Ipilimumab Combined with Nivolumab: A Standard of Care for the Treatment of Advanced Melanoma?

Matteo S. Carlino¹ and Georgina V. Long²

1. Melanoma Institute Australia, The University of Sydney, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Sydney, Australia
2. Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia

Corresponding Author: Georgina V. Long, 40 Rocklands Road, North Sydney, NSW 2060, Australia. E-mail: georgina.long@sydney.edu.au

Running Title: Combination Ipilimumab–Nivolumab for Advanced Melanoma

Disclosure of Potential Conflicts of Interest

M.S. Carlino is a consultant/advisory board member for Bristol-Myers Squibb, GlaxoSmithKline/Novartis, and MSD. G.V. Long is a consultant/advisory board member for Amgen, Bristol-Myers Squibb, GlaxoSmithKline/Novartis, Merck, Provectus Biopharmaceuticals, and Roche. No other potential conflicts of interest were disclosed.
Abstract

Ipilimumab, an inhibitor of CTLA-4 on T-cells, was the first drug to improve overall survival in patients with advanced melanoma. Subsequently, inhibitors of PD-1, including nivolumab and pembrolizumab, were shown to be superior to ipilimumab with a more favourable safety profile. The combination of ipilimumab and nivolumab is associated with a further improvement in response rate and progression free survival, however the combination is associated with an increased rate of immune related toxicities. In 2015 the FDA approved the combination for the treatment of BRAF wildtype advanced melanoma. This review will examine the preclinical rational for the combination of ipilimumab and nivolumab as well as the efficacy and toxicity data from clinical trials in patients with advanced melanoma. Finally, alternative treatment options are discussed with a focus on patient selection.
Introduction

In the last 5 years the one year overall survival (OS) of patients with advanced (stage III unresectable or stage IV) melanoma treated on phase III clinical trials has risen from 25-30% (1) to over 70%, and has resulted in the approval of at least eight drug therapies by the USA Food and Drug Administration (FDA) and in other countries around the world. This revolution is due to two independent developments in drug therapy: first, the targeted inhibition of the mitogen activated protein kinase pathway in V600 BRAF mutant melanoma; and second, the manipulation of the host immune response to tumour via inhibitors of immune checkpoints on T cells, namely the cytotoxic T lymphocyte associated protein 4 (CTLA-4) receptor and the programmed death 1 (PD-1) receptor. Now, the first combination of immune checkpoint inhibitors has had accelerated FDA approval for the treatment of BRAF wildtype advanced melanoma. This drug update reviews the preclinical and clinical studies underpinning the approval of ipilimumab, an inhibitor of CTLA-4, combined with nivolumab, an inhibitor of PD-1.

CTLA-4 Inhibition; Ipilimumab

Following activation by antigen presentation cells in peripheral lymphoid organs, T cells upregulate CTLA-4 expression. CTLA-4 is a co-inhibitory molecule which binds B7 with higher affinity than the co-stimulatory molecule CD28, and the displacement of CD28 for CTLA-4 causes the suppression of T cell activity (2). Further, CTLA-4 also reduces TCR activation induced tyrosine phosphorylation via the recruitment of the SHP-1/2 phosphatases (3). Ipilimumab, a monoclonal antibody against CTLA-4, blocks this inhibitory signal leading to increased T cell activation (Figure 1).
Ipilimumab has been shown to improve survival in two phase III studies in advanced melanoma. In the second line trial, ipilimumab alone (3mg/kg) or in combination with the glycoprotein 100 vaccine (gp100) improved the OS compared with gp100 alone (median OS gp100 alone 6.4 months vs. ipilimumab alone 10.1 months [Hazard Ratio (HR) 0.68, P<0.001] or vs. ipilimumab+gp100 10 months [HR, vs gp100 alone, 0.66, P=0.003]) (4). In the first line trial, dacarbazine combined with a higher dose of ipilimumab (10mg/kg) improved the OS compared with dacarbazine alone (11.2 months vs. 9.1 months, HR 0.72; P<0.001) (5). Despite marginal improvements in the median OS, the benefit of ipilimumab is due to the long-term duration of disease control with approximately 20% of patients surviving beyond 5 years (6). In both trials, the RECIST response rate for the ipilimumab containing arms was approximately 10%, with clinical benefit and prolonged survival seen in patients who do not undergo conventional radiological responses. Furthermore, a subset of patients may progress before they respond. This phenomenon, termed ‘pseudo-progression’, led to the development of the immune response criteria (iRC) and the need to confirm progression, in addition to traditional confirmation of response (7).

**PD-1 Inhibition; Nivolumab**

PD-1 is an inhibitory receptor expressed on cytotoxic T cells, and is a hallmark of T cell exhaustion and dysregulation. One of its ligands, PD-L1, is expressed by tumour cells in response to IFNγ produced by activated T cells (8). PD-L1 expression may also be induced by other mechanisms, for example oncogenic signalling pathways (e.g. MYC overexpression (9)), and is an area of intense research. Nivolumab is an IgG4 monoclonal antibody that inhibits PD-1 resulting in activation of the T cell response against tumour cells (Figure 1). After demonstrating initial activity in multiple tumour types, nivolumab demonstrated
superiority over both dacarbazine chemotherapy and ipilimumab in patients with advanced melanoma in three phase III studies. Nivolumab significantly improved the OS compared with dacarbazine in the first-line setting in BRAF wildtype patients (one year OS 72.9% vs 42.1%, HR 0.42, P<0.001). Nivolumab improved the response rate compared with physician’s choice chemotherapy in patients who had progressed on ipilimumab (10). Finally, in a first-line phase III study (discussed below), nivolumab had a higher response rate and prolonged PFS compared with ipilimumab irrespective of BRAF mutation status (11).

Pembrolizumab is another anti-PD-1 antibody approved in many countries around the world for the treatment of advanced melanoma. It has also demonstrated a superior response rate, PFS and OS compared with ipilimumab in a phase III clinical trial, with a similar toxicity profile to nivolumab (12).

**Combined CTLA4 and PD-1 inhibition; Ipilimumab combined with Nivolumab**

**Rationale**

The primary site of action of ipilimumab is during the induction phase of anti-tumor T cell immunity within lymphoid tissues, whereas nivolumab primarily acts at the effector phase within the tumour microenvironment (Figure 1), suggesting their effects may be additive or synergistic. In preclinical models, mice deficient in CTLA-4 develop a rapidly progressive lymphoproliferative disease which is fatal within months (13). In contrast, PD-1 deficient mice develop autoimmune disease including lupus-like arthritis and glomerulonephritis (14) or antibody-mediated cardiomyopathy (15). The differing toxicity profiles suggest that the impact of CTLA-4 and PD-1 on T cell activation and function are non-redundant.

In a melanoma mouse model CTLA-4 blockade led to increased expression of PD-1 positive tumour infiltrating lymphocytes (TILs), conversely, with PD-1 blockade CTLA-4 positive TILs
increased (16). In the same model the combination of CTLA-4 and PD-1 blockade significantly increased the cure rate in mice (16).

Clinical Efficacy

The combination of ipilimumab and nivolumab was explored in a phase I study and was initially presented and published in 2013 (17). Fifty three patients with advanced melanoma received both drugs concurrently every 3 weeks for 4 doses followed by nivolumab alone for a further 4 doses every 3 weeks, then the combination every 12 weeks for 8 doses. Four dosing schedules were explored; 1) nivolumab 0.3mg/kg + ipilimumab 3mg/kg (0.3/3mg), 2) nivolumab 3mg/kg + Ipilimumab 1mg/kg (3/1mg), 3) nivolumab 1mg/kg+ ipilimumab 3mg/kg (1/3mg), and 4) nivolumab 3mg/kg+ ipilimumab 3mg/kg (3/3mg). The 3/3mg dose cohort exceeded the maximum tolerated dose, and the 1/3mg dosing schedule was selected for further expansion. Across all concurrent dosing schedules, 21 of 52 (40%) patients responded using the modified WHO criteria, and evidence of clinical activity (defined as a radiological response or an immune-related partial response or stable disease for ≥24 weeks) was observed in 34 of 52 (65%) of patients. Compared to prior studies of single agent checkpoint inhibition the depth of response appeared substantially higher, including a 10% complete response (CR) rate at 12 weeks. Responses were observed in 9 of 17 (53%), with clinical activity (defined above) in 11 of 17 (65%) of patients in the 1/3mg cohort. The activity in the 3/1mg cohort was comparable; 6 of 15 (40%) patients responded and 11 of 15 (73%) had evidence of clinical activity (defined above). OS was updated at ASCO in 2014 with the one and two year OS rate at 84% and 72% respectively.

A subsequent first line randomized phase II study examined a slightly altered dosing regimen of ipilimumab 3mg/kg every 3 weeks combined with nivolumab 1mg/kg for four
doses followed by nivolumab 3mg/kg every 2 weeks until progression or unacceptable toxicity (Table 1). This was compared with 4 doses of ipilimumab 3mg/kg every 3 weeks combined with placebo (Checkmate 069) (18). The primary endpoint was response rate (determined via RECIST 1.1.) in BRAF\(^{V600}\) wildtype tumours. In the combination arm, 44 of 72 (61%) patients responded compared with 4 of 37 (11%) in the ipilimumab+placebo arm (P<0.001). A CR was observed in 16 patients (22%) on the combination and 0% of those on single agent ipilimumab. At the time of initial publication the median PFS was not reached in the combination arm and was 4.4 months with single agent ipilimumab (HR 0.40; P<0.001). An update reporting the OS, an exploratory endpoint, reported a one- and two-year OS of 79% and 69% in BRAF\(^{V600}\) wildtype patients treated with the combination (19). Similar differences in efficacy were observed in a smaller cohort of BRAF mutant patients.

Checkmate 067 is a first-line placebo-controlled randomized phase III study comparing three arms of treatment in 915 patients with metastatic melanoma; nivolumab combined with ipilimumab or nivolumab alone versus ipilimumab alone (Table 1) (11). The study was not powered to compare between the two nivolumab containing arms. At initial analysis, the response rate and PFS in the two nivolumab containing arms were improved compared with ipilimumab. The response rates were 58% (CR 12%), 44% (CR 9%) and 19% (CR 2%) in the combination, nivolumab and ipilimumab arms, respectively (P<0.001 for both nivolumab arms compared to ipilimumab). The combination arm was associated with an improvement in PFS compared to ipilimumab (median 11.5 versus 2.9 months, HR 0.42; P<0.001), and the PFS for the combination was numerically longer than that of nivolumab alone (median 6.9 months, HR 0.57 compared with ipilimumab; P<0.001). Of note, at the time of this preliminary analysis, 85 patients had died in the nivolumab monotherapy group, 86 in the nivolumab/ipilimumab combination group and 114 in the ipilimumab monotherapy group,
and was too immature for OS analysis. A recent update with a minimum follow-up of 18 months, found the landmark 18 month PFS was 46%, 39% and 14% for the combination, nivolumab and ipilimumab arms, respectively (20). The median duration of response had not been reached for the combination and was 22.3 and 14.4 months for the nivolumab and ipilimumab arms respectively (20).

**Clinical Efficacy and Subgroups**

Checkmate 067 is the only phase 3 randomised trial containing the combination of CTLA-4 and PD-1 inhibition, however it was not powered to compare the combination with nivolumab monotherapy, currently the most pressing question in the treatment paradigm of advanced melanoma. Pre-planned, but underpowered analysis of subgroups may suggest those that stand to benefit from the more toxic combination regimen (see Toxicity below).

Most interestingly, in patients whose tumours were PD-L1 positive (defined in this trial as ≥5% PD-L1 staining of tumor cells by immunohistochemistry in a section of at least 100 evaluable tumor cells, a ≥1% cutoff was examined), the PFS was similar in the two nivolumab containing arms (14 months in both nivolumab arms [95% CI, 9.1 to not reached] in the nivolumab alone arm and [95% CI, 9.7 to not reached] in the combination arm), but different for patients with PD-L1 negative tumours (median 11.2 months [95% CI, 8.0 to not reached] in the combination arm vs. 5.3 months [95% CI, 2.8 to 7.1] for nivolumab alone). The difference was even greater when PD-L1 negative tumours were defined by a lower cut off of ≤1%. The PD-L1 data needs to be interpreted with caution given the short follow up, lack of OS data and the fact that the study was not powered to compare the combination to single agent nivolumab.
Although Checkmate 067 was not powered to define subgroups that may specifically benefit from PD-1 inhibitor based therapy, specific subgroups of interest include those with the BRAF\textsuperscript{V600} mutation (because molecularly targeted therapies are an alternative first line strategy), an LDH > x2 upper limit of normal (ULN), and patients over 75 years of age. The data are compelling for all three subgroups, with combination ipilimumab and nivolumab superior to ipilimumab irrespective of age, LDH or mutation status (21). In patients with an LDH>2X the ULN the response rate to the combination was 38%, 22% to nivolumab, and 0% for ipilimumab (21). In the BRAF\textsuperscript{V600} mutant population the response rate to combination was 67%, which was numerically superior to the 37% and 22% response rates observed with nivolumab or ipilimumab alone, respectively.

**Toxicity**

Combination ipilimumab and nivolumab is associated with increased immune-related adverse events (irAE) as compared to either agent alone. In the phase I study, treatment-related grade 3 or 4 toxicities were seen in 53% of patients (17). In the Checkmate 067 study, treatment-related adverse events of any grade occurred in 96% of patients on the combination arm as compared to 82% and 86% in the nivolumab and ipilimumab arms, respectively (Table 1). Grade 3 or 4 treatment-related adverse events were also more common with the combination; 55% compared with 16% and 27% for nivolumab and ipilimumab, respectively. The most common grade 3 and 4 irAEs in the combination arm of CheckMate-067 study were diarrhoea (9.3%), increased transaminases (ALT 8.3%, AST 6.1%) and colitis (7.7%). Toxicities affecting more than one organ system occurred more commonly with the combination; 25% of patients had grade 2 or greater toxicities affecting
more than one organ (e.g. a patient with both GI toxicity and skin toxicity), and 7% of patients had 3 or more organ systems affected (21).

The toxicities seen with the combination were similar to those seen with either single agent, however were more frequent and of higher grade, but were manageable with standard algorithms. In Checkmate 067 toxicities led to treatment discontinuation in 36% of patients treated with the combination, 8% of patients treated with nivolumab and 15% of patients treated with ipilimumab (11). Of interest the response rates were not reduced in patients who discontinued due to toxicity, with responses seen in 68% (81/120), 85% (23/27), and 30% (14/47) of patients who discontinued treatment with the combination, nivolumab or ipilimumab respectively, responses were ongoing in approximately in 70% of patients who discontinued across all three treatment arms (21). Excluding endocrinopathies, most toxicities resolved with standard treatment algorithms, immunomodulatory agents other than steroids (e.g. infliximab) were used in 6.1%, 0.6% and 5.1% of patients treated with the combination, nivolumab or ipilimumab (11). There were no treatment-related deaths in the combination arm of Checkmate 067, however the 3 deaths (4%) in the combination arm of Checkmate 069 were potentially due to treatment (18). In an analysis of toxicity by subgroups in Checkmate 067, increased toxicity was not noted in any particular patient subgroup, including those aged >75 years (21). The generalisability of these results beyond a clinical trial patient population remains to be determined.

Alternative CTLA-4/PD-1 inhibitor combinations, sequencing, dosing and special patient populations
The phase I study of ipilimumab combined with nivolumab included a sequential cohort of patients who had received at least 3 doses of ipilimumab (last dose between 4 to 12 weeks prior to enrolment) and were treated with the standard dose nivolumab (3mg/kg) every 2 weeks. Patients with a CR or symptomatic progression after ipilimumab were excluded (17). Responses were seen in 6 of 30 (20%) of patients, and 18% of patients experienced a grade 3 or 4 treatment related adverse event (17). Sequencing of ipilimumab and nivolumab was further explored in a randomized phase II study, Checkmate 064. Patients were treated with either 12 weeks of nivolumab (cohort A) or ipilimumab (cohort B) at standard doses followed by a switch for a further 12 weeks of treatment. All patients were subsequently treated with nivolumab until progression or unacceptable toxicity (22). The rate of grade 3 or 4 treatment related adverse events at the end of 24 weeks were similar between the 2 groups, 50% and 43% for cohort A and B, respectively. The response rate at 25 weeks appeared numerically higher in cohort A (48%) as compared to cohort B which received ipilimumab first (23%). Caution is required in interpreting the results of this study given it was underpowered (70 patients each arm) and there were differences in baseline characteristics e.g. 42% of patients in the cohort A had PD-L1 positive tumors whereas only 23% were positive in cohort B. Furthermore, the time gap when switching from nivolumab to ipilimumab was 2 weeks, yet it was 3 weeks in the ipilimumab-first arm. Given the half-lives of these two drugs, the different time gap would result in a greater overlap of the two drugs in cohort A compared with cohort B.

Given the activity of the combination of ipilimumab and nivolumab in melanoma, it has now been explored in phase I/II studies in other malignancies, including renal cell carcinoma (23) and non-small cell lung cancer (24). In melanoma, two alternative dosing strategies are being compared in a randomized study; nivolumab 1mg/kg plus ipilimumab 3mg/kg versus
nivolumab 3mg/kg plus ipilimumab 1mg/kg (every 3 weeks for 4 doses in both arms) followed by a nivolumab monotherapy (Checkmate-511, NCT02714218).

Combination ipilimumab and pembrolizumab has also been explored in melanoma and renal cell carcinoma. In a phase I study, low dose ipilimumab (1mg/kg) was combined with standard dose pembrolizumab (2mg/kg) and administered every 3 weeks for 4 doses. Pembrolizumab was continued every 3 weeks for a total of 24 months, disease progression or unacceptable toxicity (25). In the phase Ib expansion cohort of 153 metastatic melanoma patients, treatment-related AEs occurred in 95% of patients, grade 3-4 treatment-related AEs occurred in 42% (grade3/4 immune related AEs in 25%), and responses were observed in 57% of patients (26). Without a head to head comparison with the ipilimumab/nivolumab combination it will be difficult to determine if a lower dose of ipilimumab in combination with a higher dose of PD-1 inhibitor maintains efficacy with less toxicity. A third combination of a CTLA-4 inhibitor tremelimumab, and a PD-L1 inhibitor durvalumab showed promising activity in initial analysis of a phase 1 study in patients with NSCLC (27).

One treatment strategy currently under investigation in clinical trials, is to commence treatment with single agent anti-PD1, and switch to combination anti-CTLA4 and anti-PD1 blockade in those who do not respond to single agent anti-PD1 therapy (NCT02731729). Such a strategy would prevent the anti-PD1 responders (approximately 40% of patients) being exposure to the increased toxicity risk of the combination. This is not yet a standard treatment option, but if successful in trials, would be very attractive to clinicians and patients.

Given its rarity, at least in Caucasian populations, data from multiple studies was combined to assess the efficacy of nivolumab and the combination of nivolumab and ipilimumab in
patients with mucosal melanoma (28). Responses were observed in 37% of patients treated with the combination, 23% of those treated with nivolumab, and 8% of those treated with ipilimumab (P=0.005 for the combination vs ipilimumab; P=0.075 for nivolumab vs ipilimumab.) The median PFS was 5.9 months, 3.0 months and 2.9 months for patients treated with the combination, nivolumab and ipilimumab respectively (P=0.12 for nivolumab vs ipilimumab, and P=0.003 for the combination vs ipilimumab).

The combination of ipilimumab and nivolumab is currently being explored in a number of melanoma subpopulations, including patients with active brain metastasis (NCT02374242, NCT02460068), those with uveal melanoma (NCT01585194) and in the perioperative setting in stage III disease (NCT02437279).

**Patient Selection and Alternative Approaches to Combination Immunotherapy**

Given the favourable toxicity profile of single agent PD-1 inhibition and the lack of OS data for the combination of nivolumab and ipilimumab, the use of PD-L1 status as a biomarker for selection of patients to forgo combined CTLA-4 and PD-1 blockade appears attractive. Although biomarkers are usually employed to select for a treatment (e.g. HER2, estrogen, progesterone in breast cancer, BRAF mutations in melanoma), not to forgo it, there may be an argument to spare a proportion of patients from the increased risk of toxicity of the combination. This is being examined in Checkmate 067, and may assist in some clinical decisions, however it is important to emphasise that the study is not sufficiently powered to compare the combination arm with nivolumab alone. Studies of human melanoma tissue taken from patients just prior to treatment with anti-PD1 therapies have identified factors associated with a response, including the presence of CD8 positive T cells (29), a clonal T cell
receptor repertoire (29) and a high level of neo-antigens, which in turn are associated with a high mutational burden in the tumour (30). It remains to be determined if such markers will be useful in selecting patients for single agent anti-PD1 therapy versus the combination. Furthermore, early during treatment biopsies may be more predictive of tumour response to anti-PD1 therapy and define subsets of patients who require a different treatment strategy (31).

The financial cost, both of the drugs and the ensuing toxicities, may impact the use of the combination around the world. A systematic examination is yet to be reported, but a rational cost benefit analysis compared with single agent is likely to require maturation of the survival data from CheckMate 067 (32). In some health systems, the combination may be cost prohibitive, however biomarker driven patient selection algorithms may minimise the financial impact.

In an effort to improve the efficacy of PD-1 inhibition, without significant increases in toxicity, multiple combinations of therapies with an anti-PD1 backbone are in clinical development or in planning, and have been reviewed elsewhere (33). Three randomized clinical trials in advanced melanoma of such combination therapies compared with anti-PD1 monotherapy warrant further discussion.

IDO1 (indoleamine 2,3 dioxygenase 1) is overexpressed in many cancers and suppresses immune responses, with preclinical evidence of synergy between IDO1 inhibition and PD-1 blockade (34). Epacadostat, an oral IDO1 inhibitor, has been trialed in combination with pembrolizumab. A preliminary analysis of the 19 patients with advanced melanoma from the phase I study reported responses in 10 patients (53%). Toxicities in all patients with solid tumors appeared comparable to single agent pembrolizumab (35). A phase III study
randomizing patients to pembrolizumab combined with epacadostat or placebo is underway (NCT02752074).

Intra-tumoral injection of Talimogene laherparepvec (T-VEC), a genetically modified and oncolytic herpes simplex virus improves durable responses (defined as objective response lasting continuously ≥ 6 months) in selected patients with unresectable stage IIIB/C and stage IV melanoma. TVEC in combination with pembrolizumab was associated with an overall response rate of 57% (unconfirmed response rate 67%) in 21 patients treated in a phase I study (36). A placebo controlled phase III study comparing TVEC combined with pembrolizumab with pembrolizumab and a matched placebo is currently underway (NCT02263508).

As both TVEC and epacadostat combined with PD-1 blockade are being compared to single agent PD-1 inhibition in phase III studies, it will remain difficult to compare these newer immune combinations with ipilimumab/nivolumab.

An alternative approach is the combination of molecularly targeted and immune therapies. In mouse models the combination of BRAF and/or MEK inhibitors is synergistic with anti-PD-1 therapy (37). In preliminary data from the phase I study of dabrafenib + trametinib in combination with pembrolizumab unconfirmed responses were seen in 9 of 15 (60%) patients (38). The phase 2 portion of this study compares dabrafenib + trametinib combined with pembrolizumab versus dabrafenib + trametinib combined with a matched placebo (NCT02130466). Given this design, and depending on the results, further studies are likely to be required to definitively determine if the triple combination is superior to the sequencing of targeted and immunotherapy. A sequencing study of combined BRAF/MEK inhibition therapy versus combined ipilimumab/nivolumab, with cross over on progression is
underway (NCT02224781). This design will help determine if the order of therapy is important, yet will not answer the question of combination versus sequencing therapies.

There is much interest in rationally selecting patients for individualized combinations of therapies based on characteristics of the patient’s tumor and the microenvironment. In one model it is hypothesized that patients could be stratified based on tumor TILs and PD-L1 expression (39). Patients whose tumors have TILs and express PD-L1 may be best served by single agent anti-PD1 treatment, given the association of these factors with response, as well as the favorable toxicity profile. Tumors that do not contain TILs may benefit from the combination of CTLA-4 and anti-PD1, to ‘bring T cells into the tumor’ (39). Tumors which do not express PD-L1 but contain TILs are hypothesized to have non PD1/PD-L1 immunosuppressive pathways and may require treatment with other checkpoint inhibitors (39).

Analysis of tumour biopsies early during treatment show an increase in the number of cytotoxic T cells and macrophages (31) in patients who respond to anti-PD-1 therapy, further a fall in circulating tumour DNA early on treatment may predict for response (40). Analysis of such early on treatment bio-markers may allow for selection of more effective individualised therapies. Novel clinical trial designs and translational studies will be required to determine if such strategies can lead to rational individualized combination treatment.

**Conclusion**

Combined CTLA-4 and PD-1 inhibition with ipilimumab and nivolumab was approved by the FDA in the USA for BRAF wildtype melanoma in the first line setting in 2015. This accelerated approval was based on the improvement in response rate and PFS compared with ipilimumab (18). The OS data from the phase III trial are eagerly awaited (11), and without
more mature data, the combination cannot yet be considered the standard of care, particularly given the high rates of immune-related toxicities compared with PD-1 inhibition alone. There may be subgroups of patients who particularly benefit from the combination (for example, patients with rapidly progressing BRAF wildtype melanoma or patients with a high baseline LDH), and validation of biomarkers, such as PD-L1 along with studies in specific patient subtypes are required to assist in patient selection. Multiple alternative immunotherapy combinations are currently in clinical development with the hope that correlative science will allow treatments to be individualised to further improve patient outcomes, with less toxicity.

References


Table 1: Efficacy and Toxicity from Randomized Trials of Ipilimumab Combined with Nivolumab

<table>
<thead>
<tr>
<th></th>
<th>Checkmate-069*</th>
<th></th>
<th>Checkmate-067</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipi (N=47)</td>
<td>Ipi/Nivo (N=95)</td>
<td>Ipi (N=315)</td>
<td>Nivolumab (N=316)</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate (%)</td>
<td>11</td>
<td>61</td>
<td>19</td>
<td>44</td>
</tr>
<tr>
<td>P value vs Ipi</td>
<td>-</td>
<td>&lt;0.001</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>0</td>
<td>22</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>4.4</td>
<td>NR</td>
<td>2.9</td>
<td>6.9</td>
</tr>
<tr>
<td>HR vs Ipilimumab</td>
<td>-</td>
<td>0.40 (95% CI 0.23-0.68)</td>
<td>-</td>
<td>0.57 (95% CI 0.43-0.76)</td>
</tr>
<tr>
<td><strong>Toxicity (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Related AE</td>
<td>93</td>
<td>91</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>24</td>
<td>54</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td><strong>Selected AEs of interest (all grades)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>13</td>
<td>23</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Hypopysitis</td>
<td>6</td>
<td>12</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>16</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Hepatic</td>
<td>4</td>
<td>28</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>59</td>
<td>71</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>17</td>
<td>47</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

* For Checkmate-069 efficacy data limited to BRAF wildtype patients (N=72 Ipi/Nivo, and N=37 Ipilimumab), toxicity data from the entire population

NR=not reached

CI=confidence interval

AE= adverse event
Figure 1: T-cell Activation by Ipilimumab and Nivolumab

MHC, major histocompatibility complex; TCR, T-cell receptor.
Figure 1:

Lymph node

Dendritic cell

T cell

Tumor cell

TCR

MHC

Anti-CTLA-4

PD-1

PD-L1

T cell attacks

Tumor antigen

CD28

CTLA-4

B7
Ipilimumab Combined with Nivolumab: A Standard of Care for the Treatment of Advanced Melanoma?

Matteo S. Carlino and Georgina V. Long

_Clin Cancer Res_ Published OnlineFirst June 23, 2016.

Updated version
Access the most recent version of this article at:

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.