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Blockade of Programmed Cell Death Protein-1 Pathway for the Treatment of Melanoma

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Abstract

Metastatic melanoma is a very deadly type of skin cancer with poor prognosis and low 5-year survival rates. Until recently, patients with metastatic melanoma had very few treatment options, which only included dacarbazine and aldesleukin. In 2011, the first checkpoint blocker, ipilimumab was approved for the treatment of unresectable metastatic melanoma but its success was eclipsed by low response rates and high incidence of adverse events. Later in 2014, anti-PD-1 antibodies, nivolumab and pembrolizumab were approved for the treatment of metastatic melanoma. With comparatively high response rates and manageable safety profile, PD-1 blockers were remarkably successful in the treatment of melanoma and also other cancer subtypes such as non-small cell lung cancer and metastatic urothelial carcinoma. This article highlights the success of anti-PD-1 antibodies, discusses the mechanism of PD-1:PD-L1/2 pathway, responses of melanoma patients to PD-1 blockers and the research on improving response rates to PD-1 blockers.

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Introduction

Melanoma is a type of skin cancer caused due to uncontrolled proliferation of melanocytes, the melanin producing cells located at the basal layer (*Stratum basale*) of skin epidermis. Though it is not the commonest type of skin cancer as it accounts for less than 5 % of all skin cancer types, it is the most deadly type of skin cancer and nearly 80 % of the skin cancer-related deaths are due to melanoma. Melanoma is more prevalent in Caucasian population and exposure to UV radiation and familial history are considered as the most common causative factors. While, primary melanoma can be easily treated by surgical resection and has a very good post-treatment prognosis rate, metastatic melanoma has poor prognosis and less than 15 % of the patients survive for 5-years. Until recently, patients with metastatic melanoma had very few treatment options with a handful of approved drugs. For decades, dacarbazine and high-dose IL-2 were the only FDA-approved drugs available for metastatic melanoma patients [1]. The approval of vemurafenib (BRAFV600E inhibitor) and ipilimumab (anti-CTLA-4 monoclonal antibody) in 2011 was a major milestone in treatment of melanoma as the drugs increased the survival rates of patients and also laid foundation for further research in immunotherapy and targeted therapy of melanoma (Figure 1). Especially, the success of ipilimumab in melanoma paved way for the monoclonal antibodies targeting PD-1 receptors [2]. In 2014, 3 years after approval of ipilimumab, 2 anti-PD-1 antibodies, pembrolizumab and nivolumab were approved for the treatment of unresectable metastatic melanoma. To date, anti-PD-1 antibodies are the most successful drugs for the treatment of melanoma and nearly 40% of patients reportedly respond anti-PD-1 therapy [3]. Combination of anti-CTLA-4 and anti-PD-1 antibodies, approved in 2015 was found to increase the response rates even further and nearly 50% of patients reportedly showed objective responses to therapy [4-6]. This present article discusses the significance of PD-1 blockade in melanoma treatment with details on checkpoint mediated regulation of T-cell activity, functions of PD-1:PD-L pathway, response rates of approved PD-1 blockers including nivolumab and pembrolizumab and details of PD-1:PD-L pathway targeting antibodies in clinical development.

Immune Checkpoints

Anti-tumor immune response mainly involves cytotoxic activity of natural killer cells (NK cells) and cytotoxic T-lymphocytes (CTLs) and cytokine-secreting activity of T-helper1 (Th1) cells. NK cells are innate immune cells that recognize tumor cells, which do not express self-antigens, whereas CTLs and Th1 cells are adaptive immune cells that are primed to recognize specific antigens on tumor cells. NK cells and CTLs induce lysis in target cells mainly by secreting perforin and granzyme B over the target cell surface. Th1 cells mainly act by amplifying the activity of NK cells and CTLs through CD40:CD40L interactions and by secreting interferon-γ (IFN- γ), a cytotoxic cytokine that is also secreted by CTLs. Excessive cytotoxic activity of effector immune cells is modulated by specialized receptors, known as checkpoints, expressed on their surface. Upon interacting with their respective ligands, checkpoints down regulate the cytotoxic activity, cytokine secretion and proliferation of effector immune cells. The main function of checkpoints is to prevent the activation of 'hyperreactive' T-cells and excessive tissue damage during immune response. Tumor cells evade immune response by expressing ligands for the checkpoint receptors. Further, the inflammatory conditions in the tumor milieu also induce checkpoint receptor expression on immune effector cells and promote immune evasion. Five checkpoint receptors including CTLA-4, PD-1, TIGIT, TIM-3 and LAG-3 are mainly targeted for the treatment of cancer and monoclonal antibodies against CTLA-4 and PD-1 are approved for the treatment of melanoma. Details of receptors and their ligands are presented in Table 1. Targeting PD-1:PD-L1 pathway has been the most successful strategy for the treatment of melanoma as seen by the remarkably higher response rates compared to other drugs. To date, 5 drugs targeting PD-1:PD-L1 have been approved for the treatment of various types of cancers and several others are in advanced stages of testing (Table 2).

PD-1:PD-L Pathway

Programmed cell death protein (PD-1 or PDCD1) is a cell surface receptor commonly expressed on activated T-cells. It was first described by Honjo and coworkers from studies on pathways of programmed cell death [7]. The cell types expressing PD-1 receptors include activated monocytes, macrophages, myeloid L1

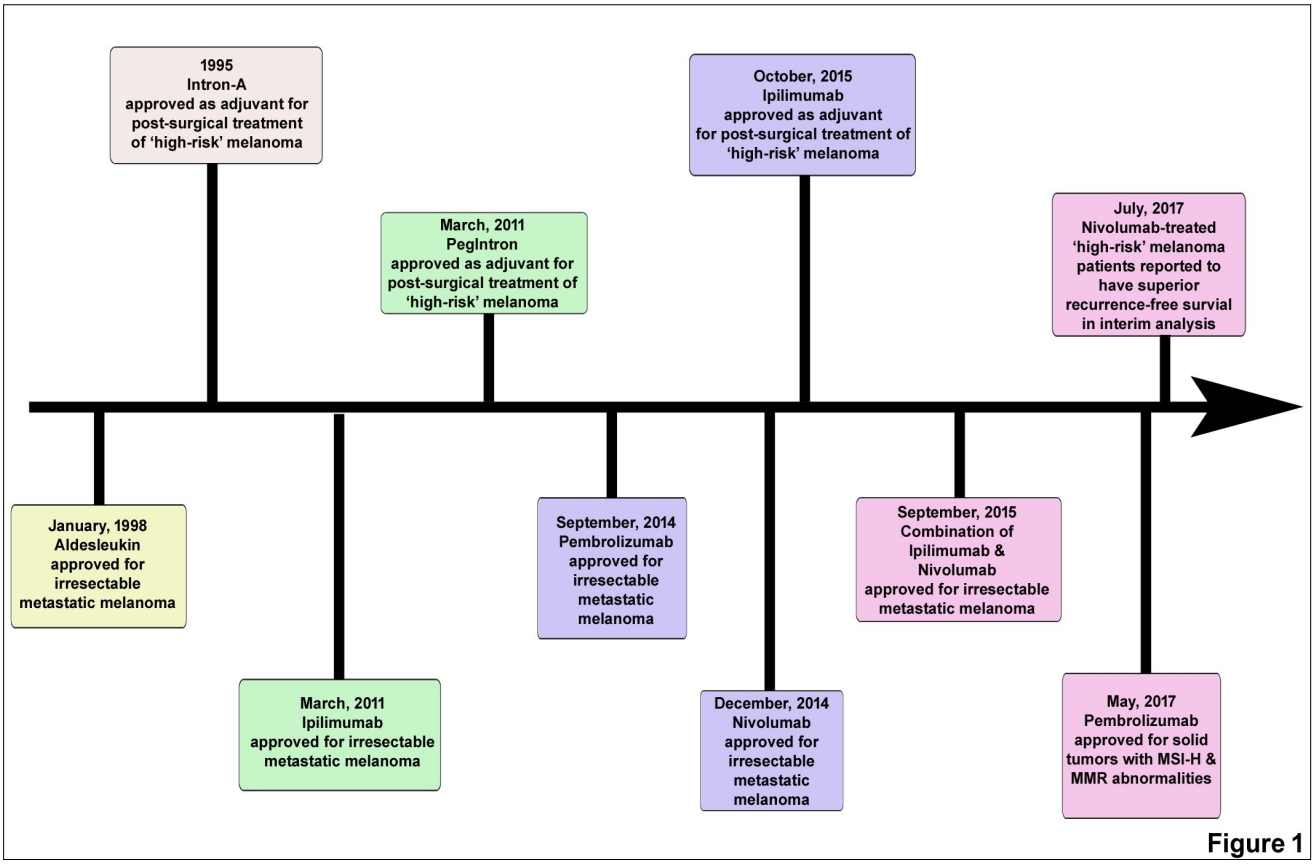

Figure 1: Milestones in the clinical development of immunotherapy of melanoma

Table 1: Commonly targeted checkpoint receptors and their ligands

Receptor	Ligands	Cells expressing receptor	Cells expressing ligands
CTLA-4	CD80 & CD86	Activated T-cells, TRegs, exhausted effector T cells	APCs
PD-1 (PDCD1 & CD279)	PD-L1 & PD-L2	Activated T-cells, TRegs, NK cells, macrophages & exhausted effector T cells	APCs, hematopoetic & nonhematopoetic cells & tumor cells
TIGIT	PVR/ CD155 & CD112	Activated T-cells, memory T-cells, TRegs, NK cells, NKT cells & exhausted effector T cells	APCs, fibroblasts, endothelial cells & tumor cells
TIM-3 (HAVCR2)	Galectin-9, Ceacam-1, HMGB-1 & phosphatidyl serine	Activated T cells, TRegs, DCs, NK cells & monocytes	APCs, tumor cells
LAG-3 (CD223)	MHC II class LSECtin Galectin-3	Activated CD4+ T-cells, TRegs, activated $CD8^+$ T-cells & NK cells	APCs Liver cells and tumor cells

Table 2: List of FDA approved drugs that target PD-1:PD-L1 pathway as of October, 2017

Drug; Target	Brand name; Marketed by	Approved indications*	Recommended dose & Route*
Nivolumab Anti-PD-1	Opdivo; Bristol-Myers Squibb	Metastatic melanoma, Metastatic Non-small cell lung cancer (NSCLC), Renal cell carcinoma (RCC), Classical Hodgkins lymphoma, Head and Neck Squamous cell carcinoma (HNSCC), Urothelial Carcinoma Microsoft Himalaya	For melanoma, NSCLC, RCC, & urothelial carcinoma: 240 mg IV infusion for every 2 weeks until disease progression or toxicity For Classical Hodgkins lymphoma & HNSCC: 3 mg/kg IV infusion for every 2 weeks until disease progression or toxicity
Pembrolizumab Anti-PD-1	Keytruda; Merck	Metastatic melanoma, Metastatic NSCLC, Classical Hodgkins lymphoma, HNSCC Microsoft Himalaya	For NSCLC, classical Hodgkins lymphoma & HNSCC: 200 mg IV infusion for every 2 weeks until disease progression, toxicity or up to 24 months For melanoma: 2 mg/kg IV infusion for every 3 weeks until disease progression or toxicity
Atezolizumab Anti-PD-L1	Tecentriq; Genentech/Roche	Urothelial carcinoma, Metastatic NSCLC	1200 mg IV infusion for every 3 weeks until disease progression or toxicity
Avelumab Anti-PD-L1	Bavencio; Pfizer	Merkel cell carcinoma, Metastatic urothelial carcinoma	10 mg/kg IV infusion for every 2 weeks until disease progression or toxicity
Durvalumab Anti-PD-L1	Imfinzi; Astrazeneca	Metastatic urothelial carcinoma	10 mg/kg IV infusion for every 2 weeks until disease progression or toxicity

