Ipilimumab in melanoma

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Abstract

The treatment of melanoma has been evolving rapidly over the past few years. Patients with BRAFv600 mutations can be treated with a combination of a BRAF-inhibitor and an MEK-inhibitor. Check point inhibitors are treatment options both for patients with BRAF wild-type tumors and BRAFv600 mutated tumors. We conducted a comprehensive review of the literature on the efficacy, predictive markers, safety, and pharmacoeconomics of ipilimumab in melanoma. Ipilimumab was approved by the Food and Drug Administration and the European Medicines Agency for the treatment of metastatic melanoma in 2011. More recently, ipilimumab was also approved by FDA in the adjuvant setting for patients with high risk, stage III melanoma. The anti-PD1 directed antibodies pembrolizumab and nivolumab are superior to single agent ipilimumab, which can is no longer be considered the standard first line treatment in metastatic melanoma.

The addition ipilimumab to nivolumab is associated with a higher response rate and a better progressen-free survival, particularly in patients with PD-L1 negative tumors, albeit at the cost of a steep increase in the incidence of grade 3-4 adverse events. Definitive survival data on this combination are pending. The optimal sequence (inhibition of BRAF and MEK followed by checkpoint inhibitor or the reverse) in patients with BRAFv600 mutated tumors is unknown.

Keywords: Ipilimumab, Melanoma, Advanced, Metastatic, Adjuvant

Introduction

The incidence of melanoma is increasing (1-4). Worldwide, about 200.000 new cases of cutaneous melanoma are diagnosed each year (1-4). The outcome depends on the stage at diagnosis (5-7). Until recently long term survival in patients with stage IV melanoma was lower than 10 %, although a more indolent and protracted course was observed in a minority of patients (5-8). Objective response rates with standard chemotherapy were consistently lower than 20 % and no proven survival benefit was demonstrated in randomized phase III trials. Long term remissions were observed in highly selected patients with high-dose interleukin-2 (5, 8, 9). However, this regimen is highly toxic and is currently rarely used.

Ipilimumab (Yervoy®) is a fully human, IgG1B monoclonal antibody directed against the Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) receptor (10). Cytotoxic T lymphocyte antigen-4 is a negative regulator of T-cell-mediated immune responses. In response to the antigenic stimulation of T cells, CTLA-4 competitively binds to B7-1 and B7-2 (CD80 and CD86) on antigen presenting cells, preventing them from binding to CD28 on T cells. As a result a co-stimulatory signal necessary for ligand-induced T-cell activation is blocked. This homeostatic mechanism intends to limit the cell-mediated immune response and to prevent nonspecific tissue damage (11-13). Blocking CTLA-4 signaling has been shown to prolong T-cell activation and to amplify T cell-mediated immunity (11). CTLA-4 blockade activates CD4-positive and CD8-positive effector cells (14).

Ipilimumab was the first immune checkpoint inhibitor reaching the clinic and was approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of metastatic melanoma in 2011. More recently, it was approved by FDA in the adjuvant setting for the treatment of patients with high risk, stage III melanoma.

Pharmacokinetics

The pharmacokinetics of ipilimumab was studied in 4 phase II studies enrolling 498 patients with advanced melanoma. Patients received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. Maximum concentration (Cmax), trough concentration (Cmin) and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Ipilimumab steady-state was reached by the third dose. The mean terminal half-life was 15 days (standard deviation [SD] 4.62). Ipilimumab clearance increased with increasing body weight and with increasing lactate dehydrogenase (LDH) at baseline. Clearance was not affected by age (range 26-86 years), gender, hepatic function (as measured by albumin and alkaline phosphatase), concomitant use of budesonide, renal function (estimated glomerular filtration rate > 22 ml/min), performance status, HLA-A2*0201 status, or prior use of systemic anticancer therapy (15). The safety and pharmacokinetic profile of either transfectoma- or a hybridoma-derived ipilimumab was studied in a phase I/II trial enrolling 88 patients with unresectable stage III or IV melanoma (16). Similar pharmacokinetic characteristics were shown with equimolar concentrations of hybridoma-derived (3 mg/kg) and transfectoma-derived (2.8 mg/kg) ipilimumab. Transfectoma-derived ipilimumab was used in subsequent clinical development. Single dosing up to 20 mg/kg was well tolerated, as were multiple doses up to 10 mg/kg on days 1, 57, and 85. No maximum-tolerated dose was established. Immune-related (ir) adverse events (AEs) were more common when ipilimumab was administered on days 1, 22, 43 and 64, particularly at a dose of 10 mg/kg. However, as these adverse events were manageable, and

considering the positive correlation between the occurrence of immune related adverse events and the clinical benefit, ipilimumab administered at a dose of 10 mg/kg every 3 weeks for four doses was suggested for further studies (16). No major PK or PD interactions were observed when ipilimumab was administered with dacarbazine or with the carboplatin/paclitaxel combination (17).

Ipilimumab in advanced melanoma

Non-randomized phase II trials, Single agent ipilimumab

O'Day et al (18) treated 155 patients, who had failed at least one prior systemic therapy, with ipilimumab, 10 mg/kg administered every 3 weeks for four doses, followed by iplimumab, 10 mg/kg administered every 12 weeks, starting at week 24. The overall response rate (ORR) and disease control rate (DCR) were 5.8% (95% confidence interval [CI] 2.7-10.7) and 27% (95% CI 20-35), respectively. Estimated 2-year overall survival (OS) rate was 32.8 % (95 % CI 25.4-40.5). Median OS was 10.2 months (95 % CI 7.6–16.3) (18).

Ipilimumab in combination with chemotherapy

In the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II trial (19, 20), 86 patients, including 20 with asymptomatic brain metastases, were treated with a combination of ipilimumab, 10 mg/kg every 3 weeks for four doses, and fotemustine, 100 mg/m² weekly for 3 weeks and subsequently every 3 weeks starting on week 9. Ipilimumab maintenance was administered every 12 weeks starting from week 24. Immune-related DCR (primary objective) was 46.5% (95% CI 35.7–57.6). The irORR was 29.1% (95% CI 19.8–39.8)(19). With a median follow-up of 39.9 months, median OS and 3-year survival rates were 12.9 months (95% CI 7.1-18.7) and 28.5% for the whole study population, and 12.7 months (95% CI 2.7-22.7) and 27.8% for patients with brain metastases, respectively (21).

Patel et al (22) enrolled 64 patients with previously untreated unresectable stage III or stage IV melanoma in a single-institution, phase II clinical trial of ipilimumab plus temozolomide. The induction phase consisted of ipilimumab, 10 mg/kg IV on day 1, and oral temozolomide 200 mg/m² on days 1-4 every 3 weeks for 4 doses. Maintenance therapy (ipilimumab 10 mg/kg every 12 weeks and temozolomide 200 mg/m² on days 1-5 every 4 weeks) started on week 12. With a median follow-up of 8.5 months, the median progression-free survival (PFS) was 5.1 months. There were 10 (15.6%) confirmed complete responses (CR) and 8 (12.5%) confirmed partial responses (PR) (22).

Ipilimumab in combination with biologicals

Ipilimumab can be safely combined with bevacizumab. Hodi et al (23) treated 46 patients with metastatic melanoma in four dosing cohorts of ipilimumab (3 or 10 mg/kg), for four doses at 3-week intervals, and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks. Inflammatory events included giant cell arteritis (n = 1), hepatitis (n = 2), and uveitis (n = 2). The disease control rate was 67.4 % with 8 partial responses (17.4 %). Median OS was 25.1 months (23).

