Ipilimumab retreatment in patients with pretreated advanced melanoma: the expanded access programme in Italy

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**Background:** Retreatment with ipilimumab has been shown to re-establish disease control in some patients with disease progression. Here, we report the efficacy and safety of retreatment with ipilimumab 3 mg kg\(^{-1}\) among patients participating in an expanded access programme in Italy.

**Methods:** Patients who achieved disease control during induction therapy were retreated with ipilimumab upon progression (3 mg kg\(^{-1}\) every 3 weeks for up to four doses), providing they had not experienced toxicity that precluded further dosing. Tumour assessments were conducted after retreatment, and patients were monitored throughout for adverse events.

**Results:** Of 855 patients treated with ipilimumab, 51 were retreated upon disease progression. Of these, 28 (55%) regained disease control upon retreatment and 42% were alive 2 years after the first induction dose of ipilimumab; median overall survival was 21 months. Eleven patients (22%) had a treatment-related adverse event of any grade during retreatment. These were generally mild-to-moderate and resolved within a median of 4 days. No new types of toxicity were reported.

**Conclusions:** For patients who meet predefined criteria, retreatment with ipilimumab is generally well tolerated and can translate into clinical benefit. This strategy should be compared with other therapeutic options in randomised controlled trials.

The annual mortality rate for patients with metastatic melanoma is increasing faster than for most other types of cancer (Lens and Dawes, 2004; Ferlay et al, 2010). Until recently, patients with unresectable stage III or stage IV (advanced) melanoma had limited treatment options and a poor prognosis, with less than one-third of patients surviving up to 1 year (Tarhini and Agostara, 2011).
Retreatment with ipilimumab in the EAP

Patients. Patients with life-threatening unresectable stage III or stage IV melanoma were eligible to be included in the EAP if they had failed to respond or were intolerant to at least one systemic therapy and if no alternative treatment option was available. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and an interval of at least 28 days since completion of treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy was recommended. Patients who progressed following either stable disease (SD) of ≥3 months duration or an initial objective response (partial (PR) or complete response (CR)) were eligible to receive retreatment with ipilimumab providing they met predefined safety criteria (no unacceptable toxicity requiring discontinuation of ipilimumab during the induction phase excepting reversible autoimmune hepatitis, medically manageable endocrinopathy or reversible dermatological toxicity). The protocol for the EAP was approved by a local independent ethics committee and all participating patients provided signed informed consent before enrolment.

Study design. During the induction phase, ipilimumab 3 mg kg⁻¹ was administered intravenously over 90 min every 3 weeks for four doses. Tumour assessments were conducted at baseline and after completion of induction therapy (Week 12), and classified according to immune-related response criteria (Wolchok et al., 2009). Clinical response was defined as an immune-related complete response (irCR) (disappearance of all index lesions), immune-related partial response (irPR) (≥50% decrease from baseline in the sum of the product of diameters of defined index lesions), immune-related progressive disease (≥25% increase from the smallest recorded sum of the product of diameters of defined index lesions), or an immune-related SD (irSD) (criteria not met for CR, PR or progressive disease). Immune-related disease control (irDC) was defined as irSD lasting ≥3 months, irPR, or irCR, and the irDC rate (irDCR) was the percentage of patients achieving irDC. Each retreatment cycle consisted of four doses of ipilimumab 3 mg kg⁻¹ given in an identical schedule to that used during the trials, were eligible for retreatment with ipilimumab 3 mg kg⁻¹.

Table 1. Retreatment with ipilimumab in previous clinical trials

| Treatment* | CA184-025 (rollover phase II study) | MDX010-20 (phase III) |
|------------|------------------------------------|----------------------|
| Ipiplimumab plus gp100 (n = 29) | Ipiplimumab (n = 9) | 0.3 mg kg⁻¹ (n = 24) | 3 mg kg⁻¹ (n = 34) | 10 mg kg⁻¹ (n = 53) |
| Retreatment dose of ipilimumab, mg kg⁻¹ | 3 | 0.3 | 3 | 10 |
| Median number of doses, n | 4 | 4 | 2 | 4 |
| BOIRR, n/n (%) | 3/23 (13) | 3/8 (38) | 28/122 (23)b | |
| DCR, n (%) | 15/23 (65) | 6/8 (75) | 59/122 (48)b | |
| irAEs, n (%) | 15 (52) | 7 (78) | 18 (75) | 23 (68) | 30 (57) |

Abbreviations: BOIRR = best overall response rate; DCR = disease control rate; irAE = immune-related adverse event.
*Treatment received during the induction phase and retreatment; patients received ipilimumab at 3 mg kg⁻¹.
bIncludes three patients who were previously treated with other doses or regimens of ipilimumab and eight patients who were retreated with ipilimumab 3 mg kg⁻¹. 
induction phase. Tumour assessments were carried out 12 weeks after initiation of retreatment. AEs, including irAEs, were monitored continuously and graded using Common Terminology Criteria for Adverse Events, version 3.0.

Objective. The aim of this analysis was to evaluate the efficacy and safety of retreatment with ipilimumab 3 mg kg\(^{-1}\) in patients with advanced melanoma outside of a clinical trial setting.

Statistical analysis. Patient and disease characteristics were analysed using descriptive statistics. Discrete variables were expressed as relative frequencies (percentages) and continuous variables as median and range. With a total of 51 patients, the largest s.e. in the response rate would be 7% (50% response rate), corresponding to a 95% confidence interval (CI) width of \(\sim \pm 14\%\). Overall survival (OS) was estimated using the Kaplan–Meier analysis.

RESULTS

Patient characteristics. Of the 855 patients participating in the Italian EAP, 126 patients had disease progression following a response to ipilimumab induction therapy but did not receive retreatment and 51 patients (6%) were retreated with ipilimumab 3 mg kg\(^{-1}\). Of these retreated patients, 31 patients had irSD lasting \(\geqslant 3\) months as their best response to induction therapy, and 20 patients had an irPR with induction therapy. Patient characteristics at the beginning of retreatment are provided in Table 2. Among the 51 patients who started a first retreatment cycle, 37 received all four doses and 2 patients began a second retreatment cycle (Table 3). Reasons for not completing all four retreatment doses comprised death \((n = 6)\), dose omission (for surgery or other reasons not including toxicity; \(n = 4)\), disease progression \((n = 3)\), and toxicity (grade 3 diarrhoea; \(n = 1\)). The median time between first induction dose and first retreatment dose was 36 weeks (range: 24–66 weeks).

Efficacy. Among the 51 patients who received retreatment with ipilimumab, two patients achieved an irCR and four an irPR with ipilimumab retreatment for an immune-related best overall response rate of 12% (3–20%). This included one patient whose best response to induction therapy had been irSD. An additional 22 patients had irSD in response to retreatment for an irDCR of 55% (41–69%). Best response to induction therapy for the 22 patients with irSD on retreatment had been an irPR in 8 patients and irSD in 14 patients (Table 4). With a median follow-up of 20 months (range: 7–33 months), median OS from the beginning of induction therapy was 21 months (95% CI: 16–26 months; Figure 1A) for patients who were retreated with ipilimumab and 13 months (95% CI: 11–15 months; \(P < 0.0001\)) for those who were not retreated (median follow-up 13 months; range: 3–29 months). The 1- and 2-year OS rates for patients given retreatment were 92% and 42%, respectively. Median OS from the start of retreatment was 12 months (95% CI: 10–14 months; Figure 1B), and the 1- and 2-year OS rates were 50 and 33%, respectively, for retreated patients.

Safety. Of the 51 patients retreated with ipilimumab 3 mg kg\(^{-1}\), drug-related toxicity had been reported in 20 patients (39%) during the induction phase, including 2 patients with a grade 3 AE (diarrhoea and thrombocytopenia) that had not precluded further dosing. Upon retreatment, 14 patients (27%) reported an AE of any grade, which were considered drug-related in 11 patients (22%; Table 5). Of these 14 patients, 7 had experienced treatment-related AEs and 3 had experienced AEs that were unrelated to ipilimumab during the induction period. Ten patients (20%) had grade 1 or 2 AEs upon retreatment, which were considered to be treatment related in 8 patients (16%). Grade 3 or 4 AEs were reported upon retreatment in 5 patients (10%) and were considered to be treatment related in 3 patients (6%) (Table 5).

