Immune checkpoint inhibitors to treat cutaneous malignancies

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Learning objectives

After completing this learning activity, participants should be able to describe the mechanism of action of checkpoint inhibitors in their antitumor effects; identify biomarkers associated with response to checkpoint inhibitors; identify the pivotal clinical trials and other data substantiating the use of checkpoint inhibitors in melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma; compare efficacy and safety profiles between checkpoint inhibitors and between tumor types; and recognize active areas of research in checkpoint blockade for cutaneous malignancies.

Disclosures

Editors

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Authors

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As the incidence of cutaneous malignancies continues to rise and their treatment with immunotherapy expands, dermatologists and their patients are more likely to encounter immune checkpoint inhibitors. While the blockade of immune checkpoint target proteins (cytotoxic T-lymphocyte—associated protein-4, programmed cell death-1, and programmed cell death ligand-1) generates an antitumor response in a substantial fraction of patients, there is a critical need for reliable predictive biomarkers and approaches to address refractory disease. The first article of this Continuing Medical Education series reviews the indications, efficacy, safety profile, and evidence supporting checkpoint inhibition as therapeutics for metastatic melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma. Pivotal studies resulting in the approval of ipilimumab, pembrolizumab, nivolumab, cemiplimab, and avelumab by regulatory agencies for various cutaneous malignancies, as well as ongoing clinical research trials, are discussed. (J Am Acad Dermatol 2020;83:1239-53.)

Key words: basal cell carcinoma; checkpoint inhibitor; CTLA-4 inhibitor; cutaneous lymphomas; cutaneous malignancies; cutaneous squamous cell carcinoma; immunotherapy; Kaposi sarcoma; melanoma; Merkel cell carcinoma; PD-1 inhibitor; PD-L1 inhibitor; skin cancer.

Immunotherapy has become a cornerstone of advanced tumor management. Via inhibition of the cytotoxic T-lymphocyte—associated protein 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1), tumor cells are targeted and destroyed by activated T cells that infiltrate the tumor microenvironment. The first of the immune checkpoint inhibitors (CPIs) approved for cutaneous malignancies was ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY); an additional 4 CPIs were later approved by regulatory agencies (nivolumab [Opdivo; Bristol-Myers Squibb], pembrolizumab [Keytruda; Merck and Co, Kenilworth, NJ], cemiplimab [Libtayo; Regeneron Pharmaceuticals, Tarrytown, NY], and avelumab [Bavencio; EMD Serono, Rockland, MA]). In addition to melanoma, CPIs are indicated for cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC). There are currently no CPIs approved for basal cell carcinoma (BCC), cutaneous lymphomas, cutaneous sarcomas, or cutaneous adnexal carcinomas (CACs).

Mechanism of action of immune checkpoint inhibitors

Ipilimumab works by blocking the negative regulator CTLA-4, resulting in increased cytotoxic T cell activation and decreased regulatory T cell immunosuppressive activity.[1] Pembrolizumab and nivolumab selectively block PD-1 receptors and suppress their expression by activated T cells, B cells, monocytes, and natural killer cells.[2] Atezolizumab, avelumab, and durvalumab inhibit binding of PD-L1 to PD-1 receptors on T cells, thereby resulting in downregulation of T cell quiescence and reinvigoration of the antitumor immune response[3] (Fig 1).

Predictive biomarkers of response to immunotherapy

Markers of tumor response to immunotherapy have been investigated,[4] and while some have been associated with increased overall survival (OS) in patients with melanoma, none have been validated. In accordance with the National Comprehensive Cancer Network (NCCN) Guidelines, PD-L1 has potential utility in identifying patients with melanoma who are more likely to respond to CPIs[5,6]; however, the routine use of PD-L1 expression is not recommended for treatment decisions.[5,7] Several additional immunotherapy biomarkers are under development for melanoma, including relative eosinophils, relative basophils, absolute monocytes, lactate dehydrogenase, and neutrophil-to-lymphocyte ratio.[8-10] The occurrence of immune-related adverse events (irAEs) has also been implicated as potentially useful in tumor response to CPIs.[11] In addition, a decrease in regulatory T cells and an increase in activated $CD8^+$ T cells have been cited.[12-14] In advanced cSCC, although PD-L1 appears to be increased in high-risk cSCC specimens compared with normal skin specimens, its levels do not appear to correlate with the antitumor activity of PD-1 blockade.[15-17] However, a higher tumor mutational burden is more commonly observed in immunocompromised cSCC patients.[18-20] No predictors of response of MCC to CPIs are available yet.

