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Checkpoint Modulation in Melanoma: An Update on Ipilimumab and Future Directions

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Abstract

Ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 antibody, was the first therapy demonstrated to improve overall survival in melanoma. Since ipilimumab's approval by the FDA in 2011, a wealth of data have amassed, helping clinicians to optimize its use. We have learned how to mitigate the adverse effects of ipilimumab, identified its effects in melanoma subpopulations such as those with brain metastases, uveal melanoma, and mucosal melanoma, discovered potential biomarkers of activity, and investigated its use in combination with other therapeutic modalities. These discoveries have paved the way for rapid development of second-generation immunomodulatory antibodies such as inhibitors of the programmed cell death 1 receptor axis. These new agents hold promise as monotherapy, but perhaps the greatest allure lies in the possibility of combining these agents in synergistic multidrug regimens.

Keywords

Ipilimumab; Checkpoint; Immunotherapy; Melanoma; Anti-programmed cell death 1

Introduction

Emerging novel immunotherapies have dramatically reshaped the treatment landscape for metastatic melanoma. Before 2010, the FDA-approved standards of care were dacarbazine and high-dose interleukin-2, neither of which had been shown to improve overall survival [1, 2]. Since then, two independent phase III trials have reported an improvement in overall survival with ipilimumab (Yervoy™, Bristol-Myers Squibb, New York, NY, USA), a fully human monoclonal antibody inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4) [3, 4]. Following these positive phase III studies, ipilimumab became a new standard of care, and

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Conflict of Interest

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was soon joined by vemurafenib, a selective B-Raf inhibitor that improves overall survival among patients with the activating V600E *BRAF* mutation [5].

Since ipilimumab's FDA approval, it has become the prototypical immunomodulatory antibody, with which a wealth of clinical data have emerged. However, the past year alone has ushered in multiple second-generation immunomodulatory antibodies. Recently, both programmed cell death 1 (PD-1) and PD-1 ligand 1 (PD-L1) inhibitors have entered the spotlight, with recent phase I clinical trials reporting promising objective response rates with little toxicity [6, 7]. Trailing just behind, numerous other checkpoint agents are being explored in phase I clinical trials with exciting potential. This review will summarize the important updates in the treatment of melanoma with ipilimumab, describe the recent data published on PD-1 and PD-L1 inhibition, and finally, introduce future studies in checkpoint modulation.

Lessons Learned from Ipilimumab

Updated Ipilimumab Experience: Durability and Safety

The phase III registration trial compared ipilimumab at a dose of 3 mg/kg with or without the gp100 peptide vaccine versus gp100 peptide vaccine alone in patients with unresectable stage III or stage IV melanoma [3]. Median overall survival in the ipilimumab and ipilimumab plus gp100 cohorts was 10.1 and 10.0 months, respectively, compared with 6.4 months for the gp100 control arm (hazard ratio 0.68, $p < 0.001$). The subsequent first-line trial comparing dacarbazine plus placebo with dacarbazine plus ipilimumab at a dose of 10 mg/kg reported overall survival of 9.1 months for dacarbazine alone versus 11.2 months in the combination arm (hazard ratio 0.72, $p < 0.001$) [4].

The Kaplan–Meier survival curves in these trials illustrate several important points about ipilimumab therapy. First, the survival curves diverged after approximately 4 months. This suggests the benefit of ipilimumab can take some time to develop, and this differs from the survival curves seen in targeted therapy, where an early survival difference has been observed [5]. The curves also reached a plateau, indicating that a subset of patients experience long-term survival, observations underscored by the differences in overall survival at 1 year and 2 years after initiation of treatment.

In addition to improving overall survival, follow-up of these trials has also demonstrated preservation of quality of life while the patient is receiving treatment. Among patients treated in the registration trial, health-related quality of life was assessed at the baseline and at 12 weeks using the previously validated QLQ-C30 questionnaire [8]. With use of this measure, quality of life was not adversely affected by treatment with ipilimumab [9]. Thus, despite the low response rates, ipilimumab stands out as an effective treatment, improving overall survival and producing durable responses, with preservation of quality of life while the patient is receiving treatment.

Although long-term data from the ipilimumab registration studies continue to be analyzed, perhaps the longest-term follow-up data of ipilimumab's effects are from an analysis of 177 patients treated in early studies of ipilimumab at the National Cancer Institute [10]. Median follow-up in these patients was 92, 84, and 71 months across the three early protocols reported, two evaluating ipilimumab in conjunction with gp100, and another evaluating ipilimumab with interleukin-2 [11–13]. A total of 15 patients experienced complete responses, with 14 of 15 patients experiencing durable complete responses that were ongoing after 54 to 99 months. Some patients who initially achieved a partial response ultimately went on to achieve a complete response. This reverberates the original message

that, indeed, a proportion of patients achieve durable disease control, and that patients can experience benefit that may not be evident on first radiographic evaluation [14].

Dosing and Sequencing of Therapy

A randomized phase II study evaluated the influence of ipilimumab dose on response rate [15]. In that study, the best overall response rate (ORR) was 11.1% in the 10 mg/kg arm, versus 4.2% in the 3 mg/kg arm and 0% in the 0.3 mg/kg arm ($p = 0.0015$). However, the incidence of immune-related adverse events was also higher in the 10 mg/kg group, with 27% versus 10% of patients requiring discontinuation of treatment in the 10 mg/kg and 3 mg/kg arms, respectively. To definitively determine the optimal dose, a phase III randomized trial comparing the two doses (10 mg/kg versus 3 mg/kg) with an overall survival end point is awaiting interim analysis (NCT01515189). The benefit of maintenance ipilimumab administered every 3 months is unknown; however, some limited data suggest that reinduction therapy with four additional doses of ipilimumab administered every 3 weeks is active in patients who progressed after initial response or initial disease stability. In the registration trial, six of 31 reinduced patients (19%) achieved an objective response, with an additional 15 patients (48%) achieving stable disease [3, 16].

With the approval of both ipilimumab and vemurafenib and no head-to-head randomized comparisons of the two drugs, the optimal sequencing is still an unanswered question. One retrospective analysis suggested inferior overall survival when vemurafenib was administered prior to immunotherapy [17]. However, it is our practice to treat *BRAF*-mutant patients with vemurafenib first when they are symptomatic or have high tumor burden at the baseline, given the greater likelihood of a rapid response with vemurafenib [18]. Additionally, a vemurafenib “induction” strategy is being evaluated for safety in a single-arm phase II trial: patients will receive vemurafenib (960mg per os twice daily) for 6 weeks followed by ipilimumab (four doses of 10 mg/kg), followed by vemurafenib at first progression (NCT01673854).

Ipilimumab and Targeted Therapy: Bevacizumab and Vemurafenib

Preclinical studies indicate that B-Raf inhibitors can increase melanoma antigen expression, decrease secretion of immunosuppressive cytokines, and induce T-cell infiltration of tumor sites while preserving T-cell function [19–21]. Additionally, the vascular endothelial growth factor inhibitor bevacizumab increases dendritic cell maturation, primes T cells, and inhibits maturation of myeloid-derived suppressor cells (MDSCs) [22, 23]. These agents, in combination with checkpoint agents, could enhance immune clearance of tumor. Bevacizumab combined with ipilimumab is currently being evaluated in a phase I trial (NCT00790010). Unfortunately the vemurafenib combined with ipilimumab phase I/II study was stopped early secondary to hepatic toxicity. [24]. Skin reactions were additionally seen in this concurrent regimen which resembled skin toxicity seen when patients were treated with vemurafenib soon after completing ipilimumab therapy [25]. It is likely that scheduling of vemurafenib and ipilimumab will be important to their overlapping toxicity profile. A strategy of vemurafenib “induction” followed by ipilimumab is being prospectively evaluated (NCT001673854).

Ipilimumab and Central Nervous System Metastases

Central nervous system (CNS) metastases occur in more than 50% of patients with advanced metastatic melanoma, and the median overall survival has been reported as 4.4 months [26, 27]. A phase II open-label trial of ipilimumab at a dose of 10 mg/kg in patients with CNS metastases served to determine whether the drug would be effective in this scenario [28]. Two parallel cohorts—neurologically asymptomatic patients not requiring corticosteroids and neurologically symptomatic patients requiring steroids—received induction therapy

followed by maintenance infusions every 3 months if clinical benefit was achieved. CNS and non-CNS responses were evaluated by both modified World Health Organization (mWHO) criteria and immune-related response criteria (irRC). The primary end point was disease control at week 12 determined by mWHO criteria (partial response, complete response, and stable disease). The study reported 18% control in asymptomatic patients versus 5% control in patients requiring steroids. Disease control rates within the CNS and outside the CNS were concordant. It is most likely that the reduced response rate and overall survival of the corticosteroid cohort was due to the overall poorer health of this study cohort. A possible detrimental effect of steroids blunting the immune response to ipilimumab, however, could also be involved. On the basis of these data, ipilimumab is a reasonable consideration for treatment of asymptomatic CNS lesions; however, more data are required to validate this approach for treatment of symptomatic lesions.

Ipilimumab and Cytotoxic Chemotherapy

Although cytotoxic chemotherapy may induce lymphopenia and immune suppression, it may also stimulate the immune system by a variety of mechanisms, such as depleting the levels of MDSCs, inducing tumor antigen release, and enhancing T-cell function [29–31]. Therefore, combination regimens with chemotherapy are actively being investigated (Table 1). The initial combination trials included a phase II study showing a trend of increased disease control with ipilimumab plus dacarbazine versus ipilimumab alone [32], and a phase III study demonstrating improved survival of patients receiving ipilimumab plus dacarbazine compared with patients receiving dacarbazine alone [4]. More recently, the Italian phase II NIBIT-M1 trial was conducted that combined ipilimumab at a dose of 10 mg/kg with fotemustine, an alkylating agent that crosses the blood–brain barrier and may prolong the time to progression of CNS metastases [33, 34]. The results were encouraging, with a favorable objective response rate compared with historical rates from the ipilimumab registration trials (29% determined by irRC, compared with 11% [3] and 15% [4] determined by mWHO criteria). Twenty patients with asymptomatic brain metastases were treated, with nine of the 20 patients (45%) experiencing an objective response and ten of the 20 patients (50%) achieving disease control. Similarly, temozolomide was tested in combination with ipilimumab at a dose of 10 mg/kg. An interim analysis demonstrated a best ORR of 28.1% as determined by irRC, with tolerable toxicity and evidence of activity in CNS metastases [35, 36].

Ipilimumab and Radiation: The Abscopal Effect

The abscopal effect describes the phenomenon of tumor regression at sites distant from the primary site of radiotherapy. This concept was demonstrated in a melanoma case report published in 1975 [37] and rests on the theory that radiation induces antigen and cytokine release, which subsequently potentiates a systemic immune response to the tumor. In the past year, two case studies have provided additional anecdotal evidence of the abscopal effect, along with associated immunologic correlates. In the first case, a patient with unresectable scalp melanoma and in-transit lesions developed complete response of both irradiated and nonirradiated lesions following external beam radiotherapy [38]. Later, after developing metastases to the skin and brain, he received concurrent ipilimumab and stereotactic brain radiotherapy, which resulted in a complete resolution of skin lesions. In the second case, a female with metastatic disease initially progressed while receiving ipilimumab with worsening disease in the spleen, soft tissue, and lymph nodes. After palliative radiotherapy for the soft tissue lesion, she later experienced disease regression within the irradiated field but more impressively also in areas outside the irradiated field, including the spleen and lymph nodes [39].

In both of these cases, antibody responses to melanoma antigens were evaluated by enzyme-linked immunosorbant assay. The scalp melanoma patient exhibited preexisting antibodies against melanoma antigen A3 (MAGEA3), which increased in titer following ipilimumab therapy with radiotherapy. Following ipilimumab therapy, the patient mounted a new response to PAS domain containing 1 (PASD1), another cancer antigen [38]. In the second patient, a serologic analysis of over 9,000 human antigens revealed ten antigenic targets that exhibited greater than fivefold increase in reactivity following radiotherapy. Additionally, the immunosuppressive MDSC population decreased after radiotherapy.

