Clinical trial results:
THE IPI – MULTIBASKET TRIAL IN ADVANCED OCULAR MELANOMA: PROSPECTIVE CLINICAL PHASE II MULTIBASKET STUDY IN OCULAR MELANOMA PATIENTS WITH ADVANCED DISEASE

Summary

EudraCT number	2010-021946-22
Trial protocol	DE
Global end of trial date	06 December 2013

Results information

Result version number	v1 (current)
This version publication date	15 November 2021
First version publication date	15 November 2021
Summary attachment (see zip file)	summary csr (multibasket-csr-summary-version-1.1-2014-12-15_blackened.pdf)

Trial information

Trial identification

Sponsor protocol code	DeCOG–MM-PAL11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01355120
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Essen
Sponsor organisation address	Hufelandstraße 55, Essen, Germany, 45147
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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	06 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2013
Global end of trial reached?	Yes
Global end of trial date	06 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To further characterize efficacy of second line ipilimumab monotherapy 3mg/kg given according to the MDX010-20 protocol in a broad range of pretreated metastatic (cutaneous, mucosal, and uveal) melanoma patients with or without prior systemic treatment seen in daily clinical practice:

- Overall survival rate at 12 months defined as the rate of patients alive 12 months after the date from the first study treatment for complete study population

Protection of trial subjects:

The treatment should be conducted exactly as described in the protocol. Any protocol deviations were reported. The recommendations of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, were observed.
Pregnant or lactating female patients were excluded from study participation. Additionally, patients with an existing myocarditis were excluded from study participation; for enrolled pateents, ECG examinations at baseline ad at week 12 and in case of evidence of myocarditis (e.g. dyspnoea, functional insufficiency) before each therapy cycle were obligatory.
The study treatment consisted of an induction and a re-induction part. After enrolment, all patients received a maximum of 4 cycles of ipilimumab monotherapy (3 mg/kg IV, q3 weeks) according to the completed Medarex study MDX-010-20 (induction treatment). Only patients who progressed following stable disease of >=3 months duration starting from diagnosis at week 12 tumor assessment or who had progressed following an initial response (partial or complete) assessed at week 12 could receive additional cycles of ipilimumab monotherapy (re-induction treatment). Re-treatment was not permitted for patients with experience of >= grade 3 gastrointestinal adverse events (AEs) or selected immune-related adverse events (irAE) or with disease progression following the first cycle of study medication. Investigators had to align to criteria defined in the protocol for skipping or discontinuing study treatment.

Background therapy:

Concomitant therapy IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; any other systemic therapy for cancer including any other experimental treatment was prohibited during study therapy.
Topical or inhalational steroids were permitted for management of symptoms due to brain metastases. In case of occurrence of irAEs, clinically necessary steroid therapy was permitted.
In case of infusion reactions associated with ipilimumab, premedication with diphenhydramine and acetaminophen could be given for subsequent doses of ipilimumab at the discretion of the investigator. If a patient experienced isolated drug fever, for the next dose, pretreatment with acetaminophen or non-steroidal anti-inflammatory agent at the investigator’s discretion was permitted.

Evidence for comparator:

Not applicable, as this was a study with one treatment arm only.

Actual start date of recruitment	23 May 2011
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	Germany: 161
Worldwide total number of subjects	161
EEA total number of subjects	161

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)	85
From 65 to 84 years	75
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

After obtaining informed consent, screening evaluations were performed to confirm eligibiliy and to obtain baseline safety data.
From 23-May-2011 (first patient in) up to 21-Sep-2012 (last patient in), 161 patients were registered by 25 hospitals in Germany.

Pre-assignment

Screening details:

The selection of patients occurred by the investigators according to the inclusion and exclusion criteria. After having informed the patient orally and in writiing about the study and after obtaining the patient's informed consent. Study treatment should begin within 14 days after registration.

Pre-assignment period milestones

Number of subjects started	171[1]
Intermediate milestone: Number of subjects	Screening: 171
Intermediate milestone: Number of subjects	Registration: 161
Intermediate milestone: Number of subjects	Treatment: 156
Number of subjects completed	156

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 13
Reason: Number of subjects	Consent withdrawn by subject: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 171 patients have been screened, however due to not fuulfilling all aligibility criteria, only 161 patients could be enrolled.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

Arms

Arm title	Treatment

Arm description:

ipilimumab monotherapy

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	L01XC11
Other name	YERVOY
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg ipilimumab administered as iv infusion, q3weeks

Number of subjects in period 1[2]	Treatment
Started	156
Completed	156

Notes:

