REVIEW

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Ipilimumab: from preclinical development to future clinical perspectives in melanoma

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The arsenal for the treatment of metastatic melanoma is limited. A new approach to therapy using checkpoint blockade has improved overall survival in this patient population. Ipilimumab a CTLA-4 monoclonal antibody is a first in class drug that has pioneered this revolution. In this review, the authors provide an account of the different stages that led to the development of ipilimumab, its approval in the clinical setting for the treatment of advanced melanoma and ongoing investigations of combinatorial immune therapy.

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Melanoma has an increasing burden of disease; according to the 2015 Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute data nearly 74,000 new cases were diagnosed in the USA, comprising approximately 4.5% of new cancer cases. The estimated number of melanoma deaths in 2015 approached 10,000 and 2.1% of Americans will develop this malignancy in their lifetime [1]. A significant number of these patients present with advanced disease, requiring more than surgical interventions. Localized disease portends to a good overall survival (OS) but the therapeutic armamentarium against regional and distant disease is far more limited. 5-year survival for advanced disease remained at less than 20% per 2011 data [2]. The need for new therapeutics and interventions continues to grow.

In 2011, ipilimumab became a US FDA-approved drug for the treatment of melanoma and ushered in a new role for immunomodulatory therapy. Ipilimumab is a first in class CTLA-4 monoclonal antibody drug and has been investigated in several different malignancies including prostate, lung and bladder cancer [3–6]. CTLA-4 is expressed on the surface of activated T-cell lymphocytes and ipilimumab binding leads to augmentation of antitumor immune activities. Activation of a T-cell requires a minimum of two signals between the lymphocyte and the antigen-presenting cell (APC). Signal 1, the classic signal, occurs between the MHC present on the APC with T-cell receptors (TCRs) present on the lymphocytes. The MHC on the APC presents an antigenic peptide to the TCR. For proper T-cell activation a second costimulatory signal is required. The prototypical second signal is between CD28 on the T cell and B-7 on the APC. Both signals are required to activate the T-cell [7].

CD-28 is a superfamily of immunoglobulins found on the majority of resting CD4⁺ T-lymphocytes and about half of CD8⁺ T-lymphocytes [8]. CTLA-4, a homolog of CD28, was initially cloned in 1987, and has an inhibitory effect on T-cell activation [9,10]. If antigen presentation with signal 1 between the MHC and the APC occurs and the costimulatory signal is between B7 on the APC

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and CTLA-4 on the T-cell, the T-lymphocyte becomes inactive. The role of ipilimumab or any anti-CTLA-4 monoclonal antibody is to occupy the CTLA-4 binding site (Figure 1). This forces B7 to bind CD28 and allows for preserved T-cell activation and continued antitumor effect [11].

Ipilimumab has been developed at an astounding pace since its inception, and along with it check-point blockade and immunomodulatory-based therapy. Indeed it sets the stage for a new exciting era in advanced melanoma management, a field with previously abysmal survival rates. In the 5 years since its FDA approval some limitations such as acquired drug resistance and autoimmune toxicities have been further elucidated, leading to additional clinical trials and drug combinations with improved efficacy of this promising agent. The goal of our review is to discuss the literature on ipilimumab in melanoma, the preclinical and clinical dataset related to this agent and the future of the drug in the context of new therapeutic paradigms presently being applied to melanoma.

Preclinical

The potential for CTLA-4 antibodies to provide antitumor effect was highlighted in a 1996 *Science* article [12]. Using a murine model and injecting a transplantable murine colon carcinoma, the researchers were able to demonstrate that CTLA-4 blockade increased the rate of tumor rejection in new or established tumors. Importantly, these effects occurred in un-manipulated wild-type tumors, further underscoring the potential of a viable pharmacologic intervention.

Homozygous CTLA-4-negative mice (CTLA-4^{-/-}) demonstrate histological evidence of early accumulation of activated lymphocytes in various tissues, including lymphoid, heart, lung, liver and pancreas. It has been observed that the majority of these mice die by 3–4 weeks of age. One postulation explaining the high rapid mortality rate is from complications of lymphoproliferative disease and lymphocytic infiltration [13,14].

To further elucidate the therapeutic potential of CTLA-4 blockade a more realistic human

Figure 1. Mechanism of action. (A) T-cell activation requires two signals; signal 1 between MHC and T-cell receptor and signal 2 between B7 molecules on the antigen receptor cell (APC) and CD28 on the T cell. (B) Activation leads to CTLA-4 upregulation and translocation to the cell surface. CTLA-4 on the T cell competitively binds to B7 on the APC leading to downregulation and T-cell inactivation. (C) Ipi blocks CTLA-4 binding with B7 allowing for ongoing activation of T cells and antitumor effect. APC: Antigen-presenting cell; Ipi: Ipilimumab.

model than murine studies needed to be investigated. Human monoclonal antibodies were developed from transgenic mice expressing human immunoglobulin genes and one in particular *10D1* showed good affinity and binding specificity. This antibody prevents ligand binding and therefore impedes CTLA-4 and B7 interaction. To further test *10D1*, the antibody was injected in a primate model with concurrent vaccination of a human melanoma cell line transfected to express granulocyte–monocyte colony-stimulating factor (GM-CSF). The group of six cynomolgus monkeys exhibited an increased humoral immune response as measured by flow cytometry and ELISA [15]. No significant side effects were noted and this helped usher a transition to human clinical trials.

From *10D1*, a CTLA-4 antibody was developed for directed immunotherapy toward human malignancies and infections [16]. The end result led to the shaping of the first in class drug ipilimumab, and with it an emerging family of immunomodulatory antibodies/immune checkpoint inhibitors for cancer treatment.

Phase I

Multiple Phase I clinical trials have been performed to evaluate safety, efficacy and pharmacokinetics of ipilimumab in different types of malignancies including metastatic melanoma. The first in human Phase I trial was done in patients with metastatic hormone refractory prostate cancer in which single dose ipilimumab of 3 mg/kg was given to 14 patients. Two patients showed >50% decline in prostate-specific antigen levels and one patient developed grade 3 rash requiring systemic steroid use [5]. Increases in CD4 and CD8 cells coexpressing HLA-DR were used as a marker of T-cell activation and suggested the possibility of T-cell activation. The pharmacokinetic profile indicated a terminal half-life of 12.5 days hence permitting a 3- to 4-week dosing design for future studies.

In an early published abstract, patients with surgically unresectable stage III or IV malignant melanoma were given 3 mg/kg of ipilimumab. Two of 17 patients had a partial response with a reduction in overall tumor size [17], and an analogous study found leukocytic infiltration with evidence of tumor necrosis observed in three of seven patients [18]. Ipilimumab was infused over a 90-min period and one acute hypersensitivity reaction was noted and treated routinely with antihistamines. Constitutional

symptoms were common in the 2–7 days after infusion and grade III liver function tests elevation in a patient with known liver metastasis was observed [18].

Later studies assessed serial dosing of ipilimumab given as 3 mg/kg every 3 weeks. 21 patients with stage IV melanoma were sought but accrual was truncated after six cases of grade III/IV autoimmune toxicity occurred in 14 enrollees. Manifestations included dermatitis, hepatitis and hypophysitis. Serial dosing in three patients did cause tumor regression, two complete and one partial response [19].

A 2006 NIH study looked at dose escalation in patients with metastatic melanoma. Outcomes looked at grade III or greater autoimmunity, other dose limiting toxicity and objective tumor response. 46 patients were divided into two cohorts; one receiving 3 mg/kg of ipilimumab with a subsequent dose escalation to 5 then 9 mg/kg. The second cohort was started at 5 mg/kg and dose escalation occurred in the same fashion to 9 mg/kg. Outcomes were observed in 16 patients (19 events) experiencing grade III/IV autoimmune events and five patients with objective clinical response. The investigators concluded escalating doses of ipilimumab demonstrated a trend toward increasing rates of autoimmunity without benefit of increased objective response rates [20].

The peak concentration (C_{max}) of ipilimumab dosed at 2.8 and 3.0 mg/kg respectively were 79.9 and 84.5 µg/ml and occurred 1 day post infusion with a half-life of approximately 350 h [21].

Phase II

Multiple Phase II trials have been done using ipilimumab as a single agent or in combination with other cytotoxic agents. At least two Phase II studies [22,23] utilized the combination of ipilimumab with dacarbazine (DTIC), one of the initial FDA-approved drugs for melanoma, with a rate of overall response to be approximately 15% [24].

Hersch *et al.* recruited 72 patients with advanced melanoma, all of whom were previously chemo naive. Patients were randomized to ipilimumab 3 mg/kg every 4 weeks for four doses plus up to six 5-day courses of DTIC 250 mg/m²/day versus ipilimumab alone. The objective response rate, a summation of partial response and complete response, was 14.3% and 5.4% in the combination arm versus the

ipilimumab alone arm respectively. Durable response rates, greater than 1 year, were greater in combination therapy [22].

A Japanese study involving higher doses of ipilimumab, 10 mg/kg plus four doses of DTIC every 3 weeks at 850 mg/m² resulted in increased adverse events without any increased benefit in terms of overall response rates (ORRs) [23].

Ipilimumab has been trialed in patients with pretreated advanced melanoma and shown to be effective and well tolerated. A single-arm study dosed ipilimumab at 10 mg/kg every 3 weeks for four doses followed by maintenance therapy in 155 patients with progressive disease and failure of at least one prior therapy. Best ORR using modified WHO criteria were 5.8% and disease control rate was 27% [25]. Wolchok *et al.* generated similar results in the 10 mg/kg arm of their study with more favorable results at this higher dose compared with 3 and 0.3 mg/kg of ipilimumab in 217 previously treated patients [26]. Patients with no disease response to prior systemic therapy may find benefit with ipilimumab immunotherapy.

Given the overall poor prognosis of melanoma in patients with brain metastasis, several Phase II studies were designed to investigate ipilimumab in this patient population [27,28]. The largest of these studies involved 72 patients; 51 in cohort A, treatment naive, who did not have recent exposure to corticosteroids and 21 in cohort B who received concurrent ipilimumab and systemic corticosteroids for amelioration of neurologic sequela from metastatic brain lesions. Both cohorts received ipilimumab at a dosage of 10 mg/kg every 3 weeks for four cycles, followed by maintenance infusions once every 12 weeks. Median survival in cohort A was 7 and 4 months in cohort B. Toxicities and adverse events occurred in expected frequencies [28]. The use of immunotherapy seems a viable alternative or complement to established treatments of surgical resection or stereotactic radiation particularly in instances of multifocal brain lesions. Interestingly, it has been hypothesized the bulk of the therapeutic effect is through T-cell activation as antibodies are not thought to cross the intact blood–brain barrier [29].

Phase III

The promising results from early studies have led to multiple Phase III trials with ipilimumab that utilized OS and progression-free survival (PFS) as primary end points. Prior to this, Phase I/II

trials of ipilimumab in melanoma had examined objective response as the main primary outcome. The change in paradigm was ushered by immunologic therapies and checkpoint blockade manifesting its benefits through disease stabilization leading to improved outcomes rather than tumor shrinkage. A meta-analysis, evaluating 42 prior studies and more than 2000 patients, supported OS as a viable and appropriate primary end point [30,31]. This benchmark end point was assessed in a seminal paper released in the *New England Journal of Medicine* in 2010. The multinational, randomized, double-blinded Phase III trial examined OS with ipilimumab in patients with previously treated metastatic melanoma. A total of 676 patients with stage III or IV melanoma and good performance status (ECOG 0 or 1) were assigned in a 3:1:1, ipilimumab plus a gp100 vaccine; ipilimumab alone; or gp100 alone [32]. Ipilimumab induction was with a dose of 3 mg/kg once every 3 weeks for four cycles. Patients who received subcutaneous vaccines received two modified HLA-A*201-restricted peptides. The study was devised with the initial primary end point being best ORR but formally amended and approved to be changed to OS in accordance with previously described meta-analysis [31]. Patients were followed up for 55 months; those who received ipilimumab had a median OS of 10.0 months, versus 6.4 months in patients who received vaccine alone. Survival in the ipilimumab cohorts at 24 months was superior to gp100 alone. There was no survival benefit between the two ipilimumab arms and results were independent of age, sex or stage [32]. Adverse events were similar to previously observed studies with the largest category being immune-related events occurring in 60% of patients treated with ipilimumab. The vast majority of these events occurred during the induction phase (initial 12 weeks) with resolution during the subsequent 12 weeks, and managed mostly with supportive measures and corticosteroid therapy [32,33]. This became the first randomized trial to show a survival benefit in patients with metastatic melanoma. Additional studies assessing ipilimumab plus DTIC in previously untreated metastatic melanoma also demonstrated increased OS when compared with DTIC alone [34].

Long-term follow-up of these and other patients in Phase III trials reporting OS is now available [35,36]. In a pooled analysis of long-term survival of patients with advanced melanoma

receiving ipilimumab, 3-year survival rates in all patients, treatment-naïve patients and previously treated patients were 22, 26 and 20%, respectively. These data were independent of drug dosage or prior treatment regimen [36].

Recent & ongoing trials of ipilimumab in melanoma

Multiple studies have recently and/or are presently investigating ipilimumab in combination with other drugs and follow-up survival rates in previously treated patients. Ipilimumab is also being investigated in several other malignancies but that is beyond the scope of this review and will not be discussed.

In a Phase I study by Wolchok *et al.*, nivolumab a humanized IgG4 anti-PD-1 monoclonal antibody in combination with ipilimumab was assessed. Patients previously treated with ipilimumab, received nivolumab every 2 weeks for up to 48 doses (sequenced regimen), this was compared with 'concurrent regimen' where nivolumab and ipilimumab were given every 3 weeks for four doses, followed by nivolumab alone every 3 weeks for four doses, subsequently the combined treatment was administered every 12 weeks for up to eight doses. thirty-three patients received sequenced treatment and 53 received concurrent therapy. The objective response rates were 20 and 40% respectively, providing the impetus for further investigations [37]. CheckMate 069, a Phase II clinical trial, randomized 142 treatment-naïve patients with unresectable stage III or IV melanoma (2:1) to combination nivolumab and ipilimumab versus ipilimumab alone, the objective response rate was 59% in the combination arm as opposed to 11% in the ipilimumab alone arm [38]. Drug-related grade 3–4 toxicity was reported more frequently in the combination arm than ipilimumab monotherapy 54 versus 24%. This included three deaths related to combination therapy according to the investigator assessment. The 2-year follow-up of this trial was recently presented at the AACR 2016 annual meeting. Median PFS at 2 years was not reached in the combination group versus 3 months in the ipilimumab alone group ($p < 0.0001$) regardless of the PD-L1 status. Consistently grade 3–4 toxicity was higher in the combination arm, but has not increased, and importantly no more treatment deaths have been reported at 2 years of follow-up [39].

Larkin *et al.* conducted a large Phase III trial in 945 patients with treatment-naïve melanoma.

This double blind study enrolled patients in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab plus placebo or ipilimumab plus placebo. The primary outcome of PFS was greatest at 11.5 months in the nivolumab plus ipilimumab group, compared with 6.9 and 2.9 months in the nivolumab plus placebo and ipilimumab plus placebo groups, again this was associated with significant grade III or IV adverse events (55%) in the combination therapy group [40]. One treatment related death was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest), but none were reported in the nivolumab plus ipilimumab group [40,41]. In a subgroup analysis using tumor PD-L1 expression with 5% cut-off, PFS was superior in the combination arm compared with either single arms in patient with tumor PD-L1 expression level $<5\%$, however in the PD-L1 positive tumors ($>5\%$), both the combination and nivolumab arms seemed comparable and superior to ipilimumab alone arm [42].

This combination therapy has emerged as the new standard of care for newly diagnosed metastatic melanoma but requires particular attention to the monitoring of autoimmune side effects [43].

GM-CSF cytokine in combination with ipilimumab have also been studied. A Phase II randomized trial assigned patients to receive ipilimumab or ipilimumab plus systemic GM-CSF (sargramostim). Two hundred and forty five patients with previously treated metastatic melanoma were equally randomized. OS for the combination group was 17.5 versus 12.7 months for ipilimumab alone and 1-year survival was nearly 70% in the combination group. There was no statistically significant difference of PFS between the groups [44]. Additional combination therapies with ipilimumab and a second agent, including a B-Raf inhibitor have been investigated [45]. Unfortunately the trial was terminated early due to substantial rates of hepatotoxicity. Further combination therapies will continue to be explored with ongoing critical assessment of efficacy versus unintended sequela.

Many other promising immunotherapy combinations are currently being tested in metastatic melanoma. One novel approach includes ipilimumab with IDO inhibitors. IDO is an enzyme that converts the essential amino acid tryptophan to kynurenine, which results in enhancement of suppressive T regulatory cells

and inhibition of the effector T cells, leading to immune suppression [46]. IDO is upregulated in many human tumors including melanoma [47], and correlates with worse clinical outcome [48]. Tumor models have shown synergistic effects between anti-CTLA-4 and IDO inhibition providing a rationale for the combination in the clinical setting [49]. In an ongoing clinical trial (NCT02073123) combining an IDO inhibitor ‘indoximod’ with a checkpoint inhibitor, the Phase I escalation part deemed the combination with ipilimumab to be safe and the recommended Phase II dose (RP2D) of indoximod has been established at 1200 mg [50]. Epcadostat another oral IDO inhibitor was tested with ipilimumab, and a dose up to 50 mg twice daily was generally well tolerated [51]. Both indoximod and epcadostat are currently being tested in clinical trials with anti-PD-1 antibodies.

Ipilimumab has been combined with oncolytic vaccine Talimogene Laherparepvec (T-VEC) in a randomized Phase II trial (NCT01740297) in unresected melanoma. Results of this trial are pending. A prior Phase III clinical trial (OPTim) randomized 436 patients with stage IIIB/ IV melanoma to single agent T-VEC or GM-CSF (2:1 ratio) with a primary end point of durable response rate lasting at least 6 months and secondary end points of OS and ORR [52]. Durable response rate was significantly higher in the T-VEC arm than the control arm (16.3 vs 2.1%, respectively, odds ratio: 8.9; $p < 0.001$), with superior ORR (26.4 vs 5.7%). There was a trend for better median OS with T-VEC (23.3 vs 18.9 months), however, not statistically significant (hazard ratio [HR]: 0.79; 95% CI: 0.62–1.00; $p = 0.051$) [52].

Ipilimumab has been studied in the adjuvant setting too, recently, results of EORTC 18071 using adjuvant ipilimumab in patients with high risk cutaneous melanoma showed statistically significant recurrence-free survival (RFS) benefit in patients with high-risk melanoma with the use of adjuvant ipilimumab. Median RFS was 26.1 months in the ipilimumab group versus 17.1 months in the placebo group [53]. A more recent follow-up data at 5.3 years were presented at the European Society for Medical Oncology October 2016 showed a 28% improvement in OS in the ipilimumab arm (HR: 0.72, $p = 0.001$). There was consistency across all end points with HR of 0.76 for RFS and distant metastases-free survival ($p < 0.001$

and $p = 0.002$) [54]. Of note a higher dose of ipilimumab at 10 mg/kg was approved in the adjuvant setting as compared with 3 mg/kg in advance melanoma. Also a prolonged schedule of every 3 weeks for four doses and then a maintenance dose every 3 months for 3 years was used in adjuvant setting as compared with current strategy of every 3 weeks dosing for up to four doses (retreatment permitted) when used as monotherapy in advanced melanoma. Adverse event related discontinuation was noted in 52% of patients and 1% treatment-related deaths, no additional toxicities or deaths were noted at 5.3 years median follow-up [54]. Although the FDA approved this therapy in October 2015 the authors themselves concluded that risk–benefit ratio will need to be discussed carefully and reviewed with patients before using this adjuvant approach.

The Phase III trial, ECOG 1609, is evaluating adjuvant ipilimumab at 10 versus 3 mg/kg versus high-dose interferon as treatment option in patients with high risk or metastatic melanoma. The trials primary end points include RFS and OS. The results of this trial are expected in 1–2 years and will help establish the key role of using ipilimumab as adjuvant therapy.

Safety & toxicity

In general, the adverse events reported with ipilimumab are manageable with supportive measures and the occasional use of systemic corticosteroids. For single-agent ipilimumab; most side effects are immune related and occur within the first 12 weeks after induction and with treatment resolve within the subsequent 3–4 months thereafter [33].

Early, in Phase I studies diarrhea and dermatitis were the most commonly reported side effects [18–20,25]. Interestingly, patients who do experience autoimmune adverse effects generally also have better clinical response to their disease [20,21]. It appears that autoimmunity correlates with drug effect.

Subsequent Phase III studies reported all grade immune related events occurring in 60–77% of patients receiving ipilimumab and grade III or IV immune events occurring in 10–20% of patients, the most common manifestations being diarrhea and hepatitis [32,34]. Occurrences of adverse events are higher in combination immune therapy verses ipilimumab alone [37–38,40]. Rates of frequently

encountered immune related adverse effects are listed in [Table 1](#). Analgesics were concomitantly given in >50% of patients in one study [33], and use of supportive medications such as antiemetics, antidiarrheals, antihistamines, antibiotics and systemic corticosteroids is also quite common. Death, though uncommon, has occurred in association with ipilimumab administration. Causes of mortality include liver failure, bowel perforation, Guillain-Barré syndrome and sepsis [33]. Rare-unexpected side effects have been reported, for instance, necrotic myelopathy has been observed and could be explained as an additional immune-mediated

adverse event [55]. An additional case reported a 52-year-old female who developed altered mental status and combative behavior that was believed to be secondary to aseptic ipilimumab-induced meningitis. Medication cessation led to rapid normalization of behaviors [56]. As use increases, we anticipate increased reporting of neurological side effects and singular events. Heightened awareness and a low threshold to suspect ipilimumab as an offending agent are warranted.

The majority of adverse events reported in the literature are immune-related and the cornerstone of treatment is systemic steroids. We treat

Table 1. Rates of immune-mediated adverse effect of ipilimumab.

Study (year)	Treatment	Type of adverse event	% reported	Grade III/VI% reported	Ref.
Hodi <i>et al.</i> (2010)	Ipilimumab	All drug related events	80%	23%	[32]
		Diarrhea	33%	5%	
		Rash	19%	1%	
		Hypophysitis	1.5%	1.5%	
		Hepatitis	1%	0%	
		Colitis	8%	5%	
Wolchok <i>et al.</i> (2013)	Ipilimumab + nivolumab	Pneumonitis	6%	2%	[37]
		Hypophysitis	4%	2%	
		Diarrhea	34%	6%	
		Colitis	9%	4%	
		Rash	55%	4%	
Eggermon <i>et al.</i> (2015)	Ipilimumab	Rash	34%	1%	[53]
		Diarrhea	41%	10%	
		Colitis	16%	8%	
		Increased liver function tests	21%	5%	
		Hypophysitis	18%	5%	
Postow <i>et al.</i> (2015)	Ipilimumab + nivolumab	Skin	71%	1%	[38]
		Gastrointestinal	51%	21%	
		Endocrine	34%	<1%	
		Hepatic	28%	15%	
		Pulmonary	12%	<1%	
	Ipilimumab	Skin	56%	0%	
		Gastrointestinal	37%	11%	
		Endocrine	17%	4%	
		Hepatic	4%	0%	
		Pulmonary	4%	2%	
Larkin <i>et al.</i> (2015)	Ipilimumab + nivolumab	Diarrhea	44%	9%	[40]
		Rash	40%	5%	
		Colitis	12%	8%	
		Increased ALT	18%	8%	
		Dyspnea	10%	<1%	
	Ipilimumab	Diarrhea	33%	6%	
		Rash	33%	2%	
		Colitis	12%	9%	
		Increased ALT	4%	2%	
		Dyspnea	4%	0%	

Table 2. Summary of ipilimumab studies in treatment of melanoma.

Study (year)	Phase	n	Study population	Regimen/treatment	End point/objective	Results	Ref.
Tchekmedyan <i>et al.</i> (2002); (abstract)	I	17	Unresectable stage III/IV malignant melanoma	Single dose ipilimumab 3 mg/kg	Safety profile; objective response	Two of 17 patients had a partial response	[17]
Hodi <i>et al.</i> (2003)	I	7	Metastatic melanoma	Single dose ipilimumab 3 mg/kg	Safety profile; objective response	Three of seven patients with tumor necrosis observed; hepatotoxicity, autoimmunity	[18]
Phan <i>et al.</i> (2003)	I	14	Stage IV melanoma	Ipilimumab 3 mg/kg every 3 weeks	Safety profile; objective response	Six cases of grade III/IV autoimmune toxicity; clinical response in three of 14 patients	[19]
Maker <i>et al.</i> (2006)	I	46	Metastatic melanoma	Ipilimumab 3 mg/kg every 3 weeks or 5 mg/kg every 3 weeks; dose escalation to 9 mg/kg	Grade III or greater autoimmunity, dose limiting toxicity and objective tumor response	16 of 46 patients grade III/IV autoimmune events; more adverse events at higher dosages; five patients with objective clinical response	[20]
Wolchok <i>et al.</i> (2013)	I	53	Unresectable stage III/IV malignant melanoma	Nivolumab plus ipilimumab every 3 weeks × 4 cycles; followed by nivolumab alone or with concurrent ipilimumab	Safety profile; objective response rate	Objective response rate nivolumab with concurrent ipilimumab 40% and nivolumab alone 20%	[37]
Postow <i>et al.</i> (2015)	I	142	Treatment-naïve unresectable stage III/IV melanoma	Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg or placebo every 3 weeks × four cycles	Safety and objective response	Objective response 61% in combination group vs 11% in ipilimumab plus placebo	[38]
Weber, Jeffery <i>et al.</i> (2008)	I/II	88	Unresectable stage III/IV malignant melanoma	Single dose ipilimumab up to 20 mg/kg; multiple doses up to 10 mg/kg	Safety and pharmacokinetic profile	Half-life of ~350 h; no maximum tolerated dose	[21]
Hersh <i>et al.</i> (2009)	II	72	Unresectable metastatic melanoma	Ipilimumab 3 mg/kg every 4 weeks for 4 doses; ± DTIC 250 mg/m ² for 5 days every 3 weeks	Safety and efficacy alone and in combination with DTIC	Objective response rate, 14.3 and 5.4% in combination arm vs ipilimumab	[22]
Yamazaki <i>et al.</i> (2015)	II	15	Previously untreated unresectable or metastatic melanoma; Japanese cohort	Ipilimumab 10 mg/kg plus DTIC 850 mg/m ² every 3 weeks × 4 doses. Then DTIC alone every 4 weeks × 4 doses	Safety and efficacy of ipilimumab plus DTIC in Japanese population	12 of 15 patients with elevated LFTs Nine of 16 discontinued medication due to toxicities; regimen poorly tolerable in population	[23]
O'Day <i>et al.</i> (2010)	II	155	Previously treated unresectable stage III/IV melanoma	Ipilimumab 10 mg/kg every 3 weeks × 4 cycles	Safety and BORR	BORR 5.8%; 1-year survival 47.2%; 2-year 32.8%; OS 10.2 months	[25]
Wolchok <i>et al.</i> (2010)	II	217	Previously treated unresectable stage III/IV melanoma	Ipilimumab either 10 mg/kg, 3 mg/kg or 0.3 mg/kg every 3 weeks × 4 cycles; then same dose once every 3 months	Best overall response rate	BORR 11.1% for 10 mg/kg, 4.2% for 3 mg/kg and 0% of 0.3%. increased rate of adverse effects with dose escalation	[26]
Margolin (2012)	II	72	Melanoma with brain metastases	Ipilimumab 10 mg/kg every 3 weeks × 4 cycles; then every 3 months up to 8 doses; cohort B on stable dose steroids	Safety and efficacy	Median survival in cohort A was 7 months and 4 months in cohort B; expected toxicity rates	[28]

BORR: Best overall response rate; DTIC: Dacarbazine; LFT: Liver function test.

Table 2. Summary of ipilimumab studies in treatment of melanoma.

Study (year)	Phase	n	Study population	Regimen/treatment	End point/objective	Results	Ref.
Hodi <i>et al.</i> (2014)	II	245	Metastatic melanoma	Ipilimumab 10 mg/kg every 3 weeks × 4 cycles ± GM-CSF on days 1–14 of 21-day cycle	Overall survival	1-year survival 52.9% ipilimumab alone vs 68.9% in combination	[44]
Hodi <i>et al.</i> (2010)	III	676	Previously treated unresectable stage III/IV melanoma	Ipilimumab 3 mg/kg every 3 weeks for 4 cycles; 3:1:1 ipilimumab plus gp100 vaccine, ipilimumab alone or gp100 alone	Overall survival	OS was 10 months in groups receiving ipilimumab and 6.4 months. In vaccine alone group. 2 years 21.6, 23.5 and 13.7%	[32]
Eggermon <i>et al.</i> (2015)	III	951	Resected high-risk stage III melanoma without prior chemo exposure	Postsurgery ipilimumab 10 mg/kg or placebo every 3 weeks × 4 cycles, then every 3 months for up to 3 years	Recurrence-free survival	Median recurrence-free survival 26.1 in ipilimumab vs 17.1 in placebo; 3-year recurrence-free survival 46.5 vs 34.8%	[53]
Robert <i>et al.</i> (2011)	III	502	Previously treated metastatic melanoma	Ipilimumab 10 mg/kg plus DTIC 850 mg/m ² or DTIC alone	Overall survival	OS ipilimumab + DTIC 11.2 months vs 9.1; 1, 2 and 3-year survival 47.3, 28.5 and 20.8% ipilimumab plus DTIC vs 36.3, 17.9 and 12.2% DTIC alone	[34]
Larkin <i>et al.</i> (2015)	III	945	Previously untreated metastatic melanoma	Nivolumab alone 3 mg/kg every 2 weeks, or 1 mg/kg nivolumab and 3 mg/kg ipilimumab every 3 weeks × 4 cycles then nivolumab 3 mg/kg every 2 weeks, or ipilimumab 3 mg/kg every 3 weeks × 4 cycles	Progression-free survival	11.5 months in combination group vs 2.9 months ipilimumab alone vs 6.9 months nivolumab alone	[40]

BORR: Best overall response rate; DTIC: Dacarbazine; LFT: Liver function test.

severe grade 3 and 4 immune-related hepatitis, pneumonitis, dermatitis, hypophysitis and others with discontinuation of immune therapy and 1 mg/kg prednisone or equivalent, with a slow taper over the course of a month after clinical or laboratory improvement. Supportive measures with loperamide and/or diphenoxylate/atropine for low-grade diarrhea are often sufficient for treatment. It is our belief that monitoring of patients on immune therapy should include a thorough history and physical examination with particular focus on bowel habits, and an in-depth dermatologic assessment, with liver function tests obtained serially. Corticosteroid therapy should be initiated early on once an infectious process has been excluded in grade III/IV autoimmune related events. Emerging data suggest that the use of systemic immunosuppression for management of immune-related adverse events does not compromise the effect of immunotherapy on OS or time to treatment failure [57].

Future perspective

Ipilimumab is the first ever checkpoint inhibitor to be approved for clinical practice in melanoma and has since transformed its prognostic outlook. With more of its use in clinics, immune-related adverse events are increasing in incidence but its early recognition will remain the key for successful management. Several clinical trials utilizing combination treatments including ipilimumab with chemotherapy, targeted therapy, adoptive T-cell transfer and vaccines for management of advanced melanoma and other malignancies are underway. These trials are also utilizing different dosing strategies of ipilimumab such as reduced dosage or increased duration between doses (e.g., 1 mg/kg every 3–4 weeks) which may reduce the incidence of immune-mediated adverse events without compromising efficacy. Combination treatment with ipilimumab and nivolumab is a current standard treatment for management of

advance melanoma but associated with greater toxicity. Immune biomarkers may help choosing treatments between monotherapy versus combination therapy thereby sparing side effects associated with combination. Resistance mechanisms to anti-CTLA-4 treatments are being recognized. Newer therapies attempting to break immune tolerance with ongoing treatment with checkpoint inhibitor are likely to make their way in the near future. We will get more data about the role of ipilimumab in the adjuvant phase once the results of ECOG 1609 are available.

Conclusion

The aggressive nature and high mortality rate associated with metastatic melanoma has long challenged practitioners and researchers alike to develop new therapies. The advent of CTLA-4 inhibitors such as ipilimumab has transformed the management of advanced melanoma (Table 2). Objective response was an early measurable benchmark and reason for optimism; however, the real excitement brought to the field was with repeated demonstration of improvement in OS.

The safety profile of ipilimumab is acceptable and manageable. Most adverse events occur early during and around induction. Following established algorithms for management has led to minimal rates of long-term side effects or medication discontinuation, but keeping high

clinical suspicion with early recognition of immune-related side effects, and timely initiation of systemic corticosteroid therapy will also need to be part of clinical practice to make this therapy successful.

Ipilimumab ushered a new paradigm in cancer treatment with immune therapy and checkpoint blockade that has become part of the new standard of care in patients with advanced and high-risk melanoma. Combined and synergistic effects on tumor immunity continue to be a rapidly growing area with new and emerging pharmaceuticals agents. Concurrent or sequential combination therapy will need to be further elucidated; and if sequential in what order or timing should administration occur. The surface of these questions are just now being exposed and answers will hopefully further advance survival in patients with advanced melanoma.

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EXECUTIVE SUMMARY

Early & late phase trials

- The burden of disease in melanoma is growing and novel therapeutic agents are needed; ipilimumab is the first US FDA-approved checkpoint inhibitor in melanoma treatment.
- Ipilimumab works on CTLA-4 and enhances T-cell activation providing antitumor effect.
- Standard induction dosing of ipilimumab is 3 mg/kg every 3 weeks for four doses.
- Meta-analysis supported overall survival as viable end point in trials with ipilimumab.
- Alone and in combination with other agents ipilimumab may increase overall survival.

Current & future studies

- Combination checkpoint blockade with ipilimumab and nivolumab is the standard of care in newly diagnosed metastatic melanoma.
- Evolving field in immunotherapy with combination and/or sequential dosing of medication.

Safety & toxicities

- Majority of toxicities occur during the first 12 weeks of starting treatment.
- Majority of side effects are immune mediated; dermatitis, hepatitis and diarrhea.
- Treatment for most of the toxicities is supportive care with the occasional use of systemic corticosteroids.

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