Clinical trial results:
A Phase I Study of Ipilimumab (Anti-CTLA-4) in Children, Adolescents, and Young Adults with Treatment Refractory Cancer

Summary

EudraCT number	2012-001141-41
Trial protocol	Outside EU/EEA
Global end of trial date	13 April 2014

Results information

Result version number	v1 (current)
This version publication date	10 February 2017
First version publication date	10 February 2017

Trial information

Trial identification

Sponsor protocol code	CA184-070

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Division of Cancer Treatment and Diagnosis (DCTD)
Sponsor organisation address	9609 Medical Center Drive, Rockville, United States, 20892
Public contact	Melinda Merchant, MD, Division of Cancer Treatment and Diagnosis (DCTD), merchanm@mail.nih.gov
Scientific contact	Melinda Merchant, MD, Division of Cancer Treatment and Diagnosis (DCTD), merchanm@mail.nih.gov

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000117-PIP02-10, EMEA-000117-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the tolerance and toxicity profile of ipilimumab at a range of doses up to, but not exceeding, the highest dose tolerated in adults in subjects ≤ 21 years of age with untreatable, refractory or relapsed solid malignant tumors and to assess the pharmacokinetics (PK) of ipilimumab administered intravenously (IV) in subjects ≤21 years of age with solid tumors refractory to standard 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	08 September 2008
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	United States: 33
Worldwide total number of subjects	33
EEA total number of subjects	0

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)	13
Adolescents (12-17 years)	12
Adults (18-64 years)	8
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

33 subjects were enrolled at a total of 3 study sites. All enrolled subjects received at least one dose of Ipilimumab.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	1mg/kg Ipilimumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	YervoyBMS-734016
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	In vitro use

Dosage and administration details:

Ipilimumab was administered IV over 90 minutes on Day 1 of each 21-day cycle for 4 cycles in the absence of dose-limiting toxicity (DLT) or disease progression. Subjects received no experimental drug therapy on Days 2 to 21 of cycles 1 through 4. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing).

Subjects who entered the maintenance phase and had confirmed PD during the maintenance treatment were eligible to receive re-induction therapy using ipilimumab at the assigned dose and schedule specified in the protocol (Day 1 of a 21-day cycle for 4 cycles). Patients who stopped maintenance treatment because of a CR and subsequently had confirmed PD were eligible to receive re-induction as well. Subjects with an initial PR or CR or SD for at least 3 months, and subsequently had PD were also eligible for re-induction. Eligible patients could receive treatment/maintenance therapy until they met off-treatment criteria.

Arm title	3mg/kg Ipilimumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	YervoyBMS-734016
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	In vitro use

Dosage and administration details:

Ipilimumab was administered IV over 90 minutes on Day 1 of each 21-day cycle for 4 cycles in the absence of dose-limiting toxicity (DLT) or disease progression. Subjects received no experimental drug therapy on Days 2 to 21 of cycles 1 through 4. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing).

Subjects who entered the maintenance phase and had confirmed PD during the maintenance treatment were eligible to receive re-induction therapy using ipilimumab at the assigned dose and schedule specified in the protocol (Day 1 of a 21-day cycle for 4 cycles). Patients who stopped maintenance treatment because of a CR and subsequently had confirmed PD were eligible to receive re-induction as

well. Subjects with an initial PR or CR or SD for at least 3 months, and subsequently had PD were also eligible for re-induction. Eligible patients could receive treatment/maintenance therapy until they met off-treatment criteria.

Arm title	5mg/kg Ipilimumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	YervoyBMS-734016
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	In vitro use

Dosage and administration details:

Ipilimumab was administered IV over 90 minutes on Day 1 of each 21-day cycle for 4 cycles in the absence of dose-limiting toxicity (DLT) or disease progression. Subjects received no experimental drug therapy on Days 2 to 21 of cycles 1 through 4. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing).

Subjects who entered the maintenance phase and had confirmed PD during the maintenance treatment were eligible to receive re-induction therapy using ipilimumab at the assigned dose and schedule specified in the protocol (Day 1 of a 21-day cycle for 4 cycles). Patients who stopped maintenance treatment because of a CR and subsequently had confirmed PD were eligible to receive re-induction as well. Subjects with an initial PR or CR or SD for at least 3 months, and subsequently had PD were also eligible for re-induction. Eligible patients could receive treatment/maintenance therapy until they met off-treatment criteria.

Arm title	10mg/kg Ipilimumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	YervoyBMS-734016
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	In vitro use

Dosage and administration details:

Ipilimumab was administered IV over 90 minutes on Day 1 of each 21-day cycle for 4 cycles in the absence of dose-limiting toxicity (DLT) or disease progression. Subjects received no experimental drug therapy on Days 2 to 21 of cycles 1 through 4. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing).

Subjects who entered the maintenance phase and had confirmed PD during the maintenance treatment were eligible to receive re-induction therapy using ipilimumab at the assigned dose and schedule specified in the protocol (Day 1 of a 21-day cycle for 4 cycles). Patients who stopped maintenance treatment because of a CR and subsequently had confirmed PD were eligible to receive re-induction as well. Subjects with an initial PR or CR or SD for at least 3 months, and subsequently had PD were also eligible for re-induction. Eligible patients could receive treatment/maintenance therapy until they met off-treatment criteria.

Number of subjects in period 1	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab
Started	3	3	14
Completed	0	0	0
Not completed	3	3	14
Adverse event, non-fatal	-	-	4
Death	-	-	-
Progressive Disease	3	3	8
Clinical Progression	-	-	1
Complicating Disease/Intercurrent Illness	-	-	1

Number of subjects in period 1	10mg/kg Ipilimumab
Started	13
Completed	0
Not completed	13
Adverse event, non-fatal	4
Death	1
Progressive Disease	8
Clinical Progression	-
Complicating Disease/Intercurrent Illness	-

Baseline characteristics

Reporting groups	
Reporting group title	1mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	3mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	5mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	10mg/kg Ipilimumab
Reporting group description: -	

Reporting group values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab
Number of subjects	3	3	14
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)	1	1	6
Adolescents (12-17 years)	0	1	5
Adults (18-64 years)	2	1	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	14.57	12.57	12.76
standard deviation	± 10.54	± 8.83	± 5.67
Gender Categorical Units: Subjects			
Female	2	1	13
Male	1	2	1

Reporting group values	10mg/kg Ipilimumab	Total	
Number of subjects	13	33	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	4	12	
Adolescents (12-17 years)	7	13	
Adults (18-64 years)	2	8	
From 65-84 years	0	0	

85 years and over	0	0	

Age Continuous Units: years			
arithmetic mean	14.18		
standard deviation	± 3.53	-	
Gender Categorical Units: Subjects			
Female	3	19	
Male	10	14	

End points

End points reporting groups

Reporting group title	1mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	3mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	5mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	10mg/kg Ipilimumab
Reporting group description: -	

Primary: Number of subjects with drug-related adverse events, adverse events leading to discontinuation, drug-related adverse events leading to discontinuation, serious adverse events, drug-related serious adverse events, and immune-related adverse events.

End point title	Number of subjects with drug-related adverse events, adverse events leading to discontinuation, drug-related adverse events leading to discontinuation, serious adverse events, drug-related serious adverse events, and immune-related adverse events.[1]

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. 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.

End point type	Primary

End point timeframe:

From first dose to 30 days after last dose

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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	14	13
Units: subjects				
Drug-related adverse events	3	3	12	12
Adverse events leading to discontinuation	0	0	4	4
Drug-related AEs leading to discontinuation	0	0	4	4
Serious adverse events	0	2	9	5
Drug-related serious adverse events	0	2	6	5
Immune-related adverse events	2	3	10	10

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - White Blood Cell Count

End point title	Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - White Blood Cell Count[2]

End point description:

