



Clinical trial results:

A Randomized, Multicenter, Double-Blind, Multinational, Phase 3 Trial Comparing the Efficacy of Ipilimumab in Addition to Paclitaxel and Carboplatin versus Placebo in Addition to Paclitaxel and Carboplatin in Subjects with Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC) with Squamous Histology

Summary

EudraCT number	2014-002604-25
Trial protocol	HU DE PL
Global end of trial date	03 May 2018

Results information

Result version number	v1 (current)
This version publication date	05 June 2019
First version publication date	05 June 2019

Trial information

Trial identification

Sponsor protocol code	CA184-153
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02279732
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb Research and Development
Sponsor organisation address	1717 West Nanjing Road, Shanghai, China, 200040
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb Research and Development, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb Research and Development, 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	03 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare overall survival (OS) of subjects with Stage IV/recurrent NSCLC of squamous histology who have been randomized to ipilimumab in addition to paclitaxel and carboplatin versus placebo in addition to paclitaxel and carboplatin and have received at least one dose of blinded study therapy.

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	15 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 268
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Singapore: 2
Worldwide total number of subjects	342
EEA total number of subjects	54

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)	0
From 65 to 84 years	229
85 years and over	113

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

342 participants enrolled, 295 were randomized to ipilimumab (148) and placebo arms (147). After chemotherapy, double blinded study treatment, which was the focus of the study, was started. Of all randomized participants, only 98 (ipilimumab arm) and 106 (placebo arm) participants received at least one dose of blinded study therapy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipi + PAC/CAR

Arm description:

Ipilimumab + paclitaxel/Carboplatin

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

Dosage and administration details:

Subjects received a dose of paclitaxel 175 mg/m² as IV solution.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a dose of Carboplatin AUC = 6 as IV solution.

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Ipilimumab 10 mg/kg as IV solution.

Arm title	Placebo + PAC/CAR
Arm description:	
Placebo + paclitaxel/Carboplatin	
Arm type	Placebo

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received a dose of paclitaxel 175 mg/m ² as IV solution.	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received a dose of Carboplatin AUC = 6 as IV solution.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received placebo matched to Ipilimumab as IV solution.	

Number of subjects in period 1^[1]	Ipi + PAC/CAR	Placebo + PAC/CAR
Started	98	106
Completed	0	0
Not completed	98	106
Adverse event, serious fatal	23	20
Disease progression	13	3
Adverse event, non-fatal	1	2
Maximum clinical benefit	1	-
Unknown	3	3
Unspecified	53	67
Study Drug Toxicity	2	-
Lost to follow-up	-	1
Subject requested to discontinue	-	1
Withdrawal by subject	2	7
Administrative reason by sponsor	-	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: 342 subjects enrolled, 295 were randomized to ipilimumab (148) and placebo arms (147). After chemotherapy, double blinded study treatment was started. Of all randomized subjects, only 98 (ipilimumab arm) and 106 (placebo arm) participants received at least one dose of blinded study therapy.

Baseline characteristics

Reporting groups

Reporting group title	Ipi + PAC/CAR
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Reporting group description:

Ipilimumab + paclitaxel/Carboplatin

Reporting group title	Placebo + PAC/CAR
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Reporting group description:

Placebo + paclitaxel/Carboplatin

Reporting group values	Ipi + PAC/CAR	Placebo + PAC/CAR	Total
Number of subjects	98	106	204
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	68	75	143
From 65-84 years	30	31	61
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	60.9	59.8	
standard deviation	± 6.89	± 8.22	-
Gender categorical			
Units: Subjects			
Female	11	13	24
Male	87	93	180
Race/Ethnicity, Customized			
Units: Subjects			
Chinese	81	80	161
Non-Chinese	17	26	43

End points

End points reporting groups

Reporting group title	Ipi + PAC/CAR
Reporting group description: Ipilimumab + paclitaxel/Carboplatin	
Reporting group title	Placebo + PAC/CAR
Reporting group description: Placebo + paclitaxel/Carboplatin	