MELANOMA

Key points

- **Ipilimumab, pembrolizumab, and nivolumab are approved for advanced melanoma**
- **In melanoma, combination therapy with nivolumab and ipilimumab results in higher OS compared with ipilimumab alone**
- **Nivolumab and pembrolizumab have each shown superior OS, with a better safety profile than ipilimumab**

Abbreviations used:

AE:	adverse event
BCC:	basal cell carcinoma
CAC:	cutaneous adnexal carcinoma
CPI:	checkpoint inhibitor
cSCC:	cutaneous squamous cell carcinoma
CTLA-4:	cytotoxic T-lymphocyte-associated protein-4
FDA:	US Food and Drug Administration
irAE:	immune-related adverse event
MCC:	Merkel cell carcinoma
ORR:	objective response rate
PD-1:	programmed cell death-1
PD-L1:	programmed cell death ligand-1
PFS:	progression-free survival

Melanoma of the skin, despite its lower prevalence compared with other cutaneous malignancies, is one of the most aggressive forms of cancer. Noninvasive melanoma (melanoma in situ) has a good surgical prognosis; however, advanced melanoma lacks curative treatment options. Three CPIs are currently available to treat advanced melanoma: ipilimumab, nivolumab, and pembrolizumab.

Ipilimumab: Anti–CTLA-4 therapy for advanced melanoma

Based on the improved OS results of the MDX010-20 phase III trial (Table I), ipilimumab (anti–CTLA-4) was approved in 2011, becoming the first CPI to be indicated for the treatment of nonresectable or metastatic melanoma (Fig 2).[21] Ipilimumab was found to elicit a dose-dependent effect on efficacy and safety measures, lending support to further studies at a dose of 10 mg/kg.[22] However, while the 10-mg/kg dosing regimen of ipilimumab does result in significantly longer OS than does ipilimumab 3 mg/kg, it also leads to an increased frequency of treatment-related adverse events.[23] In 2015, as significantly improved recurrence-free survival (RFS) for patients with completely resected high-risk stage III melanoma was observed in the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase III trial, ipilimumab was approved for this indication (Fig 2). Significantly higher rates of RFS, OS, and distant metastasis-free survival compared with placebo were observed,[24-26] and the frequency of irAEs (Table I) was consistent with that observed in advanced melanoma.[21,26] However, the adverse event (AE) profile was worse in the EORTC trial than in the MDX010-20 trial, in particular for endocrinopathies.

Pembrolizumab: Anti–PD-1 therapy for advanced melanoma

In September 2014, pembrolizumab was the first PD-1 inhibitor approved for patients with unresectable or ipilimumab-refractory advanced melanoma after treatment with a BRAF inhibitor if positive for the *BRAF* V600 mutation (Fig 2).[27] The phase I trial demonstrated that pembrolizumab was safe and efficacious at both doses of 2 mg/kg and 10 mg/kg every 3 weeks (Table II).[28] In December 2015, based on the results of the phase 3 KEYNOTE-006 trial, which showed a substantial prolonged OS,

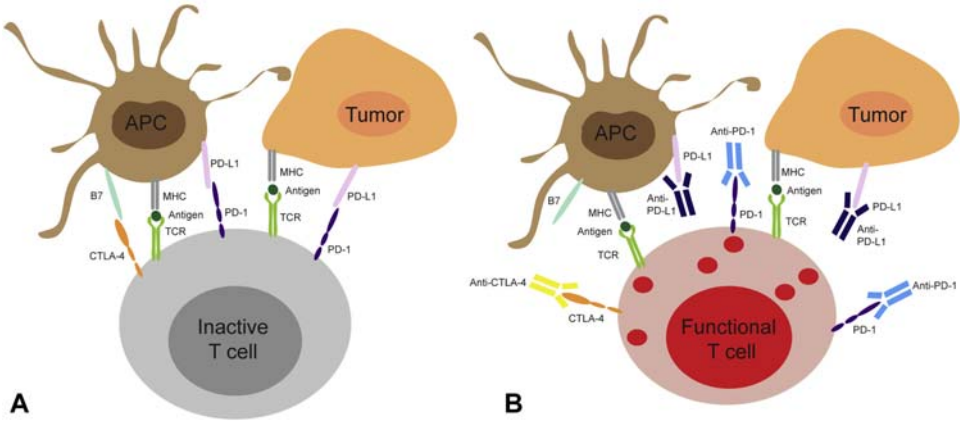

Fig 1. Immune checkpoint inhibitors reinvigorate antitumor immune responses. **A**, Cytotoxic T cells in the tumor microenvironments express high level of inhibitory receptors such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1). In the absence of immune checkpoint inhibitors, ligation of CTLA-4 and PD-1 by B7 protein or programmed cell death-1 (PD-L1) expressed by antigen-presenting cells (APCs) or tumor cells dampens the cytotoxic functions of T cells and inhibits their antitumor activity. **B**, