



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 |
| Public contact | Prof. Dr. Dirk Schadendorf, University Hospital Essen, Department of Dermatology, Hufelandstraße 55, DE-45147 Essen, 0049 2017234342, dirk.schadendorf@uk-essen.de |
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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 patients, ECG examinations at baseline and 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 \geq 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 eligibility 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 writing 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 fulfilling all eligibility 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 failure after enrolment or withdrew the informed 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 primary 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 unknown 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 unknown 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 primary 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 full range (min-max) | 63 33 to 73 | 67 34 to 84 | 63 30 to 85 |
| Gender categorical Units: Subjects | | | |
| Female | 5 | 30 | 21 |
| Male | 2 | 23 | 34 |
| Type of melanoma | | | |
| Patients with cutaneous, mucosal, unknown primary 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 full range (min-max) | 63.5 33 to 73 | 68 40 to 77 | 67 36 to 84 |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 2 | 19 |
| Male | 2 | 7 | 15 |
| Type of melanoma | | | |
| Patients with cutaneous, mucosal, unknown primary 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 full range (min-max) | 62 40 to 77 | | |
| Gender categorical Units: Subjects | | | |
| Female | 2 | | |
| Male | 11 | | |

| | | | |
|--|----|--|--|
| Type of melanoma | | | |
| Patients with cutaneous, mucosal, unknown primary 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 unknown 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 unknown 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:

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

| | | | |
|---|-------------------------|--|--|
| Erythema multiforme subjects affected / exposed occurrences (all) | 7 / 156 (4.49%) 7 | | |
| Pruritus subjects affected / exposed occurrences (all) | 21 / 156 (13.46%) 22 | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 8 / 156 (5.13%) 9 | | |
| Infections and infestations | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 7 / 156 (4.49%) 8 | | |
| Colitis subjects affected / exposed occurrences (all) | 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