Although these cases are anecdotally interesting, prospective evaluation is required to fully evaluate the possibility of synergy between radiotherapy and immunotherapy as suggested by these case reports, preclinical models, and the results of a phase I study [15, 40, 41]. Since the dose of radiotherapy likely has immunologic consequences that may be important to consider in combination with immunotherapy, we will soon initiate a randomized, phase II study to evaluate whether high dose per fraction radiotherapy is more effective than conventionally fractionated radiotherapy. Additional prospective trials of the combination of ipilimumab and radiotherapy are ongoing (Table 1).

Ipilimumab and Uveal Melanoma

Ipilimumab has recently been evaluated as a treatment for uveal melanoma, a rare melanoma subtype with a distinct genetic profile and no known systemic therapy conferring survival benefit [42, 43]. A recent single-institution review of patients receiving ipilimumab for treatment of uveal melanoma demonstrated similar response rates and adverse effects compared with those for cutaneous melanoma. At 24 weeks, the response rate determined by irRC was 5% (one of 20 patients with a partial response), with 25% of patients achieving either a response or stable disease. One patient achieved a partial response later, consistent with an immune-related response, making the ORR 10%. These responses were ongoing at the time of publication, and median overall survival was 8.6 months [44]. These findings were confirmed by several smaller series, one of which reported two of five patients with durable stable disease (15 months, more than 12 months) but no objective responses, and another which reported three of 13 patients with durable stable disease (71 weeks, 75 weeks, more than 172 weeks), but no objective responses [45, 46]. In all of the above-mentioned studies, adverse events were comparable to those of patients treated for cutaneous melanoma. These findings provide a rationale for currently accruing prospective studies, including a phase I/II trial investigating ipilimumab in both the adjuvant and the metastatic setting (NCT01585194), as well as a pilot study evaluating sequential radioembolization followed by ipilimumab therapy for treatment of liver metastases (NCT01730157).

Ipilimumab and Mucosal Melanoma

Like uveal melanoma, mucosal melanoma is a rare subtype of melanoma with genetically distinct features [47]. The efficacy of ipilimumab in mucosal melanoma is largely unknown. Recently, an experience of 70 mucosal melanoma patients treated with 3 mg/kg ipilimumab induction under a European expanded access program was reported. The response rate was 6%, with one complete response; however, 23.1% of patients achieved disease control [48]. Our experience with mucosal melanoma in patients treated at Memorial Sloan-Kettering Cancer Center, Dana-Farber Cancer Institute, and Massachusetts General Hospital shows similar response rates, with an irRC ORR of 6% and a disease control rate of 26.7% across 30 patients (unpublished data). This indicates that ipilimumab is a reasonable choice to consider in patients with mucosal melanoma, especially in patients for whom a targetable mutation such as a c-KIT mutation cannot be identified. A prospective trial of ipilimumab for treatment of mucosal melanoma is ongoing (NCT01355120).

Other CTLA-4 Agents: Tremelimumab

Another CTLA-4 antibody, tremelimumab, continues to be investigated in clinical trials. A phase II trial of tremelimumab monotherapy in 251 melanoma patients demonstrated an ORR of 6.6%, with prolonged duration of response among responders ranging from 8.9 to 29.8 months [49]. This prompted a phase III randomized trial of tremelimumab (15 mg/kg) versus dacarbazine or temozolomide [50]. Six hundred and fifty-five patients were enrolled, but after the second interim analysis, the trial was stopped for futility. Final analysis demonstrated a nonsignificant overall survival benefit of 12.6 months versus 10.7 months (hazard ratio 0.88, $p = 0.127$). Objective responses were equal (10.7% versus 9.8%); however, the median duration of response was longer in patients responding to tremelimumab (35.8 months versus 13.7 months, $p = 0.0011$). Toxicity was similar to that of ipilimumab, and seven patients (2%) died from treatment-related causes. It is possible that the lack of an overall survival benefit was due to exclusion of patients with elevated LDH levels and the fact that a number of patients in the control arm subsequently received ipilimumab.

Despite the trial's failure to demonstrate survival benefit, tremelimumab may still hold promise, particularly in combination with other therapeutics. For example, a phase II trial combining tremelimumab with interferon alfa-2b demonstrated a best ORR of 24%, with an additional 38% of subjects experiencing stable disease [51]. Overall survival was 21 months, significantly longer than reported with ipilimumab or tremelimumab monotherapy, with grade III/IV toxicities of neutropenia (17%), diarrhea/colitis (11%), liver abnormalities (11%), rash (11%), fatigue (40%), and anxiety/depression (14%). Moving forward, tremelimumab will be evaluated in combination with the anti-CD40 antibody CD-870,893, as well as in combination with other immunomodulatory therapies (NCT01103635) and as monotherapy in other malignancies.

Biomarkers for Ipilimumab

Despite the improvement in overall survival with ipilimumab, only a minority of patients experience long-term overall survival. Therefore, considerable efforts are ongoing to discover biomarkers that may predict response to ipilimumab and other immunomodulatory agents. One of the first and most thoroughly described potential biomarkers is the absolute lymphocyte count (ALC). Patients with an ALC of more than 1,000 cells per microliter 7 weeks after starting therapy exhibited increased overall survival in a single-institution cohort of patients receiving ipilimumab at a dose of 10 mg/kg [52]. Recently, the ALC was evaluated in 137 patients receiving ipilimumab at the commercial dose (3 mg/kg) and similar findings were obtained. The association between ALC and overall survival 7 weeks into ipilimumab therapy retained significance in a multivariate analysis accounting for LDH, M stage, and number of prior therapies [53]. Further work must be performed to prospectively evaluate this biomarker and determine if it could be appropriately used clinically. One foreseeable hypothesis is that this ALC cutoff could be used to determine whether a patient should continue with the commercial dose of ipilimumab or receive additional therapy or perhaps higher doses of ipilimumab.

Various correlates of cellular and humoral response have been previously examined as possible biomarkers in patients treated with ipilimumab, including antibodies and $CD8^+$ antigen-specific responses to NY-ESO-1, the percentage of $CD4^+ICOS^{hi}$ cells following treatment, expression of genes involved in immune response, and posttreatment increases the levels of in tumor infiltrating lymphocytes [54–58]. At the annual meeting of American Society of Clinical Oncology in 2012, an additional cellular marker, the percentage of MDSCs (determined as the percentage of cells that are $CD14^+$, HLA-$DR^{-/low}$ among peripheral blood mononuclear cells), was reported as being associated with overall survival

in melanoma patients treated with ipilimumab. Low MDSC quantity was associated with improved overall survival ($p = 0.002$), an effect which was associated with overall survival in a multivariate analysis when accounting for the baseline LDH level [59]. It is quite possible that a high quantity of MDSCs may be a poor prognostic factor in melanoma, regardless of therapy. Most of these biomarker analyses have been retrospective and included only small numbers of patients. Nonetheless, they highlight the potential of immunologic monitoring in patients treated with immunotherapy.

In efforts to produce a mainstream assay to predict response to therapy, an assay that evaluates antibody response to a proprietary panel of melanoma antigens such as *BRAF* and NY-ESO-1 has been developed. Among 34 patients receiving ipilimumab who were tested with the assay, most of the patients exhibited antibodies to at least one of the antigens tested (22 of 34 patients, 65%). Patients who produced antibodies to at least two antigens exhibited increased overall survival (39.4 weeks versus 16.4 weeks, $p = 0.02$) [60]. Similarly, expression array analyses of patients receiving ipilimumab were evaluated for potential use as an assay to predict immune-mediated gastrointestinal events. Twenty-seven genes were identified as differentially expressed among patients developing immune-related gastrointestinal toxicities. Expression of two neutrophil activation markers, CD177 and CEACAM1, was associated strongly with gastrointestinal events, as well as several immunoglobulin genes. These findings were confirmed in a validation cohort, indicating that expression of these genes might serve to predict gastrointestinal toxicity [61].

Targeting the PD-1 Axis

PD-1 Blockade

In 2012, preliminary investigations of PD-1 inhibitors came to fruition, demonstrating a strong signal of efficacy and safety. PD-1 signaling serves to regulate T-cell activation in peripheral tissues, limiting autoimmunity and sequelae of chronic inflammation. Inhibition of these interactions can enhance T-cell response in vitro and stimulate antitumor activity in preclinical models [62, 63]. The sentinel anti-PD-1 phase I trial evaluated the safety of nivolumab (BMS-936558), a fully human immunoglobulin G4 (IgG4) blocking monoclonal antibody, against PD-1 [6, 64]. In the most recent analysis, 106 melanoma patients were accrued, receiving doses ranging from 0.1 to 10.0 mg/kg every 2 weeks, with options for maintenance and reinduction dosing in select clinical scenarios. Unlike for ipilimumab, a dose–response correlation was not observed. All doses had acceptable safety, and a maximum tolerated dose was not defined. The objective response rate was 31% (33 of 106 patients), with an additional 6% of patients (six of 106) achieving stable disease lasting 24 weeks or more [64]. Most of the responses were durable for more than 1 year (13 of 18 patients). As with ipilimumab, some patients experienced progression or stable disease before ultimately responding to therapy. Additionally, responses to anti-PD-1 reinduction have been reported [65].

Grade III/IV drug-related toxicities occurred in 14% of patients in the trial, some with potential immune-mediated mechanisms (pneumonitis 1%, diarrhea 1%, and increased alanine aminotransferase/aspartate aminotransferase levels 2%). Frequent grade I/II adverse events included fatigue, anorexia, diarrhea, pruritus, rash, and nausea. Three treatment-related deaths occurred secondary to pneumonitis, which contrasts with ipilimumab's most frequent life-threatening toxicity of colitis. With additional experience, algorithms to address pneumonitis may mitigate progression to life-threatening pneumonitis, as has been achieved with ipilimumab and colitis [66].

In an unplanned analysis, 42 patients with pretreatment biopsies were evaluated for PD-L1 expression by immunohistochemistry. Patients with tumors expressing PD-L1 had an ORR

of 36%, versus 0% among PD-L1-negative patients ($p = 0.006$) [6]. Despite these data, we emphasize that the currently available assays have not yet been validated and prospectively evaluated. Additionally, PD-L1 and PD-1 expression is dynamic and heterogeneous, and baseline PD-L1 expression might by modified by clinical factors. Further, durable stable disease is felt to be a benefit of therapy, and whether patients with PD-L1-negative tumors achieved durable stable disease has not yet been reported.

An additional anti-PD-1 antibody, lambrolizumab (MK-3475), is currently being investigated. Interim analysis of a phase I trial investigating three dosing regimens revealed a 51% ORR by the irRC among 85 evaluable melanoma subjects. Of these, 9% experienced complete response, and 41% of patients pretreated with ipilimumab achieved an immune-related response (with no complete responses) [67]. Seven grade III/IV adverse events were reported. This trial was followed by an actively accruing phase II trial (NCT01704287) comparing lambrolizumab with the investigator's choice chemotherapy. Additional agents directed towards PD-1 are actively being investigated, including AMP-224 and CT-011 (NCT01352884, NCT01435369).

PD-L1 Blockade

PD-L1 antibodies are being developed in tandem with PD-1 antibodies. The rationale is similar: antibodies against PD-L1 impede the inhibitory interactions of PD-1 with PD-L1. Notably, PD-1 ligand 2/PD-1 interactions are spared, and PD-L1/CD80 are additionally inhibited [68]. The therapeutic significance of these differences remains to be determined.

A multicenter phase I dose-escalation trial of the PD-L1 antibody BMS-936559 provides the first compelling clinical evidence of efficacy. Two hundred and seven patients were enrolled, of whom 55 were melanoma patients. Objective responses were observed in 17% of patients(nine of 52) with melanoma, including three complete responses. Many responses were durable, with five responses lasting more than 1 year, and an additional 27% of patients achieving stable disease lasting more than 24 weeks [7]. Four trial patients experienced a response as determined by irRC that would be classified as progression by standard RECIST [69]. Benefit was observed across all doses, and a maximum tolerated dose was not achieved up to 10 mg/kg administered every 2 weeks. Grade III/IV adverse effects were observed in 9% of patients treated with the drug, with common toxicities including fatigue, emesis, infusion reaction, and lymphopenia. No treatment-related deaths were reported.

Future Perspectives: Novel Targets and Combinations

Preclinical studies suggest that concurrent blockade of immunologic checkpoints with multiple inhibitory molecules may enhance efficacy [70, 71]. The sentinel clinical trial investigating this strategy is a phase I trial combining ipilimumab with nivolumab, with clinical arms comparing various dose combinations (NCT01024231). Another trial will compare nivolumab and the combination of nivolumab with ipilimumab versus ipilimumab monotherapy (NCT01844505). Sequential monotherapy is also being investigated in a phase II trial, since clinical responses to anti-PD-1 have been observed in patients previously receiving ipilimumab (NCT01783938).

In addition to CTLA-4 and PD-1, numerous other immunologic inhibitory and activating targets have been identified preclinically, many with corresponding therapeutic antibodies that are being investigated in phase I clinical trials (Fig. 1). In murine models, these next-generation checkpoint antibodies appear to work synergistically when delivered in combination [72, 73]. Additionally, multiple other viable immune strategies could be combined with checkpoint modulators, for example, tumor vaccines, cytokine therapy,

adoptive T-cell therapy, and biochemotherapy [74–76]. A promising next step is to combine immunomodulatory agents with such strategies (Table 1).

Conclusion

Ipilimumab has paved the way for a host of next-generation immunomodulatory agents. Preliminary data on anti-PD-1 and anti-PD-L1 antibodies demonstrate response rates that exceed those of ipilimumab, with an acceptable toxicity profile. Despite decades of skepticism of immunotherapy, these agents have proven immunotherapy is a viable therapeutic strategy, both in melanoma and in other malignancies. We must continue to investigate this new class of therapeutic agents, and incorporate them into clinical practice with previously existing and novel therapies. We anticipate that work performed in 2013 will reaffirm the clinical utility of anti-PD-1 and anti-PD-L1 therapy, setting the stage for ultimate FDA approval. Additionally, clinical trials combining multiple checkpoint agents will come to fruition, allowing even more novel subsequent combination approaches.

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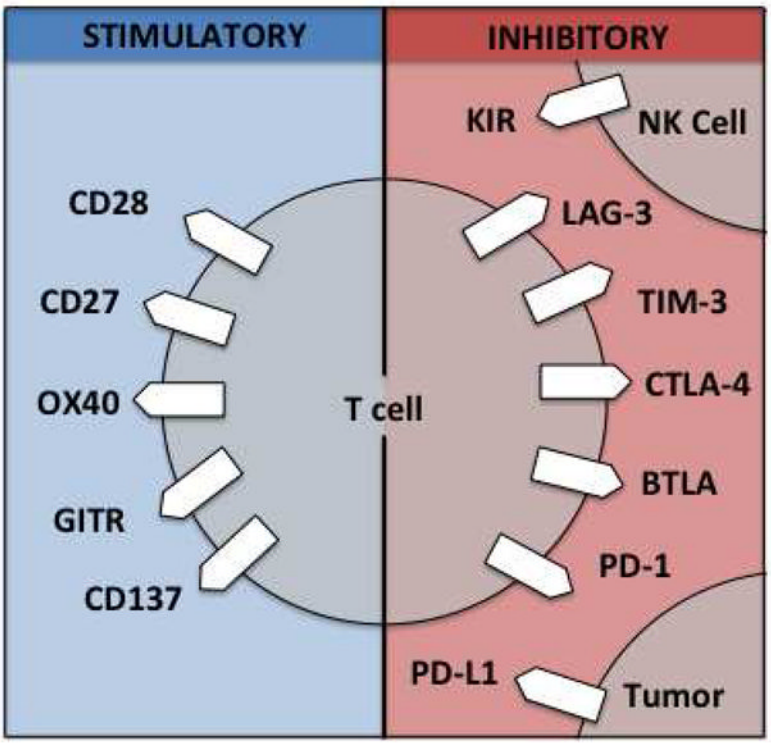

Fig. 1.

Therapeutic targets for immunoregulatory antibodies. *GITR* glucocorticoid-induced tumor necrosis factor receptor related protein, *NK cell* natural killer cell, *KIR* killer inhibitory receptor, *LAG-3* lymphocyte activation gene 3, *TIM-3* T-cell immunoglobulin- and mucin-domain containing 3, *CTLA-4* cytotoxic T lymphocyte antigen 4, *BTLA* B- and T-cell attenuator; *PD-1* programmed cell death 1, *PD-L1* programmed cell death 1 ligand 1

Table 1

Examples of active clinical trials evaluating combination strategies with checkpoint modulation

Combination	Trial identifier	Phase	Regimen
Checkpoint agents	NCT01714739	I	Anti-PD-1 + anti-KIR
	NCT01024231	I	Dose-escalation ipilimumab + nivolumab
	NCT01750580	I	Ipilimumab + anti-KIR
	NCT01844505	III	Ipilimumab vs nivolumab vs ipilimumab + nivolumab
Chemotherapy	NCT01590082	I/II	Ipilimumab + doxycycline + temozolomide
	NCT01676649	II	Ipilimumab + carboplatin/taxol in melanoma
	NCT01323517	II	Ipilimumab + ILI melphalan/dactinomycin
	NCT01740401	II	Ipilimumab + low-dose cyclophosphamide
Immunotherapy	NCT01701674	0	Ipilimumab + adoptive T-cell therapy + lymphodepletion
	NCT01629758	I	Anti-PD-1 and IL-21
	NCT01176461	I	Anti-PD1 + vaccine + montanide
	NCT01489059	I	Ipilimumab + IL-21
	NCT01838200	I	Ipilimumab + intralesionally administered BCG
	NCT01672450	I	Ipilimumab + intralesionally administered IL-2
	NCT01750983	I	Ipilimumab + lenalidomide
	NCT01810016	I	Ipilimumab + NY-ESO-1 vaccine
	NCT01103635	I	Tremelimumab + anti-CD40 (CP-870,893)
	NCT01740297	I/II	Ipilimumab +/− talimogene laherparepvec
	NCT01689870	I/II	Ipilimumab + anti-OX40
	NCT00871481	I/II	Ipilimumab + antigen-specific T cells
	NCT01409174	I/II	Ipilimumab + biochemotherapy
	NCT01743157	I/II	Ipilimumab + biochemotherapy + bevacizumab
	NCT01363206	II	Ipilimumab + GM-CSF
	NCT01708941	II	Ipilimumab +/ IFNα_{2b}
	NCT01134614	II	Ipilimumab +/− sargramostim
	NCT01302496	II	Ipilimumab + TriMix-DC
Radiotherapy	NCT01703507	I	Ipilimumab + whole-brain radiotherapy or SRS in brain mets
	NCT01497808	I/II	Ipilimumab + stereotactic body radiotherapy
	NCT01565837	II	Ipilimumab + stereotactic ablation in oligometastases
	NCT01689974	II	Ipilimumab +/− radiotherapy
Targeted therapy	NCT01767454	I	Ipilimumab + dabrafenib +/− trametenib in V600E/K+
	NCT00790010	I	Ipilimumab + bevacizumab
	NCT01738139	I	Ipilimumab + imatinib in c-KIT mutation
	NCT01633970	I	MPDL3280A + bevacizumab +/− chemotherapy
	NCT01656642	I	MPDL3280A + vemurafenib
	NCT01604889	I/II	Ipilimumab +/− INCB024360

GM-CSF granulocyte–macrophage colony stimulating factor, *IFN* interferon, *ILI* isolated limb infusion, *KIR* killer inhibitory receptor, *PD-1* programmed cell death 1, *SRS* stereotactic radiosurgery