Clinical Medicine Insights: Oncology

EXPERT REVIEW

Ipilimumab Pharmacotherapy in Patients with Metastatic Melanoma

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Abstract: Immune augmentation with ipilimumab, an anti-CTLA-4 monoclonal antibody, has joined the ranks of approved immunologic agents for the treatment of metastatic melanoma. Phase III studies of ipilimumab in metastatic melanoma have demonstrated an overall survival advantage as compared to other approved and investigational therapies. However, the adverse effects associated with this medication are unique and often require management with steroids or other immunosuppressants. In addition, the time to response differs with ipilimumab as compared to traditional chemotherapy, and alternative means of assessment of response have been proposed. In this review, we will summarize the basic science of this treatment, its preclinical evaluation, and the clinical trials leading to its approval. We will also discuss the details regarding its use, assessment of response to this drug and other immune-related therapies, and further directions for investigation.

Keywords: ipilimumab, melanoma, CTLA-4, Yervoy™

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Introduction

Immunotherapy has been a treatment modality for advanced melanoma for years. Although refractory to most traditional chemotherapeutic approaches, metastatic melanomas have shown durable responses to Aldesleukin or interleukin-2 (IL-2),[1,2] used alone or in combination with chemotherapy and other biologic treatments such as alpha interferon. The FDA has approved the high- dose interferon alpha 2b regimen for the adjuvant treatment of resected melanoma and high dose interleukin-2 for the treatment of metastatic melanoma. However, the response rates to these agents remain modest, and their use is not without controversy. Active specific immunotherapy with a variety of cellular and tumor antigen vaccines as well as dendritic cell therapy has been explored in detail, but none have shown clinical benefit in controlled clinical trials. Earlier attempts for nonspecific augmentation of anti-tumor immune responses with agents such as Bacillus Calmet Gueran (BCG) have also failed in melanoma.[3] More recently, non-tumor specific immune augmentation with ipilimumab, an anti-CTLA-4 monoclonal antibody, has joined the ranks of approved immunologic agents for the treatment of metastatic melanoma. We will review the basic science of this treatment, its preclinical evaluation, and the clinical trials leading to its approval. We will also discuss the details regarding its use, assessment of response to this drug and other immune-related therapies, and further directions for investigation.

Mechanism of Action

Recognition of tumor cells as foreign and activation of the immune response comprise key steps in the immunologic treatment of cancer.[4] The activation of T cells required for an immune response is a multiple step process. The initial interaction occurs between the antigen presenting cell displaying the antigen and the T cell receptor specific to that antigen on the T cell. Additional costimulatory receptors on the surface of the T cell then associate with ligands on the antigen-presenting cell, thereby allowing for both positive and negative adjustment of the immune response. In addition to the signal between the MHC class one molecule on the antigen presenting cell and the T cell receptor, a second signal is generated by interaction of B71 on the antigen presenting cell and CD28 on the responding lymphocyte. This process results in T cell proliferation, as well as the generation of both IL-2 and gamma interferon. The cytotoxic T-lymphocyte antigen-4 (CTLA-4, also known as CD152) receptor is one of the costimulatory receptors that has a major negative regulatory effect on the T cell. As the immune response develops, the CTLA-4 molecule is expressed on the cell surface. It out competes the interaction with B71 and results in the down regulation of the T cell response. In particular, CTLA-4 has a function in maintaining tolerance to self-antigens.[5] Only expressed after the start of T-cell activation, this molecule may therefore play a role in tumor evasion of the immune system by suppressing the immune response and allowing cancer cells to be recognized as "self." Blockade of this pathway allows proliferation of T cells to proceed, thereby permitting an anti-tumor effect.[6] Additional effects of CTLA activation include decreased expression of IL-2 and its receptors and decreased progression through the cell cycle; blockade of CTLA-4 has been proposed to mitigate these effects as well.[7,8]

Murine models of cancer have demonstrated the role of CTLA-4 in the immune system and its interaction with cancers *in vivo*. Low level expression of the CTLA-4 ligand CD80 has been associated with immunosuppression and evasion of immune surveillance in a mouse model of colon cancer.[9] In addition, anti-CTLA-4 monoclonal antibodies have been administered in murine models of colon cancer and fibrosarcoma, resulting in rapid rejection of both CD80+ tumors and tumors that did not express CTLA-4 ligands.[10] Studies of CTLA-4 antibodies in murine models of prostate cancer have also demonstrated decreased tumor growth and tumor rejection, as well as benefit in the adjuvant setting after surgical excision.[11,12] Synergistic effects protecting mice from subsequent challenge with tumor innoculation have also been observed. Study of the combination of CTLA-4 blockage and vaccination with SM1 cells engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF) showed protection of murine models against mammary carcinoma, whereas either agent alone did not prevent tumors.[13] Similarly, the addition of CTLA-4 blockade to melphelan chemotherapy enhanced its antitumor effects in MOPC-15 murine models.[14] The understanding of the mechanisms involved in the control and down-regulation of the immune response and the

role of CTLA-4 in regulation of both autoimmune and anti-tumor immune responses has resulted in the development of monoclonal antibodies to CTLA-4 as therapeutic agents for human cancer.

Preclinical Studies of CTLA-4 Blockade in Melanoma

Initial work in murine models of melanoma focused on the effects of CTLA-4 blockade in combination with other immune-based therapies. Von Elsas et al treated mice with the B16-BL6 murine melanoma with anti-CTLA-4 and irradiated tumor cells that expressed GM-CSF.[15] They found that this combination caused the rejection of 80% of newly acquired tumors; furthermore, it afforded protection against a second challenge with this tumor and was effective against established lung metastases. Additional work from the same group demonstrated that the combination of anti-CTLA-4 therapy and anti-CD25 (a molecule important in regulatory T cells) therapy with the GM-CSF vaccine resulted in maximal tumor rejection.[16] The combination of a hamster-derived anti-CTLA-4 antibody and vaccination with plasmids expressing TRP2 or gp100 also caused protection from subsequent tumor challenge in murine B16 melanoma.[17] This combination was most effective when a priming vaccination was given, followed by the antibody and the boost vaccination. Blockade of CTLA-4 with aptamers (low molecular weight ligand constructs) rather than antibodies was also shown to be efficacious in conjunction with a GM-CSF-secreting B16/F10.9 melanoma vaccine.[18]

Ipilimumab and Tremelimumab

Two anti-CTLA-4 antibodies have undergone clinical development for treatment of melanoma. Ipilimumab, previously known as MDX-010, is a fully humanized IgG1 monoclonal antibody against the extracellular domain of CTLA–4. Produced by Medarex (Princeton, New Jersey) and Bristol-Myers Squibb (New York, New York), ipilimumab is also known by the trade name Yervoy™. It was approved by the FDA for treatment of metastatic melanoma in 2011. Tremelimumab, a human IgG2 monoclonal antibody produced by Pfizer (New York, New York), has also been in clinical trials for melanoma patients. However, the phase III trial of tremelimumab did not demonstrate a significant survival benefit as compared to dacarbazine or temazolamide.[19] We will therefore focus our discussion below on the clinical studies of ipilimumab. However, the reported response rate, response duration, and toxicities of tremelimumab appear to be similar to those of ipilimumab, to the extent that different non-comparative studies can be evaluated.

Clinical Studies in Melanoma

The initial human study of ipilimumab (then known as MDX-010) was conducted by Hodi et al and published in 2003.[20] A total of nine subjects previously treated with a variety of vaccine therapies received a single infusion of MDX-010 at 3 mg/kg to determine if the biologic effects of CTLA-4 blockade seen in animal models could be reproduced in humans. Of these subjects, seven had metastatic melanoma and two had ovarian carcinoma. For the five subjects with a history of prior treatment with irradiated, autologous GM-CSF-secreting tumor cells, evidence of anti-tumor effect was observed after the dose of MDX-010. The patients with melanoma developed extensive tumor necrosis, whereas those with ovarian cancer had stabilization or reduction of CA-125 levels. Subjects with a history of vaccinations other than GM-CSF-secreting cells did not experience tumor necrosis. The clinical toxicity associated with the single dose of MDX-010 in this study was minimal. One subject experienced an acute hypersensitivity reaction during infusion, which was corrected by administration of antihistamines. Another patient with liver metastases had transient grade 3 hepatotoxicity, and other adverse effects were grade 1 or 2 systemic symptoms that usually resolved within a week of the infusion. All melanoma patients on study developed a grade 1 rash with peri-vascular T-cell infiltrates in the superficial dermis and extending into the epidermis; however, despite this evidence of an effect on melanocytes, there was no clinical evidence of vitiligo. In addition, four patients developed autoantibodies at low titers but did not have clinical manifestations of autoimmune disease. Overall, this study determined that ipilimumab had the potential to augment an immunologic memory response in human cancer patients and could possibly induce an antitumor response. In another early phase I study, Phan et al investigated the role of CTLA-4 blockade in overcoming immune tolerance and enhancing the effectiveness of two gp100 peptide vaccines in a

population of patients with metastatic melanoma.[21] Subjects received ipilimumab at 3 mg/kg followed by injection with the two peptide vaccines every three weeks. Overall, fourteen patients were accrued; most received two cycles of treatment, and the maximum number of cycles for a subject was six. Eight subjects developed clinical immune-related adverse events (irAEs) after receiving the combination of ipilimumab and gp100 peptide vaccine. The grade 3 or 4 autoimmune responses were dermatitis, enterocolitis, hypophysitis, or hepatitis. Less severe autoimmune side effects included conversion to ANA positivity and development of vitiligo. In addition, three patients had sustained objective responses to their cancers. Two patients with limited disease experienced complete responses in the initial report, and another had a partial response that included complete resolution of a subcentimeter brain metastasis. This study was updated with a total of fifty-six subjects with stage IV melanoma: in addition to the peptide vaccines, 29 subjects received 3 mg/kg of ipilimumab every three weeks and 27 subjects received an initial ipilimumab dose of 3 mg/kg, followed by 1 mg/kg every three weeks.[22] In the updated report, two subjects had complete responses and five had partial responses. The response rate was 13%, and neither response rate nor toxicity differed between the two dosing schedules. However, clinical response occurred more frequently in patients who experienced higher-grade autoimmune adverse effects (36% response rate in those with autoimmune toxicity versus 5% in those without; $P = 0.008$). Plasma concentrations of ipilimumab were not clearly correlated with either toxicity or tumor response. Despite these results, assays of cellular response did not indicate an enhancement of the effects of the peptide vaccine with the ipilimumab as compared to historical results with the vaccine alone; therefore, it was suggested that the clinical effects may have been a function of the CTLA-4 inhibition and that further investigation of the MDX-010 as a single agent should be considered.[21]

In contrast, Sanderson et al conducted another study of nineteen high-risk patients with Stage III or Stage IV melanoma who had been rendered free of disease by surgery, and they concluded that ipilimumab did enhance response to vaccination.[23] In this study, subjects were randomized to receive a multipeptide vaccine directed against gp100/MART-1/tyrosinase in conjunction with ipilimumab at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg. The primary endpoints focused on the adverse effects and tolerability of ipilimumab, and the pharmacokinetics and immunologic responses to the vaccine caused by ipilimumab. The most frequent toxicities reported were systemic, cutaneous, and gastrointestinal, with a tendency to increasing incidence and severity of toxicities with an increasing dosing level of ipilimumab. Grade 3 or 4 toxicities included diarrhea in one patient in the 1 mg/kg cohort cohort and two patients in the 3 mg/kg cohort, abdominal cramping in one patient in the 3 mg/kg cohort, and melena in one patient in the 1 mg/kg cohort. Uveitis was also noted in one patient in the 1 mg/kg cohort. In all, eight patients had toxicities that were considered of autoimmune origin. With three out of the five patients in the 3 mg/kg cohort reporting dose-limiting toxicity, the MTD in this study was therefore defined as 1 mg/kg. However, other large studies have used doses of 3 mg/kg and 10 mg/kg with no apparent increase in tolerance. The development of autoimmunity showed a possible correlation with disease response: nine of the eleven patients without autoimmune symptoms had relapse of their disease at 28 months of followup, whereas only three of the eight patients who experienced these symptoms had relapsed at that time. Relapse rates were similar between the 3.0 mg/kg and the other cohorts. Unlike the results from Phan et al, immune response to the peptide vaccinations was more frequent in this study than would be expected from historical results from the vaccine alone.

The results previously reported by Phan et al and Attia et al were combined with a dose-escalation study of ipilimumab with gp100 peptide vaccines in a report by Downey et al.[24] Thirty-eight subjects were started at 3 mg/kg ipilimumab, which was increased to 5 mg/kg and then to 9 mg/kg in the absence of response or limiting toxicity. Due to rapid disease progression for subjects at 3 mg/kg, an additional 50 subjects were enrolled starting at the 5 mg/kg dose. Response rates, overall survival, and progression-free survival did not differ between subjects on the dose-escalation study and those on the earlier studies. The more aggressive dosing strategy also did not result in significant differences in immunologic adverse effects. Of the 139 total patients, three subjects had a complete response, and 20 had a partial response. Median overall survival was 15.7 months. Analysis of prognostic factors

showed that previous therapy with interferon alpha 2B was a negative indicator, but other prior treatments did not affect response. However, bowel perforations were found to be more common in individuals who received high-dose IL-2 therapy after ipilimumab, which suggests that IL-2 therapy should be undertaken prior to use of ipilimumab in eligible patients.

Prieto et al published an update on this combined population in 2012.[25] Overall, 177 subjects received ipilimumab at varying doses with or without gp100 vaccination or IL-2. In these three studies, median overall survival ranged from 13–16 months. Complete response rates were 6%–7% for the studies with gp100 vaccination and 17% for the protocol with IL-2. Of note, nearly all of the subjects with a complete response had a sustained duration of response, ranging from 54+ to 99+ months.

The use of ipilimumab in conjunction with high-dose IL-2 was studied by Maker et al in 36 patients with metastatic melanoma.[26] Because IL-2 has been shown to increase T-regulatory cells that express CTLA-4, the addition of ipilimumab was proposed to enhance the antitumor effects of the IL-2. Dosing of the ipilimumab ranged from 0.1 mg/kg to 3 mg/kg every three weeks. The objective response rate was 22%, which was similar to the sum of the expected response rates from each drug used as a single agent. Three complete responses and five partial responses were observed; the majority of the responding patients were in the group receiving 3 mg/kg. High-grade toxicities included four patients with enterocolitis and one patient with uveitis and arthritis. Overall, the combination of these two drugs was not felt to demonstrate a synergistic effect on metastatic melanoma.

A combination phase I/II study done by Weber et al investigated the safety and pharmacokinetics of transfectoma-derived ipilimumab versus those of the established hybridoma-derived version of the drug.[27] If the effects were similar, use of the transfectoma-derived drug would allow for more efficient production. In a trial of 88 patients with unresectable stage III or stage IV melanoma, subjects received single doses of the transfectoma-derived drug (group A—single dose at 7.5, 10, 15, or 20 mg/kg), multiple doses of transfectoma- or hybridoma-derived drug (group A—multiple doses from 2.8–8 mg/kg), or multiple doses of transfectoma-derived drug at 10 mg/kg every three weeks up to 4 doses (group B). Nearly 80% of subjects had prior systemic therapy with immunotherapy or chemotherapy. The pharmacokinetic properties of the hybridoma- and transfectoma-derived anti-CTLA-4 antibodies were similar. Toxicities resembled those seen in previous studies, with rash and diarrhea each occurring in over a third of patients enrolled. All individuals who had an observable tumor response had a rash, and most had autoimmune gastrointestinal events as well. Twenty-five percent of subjects receiving multiple doses at 10 mg/kg had adverse effects that were grade 3 or higher, including one instance of grade 4 colitis and colonic perforation requiring colostomy. Most toxicities, however, could be managed with steroids and were reversible, and a maximal tolerated dose was not identified. One complete response (in group B) and three partial responses were observed, and 14 individuals had stable disease. Most of these responses were durable at 24 weeks. Some individuals had a slow or gradual onset of response, which in some cases did not become apparent until after week 12. Although comparisons among the groups were not part of the study design, the multi-dose regimen at 10 mg/kg (group B) appeared the most efficacious, with median progression-free survival and overall survival of 95 days and 405 days, respectively.

Overall, these studies indicated that multidose therapy with ipilimumab over a range of doses was reasonably well tolerated with a well-defined spectrum of predominantly autoimmune toxicities. There was a rough correlation between the dose and both the toxicity and the clinical benefit, and toxicity was associated with clinical benefit at all doses. However, the small numbers of patients at any dose and schedule and the variability in other concurrent immunotherapeutic agents as well as the variability of the clinical situations preclude any definite conclusions about dose response, dose toxicity and other factors where these issues would have been better elucidated in larger studies.

The first phase III study of ipilimumab investigated its use with and without gp100 peptide vaccine versus gp100 alone in HLA-A*0201-positive individuals with previously treated metastatic melanoma.[28] The peptide vaccine consisted of two modified HLAA*0201-restricted peptides, a gp100:209-217 (210 M) peptide and a gp100:280-288 (288 V) peptide, in an emulsion with incomplete Freund's adjuvant (Montanide ISA-51). Six hundred seventy-six subjects were

randomized in a 3:1:1 ratio to ipilimumab (3 mg/kg every three weeks for up to 4 treatments) + gp100 (1 mg of each peptide given in opposite thighs every 3 weeks), ipilimumab alone, or gp100 alone. Of these subjects, 22.8% had prior treatment with interleukin-2 therapy. Median overall survival was significantly improved in those in the combination therapy arm as compared to the gp100 arm (10.0 months versus 6.4 months, HR 0.68, $P < 0.001$), but it did not differ between the two ipilimumab-containing groups. Survival at one year was also greater for those who received ipilimumab than for those who received the vaccine only (44% versus 25%). Subgroup analyses showed no difference in survival based on age, gender, baseline lactate dehydrogenase level (LDH), metastatic substage, or prior therapy with interleukin-2. Overall response rate for ipilimumab alone was 10.9%; for the combination therapy group, it was 5.7% and for those receiving gp100 alone it was 1.5%. Benefit was also observed in individuals who underwent reinduction with ipilimumab after disease progression. The median time to progression was 2.86 months for the ipilimumab alone group and 2.76 months for both the combination therapy group and the gp100 alone group. High-grade immune-related adverse events occurred in 10%–15% of subjects in the ipilimumab-containing arms of the study and were similar in nature to those previously reported with this drug. In descending order of frequency, the grade 3 and 4 toxicities in the ipilimumab-alone arm included fatigue (6.9%), diarrhea (5.3%), colitis (5.3%), dyspnea (3.9%), anemia (3.1%), nausea (2.3%), constipation (2.3%), vomiting (2.3%), headache (2.3%), hypopituitarism (1.6%), decreased appetite (1.5%), abdominal pain (1.5%), hypophysitis (1.5%), and rash (0.8%). Fourteen subjects experienced death related to study drug. Based on these results, the authors concluded that the effect of ipilimumab on overall survival in previously-treated melanoma patients was not improved by the addition of the gp100 peptide vaccine, but it was markedly superior to that of patients getting gp100 alone and therefore a significant advance in the treatment of melanoma. Based on this study, the drug was approved by the FDA in March 2011 for the treatment of metastatic melanoma. It is also noteworthy that these results were achieved in patients who had been previously treated with chemotherapy or other immunotherapy for their metastatic disease.

As the activity of ipilimumab in the absence of vaccine was established, additional investigation focused on the use in combination with chemotherapy. Hersh et al conducted a phase II study of ipilimumab (3 mg/kg every 4 weeks) as a single agent or with dacarbazine (250 mg/m^2/day for 5 days every three weeks, up to 6 cycles) in 72 chemotherapy-naïve melanoma patients.[29] Individuals on monotherapy were allowed to cross over to combination therapy after disease progression. The pharmacokinetics of the ipilimumab were not altered by the addition of dacarbazine to the regimen. The objective response rates were 14.3% in the combination arm and 5.4% with single-agent ipilimumab. Two subjects in the combination therapy group had durable complete responses, and two subjects in the ipilimumab-alone group had durable partial responses. In addition, three subjects in the combination therapy group had partial responses but subsequently had progressive disease. Median overall survival was 14.3 months in the ipilimumab-dacarbazine group and 11.4 months in the ipilimumab-alone group; however, these differences were not statistically significant. The survival results did compare favorably with the historical results of treatment of metastatic melanoma with dacarbazine alone. As in the previous studies, most adverse events were reversible and could be managed medically. Significant adverse events were more frequent in the combination therapy arm: 22.9% of subjects in the combination treatment arm had grade 3 or higher toxicities, whereas this level of toxicity was reported in 12.8% of those on monotherapy with ipilimumab. In addition to the side effects reported in other studies, autoimmune vasculitis, adrenal insufficiency, pulmonary embolism with sepsis, steroid-refractory colitis with subsequent disseminated aspergillosis, and acute multiorgan failure were also observed in individual patients.

Based on subsequent data on optimization of dosing, the phase III trial of ipilimumab with dacarbazine used a significantly higher dose of ipilimumab. In this study by Robert et al, 502 subjects with previously untreated metastatic melanoma were randomized to dacarbazine (850 mg/m^2 every three weeks for up to 22 weeks) plus placebo or ipilimumab at 10 mg/kg every three weeks for four doses.[30] It is not clear as to why the investigators used a dose of 850 mg/m^2 of dacarbazine rather than the standard 1000 mg/m^2 or

250 mg/m^2 daily for 5 days. Individuals with stable disease or tumor response continued with the previously assigned placebo or ipilimumab every 12 weeks for maintenance therapy. Of note, individuals with elevated LDH levels were not excluded from the study; however, those with evidence of brain metastases, ocular or mucosal origin of the melanoma, or pre-existing autoimmune disease were ineligible. Individuals receiving ipilimumab and dacarbazine had significantly increased overall survival as compared to the dacarbazine-alone group (11.2 months versus 9.1 months). The hazard ratio for death was 0.72 for the combination therapy arm ($P < 0.001$). The improved efficacy over dacarbazine alone persisted over all subgroups of age, gender, performance status, substage of disease, and LDH level. Subjects who did respond to ipilimumab plus dacarbazine tended to have durable responses, with a mean duration of response of 19.3 months. High-grade adverse events were more frequent in the combination therapy arm than in the dacarbazine arm (56.3% versus 27.5%). If limited to severe immune-mediated adverse effects, 38.1% of subjects in the ipilimumab-dacarbazine group experienced these toxicities as compared to 4.4% of those in the dacarbazine-alone group. The side effect profile for ipilimumab users was similar to that noted in other studies, with several notable exceptions: no gastrointestinal perforations or hypophysitis were observed, and the incidence of elevations in hepatic enzymes was significantly higher than reported previously. The lack of colonic perforations and hypophysitis may be attributed to the increased awareness of immune-related gastrointestinal and endocrine toxicities and the early use of steroids in individuals developing these symptoms, whereas the increase in hepatic toxicity may be due to the addition of dacarbazine, which is known to be hepatotoxic in some patients, to the regimen. No drug-related deaths were seen in the combination treatment group; one subject in the dacarbazine-alone group had a fatal gastrointestinal hemorrhage.

Approval

In March 2011, ipilimumab was approved for the treatment of metastatic melanoma by the United States Food and Drug Administration. The exact FDA approved indication is for 3 mg/kg ipilimumab as an intravenous infusion every three weeks for four doses in the setting of metastatic or unresectable melanoma. Due to the unusual side effect profile associated with the drug, a Risk Evaluation and Mitigation Strategy (REMS) was implemented to provide education for health professionals regarding its use.

The European Medicines Agency approved ipilimumab in July 2011. However, at this time, the National Institute for Health and Clinical Excellence (NICE) has recommended against use of ipilimumab for the National Health Service in the United Kingdom. Issues contributing to the negative recommendation include lack of biomarkers to determine which subpopulation of melanoma patients will be expected to respond to this treatment, the severity of potential side effects of the drug, and the cost of the drug (currently the average cost per dose is $31,400 or £20,000). The public comment period on this recommendation closed recently (in November 2011), but it has been suggested that a reduction in cost through a patient access scheme might be considered.

Practical Considerations

Dosing and schedule

Although ipilimumab has been approved with dosing of 3 mg/kg, considerable controversy remains as to whether this is in fact the optimal dose. Downey et al found that efficacy and adverse effects were similar with 3 mg/kg, 5 mg/kg, and 9 mg/kg dosing of ipilimumab when given in conjunction with a peptide vaccine.[24] Weber et al found that 10 mg/kg dosing was more efficacious than single-dose regimens or multiple lower-dose regimens, but the higher dosing resulted in increased immune-related toxicity.[27] Indirect comparisons among studies seem to confirm this finding. However, neither of these studies was designed or powered to make a direct comparison regarding dosing levels. An upcoming randomized clinical trial will investigate use of 3 mg/kg versus 10 mg/kg ipilimumab in the advanced melanoma population. However, a formal, large-scale, pharmacokinetically- and pharmacodynamically- (immunostimulation or immunomodulation) driven dose-response study of this agent has never been done. The comparison of 3 and 10 mg/kg does not fulfill this need.

Use of ipilimumab beyond twelve weeks is another area of interest. Although some of the studies above offered maintenance or reinduction therapy after completion of the ipilimumab course, the optimal schedule for ipilimumab remains to be clarified.

Guidelines for Assessing Response

Overall, four response patterns have been observed with treatment with ipilimumab:[31]

1. Response in baseline lesions and no development of new lesions.
2. Stable disease, sometimes followed by a gradual decline in tumor burden.
3. Response after an initial increase in total tumor burden.
4. Response in index and new lesions after the appearance of new lesions.

The first two of these patterns fall under traditional RECIST criteria for responses; however, the second two do not. For this reason, alternative criteria have been derived from a population of 487 patients with advanced melanoma who have received ipilimumab. These immune-related response criteria (irRC) include the following:

1. Only index and measurable new lesions are assessed in the evaluation of tumor burden. (Under RECIST criteria, new lesions are not measured and new lesions are not included).
2. Response at each assessment time point is defined based on the change in tumor burden (including both index and new measurable lesions) as compared to the baseline measurements.
3. Overall response is determined from the time point assessments. irCR is complete disappearance of all lesions with no new lesions, as confirmed by repeat assessment at least 4 weeks later. irPR is characterized by a 50% or greater decrease in tumor burden relative to baseline, confirmed by repeat assessment at least 4 weeks later. irPD is indicated by a 25% or greater increase in tumor burden relative to the patient's nadir value for tumor burden, confirmed by repeat assessment at least 4 weeks later. Those who do not meet criteria for irCR, irPR, or irPD are categorized as having irSD.

These guidelines are described in further detail by Wolchok et al.[31]

Management/Prevention of Adverse Effects

Because of the prevalence of immune-related gastrointestinal effects with ipilimumab, Weber et al conducted a randomized study of the tolerability and efficacy of this drug with and without prophylactic budesonide (Entocort® EC), a nonabsorbed oral steroid, in an advanced melanoma population.[32] The addition of the steroid did not affect the incidence of diarrhea that was grade 2 or greater (32.7% with budesonide and 35.0% with placebo). The two groups had similar rates of drug-related adverse events overall, and 57% of the individuals in the budesonide group required additional steroid treatment for adverse events, as compared to 44% of those in the placebo group. Overall response rates were 12% for the budesonide group and 15.8% for the placebo group. Based on these results, use of steroids remains reserved only for treatment rather than prophylaxis of adverse events associated with ipilimumab.

Current treatment recommendations include antidiarrheal drugs and supportive care for non-bloody grade I diarrhea, with the addition of budesonide for grade 2 diarrhea and high-dose steroids for diarrhea that is bloody or grade 3 or higher.[33] Weber et al recommend 125 mg IV methylprednisolone, followed by 1–2 mg/kg/day of oral prednisone or dexamethasone 4 mg every 4 hours, for patients with grade 3 or 4 diarrhea.[34] Steroids should be tapered over at least 4 weeks in this setting. Onset of diarrhea can be abrupt, and treatment must be initiated immediately. Those who have grade I symptoms may continue to receive treatment, but therapy must be held pending resolution of the diarrhea for any higher-grade symptoms.[33] Individuals with higher-grade symptoms should be admitted to the hospital for hydration and observation. Those who do not respond to steroids after several days may require a trial of infliximab (5 mg/kg every 2 weeks);[34] failing that, surgical intervention is indicated.[33]

Steroids are a mainstay of the management of non-diarrheal immune-related side effects of ipilimumab as well.[33,34] Hepatitis usually manifests as transaminitis. For elevations of AST/ALT less than five times the upper limit of normal, skipping the ipilimumab dose until the next scheduled dose is usually sufficient once the transaminases normalize.[33] Grade 3–4 transaminitis requires a 30-day course of steroids (including IV steroids for the initial 24–48 hours, followed by oral dexamethasone 4 mg every 4 hours or prednisone 1–2 mg/kg/day) and discontinuation of the ipilimumab. Steroid tapers should again be performed over at least 30 days. Mycophenolate mofetil

(500 mg every 12 hours) may be initiated if there is no improvement with steroids.[34] Previously, infliximab was recommended for refractory grade 4 transaminitis; however, more recent recommendations indicate that this medication should be avoided as it may cause hepatotoxicity as well.[34] Hypophysitis should be evaluated by MRI of the brain and serum endocrine panel, and should be treated with appropriate hormone replacement as well as methylprednisolone 1–2 mg/kg IV, followed by prednisone 1–2 mg/kg/day, tapered off over at least 4 weeks.[33,34] The ipilimumab package insert recommends testing of thyroid function and serum chemistries at baseline and prior to each dose; however, some experts have recommended a full endocrine panel—including cortisol, adrenocorticotrophic hormone (ACTH), free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH), testosterone (men only), follicle stimulating hormone (FSH; women only), luteinizing hormone (LH; women only), prolactin (women only), and a cosyntrophin stimulation test if available—to be done prior to initiation of ipilimumab therapy.[34] Dermatologic toxicity should be managed with a 4-week steroid taper starting from 1 mg/kg/day of prednisone for grade 3 or higher toxicity; ipilimumab should be stopped for grade 4 dermatologic toxicity.[34] Grade 2 neuropathy indicates that the dose of ipilimumab should be held, whereas grade 3–4 neurologic toxicity requires discontinuation of the ipilimumab and a steroid taper over at least 4 weeks.[34] Uveitis may be managed with topical steroids such as 1% prednisolone actetate suspension for grade 1–2 toxicity, but discontinuation of the ipilimumab and a steroid taper of at least 4 weeks is indicated for higher-grade toxicity.[34]

Because of the potential toxicity and the occasional rapid onset of serious immune-related adverse events, it is essential that the treating physician, nursing staff and other health care providers be familiar with the potential toxicities. It is also essential that the patient be educated about the toxicities and that they be instructed to contact their health care providers as soon as symptoms or signs of toxicity develop. In addition, it is the practice of our clinic to call the patient at least once a week during the treatment period to inquire about their condition. This is particularly important as the patient may not necessarily connect the symptoms to the treatment and therefore may seek care from other physicians who may not be familiar with the toxicity of ipilimumab.

Role in the management of metastatic malignant melanoma

Until recently, the standard treatment options for patients with metastatic malignant melanoma were very limited. No agent had been demonstrated to prolong survival. Only three agents—dacarbazine, hydroxyurea, and IL-2—were approved to treat metastatic disease. Other agents, particularly temozolomide and taxol plus carboplatin, were widely used but not approved for this indication. However, with the approval of ipilimumab and vemurafenib, the treatment landscape has changed. Now, in our practice all patients with melanoma are tested for the BRAF V600E mutation. Those who are in good clinical condition and have disease limited to lungs and lymph nodes or skin (M1a or M1b) are often offered high-dose IL-2. Those who are positive for the mutation and who have bulky or aggressive disease are treated with vemurafenib. Those whose disease is low-volume and more slow-growing are treated with ipilimumab. At present, we do not have predictive markers of response to ipilimumab, but this remains an area of intense interest and investigation. Both vemurafenib and ipilimumab can be used and have been shown to be effective in previously treated as well as untreated patients. Of course, since neither agent is generally curative there remains a leading role for experimental therapy, particularly with protocols that use these agents in combination with other new agents.

Prospects for Future Use

With the approval of ipilimumab for the treatment of metastatic disease, attention has turned to the possibility of its use in the adjuvant setting. Sarnaik et al performed a phase II trial of adjuvant ipilimumab after resection of Stage III and Stage IV melanoma in 75 patients.[35] Of these, 25 patients received 3 mg/kg ipilimumab every 6–8 weeks for one year, and 50 patients received 10 mg/kg on the same schedule. Subjects from both groups were eligible for additional maintenance therapy, and individuals positive for HLA-A*0201 also received a peptide vaccine. Median relapse-free and overall survival had not been reached at 29.5 months, as compared to historical reports of median relapse-free survival of 7–9 months

Table 1. Incidence of selected toxicity in clinical trials of ipilimumab.

Reference	n	Dermatologic	Gastrointestinal	Endocrine
Hodi et al[20]	9	7 (78%) grade I–II	1 (11%) grade III hepatitis	–
Phan et al[21]	14	1 (7%) grade I–II 3 (21%) grade III–IV	3 (21%) grade I–II colitis 2 (14%) grade III–IV colitis 1 (7%) grade III–IV hepatitis	1 (7%) grade III–IV hypophysitis
Attia et al[22]	56	4 (7%) grade III–IV	8 (14%) grade III–IV colitis 1 (2%) grade III–IV hepatitis	1 (2%) grade III–IV hypophysitis
Sanderson et al[23]	19	7 (37%) grade I–II	4 (21%) grade I–II colitis 3 (16%) grade III–IV colitis	–
Downey et al[24]	139	40 (29%) grade I–II 8 (6%) grade III–IV	4 (3%) grade I–II colitis 24 (17%) grade III–IV colitis 2 (1%) grade III–IV hepatitis	13 (9%) grade III–IV hypophysitis
Prieto et al[25]	177	10 (6%) grade III–IV	29 (16%) grade III–IV colitis 1 (0.5%) grade III–IV hepatitis	13 (7%) grade III–IV hypophysitis
Maker et al[26]	36	–	4 (11%) grade III–IV colitis	–
Weber et al[27]	88	2 (2%) grade III–IV	1 (1%) grade III–IV hepatitis 5 (6%) grade III–IV colitis	–
Hodi et al[28]	511	6 (1%) grade III–IV	24 (5%) grade III–IV colitis	4 (<1%) grade III–IV hypophysitis
Hersh et al[29]	74	19 (26%) rash	4 (5%) colitis	–
Robert et al[30]	247	3 (1%) grade III–IV	5 (2%) grade III–IV colitis 3 (1%) grade III–IV hepatitis	–

in this population. More than one-third of patients had significant immune-related adverse events, which were similar in nature to those reported in the studies in the metastatic population. There were no treatment-related deaths. Again, individuals without a relapse were more likely to experience an immune-related adverse event than those with a relapse (48% versus 24%, $P = 0.038$). Of note, individuals with a C-reactive protein greater than 2 were found to be less likely to experience relapse than those with a lower level of this protein. Overall survival and toxicity were not significantly different between those who received 3 mg/kg and those who were given 10 mg/kg, and use of the peptide vaccine also did not affect survival.

Further investigation of ipilimumab in the adjuvant setting is ongoing. The Eastern Oncology Cooperative Group is currently enrolling for a phase III study of interferon versus ipilimumab in patients with resected Stage III and IV disease. This protocol has recently been modified to contain three adjuvant treatment arms: interferon alpha 2b (induction with 20 MU/m^2/day IV on Monday-Friday every week for 4 weeks, followed by 10 MU/m^2/day SQ three times a week for 48 weeks); high-dose ipilimumab (induction with 10 mg/kg IV every 3 weeks for 4 doses, followed by 10 mg/kg IV every 12 weeks for a maximum of 4 doses for maintenance); and low-dose ipilimumab (induction with 3 mg/kg IV every 3 weeks for 4 doses, followed by 3 mg/kg every 12 weeks for a maximum of 4 doses for maintenance). A trial of adjuvant therapy with ipilimumab has been completed in Europe as well but has not yet been reported.

Another potential area under exploration is the use of ipilimumab in the setting of brain metastases. Classically, individuals with brain metastases are excluded from clinical trial participation due to their poor prognosis. However, retrospective subgroup analysis of 12 melanoma subjects with treated brain metastases who received ipilimumab showed that two achieved a partial response and an additional three had stable disease.[36] Median overall survival in this small group was 14 months and ranged to greater than 56 months. Two subjects had grade 3 or greater central nervous system adverse events, including cerebral edema and seizures. Another case series of 10 patients from Downey et al showed complete response in one patient and partial responses in two patients with brain metastases who received ipilimumab.[24]

The results of ipilimumab treatment in metastatic melanoma have led to a flurry of additional trials. Because of the delayed onset of action with ipilimumab, combination with chemotherapeutic agents that may have a more rapid effect is an

attractive option. Current combinations under study include ipilimumab with bevicizumab, paclitaxel/carboplatin, or vemurafenib. Adding ipilimumab to other biologic therapies is another area of investigation, and studies with GM-CSF, laboratory-altered T cells, TriMix-DC vaccine, IL-21, IL-2, and other biotherapies are also in the works. The use of ipilimumab in the neoadjuvant setting or in conjunction with other treatment modalities, such as radiation therapy and isolated limb infusion, has also been proposed.

In summary, ipilimumab is the first drug to demonstrate survival benefit in the setting of metastatic melanoma. Its pattern of response and adverse effect profile are unique relative to other treatments, but understanding of these differences allows for safe and effective management of patients under this therapy. Additional applications and fine-tuning of dosing and scheduling of this medication are currently under investigation.

Author Contributions

Conceived and designed the experiments: JMJ, EMH. Analysed the data: Not applicable. Wrote the first draft of the manuscript: JMJ. Contributed to the writing of the manuscript: JMJ, LDC, EMH. Agree with manuscript results and conclusions: JMJ, LDC, EMH. Jointly developed the structure and arguments for the paper: JMJ, EMH. Made critical revisions and approved final version: JMJ, EMH. All authors reviewed and approved of the final manuscript.

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Competing Interests

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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