*-Refer to respective FDA-approved package inserts for complete information

DCs, activated CD4 and CD8 T-cells, TRegs, natural killer T-cells (NKT) cells, natural killer cells and activated B-cells [8-9]. The ligands for PD-1 receptors, PD-L1 and PD-L2 differ in their expression profile and affinity to PD-1 receptors. PD-L1 has comparatively lower affinity to PD-1 receptors and is the widely expressed ligand. It is found on T-cells, B-cells, macrophages, DCs, non-hematopoietic cell types such as vascular endothelial cells, fibroblastic reticular cells, epithelia, pancreatic islet cells, astrocytes and neurons and also on cells such as trophoblasts in the placenta, retinal pigment epithelial cells and neurons in the eye that are known to be immune privileged sites [8-9]. PD-L2 has approximately 3-fold higher affinity to PD-1 receptors compared to PD-L1 and is less widely expressed compared to PD-L1; it is seen mainly on activated macrophages and DCs [10]. PD-1:PD-L interaction results in inhibition of characteristic features of immune effector-cell response such as cell proliferation, cytokine secretion and cytotoxic ability [3]. PD-1:PD-L pathway was also shown to enhance FoxP3 expression in CD4 T-cells and promote their differentiation into induced TReg (iTReg) cells in murine models [11]. The expression of PD-L1 on cell surface is induced by IFN-γ and the pathway serves to prevent excessive tissue damage caused by immune effector cells (Figure 2) [9]. Tumor cells utilize this protective mechanism and escape immune response by expressing PD-L1. Moreover, chronic

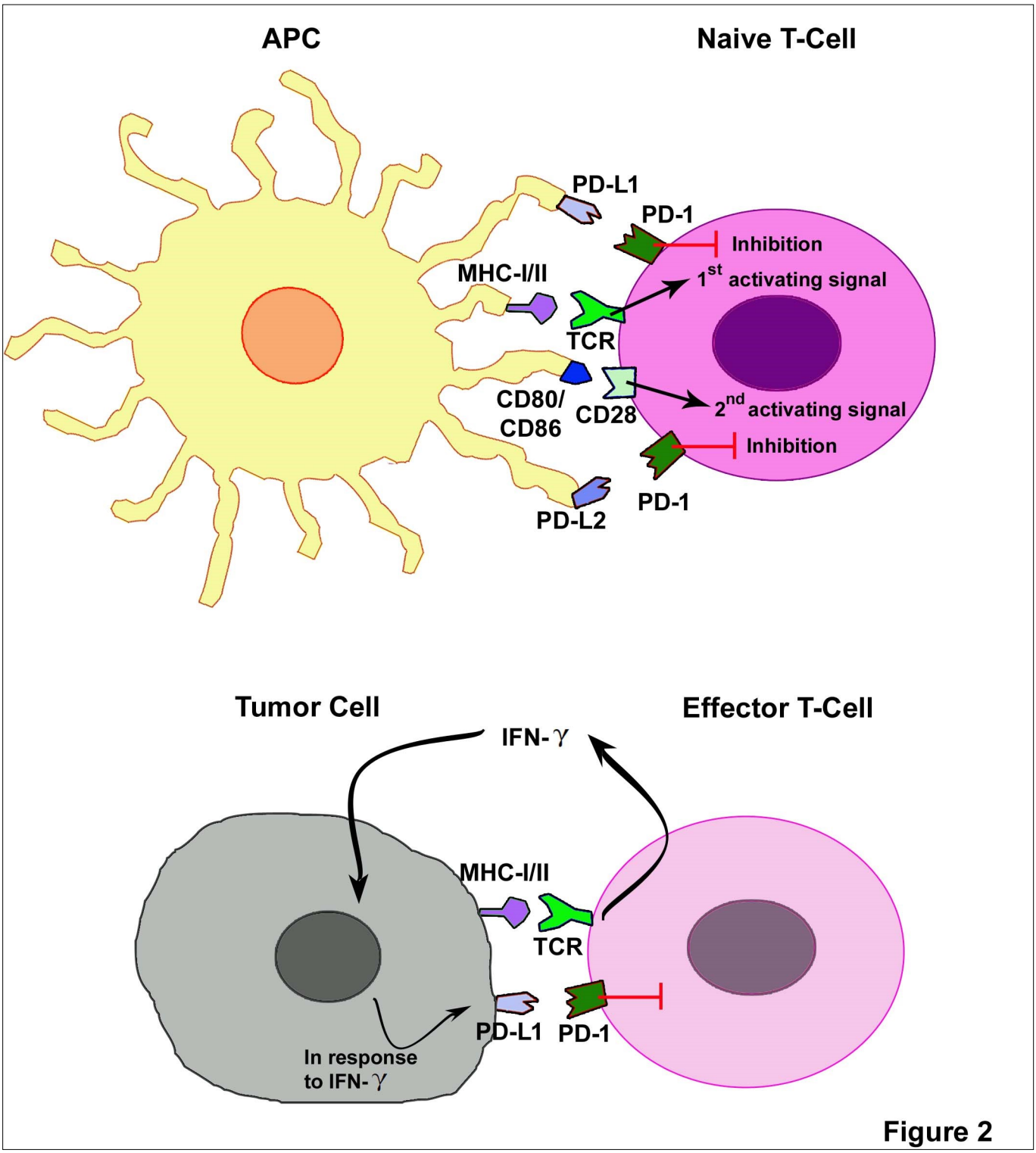

Figure 2: PD-1:PD-L1/2 pathway in the regulation of anti-tumor immune response

inflammatory conditions in the tumor microenvironment (TME) induce a dysfunctional phenotype in effector T-cells, characterized by increased expression of PD-1, decreased rate of proliferation and decreased cytotoxic ability [12]. PD-1 blockers have shown enormous potential in the treatment of melanoma and 2 anti-PD-1 monoclonal antibodies including nivolumab and pembrolizumab have been approved for the treatment of metastatic melanoma [3].

Nivolumab

Nivolumab, is a fully human anti-PD-1 IgG4 kappa immunoglobulin monoclonal antibody, developed by Bristol-Myers Squibb and marketed under the trade name 'Opdivo' [3]. It was approved by US FDA in December 2014 and its combination with ipilimumab, an anti-CTLA-4 monoclonal antibody was approved in September 2015 for the treatment of metastatic melanoma with unresectable tumors [3]. Efficacy of nivolumab in patients with advanced melanoma was tested in 2 randomized phase 3 trials (Table 3); one study compared efficacy of nivolumab with dacarbazine in patients without BRAF mutation and other study compared nivolumab treatment with investigator choice of chemotherapy in patients with advanced melanoma with or without BRAF mutation [13-14]. The first study was a double blind study, designed to analyze the overall survival (OS); previously untreated metastatic melanoma patients (n=418) were randomly assigned in a 1:1 ratio to receive nivolumab (3 mg/kg every 2 weeks plus dacarbazine-matched placebo every 3 weeks) or dacarbazine (1000 mg/m2 every 3 weeks plus nivolumab -matched placebo every 2 weeks) [13]. The results of the study reported an 1-year OS rate of 72.9 % (95 % CI, 65.5–78.9) in nivolumab group as compared to 42.1 % (95 % CI 33.0–50.9) in dacarbazine group (hazard ratio (HR) for death, 0.42; $p < 0.001$). Median progression-free survival (PFS) was reported as 5.1 months in nivolumab group and 2.2 months in dacarbazine group (HR for death or progression of disease, 0.43; $p < 0.001$). Objective response rates (ORR) in nivolumab group was reportedly 40.0% (95 % CI, 33.3–47.0) and 13.9 % (95 % CI, 9.5–19.4) in dacarbazine group (odds ratio 4.06; $p < 0.001$) [13]. The second phase 3 trial was in a multi-center and open -label setting where researchers involved in tumor assessment were masked to treatment assignment. Patients with unresectable or metastatic melanoma who progressed after ipilimumab and ipilimumab plus BRAF inhibitor therapy (if they had BRAF mutations) were randomized in a 2:1 ratio to receive either 3 mg/kg nivolumab intravenously every 2 weeks (n = 272) or investigator's choice of chemotherapy (n = 133) in the form of either single-agent dacarbazine (1000 mg/m2 every 3 weeks) or the combination of carboplatin (AUC 6 every 3 weeks) plus paclitaxel (175 mg/m2 every 3 weeks). In the patients (n = 120, nivolumab group; n = 47, chemotherapy group) who met the criterion of minimum duration of follow up (6 months) at the time of report, an ORR of 32 % (n = 38/120; 95 % CI, 23.5–40.8) was recorded in nivolumab group and 11 % (n = 5/47; 95 % CI, 3.5–23.1) in chemotherapy group (Table 3). Median PFS in nivolumab group was 4.7 months and 4.2 months in chemotherapy group; hazard ratio for death or disease progression was 0.82 (99.99% CI 0.32-2.05) [14].

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody targeting PD-1 with an IgG4 kappa immunoglobulin backbone. It is developed and marketed by Merck with the trade name 'Keytruda'. The drug was approved for treatment of unresectable and metastatic melanoma in September 2014 [15]. Similar to nivolumab, efficacy of pembrolizumab was studied in treatment-naïve as well as ipilimumab and/or BRAF inhibitor refractory melanoma patients [16-17]. In the first phase 3 study, patients with advanced melanoma were randomized and assigned in a 1:1:1 ratio to receive pembrolizumab, 10 mg/kg every 2 weeks or every 3 weeks or ipilimumab, 3 mg/kg every 3 weeks. The study reported significantly better ORRs in pembrolizumab treated patients ($p<0.001$ for both treatment regimen) compared to ipilimumab treated patients. ORR in patients receiving pembrolizumab every 2 weeks was 33.7 % (95 % CI, 28.2-39.6), every 3 weeks was 32.9 % (95 % CI, 27.4-38.7) and in patients receiving ipilimumab was 11.9 % (95 % CI, 8.3-16.3). HR for death in pembrolizumab every 2 weeks versus ipilimumab group was 0.63 (95 % CI, 0.47–0.83; $p = 0.0005$) and pembrolizumab every 3 weeks versus ipilimumab group was 0.69 (95 % CI, 0.52–0.90; $p = 0.0036$). The estimated 6-month PFS were found to be 47.3 % and 46.4 % in patients who received pembrolizumab for every 2 weeks and 3 weeks respectively, and 26.5 % in patients treated with

Table 3: Efficacy of checkpoint blockers documented in clinical trials

ose	Response rates (%) (95% CI)	Survival; OS/PFS months (95 % CI)	Hazard ratio compared to other treatment arm (95 % CI)	References
Ipilimumab (Anti-CLTA-4; Trade name: Yervoy; Bristol Myers Squibb)				
3 mg/kg Q3W	10.9% (6.3 -17.4)	Median OS: 10.1 months (8.0-13.8) Median PFS: 2.86 months (2.76-3.02) 12- & 24-month OS rate: 45.6% & 33.2% respectively	HR for death: 0.66 (0.51-0.87)	[26]
10 mg/kg Q3W	15.0% (11.8-19.5)	Median OS: 15.7 months (11.6-17.8) 12- & 24-month OS rate: 54.3% & 38.5% respectively Median PFS: 2.8 months (2.8-3.0)	HR for death: 0.84 (0.70-0.99)	[27]
10 mg/kg Q3W+Dacarbazine 850 mg/m2	15.20% (CI: NA)	Median OS: 11.2months (9.4-13.6) 12- & 24- month OS rate: 47.3 % & 28.5 % respectively	HR for death: 0.72 (0.59-0.87); HR for progression: 0.76 (0.63-0.93)	(28-29]
Nivolumab (Anti-PD-1; Trade name: Opdivo; Bristol Myers Squibb)				
3 mg/kg Q2W	31.7% (23.5-40.8)	Median PFS: 4.7 months (2.3-6.5) 6-month PFS rate: 48%	HR for disease progression, 0.82 (99.99% CI 0.32-2.05)	[14]
3 mg/kg Q2W	40.0% (33.3-47.0)	Median OS: Not Reached 12-month OS rate: 72.9% Median PFS: 5.1 months (3.5-10.8)	HR for death: 0.42 (99.79% CI, 0.25-0.73); HR for disease progression: 0.43 (95% CI, 0.34-0.56)	[13]
Pembrolizumab (Anti-PD-1; Trade name: Keytruda; Merck)				
2 mg/kg or 10 mg/kg Q3W	21% (15-28) in 2mg/kg group & 25% (19-32) in 10 mg/kg group	Median PFS: 2.9 months in both groups 6-month PFS rate: 34% in 2 mg/kg group & 38% in 10 mg/kg group	HR for disease progression 0.57 (0.45–0.73) in 2mg/kg group & 0.50 in 10 mg/kg group (0.39-0.64)	[17]

10 mg/kg Q2W or Q3W	33.7% (CI: NA) in Q2W group & 32.9% (CI: NA) in Q3W group	Median OS: Not reached for any study group 12-month OS rate: 74.1 for Q2W & 68.4% for Q3W Median PFS: 5.5 months in Q2W group & 4.1 months in Q3W group 6-month PFS rate: 47.3% in Q2W group & 46.4% in Q3W group	HR for death: 0.63 (0.47-0.83) for Q2W & 0.69 (0.52 -0.90) for Q3W; HR for disease progression: 0.58 (0.46-0.72) for Q2W & 0.58 (0.47 -0.72) for Q3W	[16]
Nivolumab and Ipilimumab combination				
Nivo-1 mg/ kg, Ipi-3 mg/ kg Q3W X4 doses followed by Nivo-3 mg/ kg Q2W	61% (49-72 in BRAF -WT patients & 52% (31-73) in BRAF-MT patients	Median PFS: Not Reached in BRAF-WT patients & 8.5 months (2.8-NE) in BRAF-MT patients	HR for disease progression or death: 0.40 (0.23-0.68) in BRAF-WT patients; 0.38 (0.15-1.00) in BRAF-MT patients	[4]
Nivo-1 mg/ kg, Ipi-3 mg/ kg Q3W X4 doses followed by Nivo-3 mg/ kg Q2W	57.6 (52.0-63.2)	Median PFS: 11.5 months (8.9-16.7)	HR for disease progression or death: 0.42 (0.31-0.57) vs Ipi group; 0.74 (0.60-0.92) vs Nivo group	[30]
Nivo-1 mg/ kg, Ipi-3 mg/ kg Q3W X4 doses followed by Nivo-3 mg/ kg Q2W	59% (48-69)	Median OS: Not reached 12- & 24-month OS rate, 73.4% & 63.8% respectively Median PFS: Not reached 12- & 24-month PFS rate, 52.5% & 51.3% respectively	HR for death: 0.74 (0.43–1.26; p=ns) HR for disease progression: 0.36 (0.22-0.56)	[5]
Nivo 3mg/ kg Q2W x6 doses, then Ipi 3mg/kg Q3W x4 doses (and vice-versa)	56% (43.3 -67.0) in Nivo followed by Ipi group and 31% (20.9-43.6) in Ipi followed by Nivo group	OS: Not reached in Nivo followed by Ipi group & 16.9 months (9.2-26.5) in Ipi followed by Nivo group 12-month OS rate: 76% & 54% respectively	HR for death: 0.48 (0.29-0.80)	[20]
Pembrolizumab and Ipilimumab combination				
2 mg/kg pembro + 1 mg/kg ipi Q3W followed by 2 mg/kg pembro Q3W up to 2-y	61% (53-69)	Median PFS: Not reached 12-month PFS rate: 69% (60-75)	ND	[6]

NA: Not available; ND: Not determined; Q2W: Dosed every 2 weeks; Q3W: Dosed every 3 weeks

ipilimumab (HR for disease progression, 0.58; p < 0.001 for both pembrolizumab regimens versus ipilimumab; 95 % CI, 0.46–0.72 and 0.47–0.72 respectively). Estimated 12-month survival rates in pembrolizumab treated patients was 74.1 % and 68.4 % (every 2 weeks and 3 weeks regimen respectively) and in ipilimumab treated patients was 58.2 % [16]. In the second study, patients with disease progression after two or more ipilimumab doses and, if BRAFV600 mutant-positive, after treatment with a BRAF or MEK inhibitor or both, were randomized in a 1:1:1 to receive pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks or investigator-choice chemotherapy [17]. The study found significant improvement in PFS in patients receiving pembrolizumab 2 mg/kg (HR 0·57, 95 % CI 0·45–0·73; p<0·0001) and pembrolizumab 10 mg/kg (HR: 0·50, 95 % CI 0·39–0·64; p<0·0001) compared to those receiving chemotherapy. 6-month PFS rate was reportedly 34 % (95% CI 27-41) in pembrolizumab 2 mg/kg group, 38 % (95 % CI 31-45) in pembrolizumab 10 mg/kg group and 16 % (95 % CI 10-22) in chemotherapy group. ORR in pembrolizumab 2 mg/kg group was 21 % (95 % CI 15-38), in pembrolizumab 10 mg/kg was 25 % (95 % CI 19-32) and in chemotherapy group was 4 % (95 % CI 2-9) [17].

Combination Therapy and Ongoing Research

Anti-PD-1 antibodies demonstrated significantly higher OS and PFS rates and ORRs in metastatic melanoma patients compared to chemotherapy, but the response rates recorded were less than 50 %. Combination immunotherapy has been suggested in order to increase the response rates and combination of nivolumab and ipilimumab has been tested in metastatic melanoma patients. In a double-blind phase 3 study, previously untreated metastatic melanoma patients (n=142) were randomly assigned in a 2:1 ratio to receive ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg/kg) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects. The study reported an ORR of 61 % (n=44/72, 95 % CI, 49-72) in ipilimumab plus nivolumab group and 11 % (n=4/37, 95 % CI, 3-25) in ipilimumab plus placebo group (odds ratio, 12.96; 95% CI, 3.91 to 54.49; p<0.001). Complete responses were recorded only in patients in the combination group (n=16, 22%) and the hazard ratio for disease progression or death associated with combination therapy compared with ipilimumab monotherapy was 0.40 (95 % CI, 0.23-0.68; p<0.001) [4]. In another phase 2 study, patients were randomized in a 2:1 ratio to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or ipilimumab 3 mg/kg plus placebo every 3 weeks for four doses, followed by nivolumab 3 mg/kg or placebo every 2 weeks until disease progression or unacceptable toxicity. 2-year OS rate at the time of median follow-up time of the study (24.5 months) was reported to be 63.8 % (95 % CI, 53.3-72.6) in the combination group and 53.6 % (95 % CI, 38.1-66.8) in the ipilimumab alone group [5]. However, while adverse effects were comparatively less frequent with nivolumab monotherapy, combination of nivolumab and ipilimumab reported drug-related grade 3 or 4 adverse events in 54 % of patients. The incidence of grade 3 or 4 colitis and increased alanine aminotransferase and aspartate aminotransferase indicating liver abnormalities, were increased by more than 5-times in the combination group [4-5, 18]. Recently, 2 cases of death due to myocarditis accompanied by myositis were reported in patients receiving ipilimumab and nivolumab combination suggesting a cautious approach in prescribing the combination [19]. Pembrolizumab and ipilimumab combination was also tested in melanoma patients and recently, a phase 1b study assessing the safety and anti-tumor activity of pembrolizumab administered at standard-dose plus ipilimumab administered at a reduced dose, reported an objective response rate of 61% (53-69) and occurrence of grade 3 or 4 adverse events in 45% of the patients [6].

In order to test if the increased incidence of adverse events could be addressed by altering the sequence of administration of nivolumab and ipilimumab, a phase 2 study was initiated in which, patients were randomly assigned in a 1:1 ratio to receive nivolumab 3 mg/kg every 2 weeks for six doses followed by a planned switch to ipilimumab 3 mg/kg every 3 weeks for four doses or the reverse sequence. The study did not find any significant difference in frequencies of treatment-related grade 3-5 adverse events between the treatment groups and found that the fraction of patients responding at week 25 was higher in patients who received nivolumab followed by ipilimumab than in patients who received the reverse sequence. Disease progression was lower and OS was better in nivolumab followed by ipilimumab group compared to the group

that received reverse sequence suggesting that though the adverse events were not effected by alterations in sequence of administration, efficacy of the combination was better when the patients received nivolumab followed by ipilimumab [20]. Combining PD-1 blockers with antibodies against checkpoints that have milder phenotype has been suggested to have less severe adverse events and TIGIT, TIM-3 and LAG-3 have been suggested as promising targets [21]. TIM-3 was recently found to be co-expressed along with PD-1 and CTLA-4 on tumor infiltrating CD8 T-cells in melanoma patients and the cells that co-expressed TIM-3, CTLA-4 and PD-1 were found to be most responsive to PD-1 therapy [22]. Research is ongoing to identify the drugs that can be safely and effectively combined with PD-1 blockers [22-24].

Summary

To summarize, approval of PD-1 blockers positively influenced the prognosis of metastatic melanoma. Compared to previously approved drugs for melanoma, including dacarbazine, aldesleukin and ipilimumab, PD-1 blockers such as nivolumab and pembrolizumab had higher objective response rates, increased the OS and PFS significantly and had lower incidences of adverse events [25]. Combination of CTLA-4 and PD-1 blockers has been suggested for patients who failed to respond to anti-PD-1 therapy; the combination was successful in increasing the response rates in patients but had severe adverse effects. Further research is needed to identify safe and effective combinations for treatment of melanoma.

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