Laboratory grades are based on Common Terminology Criteria for Adverse Events (CTC) version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[2] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	2	2	9	9
Grade 1	1	1	2	3
Grade 2	0	0	2	0
Grade 3	0	0	0	1
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Absolute Neutrophil Count

End point title	Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Absolute Neutrophil Count[3]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[3] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	12
Units: subjects				
Grade 0	2	3	11	9
Grade 1	0	0	0	2
Grade 2	1	0	1	1
Grade 3	0	0	1	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Platelet Count

End point title	Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Platelet Count[4]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[4] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	3	1	8	10
Grade 1	0	2	5	3
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Hemoglobin

End point title	Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Hemoglobin[5]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[5] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	0	0	5	1
Grade 1	2	1	4	6
Grade 2	1	0	4	4
Grade 3	0	2	0	2
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Absolute Lymphocyte Count (ALC)

End point title	Number of Subjects with Worst CTC Grade of On-study Hematology Laboratory Results - Absolute Lymphocyte Count (ALC)[6]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[6] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	3	1	5	4
Grade 1	0	0	2	2
Grade 2	0	2	4	6
Grade 3	0	0	2	0
Grade 4	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Alanine Aminotransferase (ALT)

End point title	Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Alanine Aminotransferase (ALT)[7]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[7] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	1	0	9	5
Grade 1	1	2	2	6
Grade 2	1	1	0	1
Grade 3	0	0	2	1
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Aspartate Aminotransferase (AST)

End point title	Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Aspartate Aminotransferase (AST)[8]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[8] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	2	0	11	6
Grade 1	0	3	0	4
Grade 2	1	0	1	2
Grade 3	0	0	1	1
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Total Bilibrubin

End point title	Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Total Bilibrubin[9]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[9] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	3	3	12	13
Grade 1	0	0	1	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Alkaline Phosphatase

End point title	Number of Subjects with Worst CTC Grade of On-study Liver Function Laboratory Results - Alkaline Phosphatase[10]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[10] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: subjects				
Grade 0	1	2	9	9
Grade 1	2	1	2	4
Grade 2	0	0	1	0
Grade 3	0	0	1	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Renal Function Laboratory Results - Creatinine

End point title	Number of Subjects with Worst CTC Grade of On-study Renal Function Laboratory Results - Creatinine[11]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[11] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	13	11
Units: subjects				
Grade 0	3	2	13	10
Grade 1	0	0	0	1
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Serum Chemistry Laboratory Results - Lipase

End point title	Number of Subjects with Worst CTC Grade of On-study Serum Chemistry Laboratory Results - Lipase[12]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[12] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	11	8
Units: subjects				
Grade 0	2	3	9	8
Grade 1	0	0	0	0
Grade 2	0	0	1	0
Grade 3	1	0	0	0
Grade 4	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Worst CTC Grade of On-study Serum Chemistry Laboratory Results - Amylase

End point title	Number of Subjects with Worst CTC Grade of On-study Serum Chemistry Laboratory Results - Amylase[13]

End point description:

Laboratory grades are based on CTC version 3.0 and 4.0. All treated subjects with evaluable laboratory results were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[13] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	11
Units: subjects				
Grade 0	3	3	11	11
Grade 1	0	0	1	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of On-study Deaths

End point title	Number of On-study Deaths[14]

End point description:

The total number of deaths due to any cause, that occurred within 30 days of last dose, was reported for each arm. All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to last dose plus 30 days

Notes:

[14] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	14	13
Units: subjects	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of Deaths

End point title	Number of Deaths[15]

End point description:

The total number of deaths due to any cause, including deaths that occurred off-study, was reported for each arm. All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

From Study Initiation to Study Closure (Approximately 67 months)

Notes:

[15] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	14	13
Units: subjects	3	3	5	4

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived Maximum Plasma Concentration (Cmax) Parameters of Ipilimumab

