DeCOG-MM-PAL11-Trial
THE IPI – MULTIBASKET TRIAL IN ADVANCED MELANOMA

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Prospective Clinical Phase II Multibasket Study in Melanoma Patients with advanced disease

Study drug: Ipilimumab
EudraCT-No.: 2010-021946-22
Short title: Multibasket

Clinical Study Report (Synopsis)

Final

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Study Start: 23.05.2011 – Study End: 21.09.2013

Signatures

By signing this Clinical Study Report, the undersigned authors agree with the contents of this document. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable legislation.

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List of abbreviations

ABE	Automatical Breakthrough Event
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase (SGOT)
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
BORR	Best Overall Response Rate
CBC	Complete Blood Count
CR	Complete Response
CT scan	Computed Axial Tomography scan
CTC AE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
ESR	Expedited safety report
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
irAE	immune-related adverse event (irAE)
IRB	Institutional Review Board
irBOR	Immune-Related Best Overall Response
irRC	Immune Related Response Criteria
ir – PD	Immune-Related Progressive Disease
ir – RC	Immune-Related Response Criteria
LDH	Lactat-Dehydrogenase
LFT	Liver Function Tests
LPFV	Last Patient First Visit
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OR	Overall Response
ORR	Overall Response Rate
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors

SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvate Transaminase (ALT)
SPD	Sum of the Products Diameters
SPN	Single Nucleotide Polymorphism
TA	Tumor Assessment
T. Bilirubin	Total Bilirubin
TNM Staging	Tumor, Node and Metastasis Staging
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USA	United States of America
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

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1. Overall Information

1.1 Study Title

DeCOG-MM-PAL11-Trial: The IPI – Multibasket Trial in advanced melanoma -Prospective Clinical Phase II Multibasket Study in Melanoma Patients with advanced Disease

1.2 Type of Project

Clinical trial Phase II

1.3 Sponsor / Representative

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1.6 Study Publication/Reference

Not yet available.

1.7 Study Period

First patient in: 23-05-2011
Last patient out: 21-09-2013

1.8 Study Objectives

This study was conducted 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 ocular melanoma patients with or without prior systemic treatment seen in daily clinical practice.

1.9 Primary Endpoint

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.

1.10 Secondary Endpoints

- All adverse events ≥ Grade 3 according to CTCAE, Version 4.0 criteria, that are definitely, probably, or possible related to the administration of the investigational agents will be assessed
- Overall response rate (PR+CR) according to immune-related response Criteria (ir-RC) at any time of study
- Disease control rate irDCR (rate of CR or PR or SD) according to immune-related response Criteria (ir-RC) at any time of study
- Overall response rate (PR+CR) according to RECIST criteria at any time of study
- Disease control rate (CR or PR or SD) according to RECIST criteria at any time of study
- Progression free survival, progression free survival rate at 6 months
- Overall survival
- Clinical efficacy parameter (1-year OS, ORR, DCR, PFS) according to b-raf mutational status of tumor (b-raf V600E yes versus no), NRAS mutational status of tumor (NRAS mutated yes versus no) brain metastases (brain metastases vs no brain metastases), LDH (LDH <2ULN versus LDH ≥ 2ULN) and HLA-A2 (HLA-A2 positive versus HLA-A2 negative), number of ipilimumab doses (4 doses vs less than 4 doses)

1.11 Study Design

This was an open-label, multi-center, single-arm clinical phase II study to further characterize the efficacy and safety of ipilimumab (3mg/kg) in patients with pretreated, metastatic and/or inoperable melanoma. After recruitment of sufficient numbers of cutaneous and mucosal melanoma patients in 2011 the DeCOG-MM-PAL11-Trial was continued for patients with metastatic ocular melanoma only, with or without systemic pretreatment (Amendment 1). 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 to guarantee a valid evaluation of all cohorts. Ocular melanoma was defined as melanomas originated from uvea, the choroid, the ciliary body and conjunctiva [1].

1.12 Study rational

Melanoma is the most common tumor of the skin that develops from a neoplastic transformation of melanocytes. The incidence of cutaneous melanoma is increasing at a faster rate than for any other solid tumor and is estimated as 68,000 new cases annually in the USA. Globally, the incidence of melanoma varies by region, and according to World Health Organization (WHO) over 130,000 new cases of melanoma are recognized annually around the world. Melanoma is a tumor with significant impact on society and when found to be metastatic, there is no effective treatments for most patients. Although most patients have localized disease at the time of diagnosis and are cured by surgical excision of the primary tumor, metastases can develop and most of these patients die of melanoma-associated causes. In the USA, over 8,000 deaths in 2008 were associated with melanoma.

Most melanomas develop in the skin (cutaneous melanoma). The American Joint Committee on Cancer (AJCC) classification is helpful in segregating risk for recurrence and survival in primary melanoma, especially when combined with the Breslow thickness criteria. The AJCC first published a staging schema in 1978 that incorporated primary tumor thickness, ulceration, level of invasion, regional and distant metastases subtypes and serum LDH levels that correlated with prognosis for relapse and survival [2]. For metastatic melanoma, however, there is no current classification scheme that allows to predict a response to treatment in more than 25% in a given cohort. Melanomas from any anatomic site may metastasize. The overall median survival from diagnosis of stage IV melanoma has been estimated to be 8 months. One year survival for these patients has been reported as approximately 25%, with approximately 15% of patients surviving 5 years (SEER 2009). In metastatic melanoma, chemotherapy is used mostly with palliative intent. At the begin of this study registered agents for the treatment of melanoma included the alkylating agent dacarbazine (DTIC) and high dose IL-2 (US only). The administration of dacarbazine (DTIC) was a standard treatment with response rates in the range of 5-15% and progression free survival of approximately 8 weeks [3]. Cytotoxic therapies have not been reported to prolong overall survival.

This trial was designed in light of the high unmet medical need in the treatment of metastatic melanoma and the promising clinical results derived from trials with ipilimumab. Various phase II clinical studies using ipilimumab in unresectable stage III-IV have been conducted. Results of the first pivotal phase III study MDX010-20 were published by Hodi et al. [4]. In the second phase III trial CA184-024, a different dose and treatment scheme was tested in the first-line setting [5]. Results showed little difference between groups in quality-adjusted survival during the first year of study, but after 2, 3 and 4 years follow-up for patients with extended survival, the benefits of IPI+DTIC vs PLA+DTIC for advanced melanoma continued to accrue [5].

However, due to strictly defined inclusion and exclusion criteria in phase III trials, results of registrational trials do not answer all questions regarding safety and efficacy of ipilimumab in all advanced melanoma patient cohorts seen in daily routine. E.g. on one hand, in MDX010-20 trial, only patients positive for HLA-A2 could be enrolled (since patients were randomized in a double-blind fashion in a 1:3:1 ratio to receive HLA2-restricted melanoma gp 100 peptide vaccine monotherapy, MDX-010 in combination with melanoma gp100 peptide vaccine, or MDX-010 monotherapy.) In the second phase III study CA 184-024 patients were not restricted to HLAA2+ haplotype. However, a different patient group was enrolled (first line situation) and another dosing and treatment scheme was tested (combination with DTIC; ipilimumab10mg/kg and maintenance period following induction phase for patients who benefitted from ipilimumab). Patients with primary mucosal melanoma were excluded

in CA184-024 study; patients with primary ocular melanoma were excluded in both MDX010-20 as well as in CA184-024.

This large clinical phase II trial was proposed to treat broad range of metastatic melanoma patients who have failed at least one systemic treatment regimen in advanced, non-resectable melanoma. The study aimed at gaining more information about efficacy and safety of ipilimumab in a broad range of clinically relevant pretreated patient cohorts seen in daily routine, neither addressed in MDX-010-20 study nor in CA184-024. Enrollment was not restricted to any specific HLA subtype and patients with uveal or ocular melanoma as well as cutaneous melanoma patients with or without asymptomatic brain metastases could be treated with ipilimumab as well. Potential predictive markers (ALC, B-raf mutational status) were prospectively evaluated. Wide access to ipilimumab in skin cancer-specialized clinical centers was achieved in addition to a standardized evaluation of its clinical results and of the proposed management guidelines handling the side effects. Patients were treated according to the MDX010-20 protocol with ipilimumab monotherapy 3mg/kg four times during the induction phase only. Patients benefiting from therapy (stable disease of ≥ 3 months beginning at Week 12 or patients with initial partial or complete response at Week 12 assessment) and showing no immune-related adverse events (irAE) ≥ grade 3 were eligible for treatment re-induction in the case of melanoma relapse.

The DeCOG-MM-PAL11-Trial was shortly interrupted and continued for patients with ocular melanoma only in 2011 after 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 to guarantee a valid evaluation of all cohorts. Ocular melanoma was defined as melanomas originated from uvea, the choroid, the ciliary body and conjunctiva [1].

2. Investigational medicinal product / treatment strategy

Trade name:	Yervoy®
Active substance:	Ipilimumab
CAS number:	477202-00-9
Dose:	3 mg/kg
Concentration:	200 mg
Mode of administration:	intravenous use
Duration of treatment:	10 weeks (3-weekly administration)
Storage:	Ipilimumab must be stored at a temperature ≥ 2°C and ≤ 8°C, protected from light

2.1 Comparator condition / medication

Not applicable.

3. Treatment / Invention

Ipilimumab (3 mg/kg) was administered intravenously every 3 weeks over 10 weeks. Patients with progressive disease (PD) following stable disease (SD) or an initial partial (PR) or complete response

(CR) ≥ 3 months from week 12 tumor assessment on were eligible for re-induction with ipilimumab (again 4x 3mg/kg over 10 weeks).

4. Total number of patients and Study Population

A total of 171 patients with pretreated metastatic melanoma originating from skin, mucosa, ocular or with unknown primary tumor from 25 clinics in Germany were screened for this study. 161 patients were enrolled and with a total of 5 dropouts, 156 of these patients received at least one dose of ipilimumab and could therefore be analyzed.

4.1 Analysis data set

Number of patients		171
Number of patients (ITT-Set = ITT)		156
	Patients with cutaneous melanoma	83
	Patients with mucosal melanoma	7
	Patients with MUP (melanoma with unknown primary)	13
	Patients with ocular melanoma	53
Number of patients (Response-evaluable set = RES)		104
	Patients with cutaneous melanoma	55
	Patients with mucosal melanoma	6
	Patients with MUP	9
	Patients with ocular melanoma	34

Number of patients with measurable disease at baseline determined by irRECIST and least one restaging (Response-evaluable set (irRECIST)) = irRES)		48
	Patients with cutaneous melanoma	26
	Patients with mucosal melanoma	3
	Patients with MUP	6
	Patients with ocular melanoma	13
Number of participating clinics		25

4.2 Analysis Population

Safety population (SP) = Intent-to-treat (ITT): All patients who were enrolled and received at least one dose of ipilimumab.

Response-evaluable population: 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.

Protocol violations/deviations: none

The following aspects were documented:

- Patient characteristics (e.g., sex, age, ECOG, pretreatment, tumor data)
- (Serious) Adverse events
- Immune-related adverse events
- Survival and response (e.g., PFS (rate), OS (rate), ORR, DCR, irORR, irDCR)
- (Re-)Induction therapy

- Follow-up
- Screening and registration

4.3 Inclusion criteria

1. Protocol version 1.0: histologically proven cutaneous, mucosal or uveal melanoma; Protocol version 2.0: histologically proven ocular melanoma
2. Measurable disease according to RECIST in unresectable stage III-IV
3. Minimum age of 18 years
4. Able and willing to give valid written inform consent
5. Protocol version 1.0: Must have received at least one line of prior systemic therapy for advanced malignant melanoma resulting in one of the following conditions:

   a. relapsed following response of CR, PR or SD or

   b. failed to demonstrate a response of CR. PR or SD or

   c. did not tolerate such a regime due to toxicity

   Protocol version 2.0: Patients with or without prior systemic treatment for advanced malignant melanoma are eligble.
6. In case of systemic pre-treatment, an interval of at least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy is mandatory as well as recovery from any clinically significant toxicity experienced during treatment is recommended. Prior treatment must be completed by the time of ipilimumab administration. Palliative radiation therapy outside of the brain or therapeutic radiation to the brain after the patient's condition is stabilized and systemic steroids required for the management of symptoms due to brain metastases is decreased to the lowest fixed dose possible and does not require the 28-day waiting period. Patient must have recovered from any acute toxicity associated with prior therapy.
7. Expected survival of at least six months
8. ECOG Performance Status 0, 1 or 2.
9. Within the last 2 weeks prior to study day 1 the following laboratory parameters, which should be within the ranges specified: Lab Parameter Range

White blood cells (WBC)	≥ 2500/mm3 (_ 1 2.5 x 109/L)
Absolute neutrophil count (ANC)	≥ 1000/mm3 (_ 1.0 x 109/L)
Platelets	≥ 75.000/mm3 (_ 75 x 109/L)
Hemoglobin	≥ 9 g/dL(≥ 90 g/L; may be transfused)
Creatinine	≤ 2.0 x ULN
Bilirubine total	≤ 2.0 x ULN (excepted patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
ALT, AST	≤ 2.5 x ULN for patients without liver metastases, ≤ 5 x ULN for patients with liver metastases

10. No childbearing potential or negative pregnancy test of women of childbearing potential performed within 7 days prior to the start of treatment. Women of childbearing potential (WOCP) must be using an effective method of contraception (Pearl-Index < 1, e.g. oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [diaphragm, spermicides]) throughout the study and for up to 26 weeks after the last dose of

investigational product, in such a manner that the risk of pregnancy is minimized. No men of fathering potential or men of fathering potential must be using an effective method of contraception to avoid conception throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as:

• Amenorrhea ≥ 12 consecutive months without another cause, or

• For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥ 35 mIU/mL.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or ar practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at Baseline within 7 days before the start of ipilimumab and at week 12.

4.4 Exclusion criteria

1. The patient requires concomitant therapy with any of the following: 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.
2. The patient requires chronic use of systemic corticosteroids. Systemic steroids for management of symptoms due to brain mets should be avoided if possible or subject should be stable on the lowest clinically effective dose. Topical or inhalational steroids are permitted.
3. Use of any investigational or non-registered product (drug or vaccine) other than the study treatment.
4. Active autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis).
5. Symptomatic CNS metastases (Remark: Asymptomatic stable, untreated or pretreated central nervous system (CNS) metastasis are allowed)
6. Family history of congenital or hereditary immunodeficiency
7. The patient is known to be positive for Human Immunodeficiency Virus (HIV) or other chronic infections (HBV, HCV) or has another confirmed or suspected immunosuppressive or immunodeficient condition.
8. The patient has psychiatric or addictive disorders that may compromise his/her ability to give informed consent or to comply with the trial procedures.
9. Lack of availability for clinical follow-up assessments

10. The patient has concurrent severe medical problems, unrelated to the malignancy, that would significantly limit full compliance with the study or expose the patient to unacceptable risk.
11. Other serious illnesses, e.g., serious infections requiring antibiotics or bleeding disorders
12. Patients with serious intercurrent illness, requiring hospitalization
13. For female patients: the patient is pregnant or lactating. Women of childbearing potential: Refusal or inability to use effective means of contraception
14. Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.
15. Subjects with melanoma who have another active, concurrent, malignant disease are not eligible for this trial, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix.
16. Protocol version 2.0: Previous treatment with ipilimumab

5. Results

5.1 Presentation of demographics and baseline characteristics

Table 3 of the Appendix shows the patient characteristics (ITT-Set). 57.1% of the 156 patients were male and the median age was 63 years with a range from 29 to 85 years. The predominant ECOG at baseline was 0 (66.0%), the M-Stadium M1c (81.4%), 21.8% had prior brain metastasis and all patients had the AJCC-Stadium IV. Additionally, nearly all patients had at least one prior systemic anticancer treatment in stage IV different from radiotherapy (94.9%) and the patients without treatment were solely patients with ocular melanoma.

Table 4 gives an overview of the screening and registration. A total of 171 patients had been screened, with a failure or missing result for 5.8% of the patients. Therefore, 161 patients (94.2%) were registered, but only 156 patients (91.2%) received at least one dose of ipilimumab.

5.2 Presentation of efficacy

Table 5 presents the survival and response rates according to tumor and subgroups. The PFS rate at 6 months derived by Kaplan-Meier methods was 17.3%, the OS rate at 12 months 30.4% and at 24 months 16.1% with no significant differences between the single primary tumors. The same hold true for the ORR (13.5%), DCR (35.6%), the irORR (16.7%) and the irDCR (45.8%).

Table 6 the progression-free and the overall survival. The median PFS was 2.6 months and the median OS 6.9 months. The patients with MUP had hereby the longest median PFS (3.2 months) and median OS (9.9 months), but the differences between the single primary tumors did not turn out to be significant.

A multivariate analysis revealed for patients with ocular melanoma, that the only factor independently associated with better OS was an ALC ≥ 1000/µl before the third dose of ipilimumab (week 7), i.e. patients with ALC < 1000/µl were at higher risk of death than patients with an ALC ≥ 1000/µl (hazard ratio 3.6; 95% CI 1.4-9.4) (Table 1).

Table 1: Cox regression for patients with ocular melanoma (with backward selection)

	Reference value	Estimate	STD error	p-Value	Hazard ratio	CI 95%
ALC week 7 (ALC >= 1000/µl vs. ALC < 1000/µl)	ALC >= 1000/µl	1.274	0.493	0.0097	3.576	1.361-9.392

Step	Dropped	p-Value
1	IPI	0.1911
2	LDH	0.0797

In patients with cutaneous melanoma, factors independently associated with better OS, i.e. a lower risk of death were the application of 4 doses Ipilimumab (hazard ratio 4.3; 95% CI 2.3-8.0), an ALC ≥ 1000/µl before the second dose of ipilimumab (week 4) (hazard ratio 2.0; 95% CI 1.1-3.8) and the absence of brain filiae (hazard ratio 1.9; 95% CI 1.0-3.5) (Table 2).

Table 2: Cox regression for patients with cutaneous melanoma (with backward selection)

	Reference value	Estimate	STD error	p-Value	Hazard ratio	CI 95%
IPI (4 doses vs. < 4 doses)	4 doses	1.462	0.316	<.0001	4.307°	2.319-8.002
ALC week 4 (ALC >= 1000/µl vs. ALC < 1000/µl)	ALC >= 1000/µl	0.702	0.328	0.0325	2.017	1.060-3.837
Brain filiae (No vs. Yes)	No	0.639	0.315	0.0428	1.895	1.021-3.516

° Reference 4 doses, e.g. patients with < 4 doses had a 4.307 times higher hazard rate than patients with 4 doses.

Step	Dropped	p-Value
1	LDH	0.8153

Table 7 shows the best response and the response for the restagings week 12 till week 48. First of all, only one patient (1.0%) of the reponse-evaluable set (RECIST) had CR as best response, 12.5% of the patients PR and 22.1% SD. The other 64.4% showed PD as best reponse. The share of patients with the best response CR from the patients of the response-evaluable set (irRECIST) was 2.1%, again one patient, PR 14.6%, SD 29.2% and with the best response PD 54.2%. Further details are presented in the table.

To patients who have progressed following stable disease of ≥ 3 months duration starting from diagnosis at week 12 tumor assessment or patients who have progressed following an initial response (partial or complete) assessed at week 12, additional cycles of therapy with the originally assigned treatment regimen were offered until off-treatment criteria were met, provided they met re-treatment eligibility requirements. These additional cycles were named re-induction.

Table 8 deals with the induction and re-induction therapy. For the induction therapy, the median number of doses was 4 for all primary tumors except mucosal melanoma with 3. All in all 59% of the patients received 4 doses, followed by 17.3% with 3 and 2 doses, respectively. The patients with the skipped doses did not prematurely terminate the therapy, hence 60.9% had no prematurely termination of therapy. The main reasons for the prematurely termination of therapy were death and progression, each with a share of 27.9%. Further on, only 3 patients (1.9%) with cutaneous melanoma received a re-induction therapy. The median number of doses was 4 and ranged from 4 to 8. Further on, a restaging visit at week 12 was performed for 67.3% of the patients. From these patients, 81.9% received 4 doses, followed by 13.3% with three doses, 3.8% with two doses and 1.0% with one dose. Finally death was the main reason for not performed restaging visits (for 34.6% of the patients) and especially for not performed restagings at week 12 (for 11.5% of the patients).

5.3 Presentation of safety

Table 9 gives an overview of the documented adverse events in the safety population. In addition there occurred 7 adverse events in two patients who died due to progression before receiving the first therapy. Four of them were serious. At least one adverse event was documented for 95.5% of the patients belonging to the safety population. Furthermore, 68.0% of these patients showed at least one related AE, 25.0% at least one ADR grade 3/4, 53.9% at least on immune-related AE and 21.2% at least one immune-related AE grade 3/4 and finally 59.6% at least one serious AE. Going on, 7 patients (4.5%) withdrew their informed consent and 122 patients (78.2%) died, 27% of them before week 12. The main cause of death was a progressive disease (74.4%), followed by an AE/SAE related death (33.3%).

Table 10 specifies the immune-related adverse events. 36 patients (23.1%) suffered from an immune-related dermatitis of grade 1/2, distributed among rash (7.7%), pruritus (10.3%) and other (5.1%). Further on, 30.8% of the patients showed immune-related gastrointestinal disorders of grade 1/2 and 21.8% immune-related gastrointestinal disorders of grade 3/4, 3.2% had immune-related endocrine disorders of grade 1/2 and 0.64% immune-related endocrine disorders of grade 3/4. Finally immune-related hepatobiliary disorders of grade 1/2 were documented for 4.5% of the patients and immune-related hepatobiliary disorders of grade 3/4 for 5.1%.

Table 9 provides a listing of all serious adverse events that occurred during the conduct of the study.

6. Statistical Methods

All parameters were evaluated in a descriptive manner. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For comparison of these variables, Fisher's exact test (the test is e.g. for categorical data that result from classifying objects in two different ways; it is used to examine the significance of the association (contingency) between the two kinds of classification) was used.

For continuous variables, the mean, median, standard deviation, minimum and maximum values will be given and in some cases the number of missing values. For comparison of these variables, Wilcoxon's test (the test is a non-parametric statistical hypothesis test used when comparing two independent samples according to their mean or median) was used.

Event related data like progression free survival, time to progression, duration of response and overall survival was analyzed by Kaplan Meier methods and compared using the logrank test. For the median values of progression free survival, overall survival, survival rate at 1 and 2 year and PFS rate at 6

months, the 95% confidence interval was calculated. All reported p-values are two-sided and not corrected for multiple testing.

In Addition, all results will be presented for the subgroups

- Cutaneous melanoma
- Mucosal melanoma
- MUP
- Ocular melanoma
- Cutaneous melanoma + MUP

Safety population (SP) = Intent-to-treat (ITT): All patients who were enrolled and received at least one dose of ipilimumab.

Response-evaluable population: 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.

7. Discussion

This phase II trial evaluated the efficacy and safety of ipilimumab in a cohort of patients with pretreated metastatic cutaneous, mucosal and unknown primary melanoma and in a large cohort of patients with pretreated and treatment-naïve metastatic uveal melanoma (UM) in a prospective fashion. Our findings show that ipilimumab is a treatment option for patients with advanced cutaneous melanoma seen in daily routine. Ipilimumab has limited clinical activity in patients with metastatic UM. Given the small number of patients with metastatic mucosal and unknown primary melanoma, it is not possible to determine whether ipilimumab has activity in these melanoma subgroups. The overall safety profile was consistent with previous clinical data [4,6].

There are several limitations to interpreting data from this phase II trial; 1) the single-arm, non-randomized phase II design, however, no clear standard therapy for the rare melanoma subgroups, especially for metastatic UM exists, 2) the lack of central review of imaging studies, and 3) the missing classification of tumor assessments according to immune-related response criteria [7].

The 1-year, 2-year OS rate and the DCR for patients with cutaneous melanoma was in line with the results of the pivotal phase III trial [4]. However, the median OS of 6.8 months was lower than the reported median OS of 10.1 months in the phase III trial [4]. This difference in the median OS could be related to the different performance status of the included patient population. In our study patients with a performance status 0-2 were included. In contrast, only patients with a performance status ≤1 were included in the pivotal phase III trial [4]. The 1-year OS rate of 22% for patients with UM in our study was lower than the 31% calculated for 82 patients with advanced UM who received 3mg/kg ipilimumab in the Italian EAP [8]. In the pivotal phase III trial [4] of ipilimumab patients with UM were excluded. However, the 1-year OS in this phase III trial in patients with previously treated metastatic melanoma was almost double as high as the 1-year OS for the patients with UM in our study. This difference in the 1-year OS could be related to the genetically distinct tumor biology of UM with poor prognosis at the stage of metastatic disease [9-11]. Interestingly, a more recent retrospective study assessing the OS from time of metastasis in mucosal, uveal, and cutaneous melanoma reported similar survivals in metastatic cutaneous and uveal melanoma [12]. The median OS and the DCR for patients with UM in our study were similar to previous retrospective findings [8,13]. In the Italian EAP four (5%) out of 82 patients with UM had an irPR, and additional 24 patients (29%) had irSD [8]. Recently, ipilimumab administered at a dose of 10 mg/kg has shown preliminary activity in treatment-naïve patients with

metastatic UM [14]. In this phase II trial of the Spanish Melanoma Group (GEM) the median OS, PFS rate at 6 months, the ORR and the DCR in 31 evaluable patients with treatment-naïve metastatic UM were 9.8 months, 27%, 7%, and 49%, respectively [14]. Two patients (7%) out of 31 achieved irPR and 13 (42%) had irSD. The 1-OS rate of 14% for seven patients with mucosal melanoma in our study was lower than the 35% for the 71 patients with advanced mucosal melanoma in the Italian EAP [15]. The difference in the 1-OS could be related to the small number of patients with mucosal melanoma in our study.

Given the side effects [4,16] and treatment costs [17] of ipilimumab as well as the poor prognosis of advanced melanoma with rapid clinical deterioration [9,12], early biomarkers of response would be very helpful. In our study, four doses of ipilimumab, an absolute lymphocyte count (ALC) ≥ 1000/µl at week 4 and the absence of brain metastases were factors independently associated with a better OS for patients with cutaneous melanoma. For patients with UM, an ALC ≥ 1000/µl at week 7 was the only factor independently associated with a better OS. This is in line with the results of previous studies, which reported that the rise in ALC during ipilimumab treatment at week 4 or week 7 [6,13,18] and the number of ipilimumab doses appears to correlate with OS [6]. Further confirmation of predictive biomarkers in prospective clinical trials is required. Recently, ipilimumab has been shown to improve the recurrence-free survival compared with placebo in a prospective phase III trial in patients with complete resection of stage III cutaneous melanoma [19]. A second phase III study in the adjuvant setting (NCT01274338), evaluating ipilimumab at 3 or 10 mg/kg vs high-dose interferon is still recruiting patients. The results of a further phase III trial (NCT01515189) comparing two different doses of ipilimumab (3 mg/kg vs 10 kg/KG) in patients with metastatic melanoma are still outstanding and will not be awaited before 2015. A large prospective phase I/II trial on ipilimumab in patients with locally treated UM (adjuvant arm) and metastatic UM (metastatic arm) is still recruiting patients and will not be finished before 2017 (NCT01585194). Besides CTLA-4 blockade by ipilimumab, targeting new immune checkpoint inhibitory receptors and ligands such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1), have evolved as further important targets in cutaneous melanoma [20-24]. PD-L1 expression is also found in primary and metastatic UM [25] and treatment strategies targeting PD-1/PD-L1 may also be of interest.

The encouraging results obtained using CTLA-4 or PD-1 immune checkpoint blockade in advanced-stage disease set the rationale for conducting combination treatments using the PD-1 antibody nivolumab and ipilimumab [26]. The results were promising, with an objective response rate of 53%, with a rapid tumor response and ≥ 80% reduction in tumor burden in the group treated at the maximum tolerable dose (nivolumab 1mg/kg and ipilimumab 3mg/kg) [26]. The results of the registration phase III study to compare treatment with ipilimumab versus nivolumab versus the combination of both drugs in patients with advanced-stage melanoma (NCT01844505) will not be available before 2016. Besides immunotherapy, current treatment progress in advanced melanoma has been focusing on relatively common BRAF V600 mutations (>50% melanomas [27]). The BRAF inhibitors vemurafenib and dabrafenib, the MEK inhibitor trametinib, and the combination of the MEK inhibitor, trametinib, and the BRAF inhibitor, dabrafenib have been approved for the treatment of BRAF V600-mutated metastatic melanoma based on phase II/III clinical trials [28-31]. Moreover, in BRAF V600-mutant melanoma, the combination of dabrafenib and trametinib is superior to single-agent treatment [32]. The understanding of the molecular biology of UM has led to more recent phase I/II studies investigating different kinase inhibitors as single agent [33], in combination with chemotherapy [34] or in combination with a PKC inhibitor (NCT01801358). In a randomized phase II study comparing the MEK inhibitor selumetinib with chemotherapy (temozolamide or dacarbazine) in patients with metastatic UM, the median PFS was significantly improved from 7 weeks with chemotherapy to 15.9 weeks with selumetinib. However, there was no improvement in OS. For the

patients treated with selumetinib, PFS rate at 6 months and 1-year OS rate were 23% and 42%, respectively. Recently, the PKC inhibitor, AEB071 has shown preliminary activity in metastatic UM with 72 out of 141 patients having PR/SD and a median PFS of 15 weeks [35]. A phase I/II study evaluating the combination of the MEK inhibitor MEK162 and the PKC inhibitor AEB071 in metastatic UM is currently recruiting patients (NCT01801358).

Similar to previous studies of ipilimumab at a dose of 3 mg/kg [4,36] immune-related dermatological AEs, i.e. pruritus and rash, and immune-related gastrointestinal AEs, i.e. diarrhea and colitis were the most frequent treatment-related adverse events. The rate of grade 3 and 4 treatment-related AEs in patients with cutaneous melanoma was in line with the results of the pivotal phase III trial of ipilimumab [4]. However, the rate of grade 3 and 4 treatment-related AEs in patients with UM was higher. This difference could be related to the genetically distinct tumor biology of UM with poor prognosis at the stage of metastatic disease and to the exclusion of patients with UM in the pivotal phase III trial. Immune-related gastrointestinal and hepatic AEs were the most common grade 3 and 4 irAEs in patients with UM. Consistent with our findings, grade 3 and 4 hepatic disorders were the most frequent irAEs in patients with metastatic UM treated in the Italian EAP [8]. Most of the irAEs were reversible when managed as per protocol-specific treatment guidelines and resolved with systemic glucocorticosteroid therapy. No new and unexpected safety findings were noted except the two following cases that were reported as serious adverse drug reaction, but that are not referenced in the IB of ipilimumab or SMPC of ipilimumab: there was one possible treatment-related death due to pancytopenia. Although attributed to ipilimumab, it is possible that the concomitant medication of the patient caused the pancytopenia. Additionally, one death with unknown cause was reported and the causal relationship to ipilimumab could not be excluded as per investigator.

8. Conclusion

In conclusion, ipilimumab is a treatment option for patients with advanced cutaneous melanoma seen in daily routine. For patients with UM, ipilimumab has limited clinical activity in patients. Given the small number of patients with metastatic mucosal and unknown primary melanoma, it is not possible to determine whether ipilimumab has activity in these melanoma subgroups. The ALC at week 4 and 7 appears to be an early biomarker of response and need further confirmation in randomized controlled trials. Immune-related AEs were manageable and reversible in most of the cases. Further investigations of ipilimumab and novel immune checkpoint inhibitors as well as the combination of immune checkpoint inhibitors with emerging signal transduction inhibitors in patients with cutaneous, uveal, mucosal and unknown primary melanoma in the adjuvant and metastatic setting are warranted to determine the optimal treatment time point for achieving the best clinical response.

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10. Appendix

Table 3: ITT Patient characteristics

Patient characteristics		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Number of patients		83		7		13		53		156	
Sex											
	Male	53	63.86	2	28.57	11	84.62	23	43.40	89	57.05
	Female	30	36.14	5	71.43	2	15.38	30	56.60	67	42.95
Age, years											
	Median	63		63		62		67		63	
	Range	29-85		33-73		40-77		34-84		29-85	
HLA-A2											
	Negative	2	2.41	.	.	.	.	1	1.89	3	1.92
	Positive	2	2.41	.	.	.	.	.	.	2	1.28
	Not known	79	95.18	7	100.00	13	100.00	52	98.11	151	96.79
ECOG baseline											
	0	51	61.45	2	28.57	12	92.31	38	71.70	103	66.03
	1	23	27.71	5	71.43	1	7.69	14	26.42	43	27.56
	2	9	10.84	.	.	.	.	1	1.89	10	6.41
NRas mutation											
	Not mutated	5	6.02	.	.	.	.	1	1.89	6	3.85
	Mutated	4	4.82	.	.	.	.	.	.	4	2.56
	Not known	74	89.16	7	100.00	13	100.00	52	98.11	146	93.59
B-raf mutation											
	Not mutated	29	34.94	3	42.86	5	38.46	12	22.64	49	31.41
	Mutated	17	20.48	.	.	6	46.15	.	.	23	14.74
	Not known	37	44.58	4	57.14	2	15.38	41	77.36	84	53.85
Histology											
	Missing	13	15.66	.	.	.	.	.	.	.	.
	SSM	21	25.30	.	.	.	.	.	.	.	.
	NM	29	34.94	.	.	.	.	.	.	.	.
	ALM	6	7.23	.	.	.	.	.	.	.	.
	LMM	.	.	.	.	.	.	.	.	.	.
	Others	14	16.87	.	.	.	.	.	.	.	.
Breslow											
	T1 (<= 1mm)	15	18.07	1	14.29	.	.	1	1.89	17	10.90
	T2 (>1-2mm)	18	21.69	.	.	.	.	.	.	18	11.54

Patient characteristics		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
	T3 (>2-4mm)	19	22.89	.	.	.	.	1	1.89	20	12.82
	T4 (>4mm)	19	22.89	.	.	.	.	2	3.77	21	13.46
	Not known	12	14.46	6	85.71	13	100.00	49	92.45	80	51.28
M-Stadium											
	M1a	6	7.23	.	.	3	23.08	.	.	9	5.77
	M1b	15	18.07	2	28.57	1	7.69	2	3.77	20	12.82
	M1c	62	74.70	5	71.43	9	69.23	51	96.23	127	81.41
AJCC											
	St III unresectable	.	.	.	.	.	.	.	.	.	.
	St IV	83	100.00	7	100.00	13	100.00	53	100.00	156	100.00
LDH											
	<2 ULN	67	80.72	5	71.43	11	84.62	33	62.26	116	74.36
	>= 2 ULN	16	19.28	2	28.57	2	15.38	20	37.74	40	25.64
Previous brain metastases											
	No	57	68.67	5	71.43	10	76.92	50	94.34	122	78.21
	Yes	26	31.33	2	28.57	3	23.08	3	5.66	34	21.79
Prior systemic anticancer treatment in stage IV (except radiotherapy)											
	No	.	.	.	.	.	.	8	15.09	8	5.13
	Yes	83	100.00	7	100.00	13	100.00	45	84.91	148	94.87
Immunotherapy											
	No	67	80.72	7	100.00	11	84.62	53	100.00	138	88.46
	Yes	16	19.28	.	.	2	15.38	.	.	18	11.54
	Vaccination	5	6.02	.	.	.	.	.	.	5	3.21
Small molecules											
	No	71	85.54	7	100.00	9	69.23	46	86.79	133	85.26
	Yes	12	14.46	.	.	4	30.77	7	13.21	23	14.74
	BRAF inhibitor	7	8.43	.	.	2	15.38	.	.	9	5.77
	MEK inhibitor	4	4.82	.	.	2	15.38	.	.	6	3.85
	C-KIT inhibitor	.	.	.	.	.	.	.	.	.	.
	Other	1	1.20	.	.	.	.	7	13.21	8	5.13
Extremity perfusion											
	No	62	74.70	6	85.71	9	69.23	37	69.81	114	73.08
	Yes	12	14.46	1	14.29	2	15.38	.	.	15	9.62

Patient characteristics		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Chemotherapy regimens											
	0	9	10.84	.	.	2	15.38	16	30.19	27	17.31
	1	47	56.63	6	85.71	8	61.54	25	47.17	86	55.13
	2	20	24.10	.	.	2	15.38	9	16.98	31	19.87
	≥3	7	8.43	1	14.29	1	7.69	3	5.66	12	7.69
Number of prior systemic anticancer therapies in stage IV (CT,IMT,SM without radiotherapy)											
	0	.	.	.	.	.	.	8	15.09	8	5.13
	1	42	50.60	6	85.71	8	61.54	28	52.83	84	53.85
	2	27	32.53	.	.	3	23.08	9	16.98	39	25.00
	≥3	13	15.66	1	14.29	2	15.38	4	7.55	20	12.82
	Not determinable	1	1.20	.	.	.	.	4	7.55	5	3.21

Table 4: ITT: Screening/Registration

Screening /Registration				Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%	N	%
Number of patients with screening			8		86		7		15		55		171
Screening	Failure	7	87.50	1	1.16	.	.	1	6.67	.	.	9	5.26
	Missing	1	12.50	.	.	.	.	.	.	.	.	1	0.58
Registration		.	.	85	98.84	7	100.00	14	93.33	55	100.00	161	94.15
No. of registered patients with at least one study therapy		.	.	83	96.51	7	100.00	13	86.67	53	96.36	156	91.23

Table 5: ITT: Survival/Response

Survival/Response	N	PFS rate at 6 months°			N	OS rate at 12 months°			OS rate at 24 months°			N*	ORR RECIST*			DCR RECIST*			N**	ORR irRECIST**			DCR irRECIST**		
		N	%	p		N	%	p	N	%	p		N	%	p	N	%	p		N	%	p	N	%	p
Total	156	126	17.27		155	102	30.36		118	16.05		104	11	10.58		37	35.58		48	7	14.58		22	45.83	
Cutaneous melanoma	83	68	16.33	0.68	83	49	37.79	0.58	58	22.44	0.26	55	9	16.36	0.04	16	29.09	0.24	26	6	23.08	0.14	13	50.00	0.77
Mucosal melanoma	7	6	14.29		7	6	14.29		7	0.00		6	1	16.67		3	50.00		3	1	33.33		2	66.67	
MUP	13	10	16.67		12	7	27.27		7	27.27		9	1	11.11		2	22.22		6	0	0.00		2	33.33	
Ocular melanoma	53	42	19.24		53	40	22.44		46	6.65		34	0	0.00		16	47.06		13	0	0.00		5	38.46	

°Derived by Kaplan-Meier methods (N=Number of patients who died/with progression; %=OS/PFS rate), one patient with unknown date of death skipped for evaluation of OS

* Response-evaluable set (104 patients)

** Patients with measurable lesions at baseline according to irRECIST and at least one tumor assessment at study (48 patients)

Survival/Response		N	PFS rate at 6 months°			N	OS rate at 12 months°			OS rate at 24 months°			N*	ORR RECIST			DCR RECIST			N**	ORR irRECIST			DCR irRECIST		
			N	%	p		N	%	p	N	%	p		N	%	p	N	%	p		N	%	p	N	%	p
Total		156	126	17.27		155	102	30.36		118	16.05		104	11	10.58		37	35.58		48	7	14.58		22	45.83	
Cutaneous melanoma																										
B-raf	Not mutated	29	20	30.09	0.12	29	14	50.69	0.42	18	31.11	0.46	17	7	41.18	0.005	10	58.82	0.003	6	3	50.00	0.03	5	83.33	0.27
	Mutated	17	14	15.69		17	11	30.80		12	20.53		12	1	8.33		3	25.00		9	3	33.33		4	44.44	
	Not known	37	34	5.62		37	24	30.56		28	16.98		26	1	3.85		3	11.54		11	0	0.00		4	36.36	
Brain	No metastases	57	44	20.54	0.02	57	26	50.98	< .0001	33	32.47	< .0001	42	8	19.05	0.67	13	30.95	0.73	23	6	26.09	1.0	12	52.17	1.0
	metastases	26	24	7.69		26	23	11.54		25	3.85		13	1	7.69		3	23.08		3	0	0.00		1	33.33	
LDH	< 2 ULN	67	53	18.80	0.009	67	36	42.34	.0007	45	24.31	0.002	50	8	16.00	1.0	15	30.00	1.0	23	6	26.09	1.0	12	52.17	1.0
	>= 2 ULN	16	15	6.25		16	13	18.75		13	18.75		5	1	20.00		1	20.00		3	0	0.00		1	33.33	
IPI	< 4 doses					32	27	13.46	< .0001	28	8.97	< .0001														
	4 doses					51	22	53.13		30	30.95															
ALC-Week 1	< 1000/µl					38	24	35.37	0.21	29	16.98	0.14														
	>= 1000/µl					41	22	42.14		26	28.46															
ALC-Week 4	< 1000/µl					18	14	22.22	0.002	15	11.11	0.005														
	>= 1000/µl					50	24	46.51		31	27.56															
ALC-Week 7	< 1000/µl					14	8	42.86	0.44	11	10.71	0.16														
	>= 1000/µl					39	19	46.63		23	32.64															

Survival/Response		N	PFS rate at 6 months°			N	OS rate at 12 months°			OS rate at 24 months°			N*	ORR RECIST			DCR RECIST			N**	ORR irRECIST			DCR irRECIST		
			N	%	p		N	%	p	N	%	p		N	%	p	N	%	p		N	%	p	N	%	p
Mucosal melanoma																										
B-raf	Not mutated	3	3	0.00	0.05	3	3	0.00	0.01	3	0.00	0.01	2	0	0.00	.	0	0.00	.	1	0	0.00	.	0	0.00	.
	Mutated	0	0	.		0	0	.		0	.		0	0	.		0	.		0	0	.		0	.	
	Not known	4	3	25.00		4	3	25.00		4	0.00		4	1	25.00		3	75.00		2	1	50.00		2	100.0	
Brain	No metastases	5	5	0.00	0.42	5	5	0.00	0.50	5	0.00	0.50	5	0	0.00	0.17	2	40.00	1.0	2	0	0.00	0.33	1	50.00	1.0
	metastases	2	1	50.00		2	1	50.00		2	0.00		1	1	100.0		1	100.0		1	1	100.0		1	100.0	
LDH	< 2 ULN	5	5	0.00	0.29	5	5	0.00	0.50	5	0.00	0.50	5	0	0.00	0.17	2	40.00	1.0	2	0	0.00	0.33	1	50.00	1.0
	>= 2 ULN	2	1	50.00		2	1	50.00		2	0.00		1	1	100.0		1	100.0		1	1	100.0		1	100.0	
IPI	< 4 doses					4	3	25.00	0.71	4	0.00	0.71														
	4 doses					3	3	0.00		3	0.00															
ALC-Week 1	< 1000/µl					3	2	33.33	0.99	3	0.00	0.99														
	>= 1000/µl					3	3	0.00		3	0.00															
ALC-Week 4	< 1000/µl					2	2	0.00	0.008	2	0.00	0.008														
	>= 1000/µl					5	4	20.00		5	0.00															
ALC-Week 7	< 1000/µl					1	1	0.00	0.08	1	0.00	0.08														
	>= 1000/µl					3	3	0.00		3	0.00															
MUP																										
B-raf	Not mutated	5	5	0.00	0.003	4	3	25.00	0.42	3	25.00	0.44	4	0	0.00	1.0	0	0.00	0.56	3	0	0.00	.	0	0.00	0.20
	Mutated	6	4	33.33		6	4	22.22		4	22.22		4	1	25.00		2	50.00		2	0	0.00		1	50.00	
	Not known	2	1	0.00		2	0	100.0		0	100.0		1	0	0.00		0	0.00		1	0	0.00		1	100.0	
Brain	No metastases	10	8	11.11	0.96	9	4	38.10	0.05	4	38.10	0.05	8	1	12.50	1.0	1	12.50	0.22	6	0	0.00	.	2	33.33	.
	metastases	3	2	33.33		3	3	0.00		3	0.00		1	0	0.00		1	100.0		0	0	.		0	.	
LDH	< 2 ULN	11	9	18.18	0.12	10	6	30.00	0.03	6	30.00	0.03	9	1	11.11	.	2	22.22	.	6	0	0.00	.	2	33.33	.
	>= 2 ULN	2	1	0.00		2	1	0.00		1	0.00		0	0	.		0	.		0	0	.		0	.	
IPI	< 4 doses					5	3	25.00	0.29	3	25.00	0.29														
	4 doses					7	4	25.00		4	25.00															
ALC-Week 1	< 1000/µl					5	4	20.00	0.13	4	20.00	0.13														
	>= 1000/µl					6	2	37.50		2	37.50															
ALC-Week 4	< 1000/µl					4	4	0.00	0.04	4	0.00	0.04														
	>= 1000/µl					7	3	45.71		3	45.71															
ALC-Week 7	< 1000/µl					1	1	0.00	0.008	1	0.00	0.008														
	>= 1000/µl					8	4	38.10		4	38.10															
Ocular melanoma																										
B-raf	Not mutated	12	8	33.33	0.35	12	9	25.00	0.82	10	12.50	0.74	7	0	0.00	.	3	42.86	.	3	0	0.00	.	1	33.33	.
	Mutated	0	0	.		0	0	.		0	.		0	0	.		0	.		0	0	.		0	.	
	Not known	41	34	15.00		41	31	22.00		36	4.71		27	0	0.00		13	48.15		10	0	0.00		4	40.00	

Survival/Response		N	PFS rate at 6 months°			N	OS rate at 12 months°			OS rate at 24 months°			N*	ORR RECIST			DCR RECIST			N**	ORR irRECIST			DCR irRECIST		
			N	%	p		N	%	p	N	%	p		N	%	p	N	%	p		N	%	p	N	%	p
Brain	No metastases	50	40	18.38	0.98	50	38	21.72	0.96	44	4.07	0.54	32	0	0.00	.	15	46.88	1.0	12	0	0.00	.	4	33.33	0.38
	metastases	3	2	33.33		3	2	33.33		2	33.33		2	0	0.00		1	50.00		1	0	0.00		1	100.0	
LDH	< 2 ULN	33	24	25.00	0.02	33	21	33.24	< .0001	27	9.85	< .0001	26	0	0.00	.	12	46.15	1.0	11	0	0.00	.	5	45.45	0.49
	>= 2 ULN	20	18	10.00		20	19	5.00		19	5.00		8	0	0.00		4	50.00		2	0	0.00		0	0.00	
IPI	< 4 doses					23	21	4.55	< .0001	22	0.00	< .0001														
	4 doses					30	19	35.45		24	11.82															
ALC-Week 1	< 1000/µl					17	14	15.69	0.09	15	7.84	0.11														
	>= 1000/µl					30	20	30.65		25	8.76															
ALC-Week 4	< 1000/µl					9	8	11.11	0.08	8	11.11	0.08														
	>= 1000/µl					30	23	22.50		28	0.00															
ALC-Week 7	< 1000/µl					6	6	0.00	0.006	6	0.00	0.006														
	>= 1000/µl					25	16	35.00		21	5.83															

°Derived by Kaplan-Meier methods (N=Number of patients who died/with progression; %=OS/PFS rate), one patient with unknown date of death skipped for evaluation of OS

* Response-evaluable set (104 patients)

** Patients with measurable lesions at baseline according to irRECIST and at least one tumor assessment at study (48 patients)

Table 6: ITT: PFS/OS

PFS/OS	PFS (months)							OS (months)						
	N	Death/ Progress	Censored	Mean	Median	CI 95% for Median	p	N	Death	Censored	Mean	Median	CI 95% for Median	p
Total	156	142	14	4.37	2.60	2.53-2.73		155*	121	34	10.03	6.91	5.66-8.62	
Cutaneous Melanoma	83	74	9	4.45	2.57	2.53-2.66	0.95	83	60	23	11.12	6.78	5.30-9.87	0.24
Mucosal Melanoma	7	7	0	3.56	2.76	1.51-5.72		7	7	0	8.71	9.57	1.55-11.05	
MUP	13	11	2	3.19	2.53	2.27-4.05		12*	7	5	7.82	9.90	2.27-.	
Ocular Melanoma	53	50	3	4.25	2.83	2.53-2.89		53	47	6	8.27	6.78	3.65-8.06	

*One MUP patient died, but the date of death was unknown, hence this patient cannot be investigated here.

OS		OS (months)						
		N	Death	Censored	Mean	Median	CI 95% for Median	p
Total		155*	121	34	10.03	6.91	5.66-8.62	
Cutaneous Melanoma								
LDH	< 2 ULN	67	47	20	12.29	7.93	5.66-15.07	0.005
	>= 2 ULN	16	13	3	3.25	2.11	0.63-5.03	
IPI	< 4 doses	32	28	4	4.42	2.07	1.55-4.05	< .0001
	4 doses	51	32	19	14.86	13.45	7.93-20.43	
ALC- Week 4	< 1000/µl	18	16	2	7.85	3.59	1.78-5.63	0.003
	>= 1000/µl	50	32	18	13.11	9.87	6.12-18.45	
ALC- Week 7	< 1000/µl	14	12	2	10.76	6.33	3.62-15.07	0.11
	>= 1000/µ	39	24	15	14.07	9.87	6.12-20.43	
Mucosal Melanoma								
LDH	< 2 ULN	5	5	0	9.09	9.57	6.81-11.05	0.50
	>= 2 ULN	2	2	0	7.78	7.78	1.55-14.01	
IPI	< 4 doses	4	4	0	7.37	6.96	1.55-14.01	0.71
	4 doses	3	3	0	10.50	10.89	9.57-11.05	
ALC- Week 4	< 1000/µl	2	2	0	4.18	4.18	1.55-6.81	0.008
	>= 1000/µl	5	5	0	10.53	10.89	7.11-14.01	
ALC- Week 7	< 1000/µl	1	1	0	6.81	6.81	.	0.08
	>= 1000/µ	3	3	0	9.68	10.89	7.11-11.05	

OS		OS (months)						
		N	Death	Censored	Mean	Median	CI 95% for Median	p
MUP*								
LDH	< 2 ULN	10	6	4	8.38	9.90	2.27-.	0.03
	>= 2 ULN	2	1	1	2.27	2.27	.	
IPI	< 4 doses	5	3	2	3.16	3.16	2.27-.	0.29
	4 doses	7	4	3	9.52	10.59	4.31-.	
ALC- Week 4	< 1000/µl	4	4	0	5.13	4.18	2.27-9.90	0.04
	>= 1000/µl	7	3	4	9.62	11.28	2.27-.	
ALC- Week 7	< 1000/µl	1	1	0	4.05	4.05	.	0.008
	>= 1000/µ	8	4	4	9.77	11.28	4.31-.	
Ocular Melanoma								
LDH	< 2 ULN	33	28	5	10.90	9.29	7.01-11.58	< .0001
	>= 2 ULN	20	19	1	3.41	2.52	1.45-5.69	
IPI	< 4 doses	23	22	1	4.16	2.80	1.45-6.32	< .0001
	4 doses	30	25	5	11.32	9.13	6.74-13.85	
ALC- Week 4	< 1000/µl	9	8	1	4.60	3.32	1.41-8.62	0.08
	>= 1000/µl	30	28	2	8.63	7.70	5.00-10.39	
ALC- Week 7	< 1000/µl	6	6	0	4.92	3.11	2.20-11.45	0.006
	>= 1000/µ	25	22	3	10.91	8.62	7.01-14.47	

*One MUP patient died, but the date of death was unknown, hence this patient cannot be investigated here.

Table 7: ITT: ORR/DCR

ORR/DCR		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Number of patients		83		7		13		53		156	
Response-evaluable set (RECIST)		55		6		9		34		104	
Number of patients week 24 (RECIST)		15		2		2		12		31	
Disease control rate (DCR) (CR or PR or SD) (RECIST; %)		16	29.09	3	50.00	2	22.22	16	47.06	37	35.58
	Week 12	15	27.27	3	50.00	2	22.22	16	47.06	36	34.62
	Week 24	10	66.67	1	50.00	1	50.00	7	58.33	19	61.29
Overall response rate (PR+CR) (RECIST; %)		9	16.36	1	16.67	1	11.11	0	0.00	11	10.58
	Week 12	7	12.73	1	16.67	0	0.00	0	0.00	8	7.69
	Week 24	6	40.00	1	50.00	0	0.00	0	0.00	7	22.58
Best response (RECIST)											
	Complete response (CR)	.	.	.	.	.	.	.	.	.	.
	Partial response (PR)	9	16.36	1	16.67	1	11.11	.	.	11	10.58
	Stable disease (SD)	7	12.73	2	33.33	1	11.11	16	47.06	26	25.00
	Progressive disease (PD)	39	70.91	3	50.00	7	77.78	18	52.94	67	64.42
Response-evaluable set (irRECIST)		26		3		6		13		48	
Disease control rate (irRECIST; %)		13	50.00	2	66.67	2	33.33	5	38.46	22	45.83
Overall response rate (irRECIST; %)		6	23.08	1	33.33	0	0.00	0	0.00	7	14.58
Best response (irRECIST)											
	Complete response (irCR)	1	3.85	.	.	.	.	.	.	1	2.08
	Partial response (irPR)	5	19.23	1	33.33	.	.	.	.	6	12.50
	Stable disease (irSD)	7	26.92	1	33.33	2	33.33	5	38.45	15	31.25
	Progressive disease (irPD)	13	50.00	1	33.33	4	66.67	8	61.54	26	54.17
Restaging visit 1 at week 12 (RECIST)		55		6		9		34		104	
RECIST	CR	.	.	.	.	.	.	.	.	.	.
	PR	7	12.73	1	16.67	.	.	.	.	8	7.69
	SD	8	14.55	2	33.33	2	22.22	16	47.06	28	26.92
	PD	40	72.73	3	50.00	7	77.78	18	52.94	68	65.38
Restaging visit 1 at week 12 (irRECIST)		26		3		6		13		48	
irRECIST	irCR	1	3.85	.	.	.	.	.	.	1	2.08
	irPR	4	15.38	1	33.33	.	.	.	.	5	10.42
	irSD	8	30.77	1	33.33	2	33.33	5	38.46	16	33.33
	irPD	13	50.00	1	33.33	4	66.67	8	61.54	26	54.17

ORR/DCR		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Restaging visit 2 at week 24 (RECIST)		15		2		2		12		31	
RECIST	CR	.	.	.	.	.	.	.	.	.	.
	PR	6	40.00	1	50.00	.	.	.	.	7	22.58
	SD	4	26.67	.	.	1	50.00	7	58.33	12	38.71
	PD	5	33.33	1	50.00	1	50.00	5	41.67	12	38.71
Restaging visit 2 at week 24 (irRECIST)		6		1		1		5		13	
irRECIST	Missing	1	16.67	.	.	.	.	.	.	1	7.69
	Not calculable	.	.	.	.	.	.	1	20.00	1	7.69
	irCR	.	.	.	.	.	.	.	.	.	.
	irPR	4	66.67	1	100.00	.	.	.	.	5	38.46
	irSD	1	16.67	.	.	1	100.00	2	40.00	4	30.77
	irPD	.	.	.	.	.	.	2	40.00	2	15.38
Restaging visit 3 at week 36 (RECIST)		10		1		1		4		16	
RECIST	CR	.	.	.	.	.	.	.	.	.	.
	PR	6	60.00	.	.	.	.	.	.	6	37.50
	SD	2	20.00	.	.	1	100.00	2	50.00	5	31.25
	PD	2	20.00	1	100.00	.	.	2	50.00	5	31.25
Restaging visit 3 at week 36 (irRECIST)		4		1		1		0		6	
irRECIST	Not calculable	.	.	1	100.00	.	.	.	.	1	16.67
	irCR	.	.	.	.	.	.	.	.	.	.
	irPR	1	25.00	.	.	.	.	.	.	1	16.67
	irSD	3	75.00	.	.	1	100.00	.	.	4	66.67
	irPD	.	.	.	.	.	.	.	.	.	.
Restaging visit 4 at week 48 (RECIST)		6		0		1		1		8	
RECIST	CR	.	.	.	.	.	.	.	.	.	.
	PR	4	66.67	.	.	1	100.00	.	.	5	62.50
	SD	.	.	.	.	.	.	1	100.00	1	12.50
	PD	2	33.33	.	.	.	.	.	.	2	25.00
Restaging visit 4 at week 48 (irRECIST)		3		0		1		0		4	
irRECIST	Not calculable	1	33.33	.	.	1	100.00	.	.	2	50.00
	irCR	.	.	.	.	.	.	.	.	.	.
	irPR	1	33.33	.	.	.	.	.	.	1	25.00
	irSD	1	33.33	.	.	.	.	.	.	1	25.00
	irPD	.	.	.	.	.	.	.	.	.	.

Table 8: ITT: Induction/Re-Induction

Induction/Re-Induction		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Number of patients		83		7		13		53		156	
Induction											
	Median number of doses	4		3		4		4		4	
	Range	1-4		2-4		1-4		1-4		1-4	
	4 doses	51	61.45	3	42.86	8	61.54	30	56.60	92	58.97
	3 doses	13	15.66	3	42.86	3	23.08	8	15.09	27	17.31
	2 doses	14	16.87	1	14.29	2	15.38	10	18.87	27	17.31
	1 dose	5	6.02	.	.	.	.	5	9.43	10	6.41
	Skipped one dose	1	1.20	1	14.29	.	.	1	1.89	3	1.92
Prematurely termination											
	No	52	62.65	4	57.14	8	61.54	31	58.49	95	60.90
	Yes	31	37.35	3	42.86	5	38.46	22	41.51	61	39.10
	After 3 treatments	12	14.46	2	28.57	3	23.08	7	13.21	24	15.38
	After 2 treatments	14	16.87	1	14.29	2	15.38	10	18.87	27	17.31
	After 1 treatment	5	6.02	.	.	.	.	5	9.43	10	6.41
Cause for study discontinuation/prematurely termination											
	Death	9	10.84	1	14.29	1	7.69	6	11.32	17	10.90
	Severe hematological AE	.	.	.	.	.	.	1	1.89	1	0.64
	Non-severe hematological AE	2	2.41	.	.	.	.	5	9.43	7	4.49
	Progression	10	12.05	2	28.57	1	7.69	4	7.55	17	10.90
	Other	8	9.64	.	.	1	7.69	4	7.55	13	8.33
	Patients wish	2	2.41	.	.	1	7.69	1	1.89	4	2.56
	Withdrawal of informed consent	.	.	.	.	1	7.69	1	1.89	2	1.28
Re-Induction											
	No	80	96.39	7	100.00	13	100.00	53	100.00	153	98.08
	Yes	3	3.61	.	.	.	.	.	.	3	1.92
	Number of patients with one re-induction therapy	2	2.41							2	1.28
	Number of patients with two re-induction therapies	1	1.20							1	0.64
	Median number of doses	4		.		.		.		4	
	Range	4-8								4-8	

Induction/Re-Induction		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
	1 dose	.	.	.	.	.	.	.	.	.	.
	>= 2 doses	3	3.61	.	.	.	.	.	.	3	1.92
Restaging visit at week 12 and administration of study medication											
	Patient received 4 doses and had restaging at week 12	48	57.83	3	42.86	8	61.54	27	50.94	86	55.13
	Patient received 3 doses and had restaging at week 12	7	8.43	3	42.86	1	7.69	3	5.66	14	8.97
	Patient received 2 doses and had restaging at week 12	1	1.20	.	.	.	.	3	5.66	4	2.56
	Patient received 1 dose and had restaging at week 12	.	.	.	.	.	.	1	1.89	1	0.64
	Restaging visit at week 12	56	67.47	6	85.71	9	69.23	34	64.15	105	67.31
	Restaging visit at week 24	15	18.07	2	28.57	2	15.38	12	22.64	31	19.87
	Restaging visit at week 36	10	12.05	1	14.29	1	7.69	4	7.55	16	10.26
	Restaging visit at week 48	6	7.23	.	.	1	7.69	1	1.89	8	5.13
Cause for not performed restaging visits											
	Death before staging	26	31.33	3	42.86	4	30.77	21	39.62	54	34.62
	Lost to Follow-up and death before staging	5	6.02	.	.	.	.	3	5.66	8	5.13
	Lost to Follow-up before staging	2	2.41	.	.	1	7.69	.	.	3	1.92
	Non-severe hematological adverse reaction and death before stagi	1	1.20	.	.	.	.	4	7.55	5	3.21
	Non-severe hematological adverse reaction before staging	1	1.20	.	.	.	.	1	1.89	2	1.28
	Other reason and death before staging	6	7.23	.	.	1	7.69	4	7.55	11	7.05
	Other reasons	1	1.20	.	.	.	.	.	.	1	0.64
	Patients wish and death before staging	2	2.41	.	.	1	7.69	1	1.89	4	2.56
	Progression and death before staging	9	10.84	2	28.57	.	.	4	7.55	15	9.62
	Progression before staging	1	1.20	.	.	1	7.69	.	.	2	1.28
	Severe hematological adverse reaction and death before staging	.	.	.	.	.	.	1	1.89	1	0.64
	Unknown	19	22.89	2	28.57	3	23.08	12	22.64	36	23.08

Induction/Re-Induction		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
	Withdrawal of informed consent	4	4.82	.	.	1	7.69	1	1.89	6	3.85
Cause for not performed restaging visit 1											
	Death before week 12	10	12.05	1	14.29	1	7.69	6	11.32	18	11.54
	Non-severe hematological adverse reaction before week 12	.	.	.	.	.	.	2	3.77	2	1.28
	Other reason and death before week 12	2	2.41	.	.	1	7.69	2	3.77	5	3.21
	Other reasons	4	4.82	.	.	.	.	1	1.89	5	3.21
	Patients wish and death before week 12	2	2.41	.	.	.	.	.	.	2	1.28
	Patients wish before week 12	.	.	.	.	1	7.69	1	1.89	2	1.28
	Progression and death before week 12	5	6.02	.	.	.	.	3	5.66	8	5.13
	Progression before week 12	2	2.41	.	.	.	.	.	.	2	1.28
	Unknown	1	1.20	.	.	.	.	3	5.66	4	2.56
	Withdrawal of informed consent	1	1.20	.	.	1	7.69	1	1.89	3	1.92

Table 9: SP: Adverse events

Adverse events		Cutaneous Melanoma		Mucosal Melanoma		MUP		Ocular Melanoma		Total	
		N	%	N	%	N	%	N	%	N	%
Number of patients		83		7		13		53		156	
Any AE (total)		79	95.18	6	85.71	13	100.00	51	96.23	149	95.51
Related AE (total)		57	68.67	3	42.86	11	84.62	35	66.04	106	67.95
	Grade 3/4	14	16.87	2	28.57	4	30.77	19	35.85	39	25.00
irAE (total)		40	48.19	2	28.57	10	76.92	32	60.38	84	53.85
	Grade 3/4	12	14.46	1	14.29	4	30.77	16	30.19	33	21.15
SAE (total)		48	57.83	4	57.14	7	53.85	34	64.15	93	59.62
Withdrawals of informed consent form (ICF) (total)		5	6.02	.	.	1	7.69	1	1.89	7	4.49
Death											
	Unknown	2	2.41	.	.	1	7.69	1	1.89	4	2.56
	No	21	25.30	.	.	4	30.77	5	9.43	30	19.23
	Yes	60	72.29	7	100.00	8	61.54	47	88.68	122	78.21
	Before restaging visit at week 12	19	22.89	1	14.29	2	15.38	11	20.75	33	21.15
Cause of death (multiple answers possible)											
	Therapy related	.	.	.	.	.	.	1	1.89	1	0.64
	Not therapy related	1	1.20	.	.	.	.	.	.	1	0.64
	Progressive disease	59	71.08	7	100.00	7	53.85	43	81.13	116	74.36
	AE/SAE related	27	32.53	1	14.29	4	30.77	20	37.74	52	33.33
	Not known	.	.	.	.	1	7.69	3	5.66	4	2.56

Table 10: SP: Immune-related adverse events (based on patients)

irAE	Tumor	Cutaneous melanoma				Mucosal melanoma				MUP			
	Grade	1/2		3/4		1/2		3/4		1/2		3/4	
		N	%	N	%	N	%	N	%	N	%	N	%
Number of patients					83				7				13
irDermatitis*		21	25.30	.	.	1	14.29	.	.	3	23.08	.	.
Pruritus		8	9.64	.	.	1	14.29	.	.	2	15.38	.	.
Rash		8	9.64	.	.	.	.	.	.	1	7.69	.	.
Other		5	6.02	.	.	.	.	.	.	.	.	.	.
Immune-related gastrointestinal disorders		24	28.92	15	18.07	1	14.29	1	14.29	4	30.77	4	30.77
Colitis		2	2.41	4	4.82	.	.	.	.	.	.	1	7.69
Diarrhea		17	20.48	8	9.64	.	.	1	14.29	3	23.08	1	7.69
GI perforation		.	.	1	1.20	.	.	.	.	.	.	.	.
Other		5	6.02	2	2.41	1	14.29	.	.	1	7.69	2	15.38
Immune-related endocrine disorders		4	4.82	1	1.20	.	.	.	.	.	.	.	.
Hypophysitis		3	3.61	1	1.20	.	.	.	.	.	.	.	.
Thyreoiditis		.	.	.	.	.	.	.	.	.	.	.	.
Hypothyroidism		1	1.20	.	.	.	.	.	.	.	.	.	.
Hyperthyroidism		.	.	.	.	.	.	.	.	.	.	.	.
M.Addisson		.	.	.	.	.	.	.	.	.	.	.	.
Immune-related hepatobiliary disorders		3	3.61	1	1.20	.	.	.	.	.	.	.	.
Increased S-GPT		1	1.20	.	.	.	.	.	.	.	.	.	.
Increased S-GOT		1	1.20	.	.	.	.	.	.	.	.	.	.
Increased S-GPT and S-GOT		1	1.20	.	.	.	.	.	.	.	.	.	.
Other		.	.	1	1.20	.	.	.	.	.	.	.	.
Other irAE		3	3.61	.	.	.	.	.	.	1	7.69	.	.

irAE	Tumor	Ocular melanoma				Total			
	Grade	1/2		3/4		1/2		3/4	
		N	%	N	%	N	%	N	%
Number of patients					53				156
irDermatitis*		11	20.75	.	.	36	23.08	.	.
Pruritus		5	9.43	.	.	16	10.26	.	.
Rash		3	5.66	.	.	12	7.69	.	.
Other		3	5.66	.	.	8	5.13	.	.
Immune-related gastrointestinal disorders		19	35.85	14	26.42	48	30.77	34	21.79
Colitis		3	5.66	6	11.32	5	3.21	11	7.05
Diarrhea		9	16.98	7	13.21	29	18.59	17	10.90
GI perforation		.	.	.	.	.	.	1	0.64
Other		7	13.21	1	1.89	14	8.97	5	3.21
Immune-related endocrine disorders		1	1.89	.	.	5	3.21	1	0.64
Hypophysitis		.	.	.	.	3	1.92	1	0.64
Thyreoiditis		.	.	.	.	.	.	.	.
Hypothyroidism		.	.	.	.	1	0.64	.	.
Hyperthyroidism		1	1.89	.	.	1	0.64	.	.
M.Addisson		.	.	.	.	.	.	.	.
Immune-related hepatobiliary disorders		4	7.55	7	13.21	7	4.49	8	5.13
Increased S-GPT		2	3.77	2	3.77	3	1.92	2	1.28
Increased S-GOT		1	1.89	2	3.77	2	1.28	2	1.28
Increased S-GPT and S-GOT		.	.	.	.	1	0.64	.	.
Other		1	1.89	3	5.66	1	0.64	4	2.56
Other irAE		3	5.66	1	1.89	7	4.49	1	0.64

* irDermatitis=Number of patients with irPruritus+ Number of patients with irRash + Number of patients with other irDermatitis, e.g. one patient could be counted up to three times in this category. Ditto for ir gastrointestinal disorders, ir endocrine disorders, ir hepatobiliary disorders and other irAE.

Table 11: SAE-Listing

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
1	[redacted]	[redacted]	1932	79	Male	10027433	Metabolism and nutrition disorders	10020942	Hypoalbuminaemia	Hypoalbuminemia
2	[redacted]	[redacted]	1939	72	Male	10029205	Nervous system disorders	10003591	Ataxia	Ataxia
3	[redacted]	[redacted]	1950	61	Female	10021881	Infections and infestations	10035664	Pneumonia	Pneumonia
4	[redacted]	[redacted]	1948	63	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	Progress
5	[redacted]	[redacted]	1933	78	Male	10018065	General disorders and administration site conditions	10016256	Fatigue	Fatigue
7	[redacted]	[redacted]	1934	77	Male	10017947	Gastrointestinal disorders	10003445	Ascites	Ascites
8	[redacted]	[redacted]	1950	61	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	tumor progression
9	[redacted]	[redacted]	1942	69	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10062196	Metastases to gastrointestinal tract	Gastrointestinal metastases
10	[redacted]	[redacted]	1947	64	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression
11	[redacted]	[redacted]	1939	72	Male	10017947	Gastrointestinal disorders	10000081	Abdominal pain	abdominal pain and gastric ulcer

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
	[redacted]									
11	[redacted]	[redacted]	1939	72	Male	10017947	Gastrointestinal disorders	10017822	Gastric ulcer	abdominal pain and gastric ulcer
12	[redacted]	[redacted]	1944	67	Male	10017947	Gastrointestinal disorders	10003445	Ascites	hospitalisation due to ascites
14	[redacted]	[redacted]	1966	45	Male	10022891	Investigations	10024574	Lipase increased	lipase increased
15	[redacted]	[redacted]	1965	46	Male	10018065	General disorders and administration site conditions	10049438	General physical health deterioration	Deterioration of General Condition
16	[redacted]	[redacted]	1941	70	Male	10017947	Gastrointestinal disorders	10000081	Abdominal pain	abdominal pain
17	[redacted]	[redacted]	1964	47	Female	10017947	Gastrointestinal disorders	10021328	Ileus	ileus
18	[redacted]	[redacted]	1948	63	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumor progression
19	[redacted]	[redacted]	1940	71	Male	10017947	Gastrointestinal disorders	10028813	Nausea	dizziness, faintness, nausea
19	[redacted]	[redacted]	1940	71	Male	10029205	Nervous system disorders	10013573	Dizziness	dizziness, faintness, nausea

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
19	[redacted]	[redacted]	1940	71	Male	10029205	Nervous system disorders	10042772	Syncope	dizziness, faintness, nausea
20	[redacted]	[redacted]	1942	69	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10026673	Malignant pleural effusion	Malignant Pleural effusion
21	[redacted]	[redacted]	1959	52	Female	10028395	Musculoskeletal and connective tissue disorders	10033425	Pain in extremity	Pain in extremity
22	[redacted]	[redacted]	1961	50	Female	10017947	Gastrointestinal disorders	10000081	Abdominal pain	Abdominal pain
23	[redacted]	[redacted]	1964	47	Female	10018065	General disorders and administration site conditions	10049438	General physical health deterioration	worsening general health condition
24	[redacted]	[redacted]	1964	47	Male	10029205	Nervous system disorders	10012373	Depressed level of consciousness	Depressed level of consciousness
25	[redacted]	[redacted]	1932	79	Male	10017947	Gastrointestinal disorders	10047700	Vomiting	Vomiting
26	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10009887	Colitis	Colitis
27	[redacted]	[redacted]	1948	63	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	diarrhea

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
28	[redacted]	[redacted]	1980	31	Male	10029205	Nervous system disorders	10051290	Central nervous system lesion	New brain lesion
29	[redacted]	[redacted]	1964	47	Male	10028395	Musculoskeletal and connective tissue disorders	10028372	Muscular weakness	Muscle weakness left-sides
31	[redacted]	[redacted]	1935	76	Female	10028395	Musculoskeletal and connective tissue disorders	10033425	Pain in extremity	Pain right leg
32	[redacted]	[redacted]	1932	79	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	progression of melanoma disease
33	[redacted]	[redacted]	1965	46	Male	10005329	Blood and lymphatic system disorders	10002034	Anaemia	Anemia
34	[redacted]	[redacted]	1949	62	Male	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
35	[redacted]	[redacted]	1942	69	Male	10017947	Gastrointestinal disorders	10013946	Dyspepsia	Dyspepsia
36	[redacted]	[redacted]	1955	56	Female	10040785	Skin and subcutaneous tissue disorders	10037868	Rash maculo-papular	Rash maculo-papular
37	[redacted]	[redacted]	1941	70	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of diseaseAf

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
38	[redacted]	[redacted]	1938	73	Female	10021881	Infections and infestations	10011781	Cystitis	cystitis
39	[redacted]	[redacted]	1964	47	Male	10029205	Nervous system disorders	10015037	Epilepsy	epilepsy due to brain metastases
40	[redacted]	[redacted]	1952	59	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	worsening of diahrrea
41	[redacted]	[redacted]	1935	76	Female	10021881	Infections and infestations	10040047	Sepsis	Sepsis
42	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Fatigue and Diarrhoe
42	[redacted]	[redacted]	1945	66	Female	10018065	General disorders and administration site conditions	10016256	Fatigue	Fatigue and Diarrhoe
43	[redacted]	[redacted]	1959	52	Male	10029205	Nervous system disorders	10013573	Dizziness	dizziness
44	[redacted]	[redacted]	1940	71	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	severe diarrhea
45	[redacted]	[redacted]	1942	69	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10027480	Metastatic malignant melanoma	Metastatic Malignant melanoma

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
46	[redacted]	[redacted]	1963	48	Female	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
47	[redacted]	[redacted]	1958	53	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
48	[redacted]	[redacted]	1952	59	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	worsening of diarrhea with watery stools
49	[redacted]	[redacted]	1942	69	Male	10017947	Gastrointestinal disorders	10009887	Colitis	Diarrhea / Colitis
49	[redacted]	[redacted]	1942	69	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea / Colitis
50	[redacted]	[redacted]	1964	47	Male	10029205	Nervous system disorders	10012373	Depressed level of consciousness	Depressed level of consciousness
51	[redacted]	[redacted]	1955	56	Female	10014698	Endocrine disorders	10021114	Hypothyroidism	Hypothyreodism
52	[redacted]	[redacted]	1959	52	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Progress
53	[redacted]	[redacted]	1942	69	Male	10017947	Gastrointestinal disorders	10009887	Colitis	colitis with diarrhoa
53	[redacted]	[redacted]	1942	69	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	colitis with diarrhoa
54	[redacted]	[redacted]	1952	59	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
55	[redacted]	[redacted]	1938	73	Male	10027433	Metabolism and nutrition disorders	10012601	Diabetes mellitus	Diabetes mellitus

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
56	[redacted]	[redacted]	1955	56	Male	10029205	Nervous system disorders	10015037	Epilepsy	epileptic seizure
57	[redacted]	[redacted]	1958	53	Male	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
58	[redacted]	[redacted]	1958	53	Male	10017947	Gastrointestinal disorders	10023804	Large intestine perforation	perforation- colon
59	[redacted]	[redacted]	1943	68	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	diarrhea
60	[redacted]	[redacted]	1955	56	Female	10018065	General disorders and administration site conditions	10037660	Pyrexia	Fever
61	[redacted]	[redacted]	1934	77	Male	10028395	Musculoskeletal and connective tissue disorders	10033425	Pain in extremity	pain left arm
62	[redacted]	[redacted]	1952	59	Female	10047065	Vascular disorders	10058990	Venous occlusion	acute occlusion of vein in left leg
63	[redacted]	[redacted]	1952	59	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	diarrhea, colitis with bleeding
63	[redacted]	[redacted]	1952	59	Female	10017947	Gastrointestinal disorders	10014896	Enterocolitis haemorrhagic	diarrhea, colitis with bleeding
64	[redacted]	[redacted]	1964	47	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
65	[redacted]	[redacted]	1959	52	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumorprogress
66	[redacted]	[redacted]	1932	79	Female	10038738	Respiratory, thoracic and mediastinal disorders	10013968	Dyspnoea	dyspnea
67	[redacted]	[redacted]	1941	70	Female	10022891	Investigations	10054889	Transaminases increased	Transaminase increased
68	[redacted]	[redacted]	1961	50	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	Progression
69	[redacted]	[redacted]	1928	83	Male	10027433	Metabolism and nutrition disorders	10020993	Hypoglycaemia	Hypoglycemia
70	[redacted]	[redacted]	1939	72	Female	10007541	Cardiac disorders	10003668	Atrial tachycardia	Paroxysmal atrial tachycardia
71	[redacted]	[redacted]	1958	53	Male	10028395	Musculoskeletal and connective tissue disorders	10006811	Bursitis	bursitis left arm
72	[redacted]	[redacted]	1978	33	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10025650	Malignant melanoma	disseminated metastatic melanom disease
73	[redacted]	[redacted]	1961	50	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	tumor progresssion

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
74	[redacted]	[redacted]	1956	55	Male	10018065	General disorders and administration site conditions	10049438	General physical health deterioration	progress of tumour disease , decline of general condítion
74	[redacted]	[redacted]	1956	55	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	progress of tumour disease , decline of general condítion
75	[redacted]	[redacted]	1937	74	Male	10014698	Endocrine disorders	10062767	Hypophysitis	Hypophysitis
76	[redacted]	[redacted]	1943	68	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	diarrhea
77	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10009887	Colitis	Colitis
78	[redacted]	[redacted]	1965	46	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
79	[redacted]	[redacted]	1935	76	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumor progression
82	[redacted]	[redacted]	1960	51	Male	10022891	Investigations	10004891	Biopsy tongue	biopsie and reduction of tumor burden at root of tongue
83	[redacted]	[redacted]	1937	74	Male	10037175	Psychiatric disorders	10061284	Mental disorder	Cortisonpsychoism

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
84	[redacted]	[redacted]	1956	55	Female	10017947	Gastrointestinal disorders	10000081	Abdominal pain	abdominal pain, fever, enterocolitis
84	[redacted]	[redacted]	1956	55	Female	10017947	Gastrointestinal disorders	10014893	Enterocolitis	abdominal pain, fever, enterocolitis
84	[redacted]	[redacted]	1956	55	Female	10018065	General disorders and administration site conditions	10037660	Pyrexia	abdominal pain, fever, enterocolitis
85	[redacted]	[redacted]	1948	63	Male	10017947	Gastrointestinal disorders	10000081	Abdominal pain	Abdominal pain
86	[redacted]	[redacted]	1943	68	Female	10017947	Gastrointestinal disorders	10013832	Duodenal perforation	duodenal perforation
87	[redacted]	[redacted]	1982	29	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
88	[redacted]	[redacted]	1955	56	Male	10029205	Nervous system disorders	10015037	Epilepsy	epileptic seizure
89	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
92	[redacted]	[redacted]	1958	53	Female	10017947	Gastrointestinal disorders	10009887	Colitis	Coltis
93	[redacted]	[redacted]	1955	56	Female	10018065	General disorders and administration site conditions	10049438	General physical health deterioration	General disorder, pulmonary embolism, renal failure

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
93	[redacted]	[redacted]	1955	56	Female	10038359	Renal and urinary disorders	10038435	Renal failure	General disorder, pulmonary embolism, renal failure
93	[redacted]	[redacted]	1955	56	Female	10038738	Respiratory, thoracic and mediastinal disorders	10037377	Pulmonary embolism	General disorder, pulmonary embolism, renal failure
94	[redacted]	[redacted]	1928	83	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10028980	Neoplasm	Neoplasms benign, malignant and unspecified (incl cysts and
95	[redacted]	[redacted]	1963	48	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10051696	Metastases to meninges	Meningeal metastases of malignant melanoma
96	[redacted]	[redacted]	1960	51	Male	10042613	Surgical and medical procedures	10061392	Tumour excision	Reduction of tumor burden at root of tongue
99	[redacted]	[redacted]	1945	66	Female	10005329	Blood and lymphatic system disorders	10002034	Anaemia	anemia
100	[redacted]	[redacted]	1932	79	Male	10017947	Gastrointestinal disorders	10028813	Nausea	hospitalization due to nausea
101	[redacted]	[redacted]	1934	77	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	disease progression
103	[redacted]	[redacted]	1932	79	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	disease progression
104	[redacted]	[redacted]	1973	38	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	disease progression

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
107	[redacted]	[redacted]	1964	47	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	Progress
108	[redacted]	[redacted]	1950	61	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progressed of desease
109	[redacted]	[redacted]	1941	70	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression
110	[redacted]	[redacted]	1952	59	Female	10007541	Cardiac disorders	10051093	Cardiopulmonary failure	pulmonary insufficiency due to suspected cerebral hemorrhage
111	[redacted]	[redacted]	1944	67	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Progress
112	[redacted]	[redacted]	1939	72	Male	10018065	General disorders and administration site conditions	10011906	Death	Death due to progression
113	[redacted]	[redacted]	1937	74	Female	10007541	Cardiac disorders	10061589	Aortic valve disease	aortic valve disease/stenose
113	[redacted]	[redacted]	1937	74	Female	10047065	Vascular disorders	10060965	Arterial stenosis	aortic valve disease/stenose
115	[redacted]	[redacted]	1942	69	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	Progressive disease
116	[redacted]	[redacted]	1937	74	Female	10047065	Vascular disorders	10020772	Hypertension	Hypertension
118	[redacted]	[redacted]	1949	63	Female	10019805	Hepatobiliary disorders	10019705	Hepatic pain	Pain (liver capsule)

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
119	[redacted]	[redacted]	1955	56	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of melanoma disease
120	[redacted]	[redacted]	1928	84	Male	10017947	Gastrointestinal disorders	10000081	Abdominal pain	Abdominal Pain
126	[redacted]	[redacted]	1949	63	Male	10022891	Investigations	10005364	Blood bilirubin increased	Increased Billirubin
128	[redacted]	[redacted]	1966	46	Male	10038738	Respiratory, thoracic and mediastinal disorders	10015090	Epistaxis	Nose Bleeding
129	[redacted]	[redacted]	1949	63	Female	10017947	Gastrointestinal disorders	10028813	Nausea	Pain (liver capsule) and nausea
129	[redacted]	[redacted]	1949	63	Female	10019805	Hepatobiliary disorders	10019705	Hepatic pain	Pain (liver capsule) and nausea
131	[redacted]	[redacted]	1950	61	Male	10017947	Gastrointestinal disorders	10009887	Colitis	Colitis
132	[redacted]	[redacted]	1949	63	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
133	[redacted]	[redacted]	1949	63	Female	10017947	Gastrointestinal disorders	10028813	Nausea	nausea with vomiting
133	[redacted]	[redacted]	1949	63	Female	10017947	Gastrointestinal disorders	10047700	Vomiting	nausea with vomiting

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
135	[redacted]	[redacted]	1949	63	Female	10017947	Gastrointestinal disorders	10028813	Nausea	pain (liver capsule) and nausea with vomiting
135	[redacted]	[redacted]	1949	63	Female	10017947	Gastrointestinal disorders	10047700	Vomiting	pain (liver capsule) and nausea with vomiting
135	[redacted]	[redacted]	1949	63	Female	10019805	Hepatobiliary disorders	10019705	Hepatic pain	pain (liver capsule) and nausea with vomiting
136	[redacted]	[redacted]	1936	76	Male	10037175	Psychiatric disorders	10061285	Mental disorder due to a general medical condition	Organic brain syndrome
137	[redacted]	[redacted]	1968	44	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea and collitis
138	[redacted]	[redacted]	1981	30	Female	10019805	Hepatobiliary disorders	10062000	Hepatobiliary disease	continous worsening of hepatobiliary disorders
141	[redacted]	[redacted]	1981	30	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
142	[redacted]	[redacted]	1949	63	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
143	[redacted]	[redacted]	1956	55	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10051398	Malignant neoplasm progression	progression of the malignant melanoma
144	[redacted]	[redacted]	1932	80	Female	10017947	Gastrointestinal disorders	10028813	Nausea	nausea

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
145	[redacted]	[redacted]	1932	80	Female	10018065	General disorders and administration site conditions	10028154	Multi-organ failure	multi organ failure by progress
146	[redacted]	[redacted]	1966	46	Male	10018065	General disorders and administration site conditions	10049438	General physical health deterioration	worsening general health condition
147	[redacted]	[redacted]	1966	46	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	tumour progression
148	[redacted]	[redacted]	1937	75	Female	10017947	Gastrointestinal disorders	10014893	Enterocolitis	Autoimmun-Enterocolitis
150	[redacted]	[redacted]	1948	63	Female	10018065	General disorders and administration site conditions	10003549	Asthenia	weakness
151	[redacted]	[redacted]	1936	76	Male	10018065	General disorders and administration site conditions	10011906	Death	death
152	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
153	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
154	[redacted]	[redacted]	1941	71	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	progress

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
156	[redacted]	[redacted]	1941	71	Male	10019805	Hepatobiliary disorders	10019663	Hepatic failure	death due to hepatic failure and progress
158	[redacted]	[redacted]	1960	51	Male	10021881	Infections and infestations	10040047	Sepsis	sepsis after inflammation of the left leg
159	[redacted]	[redacted]	1938	74	Female	10019805	Hepatobiliary disorders	10019705	Hepatic pain	Hepatic pain
160	[redacted]	[redacted]	1962	49	Male	10018065	General disorders and administration site conditions	10011906	Death	death due to tumorprogression
161	[redacted]	[redacted]	1934	78	Male	10019805	Hepatobiliary disorders	10036206	Portal vein thrombosis	Thrombosis portal vein right
162	[redacted]	[redacted]	1936	76	Male	10021881	Infections and infestations	10035664	Pneumonia	pneumonia
163	[redacted]	[redacted]	1936	76	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression with kidney failure
163	[redacted]	[redacted]	1936	76	Male	10038359	Renal and urinary disorders	10038435	Renal failure	progression with kidney failure
164	[redacted]	[redacted]	1956	56	Female	10017947	Gastrointestinal disorders	10000081	Abdominal pain	abdominal pain with vomiting, nausea and epigastralgia
164	[redacted]	[redacted]	1956	56	Female	10017947	Gastrointestinal disorders	10000087	Abdominal pain upper	abdominal pain with vomiting, nausea and epigastralgia
164	[redacted]	[redacted]	1956	56	Female	10017947	Gastrointestinal disorders	10028813	Nausea	abdominal pain with vomiting, nausea and epigastralgia
164	[redacted]	[redacted]	1956	56	Female	10017947	Gastrointestinal disorders	10047700	Vomiting	abdominal pain with vomiting, nausea and epigastralgia

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
166	[redacted]	[redacted]	1978	34	Male	10019805	Hepatobiliary disorders	10019663	Hepatic failure	hepatic failure
167	[redacted]	[redacted]	1948	64	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	Dyspnea due to disease progression
167	[redacted]	[redacted]	1948	64	Female	10038738	Respiratory, thoracic and mediastinal disorders	10013968	Dyspnoea	Dyspnea due to disease progression
168	[redacted]	[redacted]	1928	84	Male	10018065	General disorders and administration site conditions	10003549	Asthenia	weakeness, liver enzyme increase
168	[redacted]	[redacted]	1928	84	Male	10022891	Investigations	10060795	Hepatic enzyme increased	weakeness, liver enzyme increase
169	[redacted]	[redacted]	1948	64	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	disease progression
170	[redacted]	[redacted]	1978	34	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
171	[redacted]	[redacted]	1939	73	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
172	[redacted]	[redacted]	1969	43	Female	10022117	Injury, poisoning and procedural complications	10027091	Medication error	medication error
173	[redacted]	[redacted]	1969	43	Female	10019805	Hepatobiliary disorders	10019663	Hepatic failure	liver failure
175	[redacted]	[redacted]	1969	43	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
176	[redacted]	[redacted]	1951	61	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
177	[redacted]	[redacted]	1939	73	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumorprogression
178	[redacted]	[redacted]	1937	75	Female	10017947	Gastrointestinal disorders	10010774	Constipation	Constipation
179	[redacted]	[redacted]	1936	76	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	severe diarrhea
180	[redacted]	[redacted]	1934	78	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
182	[redacted]	[redacted]	1956	56	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
183	[redacted]	[redacted]	1937	75	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10045171	Tumour pain	Tumor pain
184	[redacted]	[redacted]	1938	74	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
186	[redacted]	[redacted]	1940	71	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumor progression
187	[redacted]	[redacted]	1936	76	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease, Sepsis

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
187	[redacted]	[redacted]	1936	76	Male	10021881	Infections and infestations	10040047	Sepsis	progression of disease, Sepsis
188	[redacted]	[redacted]	1941	71	Male	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
189	[redacted]	[redacted]	1975	36	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
190	[redacted]	[redacted]	1975	36	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
191	[redacted]	[redacted]	1975	36	Female	10017947	Gastrointestinal disorders	10012735	Diarrhoea	Diarrhea
192	[redacted]	[redacted]	1933	79	Male	10028395	Musculoskeletal and connective tissue disorders	10028372	Muscular weakness	motoric weackness one sided
193	[redacted]	[redacted]	1941	72	Male	10017947	Gastrointestinal disorders	10012735	Diarrhoea	diarrhea
194	[redacted]	[redacted]	1939	73	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression of disease
195	[redacted]	[redacted]	1964	47	Male	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Neoplasms other - tumor progression
196	[redacted]	[redacted]	1943	68	Male	10018065	General disorders and administration site conditions	10061818	Disease progression	progression
197	[redacted]	[redacted]	1937	75	Female	10018065	General disorders and administration site conditions	10061818	Disease progression	progression disease

Case-ID/SAE-ID	Site	Random-No.	Year of birth	Age on SAE	Gender	System Organ Class (Code)	System Organ Class (Term)	System Event PT Code	System Event PT Term	Event
198	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10009887	Colitis	colitis
199	[redacted]	[redacted]	1945	66	Female	10017947	Gastrointestinal disorders	10009887	Colitis	Colitis
200	[redacted]	[redacted]	1945	67	Female	10005329	Blood and lymphatic system disorders	10002034	Anaemia	Anemia
201	[redacted]	[redacted]	1945	67	Female	10005329	Blood and lymphatic system disorders	10002034	Anaemia	Anemia
202	[redacted]	[redacted]	1938	74	Female	10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10061309	Neoplasm progression	Tumorprogression
203	[redacted]	[redacted]	1958	53	Male	10017947	Gastrointestinal disorders	10019023	Haemorrhoids thrombosed	anal vein thrombosis
204	[redacted]	[redacted]	1952	59	Female	10005329	Blood and lymphatic system disorders	10033661	Pancytopenia	Pancytopenia

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
1	2011-06-08	Recovered with sequelae	Hospitalization	Not probable	210	2011-05-31	2011-05-31	[redacted]
2	2011-06-27	Recovered	Hospitalization	No	250	2011-05-26	2011-06-16	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
3	2011-07-03	Unknown	Hospitalization	Not probable	195	2011-06-23	2011-06-23	[redacted]
4	2011-07-09	Exitus	Death	Not probable	136,5	2011-05-23	2011-06-14	[redacted]
5	2011-06-24	Recovered	Hospitalization	Possible	207	2011-06-03	2011-06-28	[redacted]
7	2011-07-08	Unknown	Hospitalization	Not probable	201	2011-05-27	2011-06-17	[redacted]
8	2011-07-06	Exitus	Death	No	279	2011-06-08	2011-06-29	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
9	2011-07-15	Unknown	Hospitalization	No	294	2011-07-14	2011-07-14	[redacted]
10	2011-07-16	Exitus	Death		.	.	.	[redacted]
11	2011-07-20	Unknown	Hospitalization	No	250	2011-05-26	2011-06-16	[redacted]
12	2011-07-15	Unknown	Hospitalization	No	231	2011-07-08	2011-07-08	[redacted]
14	2011-07-25	Recovered	Hospitalization , Important medical event	Possible	255	2011-06-22	2011-07-14	[redacted]
15	2011-07-27	Recovered	Hospitalization	No	287,4	2011-07-07	2011-08-02	[redacted]
16	2011-07-11	Recovered	Hospitalization	Possible	225	2011-05-31	2011-07-20	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
17	2011-07-18	Recovered	Hospitalization	No	201	2011-07-12	2011-08-05	[redacted]
18	2011-07-27	Exitus	Death	No	294	2011-06-28	2011-07-26	[redacted]
19	2011-08-01	Recovered with sequelae	Hospitalization	Not probable	240	2011-06-20	2011-07-29	[redacted]
20	2011-07-26	Unknown	Important medical event	No	222	2011-07-21	2011-08-18	[redacted]
21	2011-08-04	Unknown	Hospitalization	Not probable	315	2011-05-24	2011-07-05	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
22	2011-08-05	Recovered	Hospitalization	Possible	201	2011-08-02	2011-10-05	[redacted]
23	2011-08-05	Recovered	Hospitalization	No	249	2011-06-09	2011-08-09	[redacted]
24	2011-08-09	Recovered	Life-threatening , Hospitalization	Not probable	338	2011-06-08	2011-07-20	[redacted]
25	2011-08-10	Unknown	Hospitalization	Possible	225	2011-08-08	2011-08-08	[redacted]
26	2011-08-11	Recovered	Hospitalization	Most likely	225	2011-05-26	2011-07-28	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
27	2011-08-03	Recovered	Hospitalization	Most likely	245,7	2011-05-31	2011-08-02	[redacted]
28	2011-08-17	Recovered	Hospitalization	No	303	2011-08-03	2011-08-03	[redacted]
29	2011-08-14	Recovered	Hospitalization	Not probable	312	2011-07-26	2011-07-26	[redacted]
31	2011-08-19	Unknown	Hospitalization	Not probable	165	2011-07-14	2011-08-04	[redacted]
32	2011-08-19	Exitus	Death	No	225	2011-08-08	2011-08-08	[redacted]
33	2011-08-19	Recovered	Hospitalization	No	286	2011-07-07	2011-08-02	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
34	2011-08-18	Recovered	Hospitalization	Most likely	246	2011-07-07	2011-07-28	[redacted]
35	2011-08-08	Unknown	Hospitalization	No	270	2011-07-14	2011-09-13	[redacted]
36	2011-08-24	Recovered	Prolongation of hospitalization	Possible	310	2011-07-13	2011-08-23	[redacted]
37	2011-08-08	Exitus	Death	No	225	2011-05-31	2011-07-20	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
38	2011-08-24	Recovered	Hospitalization	No	216	2011-06-30	2011-08-11	[redacted]
39	2011-08-27	Recovered	Hospitalization	No	297	2011-07-26	2011-08-24	[redacted]
40	2011-08-30	Recovered	Hospitalization	No	171	2011-07-19	2011-08-10	[redacted]
41	2011-08-26	Exitus	Death	Not probable	165	2011-07-14	2011-08-04	[redacted]
42	2011-08-30	Recovered	Hospitalization	Possible	225	2011-05-26	2011-07-28	[redacted]
43	2011-08-31	Unknown	Hospitalization	Most likely	283,5	2011-07-12	2011-08-02	[redacted]
44	2011-09-05	Recovered	Hospitalization	Most likely	177	2011-07-18	2011-09-26	[redacted]

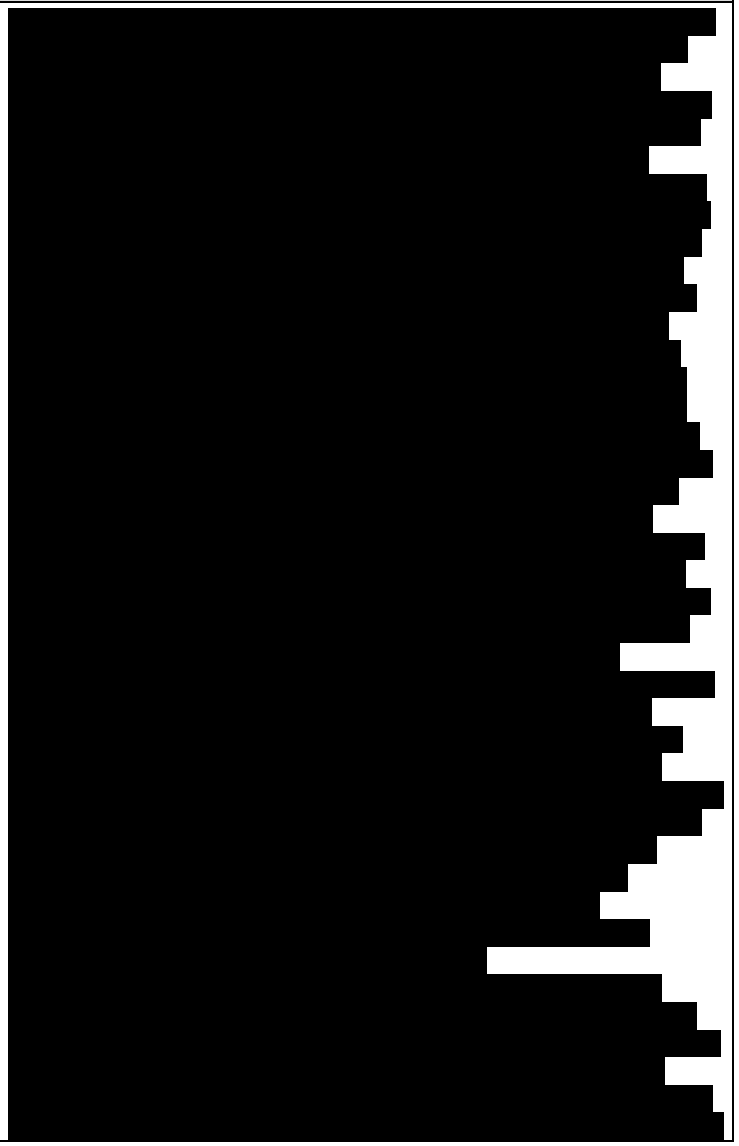
Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
45	2011-08-25	Exitus	Death	No	222	2011-07-21	2011-08-18	[redacted]
46	2011-08-31	Recovered	Hospitalization	Most likely	182,5	2011-06-27	2011-08-11	[redacted]
47	2011-09-07	Unknown	Hospitalization	Likely	250	2011-05-20	2011-07-22	[redacted]

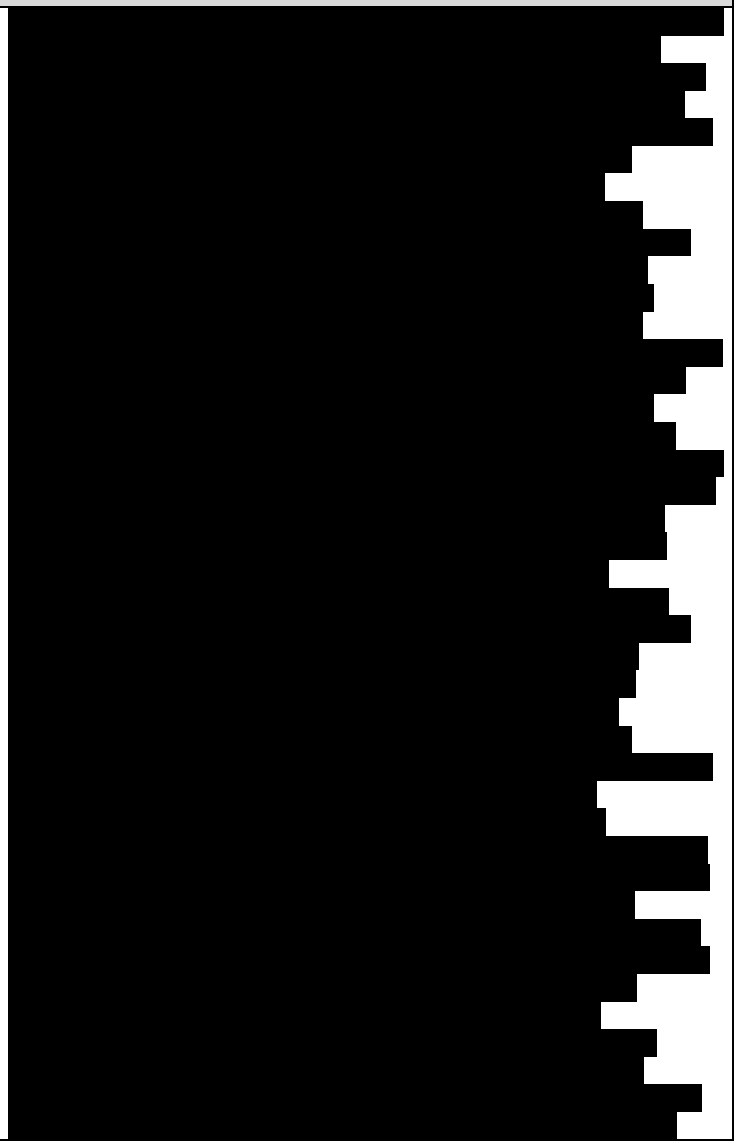
Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
48	2011-09-05	Recovered with sequelae	Hospitalization	Likely	162	2011-07-19	2011-09-02	[redacted]
49	2011-09-08	Recovered	Hospitalization	Most likely	315	2011-06-29	2011-08-31	[redacted]
50	2011-09-07	Unknown	Hospitalization	Not probable	338	2011-06-08	2011-07-20	[redacted]
51	2011-09-12	Recovered	Prolongation of hospitalization	Likely	316	2011-07-13	2011-08-23	[redacted]
52	2011-09-13	Exitus	Death	No	283,5	2011-07-12	2011-08-02	[redacted]

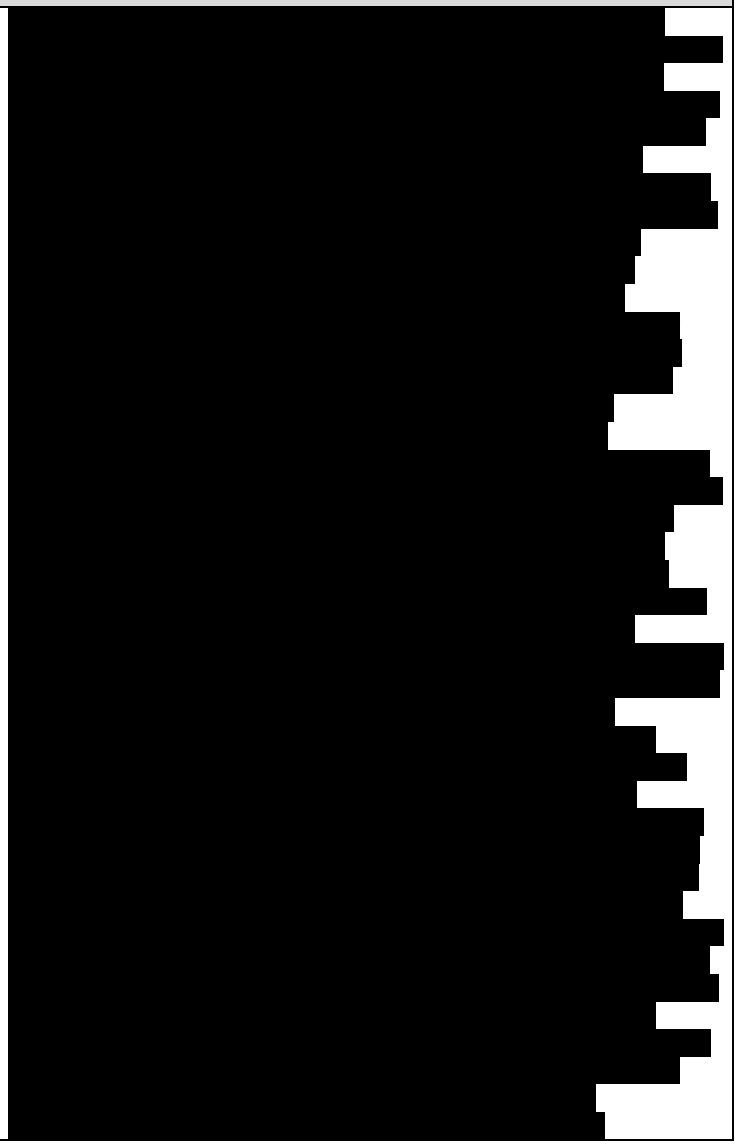
Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
53	2011-09-14	Recovered	Hospitalization	Likely	315	2011-06-29	2011-08-31	[redacted]
53	2011-09-14	Recovered	Hospitalization	Likely	315	2011-06-29	2011-08-31	[redacted]
54	2011-09-14	Exitus	Death	No	234	2011-07-13	2011-08-24	[redacted]
55	2011-09-15	Recovered	Hospitalization	No	201	2011-06-24	2011-08-25	[redacted]
56	2011-09-17	Recovered	Hospitalization	No	321	2011-08-30	2011-08-30	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
57	2011-09-14	Unknown	Hospitalization	Most likely	250	2011-05-20	2011-07-22	
58	2011-09-16	Unknown	Prolongation of hospitalization	Likely	250	2011-05-20	2011-07-22	

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
59	2011-09-19	Recovered	Hospitalization	Most likely	267	2011-08-01	2011-09-12	[redacted]
60	2011-09-19	Recovered	Hospitalization	Possible	316	2011-07-13	2011-09-15	[redacted]
61	2011-09-17	Unknown	Hospitalization	No	318	2011-06-24	2011-08-26	[redacted]
62	2011-09-16	Recovered with sequelae	Hospitalization	Not probable	162	2011-07-19	2011-09-02	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
63	2011-09-20	Unknown	Prolongation of hospitalization	Most likely	162	2011-07-19	2011-09-02	

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								[redacted]
64	2011-09-01	Exitus	Death	No	201	2011-07-12	2011-08-05	[redacted]
65	2011-09-11	Exitus	Death	No	315	2011-05-24	2011-07-05	[redacted]
66	2011-09-23	Unknown	Hospitalization	Not probable	180	2011-07-15	2011-08-26	[redacted]
67	2011-09-21	Unknown	Hospitalization	Likely	225	2011-06-28	2011-08-31	[redacted]
68	2011-09-28	Exitus	Death , Hospitalization	No	258	2011-07-25	2011-10-07	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
69	2011-09-26	Recovered	Hospitalization	No	211	2011-07-06	2011-09-06	[redacted]
70	2011-09-14	Recovered	Hospitalization	No	357	2011-07-12	2011-09-15	[redacted]
71	2011-09-17	Recovered	Hospitalization	No	252	2011-07-14	2011-09-15	[redacted]
72	2011-09-30	Unknown	Hospitalization	No	198	2011-08-15	2011-09-26	[redacted]
73	2011-10-20	Exitus	Death , Hospitalization	No	195	2011-08-02	2011-10-05	[redacted]
74	2011-10-07	Exitus	Death , Hospitalization	No	171	2011-08-31	2011-09-21	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
75	2011-10-10	Recovered with sequelae	Hospitalization	Most likely	267	2011-08-11	2011-09-08	[redacted]
76	2011-10-06	Recovered	Hospitalization	Most likely	246	2011-08-01	2011-10-05	[redacted]
77	2011-10-08	Recovered	Hospitalization	Likely	225	2011-05-26	2011-07-28	[redacted]
78	2011-09-29	Exitus	Death	No	286,5	2011-07-07	2011-08-02	[redacted]

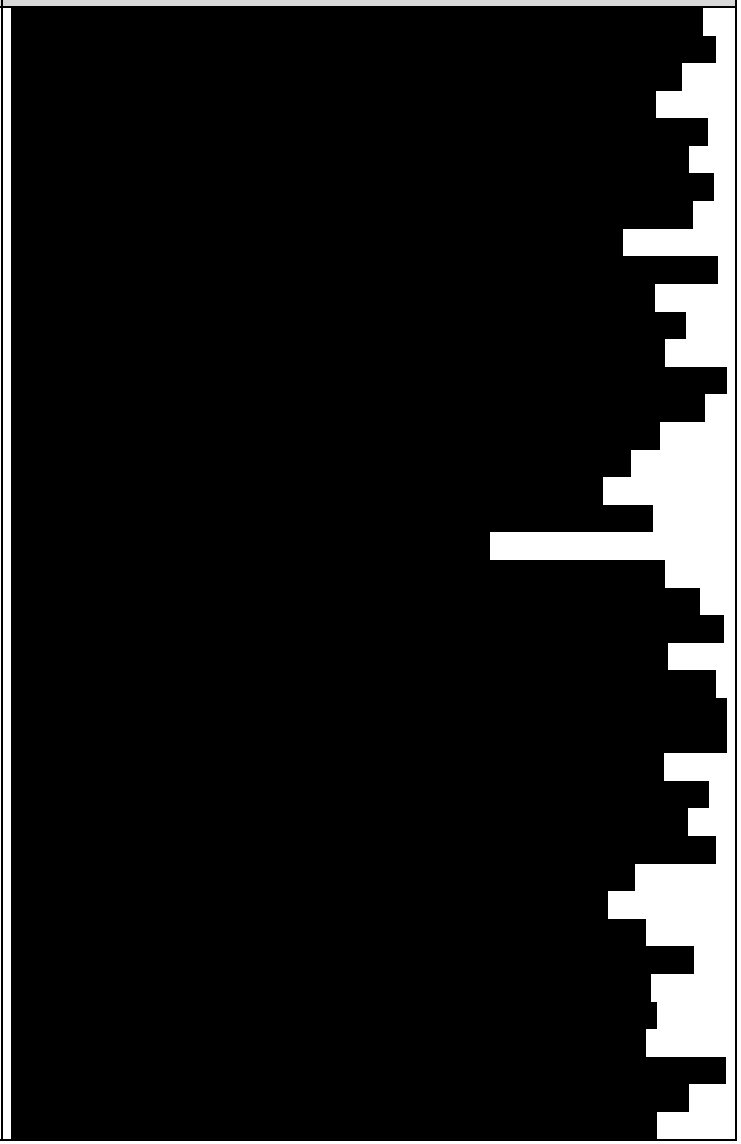
Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
79	2011-10-07	Unknown	Hospitalization	No	198	2011-08-09	2011-09-20	[redacted]
82	2011-10-05	Recovered with sequelae	Hospitalization	Not probable	228	2011-07-04	2011-09-05	[redacted]
83	2011-10-26	Recovered with sequelae	Hospitalization	Not probable	264	2011-08-11	2011-09-08	[redacted]

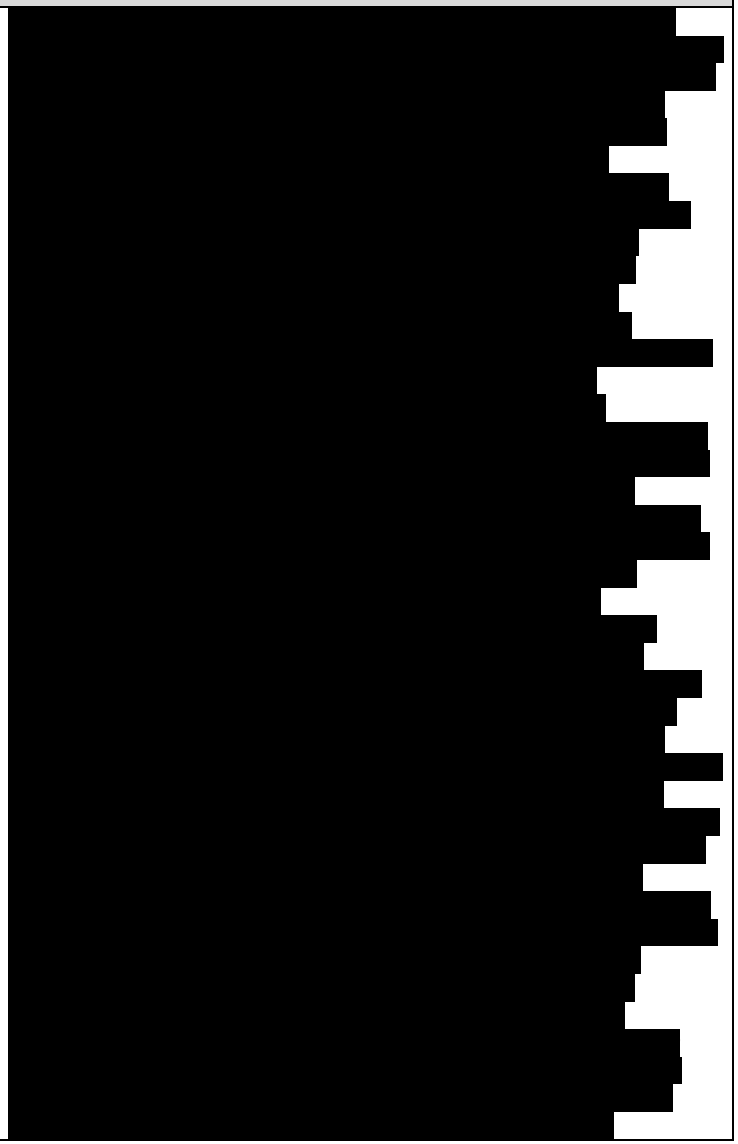
Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
84	2011-10-30	Recovered	Hospitalization	Most likely	199,8	2011-07-14	2011-09-15	[redacted]
85	2011-11-03	Unknown	Hospitalization	Possible	255	2011-05-25	2011-07-27	[redacted]
86	2011-11-04	Unknown	Hospitalization	No	252	2011-08-12	2011-09-29	[redacted]
87	2011-09-11	Exitus	Death	No	174	2011-07-21	2011-08-11	

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
88	2011-11-07	Recovered	Hospitalization	No	315	2011-08-30	2011-11-02	[redacted]
89	2011-11-11	Recovered	Hospitalization	Likely	225	2011-05-26	2011-07-28	[redacted]
92	2011-11-09	Recovered	Hospitalization , Important medical event	Likely	236	2011-07-07	2011-08-24	[redacted]
93	2011-11-11	Recovered	Hospitalization	Not probable	316	2011-07-13	2011-09-15	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
94	2011-11-07	Exitus	Death	No	211	2011-07-06	2011-09-09	[redacted]
95	2011-11-24	Unknown	Hospitalization	Not probable	182,5	2011-06-27	2011-08-11	[redacted]
96	2011-11-24	Recovered	Hospitalization	Not probable	228	2011-07-04	2011-09-05	[redacted]
99	2011-12-01	Recovered	Hospitalization	No	192	2011-11-29	2011-11-29	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
100	2011-08-04	Recovered	Hospitalization	No	225	2011-08-08	2011-08-08	[redacted]
101	2011-07-20	Exitus	Death	No	201	2011-05-27	2011-06-17	[redacted]
103	2011-06-30	Exitus	Death	No	210	2011-05-31	2011-05-31	[redacted]
104	2011-11-07	Exitus	Death	No	288	2011-07-07	2011-09-23	[redacted]
107	2011-09-11	Exitus	Death	No	338	2011-06-08	2011-07-22	[redacted]
108	2011-07-06	Exitus	Death	No	195	2011-06-23	2011-06-23	
109	2011-09-24	Exitus	Death	No	225	2011-06-28	2011-08-31	[redacted]
110	2011-10-07	Exitus	Death	No	162	2011-07-19	2011-09-02	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
								[redacted]
111	2011-07-27	Exitus	Death	No	231	2011-07-08	2011-07-08	[redacted]
112	2011-07-27	Exitus	Death	No	250	2011-05-26	2011-06-16	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
113	2011-11-22	Recovered	Hospitalization		.	.	.	
113	2011-11-22	Recovered	Hospitalization		.	.	.	
115	2011-11-22	Exitus	Death	No	271	2011-07-14	2011-09-13	[redacted]
116	2011-12-30	Recovered with sequelae	Hospitalization	Not probable	222	2011-12-16	2011-12-16	[redacted]
118	2012-01-08	Recovered	Hospitalization	No	200	2012-01-12	2012-02-09	[redacted]
119	2011-12-31	Exitus	Death	No	315	2011-08-30	2011-11-02	[redacted]
120	2012-01-10	Unknown	Hospitalization	No	232,5	2011-07-05	2011-09-07	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
126	2012-01-25	Unknown	Hospitalization	Most likely	247	2011-12-13	2012-01-05	[redacted]
128	2012-01-24	Recovered	Hospitalization	Not probable	267	2011-12-28	2012-01-18	[redacted]
129	2012-01-25	Recovered	Hospitalization	No	200	2012-01-12	2012-02-09	[redacted]
131	2011-12-22	Recovered	Hospitalization	Possible	198	2011-08-16	2011-10-28	[redacted]
132	2012-02-06	Exitus	Death	No	247	2011-12-13	2012-01-05	[redacted]
133	2012-02-06	Recovered	Hospitalization	No	200	2012-01-12	2012-02-09	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
135	2012-02-10	Unknown	Hospitalization	No	192	2012-01-12	2012-02-09	[redacted]
136	2012-02-16	Recovered with sequelae	Hospitalization	Possible	219	2011-12-21	2012-02-02	[redacted]
137	2012-01-04	Recovered	Hospitalization	Most likely	270	2011-11-14	2011-12-15	[redacted]
138	2011-09-22	Unknown	Hospitalization	No	186,6	2011-07-13	2011-09-14	[redacted]
141	2011-09-27	Exitus	Death	No	186,6	2011-07-13	2011-09-14	[redacted]
142	2012-02-20	Exitus	Death , Prolongation of hospitalization	No	192	2012-01-12	2012-02-09	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
143	2011-08-08	Exitus	Death , Hospitalization		.	.	.	[redacted]
144	2012-03-23	Unknown	Hospitalization	Possible	210	2012-02-09	2012-03-01	[redacted]
145	2012-03-24	Exitus	Death	Not probable	210	2012-02-09	2012-03-01	[redacted]
146	2012-02-02	Unknown	Hospitalization	No	267	2011-12-28	2012-01-18	[redacted]
147	2012-02-19	Exitus	Death	No	267	2011-12-28	2012-01-18	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
148	2012-03-26	Recovered	Hospitalization	Most likely	210	2012-02-09	2012-03-22	[redacted]
150	2011-06-21	Unknown	Hospitalization	Likely	136,5	2011-05-23	2011-06-14	[redacted]
151	2012-03-16	Exitus	Death	Possible	219	2011-12-21	2012-02-02	[redacted]
152	2011-08-28	Recovered	Important medical event	Most likely	255	2011-07-12	2011-08-26	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
153	2011-09-15	Recovered	Important medical event	Most likely	255	2011-07-12	2011-09-14	[redacted]
154	2012-01-09	Unknown	Hospitalization	No	270	2011-12-16	2011-12-16	[redacted]
156	2012-01-28	Exitus	Death	No	270	2011-12-16	2011-12-16	[redacted]
158	2011-11-09	Exitus	Death	No	297	2011-07-04	2011-09-06	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
159	2012-05-29	Recovered	Hospitalization	Possible	174	2012-04-04	2012-05-16	[redacted]
160	2011-08-06	Exitus	Death	No	360	2011-07-22	2011-07-22	[redacted]
161	2012-05-30	Recovered	Hospitalization	No	177	2012-03-01	2012-05-03	[redacted]
162	2012-06-04	Recovered with sequelae	Hospitalization	No	219	2012-05-07	2012-05-30	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
163	2012-06-20	Exitus	Death	No	231	2012-05-07	2012-05-30	[redacted]
163	2012-06-20	Exitus	Death	No	231	2012-05-07	2012-05-30	[redacted]
164	2012-07-10	Recovered	Hospitalization	No	192	2012-05-15	2012-07-24	[redacted]
166	2012-07-16	Unknown	Hospitalization	No	255	2012-06-28	2012-06-28	[redacted]
167	2012-07-17	Unknown	Hospitalization	No	225	2012-05-15	2012-06-27	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
168	2012-07-18	Recovered	Hospitalization	Likely	237	2012-06-08	2012-06-28	[redacted]
169	2012-07-22	Exitus	Death	No	225	2012-05-16	2012-06-27	[redacted]
170	2012-07-22	Exitus	Death	No	255	2012-06-28	2012-06-28	[redacted]
171	2012-08-09	Unknown	Hospitalization	Likely	279	2012-05-31	2012-08-02	[redacted]
172	2012-08-23	Unknown	Important medical event	No	175	2012-08-23	2012-08-23	[redacted]
173	2012-08-29	Unknown	Hospitalization	Possible	175	2012-08-23	2012-08-23	[redacted]
175	2012-09-02	Exitus	Death	No	175	2012-08-23	2012-08-23	[redacted]
176	2012-09-08	Exitus	Death	No	186	2012-07-27	2012-08-21	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
177	2012-09-10	Exitus	Death , Hospitalization	No	135	2012-07-30	2012-08-17	[redacted]
178	2012-08-27	Recovered	Hospitalization	Not probable	231	2012-08-20	2012-08-20	[redacted]
179	2012-09-16	Recovered	Hospitalization	Most likely	213	2012-08-22	2012-09-12	[redacted]
180	2012-06-20	Exitus	Death	No	174	2012-03-01	2012-05-03	[redacted]
182	2012-09-23	Exitus	Death	No	207	2012-06-26	2012-08-30	[redacted]
183	2012-09-21	Recovered	Hospitalization	Not probable	228	2012-09-10	2012-09-10	[redacted]
184	2012-10-10	Unknown	Hospitalization	Likely	207	2012-08-17	2012-09-27	[redacted]
186	2011-08-07	Exitus	Death	No	240	2011-07-29	2011-07-29	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
187	2012-07-20	Exitus	Death	No	340,05	2012-04-18	2012-06-20	[redacted]
188	2012-10-15	Recovered	Hospitalization	Likely	216	2012-07-20	2012-09-21	[redacted]
189	2011-11-06	Recovered	Important medical event	Most likely	185	2011-10-14	2011-11-03	[redacted]
190	2011-12-16	Recovered	Important medical event	Most likely	207	2011-10-14	2011-12-15	[redacted]
191	2011-11-24	Recovered	Important medical event	Most likely	216	2011-11-24	2011-11-24	[redacted]
192	2012-07-11	Unknown	Hospitalization , Important medical event	Not probable	207	2012-06-03	2012-06-28	[redacted]
193	2013-01-10	Recovered	Hospitalization	Most likely	216	2012-07-20	2012-09-21	[redacted]

Case-ID/SAE-ID	Start Date	Outcome	Reason for SAE	Ipilimumab-Causality	Ipilimumab-Dosis [mg]	Ipilimumab - Start date	Ipilimumab-Stop date	Therapy and course of SAE
194	2012-10-06	Exitus	Death	No	279	2012-05-31	2012-08-02	[redacted]
195	2011-10-03	Exitus	Death	No	297	2011-07-26	2011-08-24	[redacted]
196	2011-09-24	Exitus	Death , Hospitalization , Cancer	No	198	2011-08-08	2011-09-21	[redacted]
197	2012-03-12	Exitus	Death , Cancer	No	164,4	2011-12-16	2012-02-16	[redacted]
198	2011-12-15	Recovered	Hospitalization	Possible	192	2011-11-29	2011-11-29	[redacted]
199	2011-12-25	Recovered	Hospitalization	Possible	192	2011-11-29	2011-11-29	
200	2012-01-31	Recovered	Hospitalization	No	192	2011-11-29	2011-11-29	[redacted]
201	2012-01-20	Recovered	Hospitalization	No	192	2011-11-29	2011-11-29	
202	2012-07-14	Exitus	Death	No	174	2012-04-04	2012-05-16	
203	2011-09-07	Unknown	Hospitalization	No	250	2011-05-20	2011-07-22	
204	2011-10-07	Unknown	Life-threatening , Hospitalization	Possible	162	2011-07-19	2011-09-02	