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Tumour Review

Gaining momentum: New options and opportunities for the treatment of advanced melanoma

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ABSTRACT

Before 2011, patients with advanced or metastatic melanoma had a particularly poor long-term prognosis. Since traditional treatments failed to confer a survival benefit, patients were preferentially entered into clinical trials of investigational agents. A greater understanding of the epidemiology and biology of disease has underpinned the development of newer therapies, including six agents that have been approved in the EU, US and/or Japan: a cytotoxic T-lymphocyte antigen-4 inhibitor (ipilimumab), two programmed cell death-1 receptor inhibitors (nivolumab and pembrolizumab), two BRAF inhibitors (vemurafenib and dabrafenib) and a MEK inhibitor (trametinib). The availability of these treatments has greatly improved the outlook for patients with advanced melanoma; however, a major consideration for physicians is now to determine how best to integrate these agents into clinical practice. Therapeutic decisions are complicated by the need to consider patient and disease characteristics, and individual treatment goals, alongside the different efficacy and safety profiles of agents with varying mechanisms of action. Long-term survival, an outcome largely out of reach with traditional systemic therapies, is now a realistic goal, creating the additional need to re-establish how clinical benefit is evaluated. In this review we summarise the current treatment landscape in advanced melanoma and discuss the promise of agents still in development. We also speculate on the future of melanoma treatment and discuss how combination and sequencing approaches may be used to optimise patient care in the future.

Introduction

Despite an increase in the incidence of advanced melanoma [1,2], little progress has been made over recent decades in addressing the poor prognosis of patients or the limited treatment options available [3]. Historically, the primary aims of treatment were to reduce tumour burden and palliate symptoms, with little hope for prolonged survival. Chemotherapy remained the standard of care for advanced melanoma; objective response rates (ORRs) range from 5% to 25% for dacarbazine monotherapy and up to 45% for polychemotherapies, but none of these treatments have demonstrated improved overall survival (OS) [4,5].

More recently, extensive research has yielded a greater understanding of the epidemiology and biology of advanced melanoma, leading to the development of several new treatments with different mechanisms of action (MoAs). Six new agents have been approved in the EU, US and Japan for advanced melanoma in recent years: ipilimumab, nivolumab and pembrolizumab (immunotherapies), and vemurafenib, dabrafenib and trametinib (targeted therapies) [6–8]. These agents have dramatically improved the outlook for metastatic melanoma but have also increased the complexity of the treatment algorithm. As well as patient and disease characteristics, treatment decisions must now consider the different activity profiles of agents, balancing the desire for an immediate tumour response with symptom management and quality of life (QoL) [9]. In addition, as long-term survival has become an achievable treatment goal, the optimal measurement of clinical efficacy must be reconsidered. To this end, recommendations for how best to integrate these new agents into clinical practice are only included in more recent treatment guidelines [10–14].

This article reviews the approved treatment options for advanced and metastatic melanoma and recent data from clinical

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trials with novel regimens. It also addresses how future treatment strategies might be improved through sequencing and/or combination approaches.

Systemic treatment approaches

Approved and investigational therapies in metastatic melanoma differ in their MoAs (Fig. 1). Table 1 summarises the key properties of agents developed beyond phase I clinical trials.

Chemotherapy

Historically, systemic treatment of patients with advanced melanoma centred on cytostatic chemotherapy with dacarbazine or other alkylating agents such as temozolomide, fotemustine or taxanes [15]. Dacarbazine induces response rates (RRs) of up to 25% with no OS benefit over supportive care (median OS, 5–11 months) [5,16]. However, in comparator arms of controlled phase III trials of BRAF inhibitors, RRs for dacarbazine were only 6–9% and median OS was 9.7 months [17,18]. The most common treatment-related adverse events (AEs) with dacarbazine are nausea and vomiting, which are manageable with antiemetics in most patients [16].

Biochemotherapy combinations such as dacarbazine plus cytokines (interleukin-2 [IL-2] or interferons [IFNs]), or cisplatin/vinblastine/dacarbazine/tamoxifen (known as the Dartmouth regimen) have demonstrated superior RRs over chemotherapy alone without improved survival [19]. Furthermore, adding IL-2 to chemotherapy increases toxicity [20,21]. Polychemotherapy regimens include carboplatin/paclitaxel, CVD (cisplatin, vincristine and dacarbazine) and the BOLD regimen (bleomycin, vincristine, lomustine and dacarbazine); gemcitabine plus theosulfan is sometimes used in patients with primary ocular melanoma. Again, these combinations fail to significantly improve survival versus monochemotherapy and are therefore not considered appropriate first-line therapies [11], unless a high RR is required.

In a phase III trial, treatment with temozolomide, an oral alternative to dacarbazine, did not improve median OS in newly diagnosed patients with metastatic melanoma versus dacarbazine [22]. However, temozolomide can cross the blood–brain barrier and is widely used in patients with brain metastases [23]. Fotemustine also showed substantial activity in patients with symptomatic or asymptomatic brain metastases in a phase II trial and demonstrated superior RRs and a trend towards improved OS over dacarbazine in a phase III study [24]. Although used in

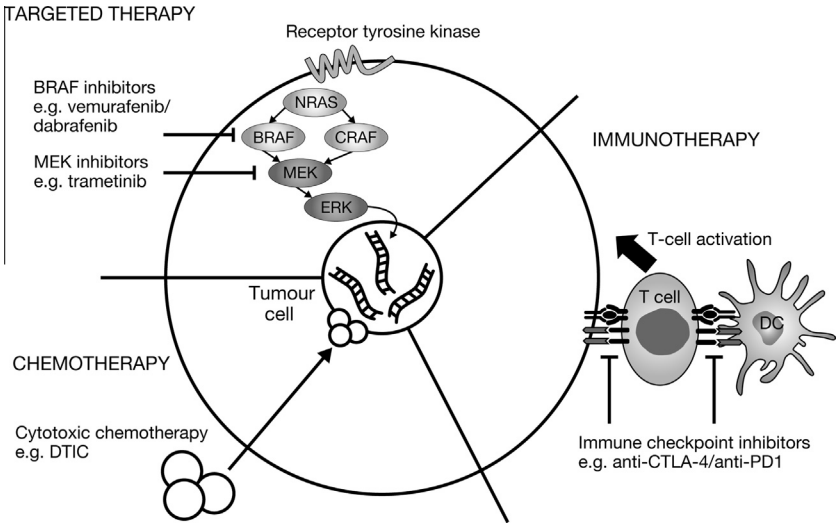

Fig. 1. Systemic therapies in advanced melanoma. *Abbreviations:* CTLA-4 – cytotoxic T-lymphocyte-associated antigen-4; DC – dendritic cell; DTIC – dacarbazine; PD-1 – programmed death 1.

Table 1
Types of antimelanoma therapy.

	Chemotherapy	Targeted therapy	Immunotherapy
MoA[a]	Direct cytotoxicity	Inhibition of MAPK signalling	Immune-related
OS advantage[a]	No	Yes	Yes
PFS advantage[a]	Yes	Yes	Small
Long-term (>2 years) survival[a]	Unknown	Unknown	Yes[b]
Common side effects[a]	Nausea, myelotoxicity	SCCs, ash, arthralgia, pyrexia, photosensitivity	irAEs[b]: colitis, endocrinopathies
Patient population[a]	All	$BRAF^{V600}$-mutation-positive	All[b]
Agents developed beyond phase I trials (highest phase)	DTIC (3)	Vemurafenib (3)	Ipilimumab (3)
	Temozolomide (3)	Dabrafenib (3)	Nivolumab (1)
	Fotemustine (3)	Trametinib (3)	Pembrolizumab (1)
	Nab-P (3)	LGX818 (1)	MPDL3280A (1)
		MEK162 (2)	BMS-936559 (1)
		Selumetinib (2)	T-VEC (3)
		Imatinib mesylate (2)	IL-2 (3)

Abbreviations: DTIC – dacarbazine; IL-2 – interleukin-2; irAE – immune-related adverse event; MAPK – mitogen-activated protein kinase; MoA – mechanism of action; Nab-P – nanoparticle albumin-bound paclitaxel; OS – overall survival; PFS – progression-free survival; SCC – squamous cell carcinoma; T-VEC – talimogene laherparepvec.

[a] Approved treatments (DTIC/vemurafenib/dabrafenib/ipilimumab).

[b] Effects are consistent with expected outcomes generally associated with immunological agents.

some EU countries, fotemustine is not European Medicines Agency (EMA)-approved.

In a more recent phase III trial, nanoparticle albumin-bound paclitaxel (nab-P) significantly improved median progression-free survival (PFS) versus dacarbazine (4.5 versus 2.8 months; hazard ratio [HR] = 0.792; $p = 0.044$), with a trend towards improved median OS at interim analysis (12.8 versus 10.7 months; HR = 0.831; $p = 0.094$) [25]. Monochemotherapy should be limited to salvage therapy in metastatic melanoma patient groups unsuitable for newer treatments or clinical trials. The combination of chemotherapy and other treatment modalities is currently being investigated in numerous clinical trials. While chemotherapy is migrating from a classical first-line treatment to palliative therapy following progression with newer antimelanoma drugs, it will remain in the treatment plan for many patients.

Targeted therapy

Several key genetic mutations have been identified that contribute to melanoma incidence and progression. An estimated 40–50% of melanomas harbour activating mutations in the BRAF oncogene, most commonly the substitution of valine to glutamic acid (V600E) or lysine (V600 K) at codon 600. In addition, mutations in NRAS have been identified in approximately 15–20% of melanomas [26,27]. The RAS and BRAF proteins regulate cellular proliferation and survival, mainly through activation of the mitogen-activated protein kinase (MAPK) pathway [28]. Indeed, the MAPK pathway can be activated via several cancer-related mechanisms, including mutations in RAS, BRAF and MEK1, loss of the tumour suppressor NF1, binding of a ligand to receptor tyrosine kinases (RTKs), or mutational activation of an RTK, leading to excessive cellular proliferation through activation of ERK1/2 [28,29]. Consequently, targeting the MAPK cascade is of interest in melanoma, and inhibitors of BRAF and its primary downstream target MEK have been developed (Table 2) [30].

BRAF inhibitors

Tumours must be screened for $BRAF^{V600}$ mutations prior to treatment to identify patients most likely to respond to BRAF inhibitors [31]. Wild-type (WT) BRAF status is an absolute contraindication for such compounds due to the potential for paradoxical activation of MAPK [32]. Vemurafenib is a potent BRAF inhibitor that is approved for patients with $BRAF^{V600}$ mutation-positive, unresectable or metastatic melanoma [31,33]. Interim analysis of a phase III trial (BRIM3) comparing vemurafenib with dacarbazine indicated early improvements in PFS and the study was unblinded to allow patients on the dacarbazine arm to cross over to vemurafenib [31]. Following an initial OS benefit with vemurafenib, subsequent follow-up showed that the HR evolved from 0.37 (95% confidence interval [CI], 0.26–0.55) to 0.70 (95% CI, 0.57–0.87) [17]. These results were verified in a phase IIIb trial of >2000 patients [34], and vemurafenib has also shown activity in patients with asymptomatic or symptomatic brain metastases [35,36].

Vemurafenib has an acceptable safety profile, with frequent yet manageable grade 1–2 AEs and few grade 3–4 AEs [31,34]. Common treatment-related AEs (>10% patients) reported in phase I–III trials included arthralgia, fatigue, rash and photosensitivity [31,34,37,38]. Vemurafenib-induced photosensitivity may be ultraviolet A-dependent; therefore, ultraviolet A-tailored sunscreens are recommended for patients at treatment initiation [39]. Patients treated with vemurafenib may require excision of new squamous-cell carcinomas (SCCs) or keratoacanthomas due to RAF inhibitor dependent activation of MAPK signalling in BRAF WT cells [31,33,40]. At present, limited data are available regarding the potential long-term ($\geqslant$2 years) survival benefit and safety of vemurafenib.

Dabrafenib, was also recently granted US Food and Drug Administration (FDA) and EMA marketing authorisation as monotherapy for $BRAF^{V600}$-mutated unresectable or metastatic melanoma. In a randomised phase III trial, dabrafenib significantly improved PFS over dacarbazine with an ORR of 50% [18]. Follow-up indicated median OS of 20.0 months versus 15.6 months with dacarbazine (HR = 0.77; 95% CI, 0.52–1.13) [41]. However, the real difference in OS cannot be assessed due to predefined crossover of progressing dacarbazine patients into the dabrafenib arm. Efficacy of dabrafenib has also been shown in patients with asymptomatic brain metastases [42].

Across five clinical studies, the most common treatment-related AEs with dabrafenib monotherapy were hyperkeratosis, headache, arthralgia and pyrexia [43]. Grade 3–4 AEs were uncommon; the incidence of phototoxic reactions or epithelial skin lesions with dabrafenib was lower than with vemurafenib in phase II and phase III trials, whereas the incidence of pyrexia was higher [18,43], although no head to head randomized data are available.

LGX818, another potent BRAF inhibitor currently in development, has shown promise in early clinical trials; a phase III study is ongoing [44,45].

Although the rapidity of response and tumour control with BRAF inhibitors has been impressive, durability of response is limited due to resistance, relapse and subsequent disease progression [46,47]. For example, in phase III trials, around 50% of patients treated with vemurafenib or dabrafenib developed disease progression within 6–7 months of starting treatment [17,41]. Data from a small number of patients suggest that continuing treatment with vemurafenib or dabrafenib beyond progression may be feasible [48,49]; however, this has not yet been confirmed in a prospective randomised trial.

MEK inhibitors

Activated BRAF phosphorylates and activates downstream MEK proteins (MEK1 and MEK2), which in turn activate ERK, leading to proliferation and survival of tumour cells. Trametinib is an orally available, highly selective allosteric inhibitor of MEK1/2 that induces tumour regression [50]. Trametinib improved PFS and OS compared with chemotherapy in a randomised phase III trial and subsequently received FDA and EMA approval for the treatment of $BRAF^{V600}$-mutated advanced melanoma [51]. The most common AEs with trametinib were rash, diarrhoea, peripheral oedema and acneiform dermatitis; no secondary skin neoplasms were diagnosed.

Further evidence supporting MEK targeting has been provided by MEK162 and selumetinib in phase II trials [52,53]. One of these trials [52] also included patients carrying NRAS mutations, which demonstrated the clinical activity of MEK162 in this patient subgroup, and a phase III trial comparing the efficacy of MEK162 with dacarbazine in patients harbouring a $NRAS^{Q61}$ mutation is currently ongoing [54].

BRAF inhibitor/MEK inhibitor combinations

Several approaches are being explored to improve durability of response to targeted therapies, including using intermittent dosing schedules to delay the selection of resistant tumour cells and combination strategies (Table 2) [55,56]. Preplanned interim data from an ongoing phase III trial (COMBI-d) in patients with $BRAF^{V600}$-mutated melanoma reported significant improvements in median PFS (9.3 months versus 8.8 months; HR = 0.75; 95% CI 0.57–0.99; $p = 0.03$) [57], ORR (67% versus 51%; $p = 0.002$) and 6-month OS (93% versus 85%; HR = 0.63; 0.42–0.94; $p = 0.02$) with first-line trametinib plus dabrafenib compared with dabrafenib alone. Furthermore, an open-label, phase III study comparing the first-line combination of dabrafenib and trametinib with vemurafenib in patients with $BRAF^{V600}$-mutated melanoma (COMBI-v)

Table 2
Targeted therapy: summary of monotherapy and combination data.

Drug[a]	MoA	ORR (%)	Median PFS (months)	Median OS (months)	1-/2-year OS (%)	Summary
Vemurafenib (phase III)	BRAF inhibitor	57	6.9	13.6	55/36[b]	Improved RR and PFS; rapid tumour regression; manageable safety profile
Dabrafenib (phase III)	BRAF inhibitor	59	6.9	18.2	63[c]/–	Improved RR and PFS; rapid tumour regression; manageable safety profile
LGX818 (phase I)	BRAF inhibitor	38	–	–	–	High RR in BRAF inhibitor naïve patients; manageable safety profile
Trametinib (phase III)	MEK inhibitor	22	4.8	–	–	OS and PFS benefit; rapid tumour regression; manageable safety profile
MEK162 (phase II)	MEK inhibitor	20	3.7	–	–	High RR; manageable safety profile
Selumetinib (+ DTIC) (phase II)	MEK inhibitor	40	5.6	13.9	–	Improved RR and PFS; no OS improvement; manageable safety profile
Imatinib mesylate (phase II)	KIT inhibitor	5–23	1.4–3.5	7.5–14	–	Improved response rates in a subset of patients
Dabrafenib plus trametinib (phase I/II)	BRAF inhibitor plus MEK inhibitor	76	9.4	–	79/–	Improved RR and PFS compared with dabrafenib monotherapy in BRAF inhibitor naïve patients; acceptable safety profile at full approved doses
Dabrafenib plus trametinib vs dabrafenib (phase III)	BRAF inhibitor plus MEK inhibitor	67	9.3	–	–	Improved ORR and PFS vs dabrafenib; manageable safety profile
Dabrafenib plus trametinib vs vemurafenib (phase III)	BRAF inhibitor plus MEK inhibitor	64	11.4	–	–	Improved ORR and PFS vs vemurafenib; safety consistent with previous studies
Vemurafenib plus cobimetinib (phase III)	BRAF inhibitor plus MEK inhibitor	68	9.9	–	–	Improved ORR and PFS vs vemurafenib; manageable safety profile
LGX818 plus MEK162 (phase Ib/II)	BRAF inhibitor plus MEK inhibitor	76	–	–	–	Encouraging RRs in 7 BRAF inhibitor-naïve patients; maximum tolerated dose not reached