End point title	Geometric Mean of Derived Maximum Plasma Concentration (Cmax) Parameters of Ipilimumab[16]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for Cmax were reported in micrograms per milliliter (ug/mL) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[16] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	13	13
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Age < 12 years	17.3 (± 99999)	51.86 (± 17.4)	93.35 (± 13.43)	193.4 (± 16.93)
Age >= 12 years	20.62 (± 12.37)	81.5 (± 99999)	90.56 (± 25.15)	203.3 (± 22.21)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived AUC(0-T) Parameters of Ipilimumab

End point title	Geometric Mean of Derived AUC(0-T) Parameters of Ipilimumab[17]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for AUC(0-T) were reported in microgram hours per milliliter (ug*hr/mL) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[17] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	12	11
Units: ug*hr/mL				
geometric mean (geometric coefficient of variation)				
Age < 12 years	2119.5 (± 99999)	4300.3 (± 11.95)	15752.2 (± 26.94)	33697.8 (± 34.79)
Age >= 12 years	1200.6 (± 259.62)	12735.9 (± 99999)	11109.9 (± 65.93)	35983.6 (± 12.9)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived AUC(0-21) Parameters of Ipilimumab

End point title	Geometric Mean of Derived AUC(0-21) Parameters of Ipilimumab[18]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for AUC(0-T) were reported in microgram hours per milliliter (ug*hr/mL) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[18] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	12	11
Units: ug*hr/mL				
geometric mean (geometric coefficient of variation)				
Age < 12 years	2554.4 (± 99999)	5273.1 (± 16.41)	16317.5 (± 19.84)	37053.1 (± 17.54)
Age >= 12 years	1356.9 (± 347.6)	16484.1 (± 99999)	12681.1 (± 72.51)	36751.3 (± 13.59)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived AUC(INF) Parameters of Ipilimumab

End point title	Geometric Mean of Derived AUC(INF) Parameters of Ipilimumab[19]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for AUC(INF) were reported in microgram hours per milliliter (ug*hr/mL) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[19] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	10	11
Units: ug*hr/mL				
geometric mean (geometric coefficient of variation)				
Age < 12 years	3126.3 (± 99999)	5913.1 (± 7.79)	24676.8 (± 38.72)	56313.1 (± 27.35)
Age >= 12 years	6542.7 (± 99999)	25105.7 (± 99999)	23170.9 (± 53.14)	52666.3 (± 24.27)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived Total Body Clearance (CL) Parameters of Ipilimumab

End point title	Geometric Mean of Derived Total Body Clearance (CL) Parameters of Ipilimumab[20]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for CL were reported in milliliter per hour per kilogram (mL/hr/kg) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[20] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	10	11
Units: mL/hr/kg				
geometric mean (geometric coefficient of variation)				
Age <12 years	0.32 (± 99999)	0.51 (± 7.79)	0.2 (± 38.72)	0.18 (± 27.35)
Age >= 12 years	0.15 (± 99999)	0.12 (± 99999)	0.22 (± 53.14)	0.19 (± 24.27)

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Derived Volume of Distribution at Steady State (Vss) Parameters of Ipilimumab

End point title	Geometric Mean of Derived Volume of Distribution at Steady State (Vss) Parameters of Ipilimumab[21]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Geometric Means for Vss were reported in liters per kilogram (L/kg) by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[21] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	10	11
Units: L/kg				
geometric mean (geometric coefficient of variation)				
Age < 12 years	0.1 (± 99999)	0.12 (± 57.1)	0.09 (± 5.07)	0.08 (± 6.41)
Age >= 12 years	0.08 (± 99999)	0.06 (± 99999)	0.07 (± 16.75)	0.08 (± 24.18)

Statistical analyses

No statistical analyses for this end point

Primary: Mean Terminal Elimination Half-life (T-half) of Ipilimumab

End point title	Mean Terminal Elimination Half-life (T-half) of Ipilimumab[22]

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Mean T-half was reported in days by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[22] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	10	11
Units: days				
arithmetic mean (standard deviation)				
Age < 12 years	8.87 (± 99999)	7.01 (± 3.07)	14.33 (± 5.3)	14.05 (± 3.44)
Age >= 12 years	14.72 (± 99999)	13.79 (± 99999)	9.82 (± 5.09)	12.74 (± 5.07)

Statistical analyses

No statistical analyses for this end point

Primary: Mean Time to Maximum Concentration (Tmax) of Ipilimumab

End point title	Mean Time to Maximum Concentration (Tmax) of

End point description:

Pharmacokinetic parameters were derived from plasma concentration vs time data for ipilimumab. Mean Tmax was reported in hours by arm and age cohort. All treated subjects with evaluable PK profiles were included in the analysis.

End point type	Primary

End point timeframe:

5 time points from Day 1 through Day 15

Notes:

[23] - 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: Only summary statistics were reported for this endpoint.

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	10	11
Units: hours				
arithmetic mean (standard deviation)				
Age < 12 years	1.58 (± 99999)	2.44 (± 0.96)	1.81 (± 0.35)	1.64 (± 0.14)
Age >= 12 years	1.69 (± 0.09)	1.93 (± 99999)	1.56 (± 0.11)	1.56 (± 0.06)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

COMPLETE RESPONSE: Disappearance of all non-measurable/non-target lesions and normalization of tumor marker levels. PARTIAL RESPONSE: Cannot be determined in patients with non-measureable disease. STABLE DISEASE: Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits. PROGRESSIVE DISEASE: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

End point type	Secondary

End point timeframe:

From first dose until disease progression/recurrence

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	14	13
Units: subjects				
Complete Response	0	0	0	0
Partial Response	0	0	0	0
Stable Disease	0	1	5	5
Progressive Disease	3	2	5	6
Not Applicable	0	0	1	1
Not Assessed	0	0	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Activated CD4+ and CD8+ T Cells

End point title	Mean Change from Baseline in Activated CD4+ and CD8+ T Cells

End point description:

Assessments of the absolute number of activated CD4+ and CD8+ T cells in peripheral blood and change from baseline by study day were made on Day 1 of Cycle 1, and Day 1 of Cycle 2. Mean percent changes from baseline are presented by arm.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 to Day 1 of Cycle 2 (Days 1 to 22)

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[24]	0[25]	9	9
Units: Percent change from baseline				
arithmetic mean (standard deviation)				
Activated CD4 T Cells	()	()	22 (± 36.82)	27 (± 63.21)
Activated CD8 T Cells	()	()	1.6 (± 48.02)	-10.5 (± 65.03)

Notes:

[24] - Summary statistics were not presented due to the limited number of subjects in this cohort.

[25] - Summary statistics were not presented due to the limited number of subjects in this cohort.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Absolutle Lymphocyte Count (ALC)

End point title	Mean Change from Baseline in Absolutle Lymphocyte Count (ALC)

End point description:

Absolute Lymphocyte Counts were evaluated in treated subjects. Mean percent changes from baseline to Day 1 of Cycle 2 are presented by arm.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 to Day 1 of Cycle 2 (Days 1 to 22)

End point values	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab	10mg/kg Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[26]	0[27]	9	9
Units: Percent change from baseline				
arithmetic mean (standard deviation)	()	()	8.5 (± 16.84)	15.6 (± 52.15)

Notes:
[26] - Summary statistics were not presented due to the limited number of subjects in this cohort.
[27] - Summary statistics were not presented due to the limited number of subjects in this cohort.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose to last dose plus 30 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	1mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	3mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	5mg/kg Ipilimumab
Reporting group description: -	
Reporting group title	10mg/kg Ipilimumab
Reporting group description: -	

Serious adverse events	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	9 / 14 (64.29%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Amylase Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatine Phosphokinase Increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Autoimmune Disorder			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision Blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device Related Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (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
Skin Infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	10mg/kg Ipilimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Amylase Increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipase Increased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Autoimmune Disorder			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaphylactic Reaction			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Eye disorders			
Photophobia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vision Blurred			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			

subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Device Related Infection				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin Infection				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	1mg/kg Ipilimumab	3mg/kg Ipilimumab	5mg/kg Ipilimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	1	4
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hot Flush			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 3 (100.00%)	2 / 14 (14.29%)
occurrences (all)	0	4	3
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 14 (28.57%)
occurrences (all)	1	1	6
Pain			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	2	1	3

Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Localised Oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Non-cardiac Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Autoimmune Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	3 / 14 (21.43%)
occurrences (all)	0	1	3
Anaphylactic Reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Perineal Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	0	0	5

Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Rhinitis Allergic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nasal Congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bronchospasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pleural Effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time ratio increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	5 / 14 (35.71%)
occurrences (all)	1	4	7
Lymphocyte count decreased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	7 / 14 (50.00%)
occurrences (all)	0	2	10
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 14 (21.43%)
occurrences (all)	1	1	9
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	4 / 14 (28.57%)
occurrences (all)	2	3	6
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	2 / 14 (14.29%)
occurrences (all)	1	2	4
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 14 (21.43%)
occurrences (all)	2	2	5
Neutrophil Count Decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	1	0	6
Haemoglobin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Platelet Count Decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	3 / 14 (21.43%)
occurrences (all)	0	2	3
Blood Bicarbonate Decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	3
International Normalised Ratio Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lipase Increased			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Amylase Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Weight Decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Blood Bilirubin Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood Creatinine Decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood Growth Hormone Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood Prolactin Abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Electrocardiogram T Wave Inversion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lymphocyte Count Increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Streptococcus Test Positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Arthropod Bite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Tracheal Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	1	3
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	4 / 14 (28.57%)
occurrences (all)	2	0	5
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	7 / 14 (50.00%)
occurrences (all)	2	3	16
Eosinophilia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 14 (21.43%)
occurrences (all)	0	0	3
Eye Swelling			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Photophobia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	5 / 14 (35.71%)
occurrences (all)	0	1	14
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	3 / 14 (21.43%)
occurrences (all)	2	1	3
Abdominal Pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	4 / 14 (28.57%)
occurrences (all)	1	2	4
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	2	1	2
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Abdominal Pain Upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rectal Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Dry Skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Rash Maculo-Papular			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Dermatitis Acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Erythema Multiforme			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Kertosis Pilaris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin Hyperpigmentation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			

subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 14 (7.14%)
occurrences (all)	1	2	3
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	4
Chromaturia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Haemoglobinuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Polyuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Diabetes Insipidus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypophysitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	3
Pain in Extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Flank Pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neck Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscular Weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Osteoporosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infections and infestations			
Oral Herpes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Device Related Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory Syncytial Virus Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	6 / 14 (42.86%)
occurrences (all)	1	2	8
Hypermagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	4 / 14 (28.57%)
occurrences (all)	1	3	5
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	3 / 14 (21.43%)
occurrences (all)	0	3	3
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 14 (14.29%)
occurrences (all)	1	2	3
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	2 / 14 (14.29%)
occurrences (all)	2	2	2
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 14 (7.14%)
occurrences (all)	1	3	1
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	3
Decreased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	10mg/kg Ipilimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hot Flush			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all)	6 / 13 (46.15%) 8		
Fatigue subjects affected / exposed occurrences (all)	5 / 13 (38.46%) 6		
Pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Chills subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Death subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Disease Progression subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Influenza Like Illness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Localised Oedema subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Non-cardiac Chest Pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Immune system disorders Autoimmune Disorder subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Anaphylactic Reaction subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Reproductive system and breast disorders			

Pelvic Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Perineal Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Rhinitis Allergic			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Nasal Congestion			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Oropharyngeal Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pleural Effusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Investigations			
Activated partial thromboplastin time ratio increased			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	11		
Lymphocyte count decreased			
subjects affected / exposed	8 / 13 (61.54%)		
occurrences (all)	10		
White blood cell count decreased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Aspartate Aminotransferase Increased			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	7		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Neutrophil Count Decreased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Haemoglobin increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Platelet Count Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood Bicarbonate Decreased			

subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
International Normalised Ratio Increased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	5			
Blood Creatinine Increased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	3			
Lipase Increased				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Amylase Increased				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Blood Creatine Phosphokinase Increased				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Weight Decreased				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Blood Bilirubin Increased				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Blood Creatinine Decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Blood Growth Hormone Abnormal				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Blood Prolactin Abnormal				
subjects affected / exposed	0 / 13 (0.00%)			
occurrences (all)	0			
Electrocardiogram T Wave Inversion				

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lymphocyte Count Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Streptococcus Test Positive			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Arthropod Bite			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Tracheal Haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Peripheral Sensory Neuropathy			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	8		
Eosinophilia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Eye Swelling			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	9		
Abdominal Pain			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Abdominal Pain Upper			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pancreatitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Rectal Haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Dry Skin			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Rash Maculo-Papular			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Dermatitis Acneiform			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Blister			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Erythema Multiforme			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Kertosis Pilaris			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin Hyperpigmentation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Chromaturia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Haemoglobinuria			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Endocrine disorders			
Diabetes Insipidus			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hypophysitis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Pain in Extremity			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		

Myalgia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Flank Pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Neck Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Muscular Weakness			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Musculoskeletal Pain			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Oral Herpes			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Device Related Infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory Syncytial Virus Infection			

subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Skin Infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	5		
Hypermagnesaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Hypophosphataemia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Decreased Appetite			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Hypoglycaemia			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Hypercalcaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2008	Archived biopsy specimen analysis applies to NCI subjects only; Clarification of urine test to include VMA and HVA combination test for subjects ≤14 years of age, and 24-hour test for subjects >14 years; Clarifications regarding endocrine testing and GH sampling, and regarding fasting for 12 hours prior to sample collection.
05 March 2009	Eligibility: changed lower limit for age from 3 to 2 years of age.
11 March 2009	Revised comprehensive adverse events and potential risks, and informed consent to include the modified risk information from CTEP. Additional eligibility criteria added to exclude subjects with autoimmune disease, including autoimmune hemolytic anemia, ulcerative and hemorrhagic colitis, endocrine disorders, sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. Clarified criteria for not receiving subsequent doses of ipilimumab if subjects experience: Non-hematologic dose limiting toxicities Immune-related adverse events possibly, probably or likely related to ipilimumab Grade 1 or 2 colitis and/or diarrhea which cannot be ascribed to another etiology and is possibly, probably or likely related to ipilimumab Grade 2 thyroid autoimmunity for Grade 2 uveitis Grade 3 or greater skin-related adverse events (regardless of causality)
25 May 2009	Revised the number of planned doses cohorts in the Phase 1 portion of the study from 4 to 3 dose levels (removed the 2 mg/kg dose cohort). Due to this revision the total number of subjects to be accrued was changed from 30 to 27 subjects.
22 July 2009	Revised exclusion criteria: Treatment with myeloid growth factors (sargramostim or filgastrim) within 72 hours prior study entry
26 January 2010	Revised exclusion criteria: No change in residual brain abnormality has been clarified to state no progression of residual brain abnormalities. Revised interval between surgery/radiotherapy and eligibility for subjects who have treated CNS metastases from 6 to 4 weeks. Pretreatment laboratories: Timing for obtaining pretreatment laboratory tests has been differentiated between those that should be collected within 72 hours (ie, hematology, LDH, ALT, AST, alkaline phosphatase, bilirubin (total and direct), BUN, creatinine, amylase, triglycerides, CPK, electrolytes, glucose, calcium, magnesium, phosphorus, uric acid, total protein and albumin) vs those collected within 4 weeks of therapy (ie, endocrine function tests, hepatitis serology, HLA typing, HAHA, anti HIV antibody and autoimmune profile (rheumatoid factor and ANA. Also for subjects with neuroblastoma: urine VMA and urine HVA, bone marrow biopsy and aspiration should be collected within 4 weeks of therapy. Baseline anti-HIV antibody added to baseline laboratory tests, to be obtained within 4 weeks of initiating the first cycle. Amylase, lipase and triglycerides have been separated from serum chemistry tests and are required to be drawn prior to every treatment cycle rather than at every laboratory draw (Cycle 1: Days 2, 4, 8, and 15, while on treatment).