[2] - 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: 156 patients received study treatment. Of the 161 enrolled patients, 5 patients were identified as screening failuire after enrolment or withdrew the indormed consent before receiving any study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
All enrolled patients who received at least one dose of study medication	

Reporting group values	Treatment	Total	
Number of subjects	156	156	
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration minus year of birth.			
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	80	80	
From 65-84 years	75	75	
85 years and over	1	1	
Age continuous			
Units: years			
median	63		
full range (min-max)	29 to 85	-	
Gender categorical			
Units: Subjects			
Female	89	89	
Male	67	67	
Type of melanoma			
Patients with cutaneous, mucosal, unknown primnary or ocular melanoma			
Units: Subjects			
Cutaneous	83	83	
Mucosal	7	7	
MUP	13	13	
Ocular	53	53	
LDH at baseline			
Units: Subjects			
LDH <2 ULN	116	116	
LDH >=2 ULN	40	40	
B-RAF mutation			
Units: Subjects			
not mutated	49	49	
mutated	23	23	
not known	84	84	

Subject analysis sets

Subject analysis set title	Treated patients_total
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were enrolled and received at least one dose of ipilimumab.

Subject analysis set title	Response-evaluable set_total
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of ocular, cutaneous, mucosal melanoma or melanoma of unkown primary; and iii) who had one baseline screening and at least one tumor assessment on study

Subject analysis set title	Treated patients_cutaneous melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients with diagnosis 'cutaneous melanoma' who received at least one dose of ipilimumab.

Subject analysis set title	Treated patients_mucosal melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients with diagnosis 'mucosal melanoma' who received at least one dose of ipilimumab.

Subject analysis set title	Treated patients_ocular melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients with diagnosis 'ocular melanoma' who received at least one dose of ipilimumab.

Subject analysis set title	Response-evaluable set_cutaneous melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of cutaneous melanoma ; and iii) who had one baseline screening and at least one tumor assessment on study

Subject analysis set title	Response-evaluable set_mucosal melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of mucosal melanoma ; and iii) who had one baseline screening and at least one tumor assessment on study

Subject analysis set title	Response-evaluable set_MUP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of melanoma of unkown primary; and iii) who had one baseline screening and at least one tumor assessment on study

Subject analysis set title	Response-evaluable set_ocular melanoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of ocular; and iii) who had one baseline screening and at least one tumor assessment on study

Subject analysis set title	Treated patients_MUP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients with diagnosis 'melanoma of unknown primary' who received at least one dose of ipilimumab.

Reporting group values	Treated patients_total	Response-evaluable set_total	Treated patients_cutaneous melanoma
Number of subjects	156	104	83
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration minus year of birth.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	80		
From 65-84 years	75		
85 years and over	1		
Age continuous			
Units: years			
median	63	65.50	63
full range (min-max)	29 to 85	30 to 85	29 to 85
Gender categorical			
Units: Subjects			
Female	67	46	30
Male	89	58	53
Type of melanoma			
Patients with cutaneous, mucosal, unknown primnary or ocular melanoma			
Units: Subjects			
Cutaneous	83	55	83
Mucosal	7	6	0
MUP	13	9	0
Ocular	53	34	0
LDH at baseline			
Units: Subjects			
LDH <2 ULN	116	90	67
LDH >=2 ULN	40	14	16
B-RAF mutation			
Units: Subjects			
not mutated	49	30	29
mutated	23	16	17
not known	84	58	37

Reporting group values	Treated patients_mucosal melanoma	Treated patients_ocular melanoma	Response-evaluable set_cutaneous melanoma
Number of subjects	7	53	55
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration minus year of birth.			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median	63	67	63
full range (min-max)	33 to 73	34 to 84	30 to 85
Gender categorical			
Units: Subjects			
Female	5	30	21
Male	2	23	34
Type of melanoma			
Patients with cutaneous, mucosal, unknown primnary or ocular melanoma			
Units: Subjects			
Cutaneous	0	0	55
Mucosal	7	0	0
MUP	0	0	0
Ocular	0	53	0
LDH at baseline			
Units: Subjects			
LDH <2 ULN	5	33	50
LDH >=2 ULN	2	20	5
B-RAF mutation			
Units: Subjects			
not mutated	3	12	17
mutated	0	0	12
not known	4	41	26

Reporting group values	Response-evaluable set_mucosal melanoma	Response-evaluable set_MUP	Response-evaluable set_ocular melanoma
Number of subjects	6	9	34
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration minus year of birth.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years			
median	63.5	68	67
full range (min-max)	33 to 73	40 to 77	36 to 84
Gender categorical Units: Subjects			
Female	4	2	19
Male	2	7	15
Type of melanoma			
Patients with cutaneous, mucosal, unknown primnary or ocular melanoma			
Units: Subjects			
Cutaneous	0	0	0
Mucosal	6	0	0
MUP	0	9	0
Ocular	0	0	34
LDH at baseline Units: Subjects			
LDH <2 ULN	5	8	26
LDH >=2 ULN	1	1	8
B-RAF mutation Units: Subjects			
not mutated	2	4	7
mutated	0	4	0
not known	4	1	27

Reporting group values	Treated patients_MUP		
Number of subjects	13		
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of registration minus year of birth.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	62		
full range (min-max)	40 to 77		
Gender categorical Units: Subjects			
Female	2		
Male	11		

Type of melanoma			
Patients with cutaneous, mucosal, unknown primnary or ocular melanoma			
Units: Subjects			
Cutaneous	0		
Mucosal	0		
MUP	13		
Ocular	0		
LDH at baseline Units: Subjects			
LDH <2 ULN	11		
LDH >=2 ULN	2		
B-RAF mutation Units: Subjects			
not mutated	5		
mutated	6		
not known	2		

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: ipilimumab monotherapy	
Subject analysis set title	Treated patients_total
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were enrolled and received at least one dose of ipilimumab.	
Subject analysis set title	Response-evaluable set_total
Subject analysis set type	Per protocol
Subject analysis set description: All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of ocular, cutaneous, mucosal melanoma or melanoma of unkown primary; and iii) who had one baseline screening and at least one tumor assessment on study	
Subject analysis set title	Treated patients_cutaneous melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled patients with diagnosis 'cutaneous melanoma' who received at least one dose of ipilimumab.	
Subject analysis set title	Treated patients_mucosal melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled patients with diagnosis 'mucosal melanoma' who received at least one dose of ipilimumab.	
Subject analysis set title	Treated patients_ocular melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All enrolled patients with diagnosis 'ocular melanoma' who received at least one dose of ipilimumab.	
Subject analysis set title	Response-evaluable set_cutaneous melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of cutaneous melanoma ; and iii) who had one baseline screening and at least one tumor assessment on study	
Subject analysis set title	Response-evaluable set_mucosal melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of mucosal melanoma ; and iii) who had one baseline screening and at least one tumor assessment on study	
Subject analysis set title	Response-evaluable set_MUP
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of melanoma of unkown primary; and iii) who had one baseline screening and at least one tumor assessment on study	
Subject analysis set title	Response-evaluable set_ocular melanoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients who received at least one dose of ipilimumab with i) measurable disease at baseline determined by irRC and RECIST; ii) histologic diagnosis of ocular; and iii) who had one baseline screening and at least one tumor assessment on study	
Subject analysis set title	Treated patients_MUP

Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients with diagnosis 'melanoma of unknown primary' who received at least one dose of ipilimumab.

Primary: Overall survival rate at 12 months

End point title	Overall survival rate at 12 months[1]

End point description:

Proportion of patients being alive or with unknown survival status 12 months after first administration of the study treatment, calculated by Kaplan Meier analysis.

End point type	Primary

End point timeframe:

12 months after the date from the first study treatment

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: No statistical analysis for the primary endpoint (= Overall survival rate at 12 months) has been specified in the protocol or the statistical analysis plan.

End point values	Treated patients_total			
Subject group type	Subject analysis set			
Number of subjects analysed	155			
Units: Subjects	102			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate according to immune-related response criteria (ir-RC)

End point title	Overall response rate according to immune-related response criteria (ir-RC)

End point description:

Proportion of patients with PR+CR as best response according to irRECIST-criteria. Any subject with irRECIST will be included in the denominator for irORR.

End point type	Secondary

End point timeframe:

Evey 12 weeks during treatment and every 3 months during Follow-up phase

End point values	Response-evaluable set_total			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: Subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (RECIST criteria)

End point title	Overall response rate (RECIST criteria)

End point description:

Proportion of patients with PR+CR as best response. Any subject of the response-evaluable population will be included in the denominator for ORR.

End point type	Secondary

End point timeframe:

Every 12 weeks during treatment and every 3 months during Follow-up

End point values	Response-evaluable set_total			
Subject group type	Subject analysis set			
Number of subjects analysed	104			
Units: Subjects	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (irRECIST)

End point title	Disease control rate (irRECIST)

End point description:

Proportion of patients with PR+CR+SD as best response according to irRECIST. Any subject with irRECIST will be included in the denominator for irDCR.

