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KS and RS are employees of Merck & Co. PK is an employee of MSD SHARP & DOHME GMBH, a subsidiary of Merck & Co., Inc. Kenilworth NJ USA. PM has served a consultant role and has been an investigator for clinical trials for MSD. PA has served a consultant/advisory role for BMS, Roche-Genentech, MSD, Novartis, Array, Amgen, Merck-Serono, Pierre Fabre, Incyte. Research funds from BMS, Roche-Genetech, Array, and has received drug supply for clinical trials (no funds) from MSD., AA has served in a consultant/advisory role for MSD, GM has received funding for travel from MSD. AH is an employee of Mapi Group (Mapi Group received budgetary compensation from Merck & Co. for the study).

Real world treatment patterns and outcomes among metastatic cutaneous melanoma patients treated with ipilimumab

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Abstract

Background: There is a scarcity of real-world data on treatment patterns and outcomes among advanced melanoma patients treated with immunotherapies including ipilimumab, an anti-CTLA-4 antibody approved since 2011.

Objective: To evaluate ipilimumab and post-ipilimumab treatment patterns and outcomes among patients with advanced melanoma in Australia, Germany, Italy and Spain following regulatory approval.

Methods: Retrospective multicentre, multinational, observational chart review study. Data were extracted from the start of ipilimumab therapy until the end of at least 40 weeks of follow-up, or death.

Results: Data from 371 patients (Australia, 103; Germany, 152; Italy, 76; Spain, 40) were analysed. Mean age was 65 years; 62% were male. Eastern Cooperative Oncology Group performance status (ECOG PS) was 0 or 1 for 94%. In 67%, ipilimumab was initially received as second-line or later therapy. Patients received on average 3.4 ipilimumab doses. The ipilimumab-refractory cohort comprised of 226 patients. Of these, 17% in Australia, 47% in Germany, 29% in Italy and 14% in Spain received another anti-melanoma treatment after ipilimumab including chemotherapy in 26% and BRAF/other kinase inhibitors in 11%. Ipilimumab-refractory patients who received post-ipilimumab treatment showed a 40% reduced hazard of dying than those not receiving treatment after ipilimumab (HR 0.60; 95% CI 0.43-0.83), after adjustment for potential confounders.

Conclusion: During the time observed, ipilimumab was mainly used as second-line or later therapy. A significant proportion of patients received post-ipilimumab therapy, most of which was chemotherapy. Nevertheless, overall survival following progression on ipilimumab treatment remained poor, highlighting the need for research to develop more effective end-of-life treatment options.

Introduction

In 2012, over 232,000 people were diagnosed with melanoma of skin with over 55,000 deaths attributed to it worldwide [1]. Cutaneous melanoma represents approximately 5% of all skin tumors but accounts for about 90% of all deaths associated with malignant neoplasms of the skin [2]. If diagnosed at an early stage, cutaneous melanoma has an excellent prognosis after local resection; however, the prognosis is very poor in the setting of metastatic disease. In a meta-analysis of 42 phase II trials conducted prior to 2006, the median survival with metastatic disease was 6.2 months and the 1-year overall survival (OS) rate was 25.5% [3].

Treatment options for advanced melanoma have improved over the past half-decade with the approval of several new classes of therapy including the checkpoint inhibitor ipilimumab, two antibodies against the programmed cell death-1 (PD-1) receptor, nivolumab and pembrolizumab, and targeted therapies including the BRAF/MEK inhibitors. Ipilimumab, a human monoclonal antibody (IgG1) that promotes antitumor immunity by blocking CTLA-4, was the first immune potentiating therapy to improve survival in patients with metastatic melanoma [4, 5] and was approved as a second-line treatment in 2011 by the United States Food and Drug Administration (FDA) and the European Commission (EC), and in 2012 by the Therapeutic Goods Administration (TGA) in Australia. In 2013, the EC approved ipilimumab as a first-line treatment.

As a result of the continually evolving treatment landscape, published guidelines for the treatment of advanced melanoma show variation and are frequently updated [6-10]. The ESMO 2015 guideline recommendations for first-line treatment of advanced melanoma included anti-PD1 therapies and, for BRAF-mutated melanomas, combinations of BRAF inhibitors with MEK inhibitors [9]. Besides the ongoing debate about the optimal treatment

sequencing, especially in BRAF-mutated patients, access to these therapies has varied significantly between countries due to differential reimbursement within national health systems. This may also contribute to a limited use of BRAF-inhibitors post-ipilimumab.

Several studies conducted among patients treated through the early access programs for ipilimumab [11-14] demonstrated similar efficacy and tolerability compared to the pivotal clinical trial for ipilimumab when administered at the approved dose of 3 mg/kg which showed a median overall survival (OS) of 10.1 months and a 10-15% incidence of Grade 3 or 4 immune-mediated adverse events (4). In 2016, data was presented comparing ipilimumab dosed at 10 mg/kg to 3 mg/kg and demonstrated that patients treated at with 10 mg/kg had improved OS relative to the 3 mg/kg dose (HR 0.84 95% CI 0.74- 0.99). However, the higher dose was associated with greater toxicity with 30% vs. 14% of patients experiencing a Grade 3-4 immune-mediated adverse event. [21]

This retrospective multi-center, multinational, observational study was conducted to characterize real-world treatment patterns and physician reported outcomes among advanced melanoma patients who initiated ipilimumab just following regulatory approval in four different health care systems: Australia, Germany, Italy and Spain. This early landmark analysis of real-world treatment patterns and outcomes represents the contemporary burden of advanced melanoma and provides a benchmark for evaluating the impact of newer immunotherapies or the potential use of the higher ipilimumab dose (10 mg/kg) on outcomes among advanced melanoma patients.

MATERIALS AND METHODS

The INTUITION (INternational STUdy on Ipilimumab Treatment utilizatION in real world clinical practice) study included advanced melanoma patients from Australia, Germany, Italy and Spain who were treated with ipilimumab. Adult (age>18 years) patients with histopathologically confirmed diagnosis of unresectable stage III/IV melanoma who received at least 1 dose of ipilimumab after local regulatory approval, an Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 and radiographic evidence of disease were eligible for enrollment. As ipilimumab had demonstrated a

distinct toxicity profile relative to other treatment options for advanced melanoma and to avoid a potential bias toward poorer outcomes and a higher rate of treatment related morbidity which could have been associated with physicians limited experience with ipilimumab when it first became available through the early access program sponsored by the manufacturer the following criteria were applied. Only patients who were treated with ipilimumab after market authorization and only experienced treatment centers which had treated a minimum of thirty advanced melanoma patients with ipilimumab and a minimum of six after local regulatory were offered participation. In order to determine whether patients were refractory to ipilimumab, access to patient charts for at least 10 months after first dose of ipilimumab was required. Patients with primary ocular or other non-cutaneous melanoma were excluded.

The index date was defined as the date of initial ipilimumab dose. Patients were considered ipilimumab-refractory if they had received at least 2 doses of ipilimumab and had investigator-reported disease progression within 24 weeks after the last ipilimumab dose.

Study design

This was a retrospective chart review study conducted at sites experienced in treating advanced melanoma patients with ipilimumab. Hospital, pharmacy and laboratory charts were reviewed from initiation of ipilimumab treatment between Sep-23rd, 2010 and Apr-18th, 2012 until the end of follow-up, or death whichever occurred earlier. All subjects initiated treatment, a minimum of 10 months earlier than site specific data abstraction cut-off date with latest cutoff Feb-18th, 2013. The study was funded by Merck & Co., Inc., Kenilworth, NJ, USA Ethics committee approvals and informed consents were obtained where required in accordance with local practice and regulations prior to any data abstraction.

Patient and disease characteristics including date and stage at primary diagnosis of melanoma and at the time of progression to metastatic disease, ECOG status, BRAF mutation status, brain metastases (yes/no), LDH, and absolute lymphocyte count (ALC) were collected at baseline and at progression post-ipilimumab. Ipilimumab treatment information was collected for all patients and included line of therapy, number of doses,

duration of therapy, date and reason for treatment discontinuation. Information on post-ipilimumab treatment was also collected.

Statistical methods

Assessment of clinical outcomes was an exploratory objective. Outcomes were described among patients receiving ≥2 ipilimumab doses and included objective response rates (ORR), defined as complete response (CR) + partial response (PR), disease control rates (DCR), defined as CR + PR + stable disease (SD), time to progression (TTP), progression free survival (PFS), OS, time to response (TTR), and duration of response (DOR) as assessed by the investigator's judgment. ORR and DCR were calculated with 2-sided exact binomial 95% confidence intervals (CIs). Patients without an imaging assessment of disease response were treated as non-responders and each patient was counted within only 1 response group. Time-to-event outcomes (TTP, PFS, OS, TTR, and DOR) and their fixed-time estimations were analyzed using the Kaplan-Meier (K-M) method. K-M median estimates and 95% CIs were calculated based on estimated variance for log transformation of the estimate. In addition, Cox regression models were used to 1) adjust hazard ratios for sex (male, female), line of ipilimumab treatment (1st line,≥2nd line), BRAF mutation status (positive vs. other including non-tested), and all of the following factors assessed at the time of progression after ipilimumab treatment: age, LDH level (elevated vs. other including non-tested), ECOG status (0, 1 or 2), and presence of brain metastases (yes, no) and 2) to derive adjusted curves for OS calculated from progressive disease following ipilimumab among ipilimumab-refractory patients with and without post-ipilimumab treatment. Patients without information on LDH or BRAF mutation status were included in the ´other´ category. Disease progression was determined based on two different methods: 1) investigator reported progressive disease and 2) imaging data, and described accordingly. Statistical analyses were conducted using SAS version 9.2 for Windows.

Results

Patients

In total, 362 patients were included between September, 23rd, 2010 (Date of earliest ipilimumab administration) and February 18th 2013 (Last site activation date) (Figure 1). At the end of data abstraction, 252 (69.6%) patients had died of which 86.1% had melanoma as primary cause of death. The mean follow-up time from the first dose of ipilimumab to the last contact date was 0.8 years (median 0.6; range 0.03-3.6 years).

Table 1 shows patient and disease characteristics at baseline/index date. The mean age was 60.6 years (range 22-88 years). A majority of patients (61.9%) were male. Percentage of patients with ECOG 0 was lowest in Australia (42.2%) and highest in Italy (68.0%). At the index date, 96.4% of patients had stage IV melanoma, and the majority (63.0%) had lung metastases while 26.8%. had brain metastases, Among those tested for LDH, 42% had an elevated LDH levels and among patients tested for BRAF mutation 35.0% tested positive.

Ipilimumab utilization

Table 2 describes the pattern of ipilimumab utilization. The majority of patients (66.9%) received ipilimumab as a second-line therapy with lower percentages in Germany and Spain (61.9% and 52.6%) versus Australia and Italy (72.5% and 76.0%). The mean time from initial melanoma diagnosis to the first dose of ipilimumab was 4.5 years (median 2.9; range 0.1-33.6 years) and mean time from diagnosis of stage IV to the index date was 1.year (median 0.6, range 0.02-15.9 years). The mean number of ipilimumab doses per patient was 3.4 (SD 1.4). Most patients (56.4%), received 4 doses of ipilimumab with the highest percentage found in Italy (74.7%) compared with other countries. A similar pattern was observed for patients completing 4 doses within 16 weeks. Ipilimumab reinduction was uncommon, but occurred more often in Australia (9.8%) than in Spain (2.6%) and Germany (1.4%), and did not occur in Italy. The mean interval between consecutive ipilimumab doses of was 21.9 days (SD 4.6); Mean duration of ipilimumab therapy was 10.1 weeks excluding reinduction (SD 3.9). Of the BRAF positive patients, 80.2% were treated with BRAF/MEK inhibitors before ipilimumab.

Treatment patterns in ipilimumab-refractory patients

In total, 226 patients were considered ipilimumab-refractory. No large differences in baseline characteristics were found compared with the overall study population, except that fewer ipilimumab-refractory patients received ipilimumab as first-line treatment (5.8% versus 9.9%). Table 3 describes the treatments administered in ipilimumab refractory patients. Of 226 ipilimumab-refractory patients, 31.9% received subsequent treatments after the last dose of ipilimumab of which most (29.6%) were administered after progression. Large differences were observed across countries in the percentage who received post-ipilimumab treatment (Australia, 16.9%; Germany, 46.9%; Italy, 28.6%; Spain, 13.6%). Post-ipilimumab treatment (before or after progression), was mostly third-line therapy (21.7%) and at least 3 additional lines were administered with a high percentage of German patients receiving at least four lines of therapy after progression. The most common post-ipilimumab chemotherapies included specific inhibitors other than dabrafenib, vemurafenib and imatinib (8.4%) fotemustine (6.6%), and paclitaxel-based regimens (8.8%), although specific types differed greatly across countries.

Treatment discontinuation or delay

Among the 362 included patients, 32 (8.8%) discontinued ipilimumab prior to receiving 4 doses. For 26 (81.3%) of these patients, the primary reason for discontinuation was treatment related toxicity (Table 2). Ipilimumab-related diarrhea and hypophysitis were the adverse events (AE) most commonly associated with treatment discontinuation (Table 5) or with a hospital admission (Table 6). Only 8 patients; 4 (3.9%) in Australia and 4 (5.3%) in Italy experienced a delay or omission of a dosing cycle due to AEs (<1% of the total number of cycles).

Treatment outcomes

Table 4 describes the treatment outcomes. Among the patients who received at least two doses of ipilimumab, 31 (9.6%) achieved an objective response, of whom 16 (51.6%) subsequently relapsed, and 72 (22.3%) showed disease control. The median

duration of response, when evaluable, was 33.6 weeks for patients in Australia and 70.0 weeks for patients in Germany.

The median time to progression was 13.3 weeks (95% CI 12.3-14.4). In most cases, disease progression was first detected by the investigator and was later confirmed by a radiographic scan. This pattern occurred most commonly in Germany (80.3%) and least often in Spain (68.6%). Up to one third of patients had disease progression detected prior to their last dose of ipilimumab which was, in most cases (89.1%), confirmed by imaging.

In total, 32.5% of the patients who received at least two doses of ipilimumab were alive at the time of data analysis and had a median survival time of 46.7 weeks. One- and two-year survival rates were, respectively, 46% (95% CI 40-51%) and 30% (25-35%). In Australia, more patients were living at the end of the study (50.6%) and for a longer time (median survival time 91.1 weeks) than in other countries (range survival rates 23.6-29.2% and range median survival times 37.1-40.2 weeks). Compared with patients without post-ipilimumab treatment, ipilimumab-refractory patients with post-ipilimumab treatment showed a longer median survival time (35.7 weeks vs 13.7 weeks (Figure 2)) from progression after ipilimumab and a 40% reduced hazard of dying (HR 0.60, 95% CI 0.43-0.83) even after adjusting for the potential confounders assessed at the time of progression (Figure 1). Excluding BRAF mutation positive patients naïve to BRAF/MEK inhibitors before ipilimumab did not change the results (HR 0.61, 95% CI 0.43-0.85).

Discussion

This study describes real-world treatment patterns and outcomes among ipilimumab-treated advanced melanoma patients. Most patients (66.9%) received ipilimumab as second-line therapy consistent with the timing of the availability of ipilimumab as a registered product (outside clinical trials and/or early access programs). Most patients received a full regimen (4 doses; 56.4%) with the highest percentage (74.7%) observed in Italy. One-and two-year survival rates were, respectively, 46% (95% CI 40-51%) and 30% (25-35%). Lower one- and two year survival rates were reported in the EAP studies using the same ipilimumab dosage of 3mg/kg [11-14]. Differences may be explained by the inclusion of patients with a worse prognosis in the EAP studies, and

the participation of experienced immuno-oncologic melanoma centers in this retrospective observational study.

Italy had the highest percentage of patients who received a full regimen. This is interesting given that a 'Payment by Result' risk sharing scheme has been implemented for ipilimumab in Italy requiring an assessment of response at 12 weeks [15] . Ipilimumab reinduction was uncommon, but was more often utilized in Australia where reinduction is included in the label and is reimbursed in contrast to the European label where it is not specified in the label and is not reimbursed [16, 17].

The percentage of ipilimumab-refractory patients who received anti-melanoma treatment after progression on ipilimumab ranged widely across countries. The highest percentage of patients who received post-ipilimumab treatment was found in Germany (47%) where treatment is reimbursed without restriction to product label, if a potentially life threatening condition cannot be adequately treated by appropriately authorized medicinal products. This practice is consistent with German melanoma patient preferences for active treatment over best supportive care [20] At the time of this study, dacarbazine/temozolomide chemotherapy was an option for first-line treatment and receipt of secondary alternative chemotherapy agents was consistent with the current practice in the setting of resistance to chemotherapy [18, 19]. Given the rapid change in the treatment landscape and displacement of ipilimumab by anti-PD1s as first line treatment options, further follow up was not undertaken for this study..

Interestingly, after adjustment for potential confounders at the time of progression, receipt of treatment post-ipilimumab was associated with a 40% reduction in the hazard of death calculated from progression after ipilimumab compared to no post-ipilimumab treatment. The results must be interpreted with caution, however, as the hypothesis for proportional hazards was rejected (P <.0001). Although the log rank test, which is rather robust to proportional hazards deviations, also indicates a difference between the two groups (p=0.0098), we cannot exclude residual variation with regard to this group of

patients having had a better prognosis and thereby potentially an increased likelihood of receiving post-ipilimumab treatment.

This observational study has several limitations. Firstly, data was abstracted based on the judgment of the treating physician. Second, differences in ipilimumab utilization between countries may be due to differences in the starting time of the study and the timing of ipilimumab approval and reimbursement. In addition, survival may have been enhanced in countries where patients are more often enrolled in clinical trials. There may be a difference in the specific type of cutaneous melanoma occurring in Australia which could explain the higher median survival time observed for Australia compared to other countries. Moreover, it is possible that BRAF mutation positive patients who received ipilimumab following a BRAF inhibitor represent a subset of all BRAF mutation positive patients with less aggressive disease. Reporting of clinical outcomes reflects real clinical practice and is not standardized so may differ between physicians and countries. Last but not least, ipilimumab was the first treatment option for advanced melanoma resulting in a survival benefit, yet its use is limited due to immune-related adverse events that warrant different handling compared to non-immune-related events, in particular immune-suppressive treatment. To avoid bias, only centers experienced in ipilimumab treatment were offered participation in this retrospective observational study. Accordingly, only 9% of patients were hospitalized due to immune-related adverse events attributable to ipilimumab, as reported by treating physicians, and may underestimate the real world challenges and impact of managing immune related adverse events.

Conclusion

In conclusion, in this observational study, ipilimumab was mostly administered second-line following chemotherapy. A significant proportion of patients received therapy post-ipilimumab, which mostly involved chemotherapy. Patients who received treatment experienced better OS than patients who received no further treatment following ipilimumab; however, OS remained poor following ipilimumab supporting the need for research to develop more effective end-of-life treatment options. Further observational

research is warranted to assess the real world impact of recent approvals of newer immune checkpoint inhibitor agents, and recent presentations on combinations, alternative doses and administration schedules of existing therapies.

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AUTHOR CONTRIBUTIONS

Conception/Design: KS, PK, RS

Collection and/or assembly of data: AA, AH, GM, PA, PM

Data analysis and interpretation: AA, AH, GM, KS, PA, PK, PM, RS

Conflict of interest statement

KS and RS are employees of Merck & Co. PK is an employee of MSD SHARP & DOHME GMBH, a subsidiary of Merck & Co., Inc. Kenilworth NJ USA. PM has served a consultant role and has been an investigator for clinical trials for MSD. PA has served in a consultant/advisory role for BMS, Roche-Genentech, MSD, Novartis, Ventana, Amgen, Array and has received drug supply for clinical trials (no funds) from MSD, AA has served in a consultant/advisory role for MSD, GM has received funding for travel from MSD. AH is an employee of Mapi Group (Mapi Group received budgetary compensation from Merck & Co. for the study).

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Table 1

Baseline patient and disease characteristics.

	Australia (N=102)	Germany (N=147)	Italy (N=75)	Spain (N=38)	Total (N=362)
Age, years					

	Australia (N=102)	Germany (N=147)	Italy (N=75)	Spain (N=38)	Total (N=362)
Mean (SD)	58.2 (15.7)	62.6 (13.4)	62.3 (13.9)	55.8 (14.3)	60.6 (14.4)
Gender, n (%)					
Female	34 (33.3)	53 (36.1)	33 (44.0)	18 (47.4)	138 (38.1)
Male	68 (66.7)	94 (63.9)	42 (56.0)	20 (52.6)	224 (61.9)
Advanced melanoma stage n (%)					
Stage III	2 (2.0)	8 (5.4)	1 (1.3)	2 (5.3)	13 (3.6)
Stage IV	100 (98.0)	139 (94.6)	74 (98.7)	36 (94.7)	349 (96.4)
Location of metastasis					
Cutaneous	45 (44.1)	50 (34.0)	19 (25.3)	12 (31.6)	126 (34.8)
Lung	65 (63.7)	89 (60.5)	53 (70.7)	21 (55.3)	228 (63.0)
Brain	29 (28.4)	50 (34.0)	14 (18.7)	4 (10.5)	97 (26.8)
Other	66 (64.7)	112 (76.2)	60 (80)	24 (63.2)	262 (72.4)
ECOG performance status, n (%)					
0	43 (42.2)	86 (58.5)	51 (68.0)	18 (47.4)	198 (54.7)
1	47 (46.1)	58 (39.5)	23 (30.7)	17 (44.7)	145 (40.1)
2	12 (11.8)	3 (2.0)	1 (1.3)	3 (7.9)	19 (5.2)
Serum LDH relative to ULN					
Missing	1 (1.0)	0	0	0	1 (0.3)
Elevated/above range	42 (41.2)	65 (44.2)	31 (41.3)	14 (36.8)	152 (42.0)
Lower/below range	5 (4.9)	0	1 (1.3)	0	6 (1.7)
Normal range	27 (26.5)	80 (54.4)	32 (42.7)	19 (50.0)	158 (43.6)
Not done	27 (26.5)	2 (1.4)	11 (14.7)	5 (13.2)	45 (12.4)
ALC range					
Missing	1 (1.0)	0	0	0	1 (0.3)
Elevated/above range	0	4 (2.7)	3 (4.0)	0	7 (1.9)
Lower/below range	25 (24.5)	42 (28.6)	14 (18.7)	13 (34.2)	94 (26.0)
Normal range	64 (62.7)	94 (63.9)	47 (62.7)	24 (63.2)	229 (63.3)
Not done	12 (11.8)	7 (4.8)	11 (14.7)	1 (2.6)	31 (8.6)
BRAF status, n (%)					
No test performed	0	12 (8.2)	3 (4.0)	1 (2.6)	16 (4.4)
Positive	29 (28.4)	53 (36.1)	29 (38.7)	10 (26.3)	121 (33.4)
BRAF V600D[a]	0	0	0	1 (10.0)	1 (0.8)
BRAF V600E[a]	20 (69.0)	27 (50.9)	25 (86.2)	6 (60.0)	78 (64.5)
BRAF V600K[a]	4 (13.8)	6 (11.3)	2 (6.9)	0	12 (9.9)
BRAF V600R[a]	1 (3.4)	0 (0.0)	0 (0.0)	0	1 (0.8)
Other[a]	0	2 (3.8)	1 (3.4)	0	3 (2.5)
Unknown if BRAF V600D,-E,-K, or –R[a]	4 (13.8)	18 (34.0)	1 (3.4)	3 (30.0)	26 (21.5)
Uncertain	2 (2.0)	0	0	1 (2.6)	3 (0.8)

	Australia (N=102)	Germany (N=147)	Italy (N=75)	Spain (N=38)	Total (N=362)
Wild-type	71 (69.6)	82 (55.8)	43 (57.3)	26 (68.4)	222 (61.3)
Earliest ipilimumab dose	Sept. 23, 2010	July 27, 2011	April 18, 2013	July 26, 2011	Sept. 23, 2010

1 ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SD, standard
2 deviation; ULN, upper limit of normal.

3 [a]Percentages are based on the number of patients who are BRAF positive.

4

5 Table 2

6 Utilization of ipilimumab.

	Australia (N=102)	**Germany (N=147)**	**Italy (N=75)**	**Spain (N=38)**	**Total (N=362)**
Time from initial melanoma diagnosis to first dose of ipilimumab, mean years(SD)	4.4 (3.8)	5.0 (5.8)	4.0 (4.2)	3.6 (5.6)	4.5 (4.9)
Time from Stage IV to first dose of ipilimumab, mean years (SD)	1.0 (1.5)	1.1 (1.8)	0.8 (0.8)	1 (1.0)	1 (1.5)
Line of initial administration of ipilimumab, n (%)					
1	10 (9.8)	20 (13.6)	2 (2.7)	4 (10.5)	36 (9.9)
2	74 (72.5)	91 (61.9)	57 (76.0)	20 (52.6)	242 (66.9)
3	16 (15.7)	27 (18.4)	12 (16.0)	12 (31.6)	67 (18.5)
4	2 (2.0)	9 (6.1)	4 (5.3)	2 (5.3)	17 (4.7)
Doses per patient, mean (SD)	3.5 (1.8)	3.2 (1.2)	3.5 (0.9)	3.2 (1.3)	3.4 (1.4)
Doses, n (%)					
1	13 (12.7)	20 (13.6)	3 (4.0)	3 (7.9)	39 (10.8)
2	19 (18.6)	22 (15.0)	9 (12.0)	10 (26.3)	60 (16.6)
3	14 (13.7)	20 (13.6)	7 (9.3)	4 (10.5)	45 (12.4)
4	46 (45.1)	82 (55.8)	56 (74.7)	20 (52.6)	204 (56.4)
5 or higher	10 (9.8)	3 (2.0)	0	1 (2.6)	14 (3.9)
Dosing interval, mean (SD) days	21.7 (1.8)	22.2 (6.9)	22.0 (2.0)	21.7 (1.7)	21.9 (4.6)
Regimen duration [a], mean (SD) weeks	14.4 (16.5)	10.7 (8.7)[b]	11.2 (2.9)	11.6 (12.4)	11.9 (11.3)
Discontinuation prior to 4 doses, n (%)	11 (10.8)	18 (12.2)	3 (4.0)	0	32 (8.8)
Main reason for discontinuation [c]					
Disease progression	1 (9.1)	0	0	0	1 (3.1)
Treatment-related toxicity	7 (63.6)	16 (88.9)	3	0	26 (81.3)
Decline in ECOG performance	1 (9.1)	1 (5.6)	0	0	2 (6.3)

status					
Patient intolerance not meeting criteria for AE	1 (9.1)	0	0	0	1 (3.1)
Other	1 (9.1)	1 (5.6)	0	0	2 (6.3)
Total No. of cycles	355	467	267	123	1212
No. of cycles delayed due to AE	2 (0.6)	3 (0.6)	3 (1.1)	0	8 (0.7)
Ipilimumab reinduction, n (%)	10 (9.8)	3 (2.0)	0	1 (2.6)	14 (3.9)
Induction regimen duration[d], mean (SD) weeks	9.6 (3.5)	10.0 (4.6)[e]	11.2 (2.9)	9.7 (3.5)	10.1 (3.9)
No. of patients treated with BRAF inhibitor, n (%)	27 (26.5)	49 (33.3)	20 (26.7)	9 (23.7)	105 (29.0)
Ipilimumab prior to BRAF inhibitor	1	17	0	1	19
Ipilimumab post BRAF inhibitor	26	32	20	8	86
No. of patients treated with MEK inhibitor, n (%)	14 (13.7)	38 (25.9)	31 (41.3)	11 (28.9)	94 (26.0)
Ipilimumab prior to MEK inhibitor	2	11	12	4	29
Ipilimumab post MEK inhibitor	12	27	19	7	65

AE-adverse events; IPI, ipilimumab; SD, standard deviation.

a Regimen duration is defined as the number of weeks from first to last dose of ipilimumab plus 21 days.

b Missing data for 2 patients.

c Percentages are based on the number of discontinuations prior to 4 doses; percentages provided when denominator > 10.

d Induction regimen duration is defined as the number of weeks from first to fourth dose or less of ipilimumab, plus 21 days.

e Missing data for 1 patient.

Table 3 Regimens used by ipilimumab-refractory patients after their last dose of ipilimumab.

	Australia (N=59	Germany (N=96)	Italy (N=49)	Spain (N=22)	Total (N=226)
No. of lines received, n (%)					
None	49 (83.1)	51 (53.1)	35 (71.4)	19 (86.4)	154 (68.1)
2	1 (1.7)	4 (4.2)	0	0	5 (2.2)
3	3 (5.1)	17 (17.7)	9 (18.4)	3 (13.6)	32 (14.2)
4	5 (8.5)	13 (13.5)	3 (6.1)	0	21 (9.3)
5 or more	1 (1.7)	11 (11.5)	2 (4.1)	0	14
Line of therapy, n (%)					
Any line[a]	10 (16.9)	45 (46.9)	14 (28.6)	3 (13.6)	72 (31.9)
Second	0	4 (4.2)	0	2 (9.1)	6 (2.7)
Third	9 (15.3)	27 (28.1)	10 (20.4)	3 (13.6)	49 (21.7)

	Australia (N=59	Germany (N=96)	Italy (N=49)	Spain (N=22)	Total (N=226)
Fourth plus	3 (5.1)	23 (24.0)	5 (10.2)	0	31 (13.7)
Common therapies[b], n (%)					
Other specific inhibitor[c]	2 (3.4)	7 (7.3)	9 (18.4)	1 (4.5)	19 (8.4)
Fotemustine	3 (5.1)	9 (9.4)	3 (6.1)	0	15 (6.6)
Paclitaxel based regimen[d]	3 (5.1)	15 (15.6)	1 (2.0)	1 (4.5)	20 (8.8)
Temozolomide	1 (1.7)	7 (7.3)	1 (2.0)	0	9 (4.0)
Vemurafenib	0	8 (8.3)	0	0	8 (3.5)
Dacarbazine	3 (5.1)	2 (2.1)	0	0	5 (2.2)
Treatment after PD, n (%)	9 (15.3)	43 (44.8)	12 (24.5)	3 (13.6)	67 (29.6)
Time from PD to start of next treatment following ipilimumab, days[e]	n = 9	n = 43	n = 12	n = 3	n = 67
Mean (SD)	166.8 (173.8)	72.7 (79.0)	62.3 (53.0)	154.3 (205.2)	87.1 (103.4)
Median (min, max)	138.0 (6, 552)	41.0 (2, 352)	36.5 (1, 161)	58.0 (15, 390)	46.0 (1, 552)

PD, progressive disease; SD, standard deviation.

[a]Including patients starting their first treatment post ipilimumab before PD.

[b]Includes therapies used in >5% of patients.

[c]Other than dabrafenib, vemurafenib and imatinib.

[d]Including paclitaxel, nab-paclitaxel, paclitaxel plus carboplatin and paclitaxel plus fotemustine plus carboplatin.

[e]Excluding patients starting their first treatment post ipilimumab before PD.

Table 4

Treatment outcomes in patients receiving ≥2 ipilimumab doses.

	Australia (N=89)	Germany (N=127)	Italy (N=72)	Spain (N=35)	Total (N=323)
Response assessment by imaging, n (%)					
CR	1 (1.1)	2 (1.6)	0	0	3 (0.9)
PR	7 (7.9)	14 (11.0)	5 (6.9)	2 (5.7)	28 (8.7)
SD	17 (19.1)	15 (11.8)	8 (11.1)	1 (2.9)	41 (12.7)
PD	41 (46.1)	58 (45.7)	32 (44.4)	12 (34.3)	143 (44.3)
Not specified	3 (3.4)	1 (0.8)	0	0	4 (1.2)
Not reported	20 (22.5)	37 (29.1)	27 (37.5)	20 (57.1)	104 (32.2)
Objective response (CR+PR), n (%)	8 (9.0)	16 (12.6)	5 (6.9)	2 (5.7)	31 (9.6)
95% CI	4.0, 16.9	7.4, 19.7	2.3, 15.5	0.7, 19.2	6.6, 13.3
Disease control (CR+PR+SD), n (%)	25 (28.1)	31 (24.4)	13 (18.1)	3 (8.6)	72 (22.3)
95% CI	19.1, 38.6	17.2, 32.8	10.0, 28.9	1.8, 23.1	17.9, 27.2

Investigator reported progression, n (%)	72 (80.9)	116 (91.3)	61 (84.7)	30 (85.7)	279 (86.4)
Patients with confirmed PD, n (%)	68 (76.4)	102 (80.3)	54 (75.0)	24 (68.6)	248 (76.8)
Patients with confirmed PD before last dose of ipilimumab, n (%)	22 (32.4)	31 (30.4)	11 (20.4)	7 (29.2)	71 (28.6)
Imaging-supported progression, n (%)	66 (74.2)	114 (89.8)	61 (84.7)	28 (80.0)	269 (83.3)
Confirmed disease progression	49 (74.2)	78 (68.4)	43 (70.5)	12 (42.9)	182 (67.7)
PFS, median (K-M), weeks	13.3	11.6	14.6	12.7	12.7
95% CI	11.0, 23.1	10.0, 12.3	11.9, 17.6	8.7, 20.0	11.9, 13.6
Criteria used to confirm PD, n (%)[a]					
Radiographic procedure	58 (85.3)	95 (93.1)	46 (85.2)	22 (91.7)	221 (89.1)
Surgical biopsy	1 (1.5)	1 (1.0)	0	0	2 (0.8)
Clinical examination	16 (23.5)	11 (10.8)	8 (14.8)	1 (4.2)	36 (14.5)
Other	5 (7.4)	1 (1.0)	2 (3.7)	1 (4.2)	9 (3.6)
TTP[b], median (K-M), weeks	15.7	12.1	15.0	12.9	13.3
95% CI	12.7, 32.3	10.6, 13.1	13.4, 20.0	8.9, 54.1	12.3, 14.4
Deaths, n (%)	44 (49.4)	97 (76.4)	51 (70.8)	26 (74.3)	218 (67.5)
OS, median (K-M), weeks	91.1	39.9	40.2	37.1	46.7
95% CI	49.7, NE	30.1, 50.3	26.0, 52.3	17.3, 77.0	38.4, 54.6
Ipilimumab-refractory patients with treatment after PD	10	45	14	3	72
Deaths, n (%)	6	36 (80.0)	11 (78.6)	2	55 (76.4)
Time from PD to death, median (K-M), weeks	57.3	36.3	27.1	56.0	35.7
95% CI	2.4, NE	26.9, 46.9	13.4, 50.9	9.3, 56.0	31.6, 46.9
Ipilimumab-refractory patients without treatment after PD	49	51	35	19	154
Deaths, n (%)	29 (59.2)	44 (86.3)	30 (85.7)	16 (84.2)	119 (77.3)
Time from PD to death, median (K-M), weeks	32.3	13.3	11.4	8.1	13.7
95% CI	14.1, NE	8.7, 24.6	4.3, 15.4	2.7, 22.3	10.7, 17.9

CI, confidence interval; CR, complete response; K-M, Kaplan-Meier estimate; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Percentages are based on patients with confirmed PD.

Table 5

Investigator-reported immune-related adverse events attributed to ipilimumab, organized by system organ class.

	Australia (N=102)	Germany (N=147)	Italy (N=75)	Spain (N=38)	Total (N=362)
System Organ Class[a] Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any adverse event	24 (23.5)	24 (16.3)	6 (8.0)	2 (5.3)	56 (15.5)
Gastrointestinal	11 (10.8)	13 (8.8)	2 (2.7)	1 (2.6)	27 (7.5)
Diarrhea	8 (7.8)	4 (2.7)	1 (1.3)	0	13 (3.6)
Bowel perforation	1 (1.0)	0	0	0	1 (0.3)
Other	3 (2.9)	10 (6.8)	1 (1.3)	1 (2.6)	15 (4.1)
Endocrine	3 (2.9)	7 (4.8)	1 (1.3)	0	11 (3.0)
Hypophysitis	3 (2.9)	6 (4.1)	0	0	9 (2.5)
Other	0	3 (2.0)	1 (1.3)	0	4 (1.1)
Skin	5 (4.9)	3 (2.0)	2 (2.7)	1 (2.6)	11 (3.0)
Rash	5 (4.9)	2 (1.4)	0	0	7 (1.9)
Pruritus	1 (1.0)	0	2 (2.7)	0	3 (0.8)
Vitiligo	0	0	0	1 (2.6)	1 (0.3)
Other	0	1 (0.7)	0	0	1 (0.3)
Liver	3 (2.9)	3 (2.0)	0	0	6 (1.7)
Abnormal liver function tests	3 (2.9)	3 (2.0)	0	0	6 (1.7)
Musculoskeletal	2 (2.0)	2 (1.4)	0	0	4 (1.1)
Arthritis	0	2 (1.4)	0	0	2 (0.6)
Other	2 (2.0)	0	0	0	2 (0.6)
Blood and lymphatic	2 (2.0)	1 (0.7)	1 (1.3)	0	4 (1.1)
Hemolytic anemia	1 (1.0)	0	0	0	1 (0.3)
Other	1 (1.0)	1 (0.7)	1 (1.3)	0	3 (0.8)
Neurologic	3 (2.9)	0	0	0	3 (0.8)
Unilateral or bilateral weakness	1 (1.0)	0	0	0	1 (0.3)
Sensory alterations	1 (1.0)	0	0	0	1 (0.3)
Other	1 (1.0)	0	0	0	1 (0.3)
Infections	3 (2.9)	0	0	0	3 (0.8)
Other	3 (2.9)	0	0	0	3 (0.8)
Eye	1 (1.0)	0	0	0	1 (0.3)
Ulveitis	1 (1.0)	0	0	0	1 (0.3)

[a]Patients may be represented in multiple systems and in multiple types within a system. System and type as reported by the investigator.

Table 6 Ipilimumab-related adverse events leading to inpatient admission.

	Australia (N=102)	Germany (N=147)	Italy (N=75)	Spain (N=38)	Total (N=362)
AE by System Organ Class[a] and preferred term					
Patients with any AE leading to inpatient admission n (%)	19 (18.6)	11 (7.5)	1 (1.3)	1 (2.6)	32 (8.8)
Gastrointestinal	9 (8.8)	6 (4.1)	1 (1.3)	1 (2.6)	17 (4.7)
Diarrhea	6 (5.9)	3 (2.0)	1 (1.3)	0	10 (2.8)
Bowel perforation	1 (1.0)	0	0	0	1 (0.3)
Other	2 (2.0)	4 (2.7)	0	1 (2.6)	7 (1.9)
Endocrine	2 (2.0)	3 (2.0)	0	0	5 (1.4)
Hypophysitis	2 (2.0)	3 (2.0)	0	0	5 (1.4)
Other	0	1 (0.7)	0	0	1 (0.3)
Skin	2 (2.0)	2 (1.4)	0	0	4 (1.1)
Rash	1 (1.0)	1 (0.7)	0	0	2 (0.6)
Pruritus	1 (1.0)	0	0	0	1 (0.3)
Other	0	1 (0.7)	0	0	1 (0.3)
Neurologic	3 (2.9)	0	0	0	3 (0.8)
Unilateral or bilateral weakness	1 (1.0)	0	0	0	1 (0.3)
Sensory alterations	1 (1.0)	0	0	0	1 (0.3)
Other	1 (1.0)	0	0	0	1 (0.3)
Blood and lymphatic	2 (2.0)	1 (0.7)	0	0	3 (0.8)
Hemolytic anemia	1 (1.0)	0	0	0	1 (0.3)
Other	1 (1.0)	1 (0.7)	0	0	2 (0.6)
Infections	3 (2.9)	0	0	0	3 (0.8)
Other	3 (2.9)	0	0	0	3 (0.8)
Musculoskeletal	2 (2.0)	0	0	0	2 (0.6)
Other	2 (2.0)	0	0	0	2 (0.6)
Liver	1 (1.0)	0	0	0	1 (0.3)
Abnormal liver function tests	1 (1.0)	0	0	0	1 (0.3)

AE, adverse events.

[a]Patients may be represented in multiple systems and in multiple types within a system. System and type as reported by the investigator.

Fig. 1. Overall survival curves from a Cox regression model in ipilimumab-refractory patients with (solid line) and without (dotted line) post-ipilimumab treatment calculated from disease progression and adjusted for sex, line of ipilimumab treatment, BRAF mutation status, and factors assessed at the time of progression: age, LDH level, ECOG status and presence of brain metastases.