Ipilimumab in combination with Inhibitors of the programmed cell death 1 ckeckpoint (PD-1)

Nivolumab and pembrolizumab are inhibitors of the programmed cell death 1 (PD-1) immune checkpoint which are superior to single agent ipilimumab in advanced melanoma. The combination of ipilimumab with nivolumab or pembrolizumab is under active investigation and might represent the main role for ipilimumab in melanoma in the near future. The addition of nivolumab to ipilimumab is feasible and is associated with a significant increase in ORR and PFS. A phase I trial

conducted by Sznol et al enrolled 53 melanoma patients who had received up to three prior systemic therapies (24). Four doses of nivolumab and ipilimumab administered every 3 weeks were followed by 4 doses of nivolumab every 3 weeks and 8 doses of nivolumab every 12 weeks. Grade 3-4 AEs occurred in 53 % of the patients. The ORR and CR rate were 41 % and 17 %, respectively. Across doses, the 1-year and 2-year OS rates were 82 % and 75 %, respectively (24). The combination of pembrolizumab, 2 mg/kg every 3 weeks up to 2 years, with 4 doses ipilimumab, 1 mg/kg every 3 weeks, has a manageable toxicity profile with grade 3-4 irAEs occurring in 20 % of the patients; ORR by central review in 107 evaluable patients enrolled in the Keynote-029 expansion cohort was 51 % (42 % PR and 9 % CR)(25) .

Randomized phase II trials

Single agent ipilimumab

Wolchok et al (26) randomized 217 patients with previously treated unresectable stage III or stage IV melanoma to receive ipilimumab at a dose of either 10 mg/kg, 3 mg/kg, or 0.3 mg/kg, every 3 weeks for four cycles, followed by maintenance therapy every 3 months. The best ORR was 11.1% (95% CI 4.9–20.7) at 10 mg/kg, 4.2% (95 % CI 0.9–11.7) at 3 mg/kg, and 0% (95 % CI 0.0–4.9) at 0.3 mg/kg (p=0.0015; trend test). Immune-related AEs were more common at the higher dose levels (26). Weber et al (27) treated 115 pre-treated and treatment-naïve patients with unresectable stage III or IV melanoma with ipilimumab, 10 mg/kg every 3 weeks for four doses, and daily blinded oral budesonide (group A) or placebo (group B) through week 16. Budesonide did not affect the rate of grade $\geq$ 2 diarrhea during the first 24 weeks of study (primary endpoint), which occurred in 32.7% and 35.0% of patients in groups A and B, respectively. Budenoside should therefore not be used prophylactically. The ORR was 12.1% in group A and 15.8% in group B. Median OS was 17.7 and 19.3 months, respectively (27). Hamid et al (28) conducted a randomized, double blind, phase II biomarker study in 82 pre-treated or treatment-naïve patients with unresectable stage III/IV melanoma. Patients were treated with ipilimumab 3 mg/kg or 10 mg/kg every 3 weeks for 4 doses. The ORR was 7.5 % and 11.9 % and the DCR was 32.5 % and 19 % for the 3 mg/kg and 10 mg/kg arms, respectively. The 1-year survival rate was 60.9% and 44.2% for 3 and 10 mg/kg ipilimumab, respectively (28).

Ipilimumab in combination with chemotherapy

Hersh et al (29) conducted a randomized phase II trial comparing ipilimumab 3 mg/kg every 4 weeks for 4 doses administered alone or in association with dacarbazine 250 mg/m²/day for 5 days for up to 6 cycles. Cross over was allowed in patients progressing on monotherapy. The objective response rate was 14.3% (95% CI 4.8–30.3) with ipilimumab plus dacarbazine and 5.4% (95% CI 0.7–18.2) with ipilimumab alone. The DCR was 37.1% (95% CI 21.5–55.1) in the ipilimumab plus dacarbazine group and 21.6% (95% CI 9.8–38.2) in the ipilimumab group. At a median follow-up of 20.9 months for ipilimumab plus dacarbazine and 16.4 months for ipilimumab alone, median OS was 14.3 months (95% CI 10.2–18.8) and 11.4 months (95% CI 6.1–15.6), respectively (29).

Ipilimumab in combination with biologicals

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase 2 trial, comparing ipilimumab, 10 mg/kg, intravenously on day 1 plus sargramostim, 250 μg subcutaneously on days 1 to 14 of a 21-day cycle, with ipilimumab alone in 245 patients with unresectable stage III or IV melanoma, who had received at least 1 prior treatment (30).

After a median follow-up of 13.3 months (range 0.03-19.9), median OS for ipilimumab plus sargramostim was 17.5 months (95% CI 14.9-not reached) vs. 12.7 months (95% CI 10.0-not reached) for ipilimumab alone. The 1-year OS rate for ipilimumab plus sargramostim was 68.9% (95% CI 60.6-85.5) compared to 52.9% (95% CI 43.6-62.2) for ipilimumab alone (stratified log-rank 1-sided p = 0.01; hazard ratio [HR] 0.64 [1-sided 90% repeated CI not applicable-0.90]). A planned interim analysis was conducted at 69.8% of expected events (104 observed with 149 expected deaths). The O'Brien-Fleming boundary was crossed for improvement in OS. There was no difference in median PFS. Grade 3 to 5 adverse events were more common with ipilimumab alone (44.9% [95% CI 35.8-54.4] vs. 58.3% [95% CI 49.0-67.2]; 2-sided p = 0.04). Most notable were differences in gastrointestinal toxicities (16.1% [95% CI 9.9-24.0] vs. 26.7% [95% CI 19.0-35.5]; p = 0.05) and pulmonary toxicities (0% [95% CI 0-3.1] vs. 7.5% [95% CI 3.5%-13.8]; p = 0.003)(30).

Talimogene laherparepvec (T-VEC) is a herpes simplex virus 1-based oncolytic immunotherapy designed to selectively replicate in tumors, produce GM-CSF, and stimulate antitumor immune responses. Chesney et al (31) reported an interim safety and efficacy analysis of an open-label randomized phase 1b/2 study of T-VEC in combination with ipilimumab. One hundred and seventy-three patients with unresectable stage IIIB-IV melanoma were randomly assigned to receive ipilimumab alone or in combination with T-VEC. T-VEC was administered at < 4 x 10^6 plaque forming units (PFU) on day 1 of week 1 and at < 4 x 10^8 PFU every 2 weeks starting on day 1 of week 4. Ipilimumab (3 mg/kg Q3 weeks x 4) was started with the 3rd dose of T-VEC.

Confirmed ORR was 35.7% with the combination and 17.5% with ipilimumab alone; unconfirmed ORR was 50% and 27.5%, respectively. Adverse events were comparable between treatment arms except for fatigue (52 % vs. 39 %), chills (51 % vs. 3 %) and pyrexia (39 % vs. 8 %), which occurred more frequently with the combination. A grade 5 autoimmune hepatitis, attributed to ipilimumab by the investigator, occurred in the combination arm (31).

Sequential or combined administration of inhibitors of the programmed cell death 1 ckeckpoint (PD-1)

Postow et al (32) randomly assigned 142 patients with previously untreated metastatic melanoma, in a 2:1 ratio, to receive ipilimumab (3 mg/kg) combined with either nivolumab (1 mg/kg) or placebo, once every 3 weeks for four doses, followed by nivolumab (3 mg/kg) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects. The rate of investigator-assessed confirmed objective response in BRAFv600 wild-type patients (primary endpoint) was 61% in the combination group versus 11% in the ipilimumab-monotherapy group (p<0.001). The CR rate was 22 % and 0 %, respectively (32). After a minimum follow up of 18 months (33), the median PFS was not reached with the combination and was 4.3 months with ipilimumab alone (HR 0.34; 95% CI 0.20- 0.57; p<0.0001). The 18-months PFS rates were 53.4 % and 8.1 %, respectively. Median OS had not been reached in either group (HR 0.56; 95 % CI 0.29-1.1; p = 0.089). Grade 3 or 4 drug-related adverse events were reported in 55% of the patients in the combination group and in 2 % of the patients in the ipilimumab-monotherapy group. Adverse events leading to discontinuation of treatment occurred in 30 % and 9 % of the patients, respectively (33).

Long et al (34) presented data from the KEYNOTE-029 expansion cohort, in which patients received pembrolizumab 2 mg/kg every 3 weeks in combination with ipilimumab 1 mg/kg every 3 weeks for 4 doses, followed by pembrolizumab 2

mg/kg every 3 weeks, until intolerable toxicity, progression, or for up to 2 years. At time of data cutoff for analysis, 107 out of 153 patients enrolled in the expansion cohort had ≥18 weeks of follow-up (median 6.4 months; range 4.3-9.4). Seventy-four percent of the patients received all 4 ipilimumab doses and 68% of the patients remained on pembrolizumab. Thirty-eight percent of the patients had ≥1 grade 3-4 drug-related AEs (DRAEs); 68% of these DRAEs resolved by data cutoff. Drug-related AEs led to discontinuation of pembrolizumab and ipilimumab in 8% of the patients, of ipilimumab alone in 10 % of the patients, and of pembrolizumab alone in 4 % of the patients; there were no treatment-related deaths. Immune-mediated AEs of any grade and of grade 3-4 severity occurred in 53% and 20% of the patients, respectively. The ORR was 57 % (5 % CR) by investigator review and 51 % (9% CR) by central review (34).

Khushalani et al (35) examined the efficacy and safety of the nivolumab-ipilimumab combination in patients with resected stage IIIC of IV melanoma. Cohort A was treated with induction therapy consisting of nivolumab, 1 mg/kg plus ipilimumab, 3 mg/kg, administered every 3 weeks for 4 doses, followed by a maintenance therapy of nivolumab, 3 mg/kg every 2 weeks, for 2 years. Toxicities during induction therapy prompted opening of cohort B, consisting of nivolumab, 3 mg/kg, plus ipilimumab, 1 mg/kg, every 3 weeks for 4 doses followed by 2 years of nivolumab, 3 mg/kg every 2 weeks. Twenty patients were treated in each cohort. Fifty percent of the patients in cohort A and 35% of the patients in cohort B were not able to complete all 4 induction doses due to toxicity. The most common cause was grade 3-4 elevated AST and/or ALT (7 patients). Four and three patients relapsed in cohort A and in cohort B, respectively. At median follow-up of 21.3 months for cohort A and 11 months for cohort B, median PFS and OS have not been reached (35).

Friedman et al (36) reported toxicity data on 64 melanoma patients treated under an expanded access program (EAP) with ipilimumab, 3 mg/kg, plus nivolumab, 1 mg/kg, administered every 3 weeks for 4 doses. At least one clinically significant irAE occurred in 90.6% of patients and 71.9% of patients required at least one course of systemic steroids. Steroid-refractory diarrhea requiring infliximab occurred in 21.9 % of patients. Only 39% of patients were able to complete all 4 doses of ipilimumab and nivolumab (36).

Prospective data on the potential role of ipilimumab after failure of an anti-PD1 directed monoclonal antibody are lacking, although some activity has been observed in small series or ad hoc subgroup or retrospective analyses (37-39). Nivolumab followed by ipilimumab with planned switch after 12 weeks of treatment appears to be a more clinically beneficial option compared with the reverse sequence, albeit with a higher frequency of adverse events (40). In a phase II trial conducted by Weber et al (40), 140 patients with advanced melanoma who had progressed after no more than one prior systemic therapy, were randomly assigned to induction with nivolumab, 3 mg/kg every 2 weeks for six doses, followed by a planned switch to ipilimumab, 3 mg/kg every 3 weeks for four doses, or the reverse sequence. After induction, both groups received nivolumab, 3 mg/kg every 2 weeks, until progression or unacceptable toxicity. After a minimum follow-up of 14 months, grade 3/4 treatment-related AEs (primary endpoint) occurred in 63% of the patients treated with nivolumab followed by ipilimumab and in 50 % of the patients receiving ipilimumab followed by nivolumab. Treatment-related grade 3/4 adverse events led to discontinuation of treatment in 25% and 27% of patients, respectively (41).

The most common treatment-related grade 3/4 AEs during the whole study period were colitis (15% vs. 20%), increased lipase (15% vs. 17%), and diarrhoea (12% vs. 7%). The proportion of patients with a response at week 25 was higher with nivolumab followed by ipilimumab than with the reverse sequence (41%; 95% CI 29.4-53.8 vs. 20%; 95 % CI 11.4-31.3). At 25 weeks, progression was reported in 38% (95 % CI 26.7-50.8) of the patients in the nivolumab followed by ipilimumab group and in 60% (95 % CI 47.6-71.5) of the patients with the reverse sequence. After a median follow-up of 19.8 months (IQR 12.8-25.7), median OS was not reached in the nivolumab followed by ipilimumab group (95% CI 23.7-not reached), whereas over a median follow-up of 14.7 months (IQR 5.6-23.9) in the ipilimumab followed by nivolumab group, median OS was 16.9 months (95% CI 9.2-26.5; HR 0.48 [95% CI 0.29-0.80]). A higher proportion of patients in the nivolumab followed by ipilimumab group achieved 12-month OS than in the ipilimumab followed by nivolumab group (76%; 95% CI 64-85 vs. 54%; 95 % CI 42-65)(40).

Phase III trials

Pretreated patients

The pivotal trial leading to approval of ipilimumab was conducted by Hodi et al. Six-hundred and seventy-six (42) HLA-A*0201–positive patients with unresectable stage III or IV melanoma, whose disease had progressed while receiving treatment containing dacarbazine, and/or temozolomide, and/or fotemustine, and/or carboplatin, and/or or interleukin-2 for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to treatment with an induction course of ipilimumab, 3 mg/kg, plus a gp100 peptide vaccine, or ipilimumab, 3 mg/kg, plus gp100 placebo, or gp100 plus ipilimumab placebo, all administered once every 3 weeks for four adminitrations. The median OS (primary endpoint) in the ipilimumab-plus-gp100 group was 10.0 months (95% CI 8.5-11.5), as compared with 6.4 months (95% CI 5.5-8.7) in the gp100-alone group (HR 0.68; p<0.001). The median OS in the ipilimumab-alone group was 10.1 months (95% CI 8.0- 13.8) (HR vs. gp100 0.66; p=0.003). No difference in OS was observed between the two ipilimumab groups (HR 1.04; p=0.76) The median PFS was 2.8 months (95% CI 2.7-2.8) with ipilimumab plus gp100, 2.9 months (95% CI 2.8-3.0) with ipilimumab plus placebo, and 2.8 months (95% CI 2.73-2.83) with gp100 plus placebo (42). Survival rates at 2 and 3 years were 25% and 25% with ipilimumab alone and 19% and 15% with ipilimumab plus gp100 (43), respectively. As compared to gp100 alone, ipilimumab had no negative impact on health related quality of life (HRQoL) during the treatment induction phase (44). Patients who derived clinical benefit from treatment (CR, PR, SD) lasting ≥3 months from week 12, were eligible for retreatment. Best overall response rates (CR + PR) for 31 retreatment-eligible patients were 13.0% and 37.5%, in the ipilimumab plus gp100 and ipilimumab plus placebo groups respectively, and DCRs were 65.2% and 75.0%, respectively (45).

Previously untreated patients

Robert et al (46) conducted a randomized, double-blind, placebo-controlled phase III trial in untreated metastatic melanoma patients. Four-hundred and fifty-two patients received dacarbazine 850 mg/m² in combination with either placebo or ipilimumab, 10 mg/kg given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22. Patients who derived clinical benefit and who had no dose limiting toxic effects, subsequently received ipilimumab or placebo maintenance therapy every 12 weeks. The median OS in the combined treatment arm was 11.2 months (95% CI

9.4-13.6), as compared to 9.1 months (95% CI 7.8-10.5) with dacarbazine plus placebo (HR 0.72; p < 0.001). Overall survival rate with the combination was higher at 1 year (47.3 % vs. 36.3 %), at 2 years (47.3% vs. 36.3%), and at 3 years (20.8% vs. 12.2%) (46). Improved OS was observed regardless of age, sex, ECOG performance status, baseline serum LDH, and substage of metastatic disease. The ORR with dacarbazine plus ipilimumab was 15.2 % vs. 10.3 % with dacarbazine plus placebo (p = 0.09). The DCR was 33.2 % and 30.2 %, respectively (p = 0.42). The HR for progression was 0.76 (p = 0.006) (46). During the first year of study, there was little difference between groups in quality-adjusted survival. The quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) difference was 0.50 months (p= 0.033) favoring ipilimumab after 1 year. The Q-TWiST difference was 1.5 months after 2 years of follow-up (p=0.009), 2.4 months after 3 years (p=0.005) and 3.3 months after 4 years of follow-up (p=0.007)(47).

Maio et al (48) conducted a milestone survival analysis with a minimum follow-up of 5 years in all patients included in this trial. The 5-year survival rate was 18.2% (95% CI 13.6-23.4) for patients treated with ipilimumab plus dacarbazine versus 8.8% (95% CI 5.7-12.8) for patients treated with placebo plus dacarbazine (p = 0.002). A plateau in the survival curve began at approximately 3 years, demonstrating a durable survival benefit with ipilimumab. In patients who survived at least 5 years and continued to receive ipilimumab, grade 3 or 4 irAEs were observed exclusively in the skin (48). The durability of long-term survival with ipilimumab is supported by a pooled analysis by Schadendorf et al (49), which involved OS data for 1,861 patients (previously treated 1,257; treatment naïve 604) from 10 prospective and two retrospective studies of ipilimumab, including two phase III trials. Most patients received ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706). Median OS was 11.4 months (95% CI 10.7-12.1 months). The survival curve also started to plateau at year 3, with follow-up of up to 10 years. Three-year survival rates were 22%, 26%, and 20%, for all patients, treatment-naive patients, and previously treated patients, respectively. In a secondary analysis of OS data (n = 4,846) with an additional 2,985 patients from an EAP, median OS was 9.5 months (95% CI 9.0-10.0), with a plateau at 21% in the survival curve beginning at year 3 (49).

Results of the dose-ranging phase 2 trial suggested a better OS but a higher incidence of treatment-related grade 3-4 adverse events with ipilimumab 10 mg/kg as compared to ipilimumab 3 mg/kg. In fulfillment of a company's commitment to the Food and Drug Administration, Ascierto et al (50) conducted a randomized, double-blind phase III trial in 727 patients with untreated or previously treated unresectable stage III or IV melanoma who had not received prior BRAF or immune checkpoint inhibitors. Patients were randomly assigned to receive 4 administrations of ipilimumab at either 10 m/kg or 3 mg/kg administered every 3 weeks. Upon disease progression, patients who had experienced clinical benefit could be re-induced with ipilimumab at the initial dose and schedule. Patients were stratified by stage, prior treatment and performance status.

At a minimum follow-up of ~43 months, ipilimumab 10 mg/kg signify-cantly improved OS (primary endpoint) vs. 3 mg/kg. Median OS (primary endpoint) was 15.7 months (95 % CI 11.6-17.8) with 10 mg/kg vs. 11.5 months (95 % CI 9.9–13.3) with 3 mg/kg (HR 0.84 [95 % CI 0.70-0.99]; p = 0.04). Overall survival rates at one year were 54.3 % (95 % CI 49.0–59.3) and 47.6 % (95 % CI 42.4–52.7), respectively. Two-year and 3-year OS rates (38.5 % [95 % CI 33.4–43.5] vs. 31 % [95 % CI 26.2–35.8] and 31.2 % [95 % CI 26.4–36.0] vs. 23.2 % [95 % CI

18.9–27.7], respectively), were also higher with 10 mg/kg. Ipilimumab 10 mg/kg was associated with higher rates of treatment-related grade 3-5 AEs (34.3% vs. 18.5%), grade 3-5 AEs leading to discontinuation (26.1% vs. 16.0%), and grade 3-5 irAEs (33.5% vs. 17.4%). Mortality was 1.1 % and 0.6 %, respectively. Deaths attributed to ipilimumab occurred in 1.1 % of the patients with 10 mg/kg vs. 0.6 % with 3 mg/kg (50).

High risk completely resected stage III melanoma

EORTC (51, 52) conducted a double-blind, phase 3 trial in patients with stage III, adequately resected, cutaneous melanoma (excluding patients with lymph node metastasis ≤1 mm or in-transit metastasis) who had not received previous systemic therapy for melanoma. Nine hundred and fifty-one patients were randomly assigned (1:1) to receive ipilimumab, 10 mg/kg, or placebo every 3 weeks for four doses, followed by one administration every 3 months for up to 3 years. Randomization was stratified by disease stage and geographical region. The primary endpoint was recurrence-free survival (RFS), assessed by an independent review committee, and analyzed by intention to treat. At a median follow-up of 2.74 years (IQR 2.28-3.22), median RFS was 26.1 months (95% CI 19.3-39.3) in the ipilimumab group vs. 17.1 months (95% CI 13.4-21.6) in the placebo group (HR 0.75; 95% CI 0.64-0.90; p=0.0013); 3-year RFS rate was 46.5% (95% CI 41.5-51.3) and 34.8% (30.1-39.5), respectively. The most common grade 3-4 irAEs in the ipilimumab group were gastrointestinal (16% vs. <1%), hepatic (11% vs. <1%), and endocrine (8% vs. none). Adverse events led to discontinuation of treatment in 52% of patients who started ipilimumab. Five (1%) participants died because of DRAEs in the ipilimumab group (3 due to colitis, 1 because of myocarditis, and one because of multi-organ failure with Guillain-Barré syndrome).

At a median follow-up of 5.3 years (53), the 5-year RFS rate was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (HR 0.76; 95% CI 0.64-0.89; p < 0.001). The 5-year OS rate was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (HR 0.72; 95.1% CI 0.58-0.88; p=0.001). The rate of distant metastasis-free survival at 5 years was 48.3% in the ipilimumab group, as compared with 38.9% in the placebo group (HR 0.76; 95.8% CI 0.64-0.92; p=0.002)(54).

Ipilimumab and/or anti-PD1

Robert et al (55) randomly assigned 834 patients, in a 1:1:1 ratio, to receive pembrolizumab, 10 mg/kg, either every 2 weeks or every 3 weeks, or four doses of ipilimumab, 3 mg/kg, every 3 weeks. Co-primary end points were PFS and OS. Efficacy was similar in the two pembrolizumab groups. The estimated 6-month PFS rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (HR 0.58; p<0.001 for both pembrolizumab regimens versus ipilimumab; 95% CI 0.46-0.72 and 0.47-0.72, respectively). Estimated 12-month OS rates were 74.1%, 68.4%, and 58.2%, respectively (HR for pembrolizumab every 2 weeks 0.63; 95% CI 0.47-0.83; p = 0.0005; HR for pembrolizumab every 3 weeks 0.69; 95% CI 0.52-0.90; p = 0.0036). After a median follow up of 22.9 months, median OS was not reached for pembrolizumab vs. 16.0 months with ipilimumab. Estimated 24-months OS rates were 55% and 43 % (HR 0.68; 95 % CI 0.53-0.86, 0.87; p = 0.008) with pembrolizumab and ipilimumab, respectively (56). The response rate was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (p<0.001 for both comparisons). Moreover, rates of grade 3-5 treatment-related AEs were lower in the

pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) (55).

In Check Mate 067 (57), 945 previously untreated patients with unresectable stage III or IV melanoma were randomly assigned, in a 1:1:1 ratio, to nivolumab, 3 mg/kg every 2 weeks plus ipilimumab-matched placebo, or nivolumab, 1 mg/kg every 3 weeks plus ipilimumab 3mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks, or ipilimumab, 3 mg/kg every 3 weeks for 4 doses plus nivolumab-matched placebo. Randomization was stratified according to tumor PD-1 ligand (PD-L1) status, BRAF mutation status, and stage. Progression-free survival and OS (co-primary endpoints) were compared between the nivolumab group or the nivolumab-plus-ipilimumab group and the ipilimumab group. The study was not designed for a formal statistical comparison between the nivolumab group and the nivolumab-plus-ipilimumab group. At a median follow-up ranging from 12.2 to 12.5 months across the three groups, the median PFS was 11.5 months (95% CI 8.9-16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI 2.8-3.4) with ipilimumab (HR 0.42; 99.5% CI 0.31 -0.57; p<0.001), and 6.9 months (95% CI 4.3-9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57; 99.5% CI 0.43-0.76; p<0.001). In patients with tumors positive for the PD-1 ligand (PD-L1), the median PFS was not reached in the nivolumab-plus-ipilimumab group, and was 22.0 months in the nivolumab group and 3.9 months in the ipilimumab group, respectively. In patients with PD-L1-negative tumors, PFS was 11.1 months in the combination therapy, 5.3 months with nivolumab alone and 2.8 months with ipilimumab alone. Treatment-related grade 3- 4 AEs occurred in 19.8% of the patients in the nivolumab group, in 56.5% of the patients in the nivolumab-plus-ipilimumab group, and in 27.0% of the patients in the ipilimumab group (57, 58).

Particular populations

Patients with brain metatastases

Anecdotal reports suggest activity of ipilimumab in melanoma brain metastases (59, 60). Margolin et al (61) enrolled 72 patients with melanoma and brain metastases into an open label phase II study. Patients in cohort A (N = 51) were neurologically asymptomatic and were not receiving corticosteroid treatment at study entry while patients in cohort B (N = 21) were symptomatic and on a stable dose of corticosteroids. Patients were to receive four 3-weekly doses of ipilimumab, 10 mg/kg.

Individuals who were clinically stable at week 24 were eligible to receive ipilimumab 10 mg/kg every 12 weeks as a maintenance therapy. After 12 weeks, nine patients in cohort A exhibited disease control (18%; 95% CI 8-31), as did one patient in cohort B (5 %; 95 % CI 0.1-24). When the brain alone was assessed, 12 patients in cohort A (24%; 95 % CI 13-38) and two patients in cohort B (10%; 95 % CI 1-30) achieved disease control. No unexpected toxic effects were observed. In the NIBIT-M1 trial, 20 with asymptomatic brain metastases were included. The irORR and irDCR in the brain were 25 % and 50 %, respectively (19). Of 855 patients participating in the ipilimumab EAP in Italy, 146 had asymptomatic brain metastases. After a median follow-up of 20 months (range 1-29+), median OS was 4.3 months (95 % CI 3.4–5.2). The global DCR was 27%, including 4 patients with a CR and 13 with a PR. Median PFS and OS were 2.8 and 4.3 months, respectively, and approximately one-fifth of patients were alive 1 year after starting ipilimumab (62).

Ipilimumab and radiotherapy

Multiple reports and preclinical data suggest radiotherapy and immunotherapy may synergize to generate "abscopal" responses outside the radiation field (63-65). Silk et al (66) analyzed the records of melanoma patients with brain metastases

who were treated with whole brain radiation therapy or stereotactic radiosurgery (SRS) between 2005 and 2012 at Ann Arbor, University of Michigan Comprehensive Cancer Center, and identified 70 patients, 33 of whom received ipilimumab and 37 who did not. The 33 patients who received ipilimumab had a median OS of 18.3 months (95% CI 8.1-25.5), compared with 5.3 months (95% CI 4.0-7.6) for the 37 patients who did not receive ipilimumab (66). From 2005 to 2011, 46 patients with melanoma received ipilimumab (3 mg or 10 mg/kg) and underwent single-fraction SRS for brain metastasis at Memorial Sloan-Kettering Cancer Center (67). A total of 113 metastases (91% intact, 9% postoperative) were treated with a median dose of 21 Gy (range 15-24 Gy). Fifteen patients received SRS during ipilimumab, 19 received SRS before ipilimumab, and 12 received SRS after ipilimumab. Overall survival was significantly associated with the timing of SRS/Ipilimumab (p=0.035). Patients treated with SRS during or before ipilimumab had better OS and less regional recurrences than did those treated with SRS after ipilimumab. Stereotactic radiosurgery during ipilimumab yielded a trend toward less local recurrence than did SRS before or after ipilimumab (67).

Chandra et al (68) evaluated 47 consecutive metastatic melanoma patients treated with ipilimumab and 65 courses of radiation. Responses of index lesions outside the radiation field were compared before and after radiotherapy. Index lesions shrank in 7 instances prior to radiation therapy (11%), compared with 16 instances (25%) after radiation therapy; in 11 of the latter instances (69%), the index lesion had been increasing in size prior to radiotherapy ($p = 0.03$). In 68% of cases, radiotherapy was associated with an improved rate of index lesion response ($p = 0.006$). Radiation fraction size ≤ 3 Gy was associated with favorable index lesion response ($p = 0.014$).

Qin et al (70) conducted a retrospective analysis of 88 consecutive melanoma patients treated with ipilimumab at Duke University Medical Center. Patients were categorized as having received radiotherapy (n = 44) or not (n = 44). There was no significant difference in OS, PFS and in both immune-related and non–immune-related toxicity ($p = 0.67$). Patients who received ipilimumab prior to radiotherapy had an increased duration of irradiated tumor response compared with patients receiving ipilimumab after radiotherapy (74.7% vs. 44.8% at 12 months; log-rank $p = 0.01$) (69).

In a retrospective analysis of 101 patients, Koller et al (70) found a significant increase in median OS (21 months vs. 10 months) and in CR rate (25.7% vs. 6.45%) in patients who were treated with ipilimumab and concurrent radiation therapy vs. patients treated with ipilimumab alone (70). The Mel-Ipi-Rx phase 1 (71) study aimed to determine the maximum tolerated dose (MTD) and safety profile of RT combined with ipilimumab in patients with metastatic melanoma. A 3 + 3 dose escalation design was used with 9, 15, 18 and 24 Gy of RT (in 3 fractions) at week 4 combined with ipilimumab 10 mg/kg every 3 weeks for 4 doses. Patients with evidence of clinical benefit at week 12 were eligible for maintenance ipilimumab, 10 mg/kg every 12 weeks, starting at week 24. Dose limiting toxicities occurred in 2/6 pts in the cohort receiving 15 Gy and the MTD in this design was determined at 9 Gy (71). GRAY-B (72) is an open label multicenter phase 2 study in patients with melanoma and brain metastases. Patients are treated with ipilimumab 3 mg/kg Q3w and whole brain radiotherapy, 30 Gy in 10 fractions or equivalent. Eligible are patients presenting a first episode of brain metastasis with Karnofsky performance status > 70 % and not requiring dexamethasone >16 mg or equivalent. A preliminary analysis after recruitment of

43 patients was presented. There were no unexpected safety issues (72). Patel et al (73) retrospectively compared the safety and efficacy of ipilimumab and SRS to SRS alone in 44 consecutive patients with newly diagnosed melanoma brain metastases. No difference in symptomatic radiation necrosis or hemorrhage was identified between cohorts. In this institutional experience the combined treatment regimen was not associated with improved outcome (73). Late symptomatic radionecrosis of brain without evidence of active tumor has been reported after SRS and ipilimumab (74).

Uveal melanoma

Ipilimumab has limited activity in patients with metastatic uveal melanoma. In a phase II study by the Dermatologic Cooperative Oncology Group (DeCOG), 45 pretreated and 8 treatment-naïve patients received ipilimumab at a dose of 3 mg/kg every 3 weeks for up to 4 doses. One-year and 2-year OS rates were 22% and 7%, respectively. Median OS was 6.8 months (95% CI 3.7-8.1) and median PFS was 2.8 months (95% CI 2.5-2.9). The disease control rate at weeks 12 and 24 was 47% and 21%, respectively. There were no objective responses (75). In 82 assessable pre-treated patients with advanced uveal melanoma receiving ipilimumab 3 mg/kg through an EAP, median OS and PFS were 6.0 months and 3.6 months, respectively. The 1-year OS and PFS rates were 31% and 11%, respectively (76). Luke et al identified 39 patients with uveal melanoma in a multicenter, retrospective analysis of 4 hospitals in the United States and Europe. Median OS was 9.6 months (95% CI 6.3-13.4; range 1.6-41.6)(77). Danieli et al (78) assessed the activity and safety of ipilimumab 10 mg/kg in 13 pretreated patients with metastatic uveal melanoma participating in a multicenter EAP. No objective responses were observed, two patients had SD, with a third patient achieving SD after initial progressive disease. Median OS was 36 weeks (range 2-172+ weeks).

Only 12 of 22 (55%) uveal melanoma patients treated with ipilimumab, 3 mg/kg, by the Dutch Working Group on immunotherapy of Oncology (WIN-O) in a named patient program (NPP) (55%) completed the planned 4 infusions. One patient had a PR according to RECIST and another patient had SD according to irRC (79).

Mucosal melanoma

Of 855 patients participating in the EAP in Italy, 71 had metastatic, mucosal melanoma. With a median follow-up of 21.8 months, the response rate was 12% and the immune-irDCR was 36% (79). Postow et al (80) performed a multicenter, retrospective analysis of 33 patients with unresectable or metastatic mucosal melanoma treated with ipilimumab. Durable responses to ipilimumab were observed, but the overall response rate was low. The median OS was 6.4 months (range: 1.8-26.7 months).

Elderly patients

Several retrospective analyses suggest that ipilimumab at a dose of 3 mg/kg can be safely used in elderly patients. Shaw et al (81) found grade 3-5 AEs in 25% of the >70 year old patients with advanced melanoma, which is comparable to the entire population of ipilimumab-treated patients (81). Mian et al (82) analysed irAEs in 858 >65 year old patients with melanoma treated with ipilimumab. The incidence of irAEs (60%) in this elderly population was also comparable to the incidence observed in the total population of ipilimumab-treated melanoma patients (82).

Response evaluation

Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria, designed to detect the effects of cytotoxic agents, may not provide adequate tools for the

assessment of immunotherapeutic agents (83). Novel immune-related response criteria (irRC) for the evaluation of anti-tumor responses with immunotherapeutic agents have been proposed (83, 84). In a detailed analysis of the phase II data with ipilimumab, four distinct response patterns, which were all associated with a favorable survival, were observed: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions (83).

Adverse events

The most common adverse events are immune-related. The most common irAEs affect the skin and the gastro-intestinal tract, including diarrhea and colitis (85-93), which can lead to bowel perforations (94-96) and require prompt management according to published guidelines (97). In daily practice, about a third of the patients require systemic corticosteroids for an irAE and about 10 % also require anti-TNFα therapy. Treatment efficacy seems not to be affected by the occurrence of irAEs or the need for systemic corticosteroids (98, 99). In contrast, in a retrospective single-center analysis of 45 patients treated with ipilimumab under a French Temporary Authorization for Use (TAU) protocol, OS was poorer in patients receiving corticosteroids at baseline (100).

Commonly reported, potentially life-threatening, irAEs also include immune-related inflammation of the endocrine system organs, particularly hypophysitis (101-109) and (late) (pan) hypopituitarism, adrenal insufficiency (110, 111), and hyper- or hypothyroidism (112, 113), and hepatotoxicity (114). Practical guidelines to help the oncologist in the clinical care of patients under immune check point blockade (ICB), including ipilimumab, have been proposed (115, 116). Before starting ICB, onco-logists must identify potential risk factors that could favor the emergence of irAEs, including personal and family history of autoimmune diseases.

Patients should be educated about signs of organ inflammation that would require prompt referral, and patients and their health care providers should be informed of the specific risks of ICB toxicities. Patients must be closely monitored for signs or symptoms of dysimmune toxicities prior to each administration. Dysimmune toxicities can develop at any time. Skin (5 weeks), gastrointestinal (7.3 weeks), and hepatic (7.7 weeks) toxicities commonly occur early, whereas pulmonary (8.9 weeks), endocrine (10.4 weeks), and renal (15.1 weeks) toxicities usually occur later after the start of ICB. However, confidence interval may vary widely among organs: 0.1–57 weeks for skin; 0.1–37.6 weeks for gastrointestinal (117). Patients who develop an irAE should be closely monitored and appropriate treatment should be initiated promptly according to published algorithms (115, 116). Resolution of severe ipilimumab-induced hepatitis has been described after antithymocyte globulin therapy (118) or a triple immunosuppressant therapy with antithymocyte globulin, mycophenolate mofetil, and steroids (119). As ipilimumab is used more widely, more and new particular adverse events are being reported affecting virtually all organs of the body (87, 96, 108, 111, 113, 120-177). Macrolides seem to have a therapeutic anti-inflammatory potential in the case of mild to moderate pulmonary ipilimumab-induced irAEs (178). Ipilimumab can be considered in patients with preexisting autoimmune disorders although exa-cerbations of the autoimmune disease necessitating systemic corticosteroids can occur in about a quarter of the patients (179). Ipilimumab may induce a severe relapse of multiple sclerosis (180). Ipilimumab has been safely administered

to patients with pre-existing hepatitis B or C infection (181-183), to liver and kidney transplant recipients (184-186), although renal allograft rejection has been reported after nivolumab after prior treatment with ipilimumab (187), and to patients with end stage renal disease (188).

Prognostic and predictive markers

Unfortunately, thus far prospectively validated prognostic or predictive markers for metastatic melanoma patients treated with ipilimumab are lacking.

Baseline factors

Baseline factors with potential prognostic or predictive value, based on retrospective analyses, include soluble CTLA4, absolute neutrophil count (ANC), neutrophil-to-lymphocyte ratio (NLR), frequencies of circulating myeloid-derived suppressor cells (MDSC), C-reactive protein (CRP), LDH, soluble CD25 (sCD25), and peripheral γδ T-cells especially Vδ1+ and Vδ2+ cells. Leung et al (189) found that higher soluble CTLA4 levels (sCTLA4) levels correlated both with response and improved survival in patients treated with ipilimumab in a small patient cohort. In contrast, sCTLA4 levels did not correlate with survival in patients who did not receive ipilimumab. High baseline neutrophil-to-lymphocyte ratio is correlated with a poor outcome (190, 191).

Ferrucci et al (192) analyzed prospectively collected data from 720 advanced melanoma patients treated with ipilimumab 3 mg/kg within the Italian EAP. Baseline ANC and derived neutrophil-to-lymphocyte ratio (dNLR) were significantly associated with the outcome of ipilimumab-treated melanoma patients, both in terms of disease progression and death. Prognosis worsened for each elevated variable. Patients with both ANC $\geq$ 7500 and dNLR $\geq$ 3 had a significantly and independently increased risk of death and of progression (HR = 4.10; 95% CI 3.08-5.46) compared with patients with both lower ANC and dNLR, suggesting that a neutrophil-based index may help risk-group stratification (192).

Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab (165). Wistuba-Hamprecht et al (193) found that patients under ipilimumab treatment with higher frequencies of Vδ1+ cells (≥30%) had poorer OS, whereas, higher frequencies of Vδ2+ cells (≥39%) were associated with longer OS and in addition decreasing frequencies of Vδ2+ cells showed worse OS (193).

Sade-Feldman et al (194) suggest the use of CD33+CD11b+HLA-DR- MDSCs as a possible prognostic and predictive biomarker in patients with stage IV melanoma after treatment with ipilimumab. Low levels of MDSCs prior to ipilimumab treatment correlated with an objective clinical response, long-term survival, increased CD247 expression in T-cells and an improved clinical status. Kaplan-Meier and log-rank tests were performed on 56 patients with metastatic melanoma. Median OS was 6.5 months in patients with MDSCs > 55.5% vs. 15.6 months in patients with lower MDSCs ($p < 0.0003$)(194).

In a cohort of 209 patients with advanced cutaneous melanoma treated with ipilimumab in the Netherlands and the United Kingdom, a baseline signature of low LDH, low absolute monocyte count (AMC), and low MDSC as well as high absolute eosinophil counts (AEC), high regulatory T cells (Tregs), and high RLC was associated with a favorable outcome (195). In a cohort of 95 patients treated with ipilimumab 3 mg/kg, disease control and survival were significantly associated with decreasing levels of LDH, CRP, and FoxP3/regulatory T cells, and increasing absolute lymphocyte count, between baseline and the end of dosing (196). The CARAMEL study (197) is a retrospective multicenter study which enrolled 120 patients with histologically confirmed metastatic melanoma treated with ipilimumab. Patients with low serum LDH

levels at baseline had significantly longer PFS ($p = 0.018$) and OS ($p < 0.05$). Higher NLR ($p = 0.043$) and platelets/lymphocyte ratio (PLR) ($p < 0.05$) were associated with a worse PFS. Women had shorter OS ($p = 0.002$) and PFS ($p = 0.003$) compared with men. The presence of >3 sites of metastases was associated with a worse OS ($p < 0.04$) and PFS ($p < 0.03$) (197).

Fatty infiltration of muscle appears as low radiographic density (also called skeletal muscle density, SMD) on computed tomography imaging. Its presence is prognostic of outcomes across cancers. In a single center, retrospective study (198), advanced melanoma patients treated with ipilimumab at the University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, patients with low SMD had significantly poorer median PFS (2.4 vs. 2.7 months, HR 1.76, $p = 0.008$) and OS (5.4 vs. 17.5 months, HR 2.47, $p = 0.001$) compared to patients with SMD above the cut-point and ORR trended in favor of higher SMD (17.9 vs. 3.3%, $p = 0.051$). The prevalence of high NLR was higher in low SMD patients (39 vs. 21%, $p = 0.049$), suggesting that SMD may be related to an underlying inflammatory state (198).

Baseline IL-17 level was significantly associated with the later development of severe diarrhea/colitis while the combination of baseline TGF-β1 and IL-10 levels were associated with therapeutic clinical outcome after neoadjuvant ipilimumab (199).

In 262 metastatic melanoma patients receiving ipilimumab, baseline serum concentrations of sCD25 represented an independent indicator of OS, with high levels predicting resistance to therapy (200). Using genome-wide somatic neo-epitope analysis and patient-specific HLA typing, Snyder et al (201) elucidated a neo-antigen landscape that is specifically present in tumors with a strong response to CTLA-4 blockade. Mutational load was associated with the degree of clinical benefit ($p = 0.01$) but alone was not sufficient to predict benefit.

Using genome-wide somatic neo-epitope analysis and patient-specific HLA typing, they identified candidate tumor neo-antigens for each patient. Predicted neo-antigens activated T cells from the patients treated with ipilimumab. Their findings define a genetic basis for benefit from CTLA-4 blockade in melanoma and provide a rationale for examining exomes of patients for whom anti-CTLA-4 agents are being considered (201).

NY-ESO-1 is an intracellular antigen which is expressed in 30% to 40% of stage III and IV melanoma. Yuan et al analyzed NY-ESO-1 serum antibody by Enzyme-Linked Immuno Sorbent Assay (ELISA) in 144 ipilimumab-treated melanoma patients. Sixteen percent were seropositive at baseline and 22% were seropositive following treatment. Patients with pre-existing antibody responses to NY-ESO-1 or who showed a sero-conversion to NY-ESO-1 during ipilimumab treatment were nearly twice as likely to experience clinical benefit as compared with NY-ESO-1–seronegative patients. Furthermore, in NY-ESO-1–seropositive patients, the presence of peripheral CD8+ T-cell responses to NY-ESO-1 was highly correlated with clinical benefit to ipilimumab (202). Baseline CRP ($p <0.05$) correlated with OS in a cohort of pretreated patients who received ipilimumab in the context of an EAP (203). Ji et al (204) performed a gene expression profiling on tumor biopsies collected from 45 melanoma patients before and 3 weeks after the start of treatment in a phase II clinical trial of ipilimumab, 3 or 10 mg/kg administered every 3 weeks. Patients with high baseline expression levels of immune-related genes were more likely to respond favorably to ipilimumab. Pre-treatment serum VEGF is inversely associated with clinical response and overall survival in advanced melanoma patients treated with ipilimumab (205). Gene expression

profiling of peripheral blood using Affymetrix gene chip HT-HG-U133A might potentially identify either differential gene expression or different changes of gene expression after ipilimumab administration between patients with or without grade $\geq$ 2 immune-related adverse events (206).

Retrospective analyses suggest that NRAS mutations are associated with increased benefit from immune-based therapies including ipilimumab (207, 208). No association between BRAFv600E mutation status and durable disease control was detected a retrospective study which analyzed the BRAFv600E mutation status in tumor biopsies of 80 patients treated with ipilimumab (209). In this context, it should be stressed that the combined use of ipilimumab and a BRAF inhibitor is not recommended. A phase I study of the concurrent administration of vemurafenib and ipilimumab was halted prematurely because of unacceptable liver toxicity (210). A retrospective analysis of four phase II trials of ipilimumab found no indication for a different outcome according to HLA subtype (211). In an exploratory study of patients with metastatic melanoma being treated with ipilimumab, pre-treatment morphomic analysis (psoas density and spine-fascia distance) correlated with response and survival (212). A prospective study showed a significant and independent association between low baseline IL-6 serum levels (OR = 2.84, 95% CI 1.34-6.03, p= 0.007) and irAEs, suggesting that IL-6 serum levels might be a predictive marker for irAEs (213).

Prior treatment

Retrospective data not unexpectedly suggest that OS in treatment-naïve patients receiving ipilimumab is longer than in pretreated patients (214). Data from clinical trials and EAPs suggest ipilimumab confers a consistent survival benefit and has a similar safety profile across different age groups, including patient aged over 70 years (215). Prior therapy with IFNa-2b seems to be a negative prognostic factor, whereas prior high-dose interleukin-2 does not significantly affect the probability of response (216). In a retrospective analysis, prior treatment with immunotherapy did not appear to negatively influence response to BRAF inhibitors. However, outcomes for immunotherapy with ipilimumab following BRAF-inhibitor discontinuation were poor (217, 218). Data from the Italian cohort of an EAP also suggest that patients who receive ipilimumab first do better than those who are first treated with a BRAF inhibitor (218). Randomized controlled trials are needed to define the optimal sequencing of state of the art immunotherapy and the combined inhibition of BRAF and MEK.

Dynamic factors under ipilimumab treatment

An increase in absolute lymphocyte counts (ALC) is a potential surrogate marker of ipilimumab activity during the induction phase of treatment. In an analysis of advanced refractory melanoma patients treated with ipilimumab 3 mg/kg or 10 mg/kg at the Memorial Sloan-Kettering Cancer Center, the ALC after 2 ipilimumab administrations appeared to correlate with clinical benefit and OS (219, 220). Pierret et al (221) also observed a sustained increase in ALC and percentage of lymphocytes in the total white blood cell count in responding patients but in none of the non-responding patients.

In a cohort of patients included in an EAP, stable or decreasing ALC were associated with lack of clinical benefit while patients with an ALC > 1500/µL had an increased OS compared with those having an ALC < 1500/µL (222). Pre-treatment myeloid derived suppressor cells quantity may predict clinical response following ipilimumab therapy, independently of pre-treatment or week 7 ALC and pre-treatment LDH (223). Increased levels of ALC observed at 2-8 weeks after initiation of ipilimumab and delayed

increased levels of CD4+ and CD8+ T cells reflect changes associated with positive outcome (195). Some authors reported a positive association between the occurrence of irAEs and objective, durable clinical responses (216, 224).

In a prospective phase II trial by Hamid et al (28), immunohistochemistry and histology on tumor biopsies revealed significant associations between clinical activity and high baseline expression of FoxP3 ($p = 0.014$) and indoleamine 2,3-dioxygenase ($p = 0.012$), and between clinical activity and increase in tumor-infiltrating lymphocytes (TILs) between baseline and 3 weeks after start of treatment ($p = 0.005$)(28). Changes in the number of circulating of inducible T cell co-stimulator (ICOS) on CD4(+) and CD8(+) T cells ICOS(+) T cells or ratio between ANC and NLR during ipilimumab treatment might represent early markers of response (225).

An early increase in eosinophil count during the treatment with ipilimumab has been associated with an improved clinical response whereas elevated amounts of monocytic MDSC, neutrophils, and monocytes were found in non-responders as compared with basal levels and with responding patients (226). Retseck et al (228) analyzed the peripheral blood mononuclear cells (PBMC) of 18 patients with locally/regionally advanced melanoma. The results showed that an increase in Treg suppressive function was associated with a statistically significant decrease in PFS ($p=0.02$) six weeks after treatment with ipilimumab (227). (18)F-FDG PET/CT after two cycles of ipilimumab is highly predictive of the final treatment outcome in patients with progressive or stable metabolic disease (228)

Regulatory status and recommended dose

Ipilimumab has been approved by the FDA and EMA for the treatment of advanced (unresectable or metastatic) melanoma, and by the FDA for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy (15, 227). The recommended induction regimen in patients with advanced unresectable or metastatic melanoma is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumor response should be conducted only after completion of induction therapy. The currently approved dose of ipilimumab is 3 mg/kg infused over 90 minutes, although administration over 30 minutes also appears to be safe (228), and although the recently presented trial by Ascierto et al (50) demonstrating a better outcome with the 10 mg/kg dose might lead to an adaptation of the Summary of Product Characteristics.

The recommended dose in the adjuvant setting is 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity. The combination of nivolumab (Opdivo®) and ipilimumab is also approved by the FDA and EMA in patients with unresectable or metastatic melanoma (227).

Conclusions

Single agent ipilimumab induces durable responses beyond 3 years in about 20 % of the metastatic melanoma patients. Ipilimumab is associated with irAES which can affect every organ of the body and which require prompt and adequate management according to the published guidelines. Unfortunately, not a single predictive factor for response or toxicity has been validated prospectively.

Ipilimumab at a dose of 10 mg/kg improves RFS and OS in patients with high risk, stage III melanoma. The relative efficacy of iplimumab compared to interferon is unknown. More recently, the anti-PD1 directed monoclonal pembrolizumab and nivolumab were approved for patients with unresectable, metastatic melanoma, based on randomized phase III trials demonstrating superiority over single agent ipilimumab. The addition ipilimumab to nivolumab is associated with a higher response rate and a better PFS, particularly in patients with PD-L1 negative tumors. However, the grade 3/4 toxicity rate with the combination quadruples. The role of ipilimumab after failure of an anti-PD1 directed monoclonal antibody is unclear as data from prospective trials are lacking.

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