End point type	Secondary

End point timeframe:

Staging examinations should be performed every 12 weeks during treatment and every 3 months during follow-up period

End point values	Response-evaluable set_total			
Subject group type	Subject analysis set			
Number of subjects analysed	48			
Units: Subjects	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (RECIST)

End point title	Disease control rate (RECIST)

End point description:

Proportion of patients with PR+CR+SD as best response according to RECIST. Any subject of the response-evaluable population will be included in the denominator for DCR.

End point type	Secondary

End point timeframe:

Every 12 weeks during treatment and every 3 months during Follow-up

End point values	Response-evaluable set_total			
Subject group type	Subject analysis set			
Number of subjects analysed	104			
Units: Subjects	37			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS rate at 6 months

End point title	PFS rate at 6 months

End point description:

Proportion of patients being alive or with unknown survival status and without progress or not known to progress 6 months after their first administration of the study treatment, calculated by Kaplan-Meier.

End point type	Secondary

End point timeframe:

6 months after first administration of study treatment.

End point values	Treated patients_total			
Subject group type	Subject analysis set			
Number of subjects analysed	156			
Units: Subjects	126			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was measured from the date of the first ipilimumab dose given on-study until date of death. Survival time for subjects, whose date of death is unknown, were censored at the date of last contact. Overall survival was analysed by the Kaplan Meier method

End point type	Secondary

End point timeframe:

From start of study treatment until death of patient or end of study whichever occurred first.

End point values	Treated patients_total			
Subject group type	Subject analysis set			
Number of subjects analysed	155			
Units: months				
median (confidence interval 95%)	6.91 (5.66 to 8.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS

End point title	PFS

End point description:

Progression was determined according to RECIST v1.1 criteria by the respective trial sites. Progression-free survival was calculated by Kaplan-Meier-Analysis. For patients without progress and not known to have died, PFS time was censored at the date of last contact.

End point type	Secondary

End point timeframe:

From start of study therapy until progression or death of any cause, whatever occurred first.

End point values	Treated patients_total			
Subject group type	Subject analysis set			
Number of subjects analysed	156			
Units: Months				
median (confidence interval 95%)	2.6 (2.53 to 2.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 12 months according to type of melanoma

End point title	Overall survival rate at 12 months according to type of melanoma

End point description:

Proportion of patients being alive or with unknown survival status 12 months after first administration of the study treatment, calculated by Kaplan Meier method, analyzed per type of melanoma

End point type	Secondary

End point timeframe:

12 months after the date from the first study treatment

End point values	Treated patients_cutaneous melanoma	Treated patients_mucosal melanoma	Treated patients_ocular melanoma	Treated patients_MUP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	7	53	12
Units: Subjects	49	6	40	7

Statistical analyses

Statistical analysis title	OS rate at 12 months by type of melanoma
Comparison groups	Treated patients_mucosal melanoma v Treated patients_cutaneous melanoma v Treated patients_ocular melanoma v Treated patients_MUP
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.58 [2]
Method	Fisher exact

Notes:

[2] - No significant differnce between the types of primary melanoma

Secondary: ORR (RECIST) according to melanoma type

End point title	ORR (RECIST) according to melanoma type

End point description: Proportion of patients according to type of melanoma with PR+CR as best response.	
End point type	Secondary
End point timeframe: Every 12 weeks during treatment and every 3 months during Follow-up	

End point values	Response-evaluable set_cutaneous melanoma	Response-evaluable set_mucosal melanoma	Response-evaluable set_MUP	Response-evaluable set_ocular melanoma
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	6	9	34
Units: Subjects	9	1	1	0

Statistical analyses

Statistical analysis title	ORR (RECIST) by type of melanoma
Comparison groups	Response-evaluable set_cutaneous melanoma v Response-evaluable set_mucosal melanoma v Response-evaluable set_MUP v Response-evaluable set_ocular melanoma
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Fisher exact

Secondary: PFS according to type of melanoma

End point title	PFS according to type of melanoma
End point description:	
End point type	Secondary
End point timeframe: From start of study therapy until progression or death of any cause, whatever occurred first, by type of melanoma	

End point values	Treated patients_cutaneous melanoma	Treated patients_mucosal melanoma	Treated patients_ocular melanoma	Treated patients_MUP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	7	53	13
Units: months				
median (confidence interval 95%)	2.57 (2.53 to 2.66)	2.76 (1.51 to 5.72)	2.83 (2.53 to 2.89)	2.53 (2.27 to 4.05)

Statistical analyses

Statistical analysis title	PFS_by melanoma type
Comparison groups	Treated patients_cutaneous melanoma v Treated patients_mucosal melanoma v Treated patients_ocular melanoma v Treated patients_MUP
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.95
Method	Wilcoxon (Mann-Whitney)

Secondary: OS_according to melanoma type

End point title	OS_according to melanoma type

End point description:

End point type	Secondary

End point timeframe:

From start of study treatment until death of patient or end of study whichever occurred first.

End point values	Treated patients_cutaneous melanoma	Treated patients_mucosal melanoma	Treated patients_ocular melanoma	Treated patients_MUP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	7	53	12
Units: Months				
median (confidence interval 95%)	6.78 (5.30 to 9.87)	9.57 (1.55 to 11.05)	6.78 (3.65 to 8.06)	9.90 (2.27 to 9999999)

Statistical analyses

Statistical analysis title	OS_type of melanoma
Comparison groups	Treated patients_cutaneous melanoma v Treated patients_mucosal melanoma v Treated patients_ocular melanoma v Treated patients_MUP

Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.24 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - No differences in OS between the tumor types

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs were reported from date of written informed consent until end date of treatment, for serious adverse events the time period was extended to 70 days post last treatment.

Adverse event reporting additional description:

All AEs and SAEs, whether related to study treatment or not, should be recorded within the above mentioned time periods. Additionally, the investigator should notify the sponsor of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.02

Reporting groups

Reporting group title	Treated patients_total_Safety

Reporting group description:

All patients who were enrolled and received at least one dose of ipilimumab.

Serious adverse events	Treated patients_total_Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 156 (59.62%)		
number of deaths (all causes)	122		
number of deaths resulting from adverse events	52		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to gastrointestinal tract			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neoplasm				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neoplasm progression				
subjects affected / exposed	15 / 156 (9.62%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 13			
Tumour pain				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arterial stenosis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous occlusion				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				

Tumour excision			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	3 / 156 (1.92%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		
Disease progression			
subjects affected / exposed	29 / 156 (18.59%)		
occurrences causally related to treatment / all	0 / 30		
deaths causally related to treatment / all	0 / 29		
Fatigue			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Multi-organ failure			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy tongue			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			

subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic valve disease			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Central nervous system lesion				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	7 / 156 (4.49%)			
occurrences causally related to treatment / all	4 / 7			
deaths causally related to treatment / all	0 / 0			

Ascites			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	9 / 156 (5.77%)		
occurrences causally related to treatment / all	13 / 13		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	14 / 156 (8.97%)		
occurrences causally related to treatment / all	20 / 21		
deaths causally related to treatment / all	0 / 0		
Duodenal perforation			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids thrombosed				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	5 / 156 (3.21%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Hepatic pain				

subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disease			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal vein thrombosis			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Endocrine disorders			
Hypothyreodism			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cystitis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Metabolism and nutrition disorders				
Diabetes mellitus				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treated patients_total_Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 156 (95.51%)		
Investigations			
GGT increased			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	9		
Nervous system disorders			
Insomnia			
subjects affected / exposed	7 / 156 (4.49%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 156 (5.77%)		
occurrences (all)	13		
General disorders and administration site conditions			
Back pain			
subjects affected / exposed	10 / 156 (6.41%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	14 / 156 (8.97%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	37 / 156 (23.72%)		
occurrences (all)	42		
Fever			
subjects affected / exposed	13 / 156 (8.33%)		
occurrences (all)	14		
Decreased appetite			

subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 8		
Headache subjects affected / exposed occurrences (all)	12 / 156 (7.69%) 15		
Pain subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 16		
Pain in extremity subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 8		
Tumour pain subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 8		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 7		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	16 / 156 (10.26%) 19		
Diarrhoea subjects affected / exposed occurrences (all)	44 / 156 (28.21%) 67		
Nausea subjects affected / exposed occurrences (all)	17 / 156 (10.90%) 20		
Stomach pain subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 7		
Vomiting subjects affected / exposed occurrences (all)	12 / 156 (7.69%) 16		
Skin and subcutaneous tissue disorders			

Erythema multiforme subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 7 21 / 156 (13.46%) 22 8 / 156 (5.13%) 9		
Infections and infestations Arthralgia subjects affected / exposed occurrences (all) Colitis subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 8 6 / 156 (3.85%) 7		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	13 / 156 (8.33%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2011	Recruitment was continued only for patients with ocular melanoma because sufficient numbers of cutaneous and mucosal melanoma patients had already been recruited. In order to allow the separate subgroup analysis as planned in the protocol for ocular melanoma it was mandatory to focus the recruitment to this patient population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported