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REVIEW

Interleukin-2, Ipilimumab, and Anti-PD-1: clinical management and the evolving role of immunotherapy for the treatment of patients with metastatic melanoma

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ABSTRACT

Treatment of metastatic melanoma has changed dramatically in the past 5 years with the approval of six new agents (vemurafenib, dabrafenib, trametinib, ipilimumab, pembrolizumab, and nivolumab) by the US Food and Drug Administration (FDA). This review will compare the immunotherapies recently approved by the FDA (ipilimumab, nivolumab and pembrolizumab) with the long-approved immunotherapy, interleukin-2. Additional consideration will be given to the evolving landscape, including the opportunities for combination regimens. Immunotherapies have distinct mechanisms of action and unique response kinetics that differ from conventional cytotoxic and targeted therapies, and have a range of adverse events that can be safely managed by experienced health-care providers. Data suggest immunotherapies can result in long-term survival in a proportion of patients. This dynamic and evolving field of immunotherapy for melanoma will continue to offer challenges in terms of optimal patient management for the foreseeable future.

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Introduction

Skin cancer is the most commonly diagnosed malignancy, and melanoma is the most serious form of skin cancer. The annual incidence of melanoma has been increasing at an alarming rate for the past 50 years.[1]Current projections estimate a 400% increase in the incidence of melanoma in men and a nearly 800% increase in women under the age of 39 years compared with historic incidence rates.[2] The lifetime risk of developing melanoma is now 1 in 50 white Americans, and it is anticipated that there will be 76,100 new cases of melanoma and 9710 melanoma-related deaths in the United States in 2014.[3,4] Early detection and surgical management of early-stage melanoma are associated with 5-year survival rates of over 90%, but once the disease metastasizes to regional lymph nodes, the 5-year survival drops to 50%; metastatic disease in visceral organs is associated with a median survival of 9–12 months and an estimated 3-year survival rate of 15%.[5]

The treatment of metastatic melanoma has changed dramatically in the past few years with the approval by the US Food and Drug Administration (FDA) of six new agents since 2011 (vemurafenib, dabrafenib, trametinib, ipilimumab, pembrolizumab, and nivolumab). Currently, the systemic management of metastatic melanoma may include agents classified as cytotoxic chemotherapy (dacarbazine), molecularly targeted therapy (vemurafenib, dabrafenib, trametinib), or immunotherapy (aldesleukin or interleukin-2 [IL-2], ipilimumab, nivolumab, and pembrolizumab). Although chemotherapy is still used to treat melanoma, the low overall survival (OS), reported as 6 months or less, makes this option less appealing in most cases.[6] Targeted therapies (vemurafenib, dabrafenib, and trametinib) are only approved for use in melanoma harboring a mutation in *BRAF* V600E or V600K. While these drugs have been associated with a relatively high objective response rate (ORR) in patients (approximately50%),[7,8] resistance and eventual disease recurrence are common.[9] In contrast, immunotherapy agents have been associated with durable long-term survival in a proportion of patients, although response rates, particularly with IL-2 and ipilimumab, are relatively low (11–40% across all approved immunotherapies) compared with targeted therapy.[10–17]

Ipilimumab, a monoclonal antibody directed against the immune checkpoint receptor cytotoxic T-lymphocyte antigen 4 (CTLA-4), was initially approved by the FDA in 2011, and was subsequently approved in many other countries worldwide. The success of ipilimumab, which was the first agent to improve the overall survival of patients with advanced melanoma in a phase III trial,[18,19] encouraged the development of agents designed to inhibit other immune checkpoint pathways such as programmed cell death-1 (PD-1).[20] Pembrolizumab and nivolumab, two different monoclonal antibodies directed against PD-1, were approved by the FDA in 2014 for the treatment of metastatic melanoma in patients who had failed ipilimumab and, if they had a BRAF V600 mutation, had also progressed on BRAF inhibitor therapy.[21,22] On June 19, 2015, nivolumab was approved in the European Union for the treatment of unresectable or metastatic melanoma (untreated or previously treated), regardless of BRAF mutation status; pembrolizumab was subsequently approved in the European Union on July 22, 2015, for the same indication. All three checkpoint inhibitors, as well as high-dose (HD) IL-2, are recommended for first- and second-line treatment of advanced melanoma by the National Comprehensive Cancer Network (NCCN) guidelines, with treatment choice depending on evaluation of the individual patient.[23]

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This review will compare the pharmacology of all currently approved immunotherapy agents, with a focus on IL-2, ipilimumab, nivolumab and pembrolizumab. These four agents have distinct mechanisms of action, unique kinetics of response, and a range of adverse events (AEs) associated with their mechanism of action that can be safely managed by experienced health-care providers. Since the clinical management of melanoma patients receiving immunotherapy differs from that of patients receiving conventional cytotoxic and targeted therapies, we discuss clinical management guidelines for safe administration and patient monitoring of these novel agents. With an increasing array of treatments available for advanced melanoma, we consider factors that influence choice of treatment for an individual patient. Finally, we discuss the evolving treatment landscape of melanoma, including the opportunities for combination therapy.

Pharmacology of immunotherapy agents used to treat melanoma mechanism of action

Tumor development and the scope for immunotherapy

Tumors develop when the immune system fails to eradicate cells which, having acquired numerous somatic mutations, no longer have a normal phenotype and can expand uncontrollably. Dysregulation of the immune system, which may be caused in part by immunogenic changes in the tumor cells, can play a major role in tumor growth, allowing the tumor cells to avoid immune-mediated detection and destruction.[24–26] In addition to lack of immunological recognition, tumors may escape immunosurveillance by the induction of central or peripheral immune tolerance. The range of mechanisms employed by tumors to evade immune destruction lends itself to different approaches for immunotherapy.