| Table 2. Patient characteristics before retreatment \((N = 51)\) |
| --- |
| Characteristic | \(n\) (%)
| Median age, years (range) | 61 (19–85)
| Gender, \(n\) (%) | Male 24 (47) Female 27 (53)
| ECOG performance status, \(n\) (%) | 0 36 (71) 1 15 (29) Time from diagnosis, months (range) 50 (4–199)
| Number of prior therapies (excluding ipilimumab), \(n\) (%) | \(\leqslant 1\) 22 (43) \(\geqslant 2\) 20 (39) \(\geqslant 3\) 9 (18)
| Types of previous therapy | \(n\) (%) Dacarbazine 26 (51) Fotemustine 18 (35) Platinum-based chemotherapy 27 (53) BRAF inhibitor 1 (2) Temozolomide 10 (20) Patients with brain metastases, \(n\) (%) 3 (6) Patients with liver metastases, \(n\) (%) 16 (31)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

| Table 3. Overview of retreatment |
| --- |
| Ipilimumab 3 mg kg\(^{-1}\) | Patients, \(n\) (%)
| Started first retreatment cycle | 51
| Number of doses received | \(\leqslant 1\) 4 (8) 2 doses 2 (4) Three doses 8 (16) Four doses 37 (72)
| Started second retreatment cycle | 2 (4)

| Table 4. Tumour response among retreated patients \((N = 51)\) |
| --- |
| Response after induction according to irRC | irCR irPR irSD irPD
| Patients, \(n\) (%) | 0 0 1 1 4 7 0 14 16

Abbreviations: irCR = immune-related complete response; irPR = immune-related partial response; irSD = immune-related stable disease; irPD = immune-related progressive disease.
The most common treatment-related AEs of any grade experienced upon retreatment were pruritus, diarrhoea, and fatigue. For the three patients who had Grade 3 or 4 treatment-related AEs, these included hypokalaemia, which was controlled, enabling the patient to undergo a second retreatment cycle; diarrhoea, which was observed after the third cycle of retreatment causing the patient to discontinue treatment with ipilimumab. The third patient had pancytopenia 4 months after completing the fourth dose of ipilimumab retreatment, and a bone marrow biopsy performed 1 month later showed a hyperplasia of immature myeloid series. The patient’s symptoms improved with steroids, erythropoietin and blood transfusions and she was able to receive dacarbazine for disease progression.

Grade 3 AEs considered unrelated to treatment were an acute abdomen after the first cycle of retreatment, which resolved in 10 days, and one case of pain (not specified) that occurred after the first cycle of retreatment; these patients were both able to continue ipilimumab retreatment. Treatment-related AEs were experienced at a similar frequency during retreatment compared with induction, and no new types of toxicity were observed. Treatment-related AEs were generally reversible with treatment as per protocol-specific guidelines, with a median time to resolution of 4 days (range: 1–21).

**DISCUSSION**

The reported efficacy and safety profile of ipilimumab retreatment in this EAP is consistent with previously observed outcomes (Table 1) (Margolin et al, 2013; Neyns et al, 2013; Robert et al, 2013). For example, among 38 patients retreated with ipilimumab with or without gp100 in a phase III trial, 65–75% re-established DC and 61% survived for > 2 years from initial randomisation at study entry (Hodi et al, 2010; Robert et al, 2013). Similarly, of 122 patients who achieved DC in one of several completed phase II trials and subsequently progressed, 48% regained DC after retreatment with ipilimumab (Neyns et al, 2013). In the US EAP, median OS from the first ipilimumab dose was 21.1 months for the 108 patients who were retreated with ipilimumab 3 mg kg⁻¹ upon disease progression compared with 7.6 months for all 2155 patients who were treated in the EAP (Margolin et al, 2013).

Compared with DCRs of 48–75% among retreated patients in clinical trials (Neyns et al, 2013; Robert et al, 2013), approximately half the patients retreated with ipilimumab in this analysis regained DC. Interestingly, the DCR was higher among retreated patients in our analysis than had previously been reported following initial induction therapy with ipilimumab 3 mg kg⁻¹ in clinical trials (Hodi et al, 2010; Wolchok et al, 2010; Hamid et al, 2011; Hersh et al, 2011). However, this may be because the patients included in this analysis were those who had previously benefited from induction therapy with ipilimumab, suggesting that they had tumours or immune systems that were more responsive to ipilimumab (Robert et al, 2013).

The response of some patients to ipilimumab is improved upon retreatment compared with induction, possibly because of the time it can take to mount an immune response against the tumour. For example, in the phase III trial MDX010-20, 3 out of 21 patients whose best response to induction therapy was SD had a PR following retreatment with ipilimumab plus gp100 or ipilimumab alone (Robert et al, 2013). In addition, in this analysis of EAP data, 1 patient with irSD as their best response to induction therapy went on to have an irPR with retreatment.

The precise mechanism by which retreatment with ipilimumab induces renewed or even deeper antitumour activity is unclear. In patients who progress after an initial response to ipilimumab, it is possible that new lesions develop with a novel antigen repertoire that is not recognised by the existing T-cell population, thereby allowing their escape and continued proliferation (Reiman et al, 2007). Retreatment with ipilimumab may result in the expansion of T-cell clones specific for the new antigen repertoire, thus reactivating the antitumour immune response. Alternatively, ipilimumab may amplify immune adaptation through shifting T-cell responses, a mechanism for overcoming immune tolerance that has been observed in a long-term survivor of metastatic melanoma in the absence of immunotherapy (Yamshchikov et al, 2005). In addition, it has been shown that the effectiveness of continuous immunotherapy may be counteracted by large numbers of immunosuppressive cells in the tumour microenvironment (Stewart et al, 2004), or the induction of functionally corrupt

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**Table 5. Treatment-related AEs experienced upon retreatment (N = 51)**

| Treatment-related AE      | Any grade | Grade 3/4 |
|---------------------------|-----------|-----------|
| Total                     | 11 (22)   | 3 (6)     |
| Diarrhoea                 | 2 (4)     | 1 (2)     |
| Pruritus                  | 4 (8)     | 0         |
| Liver toxicity            | 1 (2)     | 0         |
| Fatigue                   | 2 (4)     | 0         |
| Hypothyroidism            | 1 (2)     | 0         |
| Hypokalaemia              | 1 (2)     | 1 (2)     |
| Bone marrow aplasia       | 1 (2)     | 1 (2)     |

Abbreviation: AE = adverse event.
memory T cells (Klebanoff et al, 2006). Following completion of ipilimumab induction therapy, the balance between immune effector and regulatory cells, together with the function of the immune state, may be ‘reset’ and potentially more conducive to subsequent treatment.

In the current analysis, ipilimumab retreatment was generally well tolerated with most patients receiving the full four doses of retreatment. In line with other reports (Margolin et al, 2013; Neyns et al, 2013; Robert et al, 2013), the frequencies of treatment-related AEs observed during retreatment were similar to those observed during induction, and no new types of toxicities were reported. Within the EAP, retreatment-related AEs resolved quickly and effectively with treatment as per protocol-specific guidelines, suggesting that retreatment with ipilimumab is safe outside of a clinical trial setting. Indeed, established management algorithms appear to be applicable to AEs that develop during ipilimumab retreatment as well as those that emerge during induction therapy.

As we develop a greater understanding of the mechanisms of tumour immunoediting and immune escape, it is important to identify how immune-based approaches can be designed to limit or overcome these processes. In addition to retreatment upon disease progression, in some trials patients with an objective tumour response or SD after the induction period have received an additional dose of ipilimumab every 12 weeks as ‘maintenance therapy’ for as long as tolerated, until progressive disease. A notable proportion of patients who received maintenance therapy in a phase III trial had long-term survival of >5 years, indicating that this approach is also feasible and warrants further evaluation (Maio et al, 2013).

This EAP has demonstrated that retreatment with ipilimumab can be effective in patients who progress after achieving initial clinical benefit with ipilimumab treatment. A retreatment response rate of 12% and irDCR of 55% is encouraging, suggesting that retreatment with ipilimumab can translate into further clinical benefit. However, the small sample size means that further prospective data are needed to confirm the safety and efficacy of retreatment protocols. Further evaluation of this strategy is required in randomised controlled clinical trials to help define the potential benefit for patients.

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CONFLICT OF INTEREST

VC-S has received travel expenses for medical meetings and conferences and honoraria for advisory boards and consultancy from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme and Roche-Genentech. PAA has served in a consultancy/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche-Genentech, GlaxoSmithKline, Amgen and Celgene; he has also received research funding from Bristol-Myers Squibb, and honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche-Genentech and GlaxoSmithKline. MM has had an advisory role and received funding for communication programmes from Bristol-Myers Squibb, Roche-Genentech and Merck Sharp & Dohme and has received research funding from Bristol-Myers Squibb. PM has served in an advisory role for Bristol-Myers Squibb, GlaxoSmithKline, Novartis and Roche-Genentech. AT received honoraria and travel support from Bristol-Myers Squibb for advisory board participation. PQ has received honoraria from and served as a consultant and in an advisory role for Bristol-Myers Squibb, GlaxoSmithKline and Roche-Genentech. MDV has served as a consultant or in an advisory role for Merck Sharp & Dohme/Schering-Plough and GlaxoSmithKline; he has received research funding from Celgene, Novartis and Roche. The remaining authors declare no conflict of interest.

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