Primary: Overall Survival (OS) of all Randomized Subjects Who Received at Least one Dose of Blinded Study Therapy

End point title	Overall Survival (OS) of all Randomized Subjects Who Received at Least one Dose of Blinded Study Therapy ^[1]
End point description: OS is defined as the time from the date of randomization 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. Analysis population included all enrolled subjects who were randomized and received at least 1 dose of blinded study therapy. Here '99999' signifies data not available. The sponsor decided to discontinue enrollment and randomization in the study CA184-153 effective 25-Sep-2015. As a result, the primary endpoint was not analyzed for study CA184-153.	
End point type	Primary
End point timeframe: Approximately 43 months post study start	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The sponsor decided to discontinue enrollment and randomization in the study effective 25-Sep-2015. As a result, the primary endpoint was not analyzed for study.

End point values	Ipi + PAC/CAR	Placebo + PAC/CAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	106		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival of all Randomized Subjects

End point title	Overall Survival of all Randomized Subjects
End point description: OS is defined as the time from the date of randomization until the date of death. For those participants who have not died, OS was censored on the last date the participant was known to be alive. All randomized subjects included all enrolled subjects who were randomized to a treatment arm. Here '99999' signifies data not available. The sponsor decided to discontinue enrollment and randomization in the study CA184-153 effective 25-Sep-2015. As a result, the primary endpoint was not	

analyzed for study CA184-153.

End point type	Secondary
End point timeframe:	
Approximately 43 months post study start	

End point values	Ipi + PAC/CAR	Placebo + PAC/CAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Among all Randomized Subjects who Received at Least one Dose of Blinded Study Therapy Using Modified World Health Organization (mWHO) Criteria

End point title	Progression-free Survival (PFS) Among all Randomized Subjects who Received at Least one Dose of Blinded Study Therapy Using Modified World Health Organization (mWHO) Criteria
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End point description:

PFS is defined as the time between the date of randomization and the date of progression per mWHO criteria or death, whichever occurs first. A subject who died without reported progression per mWHO criteria was considered to have progressed on the date of death. For those subjects who remained alive and had not progressed, PFS was censored on the date of last evaluable tumor assessment. For those subjects who remained alive and had no recorded post-baseline tumor assessment, PFS was censored on the day of randomization. Analysis population included all enrolled subjects who were randomized and received at least 1 dose of blinded study therapy. Here '99999' signifies data not available. The sponsor decided to discontinue enrollment and randomization in the study CA184-153 effective 25-Sep-2015. As a result, the primary endpoint was not analyzed for study CA184-153.

End point type	Secondary
End point timeframe:	
Up to 43 months	

End point values	Ipi + PAC/CAR	Placebo + PAC/CAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	106		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of blinded study therapy and 90 days after last dose of blinded study therapy
(Approximately 43 months assessed up to May 2018)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Ipilimumab + Carboplatin/Paclitaxel
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Reporting group description:

Participants received a dose of paclitaxel 175 milligram per meter square (mg/m²) and Carboplatin area under the curve (AUC) equal to (=) 6 as intravenous (IV) solution for up to 6 doses starting at randomization. Participants received Ipilimumab 10 milligram per kilogram (mg/kg) as IV solution every 3 weeks (Q3W) for up to 4 doses starting at cycle 3 during induction phase and every 12 weeks (Q12W) during maintenance phase beginning 9 weeks after last ipilimumab induction dose for a maximum treatment period of 3 years from the first dose of blinded study therapy.

Reporting group title	Placebo + Carboplatin/Paclitaxel
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Reporting group description:

Participants received a dose of paclitaxel 175 mg/m² and Carboplatin AUC = 6 as IV solution for up to 6 doses starting at randomization. Participants received placebo matched to Ipilimumab as IV solution Q3W for up to 4 doses starting at cycle 3 during induction phase and Q12W during maintenance phase beginning 9 weeks after last placebo induction dose for a maximum treatment period of 3 years from the first dose of blinded study therapy.

Serious adverse events	Ipilimumab + Carboplatin/Paclitaxel	Placebo + Carboplatin/Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 98 (40.82%)	33 / 106 (31.13%)	
number of deaths (all causes)	15	9	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
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	7 / 98 (7.14%)	4 / 106 (3.77%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 7	0 / 4	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	1 / 98 (1.02%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 98 (3.06%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 98 (4.08%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 98 (1.02%)	4 / 106 (3.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 98 (2.04%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza a virus test positive			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar ischaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraplegia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 98 (3.06%)	4 / 106 (3.77%)	
occurrences causally related to treatment / all	4 / 5	4 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 98 (1.02%)	3 / 106 (2.83%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 98 (0.00%)	3 / 106 (2.83%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Leukopenia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 98 (2.04%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 98 (1.02%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 98 (2.04%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 98 (1.02%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 98 (2.04%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (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			

Acute kidney injury			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothalamo-Pituitary disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary hypothyroidism			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (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			
Back pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
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	1 / 98 (1.02%)	0 / 106 (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	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial toxemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 98 (4.08%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 98 (6.12%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	3 / 6	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 98 (1.02%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab + Carboplatin/Paclitax el	Placebo + Carboplatin/Paclitaxe l	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 98 (93.88%)	89 / 106 (83.96%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 98 (14.29%)	14 / 106 (13.21%)	
occurrences (all)	16	15	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 98 (12.24%)	10 / 106 (9.43%)	
occurrences (all)	12	12	
Blood albumin decreased			
subjects affected / exposed	6 / 98 (6.12%)	2 / 106 (1.89%)	
occurrences (all)	7	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 98 (5.10%)	0 / 106 (0.00%)	
occurrences (all)	5	0	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	6 / 98 (6.12%)	1 / 106 (0.94%)	
occurrences (all)	6	1	
Haemoglobin decreased			
subjects affected / exposed	35 / 98 (35.71%)	28 / 106 (26.42%)	
occurrences (all)	53	44	
Neutrophil count decreased			
subjects affected / exposed	7 / 98 (7.14%)	7 / 106 (6.60%)	
occurrences (all)	21	15	
Platelet count decreased			
subjects affected / exposed	16 / 98 (16.33%)	8 / 106 (7.55%)	
occurrences (all)	28	11	
Red blood cell count decreased			
subjects affected / exposed	11 / 98 (11.22%)	2 / 106 (1.89%)	
occurrences (all)	15	2	
Weight decreased			
subjects affected / exposed	12 / 98 (12.24%)	3 / 106 (2.83%)	
occurrences (all)	13	3	
White blood cell count decreased			

subjects affected / exposed occurrences (all)	14 / 98 (14.29%) 31	15 / 106 (14.15%) 28	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 98 (6.12%)	6 / 106 (5.66%)	
occurrences (all)	6	6	
Hypoaesthesia			
subjects affected / exposed	12 / 98 (12.24%)	7 / 106 (6.60%)	
occurrences (all)	13	8	
Neuropathy peripheral			
subjects affected / exposed	7 / 98 (7.14%)	4 / 106 (3.77%)	
occurrences (all)	7	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	34 / 98 (34.69%)	35 / 106 (33.02%)	
occurrences (all)	53	46	
Erythropenia			
subjects affected / exposed	10 / 98 (10.20%)	8 / 106 (7.55%)	
occurrences (all)	12	9	
Leukopenia			
subjects affected / exposed	36 / 98 (36.73%)	42 / 106 (39.62%)	
occurrences (all)	64	107	
Lymphopenia			
subjects affected / exposed	4 / 98 (4.08%)	7 / 106 (6.60%)	
occurrences (all)	4	13	
Neutropenia			
subjects affected / exposed	36 / 98 (36.73%)	47 / 106 (44.34%)	
occurrences (all)	72	102	
Thrombocytopenia			
subjects affected / exposed	27 / 98 (27.55%)	30 / 106 (28.30%)	
occurrences (all)	37	49	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 98 (6.12%)	9 / 106 (8.49%)	
occurrences (all)	7	10	
Chest pain			

subjects affected / exposed occurrences (all)	4 / 98 (4.08%) 5	6 / 106 (5.66%) 9	
Fatigue subjects affected / exposed occurrences (all)	17 / 98 (17.35%) 24	16 / 106 (15.09%) 21	
Pain subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 6	3 / 106 (2.83%) 5	
Pyrexia subjects affected / exposed occurrences (all)	14 / 98 (14.29%) 21	6 / 106 (5.66%) 7	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	11 / 98 (11.22%) 15	10 / 106 (9.43%) 13	
Diarrhoea subjects affected / exposed occurrences (all)	22 / 98 (22.45%) 26	11 / 106 (10.38%) 15	
Nausea subjects affected / exposed occurrences (all)	11 / 98 (11.22%) 14	17 / 106 (16.04%) 25	
Vomiting subjects affected / exposed occurrences (all)	10 / 98 (10.20%) 10	10 / 106 (9.43%) 14	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	12 / 98 (12.24%) 16	9 / 106 (8.49%) 9	
Dyspnoea subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 8	4 / 106 (3.77%) 4	
Haemoptysis subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	7 / 106 (6.60%) 7	
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 3	8 / 106 (7.55%) 9	
Pruritus subjects affected / exposed occurrences (all)	13 / 98 (13.27%) 15	0 / 106 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	17 / 98 (17.35%) 20	2 / 106 (1.89%) 2	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 98 (8.16%) 8	4 / 106 (3.77%) 5	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 98 (3.06%) 4	8 / 106 (7.55%) 9	
Back pain subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	3 / 106 (2.83%) 3	
Pain in extremity subjects affected / exposed occurrences (all)	10 / 98 (10.20%) 14	7 / 106 (6.60%) 11	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	27 / 98 (27.55%) 35	17 / 106 (16.04%) 20	
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 6	1 / 106 (0.94%) 1	
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 8	9 / 106 (8.49%) 13	
Hyponatraemia subjects affected / exposed occurrences (all)	5 / 98 (5.10%) 5	3 / 106 (2.83%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2014	The main reason for of this amendment was to align the CA184-153 protocol with the CA184-104 protocol that is to update the study primary endpoint, modify secondary endpoints, implement a dosing limit of ipilimumab in the study to 3 years, and incorporate other minor changes for consistency and clarity.
11 December 2014	The main reason of this amendment was to include the Neutralizing AntiBody (NAb) test in this study.
24 November 2015	The CA184104 study achieved Database Lock on 01-Sep-2015 for the analysis of the primary endpoint of Overall Survival (OS) among subjects who received at least one dose of blinded study therapy. Unfortunately, the trial did not meet the primary endpoint, failing to demonstrate a statistically significant improvement in OS among subjects who received at least one dose of ipilimumab in combination with chemotherapy compared to those receiving at least one dose of placebo in combination with chemotherapy. As CA184153 study has exactly the same study design, including the study population, the treatment schedule and the primary endpoint, it is unlikely the study result will show any overall survival benefit. In order to prevent exposure of additional subjects to ipilimumab-related toxicity in the absence of clinical benefit, the sponsor has decided to discontinue enrolment and randomization in the CA184153 trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 September 2015	Global study CA184104 did not meet the primary endpoint, failing to demonstrate a statistically significant improvement in overall survival (OS) among subjects who received at least one dose of ipilimumab in combination with chemotherapy compared to those receiving at least one dose of placebo in combination with chemotherapy. As study CA184153 has exactly the same study design, including the study population, the treatment schedule and the primary endpoint, it was unlikely that the study would show any overall survival benefit, therefore, the sponsor decided to discontinue enrollment and randomization in the study CA184153 effective 25-Sep-2015.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to early termination of the study, the efficacy endpoints were not analyzed for this study. The final clinical study report (CSR) is in synoptic format and reports safety data.

Notes:

