Title: The Antitumor Immunity of Ipilimumab: (T cell) Memories to Last a Lifetime?

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Summary:

Ipilimumab has demonstrated an overall survival benefit in two randomized phase III studies. A minority of patients achieve long-term disease control, highlighting the potential of this immunotherapeutic approach. Ongoing efforts continue to characterize these patients’ unique clinical courses and correlate their responses with underlying mechanisms of antitumor immunity.

Article Body:

In this issue of Clinical Cancer Research, Prieto et al. report long-term follow-up data for 177 patients treated with ipilimumab on some of the earliest trials in its development.[1] Their results underscore the remarkable, durable benefits a subset of melanoma patients achieve from ipilimumab, hint at the promise of combining ipilimumab with interleukin-2 (IL-2), and raise the provocative question of whether, in some patients, metastatic melanoma can be cured.

Ipilimumab (Yervoy™, Bristol-Myers Squibb, Princeton, NJ) is a fully human monoclonal antibody that blocks cytotoxic T lymphocyte antigen 4 (CTLA-4). Following T cell activation, CTLA-4 is recruited to the plasma membrane where it functions in an auto-regulatory role, attenuating T cell activation and proliferation through several mechanisms.[2] Although CTLA-4 plays an essential role in maintaining immunologic tolerance, in the setting of malignancy, CTLA-4 may restrain effective antitumor immunity. As shown in figure 1, antibodies that block CTLA-4, such as ipilimumab, release T cells from this immunologic checkpoint and may enable them to exert their full antitumor effect.

Ipilimumab has been shown to confer an overall survival benefit in two phase III trials.[3, 4] The objective response (OR) rate is modest, around 10%,[3] but a portion of patients enjoy durable disease control. Though distinct in mechanism of action and side effect profile, the pattern of durable responses induced by ipilimumab is similar to the pattern described for a subset of patients who received IL-2.[5]
Prieto et al. have assembled the largest reported long-term clinical experience with ipilimumab. By providing updated data from three previously published studies: ipilimumab with gp100 vaccination (protocol 1);[6] ipilimumab with concomitant IL-2 (protocol 2);[7] and ipilimumab via a strategy of intra-patient dose escalation (+/- gp100) until response or intolerable side effects (protocol 3)[8], the authors evaluate a total of 177 patients treated with ipilimumab with a median follow-up of 92, 84, and 71 months, respectively. The clinical and correlative implications of the data presented are profound and stress several important themes that have arisen during ipilimumab’s development, especially highlighting the exceptional durability of responses.

The authors offer robust data to support the finding that patients who achieve a response after treatment with ipilimumab are likely to be alive many years later. In their population, a total of 15 patients ultimately achieved a complete response (CR). The durability of responses among patients who attain a CR is remarkable; all except one are ongoing with the longest lasting 99+ months (median 83 months). Considering these patients “cured” is tempting but should be approached cautiously as one patient did relapse after a CR lasting 42 months. How this patient’s tumor escaped after induction of a seemingly effective antitumor immune response underscores the complex relationship between tumor and host immunity. Did the patient’s immune response select for tumor cells with reduced immunogenicity? Did the tumor microenvironment shift in the favor of immune suppression? Do patients ever achieve tumor eradication or is an ongoing memory response required to hold microscopic disease in check? Cases of durable partial responses (PR) may support the notion that an ongoing active immune response continues to control disease for years. In long-term follow up, nine PRs are still alive years after initiating treatment, with three patients maintaining a stable PR without further treatment and the remainder benefiting from subsequent treatments.
Delayed response kinetics are a hallmark of ipilimumab and Prieto et al. provide a more robust description of this phenomenon than has been previously available. Among the 15 patients who ultimately achieved a CR, an average 30 months was required to reach this endpoint. In one case, a patient achieved a CR 70 months, nearly 6 years, after starting treatment. These observations emphasize the variability of response patterns and the wide window of time for ipilimumab to affect tumor burden. These responses may be best evaluated by the use immune-related response criteria (irRC), an adaptation of the World Health Organization criteria, which were designed to accommodate the delayed kinetics and variability of responses to ipilimumab.[9]

One important consideration in interpreting these findings is the fact that many of these CRs received more than 4 doses of ipilimumab (range 3-11), the dosing currently approved by the FDA for commercial use. The influence of this additional ipilimumab on the accomplishment of a CR or the likelihood of a delayed response requires further study.

Unfortunately only a subset of patients experience long-term disease control from ipilimumab, and identifying which patients are likely to benefit has been an ongoing goal. The absolute lymphocyte count (ALC) has previously been reported to associate with benefit from ipilimumab treatment,[10] and Prieto et al.’s results are consistent with this observation. They found that an increase in ALC after the first ipilimumab dose was associated with response.[1] HLA status did not appear to distinguish patients who benefit as there was no difference in the response rate to ipilimumab for the HLA-A*201-positive patients compared to HLA-A*201-negative patients. This is consistent with our retrospective analysis and in line with ipilimumab’s proposed HLA-independent mechanism of action.[11]

While ipilimumab confers impressively durable disease control for those who respond, a majority of patients do not respond. Ongoing efforts to increase the number of patients who benefit from ipilimumab are focused on combining ipilimumab with chemotherapy, targeted therapy, or other
immunotherapies. Prieto et al. report on long-term follow up of patients treated with ipilimumab in combination with IL-2. The high OR rate of 25% (CR 17%) of this combination approach is intriguing but may have been influenced by the selected patient population. Ultimately, measuring the benefit of this combination against the toxicities of receiving both agents requires a randomized trial, as the authors suggest. Notably, the typical immune-related adverse events (irAEs) observed with ipilimumab do not appear more common in this combination, although in this study most patients received lower doses of ipilimumab (< 3 mg/kg). Patients treated in protocols 1 and 3 (without IL-2) who were previously treated with IL-2 had similar response rates to ipilimumab as patients who had not previously received IL-2. This implies that tumors resistant to IL-2 can retain sensitivity to ipilimumab and may suggest a complementary mechanism of action.

Four patients who progressed on ipilimumab achieved CRs after adoptive cell transfer (ACT).[12] The possible benefit these patients received from prior ipilimumab on the subsequent success of ACT is unclear. Nonetheless, since the persistence of infused cells is important in ACT and ipilimumab may have a role in potentiating the longevity of these cells, additional research will continue to evaluate this combination approach. One study is already underway (NCT00871481). Lastly, the authors observe no significant benefit in combining ipilimumab with a vaccine comprised of two gp100 peptides emulsified in Montanide ISA-51, similar to results from the separate, large randomized phase III trial.[3]

Ipilimumab has set a new standard of care for patients with melanoma. This important long-term analysis of patients treated on some of the earliest trials in ipilimumab’s development demonstrates the true promise of ipilimumab, in its ability to engender long-lasting antitumor responses. For a subset of patients, ipilimumab appears tantalizingly close to a cure. Understanding the immunologic features that identify patients who benefit and finding complementary therapies that
enhance the activity of ipilimumab are important next steps to expanding the number of patients who benefit from this promising therapy.

**Figure Legend:**

T cell activation requires two signals as shown by arrow in panel A. One signal involves the T cell receptor (TCR) recognizing a peptide antigen bound to a major histocompatibility complex (MHC) on the surface of an antigen presenting cell (APC). The second signal involves co-stimulation through the interaction of CD28 on T cells with B7 (B7-1/CD80, B7-2/CD86) molecules on APCs. Upon T cell activation, panel B shows that cytotoxic T lymphocyte antigen 4 (CTLA-4) is recruited to the plasma membrane and functions in an inhibitory role, binding with higher affinity than CD28 to B7. Through several mechanisms, this binding results in inhibition of T cell activation and function. Panel C shows that ipilimumab binds to CTLA-4 and blocks its inhibitory role. By disabling the inhibitory functions of CTLA-4, ipilimumab enhances T cell activity.


A T cell
+ +

TCR

APC

B T cell
+ +

CD28

CTLA-4

T cell inhibition

Peptide/MHC

B7

Iplimumab

T cell activation

C T cell
+ +

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