Review of immunotherapy in melanoma

Surein Arulananda,1,2,3 Elizabeth Blackley,1 Jonathan Cebon1,2,3

1. Department of Medical Oncology, Austin Health, Heidelberg, Victoria, Australia.
2. Cancer Immunobiology Laboratory, Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia.
3. School of Cancer Medicine, La Trobe University, Bundoora, Victoria, Australia.

Email: Jonathan.Cebon@onjcri.org.au

Abstract

The prognosis of patients with metastatic melanoma in Australia has changed dramatically since the introduction of immune checkpoint inhibitors. Ipilimumab, which targets cytotoxic T lymphocyte-associated protein 4 (CTLA-4) was the first agent introduced on the scene. Subsequently nivolumab and pembrolizumab which bind to the programmed death protein 1 (PD-1) have proven to be more effective and less toxic than ipilimumab and form the mainstay of treatment for patients with advanced melanoma. The combination of nivolumab or pembrolizumab with ipilimumab have resulted in improved response rates and survival outcomes with the cost of added immune mediated toxicities. Recently reported trials have shown benefit of adjuvant immunotherapy post resection of high-risk disease. This review will explore the pivotal clinical trial data that has led to regulatory approval for use of these immunotherapy agents in Australia and some of the clinical trial results currently reported for novel combination therapies.

Therapeutic cancer immunology is revolutionising the treatment of cancer and improved outcomes are being reported across a wide range of malignancies. Melanoma has led the race to approval - with pivotal trials leading to global registration and subsequent Therapeutic Goods Administration (TGA) approval and Pharmaceutical Benefit Subsidy (PBS) for advanced disease in Australia.

Australia has the highest incidence and mortality rates from cutaneous melanoma globally.1 The incidence has increased from 27 cases per 100,000 people in 1982 to 50 cases per 100,000 people in 2013.2 Importantly the five year relative survival from melanoma in Australia has improved from 86% in the mid 1980’s to 90% in 2013.2 This is likely due to increased public awareness and earlier detection of melanomas although also in part due to the introduction of modern immunotherapies and kinase inhibitors.

Cancer immunosurveillance, described by Thomas and Burnet in 1957, suggests that the immune system controls and eliminates the development of nascent malformed cells.3,4 However, some tumours escape elimination by various mechanisms, including recruiting immunosuppressive T regulatory lymphocytes,5 interferon-gamma mediated upregulation of programmed death-ligand 1 (PD-L1) within the tumour microenvironment and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) expression on CD4+, CD8+ and T regulatory lymphocytes.6,7 In order to achieve an immune-mediated anti-cancer response, there needs to be migration of CD8+ cytotoxic T lymphocytes (CTL) into the tumour.

The constant engagement of PD-L1 with the programmed cell death protein 1 (PD-1) receptor on CD4+ and CD8+ T lymphocytes leads to T cell exhaustion.8 Antibodies against the PD-1 receptor (pembrolizumab and nivolumab) block this interaction and restores antitumour immunity.9 CTLA-4, a receptor on CD4+ and CD8+ T lymphocytes, provides an alternative molecule for B7 on dendritic cells to bind to and thereby blocks the stimulatory signal. This provides homeostatic regulation and is upregulated when the T cell is stimulated to divide.10 This effect occurs predominantly in secondary lymphoid organs as compared to the tumour microenvironment. CTLA-4 inhibitor (ipilimumab) blocks...
this interaction and enhances the proliferation of antigen-specific lymphocytes by enhancing co-stimulation.\textsuperscript{10}

Excitement surrounds these immune checkpoint inhibitors due to their ability to induce durable and deep objective responses. These drugs are available in Australia for patients with metastatic melanoma, with ipilimumab reimbursed by the PBS in 2013, pembrolizumab in 2015 and nivolumab in 2016. Given the single-agent activity of immune checkpoint inhibitors, multiple studies investigating combination approaches have now been launched, including the combination of ipilimumab and nivolumab, which is currently available on a compassionate access scheme. This review will summarise the evidence leading to the PBS reimbursement of the currently available agents and highlight various exploratory combination approaches in metastatic melanoma and in the adjuvant setting with the results from the pivotal studies highlighted in table 1.

**Anti-CTLA-4 therapy**

Ipilimumab was the first modern immune checkpoint inhibitor to be tested in clinical trials. In the phase 3 trial by Hodi et al, patients who had received at least one prior line of chemotherapy or interleukin-2 were randomised to four cycles of ipilimumab 3mg/kg, plus a gp100 peptide vaccine; ipilimumab; or gp100.\textsuperscript{11} The study met its co-primary end-points of overall response rate (ORR) and overall survival (OS). The ORR were 5.7% (ipilimumab plus gp100), 10.9% (ipilimumab) and 1.5% (gp100) while the median OS was 10 months (95% confidence interval [CI], 8.5 - 11.5) in the ipilimumab plus gp100 group compared to 6.4 months (95% CI, 5.5 - 8.7) in the gp100 group (Hazard ratio [HR], 0.68; P<0.001). The median OS in the ipilimumab group was 10.1 months (95% CI, 8.0 - 13.8) compared to gp100 (HR, 0.66; P=0.003). No OS difference was detected between the two ipilimumab groups (HR, 1.04; P=0.76). Importantly, the landmark survival rates at one and two years were 43.6% and 21.6% (ipilimumab plus gp100), 45.6% and 23.5% (ipilimumab) and 25.3% and 13.7% (gp100). The gp100 vaccine has not been adopted into routine clinical practice to its lack of added benefit in addition to ipilimumab.

Long term survival results have been pooled from two phase 3 studies and ten prospective and retrospective phase 2 ipilimumab studies.\textsuperscript{12} Among the 1861 patients treated with ipilimumab, the median OS was 11.4 months (95% CI, 10.7 - 12.1 months) and three year OS rate was 22% (95% CI, 20% - 24%). 254 of these patients were followed for a median of 5.7 years and one individual patient to 9.9 years. Excitingly, the curves plateaued after three years, suggesting that unprecedented long term survivals can be achieved in a population with advanced melanoma.

While ipilimumab increases anti-tumoral immune activity, it also impairs self-immune tolerance and can result in autoimmune side effects or immune related adverse events (IrAE). In Hodi’s study, there were 56% IrAE in the ipilimumab plus gp100 group and 61% in the ipilimumab group.\textsuperscript{11} The grade 3-4 events were 10.2% and 14.5% respectively. The typical grade 3-4 IrAE noted included rash, colitis endocrinopathies, primarily thyroid related disorders and hypophysitis, and liver function derangement. These side effects were generally treated effectively by early administration of corticosteroids.

**Anti-PD-1 therapy**

Not long after the emergence of ipilimumab, anti-PD-1 therapy made its way into the clinical trial landscape. Following on from early phase studies in melanoma, a second line study of nivolumab 3mg/kg versus chemotherapy in patients with metastatic melanoma who had received ipilimumab or a BRAF inhibitor (if BRAF-mutated) was tested in a phase 3 study.\textsuperscript{13} The OS analysis was subsequently updated by Larkin et al. in 2017.\textsuperscript{14} The study met one of its primary endpoints of ORR which was 27% (95%CI, 22 - 33) with nivolumab and 10% (95%CI, 5 - 16) with chemotherapy. Interestingly, the study did not meet its co-primary endpoint of median OS which was 15.7 months (95%CI, 12.9 - 19.9) with nivolumab compared to 14.4 months (95%CI, 11.7 - 18.2) with chemotherapy (HR, 0.95; 95% CI 0.73 - 1.24). Importantly, there was a trend to improvement in the two year landmark survival of 38.7% (95%CI, 32.8% - 44.5%) with nivolumab compared to 33.9% (95%CI, 25.8% - 42.1%) with chemotherapy. A number of factors could have led to this result including the high cross over rate to anti-PD-1/PD-L1 therapy of 41% in the chemotherapy-treated patients compared to 11% in the nivolumab arm crossing over to chemotherapy. Additionally, an increased proportion of patients in the nivolumab group had poor prognostic factors including elevated LDH and brain metastases.
Nevertheless, the median duration of response was far superior with nivolumab at 31.9 months (95% CI, 25.9 - 31.9) compared to 12.8 months (95% CI, 3.0 - NR) with chemotherapy establishing that anti-PD-1 therapies can provide durable responses.

Subsequently, pembrolizumab 10mg/kg every two weeks or three weeks (2 years) was compared head to head with ipilimumab 3mg/kg (four doses) in the first line setting in Keynote-006, a phase 3 study regardless of BRAF mutation status. The final OS results were recently published by Schachter et al. in 2017. The study had met its co-primary end points of progression free survival (PFS) and OS at interim analysis. In the final analysis, the median OS was not reached in both pembrolizumab groups (22.1 months to not reached in the two-week group and 23.5 months to not reached in the three-week group) compared to 16 months (range 13.5 to 22) in the ipilimumab group. At the landmark survival of two years, the survival rate was 55% (95% CI, 49 - 61) in the two-week group, 55% (95% CI, 49 - 61) in the three-week group and 43% (95% CI, 37 - 49) in the ipilimumab group. Both pembrolizumab groups were superior to the ipilimumab group with a HR of 0.68 (95% CI, 0.53 – 0.87; p=0.0009) for the two-week schedule and HR 0.68 (95% CI, 0.53 - 0.86; p=0.0008) for the three-week group versus ipilimumab. There was no difference between the pembrolizumab groups (HR 1.01, p=0.93). All the subgroups favoured pembrolizumab including the BRAF mutant group.

Another key feature of anti-PD-1 therapies is that the rate of IrAEs is less than occurs with ipilimumab. In Keynote-006, the IrAE rate was 82% (grade 3-4, 17%) in the pembrolizumab two-week group, 77% (grade 3-4, 17%) in the three-week group and 74% (grade 3-4, 20%) in the ipilimumab group. The most common grade 1-2 side effects were fatigue, pruritus, arthralgias, diarrhoea and rash, while the grade 3-4 IrAE included hypothyroidism, hyperthyroidism, colitis, hepatitis, pneumonitis and hypophysitis in the order of 1% or less in the pembrolizumab groups. In the ipilimumab group, grade 3-4 colitis was significantly higher at 7% while the rate of hepatitis, hyperthyroidism, hypophysitis, pneumonitis and nephritis was around 1% or less. The IrAE rate with nivolumab was similar in CheckMate-037 with 14% grade 3-4 events, consisting of rash, thyroid dysfunction, hepatitis and diarrhoea.

Pembrolizumab and nivolumab have both shown to provide durable control and improve long term survival rates in patients with advanced melanoma regardless of their BRAF mutation status with a superior toxicity profile compared to ipilimumab. Longer term follow-up to 10 years would be intriguing at elucidating if indeed the majority of these patients derive long term remission without requiring ongoing anti-cancer therapies.

**Combination anti-PD-1 and anti-CTLA-4 therapy**

Despite ground-breaking response and survival rates seen with single agent anti-PD-1 and anti-CTLA-4 inhibitors, there were still a large proportion of melanoma patients who did not survive their disease. Naturally, interest in combining these therapies emerged. CheckMate-067 was a large three-arm, double-blind phase 3 study randomising 945 treatment naïve patients to nivolumab 3mg/kg every two weeks, nivolumab 1mg/kg every three weeks plus ipilimumab 3mg/kg every three weeks for four doses, followed by nivolumab 3mg/kg every two weeks or ipilimumab 3mg/kg every three weeks for four doses. Of note, 31.5% were BRAF mutant. While the study was not statistically powered to compare nivolumab plus ipilimumab versus nivolumab, the data offers insight into these treatment options.

The study met its co-primary end point of PFS, with a median of 6.9 months (95% CI, 4.3 - 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 - 16.7) in the nivolumab plus ipilimumab group and 2.9 months (95% CI, 2.8 - 3.4) in the ipilimumab group. Significantly longer PFS was observed in the nivolumab plus ipilimumab compared to ipilimumab group (HR, 0.42; 99% CI, 0.31 - 0.57, p<0.001) and in the nivolumab compared to ipilimumab group (HR, 0.57; 99%CI, 0.43 - 0.76, p<0.001). The HR for the comparison between the nivolumab plus ipilimumab and nivolumab group was 0.74 (95% CI, 0.60 - 0.92). ORR was also improved at 43.7% (95% CI, 38.1 - 49.3) in the nivolumab group and 57.6% (95% CI, 52.0 - 63.2) in the nivolumab and ipilimumab group compared to 19.0% (95%CI, 14.9 - 23.8) in the ipilimumab group.

The OS results were subsequently updated by Wolchok et al. in 2017. The median OS was not reached in the nivolumab plus ipilimumab group compared to 19.9 months (95% CI, 17.1 - 24.6) in the ipilimumab group (HR, 0.55, 98%CI, 0.42 - 0.72, p<0.0001) and not reached (95% CI, 29.1 - NR) in
the nivolumab group compared to the ipilimumab group (HR, 0.65, 98% CI, 0.48 - 0.81, p<0.0001). The HR was 0.88 (95% CI, 0.69 - 1.12) in the nivolumab plus ipilimumab compared to the nivolumab group. The benefit was seen across all subgroups including those with elevated LDH and tumours with BRAF mutations. Intriguingly, the HR between nivolumab plus ipilimumab compared to nivolumab in BRAF mutant patients was 0.71 (95% CI, 0.45 - 1.13), as compared to 0.97 (95%CI, 0.74 - 1.28) in the BRAF wildtype patients. Another key finding was the two-year landmark survival rates in the BRAF mutant group (71% with nivolumab plus ipilimumab, 62% with nivolumab and 51% with ipilimumab) and in the BRAF wildtype group (61% with nivolumab plus ipilimumab, 57% with nivolumab and 42% with ipilimumab).

This increase in efficacy came with an associated increased toxicity profile with 55% of patients receiving combination immunotherapy experiencing a grade 3 or 4 IrAE compared to 16.3% in the nivolumab and 27.3% in the Ipilimumab groups. Consistent with previous literature, the most common adverse events were diarrhoea, colitis and deranged liver function tests. 83.4% of patients in the combination therapy arm required immune modulatory agents compared with 47% in the nivolumab, and 55.9% in the Ipilimumab groups.

Keynote-029, an open-label, multi-centre phase Ib combination study of pembrolizumab and ipilimumab enrolled 153 patients to pembrolizumab 2mg/kg and ipilimumab 1mg/kg three weekly for four doses followed by pembrolizumab 2mg/kg three weekly. The ORR was 61% (95%CI, 53 - 69). 27% of patients experienced grade 3-4 IrAE with typical toxicities of rash, colitis, hepatitis, pancreatitis and endocrinopathies.

It is apparent from both these studies that addition of ipilimumab to an anti-PD-1 antibody leads to impressive ORR. Nevertheless, the trade-off is added toxicity, although the lower IrAE rate in Keynote-029 compared to CheckMate-067, could be explained by the lower dose of ipilimumab used. It is yet to be seen if using a lower dose of ipilimumab in combination with pembrolizumab or nivolumab leads to similar overall survival rates as a compromise for lower toxicities.

Immunotherapy in the adjuvant setting

Given the impressive response rates and survival data with immunotherapy in the treatment of metastatic disease, it was a natural progression to assess its utility in the adjuvant setting.

After promising results in a phase 2 trial, the EORTC 18071 trial, a phase 3 double blind, randomised control trial accrued over 900 patients. Randomisation was stratified by disease stage (IIIA, IIIB, IIIC) and subjects were randomised 1:1 to either ipilimumab 10mg/kg or placebo every three weeks for four doses, then every three months for up to three years, disease recurrence or unacceptable toxicity.

Eggermont et al reported in late 2016 that the primary endpoint of relapse free survival (RFS) was met, with RFS of 40.8% in the ipilimumab group compared to 30.3% in the placebo group (HR for recurrence or death 0.76). The secondary end point of OS was also met with five-year median OS of 48.3% in the ipilimumab group and 38.9% in the placebo group (HR = 0.72, 95.1% CI, 0.58 to 0.88; P=0.001). As expected rates of IrAEs were greater in those receiving ipilimumab with grade 3 or 4 toxicity at 41.6% vs 2.7% in the placebo group.

Following on from this, the CheckMate-238 study published by Weber et al. in 2017, compared the same dosing schedule of ipilimumab with nivolumab 3mg/kg every two weeks for up to one year. Although median RFS has not yet been reached in either arm, the trial was halted early due to the superiority of nivolumab. In the planned interim analysis at a minimum follow-up of 18 months, the rate of RFS was significantly improved with nivolumab (66.4%) compared with ipilimumab (52.7%), (HR, 0.65, P <0.0001). The increase in RFS was seen across all subgroups, regardless of PD-L1 or BRAF mutation status. Nivolumab also had a favourable toxicity profile compared to ipilimumab with 14% vs 46% grade 3-4 adverse events and 10% discontinuation rate vs 43% in the ipilimumab arm.

Follow up of both trials is ongoing, however the interim analyses provide promising adjuvant treatment options in locally advanced melanoma, an area of previously unmet need.
Conclusion

Immunotherapeutics such as anti-PD-1 and anti-CTLA antibodies have revolutionised the treatment outcomes of patients with metastatic melanoma providing durable remissions with improved tolerability. The role of immunotherapy in the adjuvant setting has recently been reported with studies showing improved RFS, however longer follow up is needed to fully assess the magnitude of survival benefit. Immune related adverse events whilst not uncommon, have generally proven to be effectively managed with corticosteroids. Combinations of anti-PD-1 and anti-CTLA-4 inhibitors provide increased response rates and PFS however comes at the expense of higher rates of adverse events. Larger, randomised trials of novel checkpoint inhibitors both as single agents and in combination with anti-PD-1 are required to establish the long term efficacy and toxicity however they provide a promising approach for therapy via heightened stimulation of the T cell immune response.
### Table 1: Summary of pivotal immunotherapy melanoma studies

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Trial name</th>
<th>Phase</th>
<th>Treatment</th>
<th>Treatment Line</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodi et al (2010)</td>
<td>MDX010-20</td>
<td>III</td>
<td>Ipi/gp100 or ipi/placebo or gp100/placebo</td>
<td>Second or later</td>
<td>OS: 10.1 vs 10 vs 6.5 months</td>
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<td></td>
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<td>(post chemo or</td>
<td>HR ipi vs gp100: 0.66 p=0.003</td>
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<td></td>
<td></td>
<td>IL-2)</td>
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<tr>
<td>Robert et al (2011)</td>
<td>CA184-024</td>
<td>III</td>
<td>Ipi/dacarbazine or dacarbazine</td>
<td>First line</td>
<td>OS: 11.2 vs 9.1 months</td>
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<td>HR 0.72 p= &lt;0.001</td>
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<tr>
<td>Larkin et al (2017)</td>
<td>CHECKMATE 037</td>
<td>III</td>
<td>Nivo versus chemo</td>
<td>Second line*</td>
<td>OS: 15.7 vs 14.4 months</td>
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<tr>
<td>Schacter et al (2017)</td>
<td>KEYNOTE 006</td>
<td>III</td>
<td>Pembro 2 weekly or pembro 3 weekly or ipi</td>
<td>First line</td>
<td>OS: NR vs NR vs 16 months</td>
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<td></td>
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<td>HR pembro 2w vs ipi 0.68 p=0.0009</td>
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<td>HR pembro 3w vs ipi 0.68 p=0.0008</td>
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<tr>
<td>Larkin et al (2015)</td>
<td>CHECKMATE 067</td>
<td>III</td>
<td>Nivo/iPi or nivo or Ipi</td>
<td>First line</td>
<td>PFS: 11.5 vs 6.9 vs 2.9 months</td>
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<td>OS: NR vs NR vs 20.0 months</td>
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<td>HR nivo/ipi vs ipi 0.55 p&lt;0.0001</td>
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<td>HR nivo vs ipi -.63 p&lt;0.0001</td>
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<td>I</td>
<td>Pembro/Ipi</td>
<td>First line</td>
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<td>I</td>
<td>Pembro + T-VEC</td>
<td>First line</td>
<td>ORR: 57%</td>
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<tr>
<td>Gangadhar et al (2016)</td>
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<td>I</td>
<td>Pembro + IDO1 inhib</td>
<td>Any line**</td>
<td>ORR 74% in first line</td>
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*Prior targeted therapies allowed

**Excluding prior immune checkpoint inhibitors
References