investigational medicinal product name	Tegafur/Gimeracil/Oteracil potassium or S-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuation of S-1 dose used during the lead-in chemotherapy, administered orally as per standard of care until disease progression or toxicity.

Number of subjects in period 1[1]	Ipilimumab	All Best Supportive care (BSC)
Started	57	57
Completed	57	51
Not completed	0	6
Consent withdrawn by subject	-	4
No longer met criteria	-	2

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 143 subjects who were enrolled in the study, 114 were randomised. 29 subjects were not randomised due to: 26 no longer met study criteria; 2 withdrew consent, 1 other reason.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab

Arm description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab 10 mg/kg of body weight was administered intravenously, over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression.

Arm title	All Best Supportive care (BSC)

Arm description:

All BSC includes both active and non-active BSC. Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation to this study), but no other active systemic anti-cancer treatment. In non-active BSC, the fluoropyrimidine used during lead-in chemotherapy was not continued on study and no other chemotherapy or active treatment was used.

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuation of Capecitabine dose used during the lead-in chemotherapy, administered orally as per standard of care until disease progression or toxicity.

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Continuation of 5-FU dose used during the lead-in chemotherapy, administered intravenously as per standard of care until disease progression or toxicity.

Investigational medicinal product name	Tegafur/Gimeracil/Oteracil potassium or S-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuation of S-1 dose used during the lead-in chemotherapy, administered orally as per standard of care until disease progression or toxicity.

Number of subjects in period 2	Ipilimumab	All Best Supportive care (BSC)
Started	57	51
Completed	3	2
Not completed	54	49
Non-Specified	1	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	2
Poor/Non-Compliance	-	1
Adverse event, non-fatal	3	-
Maximum Clinical Benefit	-	1
Study Drug Toxicity	9	5
Lost to follow-up	-	1
Subject Request	-	1

Disease Progression	39	36

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab

Reporting group description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Reporting group title	All Best Supportive care (BSC)

Reporting group description:

All BSC includes both active and non-active BSC. Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation to this study), but no other active systemic anti-cancer treatment. In non-active BSC, the fluoropyrimidine used during lead-in chemotherapy was not continued on study and no other chemotherapy or active treatment was used

Reporting group values	Ipilimumab	All Best Supportive care (BSC)	Total
Number of subjects	57	57	114
Age, Customized Units: subjects			
Less than (<) 65 years of age	28	35	63
Greater, equal to (>=) 65 years of age	29	22	51
Age Continuous Units: years			
median	65	62	
full range (min-max)	34 to 86	32 to 80	-
Gender, Male/Female Units: subjects			
Female	21	16	37
Male	36	41	77
Region of Enrollment Units: Subjects			
Russian Federation	1	1	2
Singapore	1	1	2
Hong Kong	1	0	1
United States	8	6	14
Japan	7	5	12
Taiwan	1	0	1
Poland	0	2	2
Korea, Republic of	21	24	45
Italy	11	8	19
France	3	5	8
Germany	1	0	1
Spain	2	5	7

End points

End points reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Reporting group title	All Best Supportive care (BSC)

Reporting group description:

All BSC includes both active and non-active BSC. Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation to this study), but no other active systemic anti-cancer treatment. In non-active BSC, the fluoropyrimidine used during lead-in chemotherapy was not continued on study and no other chemotherapy or active treatment was used

Reporting group title	Ipilimumab

Reporting group description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Reporting group title	All Best Supportive care (BSC)

Reporting group description:

All BSC includes both active and non-active BSC. Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation to this study), but no other active systemic anti-cancer treatment. In non-active BSC, the fluoropyrimidine used during lead-in chemotherapy was not continued on study and no other chemotherapy or active treatment was used.

Primary: Immune-related Progression Free Survival (irPFS) as Per Assessment of a Blinded Independent Review Committee (IRC) According to Immune Related Response Criteria (irRC) Guidelines

End point title	Immune-related Progression Free Survival (irPFS) as Per Assessment of a Blinded Independent Review Committee (IRC) According to Immune Related Response Criteria (irRC) Guidelines

End point description:

irPFS is defined as the time between the randomisation date and the time of disease progression per irRC or death, whichever occurs first. irRC criteria=Measurable new lesions: incorporated into the tumor burden (eg, added to the index lesions); do not define progression unless the total measurable tumor burden increases by the required amount (25%). New non-measurable lesions: not considered progression if the total measurable tumor burden is stable or shrinking. irPFS was measured in months. The analysis was performed in all the subjects who were randomised.

End point type	Primary

End point timeframe:

Randomisation up to 91 irPFS events (Approximately 19 months)

End point values	Ipilimumab	All Best Supportive care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Months				
median (confidence interval 95%)	2.924 (1.61 to 5.158)	4.895 (3.45 to 6.538)		

Statistical analyses

Statistical analysis title	irPFS as per assessment of blinded IRC
Comparison groups	All Best Supportive care (BSC) v Ipilimumab
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0972 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.439
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.085
upper limit	1.908

Notes:

[1] - Significance level used: 0.2

Secondary: Progression Free Survival (PFS) Per Modified World Health Organization (mWHO) Criteria

End point title	Progression Free Survival (PFS) Per Modified World Health Organization (mWHO) Criteria

End point description:

PFS per mWHO was defined as the time between the randomisation date and the time of disease progression per mWHO criteria or death, whichever occurred first and was measured in months. mWHO criteria: New lesions always mean progression; Changes in non-measurable lesions contribute in the definitions of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD). The analysis was performed in all the subjects who were randomised.

End point type	Secondary

End point timeframe:

Randomisation up to 91 irPFS events (Approximately 19 months)

End point values	Ipilimumab	All Best Supportive care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Months				
median (confidence interval 95%)	2.727 (1.446	4.895 (3.45 to		

to 2.957)	6.078)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from the date of randomisation until the date of death. For those subjects who have not died, OS was censored on the last date the subject was known to be alive. Here, 99999 signifies data not estimable since the largest observation was censored.

End point type	Secondary

End point timeframe:

Randomisation up to end of study, April 2015 (Approximately 28 months)

End point values	Ipilimumab	All Best Supportive care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	51		
Units: Months				
median (confidence interval 95%)	12.68 (10.51 to 18.92)	12.06 (9.33 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Immune-Related Best Overall Response (irBOR)

End point title	Percentage of Subjects With Immune-Related Best Overall Response (irBOR)

End point description:

IrBOR rate was defined as the number of subjects whose Immune-related Best Overall Response (irBOR) criteria was Immune-related Complete Response (irCR) or Immune-related Partial Response (irPR), divided by the total number of subjects. The immune-related sum of products of diameters (irSPD) incorporates - in addition to the index lesions - measurable new lesions that may have developed on-study, providing an assessment that includes both index and new lesions. irCR=Complete disappearance of all tumor lesions (both index and non-index lesions with no new measurable/unmeasurable lesions). irPR=A 50% or greater decrease, relative to baseline of the irSPD, (based on irSPD of all index lesions and any measurable new lesions). The analysis was performed in all the subjects who were randomised.

End point type	Secondary

End point timeframe:

Randomisation up to 91 irPFS events (Approximately 19 months)

End point values	Ipilimumab	All Best Supportive care (BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percentage of subjects				
number (not applicable)	1.8	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of study treatment up to 90 days after the last dose of the study drug

Adverse event reporting additional description:

Study initiated: July 2012; End of Study: April 2015

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Ipilimumab 10 milligram per kilogram body weight (mg/kg) solution intravenously (IV), over 90 minutes, once every 3 weeks for 4 doses, then 10 mg/kg every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose). The option of re-introduction, defined as an additional 4 doses of ipilimumab (a dose of 10 mg/kg every 3 weeks) was allowed only at discretion of the investigator if criteria for re-induction were met.

Reporting group title	Active Best Supportive Care (BSC)

Reporting group description:

Active BSC includes the continuation of the fluoropyrimidine that was used during the lead-in chemotherapy (prior to randomisation)

Reporting group title	Non-Active BSC

Reporting group description:

Non-Active BSC involves supportive care with cessation of chemotherapy (no active drug).

Serious adverse events	Ipilimumab	Active Best Supportive Care (BSC)	Non-Active BSC
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 57 (54.39%)	19 / 45 (42.22%)	1 / 6 (16.67%)
number of deaths (all causes)	25	24	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Malignant neoplasm progression			
subjects affected / exposed	0 / 57 (0.00%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Gastrointestinal cancer metastatic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Disease progression			
subjects affected / exposed	6 / 57 (10.53%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 57 (1.75%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Malaise			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 57 (0.00%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 57 (1.75%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 57 (5.26%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 57 (1.75%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 57 (3.51%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	3 / 57 (5.26%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 57 (12.28%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	7 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystocholangitis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	2 / 57 (3.51%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorder			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Myalgia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 57 (3.51%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 57 (7.02%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 57 (12.28%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 57 (3.51%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ipilimumab	Active Best Supportive Care (BSC)	Non-Active BSC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 57 (96.49%)	42 / 45 (93.33%)	4 / 6 (66.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 57 (3.51%)	2 / 45 (4.44%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 57 (15.79%)	7 / 45 (15.56%)	0 / 6 (0.00%)
occurrences (all)	16	9	0
Pain			
subjects affected / exposed	3 / 57 (5.26%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Influenza like illness			
subjects affected / exposed	0 / 57 (0.00%)	3 / 45 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Asthenia			
subjects affected / exposed	12 / 57 (21.05%)	7 / 45 (15.56%)	0 / 6 (0.00%)
occurrences (all)	15	10	0
Chest pain			
subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Chills			
subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
Oedema peripheral			
subjects affected / exposed	8 / 57 (14.04%)	5 / 45 (11.11%)	0 / 6 (0.00%)
occurrences (all)	9	5	0
Fatigue			
subjects affected / exposed	26 / 57 (45.61%)	9 / 45 (20.00%)	0 / 6 (0.00%)
occurrences (all)	28	9	0
Mucosal inflammation			

subjects affected / exposed	0 / 57 (0.00%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	1 / 57 (1.75%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Productive cough			
subjects affected / exposed	3 / 57 (5.26%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Dyspnoea			
subjects affected / exposed	6 / 57 (10.53%)	5 / 45 (11.11%)	0 / 6 (0.00%)
occurrences (all)	6	5	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	5 / 57 (8.77%)	6 / 45 (13.33%)	0 / 6 (0.00%)
occurrences (all)	7	6	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 57 (0.00%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Insomnia			
subjects affected / exposed	5 / 57 (8.77%)	6 / 45 (13.33%)	0 / 6 (0.00%)
occurrences (all)	6	6	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 57 (15.79%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	10	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 57 (15.79%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	11	2	0
Weight decreased			
subjects affected / exposed	11 / 57 (19.30%)	5 / 45 (11.11%)	0 / 6 (0.00%)
occurrences (all)	11	5	0
Haemoglobin decreased			

subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Weight increased			
subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	1 / 6 (16.67%)
occurrences (all)	3	1	1
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 57 (8.77%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	5	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 57 (10.53%)	1 / 45 (2.22%)	1 / 6 (16.67%)
occurrences (all)	7	1	1
Headache			
subjects affected / exposed	4 / 57 (7.02%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Neuropathy peripheral			
subjects affected / exposed	10 / 57 (17.54%)	7 / 45 (15.56%)	0 / 6 (0.00%)
occurrences (all)	10	7	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 57 (3.51%)	7 / 45 (15.56%)	0 / 6 (0.00%)
occurrences (all)	2	7	0
Anaemia			
subjects affected / exposed	12 / 57 (21.05%)	5 / 45 (11.11%)	0 / 6 (0.00%)
occurrences (all)	16	8	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 57 (21.05%)	16 / 45 (35.56%)	0 / 6 (0.00%)
occurrences (all)	14	18	0
Dysphagia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	2 / 6 (33.33%)
occurrences (all)	0	1	2

Abdominal pain upper			
subjects affected / exposed	6 / 57 (10.53%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences (all)	7	4	0
Constipation			
subjects affected / exposed	10 / 57 (17.54%)	12 / 45 (26.67%)	0 / 6 (0.00%)
occurrences (all)	11	13	0
Dyspepsia			
subjects affected / exposed	5 / 57 (8.77%)	3 / 45 (6.67%)	0 / 6 (0.00%)
occurrences (all)	5	4	0
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 57 (5.26%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	19 / 57 (33.33%)	16 / 45 (35.56%)	0 / 6 (0.00%)
occurrences (all)	29	18	0
Vomiting			
subjects affected / exposed	17 / 57 (29.82%)	12 / 45 (26.67%)	0 / 6 (0.00%)
occurrences (all)	24	10	0
Abdominal distension			
subjects affected / exposed	3 / 57 (5.26%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Diarrhoea			
subjects affected / exposed	19 / 57 (33.33%)	9 / 45 (20.00%)	0 / 6 (0.00%)
occurrences (all)	36	12	0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	4 / 57 (7.02%)	8 / 45 (17.78%)	0 / 6 (0.00%)
occurrences (all)	3	16	0
Pruritus			
subjects affected / exposed	25 / 57 (43.86%)	3 / 45 (6.67%)	0 / 6 (0.00%)
occurrences (all)	31	3	0
Rash			

subjects affected / exposed	15 / 57 (26.32%)	2 / 45 (4.44%)	1 / 6 (16.67%)
occurrences (all)	18	2	1
Dry skin			
subjects affected / exposed	3 / 57 (5.26%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Alopecia			
subjects affected / exposed	3 / 57 (5.26%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 57 (7.02%)	0 / 45 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 57 (7.02%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	9	2	0
Arthralgia			
subjects affected / exposed	3 / 57 (5.26%)	4 / 45 (8.89%)	0 / 6 (0.00%)
occurrences (all)	4	6	0
Back pain			
subjects affected / exposed	6 / 57 (10.53%)	3 / 45 (6.67%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Bone pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	2 / 57 (3.51%)	2 / 45 (4.44%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Neck pain			
subjects affected / exposed	2 / 57 (3.51%)	0 / 45 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 57 (36.84%)	14 / 45 (31.11%)	0 / 6 (0.00%)
occurrences (all)	24	15	0
Hypokalaemia			

subjects affected / exposed	8 / 57 (14.04%)	2 / 45 (4.44%)	0 / 6 (0.00%)
occurrences (all)	9	2	0
Hyponatraemia			
subjects affected / exposed	3 / 57 (5.26%)	1 / 45 (2.22%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Hypoalbuminaemia			
subjects affected / exposed	5 / 57 (8.77%)	5 / 45 (11.11%)	0 / 6 (0.00%)
occurrences (all)	6	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2012	The main purpose of the amendment was: • To modify the acceptable lead-in chemotherapy to allow a larger Japanese patient population to be included; • To add/clarify information on the women of Childbearing Potential (WOCBP) as per the most recent BMS policy; • To add specific language for immune-mediated Adverse Reactions; • To remove the mandatory bone scans; • Other administrative changes.
31 January 2013	The main purpose of the amendment was: • To allow subjects with a platelet count between 100,000 and 75,000 to enter the trial; • To add an additional acceptable lead-in chemotherapy • To add/clarify information on the definition of WOCBP; • Other minor changes to correct and/or clarify protocol requirements; • The amendment was applicable to all subjects; • The amendment will not impact data analysis.
08 May 2013	The main purpose of the amendment was: • To modify the requirement for local lab Free T3 and T4 testing at Screening from required to obtained if available, otherwise Total T3 and T4 testing is acceptable. • To allow Magnetic resonance imaging of the chest and remove the requirement for using the same scanner. • To remove the stipulation of not carrying out the interim analysis in case the timing of the interim analysis is within 6 months of the planned date of the primary analysis. • Other minor changes to correct and/or clarify protocol requirements.
28 March 2014	The main purpose of the amendment was to limit dosing of ipilimumab in the study to 3 years. The guidance for WOCBP was also clarified as per the most recent BMS policy. Other minor changes to correct and/or clarify protocol requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported