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Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma

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ABSTRACT

Historically, the median overall survival for patients with stage IV melanoma was less than 1 year and the 5-year survival rate was ~10%. Recent advances in therapy have raised 5-year survival expectations to ~20%. Notably, a subset of melanoma patients who receive immunotherapy with high-dose interleukin-2, and now ipilimumab, can achieve long-term survival of at least 5 years. A major goal in melanoma research is to increase the number of patients who experience this overall survival benefit. In this review, we discuss the attributes of immunotherapy and newer targeted agents, and consider how combination strategies might improve the chances of achieving durable benefit and long-term survival. We also discuss three areas that we believe will be critical to making further advances in melanoma treatment. To better understand the clinical profile of patients who achieve long-term survival with immunotherapy, we first present data from ipilimumab clinical trials in which a subset of patients experienced durable responses. Second, we discuss the limitations of traditional metrics used to evaluate the benefits of immunotherapies. Third, we consider emerging issues that clinicians are currently facing when making treatment decisions regarding immunotherapy. A better understanding of these novel treatments may improve survival outcomes in melanoma, increase the number of patients who experience this overall survival benefit, and inform the future use of these agents in the treatment of other cancer types.

Introduction

Survival outcomes for patients with stage IV melanoma have traditionally been poor. With standard therapies such as dacarbazine (DTIC), median overall survival (OS) is 6–10 months and the 5-year survival rate is ~10% [1,2]. The recent availability of ipilimumab and BRAF pathway targeted agents has raised survival expectations and shifted the treatment paradigm for melanoma. An important challenge for the melanoma community is how to incorporate these new treatments into day-to-day clinical decision making to maximize the chances that a patient will experience long-term benefit. In this review, we discuss the clinical attributes of immunotherapy and BRAF pathway targeted agents when used as monotherapy and their potential to be used in combination regimens. We also discuss the following issues that will be critical to making further advances in melanoma treatment: (1) characteristics of patients who achieve long-term survival with immunotherapy, (2) the need for improved clinical trial endpoints that fully capture the clinical benefits of immunotherapy, and (3) emerging questions in need of answers to

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ensure that appropriate treatment decisions are made about immunotherapy.

New treatments: immunotherapy and targeted therapy

Immunotherapy

Initial attempts to improve outcomes in patients with advanced melanoma focused on the use of high-dose interleukin-2 (HD IL-2), a cytokine that induces T-cell activation and proliferation [3]. The rationale for using HD IL-2 to treat advanced melanoma was based in part on two observations that suggest involvement of the immune system in the natural history of melanoma. First, a small proportion of patients experience spontaneous tumor regression in primary, but not metastatic, tumors in the absence of systemic intervention, suggesting that melanoma may be an immunologically modulated malignancy [4]. Second, HD IL-2 demonstrated promising antitumor activity in murine models [5].

HD IL-2 was evaluated in a series of phase II melanoma trials. In a US National Cancer Institute study, while only 7% of melanoma patients treated with HD IL-2 achieved complete regression, responses were maintained for up to 91+ months [6]. In eight phase II melanoma trials of HD IL-2, the objective response rate was 16% with response durations ranging from 1.5 to more than 122 months [7,8]. In a randomized, phase III study, the objective response rate was 6% among 93 patients treated with HD IL-2 [9]. Although HD IL-2 may provide durable responses of over 10 years in some patients, its use is limited by severe toxicity that can affect multiple organ systems (e.g., cardiovascular, respiratory, nervous, renal, digestive, and skin) [10]. For this reason, HD IL-2 is generally reserved for selected patients who are treated as inpatients at specialty centers. The toxicities associated with HD IL-2 have prompted investigations of low-dose IL-2 (LD IL-2) regimens. Although LD IL-2 is less toxic than HD IL-2 [10], it has failed to produce complete and durable response in melanoma clinical trials [11,12]. Despite these limitations, the experience with HD IL-2 provides proof-of-concept that modulation of the immune system might offer durable clinical benefit in melanoma. In the era of more tolerable immunotherapies, the role of single-agent HD IL-2 remains to be determined, but T-cell agonist strategies with more limited toxicities will likely play a role in future combination regimens.

Improvements in our understanding of tumor immunology have led to the development of targeted immunotherapies aimed at specific immune-checkpoints. Immune-checkpoints that are currently being targeted in melanoma include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1). CTLA-4 and PD-1 are inhibitory receptors with nonoverlapping roles in modulating the adaptive immune response. CTLA-4 acts primarily early in the immune response to regulate T-cell proliferation and migration to the tumor, whereas PD-1 and its ligand PD-L1 regulate T-cell activation and proliferation at the tumor site [13].

Ipilimumab, which targets CTLA-4, was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency in 2011 for the treatment of unresectable or metastatic melanoma. A survival benefit with ipilimumab was demonstrated in two randomized, controlled phase III trials (MDX010-20 and CA184-024) [14,15]. In study MDX010-20, previously treated melanoma patients received ipilimumab 3 mg/kg plus the melanoma peptide vaccine gp100, ipilimumab 3 mg/kg alone, or gp100 alone [14]. The median OS for these treatment groups was 10.0, 10.1, and 6.4 months, respectively. The hazard ratio (HR) for death compared with gp100 alone was 0.68 ($p < 0.001$) for the ipilimumab plus gp100 group and 0.66 ($p = 0.003$) for the ipilimumab-alone group. In study CA184-024, previously untreated patients received ipilimumab 10 mg/kg plus DTIC or DTIC plus placebo [15]. The median OS for these treatment groups was 11.2 and 9.1 months, respectively (HR, 0.72; $p < 0.001$).

Data from these and other clinical trials suggest that a proportion of patients treated with ipilimumab can achieve survival of at least 5 years. In study CA184-025, a companion study of extended ipilimumab treatment in patients who received ipilimumab in previous phase II trials, 5-year survival was 16.5% to 17.0% for ipilimumab 3 mg/kg and 17.6% to >49% for ipilimumab 10 mg/kg [16]. In study CA184-024, 5-year survival was 18.2% for ipilimumab plus DTIC versus 8.8% for DTIC plus placebo [17]. A meta-analysis of pooled OS data from ipilimumab trials, which included data from 1861 melanoma patients, reported a 3-year OS rate of 22% (95% CI, 20–24%); furthermore, a plateau in the pooled Kaplan–Meier curve began at approximately 3 years after initiation of therapy, and extended through follow-up of as long as 10 years [18]. Importantly, some patients included in the pooled analysis were no longer receiving treatment, suggesting that treatment-free survival is possible with ipilimumab.

The success of ipilimumab was closely followed by the development of additional immune-checkpoint inhibitors, including nivolumab and pembrolizumab (MK-3475), which target PD-1. These agents have demonstrated clinical activity in early clinical trials and are being explored in ongoing phase III studies (Table 1). In a phase 1 study of nivolumab, 28% (26 of 94) of patients with melanoma showed an objective response that lasted from 1.9 to 24.9 months [19]. A phase Ib study of pembrolizumab reported an objective response rate of 38% among 117 evaluable patients [20]. Whether responses to nivolumab and pembrolizumab will be similarly durable to responses to ipilimumab remains to be determined, but preliminary evidence suggests that this may be the case [21,22].

Preliminary data from phase I clinical trials suggest that antibody-mediated targeting of PD-L1 may also be an effective melanoma treatment strategy (Table 1). Among 52 evaluable patients treated with BMS-936559 (MDX 1105), 9 (17%) achieved an objective response and 14 (27%) had stable disease (SD) lasting 24 weeks or more [23] (NCT00729664). Antibody-mediated blockade of PD-L1 with MPDL3280A, another PD-L1 inhibitor, was associated with objective responses in 9 of 35 evaluable patients, with all responses ongoing or improving at the time of tumor assessment [24] (NCT01375842). A phase I clinical trial is also underway to evaluate the PD-L1 inhibitor MEDI4736 in several advanced tumor types including melanoma (NCT01693562).

Targeted therapy

Concurrently with the development of the newer immunotherapies, a better understanding of the biology of melanoma has led to the development of molecular targeted therapies. The mitogen-activated protein kinase (MAPK) pathway is one of the major signaling networks involved in melanoma tumorigenesis [25]. A major driver of this pathway is BRAF, which can initiate a cascade of events including phosphorylation and activation of MEK. BRAF mutations are found in ~50% of melanomas, with most (70–95%) consisting of a V600E substitution, while a smaller proportion (5–30%) are V600K substitutions [26]. Along with ipilimumab, agents that target BRAF and MEK have now emerged as key treatments for advanced melanoma.

Vemurafenib, an inhibitor of mutant BRAF, was approved by the FDA in 2011 for the treatment of melanoma patients harboring the BRAF V600E mutation based on improved OS versus DTIC in the BRIM-3 phase III study [27]. At a median follow-up of 10.5 months for vemurafenib and 8.4 months for DTIC, median OS was 13.2 and 9.6 months, respectively (HR, 0.62) [28]. One-year OS rates were 55% and 43% in patients treated with vemurafenib

Table 1
Selected on-going immunotherapy trials in advanced melanoma.[a]

Agents (target)	NCT No.	Phase	Study arms[b]	Expected enrollment	Primary outcomes	Year initial results expected
Single-agent immunotherapy						
Nivolumab (PD-1)	NCT01721746 (CheckMate 037)	3	Arm 1: Nivo Arm 2: DTIC or CBDCA + PTX	390	ORR, OS	2015
	NCT01721772 (CheckMate 066)	3	Arm 1: Nivo + PCB for DTIC Arm 2: DTIC + PCB for nivo	410	OS	2015
	NCT01844505 (CheckMate 067)	3	Arm 1: Nivo + PCB for ipi + PCB for nivo Arm 2: Nivo + ipi + PCB for nivo Arm 3: Ipi + PCB for nivo	915	OS	2016
Pembrolizumab (PD-1)	NCT01295827 (P07990/MK-3475-001)	1	Dose-escalation phase: Arm 1: Pembro (1) Arm 2: Pembro (3) Arm 3: Pembro (10) Comparison of two dosing regimens: Arm 1: Pembro (q2wk *vs.* q3wk) Comparison of two doses: Arm 1: Pembro (low dose) Arm 2: Pembro (high dose)	1067	Safety, tumor response, DCR, biomarker	2015
	NCT01704287 (P08719/MK-3475-002)	2	Arm 1: Pembro (low dose) Arm 2: Pembro (high dose) Arm 3: CBDCA + PTX, PTX, DTIC, or tem	510	PFS, OS	2015
	NCT01866319 (MK-3475-006 AM1)	3	Arm 1: Pembro (regimen 1) Arm 2: Pembro (regimen 2) Arm 3: Ipi	645	PFS, OS	2014
MDX1105 (PD-L1)	NCT00729664 (CA210-001)	1	Arm 1: MDX1105 (0.1) Arm 2: MDX1105 (0.3) Arm 3: MDX1105 (1.0) Arm 4: MDX1105 (3.0) Arm 5: MDX1105 (10.0)	286	MTD, DLT	2013
MPDL3280A (PD-L1)	NCT01375842 (PCD4989g)	1	Arm 1: MPDL3280A	344	DLT	2014
MEDI4736 (PD-L1)	NCT01693562 (CD-ON-MEDI4736-1108)	1	Arm 1: MEDI4736 q2wk Arm 2: MEDI4736 q3wk Arm 3: MEDI4736 dose expansion	220	DLT, safety	2015
Immunotherapy combinations						
Agents	NCT No.	Phase	Study arms[b]	Expected enrollment	Primary outcomes	Year initial results expected
Dual immunotherapy						
Ipilimumab and nivolumab	NCT01024231 (CA209-004)	1	Arm 1: Nivo (0.3) + ipi (3.0) Arm 2: Nivo (1.0) + ipi (3.0) Arm 3: Nivo (3.0) + ipi (3.0) Arm 4: Nivo (10.0) + ipi (3.0) Arm 5: Nivo (10.0) + ipi (10.0) Arm 6: Nivo (1.0) Arm 7: Nivo (3.0) Arm 8: Nivo (1.0) + ipi (3.0), then nivo (3)	136	Safety	2014
	NCT01783938 (CheckMate 064)	2	Arm 1: Nivo (3), then ipi (3) Arm 2: Ipi (3), then nivo (3)	100	Safety	2014
	NCT01844505 (CheckMate 067)	3	Arm 1: Nivo + PCB for ipi + PCB for nivo Arm 2: Nivo + ipi + PCB for nivo Arm 3: Ipi + PCB for nivo	915	OS	2016
Ipilimumab and other immunotherapy	NCT01134614 (E1608)	2	Arm 1: Ipi + GM-CSF Arm 2: Ipi	220	OS	2013
	NCT01708941 (ECOG-E3611)	2	Arm 1: Ipi (10) + HDI Arm 2: Ipi (10) Arm 3: Ipi (3) + HDI Arm 4: Ipi (3)	88	PFS	2014

Immunotherapy plus targeted therapy						
Ipilimumab and BRAF inhibitor	NCT01400451 (CA184-161)	1	Arm 1: Ipi + vem	50	Safety	2013
	NCT01767454 (115984)	1	Arm 1: Dab + ipi	72	Safety	2014
			Arm 2: Dab + tram + ipi			
	NCT01673854 (CA184-240)	2	Arm 1: Vem, then ipi	45	Safety	2013
Immunotherapy plus chemotherapy						
Ipilimumab and various cytotoxics	NCT01409174 (2011-0073)	1/2	Arm 1: Ipi + tem, + cis, + IFN, or + IL-2	64	Tumor response	2017
	NCT01676649 (CA184-195)	2	Arm 1: CBDCA + PTX + ipi (regimen 1)	30	Safety	2014
			Arm 2: CBDCA + PTX + ipi (regimen 2)			
Immunotherapy plus radiotherapy						
Ipilimumab and radiotherapy	NCT01703507 (2012-43)	1	Arm 1: Ipi + WBRT	24	MTD	2017
			Arm 2: Ipi + SRS			
	NCT01689974 (S12-02746)	2	Arm 1: Ipi	100	Tumor response	2014
			Arm 2: Ipi + radiotherapy			

CBDCA, carboplatin; cis, cisplatin; dab, dabrafenib; DCR, disease control rate; DLT, dose-limiting toxicity; DTIC, dacarbazine; fot, fotemustine; GM-CSF, granulocyte macrophage colony-stimulating factor; HDI, high-dose interferon; IFN, interferon alpha-2b; IL-2, interleukin-2; ipi, ipilimumab; irDCR, immune-related disease control rate; MTD, maximum tolerated dose; nivo, nivolumab; ORR, objective response rate; OS, overall survival; PCB, placebo; Pembro, Pembrolizumab; PFS, progression-free survival; PTX, paclitaxel; q2wk, every two weeks; q3wk, every three weeks; SRS, stereotactic radiosurgery; tem, temozolomide; tram, trametinib; vem, vemurafenib; *vs.* versus; WBRT, whole-brain radiotherapy.

[a] Table includes trials that have not yet reported primary data (ClinicalTrials.gov, accessed January 2014).

[b] For some agents, doses are listed in parentheses in mg/kg.

and DTIC, respectively. In the BRIM-2 phase II study of previously treated melanoma patients, median OS was 15.9 months with vemurafenib treatment [29]. Data suggest that a subset of melanoma patients with BRAF V600 mutation may achieve survival up to 3 years with continuous, twice-daily vemurafenib treatment. In the BRIM-1 phase I study, 26% of patients treated with vemurafenib were alive at 3 years [30]. Vemurafenib treatment is associated with high response rates, but similar to experience with other therapies based on oncogene-targeted small molecules, responses require persistent drug administration and are usually of limited duration (median of 6.7 months [29]) due to the emergence of tumor resistance [31,32].

The melanoma armamentarium expanded again with the FDA approval of dabrafenib and trametinib. Dabrafenib was approved for patients with unresectable or metastatic melanoma harboring the BRAF V600E mutation based on results from a phase III trial showing improved median progression-free survival (mPFS) versus DTIC (5.1 months for dabrafenib *vs.* 2.7 months for DTIC; HR, 0.30; $p < 0.0001$) [33]. The MEK inhibitor trametinib was approved for melanoma patients harboring a BRAF V600E or V600K mutation based on results from a phase III trial showing improved mPFS versus DTIC or paclitaxel (4.8 months for trametinib *vs.* 1.5 months for DTIC or paclitaxel; HR, 0.45; $p < 0.001$) [34]. In 2014, the FDA approved the use of dabrafenib in combination with trametinib for patients with BRAF V600E- or V600K-mutated melanoma, making dabrafenib/trametinib the first FDA-approved targeted combination therapy for this disease [35]. FDA-approval of dabrafenib/trametinib combination therapy was based on an improved overall response rate (ORR) and median duration of response versus dabrafenib monotherapy in a phase I/II trial (ORR: 76% for dabrafenib/trametinib combination *vs.* 54% for dabrafenib monotherapy; median duration of response: 10.5 months for dabrafenib/trametinib combination *vs.* 5.6 months for dabrafenib monotherapy). The FDA approval of dabrafenib/trametinib combination therapy is contingent on results of an ongoing phase III trial (Combi-D, NCT01584648). Survival follow-up data from the above-mentioned studies continue to mature, with the extent of the potential survival benefit for combined dabrafenib and trametinib treatment not yet determined.

Immunotherapy and targeted therapy have clinical profiles with distinct attributes (Table 2). Although both treatment strategies offer the potential for durable response and long-term survival, current data suggest that patients must remain on treatment to achieve these outcomes with targeted therapy, whereas treatment-free survival and durable response are at least possible with immunotherapy. The following limitations have been observed for some, but not all, immunotherapies: low response rates, delayed onset of effect, and immune-related toxicity that must be managed carefully. In addition, it is difficult to predict which patients will respond to immunotherapy. By contrast, targeted therapies are associated with high response rates, rapid onset of effect, and side effects that are generally reversible after dose adjustment. However, these treatments require continuous, twice-daily dosing; may elicit resistance within 6–8 months; and generally do not provide long-lasting benefit after the therapy is discontinued. Strategies that capitalize on the strengths and overcome the weaknesses associated with these treatments are needed and might possibly be achieved through combination and/or sequencing regimens.

Immunotherapy combination strategies

Immunotherapies in combination and sequenced regimens are being evaluated for their potential to achieve greater survival benefit in advanced melanoma (Table 1). One area of active research is

combined blockade of CTLA-4 and PD-1 pathways. The rationale for this approach is supported by the concept that immune cells often express multiple immune-checkpoints with non-overlapping mechanisms of action (Fig. 1) [37].

Ipilimumab in combination with nivolumab is being studied in melanoma clinical trials (Table 1). A phase melanoma I study (NCT01024231) identified 3 mg/kg ipilimumab and 1 mg/kg nivolumab as the maximum tolerated doses for the concurrent regimen [38]. Among evaluable patients treated at these doses ($n = 17$), the objective response rate was 53%, and the disease control rate was 65%, with two patients showing rapid response ($\geqslant$80% tumor reduction at their first scheduled assessment). Among patients treated with the concurrent regimen ($n = 52$), 21 had confirmed objective response ranging from 6+ to 72+ weeks, with ongoing response observed in 91% of these patients. The most common grade 3/4 treatment-related adverse events (AEs) were increased aspartate aminotransferase (13%), increased alanine aminotransferase (11%), and elevated lipase (13%). Although the incidence of immune-related toxicity was greater for this combination than for either single agent, grade 3/4 toxicities were usually reversible through application of standard immunosuppression-based algorithms. This combination is being further explored in phase II (NCT01783938) and phase III (NCT01844505) trials in melanoma (Table 1) and in other tumor types (e.g., renal cell carcinoma [NCT01472081]; breast cancer, gastric cancer, pancreatic adenocarcinoma, and small cell lung cancer [NCT01928394]; recurrent glioblastoma [NCT02017717]; non-small cell lung cancer [NCT01454102]; and colon cancer [NCT02060188]).

Ipilimumab in combination with other immunotherapies is also being studied (Table 1). An ongoing phase II trial is evaluating ipilimumab plus granulocyte macrophage colony-stimulating factor (GM-CSF) versus ipilimumab alone (NCT01134614). Interim data from this trial suggest that the addition of GM-CSF to ipilimumab decreases the incidence of high-grade AEs, particularly those related to pulmonary and gastrointestinal function [39]. Ipilimumab with or without high-dose interferon (HDI) is also being evaluated in a phase II study (NCT01708941).

Ipilimumab is also being combined with BRAF/MEK inhibitors in clinical trials [40] (Table 1). The rationale for this approach is based in part on data from preclinical studies, which suggest that inhibition of the MAPK pathway has a beneficial effect on the tumor immune microenvironment [41]. A phase I trial (NCT01400451) of concurrent ipilimumab and vemurafenib was prematurely closed due to dose-limiting hepatotoxicity, suggesting that safety issues may limit the use of this combination regimen [42]. An ongoing phase II study will evaluate the sequential use of ipilimumab and vemurafenib (NCT01673854) [43]. Ipilimumab plus dabrafenib with or without trametinib will also be evaluated in a phase I study (NCT01767454).

Ipilimumab combined with standard cytotoxics is also being investigated in melanoma clinical trials (Table 1). In study CA184-024, ipilimumab plus DTIC was associated with higher rates of hepatotoxicity and lower rates of enterocolitis than those previously reported with either agent alone, suggesting that the toxicity profile with this combination strategy is not simply additive of these two agents [15]. These data highlight the fact that predicting toxicity with combinations of ipilimumab may not be straightforward. In a single-arm, phase II study of ipilimumab plus fotemustine (NCT01654692), the immune-related disease control rate was 46.5% in melanoma patients ($N = 86$) and 50% in patients with asymptomatic brain metastases ($N = 20$) [44]. This combination strategy is being further explored in an ongoing phase III study (EUDRACT 2012-004301-27). A phase I/II trial will evaluate ipilimumab combined with temozolomide, cisplatin, interferon α-2b, or IL-2 (NCT01409174), and a phase II trial will evaluate ipilimumab combined with carboplatin/paclitaxel (NCT01676649).

Ipilimumab in combination with radiotherapy is also being explored as a potential treatment for advanced melanoma (Table 1). The clinical benefits associated with radiotherapy are generally attributed to improved local tumor control; however, recent reports suggest that radiotherapy administered locally may improve antitumor immunity globally [45], extending the application of radiotherapy beyond its traditional role in local tumor control [46]. For example, ipilimumab in combination with radiotherapy has been shown to induce an abscopal effect [45], a phenomenon in which tumor regression occurs at a site distant from the primary site of radiotherapy. The therapeutic potential of this treatment combination is being further explored in ongoing clinical trials. A phase 1 study is investigating the maximum tolerated dose of ipilimumab plus radiotherapy in melanoma patients with brain metastases (NCT01703507). A phase 2 study is evaluating response rates associated with ipilimumab alone versus ipilimumab plus radiotherapy (NCT01689974).

Data derived from these studies will help determine which treatment regimens are most likely to improve survival outcomes in patients with advanced melanoma. However, additional work on the appropriate selection of patients is also needed to maximize the potential for immunotherapy to improve survival outcomes. For this reason, another important area of research is characterizing patients who might achieve extended survival (e.g., OS at a particular landmark such as 3 or 5 years) with ipilimumab, with the ultimate goal of identifying biomarkers that may predict patient response and survival.

Characterizing long-term survivors

Long-term survivors among ipilimumab-treated patients have included those who achieve complete response (CR), partial response (PR), SD, and, in some cases, progressive disease (PD) according to modified World Health Organization (WHO) criteria [47]. Some patients with PD may actually develop a response or SD over time, possibly reflecting the long time required to build antitumor immunity in some patients. Unlike with cytotoxic agents, SD appears to be an important endpoint for ipilimumab since these patients may still achieve long-term disease control and/or survival. An important issue related to SD is whether this response category represents true residual disease or fibrotic tissue with no residual tumor. In some cases, tumoral masses may appear to show incomplete regression, when in fact the remaining abnormal tissue is attributable to residual fibrosis. In these cases, an incorrect assessment of the tumor response could lead to an underestimation of the treatment effect [48]. Although imaging techniques can help to distinguish masses with viable tumor from those with fibrosis [48], false positives are still possible because the tumor masses being evaluated often contain a dynamic mixture of metastatic tumor and immunotherapy-induced inflammation [49]. Relying on response rates alone as a surrogate may underestimate eventual survival outcomes.

Durable responses to ipilimumab do not appear to be associated with known prognostic factors or BRAF-mutation status. Subgroup analyses from phase III ipilimumab trials suggest that the effect of ipilimumab on OS is independent of factors such as age, sex, baseline lactate dehydrogenase levels, and M stage of disease, as well as prior IL-2 therapy and ECOG performance status [14,15]. A prospective phase II trial has also demonstrated the activity of ipilimumab at an investigational dose of 10 mg/kg in patients with brain metastases, particularly when these metastases are stable and asymptomatic [50]. Data from an Italian expanded access program suggest that ipilimumab is an effective treatment for advanced melanoma regardless of BRAF-mutation status. In this study, the immune-related disease control rate among

Table 2
Attributes of immunotherapy and targeted therapy.

Immunotherapy	Targeted therapy
Strengths: • Potential for durable response • Potential for long-term survival, potentially off treatment	Strengths: • Potential for durable response, on treatment • Potential for long-term survival, on treatment • High response rates • Rapid onset of effect
Weaknesses: • Low response rates[a,b] • Delayed onset of effect[a] • Immune-related toxicity that must be carefully managed[a] • Difficulty predicting patient responders	Weaknesses: • Continuous, twice-daily dosing • May elicit resistance within 6–8 months • Rare evidence of durable response (off treatment)
Examples: • HD IL-2 • Ipilimumab targeting CTLA-4 • Investigational agents targeting PD-1 pathway - Nivolumab - Pembrolizumab - MDX1105 - MPDL3280A	Examples: - Vemurafenib (BRAF inhibitor) - Dabrafenib (BRAF inhibitor) - Trametinib (MEK inhibitor) - Dabrafenib/trametinib combination
Evidence of durable benefit? • HD IL-2 –Durable remission up to 10 yrs in ~10% of pts[c] • Ipilimumab –Long-term survival up to 10 yrs in ~20% of pts[d]	Evidence of durable benefit? • Survival data are not mature

[a] These attributes have been observed with some, but not all, immunotherapies.
[b] Response rates according to RECIST criteria.
[c] Atkins et al. 2000 [8].
[d] Schadendorf et al. 2013 [18].

BRAF-mutation positive ($n = 169$) and BRAF-mutation negative ($n = 291$) patients was 38% and 39%, respectively, with a median duration of irDC of 13.1 months [51].

Extensive research has been performed to identify potential biomarkers that can predict response to ipilimumab. These studies have focused on absolute lymphocyte count (ALC), serum S100B levels, tumor-infiltrating lymphocytes, and molecular tumor signatures [52–56]. In a retrospective analysis of 51 ipilimumab-treated patients with advanced melanoma, patients with high ALC levels ($\geqslant 1000/\mu l$) after two ipilimumab treatments had improved median OS compared to patients with low ALC levels ($<1000/\mu l$) (median OS: 11.9 months with high ALC *vs.* 1.4 months with low ALC) [54]. In another study, ipilimumab-treated patients with an NY-ESO-1-specific CD8+ T-cell response experienced a significant survival advantage compared to patients without such a response [53]. Data from a small cohort ($N = 27$) of melanoma patients treated with ipilimumab in an expanded access program suggest that increased circulating levels of inducible T-cell costimulator-positive T-cells are associated with improved survival at week 7 of treatment [56]. The ratio between absolute neutrophil and lymphocyte counts was also identified as a potential predictive marker of survival in this study. Although some of these data are compelling, additional work is needed to help clarify the predictive value of putative biomarkers in melanoma. Interested readers are referred to other reviews for a more in-depth treatment of this topic [57–60]. In addition to improved patient selection, refined methods of assessment are also needed to fully capture the clinical benefit of immunotherapies.

Refining assessment of clinical benefit

Assessment of antitumor response in immunotherapy trials has been challenging because both conventional and nonconventional response patterns have been observed. Conventional response patterns include CR with an immediate reduction in tumor burden and SD followed by reduction in tumor burden. Nonconventional response patterns, which are unique to immunotherapy treatment, include response following an initial increase in tumor burden ("pseudoprogression") and response in the presence of new lesions. Conventional response patterns rely on tumor shrinkage to demonstrate antitumor response and are captured by WHO criteria and Response Evaluation Criteria in Solid Tumors. Nontraditional response patterns, which may not directly relate to tumor shrinkage, may be missed when using these traditional metrics. The need to fully capture the clinical benefit of these drugs has led to the development of immune-related response criteria [61].

The kinetics of antitumor immune response also have important implications for evaluation of survival endpoints in immunotherapy trials. Kaplan–Meier curves from immunotherapy trials consistently show a delay in the separation of OS curves between treatment and control arms, which could reflect the time needed for an immune response to translate into a survival effect. In study MDX010-20, a separation in OS curves between ipilimumab arms and the control arm was not observed until 3 months after treatment [14] (Fig. 2). The challenge associated with delayed OS curve separation is that it increases the statistical power necessary to differentiate the treatment and control arms. A recent analysis of immunotherapy trials estimated that more than 2700 patients would be necessary to achieve statistical power to detect a significant difference between OS curves that showed a delayed separation of up to 6 months [63]. An alternative approach might be to design a trial in which landmark analysis is used to assess survival. However, there are also challenges associated with this approach, including the long time required for all patients to reach the landmark.

Median OS and landmark analysis may not fully capture the survival benefit of ipilimumab. For example, in the previously mentioned meta-analysis of ipilimumab survival data, median OS (11.4 months [95% CI, 10.7–12.1]) and landmark survival at 3 years (22%) by themselves do not fully portray the complete survival benefit that may be achieved with ipilimumab [18]. In the pooled analysis, a plateau in the Kaplan–Meier curve began at approximately 3 years and extended through follow-up of as long as 10 years, suggesting that in ipilimumab clinical trials, approximately 20% of patients with advanced melanoma experienced long-term survival benefit.

In order to fully characterize the survival pattern associated with immunotherapy treatment, additional statistical models to assess

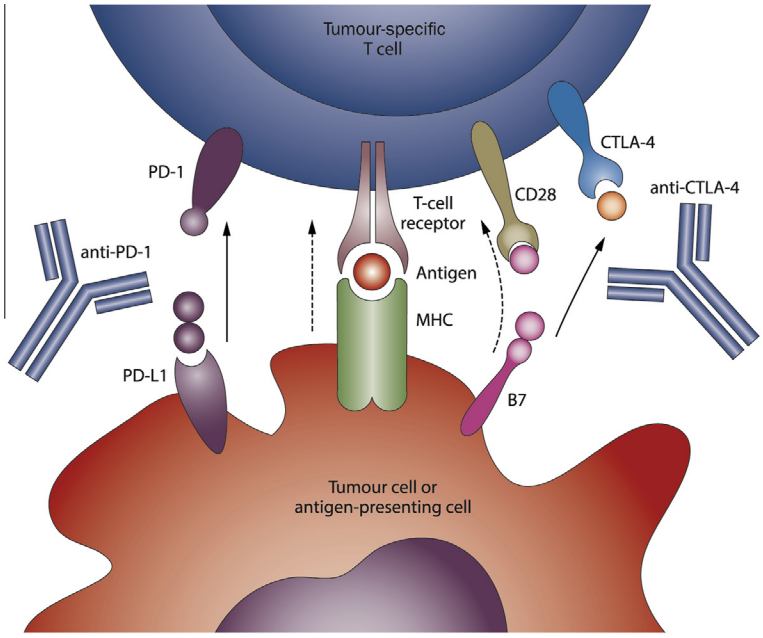

Fig. 1. Combined immune-checkpoint inhibition for melanoma treatment. Immune cells and tumor cells express multiple immune-checkpoints, which are being targeted for melanoma treatment. Ipilimumab, an anti-CTLA-4 antibody, increases the number of activated T-cells migrating to attack the tumor by restoring an essential co-stimulatory signal required to activate a T-cell immune response. Nivolumab, an anti-PD-1 antibody, prevents T-cell inactivation and promotes T-cell reactivation by disrupting the interaction between PD-1 and its ligand, PD-L1. Since ipilimumab and nivolumab target two distinct immune-checkpoint pathways that mediate different aspects of the adaptive immune response, combined immune-checkpoint inhibition with these agents may produce a more comprehensive immune response than that which can be produced with either agent alone. CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1. Figure reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology, Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nat Rev Clin Oncol 2014;11(1):24–37, copyright© 2014. [36].

survival are needed. Ideally, future immunotherapy trials should prospectively incorporate landmark analysis, conditional probability of survival at specific time points, probability of relapse, and other nontraditional metrics to describe HRs as a function of time to provide a more accurate assessment of immunotherapy treatment. Also helpful will be future clinical trials testing neoadjuvant therapy with these agents, as used successfully in breast cancer, to provide a better assessment of the pathological response histologically, as well as allowing examination of biomarker expression on residual tumor.

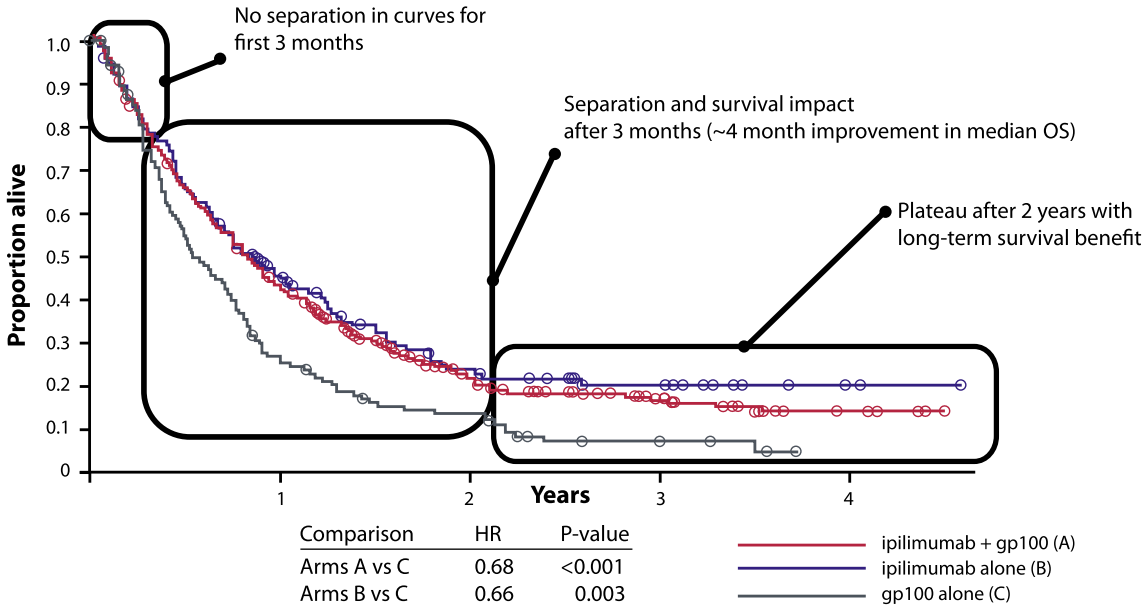

Fig. 2. Kaplan–Meier analysis of overall survival in study MDX010-20. A separation in the Kaplan–Meier curves between the ipilimumab arms and the control arm is observed after 3 months of treatment. A plateau in the Kaplan–Meier curves for the ipilimumab arms is observed after approximately 2 years of treatment. gp100, glycoprotein 100 melanoma peptide vaccine; HR, hazard ratio; OS, overall survival. Figure adapted with permission from Massachusetts Medical Society and John Wiley & Sons, Inc., from New England Journal of Medicine, Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma, vol. 363, p. 716, copyright © 2010 Massachusetts Medical Society [14] and from Annals of the New York Academy of Sciences, Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma, Wolchok JD, Hodi FS, Weber JS, Allison JP, Urba WJ, Robert C, et al, vol. 1291, p. 6, copyright © 2013 [62]; permission conveyed through Copyright Clearance Center, Inc..

Emerging questions for immunotherapy treatment

As the treatment landscape for melanoma becomes increasingly complicated, clinicians who treat advanced melanoma will require more information regarding the use of immunotherapies and other agents in order to provide the greatest benefit/risk for their patients. There are a number of emerging questions that need to be addressed to help clinicians make treatment decisions regarding immunotherapy.

Since the majority of long-term immunotherapy data in melanoma is with ipilimumab, it is possible, but not confirmed, that the experience with this agent can be applied to immunotherapy for melanoma in general. While data from ipilimumab clinical trials suggest that CTLA-4 blockade produces durable response patterns in a subset of melanoma patients, it is not yet known whether PD-1 blockade or combined CTLA-4/PD-1 blockade will have a similar effect. In a phase III study, ipilimumab 3 mg/kg was active regardless of burden of disease and number/sites of metastases, including metastases to the brain [14]. However, central nervous system involvement in melanoma is frequently responsible for treatment failure and death [64]; therefore, the effectiveness of ipilimumab in melanoma patients with brain metastases continues to be explored [43,49,65] (EUDRACT Number 2012-004301-27). Data derived from ipilimumab clinical trials also suggest that clinical responses may be delayed, raising the concern that the underlying disease may progress before an elicited immune response can counter the disease process. Given this possibility, it may be important for the treating physician to consider disease tempo when making treatment decisions related to immunotherapy.

Because the subpopulation that experiences long-term benefit with ipilimumab remains to be effectively characterized, another challenge is deciding when to move a patient who is receiving ipilimumab on to the next therapy. Prescribers who are experienced with ipilimumab cite anecdotal evidence that not only histological/radiological data, but also patient performance status, are valuable in determining whether a patient is doing well on ipilimumab or whether another therapy is needed. A related challenge is determining whether immunotherapy or targeted agents should be used in the first-line setting [66]. Prospective sequence trials will be needed to determine which treatment regimens are optimal for providing long-term survival benefit.

Whether relapsing patients should receive retreatment, a different agent, or a combination of agents also remains to be determined. Patients who progress after ipilimumab therapy may subsequently benefit from retreatment [14,56]. The National Comprehensive Cancer Network endorses consideration of retreatment with ipilimumab for patients who experience progression following initial clinical response or SD > 3 months, provided there are no contraindications such as history of severe autoimmune disease or toxicity [67]. The contribution of retreatment to overall survival remains to be determined.

Summary

Advances in immunotherapy and targeted therapy have revolutionized the treatment landscape for advanced melanoma, raising survival expectations beyond those historically anticipated with this disease. The benefits associated with these new therapies are accompanied by limitations, which may be overcome by using novel combination strategies. In order to maximize the impact of immunotherapy in melanoma treatment, several important issues need to be addressed. Biomarkers are needed to identify patients who are most likely to respond to immunotherapy. In addition, improved clinical trial endpoints are needed to fully capture the clinical benefits associated with immunotherapy. Finally, best practices need to be established to optimize the outcomes that can be achieved with immunotherapy and targeted therapy.

Conflict of interest

D. McDermott has served on advisory boards for Bristol-Myers Squibb, Merck, and Roche. C. Lebbé has served on advisory boards for Bristol-Myers Squibb, Roche, GlaxoSmithKline, and Novartis. F.S. Hodi has received clinical trial research support from Bristol-Myers Squibb, Merck, and Genentech (paid to author's institution); technology from Bristol-Myers Squibb (assigned to and licensed by author's institution); and is a non-paid consultant for Bristol-Myers Squibb, Merck, and Genentech. M. Maio has received research grants from Bristol-Myers Squibb and served on advisory boards for Bristol-Myers Squibb. J.S. Weber has received clinical trial research support from Bristol-Myers Squibb (paid to author's institution) and served on advisory boards for Bristol-Myers Squibb. J.D. Wolchok is a consultant and advisory board member for Bristol-Myers Squibb, Merck, and MedImmune. J.A. Thompson has received clinical trial research support from Bristol-Myers Squibb and Merck (paid to author's institution). C.M. Balch has received honoraria from Merck and is a consultant for Amgen.

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