The end of the beginning: PD-1 inhibition as the new standard of care first-line immunotherapy in metastatic melanoma

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Historically, treatment options for metastatic melanoma (MM) have been limited, yielding a median overall survival (OS) of 8–10 months and a 5-year survival of less than 10% [1]. These dismal results have been radically improved due to the dramatic advances in immunotherapy for MM. The immunotherapy revolution began with the CTLA-4 inhibitor ipilimumab (Bristol-Myers Squibb, NY, USA), the first medication to show an OS benefit in MM [2,3]. Subsequently, the two PD-1 inhibitors, nivolumab (Bristol-Myers Squibb) and pembrolizumab (Merck, NJ, USA), have demonstrated efficacy in ipilimumab-treated and naïve patients, giving physicians an array of immunotherapeutic strategies (see [Table 1](#) summary of trials) [4–10]. In 2015, clinical trials testing head-to-head and immunotherapy combinations have been reported, thus marking the beginning of the second phase of the immunotherapy revolution. Herein, we review the data in the individual, comparative and combination studies, which collectively establish PD-1 inhibition as the new choice for first-line immunotherapy in MM.

Immune checkpoint inhibitors in MM

The efficacy of ipilimumab was established by two randomized Phase III clinical trials. The pivotal CA184-020 study randomized 676 patients to a ipilimumab plus glycoprotein 100 (gp100) vaccine, ipilimumab alone or gp100 alone in patients previously treated with chemotherapy or IL-2 [3]. Median OS was superior for ipilimumab at 10 months versus 6.4 months for gp100 alone [3]. The second study, CA184-024, randomized 502 patients to dacarbazine with ipilimumab or placebo. The ipilimumab arm demonstrated a median OS of 11.2 months and a 5-year OS of 18% [2]. Perhaps most significantly, long-term survival in a pooled analysis of 1861 patients from both trials and eight other prospective trials found a 10-year OS of 21%, with a plateau in OS reached at 3 years [11]. The potential for 10-year OS remains a tremendous advance; the majority of patients receive no benefit from ipilimumab with an overall response rate (ORR) of 11–19% and a median progression-free survival (PFS) of 2–3 months (see [Table 1](#) trial summary) [2–5,8].

Subsequently, the PD-1 inhibitors showed good response in Phase I trials [7,12] (see [Table 1](#))

KEYWORDS

- ipilimumab • metastatic melanoma • nivolumab
- PD-1 antibody
- pembrolizumab

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Table 1. Selected clinical trial for immune checkpoint inhibitors.

Study	Arms	ORR	PFS	OS	Safety outcomes (CTCAE)	Ref.
<i>Ipilimumab first-line immunotherapy studies</i>						
CA184-020 Hodi <i>et al.</i> Phase III (n = 127)	IPI/gp100 IPI or gp100 alone	IPI: 10.9%	IPI: 2.9 months	IPI: 10 months	Any grade: 97% Any irAE: 61% Grade 3+: 15%	[3]
CA184-024 Robert <i>et al.</i> Phase III (n = 250)	IPI/DTIC DTIC	IPI/DTIC: 15% DTIC: 10% mDOR: 19 months	24% risk reduction in progression	IPI/DTIC: 11.2 months (5-year OS: 18%) DTIC: 9 months	Any grade: 99% Any irAE: 78% Grade 3+: 42%	[2]
<i>Post-ipilimumab treated, PD-1 inhibitor trials, PEM & NIV</i>						
KEYNOTE-001 Phase I (n = 655)	PEM 2 mg/kg q3W 10 mg/kg q3W 10 mg/kg q2W	All: 34% IPI-T: 29% IPI-N: 38% CR: 6% mDOR: NR	All: 5.2 months IPI-T: 4.9 months IPI-N: 5.4 months	1 year: 67% 2 years: 50%	Any grade: 83% Grade 3+: 14%	[7]
KEYNOTE-002 Phase II (n = 540)	PEM 2 mg/kg q3W 10 mg/kg q3W Chemo	PEM 2 mg/kg: 21% 10 mg/kg: 26% Chemo: 4%	6-month PFS 2 mg/kg: 34% 10 mg/kg: 38% Chemo: 16%	NR	Any grade: 68–74% Grade 3+: 11–14%	[13]
Topalian <i>et al.</i> Phase I (n = 107)	NIV dose escalation 0.1–10 mg/kg q2W	NIV 3 mg/kg 41%	NIV: 3.7 months	NIV: 16.8 months	Any grade: 54% Grade 3+: 22%	[12]
CheckMate-037 Phase III (n = 272)	NIV 3 mg/kg q2W Chemo	NIV: 32% Chemo: 11%	NIV: 4.7 months Chemo: 4.2 months	NR	Any grade: – NIV: 68% – Chemo: 80% Grade 3+: – NIV: 9% – Chemo: 31%	[10]
<i>First-line PD-1 inhibitor trials, PEM & NIV</i>						
KEYNOTE-006 Phase III (n = 834)	PEM 10 mg/kg q2W 10 mg/kg q3W IPI	PEM q2W: 34% q3W: 33% IPI: 12%	PEM: 6-month PFS q3W: 47% q2W: 46% IPI: 27%	PEM: 12-month OS q3W: 74% q2W: 68% IPI: 58%	Any grade: – PEM: 73–80% – IPI: 73% Grade 3+: – PEM: 12% – IPI: 20%	[8]
CheckMate-066 Phase III (n = 418)	NIV 3 mg/kg q2W DTIC	NIV: 40% DTIC: 14%	NIV: 5.1 months DTIC: 2.2 months	NIV 1 year: 73% DTIC: 10.8 months	Any grade: – NIV: 74% – DTIC: 76% Grade 3+: – NIV: 12% – DTIC: 18%	[6]
Sznol <i>et al.</i> Phase I (n = 53)	IPI/NIV	IPI/NIV: 42% CR: 17% DOR: NR	NR	IPI/NIV 2-year OS: 75%	NR IPI/NIV: 62%	[16]
Checkmate 067 Phase III (n = 945)	IPI/NIV, NIV or IPI alone	IPI/NIV: 58% NIV: 44% IPI: 19%	IPI/NIV: 11.5 months NIV: 6.9 months IPI: 2.9 months	NR	Any grade: – IPI/NIV: 96% – NIV: 82% – IPI: 86% Grade 3+: – IPI/NIV: 55% – NIV: 16% – IPI: 27%	[4]

Chemotherapy arms included carboplatin plus paclitaxel, paclitaxel alone, dacarbazine or temozolomide.

CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; DOR: Duration of response; DTIC: Dacarbazine; gp100: Glycoprotein 100 vaccine; IPI: Ipilimumab; irAE: Immune-related adverse event; mDOR: Median duration of response; NIV: Nivolumab; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PEM: Pembrolizumab; PFS: Progression-free survival; q2w: Every 2 weeks; q3w: Every 3 weeks.

Table 1. Selected clinical trial for immune checkpoint inhibitors (cont.).

Study	Arms	ORR	PFS	OS	Safety outcomes (CTCAE)	Ref.
First-line PD-1 inhibitor trials, PEM & NIV (cont.)						
Checkmate 069 Phase III (n = 142)	IPI/NIV IPI	IPI/NIV: 61% (CR: 22%) IPI: 11% (CR: 0%)	<i>BRAF</i> wild-type IPI/NIV: NR IPI: 4.4 months <i>BRAF</i> ^{V600} IPI/NIV: 8.5 months IPI: 2.7 months	NR	Any grade: – IPI/NIV: 91% – IPI: 93% Grade 3+: – IPI/NIV: 51% – IPI: 11%	[5]

Chemotherapy arms included carboplatin plus paclitaxel, paclitaxel alone, dacarbazine or temozolomide.

CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; DOR: Duration of response; DTIC: Dacarbazine; gp100: Glycoprotein 100 vaccine; IPI: Ipilimumab; irAE: Immune-related adverse event; mDOR: Median duration of response; NIV: Nivolumab; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PEM: Pembrolizumab; PFS: Progression-free survival; q2w: Every 2 weeks; q3w: Every 3 weeks.

and moved on to second-line studies versus chemotherapy in ipilimumab-treated patients. The KEYNOTE-002 Phase II trial of 540 patients of pembrolizumab (2 or 10 mg/kg doses every 3 weeks) versus investigators' choice of chemotherapy showed an ORR of 21, 26, 4% and a 6-month PFS of 34, 38, and 16% respectively [13]. The CheckMate-037 trial showed nivolumab was superior to investigator's choice chemotherapy, offering an ORR of 31.7% (38/120) versus 10.6% (5/47) and a PFS of 4.7 months versus 4.2 months [10]. Both trials showed durability for PD-1 inhibitors and a more than threefold increase in ORR, leading to regulatory approval for both drugs in ipilimumab-treated patients.

First-line trials in ipilimumab-naïve population in MM

CheckMate-066 was reported in 2014 and tested nivolumab versus dacarbazine as first-line therapy for *BRAF* wild type melanoma. This 418 patient Phase III study showed a PFS advantage for nivolumab of 5.1 versus 2.2 months and a 1-year of OS 73 versus 42% [6]. However, since the chemotherapy was used as the control arm and long-term results are not yet known, ipilimumab remained an option for first-line therapy. In 2015, KEYNOTE-006 was presented. In this randomized Phase II study, 834 patients were treated with pembrolizumab (10 mg/kg every 2 weeks) versus ipilimumab, with pembrolizumab demonstrating a threefold increase in ORR (34 versus 12%) and a nearly doubled 6-month PFS (47 versus 26.5%) with durable responses on parallel with ipilimumab (see Table 1) [8,14]. Shortly thereafter, the three arm CheckMate-067 trial randomized 945 patients to combination nivolumab plus ipilimumab or nivolumab monotherapy, with each arm compared to the control arm

of ipilimumab monotherapy [4]. In comparing nivolumab to ipilimumab monotherapy, PFS for nivolumab was superior at 6.9 versus 2.9 months and an ORR of 43.7 versus 19% [4]. Adverse events (AEs) are less with PD-1 inhibitors. Grade 3–4 AE were seen in 10–13% with pembrolizumab [8] and 16% with nivolumab [4], compared to 20–27% with ipilimumab [4,8]. Thus, the PD-1 inhibitors have improved responses, survival and side effect profiles compared with ipilimumab.

The improved ORR and PFS trends for PD-1 inhibitors are translating into an OS benefit. First-line trials show improved 1-year OS for nivolumab of 73% [6] and pembrolizumab 68–74% (2 and 10 mg/kg) [8] over ipilimumab's median OS of 11.4 months [11]. The OS data for CheckMate-067 are pending, although prior experience justifies optimism that OS will also be superior to ipilimumab. Second-line trials have shown improved OS for nivolumab at 2 years of 48% [15] and pembrolizumab at 2 years of 50% [7]. There is also a doubling of survival with second-line nivolumab of 41% at 3 years [15], the same time point ipilimumab began to show a plateau on the survival curve with an OS of 21% [11]. Whether there will be a plateau of survival for PD-1 inhibitors is yet to be seen.

First-line combination nivolumab plus ipilimumab versus nivolumab monotherapy

The combination of nivolumab and ipilimumab has previously demonstrated increased OS with 1- and 2-year OS rates of 82 and 75% in a Phase I study, but with significant added toxicity [9,16]. The combination arm of CheckMate-067 suggests that the benefit of the combination over nivolumab monotherapy may be limited to PD-L1 negative patients. PD-L1 IHC positive tumors (defined as >5%) had a median PFS of 14 months

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in both the combination and nivolumab monotherapy groups, compared to a median PFS in PD-L1 negative tumors of 11.2 and 5.3 months, respectively [4]. The ORR among PD-L1 positive tumors was 72.1 versus 57.5%, whereas in PD-L1 negative tumors it was 54.8 versus 41.3% [4]. Therefore, although the study was not powered to compare the combination to nivolumab monotherapy, nor to compare the effect of PD-L1 staining on these arms, the results suggest that the benefit of combination therapy may be limited to PD-L1 IHC negative tumors, and that nivolumab monotherapy is equivalent to combination therapy in PD-L1 positive melanoma.

The combination arm increased toxicity over either monotherapy arm in line with prior studies. Grade 3+ AEs were more common in the combination (55%) than nivolumab (16%) or ipilimumab (27%) [4]. Common AEs were diarrhea 44%, fatigue 35% and pruritus 33% [4]. Combination therapy frequently had AEs in more than one organ, which is uncommon in monotherapy. Importantly, there were no deaths from the combination therapy, suggesting that increased physician awareness of the management of immune mediated toxicities is translating into better outcomes. Patients discontinued the study due to treatment-related AEs in 36.4% of the combination arm, 7.7% of the nivolumab arm and 14.8% of the ipilimumab arm [4]. The most frequent reason for discontinuation of the combination was toxic effects in 38% of patients (120/313), compared to progressive disease from

nivolumab in 49% (154/313) as well as from ipilimumab monotherapy in 65% of patients (202/313) [4]. The median number of doses for the combination was 4 doses of each nivolumab and ipilimumab with 47% (147/313) having received >4 doses of nivolumab [4].

Conclusion

The treatment of advanced melanoma has now progressed to an era of comparative efficacy studies between agents with proven OS benefit. The data from first-line studies comparing first-line PD-1 inhibitor therapy to ipilimumab now firmly establishes PD-1 inhibitors as the preferred first-line choice. Whether ipilimumab should be used in combination as first-line therapy remains a topic for debate, and whether ipilimumab retains efficacy in the second-line setting is unknown. Future studies will need to further define the appropriate biomarkers for treatment selection, as well as the role of sequencing of targeted therapies with immunotherapy.

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