IL-2

IL-2 was initially identified in 1976 as a soluble factor in the supernatant of activated lymphocyte cultures that selectively stimulated the in vitro proliferation and survival of normal human T cells.[27] The first use of IL-2 first as immunotherapy for metastatic cancer was to generate and expand ex vivo populations of lymphokine-activated killer cells for adoptive T-cell transfer.[28] However, it soon became clear that IL-2 alone was capable of mediating tumor regression,[29] which ultimately led to the clinical trials that support the current use of high-dose (HD) IL-2 monotherapy for advanced melanoma.[30]

Although the precise mechanism of IL-2 -mediated tumor regression has not been characterized, it seems to involve the induction and augmentation of the inherent antitumor activity of $CD8^+$ cytotoxic T lymphocytes and the cytolytic activity of natural killer cells.[31] However, IL-2 also has a critical role in the activation of immunosuppressive regulatory T cells (Tregs).[32] These cells normally act to preserve peripheral T-cell tolerance and prevent autoimmunity, but they can also blunt lymphocyte-mediated tumor rejection. Thus, although HD IL-2 is capable of bolstering the activity of antitumor effector T cells, this effect may be counteracted in some patients by the concomitant activation of Tregs. Patients who respond to IL-2 seem to experience a transient reduction in circulating Tregs, whereas the Treg levels among nonresponders remain stable or increase after treatment.[33]

Immune checkpoint inhibitors

From a therapeutic perspective, the checkpoint receptors are some of the most promising elements recently implicated in cancer immune system dysregulation. These receptors play a major role in maintaining self-tolerance and limiting the extent of immune responses to infection, but can be exploited by tumors as an important immune resistance mechanism.[20]

The process of T-cell activation is a complex balance of stimulatory and inhibitory signals. In brief, T-cell activation requires that a T-cell receptor recognizes and binds to antigen on a major histocompatibility complex molecule, and that there is a costimulatory signal from a B7 molecule on the surface of the antigen-presenting cell binding to CD28 on the T cell. CTLA-4, a homolog of CD28, is expressed on the T-cell surface and also binds B7, but results in T-cell inhibition. Ipilimumab is a fully human, anti-CTLA-4 monoclonal antibody designed to block the CTLA-4 immune checkpoint and thereby augment antitumor T-cell responses (Figure 1).[37,38] Additional data also suggest that depletion or blockade of the activity of Tregs may contribute to the antitumor effects of ipilimumab.[38]

In addition to the CTLA-4 pathway, the immune system has a number of other inhibitory or checkpoint pathways that regulate T-cell activity in different ways to provide a natural counterbalance to costimulatory pathways, limiting the size and duration of a T-cell response and preventing damage to normal tissue.[39] One of these, the PD-1 receptor, is also expressed on activated T cells; however, unlike CTLA-4 expression which occurs early during T cell activation, PD-1 is typically upregulated after prolonged T cell receptor stimulation during an ongoing immune response (Figure 1).[34] While CTLA-4 limits T cell activation and clonal expansion, the main function of PD-1, when bound to one of its ligands (PD-L1 or PD-L2), is to limit effector T cell function in the tumor microenvironment.[20,35,36] PD-L1 and PD-L2 are expressed on a variety of hematopoietic and non-hematopoietic cells; PD-L1 is also commonly expressed by melanomas and many other tumor types.[20,40,41] PD-L1 expression by tumor cells appears to facilitate immune evasion, inhibiting T cell activation and lysis of tumor cells and, in some cases, leading to increased tumor-specific T cell death; increased PD-1 expression on tumor infiltrating lymphocytes may also contribute to tumor immunosuppression.[42] Like CTLA-4, PD-1 is also expressed by Tregs[35,42] and may be required for the suppressive function of these cells.[43]

Nivolumab, a fully human IgG4 anti-PD-1 monoclonal antibody, has been shown in preclinical studies to potently enhance cytokine production and stimulate antigen-specific T-cell responses.[44] Pembrolizumab, a humanized anti-PD-1 IgG4-kappa isotype monoclonal antibody, showed preclinical antitumor activity in a range of tumor types.[45]

Clinical efficacy and response patterns

Key efficacy data for each of the immunotherapy agents approved by the FDA for the treatment of advanced melanoma are summarized in Table 1.

High dose IL-2

HD IL-2 was approved by the FDA in 1998 for the treatment of metastatic melanoma based on its ability to induce a durable objective response in a small subset of patients treated in phase

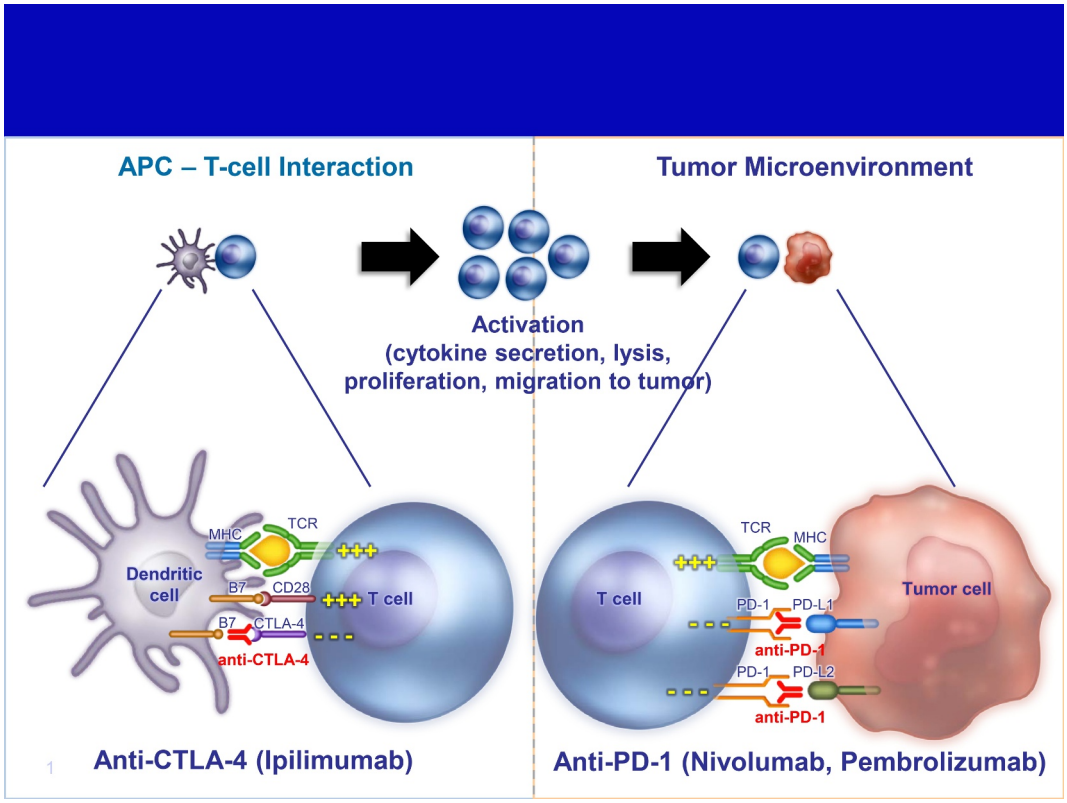

Figure 1. Blockade of CTLA-4 and PD-1: distinct immune checkpoint molecules. Upon antigen presentation by APCs (eg, dendritic cell) via the TCR, T cells become activated or suppressed depending on secondary signaling through CD28 or CTLA-4, respectively. Ipilimumab is a fully human, monoclonal antibody designed to block the immune checkpoint inhibitor, CTLA-4, permitting increased signaling through CD28 and sustained T-cell activation. Unlike CTLA-4 expression which occurs early during T cell activation, the PD-1 receptor is typically upregulated after prolonged T cell receptor stimulation during an ongoing immune response.[34] While CTLA-4 limits T cell activation and clonal expansion, the main function of PD-1, when bound to one of its ligands (PD-L1 or PD-L2), is to limit effector T cell function in the tumor microenvironment.[20,35,36] Anti-PD-1 antibodies block the interaction between PD-1 and its ligands, thereby interfering with inhibitory signaling between tumor cells and T cells within the tumor microenvironment. APC, antigen presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor. Adapted from an oral presentation at the 2013 Annual Meeting of the American Society of Clinical Oncology [*Callahan MK Peripheral and tumor immune correlates in patients with advanced melanoma treated with combination nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab. J Clin Oncol 31, 2013 (suppl; abstr 3003)*].

II studies.[30] No phase III trials comparing HD IL-2 to other treatments, providing an assessment of relative impact on OS, have been done. In a pooled analysis of 270 patients with metastatic melanoma treated with HD IL-2 in eight phase II clinical trials, the overall ORR was 16% (95% confidence interval [CI], 12–21%), with 6% achieving a complete response and 10% achieving a partial response.[30] The median duration of response was 8.9 months among all responders, and had not been reached but exceeded 59 months for complete responders.[46] None of the patients responding for over 30 months progressed at any point thereafter, suggesting that treatment was, effectively, curative. Long-term follow-up data show that over 80% of complete responders remain disease-free at 17 to 253 months of follow-up, with median duration of response more than 176 months.[47] Most responses to IL-2 usually occur early; in one report, 90% of responders to IL-2 demonstrated some tumor regression after the first course of therapy.[48]

Ipilimumab

Approval of ipilimumab for the treatment of advanced melanoma was based on data from two phase III studies that demonstrated significant improvements in OS. MDX010-20 was a placebo-controlled, randomized trial of 676 patients with previously treated unresectable or metastatic melanoma who received ipilimumab 3 mg/kg alone, ipilimumab 3 mg/kg in combination with the peptide vaccine gp100, or gp100 alone. Median OS was significantly greater with ipilimumab plus gp100 compared with gp100 alone (10.0 months vs 6.4 months; hazard ratio [HR] = 0.68; $P< .001$) and with ipilimumab monotherapy compared with gp100 alone (10.1 months vs 6.4 months; HR = 0.66; $P= .003$).[18] Follow-up analysis from this study showed the survival rate was 25% at both 2 and 3 years for patients who received ipilimumab alone.[12]

In study CA184-024, dacarbazine plus ipilimumab (10 mg/kg) was compared with dacarbazine alone in treatment-naive patients with advanced melanoma. OS rates were higher with the combination at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%), and 3 years (20.8% vs 12.2%) (HR for death = 0.72; $P< .001$).[19] The most recent data from this study show that twice as many people who received the ipilimumab combination were alive at 5 years as those receiving dacarbazine only (18.2% vs 8.8%; $P= .002$).[49] A recent pooled analysis of data from 1861 patients across 12 ipilimumab studies showed the median OS was 11.4 months, with 22% of the patients alive after 3 years, and most remaining in remission thereafter with follow-up of up to 10 years (Figure 2).[13]

Patients treated with ipilimumab have shown heterogeneous response patterns, some of which differ from responses seen with chemotherapy and HD IL-2, presumably due to the unique mechanism of action of ipilimumab and the time it can take for

Table 1. Key clinical efficacy data for FDA-approved immunotherapy agents for advanced melanoma.

Agent	Trial phase	Population/study design	N	ORR	Survival	Reference(s)
HD IL-2	II	94% stage IV; 46% previously treated with systemic therapy; pooled analysis of 8 trials	270	16%	mOS 12.0 months	30,46
	NA	Consecutive pts with stage IV disease; most previously treated	305	13%	mOS 12.8 months 2-yr OS 27% 4-yr OS 16%	47
Ipilimumab	III	Previously treated, unresectable stage III/IV; IPI + gp100 vs IPI vs gp100 (3:1:1 ratio)	676	IPI + gp100 vs IPI vs gp100: 5.7% vs 10.9% vs 1.5%	IPI + gp100 vs IPI vs gp100: mOS 10.0 vs 10.1 vs 6.4 months IPI + gp100 vs IPI: 2-yr OS: 19% vs 25% 3-yr OS: 15% vs 25%	12, 18
	III	Previously untreated stage IV; IPI + DTIC vs DTIC + placebo (1:1)	502	IPI + DTIC vs DTIC: 15.2% vs 10.3%	IPI + DTIC vs DTIC: mOS: 11.2 vs 9.1 months 2-yr OS: 28.5% vs 17.9% 5-yr OS: 18.2% vs 8.8%	19, 48
Nivolumab	III	Stage IIIC/IV melanoma after failure of anti-CTLA-4 therapy, and BRAF inhibitor if *BRAFV*^{600} mutation-positive; NIVO vs investigator choice of chemotherapy	405	NIVO vs chemotherapy: 31.7% vs 10.6%	OS data not mature	17
	III	Unresectable, treatment-naïve; NIVO vs DTIC	418	NIVO vs DTIC: 40.0% vs 13.9%	NIVO vs DTIC: 1-yr OS: 72.9% vs 42.1%	15
Pembrolizumab	I	Unresectable disease, IPI-refractory; expansion cohort, pembrolizumab 2 vs 10 mg/kg Q3W	173	26% (both doses)	2 vs 10 mg/kg pembrolizumab: 1-yr OS: 58% vs 63%	49
	III	≤1 previous treatment for unresectable stage III/IV disease; pembrolizumab 10 mg/kg Q2W vs 10 mg Q3W vs IPI	834	Q2W vs Q3W vs IPI: 33.7% vs 32.9% vs 11.9%	Q2W vs Q3W vs IPI: 1-yr OS: 74.1% vs 68.4% vs 58.2%	16

DTIC, dacarbazine; HD, high dose; IPI, ipilimumab; mOS, median overall survival; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; pts, patients; Q2(3)W, every 2 (or 3) weeks; yr, year.

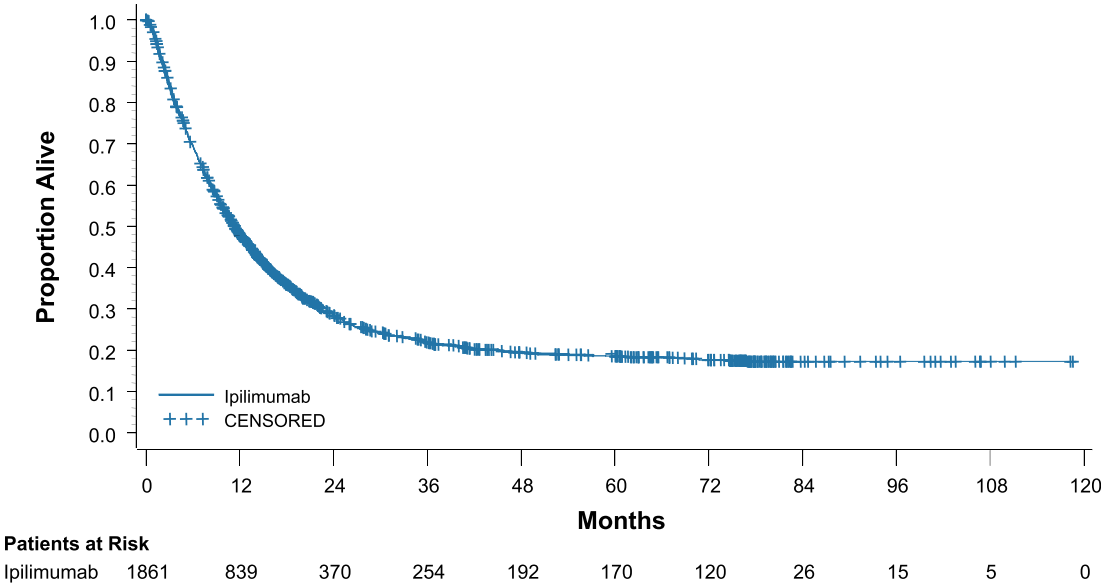

Figure 2. Overall survival with ipilimumab in a pooled analysis. In a group of 1861 patients treated with ipilimumab, median OS was 11.4 months and the 3-year OS rate was 22%.[13] CI, confidence interval. Reprinted with permission by the American Society of Clinical Oncology.

a patient to develop a clinically effective immune response.[50,51] Responses may be delayed for many weeks and may even occur after apparent disease progression. In patients with advanced melanoma, the median time to response was 2.86 months in a phase III trial.[16] So far, four distinct variations have been recorded: (1) response in baseline (index) lesions; (2) a slow, steady decline in tumor burden; (3) response after an increase in tumor burden; and (4) response in index and new lesions accompanied by the appearance of other new lesions. While all four patterns have been associated with favorable survival, patterns (3) and (4) may be unfamiliar to many treating oncologists and also are not well-characterized by standard response assessment criteria; instead, 'immune-related' response criteria have been proposed.[50,51]

The potential for these unconventional patterns of response may lead to inaccurate response assessment using conventional tumor response criteria, or if assessment occurs too soon. Initial assessment is currently recommended after the 12-week induction phase of treatment. Scans should be repeated 2 weeks after the last treatment and again a month later to confirm response.[52]

Nivolumab and pembrolizumab

Nivolumab and pembrolizumab were both approved for the treatment of unresectable or metastatic melanoma on the basis of data from phase I trials showing relatively high response rates and long duration of responses, lasting more than two year in some cases.[53,54] Recent landmark analysis of the nivolumab phase I trial showed 1-, 2-, and 3-year survival rates of 63%, 48%, and 41%, and median OS of 17.3 months for patients with advanced melanoma (n = 107).[14] Similarly, a pooled analysis of 411 patients treated with pembrolizumab in a phase I study showed a 1-year OS rate of 69%.[55]

Several phase III trials with nivolumab and pembrolizumab have now been reported, with the results confirming the early promise of both agents. In a phase III trial of patients previously treated with ipilimumab, the objective response rate (ORR) was approximately 32% in patients randomized to nivolumab (3 mg/kg) and 11% in those receiving chemotherapy; overall survival data were not mature at the time of analysis.[17] In patients with previously untreated metastatic melanoma without *BRAF* mutation, nivolumab (3 mg/kg) significantly improved OS compared with dacarbazine (HR for death = 0.42; $P < .001$).[15] The OS rate at 1 year for nivolumab vs dacarbazine was 72.7% vs 42.1%; median OS had not been reached in the nivolumab group and was 10.8 months in the dacarbazine group. The study was terminated early after this interim analysis so that patients receiving dacarbazine could be switched to nivolumab.

A phase III trial has now compared the efficacy of two different dosing schedules of pembrolizumab (10 mg/kg) with ipilimumab (3 mg/kg) in advanced melanoma.[16] Patients randomized to pembrolizumab had significantly improved OS compared with those randomized to ipilimumab, regardless of which schedule was used. The HR for death for pembrolizumab given every two weeks (Q2W) when compared with ipilimumab was 0.63 (95% CI: 0.47, 0.83; $P< .0005$) and for pembrolizumab given every three weeks (Q3W) was 0.69 (95% CI: 0.52, 0.90; $P= .036$). One-year overall survival rates were 74.1%, 68.4%, and 58.2% in the pembrolizumab Q2W, pembrolizumab Q3W, and ipilimumab groups, respectively; median OS was not reached in any group. Pembrolizumab benefited all subgroups analyzed, with the exception of patients with PD-L1-negative tumors.

As with ipilimumab, anti-PD-1 therapy has been associated with unconventional or 'immune-related' responses in patients with melanoma, although the majority of responses meet traditional RECIST criteria.[15,17,54] Most responses have been detected at the first assessment (8–12 weeks after starting treatment), but responses occurring as late as 8 months after starting treatment have also been reported.[15–17] Because unconventional responses may occur, trial protocols with nivolumab or pembrolizumab typically allowed continued treatment in patients with possible tumor progression provided other clinical parameters were favorable.[15–17]

Dosing and patient selection

IL-2

IL-2 is administered in an inpatient setting as a high-dose (600,000 or 720,000 IU/kg) intravenous bolus infusion given over 15 minutes via a centrally placed catheter. Distribution and elimination are relatively rapid, and the drug is ultimately metabolized and excreted by the kidneys.[56] A course of therapy generally consists of 2 inpatient treatment cycles separated by 9–14 days of rest. During each cycle, up to 14 doses are administered every 8 hours, typically until the onset of significant toxicity – most of which quickly resolves upon treatment cessation because IL-2 has a short half-life. Doses may be held for significant toxicity. Reduced doses are not generally given because IL-2 is maximally effective when delivered with a high-dose, bolus administration regimen.[57] Progressive disease after a course of HD IL-2 represents treatment failure and is generally a contraindication to further therapy.

The success of IL-2 is partly determined by careful selection of patients who can tolerate treatment. Contraindications have traditionally included poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status ≥2), untreated brain metastases, infection, pleural effusions, ascites, and the presence of significant cardiac, pulmonary, or autoimmune disease.

Ipilimumab, nivolumab and pembrolizumab

Ipilimumab is administered as a 90-min intravenous infusion at a dose of 3 mg/kg every 3 weeks for 4 doses over a total period of 12 weeks (induction phase).[52] Ipilimumab can be safely administrated in the ambulatory setting. Ipilimumab retreatment is an option in progressing patients who experienced an objective response or stability lasting at least 3 months and had no serious treatment-related toxicity with their initial ipilimumab treatment.[23]

Nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks at a dose of 3 mg/kg, and pembrolizumab is administered at a dose of 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks; both drugs are continued until disease progression or unacceptable toxicity.[21,22] No pre-medication is needed for infusion of these agents and infusion-related reactions are rare.[21,22]

There are no specific contradictions to ipilimumab, nivolumab or pembrolizumab use in their respective FDA labels. However, like IL-2, none of these agents has been studied in patients with autoimmune diseases.[21,22,52] All immunotherapies need to be given with caution in patients with underlying autoimmune disease.

Safety

IL-2

Most HD IL-2 toxicities are preventable, are easily managed by an experienced provider, and are nearly all reversible. Comprehensive screening guidelines and management algorithms have reduced the risk of treatment-related mortality to virtually zero.[58] The main AE associated with HD IL-2 is capillary leak syndrome (CLS), which manifests clinically with persistent hypotension, edema, and low urine output. CLS develops within hours of the first infusion and is caused by a combination of systemic vasodilation and increased vascular permeability resulting in plasma extravasation and third space fluid sequestration. Management involves careful fluid replacement with the goal of maintaining adequate intravascular volume without causing pulmonary edema. If adequate volume cannot be maintained through fluid replacement, vasopressor support may be necessary.

Other common systemic AEs, such as fevers, myalgias, and nausea, are managed prophylactically and almost always subside within hours after treatment is stopped. One of the few potential long-term AEs of IL-2 is autoimmune thyroiditis leading to hypothyroidism, which occurs in up to one-third of patients and may require hormone replacement therapy.[59] Autoimmune vitiligo has also been seen following IL-2 therapy, although this is often not reported or sought by clinicians as part of the post-treatment assessment.[30,59–64]

Ipilimumab, nivolumab and pembrolizumab

Most toxicities associated with immune checkpoint inhibitors are of mild to moderate severity and reversible, but serious AEs and, rarely, fatalities can also occur.[15–18,65] Phase III data suggest that, overall, the incidence and severity of treatment-related AEs reported with ipilimumab are slightly higher than those reported with nivolumab;[15,17,18,65] rates with ipilimumab may also be higher than those reported with pembrolizumab, but phase III data using the approved dose of pembrolizumab (2 mg/kg) are lacking. Reported rates of any-grade and grade 3/4 treatment-related AEs range from 73% to 86% and 20 to 27%, respectively, for ipilimumab,[16,18,65] and from 59% to 82% and 9 to 16%, respectively, for nivolumab.[15,17,65] Using pembrolizumab 10 mg/kg, the reported rate of any treatment-related AEs was 76% and of grade 3/4 AEs was 12%.[16]

The immune activation induced by each of the three approved immune checkpoint inhibitors has been associated with various immune-related AEs (irAEs). These irAEs include, most notably, cutaneous, gastrointestinal, hepatic, and endocrine AEs, as well as (more rarely) pulmonary and renal toxicity (Table 2).[15–18,65–71] In addition, ipilimumab can cause severe neurological irAEs, including sensory and motor neuropathy, Guillain-Barré syndrome, and myasthenia gravis.[52,72] However, most irAEs in clinical trials were of mild or moderate severity. The incidence and severity of gastrointestinal irAEs, and in particular of colitis, appear higher with ipilimumab than with either nivolumab or pembrolizumab, while the incidence (but not severity) of endocrine irAEs is slightly higher with the anti-PD-1 antibodies than with ipilimumab (Table 2). In nivolumab clinical trials, AEs were similar in treatment-naïve patients and those who had received prior ipilimumab,[15,17] suggesting that the safety profile of nivolumab is unaffected by previous exposure to ipilimumab therapy.

Guidelines for management of irAEs are available for approved immune checkpoint inhibitors,[15,17,18,73–82] and are summarized in Tables 3 and 4 for ipilimumab and nivolumab, respectively. Although precise recommendations vary with irAE and agent, general principles for management include vigilance with close patient monitoring, prompt intervention, withholding treatment until symptoms subside, and use of corticosteroids when appropriate.[15,17,72–74] In the event of a severe irAE, prompt treatment with systemic corticosteroids

Table 2. Comparison of key immune-mediated adverse events with ipilimumab, nivolumab and pembrolizumab as reported in phase III trials, by organ category.

		Ipilimumab[b]		Nivolumab[c]		Pembrolizumab[d]	
Organ category	irAE (%)[a]	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin	Pruritus	24–35	0–<1	16–19	0–<1	14	0
	Rash	14–33[e]	1–2	15–26[e]	0–1	14	0
Gastrointestinal	Diarrhea	23–33	3–6	11–19	<1–2	16	2
	Colitis	8–12	5–9	1	<1–1	3	2
Endocrine	Hypothyroidism	2–4	0	4–9	0	9	<1
	Hyperthyroidism	1–2	0–<1	2–4	0	5	0
	Hypophysitis	2–4	2	<1–1	<1	1	<1
Hepatic	Hepatitis	1	0–<1	NR	NR	1	1
	ALT increased	2–4	0–2	1–4	1	NR	NR
	AST increased	1–4	0–1	1–4	<1–1	NR	NR
Pulmonary	Pneumonitis	<1–2	<1	1–2	0–<1	1	<1
Renal	Blood creatinine increased	NR	NR	<1–1	0	NR	NR
	Renal failure	NR	NR	NR/1[f]	NR/<1[f]	NR	NR

ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; NR, not reported
[a]Key events only listed for each organ category
[b](N = 131)[18; 16]; (N = 311)[65]
[c](N = 206)[15]; (N = 268)[17]; (N = 313)[65]
[d](N = 555)[16]; note that the dose of pembrolizumab used in this trial (10 mg/kg) was higher than the approved FDA dose (2 mg/kg)
[e]Includes the terms 'rash' and 'rash maculo-papular'
[f]Includes the terms 'renal failure' and 'renal failure acute', where both were reported

Table 3. Monitoring and management of common or potentially severe immune-related adverse events associated with ipilimumab.

Adverse Event	Monitoring	Management
Gastrointestinal	Associated with diarrhea and colitis Routinely ask patients they have experienced any changes in normal bowel habits Continued vigilance is necessary during and after treatment to prevent severe colitis, particularly if diarrhea worsens or does not improve following steroid therapy	Discontinue ipilimumab until symptoms either resolve completely or are reduced to mild severity; if symptoms continue for over 1 week, give systemic corticosteroids (eg, prednisone 0.5 mg/kg/d or equivalent) Permanently discontinue ipilimumab if patients experience severe colitis or if corticosteroids cannot be reduced to prednisone 7.5 mg (or equivalent) per day Consider infliximab for severe colitis where steroids are not effective[75–77]
Hepatic	Evaluate hepatic function before each administration; even in the absence of clinical symptoms	Delay ipilimumab in patients with moderate elevation in AST or ALT (>2.5 to ≤5 times ULN) or moderate elevation in total bilirubin (>1.5 to ≤3 times ULN) Permanently discontinue ipilimumab if severe elevation in AST or ALT (>5 times ULN) or total bilirubin (>3 times ULN), and administer corticosteroids while nonimmune-related causes are ruled out
Cutaneous	Various inflammatory symptoms affecting the skin, most commonly pruritus and rash, may occur Severe reactions reported, including Stevens-Johnson syndrome or toxic epidermal necrolysis[78]	Withhold ipilimumab for moderate dermatitis and give topical or systemic corticosteroids if symptoms do not improve within 1 week. Continue ipilimumab if symptoms resolve or improve such that only mild, localized symptoms are present, and if the systemic corticosteroid dose is prednisone ≤7.5 mg (or equivalent) per day For severe reactions, permanently discontinue ipilimumab and start systemic corticosteroids, tapering for ≥1 month when symptoms are controlled
Neurological	Sensory and motor neuropathy, Guillain-Barré syndrome, myasthenia gravis, and other neurological disorders described in case reports[79,80]	Withhold ipilimumab while moderate symptoms (which do not impede daily activities) are managed appropriately; resume ipilimumab following resolution of symptoms or return to baseline Permanently discontinue ipilimumab if the immune-related neuropathy affects daily activities, and consider systemic corticosteroids and/or other medically appropriate interventions
Endocrinopathies	Associated with various endocrinopathies, including hypopituitarism, adrenal insufficiency, hypothyroidism, and hypophysitis Symptoms of neuroendocrine deficiencies may be subtle; ask patients to report symptoms such as fatigue, headache, changes in mental status or bowel movements, and abdominal pain[81,82]	If symptoms indicate a potential endocrinopathy, withhold ipilimumab while endocrine function is evaluated Administer systemic corticosteroids and consider radiographic pituitary gland imaging Start appropriate hormone-replacement therapy if needed Ipilimumab therapy may be resumed when symptoms have resolved or returned to baseline and corticosteroids have been reduced to prednisone ≤7.5 mg (or equivalent) per day

ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal

(for example, prednisone typically administered at a dose of 1 to 2 mg/kg/d or equivalent) is recommended. For some grade 3 and all grade 4 irAEs, permanent discontinuation of the relevant immune checkpoint inhibitor is recommended. In the case of ipilimumab, treatment should also be permanently discontinued if symptoms persist such that the full treatment course cannot be completed within 16 weeks of initiation.[72] Any irAEs would generally emerge before the last dose of the treatment course, although hepatitis and endocrinopathies have been reported after the last dose of drug.[70]

Table 4. Management and follow-up of immune-related adverse events associated with nivolumab (adapted from Robert 2015a[15] and Bristol-Myers Squibb 2015[74]).

Organ category and associated irAEs	Grade of irAE[a]	Management	Follow-up
Gastrointestinal			
• Diarrhea • Colitis	Grade 2	• Withhold nivolumab • Symptomatic treatment	If persists >5-7 days or recurs: • 0.5–1 mg/kg/day MP[b] or oral equivalent If worsens or persists >3-5 days with oral steroids: • Treat as grade 3–4
	Grade 3–4	• Grade 3: withhold nivolumab • Grade 4: permanently discontinue nivolumab • 1–2 mg/kg/day MP[b] or IV equivalent • Consider lower GI endoscopy	If persists >3-5 days or recurs: • Add non-corticosteroid immunosuppressive medication (e.g., infliximab)
Hepatic			
• Transaminase elevation • Total bilirubin elevation • Hepatitis	Grade 2	• Withhold nivolumab • Monitor every 3 days • 1–2 mg/kg/day MP[b] IV or IV equivalent	If persists >5-7 days or worsens: • 0.5–1 mg/kg/day MP[b] or oral equivalent
	Grade 3–4	• Permanently discontinue nivolumab • Monitor every 1–2 days • 1–2 mg/kg/day MP[b] IV or IV equivalent • Consult gastroenterologist	If does not improve in 3–5 days, worsens or rebounds: • Add non-corticosteroid immunosuppressive medication
Skin			
• Rash • Pruritus	Grade 1–2	• Continue nivolumab • Symptomatic treatment (eg antihistamines, topical steroids)	If persists >1–2 weeks or recurs: • Consider skin biopsy • Withhold nivolumab • Consider 0.5–1 mg/kg MP/day[b] or oral equivalent If worsens: • Treat as grade 3–4
	Grade 3–4	• Withhold or discontinue nivolumab • 1–2 mg/kg/day IV MP[b] or IV equivalent • Consider skin biopsy • Consult dermatologist	Can resume nivolumab if resolution to grade 1
Endocrine			
• Hypothyroidism • Hyperthyroidism • Hypophysitis	Symptomatic	• Continue nivolumab for hypothyroidism/hyperthyroidism • Withhold nivolumab for other endocrinopathies with abnormal lab/pituitary scan • Evaluate endocrine function • Consider pituitary scan • Consider endocrinology consult Normal labs/pituitary scan • Repeat labs in 1–3 weeks • Repeat MRI in 1 month Abnormal labs/pituitary scan • Initiate replacement hormone therapy	If improves (with or without hormone replacement): • Resume nivolumab • Continue standard monitoring • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
	Suspected adrenal crisis	• Withhold nivolumab • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	
Renal			
• Elevated serum creatinine • Nephritis • Renal dysfunction	Grade 2–3	• Withhold nivolumab • Monitor creatinine every 2–3 days • 0.5–1 mg/kg/day MP[b] IV or oral equivalent • Consider renal biopsy	If elevations persist >7 days or worsen: • Treat as grade 4
	Grade 4	• Permanently discontinue nivolumab • Daily creatinine monitoring • 1-2 mg/kg/day MP[b] IV or IV equivalent • Consult nephrologist • Consider renal biopsy	
Pulmonary			
• Pneumonitis	Grade 2	• Withhold nivolumab • Daily symptom monitoring • Pulmonary and infectious disease consults • Consider bronchoscopy, lung biopsy • 1–2 mg/kg /day IV MP[b] or oral equivalent	Re-image every 1–3 days If not improving after 14 days or worsening: • Treat as grade 3–4
	Grade 3–4	• Permanently discontinue nivolumab • Hospitalize • Pulmonary and infectious disease consults • Consider bronchoscopy, lung biopsy • 2–4 mg/kg/day MP[b] IV or IV equivalent	If not improving after 48 hours or worsening: • Add additional non-corticosteroid immunosuppression (infliximab, cyclophosphamide, mycophenolate)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0
[b]If improves to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections; nivolumab therapy can be resumed for mild-to-moderate imAEs that have returned to baseline
IV = intravenous; MP = methylprednisolone

The available data from nivolumab and ipilimumab phase III trials showed that 70–100% of grade 3/4 irAEs resolved successfully using recommended management guidelines and immune modulatory medication.[15,17,65] Unlike most irAEs observed with immune checkpoint inhibitors, endocrinopathies associated with treatment may be irreversible, but can be managed with hormone replacement therapy (without corticosteroids); usually, no interruption in immune checkpoint inhibitor therapy should be necessary.[15,17,18,73,74]

Considerations for immunotherapy patient selection and sequencing strategies

Patients who may be unsuited for immunotherapy

Immunotherapy has the potential for long-term survival in patients with advanced melanoma. Patients may not be ideal candidates for IL-2 or ipilimumab, if they have rapidly progressive disease;[23] such patients may not tolerate treatment well, or may have insufficient predicted survival in which to achieve a response. In this type of patient, nivolumab and pembrolizumab are options or, if a *BRAF* mutation is present, one might consider attempting to halt the progression with a BRAF inhibitor initially, with the goal of switching to immunotherapy.[23] Other patients who are not good candidates for immunotherapy include those with underlying autoimmune diseases, patients with uncontrolled brain metastases, and patients with poor performance status (ECOG 3–4).

Patients who may be unsuited for IL-2

In addition to the patients mentioned above, patients with poor lung function (less than 75% of predicted forced expiratory volume in 1 second [FEV1]), poor renal function, ascites, or pleural effusions should not receive IL-2. The presence of reversible cardiac ischemia is also a contraindication for IL-2 therapy, so patients with a smoking history, those aged >50 years, and those with a family history of coronary disease should have a nuclear stress test or stress echocardiogram before therapy. Lack of access to an experienced IL-2 center may additionally prevent treatment.

Patients who may be unsuited for ipilimumab, nivolumab or pembrolizumab

Overall, more patients are candidates for ipilimumab therapy than for HD IL-2. Patients must be able to wait 9–12 weeks for a tumor response, tolerate the potentially severe immune-related side effects, and tolerate high doses of steroids for several weeks. For example, a frail elderly patient may be unable to tolerate severe colitis, even if identified and treated promptly.

Apart from individuals with autoimmune diseases, no specific types of patient are known to be unsuited to treatment with nivolumab or pembrolizumab. The decision to treat should be made on an individual patient basis taking potential risk factors into account. No dose adjustment of either agent is required in patients with renal or hepatic impairment.[21,22] For all three agents, use in pregnant women bears risk to the fetus, and safety has not been established in pediatric populations.[21,22,52]

Which Immunotherapy to Use First?

The choice of which immunotherapy to use first must be made with each individual patient, taking into account all of the factors discussed above. Clearly, more patients may be suited to treatment with immune checkpoint inhibitors than with HD IL-2, with its requirement for extremely careful patient selection to minimize risk of excessive toxicity. Furthermore, based on the data currently available, the chances of long-term benefit appear greater with immune checkpoint inhibitors than with HD IL-2, based on much more rigorous testing in phase III trials. With survival curves for ipilimumab plateauing at 3 years, approximately 20% of patients may expect long-term survival.[13,49] Furthermore, long-term survival appears higher with treatment-naïve patients (26%) than previously treated patients (20%),[13] which would favor using ipilimumab (or nivolumab or pembrolizumab, if long-term survival data sustain the early promise of these agents) rather than HD IL-2. With HD IL-2, long-term survival seems dependent on achieving a complete response, reported in only approximately 6% of patients.[30,46] In contrast, some guidelines have advocated for IL-2 treatment as first-line therapy in appropriate patients because of the higher complete response rate and better outcomes in patients with a better underlying performance status.[10]

One potential disadvantage of using immune checkpoint inhibitors before IL-2 is the longer time to response. With HD IL-2, response is evident within approximately 6 weeks, but with all three immune checkpoint inhibitors, 8–12 weeks, or sometimes longer, may be needed. Certain irAEs with immune checkpoint inhibitors (with a bigger risk of grade 3/4 irAEs associated with ipilimumab than with nivolumab or pembrolizumab[83]) may affect subsequent therapy with HD IL-2 or other immunotherapy and may limit enrollment in clinical trials. Any toxicity requiring a prolonged course of steroids would delay or prevent the initiation of an alternative immunotherapy, and further immunotherapy would be complicated for patients with hypophysitis (secondary to use of ipilimumab) requiring long-term steroids. Even if an irAE on ipilimumab resolves, patients may be predisposed to experience similar or more severe irAEs with IL-2.[84] In contrast, prior IL-2 therapy does not seem to affect tolerability or response to ipilimumab.[85,86] Neither clinical response nor progression-free survival with IL-2 has been able to predict a benefit with subsequent ipilimumab.[87]

Immunotherapy for patients with noncutaneous melanoma

Information regarding IL-2 activity in metastatic, noncutaneous melanoma is sparse. Recently, data from multiple studies have shown improved OS with ipilimumab in patients with metastatic uveal melanoma.[88–92] The largest study with the most patients with metastatic uveal melanoma (n = 82) showed

a 1-year survival rate of 31%.[88] Data also suggest ipilimumab has activity in patients with metastatic mucosal melanoma.[92–94] An analysis of 71 patients with metastatic mucosal melanoma treated with ipilimumab showed a 1-year survival rate of 35%.[93] To date, the use of anti-PD-1 antibodies in noncutaneous melanoma has been limited, but the available data suggest antitumor activity with a similar toxicity profile to that previously reported.

Among seven patients with metastatic uveal melanoma who received pembrolizumab as part of Merck's expanded access program, one patient each had a complete response, a partial response, and stable disease; median progression-free survival (PFS) at data-cutoff was 12.2 weeks and two patients were still receiving therapy without progression.[95] A case report of a patient with metastatic mucosal melanoma treated with pembrolizumab showed that this patient discontinued treatment with severe hypothyroidism, rhabdomyolysis, and acute kidney injury, but remained in near complete response 14 months after stopping treatment.[96] A phase II study to investigate the role of pembrolizumab in patients with advanced uveal melanoma is planned (NCT02359851), while another phase II study of nivolumab in combination with ipilimumab for uveal melanoma is currently recruiting patients (NCT01585194).

Evolution of immunotherapy for advanced melanoma

The evidence for long-term survival with HD IL-2 and, more recently, ipilimumab reinvigorated the development and evaluation of immunotherapies for a range of tumors types, including melanoma. PD-1 checkpoint inhibitors are now clinically proven, with pembrolizumab and nivolumab approved for the treatment of advanced melanoma, Two other agents targeting the PD-1 pathway (MEDI4736, and MPDL3280A) are in phase III clinical development for different tumor types, with additional agents in earlier stages of development.

The development of agents designed to inhibit different immune checkpoints provides the opportunity to evaluate the safety and activity of sequential or concurrent combination regimens. In theory, combining immunotherapies with the goal of overcoming more than one immunosuppressive mechanism has the potential to provide a more comprehensive antitumor immune response than might be achieved with single-agent therapy.[20,97] In a phase Ib/II clinical trial, patients with metastatic melanoma treated with standard HD IL-2 and escalating doses of ipilimumab reported an initial ORR of 22%.[98] On further follow-up, the response rate increased to 28%, likely reflecting the delayed kinetics of response observed with ipilimumab, and 17% of patients achieved a complete response, suggesting potential benefit for combining IL-2 and ipilimumab.[99]

Phase III data have recently confirmed preclinical and early phase clinical results which suggested that sequential or concurrent combination therapy with immune checkpoint inhibitors might be superior to monotherapy treatment.[65,100–102] In a double-blind, placebo-controlled phase III trial, treatment with a combination of nivolumab and ipilimumab was compared with ipilimumab monotherapy; the trial also included a nivolumab monotherapy arm.[65] Overall survival data are not yet available, but PFS with nivolumab plus ipilimumab was significantly longer than with ipilimumab monotherapy (median 11.5 vs 2.9 months; HR for death or disease progression 0.42; 99.5% CI, 0.31 to 0.57; $P< .001$). Although the study was not designed for formal comparison of the nivolumab group and the nivolumab plus ipilimumab group, median PFS with nivolumab was 6.9 months and the HR for the comparison was 0.74 (95% CI, 0.60 to 0.92). Subgroup analysis showed consistently longer PFS with nivolumab or with nivolumab plus ipilimumab than with ipilimumab, with subgroups including those defined by PD-L1 status and *BRAF* mutation status. Combination therapy was, however, associated with greater toxicity; the rate of grade 3/4 AEs was 55%, 16% and 27% for the combination, nivolumab alone, and ipilimumab alone, respectively. Given that, in a phase I trial using a concurrent regimen with various doses of nivolumab (1 or 3 mg/kg) plus ipilimumab (0.3, 1, or 3 mg/kg) 2-year OS was 79%,[103] it will be interesting to see whether the phase III efficacy results translate into an OS benefit with the combination.

Immune checkpoint inhibitors seem likely to form a key part the management of patients with advanced melanoma for many years to come. However, other types of immunotherapy are also being developed which in the future may play a role in treating this tumor, either alone or in combination with currently approved agents. For example, two ongoing phase I trials are investigating the activity of ipilimumab combined with, respectively, varlilumab (CDX-1127), an anti-CD27 monoclonal antibody that induces activation and proliferation of human T-cells when combined with T-cell receptor stimulation (NCT02413827), or MGA271, an anti-B7-H3 monoclonal antibody that mediates antibody-dependent cellular cytotoxicity and which has shown antitumor activity in preclinical studies (NCT02381314).[104] Finally, since adenosine is known to play a key role in regulating melanoma progression, immune checkpoint inhibition may be enhanced by blockade of the adenosine A2a receptor (A2aR), which plays a critical role in the regulation of T-cell function.[105,106] Several A2aR antagonists have shown encouraging antitumor activity in preclinical development in combination with either anti-PD-1 or anti-CTLA-4 agents,[107] with a number in clinical development for non-cancer indications; a phase I study of the adenosine A2aR antagonist, PBF-509, is also ongoing in patients with non-small cell lung cancer (NCT02403193).

Conclusion

The decision of which immunotherapy to begin treatment with in eligible patients – IL-2, ipilimumab, pembrolizumab, or nivolumab – should be made based on expected benefit versus risk. All four therapies offer the possibility of extended survival in some patients. IL-2 is the only immunotherapy known to be associated with a "cure", albeit in a small number of patients, yet some patients treated with ipilimumab experience long-term survival up to 10 years. Pembrolizumab and nivolumab are currently the only agents approved by the FDA for use after progression on or intolerance to ipilimumab and a BRAF inhibitor (for patients with mutated *BRAF*). However, this guidance may change

rapidly, as phase III studies have demonstrated that treatment with a PD-1 checkpoint inhibitor is superior to ipilimumab in the first or second-line setting and that the combination of ipilimumab and nivolumab is superior to either agent alone in the first-line setting. Indeed, nivolumab monotherapy was approved in 2015 in the EU for the treatment of advanced melanoma in both the first- and second-line settings.

To enable individual patients to achieve maximal benefit from these immunotherapy agents, prompt identification and management of AEs (including irAEs) are critical. Most AEs are reversible with appropriate management and do not prevent continuation of immunotherapy for advanced melanoma.

As more checkpoint inhibitors and other immunotherapies are developed, the opportunities for combination or sequential therapy will increase rapidly. Consequently, the dynamic and evolving field of immunotherapy for melanoma will continue to offer challenges in terms of optimal patient management for the foreseeable future.

Abbreviations

AEs	adverse events
ALT	alanine transaminase
AST	aspartate transaminase
CI	confidence interval
CLS	capillary leak syndrome
CNS	central nervous system
CTLA-4	cytotoxic T-lymphocyte antigen 4
EKG	electrocardiogram
FDA	Food and Drug Administration
HD	high dose
HR	hazard ratio
Il-2	interleukin-2
irAEs	immune-related AEs
IV	intravenous
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NSAIDs	nonsteroidal anti-inflammatory drugs
OS	overall survival
PD-1	programmed death-1
SBP	systolic blood pressure
TCR	T cell receptor
Tregs	regulatory T cells
ULN	upper limit of normal

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