Ipilimumab: an Anti-CTLA-4 Antibody for Metastatic Melanoma

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Running title: Ipilimumab for Metastatic Melanoma

Abstract

Ipilimumab (MDX-010, Yervoy ®), a fully human monoclonal antibody against Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), was recently approved by the U.S. Food and Drug Administration for the treatment of metastatic melanoma. In both early and late phase trials, Ipilimumab has demonstrated consistent activity against melanoma. For example, in a randomized phase III trial that enrolled patients with previously treated, metastatic disease, ipilimumab, with or without a peptide vaccine, improved overall survival (OS): median OS was 10.1 and 10.0 months in the ipilimumab and ipilimumab plus vaccine arms respectively, versus 6.4 months in the vaccine alone group. (hazard ratio 0.68, p ≤ 0.003) Serious (grade 3 - 5) immune related adverse events occurred in 10-15% of patients. Thus, while providing a clear survival benefit, ipilimumab administration requires careful patient monitoring and sometimes necessitates treatment with immune-suppressive therapy. Here, we review the mechanism of action, preclinical data and multiple clinical trials which led to the FDA’s approval of ipilimumab for metastatic melanoma.

Basic Science and Preclinical Development

T cells, both CD4 (helper) and CD8 (cytotoxic), contribute to the adaptive immune response against pathogens and tumors, and activation and recruitment of specific T cells is a complex process. For a T cell to become fully activated (and subsequently proliferate and mediate effector function) at least two receptor / ligand interactions are required. The first of these occurs when the T cell’s unique receptor recognizes its cognate ligand, a short peptide presented in the context of a major histocompatibility complex (MHC) molecule. This interaction is exquisitely specific, and if a good fit occurs, T cell activation is initiated. However, full activation of a CD4 or CD8 T cell requires a second signal transmitted by co-stimulatory molecules present on the same antigen-presenting cell that expresses the peptide / MHC. This second signal is transmitted from co-stimulatory molecules (B7-1 and/or B7-2) to a receptor on T cells known as CD28. Only when both signals are received and integrated does a specific T cell proliferate, acquire effector function, and migrate to sites of antigen expression.
CTLA-4 was first cloned in 1987. Subsequent studies showed this molecule to be a homolog of CD28, suggesting that CTLA-4 might serve, along with CD28, as a co-stimulatory molecule. However, several other studies provided opposing results, and for some time it was not clear whether CTLA-4 transmitted a stimulatory or inhibitory signal to T cells. The generation of mice lacking CTLA-4 solved this conundrum; knockout mice developed a progressive accumulation of activated T cells, and died approximately 3-4 weeks after birth of lymphoproliferative disease. These and other results suggested that blockade of CTLA-4 using a monoclonal antibody could augment an adaptive immune response to an infectious agent or an evolving tumor. The seminal study in this area showed that CTLA-4 blockade could attenuate the growth of several implanted murine tumors, consistent with the model shown in Figure 1. On an immunological basis, this model of T cell activation, and of CTLA-4’s function, represents a significant simplification; a more complete description can be found in several relevant reviews.

Early Clinical Development

In order to translate these findings into a clinical setting, the Medarex Corporation generated a series of monoclonal antibodies using a unique transgenic mouse (HuMAb), in which the endogenous murine immunoglobulin genes have been knocked out and replaced with human loci. Immunization of these mice results in fully human monoclonal antibodies devoid of murine sequences that can lead to infusion reactions. The clinical development of MDX-010 was recently reviewed; only several selected trials most relevant to the current FDA approval in melanoma will be outlined here.

Initial phase I studies included both single and repetitive dosing regimens and demonstrated safety and an intriguing suggestion of efficacy. Subsequent trials at the National Cancer Institute administered ipilimumab, first at 3 mg/kg along with a gp100 multi-peptide vaccine, and then at doses between 1 and 3 mg/kg. Investigators observed sustained responses (>2 years) in several patients. Immune related adverse events were also seen and seemed to correlate with clinical response. An important phase I/II study to determine the pharmacokinetic profile of MDX-010 was conducted in patients with metastatic melanoma. A secondary endpoint of this study (MDX-015) was clinical activity, and the study included both single and multiple-dosing regimens. Escalating single doses of up to 20 mg/kg were examined, as well as every 3 week dosing at 10 mg/kg. Although the study was not adequately powered to compare regimens, the group of patients receiving 10 mg/kg every 3 weeks had the highest disease control rate. This study also confirmed the toxicity profile noted in earlier trials.
with 19% of patients demonstrating grade 3 or 4 adverse events. Many of these events were immune-related (irAEs), predominantly colitis, rash, and liver function abnormalities. In this study, irAEs appeared to be somewhat correlated with response, and were observed in 13 of 14 patients with stable disease, as well as in all 4 of the patients with an objective response.

Based partially on these findings, a randomized, multi-institution, double-blind dose-ranging study was performed.\(^{(10)}\) This study (CA184-022) enrolled 217 patients with previously treated metastatic melanoma, randomizing them to doses of 0.3, 3, or 10 mg/kg MDX-010, administered every 3 weeks. Patients without progressive disease at week 24 entered into a maintenance phase in which MDX-010 continued to be administered every 12 weeks. The primary endpoint of this study was efficacy. Best Overall Response Rate (BORR) was 0%, 4.2% and 11.1% in the 0.3 mg/kg, 3 mg/kg and 10 mg/kg groups respectively. Survival data were encouraging, with 30% of patients in the 10 mg/kg cohort alive at 2 years, as opposed to 18% in the 0.3 mg/kg cohort. IrAEs were again noted in 0, 5 and 18% of patients in the three dose cohorts. This study supported the efficacy of MDX-010, and reinforced the every 3 week dosing regimen that was subsequently adapted for phase III investigation.

In terms of combination studies, the safety and efficacy of ipilimumab administered with dacarbazine was first investigated in a phase II trial that randomized 72 chemotherapy-naïve patients to receive ipilimumab at 3 mg/kg every 4 weeks for four doses either alone or with dacarbazine.\(^{(11)}\) The primary endpoint, 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, i.e. there was a trend toward an increased response rate in the combination treatment group.

**Late Stage Development**

A pivotal phase III trial of MDX-010 was reported positive in 2010.\(^{(12)}\) This study randomized 676 HLA-A*0201-positive, previously treated melanoma patients 1:3:1 to ipilimumab alone, ipilimumab plus a gp100 vaccine, or gp100 vaccine alone. Mirroring the phase II schedule, ipilimumab was administered every 3 weeks for up to four doses at 3 mg/kg. The primary endpoint of this study, OS, was significantly better in the groups receiving ipilimumab than in the group receiving gp100 vaccine alone: median OS was 10.1 and 10.0 months in the ipilimumab and ipilimumab plus vaccine arms respectively, versus 6.4 months in the vaccine alone group. (hazard ratio 0.68, p≤0.003) BORR was 10.9% in the ipilimumab alone cohort, as compared with 5.7% in the ipilimumab plus vaccine group, and 1.5% for vaccine alone. The longitudinal survival benefit suggested by phase II studies was confirmed, with 22% of ipilimumab alone
patients alive at 24 months, versus 24% for ipilimumab plus vaccine and 14% for vaccine alone. The rate of grade 3 / 4 irAEs was also comparable to previous studies: 10-15% in the ipilimumab groups, as compared to 3% in the gp100 group. This study was especially significant in that it was the first randomized study ever to show a survival benefit in patients with metastatic melanoma.

Similarly positive results were seen when ipilimumab was administered as first-line therapy.(13) In a randomized phase III study, 502 patients with previously untreated metastatic melanoma were randomized 1:1 to ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m²) or dacarbazine plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22. Patients with an objective response or stable disease and no dose-limiting adverse effects received maintenance ipilimumab or placebo every 12 weeks thereafter. Overall survival, the primary endpoint of the trial, in the ipilimumab-dacarbazine group was 47%, as compared to 36% in the dacarbazine alone group. At three years, relative survival rates were 21 and 12% respectively (hazard ratio for death 0.72, p< 0.001). Grade 3 / 4 adverse events were noted more frequently than in trials not involving chemotherapy (56% ipilimumab plus dacarbazine, 28% dacarbazine alone). Interestingly, the pattern of irAEs was different, with more frequent hepatotoxicity (approximately 20%) and less frequent colitis (2%). Overall, this study was important in bringing ipilimumab into the first line setting for metastatic melanoma, as well as in showing that the patterns of toxicity of this agent might vary depending on the context in which it is administered. It should be noted that, although this study provided information about safety and tolerability of ipilimumab dosed at 10 mg/kg, the FDA approved the drug at a dosage of 3 mg/kg.

Integration of Ipilimumab into the Melanoma Treatment Paradigm

Currently, therapeutic options for patients with unresectable AJCC stage III or stage IV melanoma are few. Chemotherapy regimens include paclitaxel alone or with a platinum agent, temozolomide, or dacarbazine. Immune therapies include dacarbazine-or temozolomide-based biochemotherapy and high-dose interleukin-2 (IL-2), which results in clinical responses in approximately 15-20% of patients, with about one-third of those experiencing durable, complete responses.(14, 15) Administration of IL-2, however, is limited to patients with an excellent performance status who have no evidence of cardiac dysfunction or active central nervous system metastases. Given these constraints, the addition of ipilimumab to the therapeutic armamentarium is particularly welcome in that it expands the patient population who can receive immunotherapy. Indeed, the National Comprehensive Cancer Network (NCCN) has added ipilimumab as a category 1 recommendation in its guidelines of systemic therapy options for advanced or metastatic melanoma.
In clinical practice, the order with which a patient receives different therapies may become relevant, particularly if irAEs are encountered. Although high-dose IL-2 administration may be complicated by side effects around the time of drug delivery, those side effects generally resolve completely within several weeks. The same is not true with certain of the irAEs seen with ipilimumab. Some patients who develop ipilimumab-related pan-hypopituitarism, for example, will require long-term replacement with multiple steroid hormones, potentially disqualifying them from receiving IL-2. It may make sense, then, in patients who could tolerate either IL-2 or ipilimumab as initial therapy, to consider beginning treatment with IL-2.

The irAEs associated with ipilimumab treatment (Table 1) require careful patient selection as well as thorough and frequent patient monitoring. The NCCN guidelines note that “Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders”. Bristol-Myers Squibb, in collaboration with the FDA, has developed a Risk Evaluation and Mitigation Strategy (REMS) program, designed to facilitate early identification and appropriate management of patients with moderate or severe immune related adverse effects. In addition, comprehensive toxicity management algorithms have been developed, and are included in the ipilimumab package insert. It is important to note that the vast majority of these irAEs are reversible with early intervention. Moreover, it appears that the majority of anti-tumor responses persist despite corticosteroid therapy.

A further unresolved question involves the concept of ipilimumab maintenance therapy. It should be noted that in the ipilimumab + dacarbazine trial, patients who had stable disease or an objective response and no dose limiting toxic effects after receiving four doses of ipilimumab (10mg/kg) at weeks 1, 4, 7 and 10 received ipilimumab or placebo every 12 weeks thereafter as maintenance therapy. This was administered until disease progression, development of toxicities, or conclusion of the study. This design was similar to that used in the aforementioned phase II trial CA184-022. Likewise, Hodi et al offered additional courses of a participant’s assigned treatment (reinduction) to patients with stable disease for 3 months’ duration after week 12 or a confirmed partial or complete response. Ipilimumab in that study was dosed at 3mg/kg. FDA approval for ipilimumab does not include maintenance dosing. Although maintenance or reinduction therapy has been included in the above studies and in several non-melanoma trials (e.g. CA184-043 and -095 for prostate cancer), the role of either is still unclear.

Future Directions
In addition to its documented activity in metastatic melanoma, ipilimumab has shown early evidence of clinical activity in several additional tumor types, including renal cell, lung and prostate cancers. Two ongoing randomized phase III studies are evaluating ipilimumab in patients with metastatic castrate resistant prostate cancer (mCRPC) either before (CA184-095) or after (CA184-043) administration of docetaxel. In addition, phase II studies combining ipilimumab with standard chemotherapy or other immunotherapy modalities are ongoing in a number of tumor types.

Combining ipilimumab with targeted therapy, such as the BRAF inhibitor vemurafenib, will almost certainly become an area of active investigation in the near future. A recent report by Chapman et al showed improved survival for stage IV melanoma patients treated with vemurafenib compared to standard chemotherapy with dacarbazine.(17) At six months, OS was 84% in the vemurafenib group and 64% in the dacarbazine group. Vemurafenib has a remarkably high response rate (48% for vemurafenib versus 5% for dacarbazine) in patients with V600E mutated melanoma and, thus, may be well-suited to decrease or mitigate a tolerogenic tumor burden. Additionally, in vitro data suggesting that vemurafenib does not lead to decreased adaptive immunity(18) lends further support to the upcoming trial of vemurafenib plus ipilimumab for patients with BRAF mutation-positive melanoma.

Another interesting issue for the future development of ipilimumab involves its combination with cancer vaccines. Indeed, many of the preclinical studies of this agent showed remarkable enhancement of activity when combined with anti-cancer vaccines, particularly with cell-based vaccines secreting GM-CSF. Some of the earliest published data in this regard showed that the combination of anti-CTLA-4 plus GVAX was able to cure established, poorly immunogenic B16 melanomas – a result not achievable with either agent alone.(19) However, these results were not reflected in the pivotal phase III trial discussed above.(12) This apparent discrepancy most likely stems from the nature of the gp100 vaccine employed: two epitopes administered subcutaneously in incomplete Freund’s adjuvant. Comparative data supporting the clinical efficacy of this particular gp100 vaccine were not striking; in a randomized phase III trial in combination with IL-2 the vaccine showed a small but statistically significant improvement in progression free survival (2.2 versus 1.6 months), but no significant improvement in overall survival.(20) It is critically important to note that negative data derived from one particular vaccine should not be misinterpreted as providing evidence that other ipilimumab / vaccine combinations could not confer additive or synergistic efficacy.

With BORRs in the 10-15% range in most published studies, ipilimumab is not effective in the vast majority of patients treated. In addition, the significant rate of immune-related and other adverse events compels the development and prospective validation of a predictive biomarker, allowing pre-treatment selection of patients likely to benefit from treatment. Unfortunately, no such marker appears imminent, despite the
approximately 3500 patients treated with this agent to date. Some insight in this area was provided by the recent observation that patients with an absolute lymphocyte count (ALC) ≥1000/microL after two ipilimumab treatments had a significantly improved clinical benefit rate and median OS compared with patients whose ALC was <1000/microL. Future studies, perhaps involving paired tumor biopsy analysis or serum antibody profiling, are clearly needed in order to identify those patients whose disease is most likely to respond to ipilimumab.

Conclusions

The development and FDA approval of ipilimumab represents a major step forward in cancer immunotherapy. While multiple phase III trials confirm a survival benefit for this agent, perhaps the most compelling data are those showing a small but significant proportion of patients with metastatic melanoma surviving 2 and even 3 years from the time of treatment initiation. Given the significant rate of irAEs, clinical application of ipilimumab is challenging and requires careful monitoring and prompt attention to potential adverse events. Future clinical research will likely address the development and verification of predictive biomarkers, permitting the identification of a subgroup of patients most likely to derive clinical benefit. Perhaps more exciting, though, is the potential for additive and/or synergistic efficacy, achieved by combining ipilimumab with either targeted agents such as vemurafenib, with radiation therapy, or perhaps with cancer vaccines that optimally prime a tumor-specific T cell response.
Table 1: Presentation of Immune Related Adverse Events

<table>
<thead>
<tr>
<th>AREA AFFECTED</th>
<th>SYMPTOMS AT PRESENTATION</th>
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<tbody>
<tr>
<td>Colon</td>
<td>Diarrhea, abdominal pain, blood in stools, increased frequency of stools, nausea, vomiting, or constipation, with or without fever. Complications may include intense bleeding, bowel perforations, intense diarrhea or need for colectomy.</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash, usually maculopapular and often accompanied by significant, generalized pruritus</td>
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<tr>
<td>Liver</td>
<td>Right upper quadrant abdominal pain, nausea, vomiting, elevated AST/ALT or hyperbilirubinemia in the absence of clinical symptoms</td>
</tr>
<tr>
<td>Neuro</td>
<td>Muscle weakness or sensory neuropathies, Guillain-Barré Syndrome</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Nonspecific symptoms including headache, visual-field defects, behavioral changes, decreased libido, fatigue, new onset of atrial fibrillation, weakness, asthenia, anorexia, nausea and vomiting, lethargy, impotence, amenorrhea, fever, coma, hypotension, hypoglycemia, hyponatremia, and eosinophilia.</td>
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Figure Legend:

Figure 1:

A. Melanoma cells express proteins such as gp100, MART-1, tyrosinase (and others) which may be processed and presented by antigen-presenting cells. T cell recognition of peptide antigens derived from these proteins can potentially drive an anti-tumor immune response. For such tumor-directed T cells to become activated, two signals are required. The first signal (Signal 1) occurs when the peptide antigen is recognized by the T cell receptor on antigen-specific T cells. This recognition is exquisitely specific. However, for full T cell activation, proliferation, and effector function a second signal (Signal 2) is needed. This signal is typically mediated by the interaction between co-stimulatory molecules like B7.1 and B7.2 on antigen presenting cells and CD28 on T cells. In reality, the situation is more complex, and Signal-2 is derived from the integration of several positive and negative events.

B. Under certain conditions, T cells up-regulate the cell surface molecule CTLA-4, which binds to B7.1 and 2 with greater affinity than CD28 does. This series of events effectively “hijacks” Signal 2, resulting in a situation in which specific T cells cannot be fully activated.

C. Ipilimumab (and other anti-CTLA-4 antibodies) bind to CTLA-4 on the cell surface, effectively blocking the interaction between CTLA-4 and B7.1 / B7.2. This leads to interruption of the negative signal mediated by CTLA-4, to the resumption of Signal 2, and to a relative restoration of T cell activation.

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Conflicts of Interest:

EJL – none. CGD has served as a paid consultant to Bristol Myers Squibb, and, through Johns Hopkins University, has licensed patents to that entity.

References


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