Abbreviations: DTIC – dacarbazine; MoA – mechanism of action; ORR – objective response rate; OS – overall survival; PFS – progression-free survival; RR – response rate.
[a] Results cannot be directly compared.
[b] Based on a phase I study including a small number of patients.
[c] OS at 15 months.

showed a significant improvement in OS with combination therapy versus vemurafenib (HR = 0.69; 95% CI 0.53–0.89; $p = 0.005$) [58]; 1-year OS was 72% with the combination versus 65% with vemurafenib while median PFS was 11.4 and 7.3 months, respectively (HR = 0.56; 95% CI 0.46–0.69; $p < 0.001$). Collectively, these results suggest that dabrafenib/trametinib combination therapy can attenuate resistance to BRAF inhibition and this combination has been approved in the US for $BRAF^{V600}$-mutated advanced melanoma; approval in the EU is expected in 2015 [59,60]. It is, however, also important to note that this combination has limited efficacy in patients already resistant to BRAF inhibitors [55,61].

In clinical studies to date, dabrafenib 150 mg plus trametinib 2 mg has been well tolerated, albeit with an altered safety profile versus dabrafenib monotherapy [55,62]. In the COMBI-d study, first-line combination therapy was associated with increased pyrexia (51%) compared with dabrafenib alone (28%), and fewer cutaneous hyperproliferative events (cutaneous SCC: 2% versus 9%; hyperkeratosis: 3% versus 32%) [57]. The number of dose interruptions/reductions was also increased with dabrafenib and trametinib versus dabrafenib alone. In the COMBI-v study, rates of severe AEs and study-drug discontinuations were similar between groups [58]. The combination arm had a comparable safety profile to that of the COMBI-d study, while in the vemurafenib arm, as expected, a higher rate of photosensitivity was observed.

Potential synergistic effects of another MEK inhibitor, cobimetinib, and vemurafenib have been investigated in a phase III trial. Interim results show median PFS of 9.9 months with the combination versus 6.2 months for vemurafenib alone (HR = 0.51; 95% CI 0.39–0.68; $p < 0.0001$), with ORRs of 68% and 45%, respectively ($p < 0.001$) [63]. Vemurafenib and cobimetinib was associated with a higher incidence of diarrhoea (28% versus 56%) as well as a slightly higher incidence of grade 3 or higher AEs compared with vemurafenib (65% versus 59%).

The combination of LGX818 and MEK162 is also being investigated in early-stage clinical trials [64].

Other BRAF inhibitor combinations may also be effective in patients with specific melanoma subtypes and trials with BRAF inhibitors in combination with therapies including PI3K, mTOR and Akt inhibitors are ongoing [65–67].

KIT inhibitors

Binding of stem cell factor to the tyrosine kinase receptor c-KIT activates multiple signalling pathways involved in cell proliferation and survival, including PI3K/Akt and MAPK [68]. Although melanomas arising from non-chronically sun-damaged skin frequently harbour BRAF mutations, these are much less frequent in melanomas arising from other sites. Conversely, activating mutations in c-KIT occur in up to 20% of acral, mucosal and chronically sun-damaged melanomas, with the highest mutation rate found in vulvo-vaginal melanoma [69,70]. c-KIT inhibitors such as imatinib, dasatinib and sunitinib have demonstrated clinical activity in several studies in patients harbouring c-KIT mutations [71–74].

However, there is a broad spectrum of mutations in c-KIT, of which, only specific mutations may be therapeutically relevant; indeed, RRs observed with imatinib in a phase II trial were highest in patients with mutations at codons 576 and 642 of exons 11 and 13, respectively [72]. Several clinical trials are investigating KIT inhibitors in c-KIT mutated melanoma, either as monotherapy or in combination with chemotherapies, immunotherapies or other targeted agents [75].

In summary, several targeted approaches have shown improvements in clinical endpoints, including OS, in patients with specific oncogenic mutations. Consequently, mutational testing is a prerequisite for informed treatment decisions in metastatic melanoma [12]. In patients with $BRAF^{V600E}$-mutated melanoma, BRAF inhibitors can provide rapid tumour reduction and symptom relief, outcomes critical for patients requiring an urgent response. However, responses are often transient due to acquired resistance, and long-term data, which are of utmost importance for informed treatment decisions, are currently limited. A major focus of future research will be the management of side effects associated with targeted agents and the development of strategies to provide more durable clinical benefits. Determining the best sequencing or combination strategies using multiple targeted agents and/or combinations with other approaches provide the most promise for improved long-term outcomes.

Immunotherapy

Early immunotherapies

Immunotherapies for melanoma have been extensively studied (Table 3), based on robust evidence that the immune system is involved in tumour control [76]. Several immunotherapeutic strategies have demonstrated antitumour activity in metastatic melanoma although, until recently, no agent had prolonged OS in the clinical trial setting.

Immunotherapies may be divided into four groups based on specific/nonspecific and active/adoptive approaches. Active therapies rely on an endogenous immune response whereas adoptive therapies use immune components that are developed ex vivo [76]. Nonspecific, active approaches include infusion with cytokines such as IFN-α or IL-2. High-dose IL-2, FDA-approved in 1998 for advanced melanoma, has demonstrated durable complete responses in a small number of patients. However, its use is associated with major toxicities including fever, chills, hypotension and cardiac arrhythmias [77]. Adoptive cell therapy (ACT), or the infiltration of large numbers of autologous tumour-infiltrating lymphocytes (TIL), can also induce durable tumour regression but its widespread use is limited by cost and time limitations [78–80]. There are ongoing phase III programs to evaluate the activity of TIL-based ACT compared with ipilimumab in a prospective

Table 3
Immunotherapy: summary of monotherapy and combination data.

Drug[a]	MoA	ORR (%)	Median PFS (months)	Median OS (months)	1-/2-year OS (%)	Summary
IL-2	Cytokine	16	13.1	11.4	–	Durable response in a small number of patients; no OS benefit assessed; significant risk of toxicity
Ipilimumab (phase III)	Anti-CTLA-4	11	2.9	10.1	46/25[b]	Proven OS benefit; durable disease control; long-term survival of >5 years in some patients; manageable safety profile (grade 3–4 drug-related AEs, 33%)
Nivolumab (phase I)	Anti-PD-1	32	3.7	17.3	63/48	High RR and median OS; manageable safety profile
Nivolumab (phase III) pretreated	Anti-PD-1	32	–	–	–	Superior efficacy to investigator's choice of chemotherapy; grade 3–4 drug-related AEs less frequent vs chemotherapy (9% vs 31%)
Nivolumab (phase III) previously untreated	Anti-PD-1	40	5.1	–	72.9/–	Superior efficacy to dacarbazine; grade 3–4 drug-related AEs less frequent vs dacarbazine (12% vs 18%)
Pembrolizumab[c] (phase I)	Anti-PD-1	24	5.5	–	58/–	High RR; manageable safety profile
Pembrolizumab[c] (phase II)	Anti-PD-1	21	–	–	–	Median PFS was significantly improved vs chemotherapy; grade 3–5 drug-related AEs lower (11%) vs chemotherapy (26%)
BMS-936559 (phase I)	Anti-PD-L1	17	–	–	–	High RR; manageable safety profile
MPDL3280A (phase I)	Anti-PD-L1	29	–	–	–	High RR and DCR; manageable safety profile
T-VEC (phase III)	GM-CSF production	26	–	23.3	74/50	Durable RR benefit; trend towards improved OS; manageable safety profile
Ipilimumab plus IL-2[d] (phase I)	Anti-CTLA-4 plus cytokine	25	–	16	–	Durable tumour control in some patients; no evidence of synergistic effect; acceptable safety profile
Ipilimumab plus PEG-IFN α-2b (phase I)	Anti-CTLA-4 plus cytokine	42	–	16.6	56/–	High RR and median OS; manageable safety profile
Ipilimumab plus T-VEC (phase I)	Anti-CTLA-4 plus GM-CSF production	41	–	–	–	High RR; manageable safety profile
Ipilimumab plus GM-CSF (phase II)	Anti-CTLA-4 plus WBC growth factor	19	3.1	17.5	69/–	Improved OS compared with ipilimumab monotherapy; reduced incidence of high grade AEs
Ipilimumab plus nivolumab[e] (phase I)	Anti-CTLA-4 plus anti-PD-1	40	–	–	85/79	Improved RR and 1-year OS compared with monotherapies; manageable safety profile with ipilimumab 3 mg/kg plus nivolumab 1 mg/kg

Abbreviations: AE – adverse event; CTLA-4 – cytotoxic T-lymphocyte-associated antigen-4; DCR – disease control rate; GM-CSF – granulocyte–macrophage colony-stimulating factor; IL-2 – interleukin-2; MoA – mechanism of action; ORR – objective response rate; OS – overall survival; PD-1 – programmed death 1; PD-L1 – programmed death ligand 1; PEG-IFN α-2b – pegylated interferon α-2b; PFS – progression-free survival; RR – response rate; T-VEC – talimogene laherparepvec; WBC – white blood cell.

[a] Results cannot be directly compared.
[b] Among 95 patients with ⩾2 years follow-up.
[c] 2 mg/kg.
[d] With extended follow-up.
[e] Concurrent therapy.

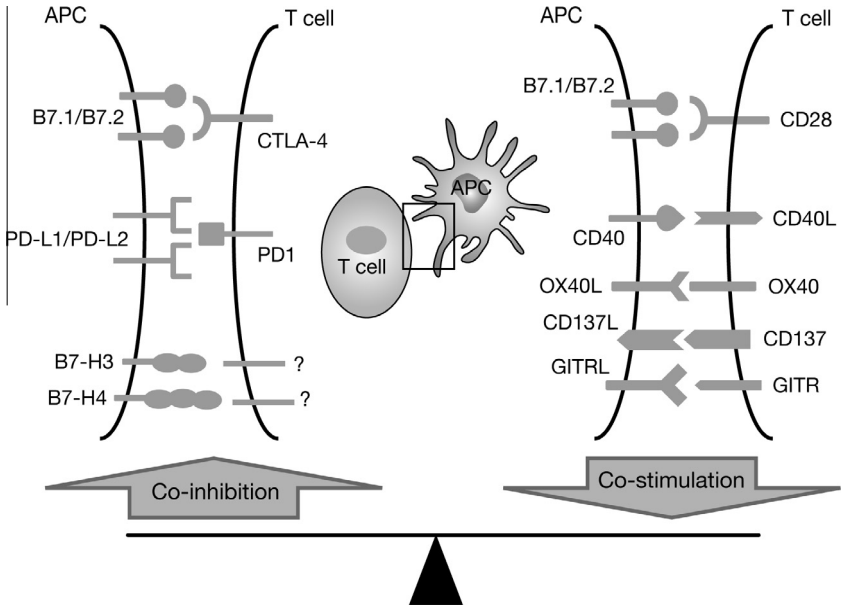

Fig. 2. Immune checkpoint regulators Inhibitory and stimulatory checkpoints of immune regulation. *Abbreviations:* APC – antigen presenting cell; CTLA-4 – cytotoxic T-lymphocyte-associated antigen-4; PD-1 – programmed death 1; PD-L1/2 – programmed death ligand 1/2.

randomized setting (NCT02278887). Results of such trials are eagerly awaited to better define the place of ACT in our armamentarium [76].

Other active immune strategies include vaccination with irradiated whole-tumour cells or dendritic cells loaded with tumour-associated antigens that can prime the immune system to attack tumour cells and, more recently, monoclonal antibodies specific to T-cell receptors that regulate the immune response [81].

Immune checkpoint inhibitors

The amplitude and quality of T-cell responses against neoplastic cells is regulated by a balance between co-stimulatory and co-inhibitory signals at key points within the immune cascade (Fig. 2). These immune checkpoints are crucial for the maintenance of self-tolerance and prevent damage to the body's normal tissues during an immune response. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) are inhibitory checkpoint receptors expressed on T cells that inhibit T-cell activity on engaging with their respective ligands (B7.1/B7.2 for CTLA-4 and PD-L1/PD-L2 for PD-1) [82].

Inhibiting immune checkpoints constitutes a novel approach to immuno-oncology by releasing the natural braking mechanism and engaging the adaptive immune system. Checkpoint inhibitors offer a number of clinical advantages in comparison with other therapy types, including a greater duration of immune response than cytokines (e.g., IL-2 and IFN-α) [83,84], and a lower susceptibility to resistance than chemotherapy and molecular targeted therapies [85,86].

The approval of ipilimumab, a fully human monoclonal antibody directed against CTLA-4, in 2011, represented a significant breakthrough in the treatment of advanced melanoma [87,88]. By blocking CTLA-4, ipilimumab potentiates T-cell proliferation, activation and intratumoural infiltration, leading to increased tumour cell death [85]. In the registrational phase III trial, ipilimumab 3 mg/kg, with or without a gp100 peptide vaccine, significantly improved OS in patients with pretreated advanced melanoma compared with the gp100 vaccine alone (median OS 6.4 months). With a maximum follow-up of 55 months, median OS was 10.1 months in patients treated with ipilimumab plus gp100 (HR versus gp100 alone: 0.68; $p < 0.001$) and 10.1 months (HR versus gp100 alone: 0.66; $p = 0.003$) with ipilimumab plus placebo [89]. In a further phase III trial, adding ipilimumab 10 mg/kg to dacarbazine significantly improved OS versus dacarbazine monotherapy in treatment-naïve patients [90]. Further evidence for the efficacy of ipilimumab in the first-line setting is provided by two retrospective US observational studies and pooled survival analysis of data from chemotherapy-naïve patients treated in phase II or phase III clinical trials [91–93]. Consequently, ipilimumab is approved for the first-line treatment of advanced melanoma in the US and many countries in the EU.

Response patterns with ipilimumab differ from those observed with other agents, which may be due to a slower onset of activity resulting from the time taken to activate and build an immune response [94]. Thus, prior to disease stabilisation or regression, some patients may experience tumour progression or pseudoprogression, an apparent progression owing to immune cell infiltration and inflammation [95]. Although objective responses with ipilimumab monotherapy in clinical trials are less frequent than reported with targeted agents [89,96,97], many patients treated with ipilimumab have long-lasting stable disease that may reflect prolonged survival [98–100]; this may result from ongoing immune system activation, persisting for months to years after initial treatment [79]. Thus, the methods employed to assess treatment efficacy in melanoma are evolving to reflect the unique properties of immuno-oncology agents. For instance, immune-specific criteria, as opposed to traditional methods for assessing treatment responses such as Response Evaluation Criteria in Solid Tumours (RECIST), may be more appropriate.

Follow-up data from phase II/III trials further demonstrate long-term survival with ipilimumab; approximately one-fifth of patients survive $\geqslant$2 years. Regardless of prior treatment, survival rates with ipilimumab plateau after 2–3 years, with a meaningful proportion of patients surviving >5 years [101–103]. In a pooled analysis of OS data from nearly 2000 patients treated in phase II/III trials, OS remained approximately 20% for up to 10 years, across different doses and lines of therapy [104]. The survival benefit observed with ipilimumab within clinical trials is independent of mutation status (e.g., BRAF, NRAS) and appears to be consistent across all patient subpopulations. This includes those with noncutaneous (uveal or mucosal) melanoma and those that are harder to

treat (for example elderly patients and those with elevated LDH, M1c disease or stable brain metastases), although retrospective data from some centres indicate that patients with elevated LDH might have a low probability of achieving the goal of long-term survival [89,90,102,105–114].

Recent investigations using whole-exome sequencing demonstrated that mutational load was significantly associated with survival benefit from ipilimumab therapy, although mutational load alone did not predict response to treatment in all cases [115]. Mutational load does, however, directly correlate with the emergence of novel antigenic epitopes from mutated proteins. In several tumour-types, T-cell reactivity against these often patient and tumour-specific neo-epitopes has been identified as essential for a successful tumour immune response [116]. Recently, a neo-epitope signature was identified in patients achieving long term benefit from CTLA-4 blockade that was predictive of survival independently from the overall mutational load, and could, if corroborated in a larger set of samples, be one of the first useful biomarkers for such a therapy [115].

Due to its immune MoA, most treatment-related AEs with ipilimumab are inflammatory in nature, commonly affecting the skin or gastrointestinal tract [89,90,97,117–120], and can be managed effectively using product-specific treatment guidelines. Early recognition of these AEs and appropriate initiation of supportive care are critical to maximise the benefit of treatment and reduce the risk of severe or life-threatening complications, which may involve the gastrointestinal, liver, skin, nervous, endocrine or other organ systems [121–123].

The success of ipilimumab has supported development of agents directed against other immune-regulatory checkpoints, including PD-1. Whereas CTLA-4 is activated primarily through the association between an antigen-presenting cell and T cell in the periphery followed by distribution of activated T cells to tumour sites, PD-1 is principally believed to inhibit effector T-cell activity in the effector phase within tissue and tumours [124]. PD-1 is also more broadly expressed than CTLA-4, and is found on activated B cells, natural killer cells, activated T cells, Tregs, CD8+ T cells and activated CD4+ cells [125]. Thus, while CTLA-4 signalling alters the early phase of activation of naïve or memory T cells, PD-1 signalling limits effector phases from T cells [126].

Consequently, monoclonal antibodies against PD-1 or its ligand PD-L1 have shown higher response rates and lower rates of AEs in early clinical trials in melanoma than have been shown in previous trials with anti-CTLA-4 agents [127,128]. There are therefore a growing number of monoclonal antibodies targeting PD-1 or PD-L1 in clinical development, with several larger scale trials nearing completion.

The FDA recently granted accelerated approval of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This approval was on the basis of promising early data from a phase Ib trial that showed an ORR (assessed by RECIST) of 24% with pembrolizumab 2 mg/kg every 3 weeks in ipilimumab-pretreated patients [7]. After median follow-up of 8 months, pembrolizumab was also well tolerated, and promising results were shown in several other clinical endpoints including median PFS (pembrolizumab 2 mg/kg: 22 weeks; 10 mg/kg: 14 weeks) and 1-year OS (58% and 63%, respectively) [129]. Preliminary data from a phase II study evaluating pembrolizumab versus investigator's choice of chemotherapy in pretreated patients with advanced melanoma were also recently presented [130]. PFS was significantly improved in both the 2 mg/kg and 10 mg/kg pembrolizumab groups compared with chemotherapy ($p < 0.00001$ for both comparisons), with 6-month PFS rates of 34%, 38% and 16%, respectively. ORR was 21% with 2 mg/kg pembrolizumab, 25% with 10 mg/kg and 4% with chemotherapy ($p < 0.0001$ for both comparisons). Rates of grade 3–5 drug-related AEs were higher with chemotherapy (26%) than with 2 mg/kg (11%) and 10 mg/kg (14%) pembrolizumab. Similar efficacy and safety has been shown with 2 mg/kg versus 10 mg/kg pembrolizumab in clinical trials to date, thus favouring the lower dose of 2 mg/kg approved by the FDA [7,129,131]. Data from a phase III trial comparing pembrolizumab with ipilimumab in treatment-naïve patients is expected to be presented in early 2015 (NCT01866319).

Nivolumab, a fully human monoclonal antibody that potently blocks PD-1 to prevent its binding to both PD-L1 and PD-L2, recently received accelerated approval for the treatment of unresectable melanoma in Japan and the US [7,8]. In a phase I dose-escalation study of nivolumab (0.1, 0.3, 1, 3 or 10 mg/kg) in patients with solid tumours, ORR was 41% in the 3 mg/kg cohort; median OS was 20.3 months and median PFS was 9.7 months, with at least 1 year of follow-up for all patients [132]. At present, nivolumab is the only anti-PD-1 antibody for which long-term survival data are available, with 1-, 2-, 3- and 4-year survival rates of 63%, 48%, 42% and 32%, respectively, among all dose cohorts. Results from the first phase III trials of nivolumab were recently presented. In patients with advanced melanoma progressing after anti-CTLA-4 therapy, confirmed ORR (RECIST) was 32% with nivolumab (3 mg/kg) and 11% with investigator's choice of chemotherapy, with median time to response of 2.1 and 3.5 months, respectively [133]. Responses to nivolumab were observed irrespective of BRAF status, prior ipilimumab benefit, and in patients with poor prognostic factors [134]. Responses were observed in patients with positive and negative tumour PD-L1 status, although PD-L1 positive patients had a higher response rate (44% versus 20%). Grade 3–4 drug-related AEs (9% versus 31%) and discontinuations due to drug-related AEs (2% versus 8%) were less frequently observed with nivolumab than chemotherapy. The majority of drug-related AEs were of a low grade and manageable using recommended treatment algorithms. In a second phase III study of nivolumab (3 mg/kg) in previously untreated patients with advanced BRAF WT melanoma, OS at 1 year was 72.9% with nivolumab versus 42.1% with dacarbazine (HR = 0.42; 99.79% CI 0.25–0.73; $p < 0.001$) [136]. Median PFS was 5.1 months and 2.2 months, respectively (HR = 0.43; 95% CI 0.34–0.56; $p < 0.001$), while ORR (RECIST) was 40.0% and 13.9%, respectively ($p < 0.001$). The safety profile of nivolumab was acceptable, manageable and consistent with its profile in pretreated patients. Common AEs with nivolumab included fatigue, pruritus and nausea; drug-related grade 3–4 AEs were less frequent with nivolumab than dacarbazine (11.7% versus 17.6%).

Two studies have evaluated the efficacy and safety of the anti-PD-L1 antibodies, BMS-936559 and MPDL3280A. Among 52 patients treated with BMS-936559 (0.3–10 mg/kg), ORR across all doses was 17%. Antitumour responses or prolonged stable disease were observed even in heavily pretreated patients [127,136]. ORR in 38 melanoma patients who received MPDL3280A 1–20 mg/kg was 29% [137]. Both of these treatments were well tolerated, with most AEs being low grade [136,138].

Another immunotherapy in development is talimogene laherparepvec (T-VEC), an HSV-1 based oncolytic therapy designed to replicate selectively in tumour cells, leading to their lysis, and to produce granulocyte–macrophage colony-stimulating factor (GM-CSF) to stimulate antitumour immune responses. Since T-VEC is injected directly into the tumour tissue, only patients with injectable (cutaneous or subcutaneous) lesions were included in a randomised phase III trial comparing T-VEC and subcutaneously administered GM-CSF in advanced melanoma. Preliminary results suggested T-VEC improves durable RRs compared with GM-CSF and has an acceptable safety profile [139], although a significant improvement in OS was not seen, despite an increase of 4.4 months

with active therapy ($p = 0.051$). However, the outcome of this study needs to be interpreted with caution due to the comparator, GM-CSF, not being injected in the same way (intralesionaly) as TVEC and furthermore, not being an accepted treatment for metastatic melanoma.

Many immuno-oncology drugs are in clinical development, with ipilimumab, pembrolizumab and nivolumab having the most mature clinical evidence. The potential long-term benefits of immune checkpoint inhibitors necessitate reassessment of how clinical success is measured. Durable disease control can substantially increase life expectancy, an outcome as important as an objective response. Emerging data suggest that immunotherapies may be most effective when used early during the course of advanced melanoma, provided patients are expected to survive long enough to complete induction therapy [89,93,107–110,112,140–144]. An important area for future research will be to identify and validate potential biomarkers to select patients most likely to benefit from treatment and achieve long-term clinical benefit with immunotherapy [96,145,146].

Combination immunotherapies

Combination strategies are a key focus of ongoing immuno-oncology research (Table 3). A phase I/II trial of ipilimumab plus IL-2 showed no evidence of synergy (ORR 25%) [103,146]. A phase I trial investigating IL-21 combined with ipilimumab or nivolumab is recruiting patients following preclinical studies that showed enhanced antitumour activity with this approach in murine tumour models [147].

Ipilimumab has also been investigated in combination with a range of other immunotherapies in patients with advanced melanoma. Phase I studies of ipilimumab in combination with PEG-interferon α-2b, T-VEC or the indoleamine 2,3-dioxygenase 1 inhibitor, INCB024360, have all shown manageable tolerability profiles and promising response rates [148–150]. Promising results have also been reported from a phase II trial evaluating the efficacy and safety of ipilimumab plus GM-CSF versus ipilimumab monotherapy; OS was improved and the incidence of high-grade AEs was reduced with combination therapy although there was no difference in PFS [151]. Several clinical studies are also planned or ongoing to evaluate the combined use of ipilimumab or nivolumab with other vaccine-based therapies (e.g., NY-ESO-1, dendritic vaccines, Tri-Mix) in advanced melanoma.

There is also a strong rationale for combining immune checkpoint inhibitors with complimentary MoAs. Indeed, preclinical studies and early clinical trial data suggest that concurrent ipilimumab and nivolumab can induce rapid and deep responses. In a phase I trial, patients who received concurrent nivolumab (0.3, 1 or 3 mg/kg) and ipilimumab (1 or 3 mg/kg) showed an ORR of 40% and 1-year OS of 85%. Although there was a significantly higher incidence of grade 3–4 AEs with combination therapy than recorded previously with either drug as monotherapy, there were no new safety signals and AEs could be managed using standard protocols. In subgroup analyses, concurrent administration of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg showed 1- and 2-year OS rates of 94% and 88%; furthermore, the response rate of a further 41 patients who received ipilimumab 3 mg/kg plus nivolumab 1 mg/kg was similar and consistent regardless of tumour BRAF mutation or PD-L1 expression status [152]. In the same study, patients who received nivolumab 1 or 3 mg/kg sequentially after standard ipilimumab therapy showed a 1-year OS rate of 70%, which is consistent with reported nivolumab monotherapy data [153]. Interestingly, residual plasma ipilimumab levels were positively associated with the response to subsequent nivolumab. Thus, concurrent therapy with ipilimumab 3 mg/kg plus nivolumab 1 mg/kg has been selected for investigation in phase III trials compared with nivolumab or ipilimumab monotherapy [154].

Two phase I trials will investigate the use of either ipilimumab or nivolumab in combination with lirilumab, an antibody directed against killer cell immunoglobulin-like receptors (KIRs) [155,156]. Lirilumab potentiates endogenous immune responses by blocking signalling through inhibitory KIRs and had an acceptable safety profile in a phase I monotherapy trial; data are expected in 2015.

Clinical application of available treatments

The best approach for incorporating recent additions to the melanoma treatment armamentarium into clinical practice needs to be considered. The distinct mechanisms of action and activity profiles of approved agents can impact treatment choice. Therefore, treatment decisions should consider genetic information and clinical parameters to optimise individual patient care.

Targeted agents offer rapid responses and prevent 'early deaths' in BRAF-mutated patients; however, resistance usually develops [17,18,46]. By contrast, immunotherapy offers the possibility of long-term survival but requires time to maximise such possibilities [94,95,101–104]. Available data suggest that around 40% of patients who fail treatment with a BRAF inhibitor undergo rapid disease progression and are unable to complete therapy with another line of treatment. Conversely, prior treatment with ipilimumab does not appear to compromise the efficacy of subsequent BRAF inhibitor treatment. Thus, using ipilimumab before BRAF inhibition in patients with more indolent disease may offer the best sequencing strategy to promote long-term survival [98,142–144]. 'Smart' sequencing will be important as other investigational agents and/or combinations become available in the future.

The complimentary MoAs of immunotherapies and targeted agents may lead to synergism when combined. However, concurrent treatment with immune checkpoint inhibitors and vemurafenib may not be feasible due to hepatotoxicity [138,157]. Nevertheless, combination studies with ipilimumab and the BRAF inhibitor dabrafenib, either alone or in combination with the MEK inhibitor trametinib, are ongoing. Preliminary data showed that the triple-combination led to early bowel perforation in 2 patients and will therefore not be pursued further; the combination of dabrafenib and ipilimumab appeared tolerable. At the same time, early combination studies of targeted agents and PD-1 targeting drugs are in progress.

Alternative sequencing approaches are also under investigation, including a phase III study of sequential treatment with dabrafenib plus trametinib and ipilimumab plus nivolumab (NCT02224781).

Conclusions

The recent approvals of several targeted and immuno-oncology agents have provided renewed hope for patients with metastatic melanoma. There are now several treatment options available, with several other agents in the pipeline. To maximise clinical benefit, the strategies for integrating new treatment options into existing guidelines need to be optimised and aligned with long-term individual patient goals. Future research is likely to focus on improving treatment outcomes through combination approaches and/or smart sequencing strategies. Greater understanding of how to overcome mechanisms of resistance or immunosuppression and the identification of biomarkers to inform treatment selection may help to transform the outcomes of patients.

Conflict of interest statement

Olivier Michielin and Christoph Höller have had a speaker and/or advisory role for Bristol Myers-Squibb, Roche, GlaxoSmithKline, Amgen and Novartis.

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