15 March 2010	Eligibility: Removed positive ANA from eligibility exclusion criteria Changed language of Comprehensive Adverse Events and Potential Risk (CAEPR) list to reflect CTCAE version 4.0. In addition revised the risk profile of ipilimumab to CAEPR Version 2.3. Added dose level 4 (10 mg/kg) to the dose escalation schema. Added language to expand the cohort of subjects receiving the highest dose tolerated to include at least four subjects 12 years of age or older (to obtain additional data regarding tolerability). Under Statistical Considerations: the expected accrual for the dose escalation was increased from 15 to 18 subjects.
26 April 2010	Clarified that the dose escalation (Phase 1 part of this study): consists of 4 and not 5 dose levels by removing the dose level -1 (0.5 mg/kg) cohort expected number of subjects to be accrued in the dose escalation phase is 24 and not 18 subjects.
08 June 2010	Eligibility: Baseline HIV and hepatitis serology changed from 4 to 12 weeks of initiation of first cycle. For subjects who received irradiation (for CNS metastasis), time to have completed therapy changed from 4 weeks to 1 week prior to enrollment. Changed the location of where ipilimumab can be administered from and in-patient setting to an out-patient setting Changed the monitoring of vital signs at Cycle 1 from the first 24 hours to the first 6 hours. Revised algorithm for management and assessment of diarrhea, hepatoxicity, and general recommendations for the management of immune-related adverse events. Under 'Background' revised definition of high-risk neuroblastoma from >1 year to 18 months with metastatic disease. Clarified RECIST Criteria to state that tumor markers alone cannot be used to assess response with the exception or neuroblastoma.
01 August 2010	Changed CTCAE criteria to be used from version 3.0 to 4.0 with effective start date 01-Aug-2010. Cite version change under the following: definitions of dose limiting toxicities reporting changes in blood pressure off-treatment criteria toxicity criteria
27 August 2010	Removed vital signs monitoring at 8, 16, and 24 hours after ipilimumab administration.
07 February 2011	Added normal ranges for non-hematologic dose limiting toxicities for ALT, AST, and GGT. For alkaline phosphatase, normal ranges by age and gender were added.
01 September 2011	Removed exclusion criterion "subjects requiring supplemental oxygen"
28 September 2011	Updated the risk information for ipilimumab per CAEPR version 2.4. New risk: rare but serious bleeding disorder cause by autoantibodies potentially life threatening condition affecting less than 10% of the skin in which cell deaths causes epidermis (outer layer) to separate from dermis (middle layer) Increased risk attribution: inability of the adrenal glands to produce a normal quantity of hormones abnormally high or abnormally low levels of thyroid gland hormone changed from 'reported but undetermined' to 'rare but serious': inflammation of the heart muscle

30 November 2011	Expanded the cohort of subjects at the highest maximum tolerated dose (5 mg/kg) to include 6 subjects <12 years of age. Revised inclusion criterion: hematologic function of transfusion independent platelet count from ≥75,000 µL to ≥50,000µL. normal bilirubin from 'direct' to 'total' Revised overall study design to allow maintenance therapy past 2 years provided that subjects continue to experience clinical benefit. Added section describing ipilimumab treatment during maintenance in those subjects who undergo resection and malignant metastases during this phase.
16 December 2011	Added language to expand the number of subjects to be included in the planned cohort expansion of the 5 and 10 m/kg doses to include 6 subjects <12 years of age.
18 January 2012	Allowed subjects to receive reinduction with 4 doses of ipilimumab at assigned dose followed by another maintenance phase for subjects who have progressed during maintenance therapy.
17 May 2012	Eligibility: changed lower limit for age from 2 to 1 year of age.
25 June 2013	Eligibility: A subject with viral hepatitis or HIV was to be excluded from study, but serology was not required unless infection was clinically suspected

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported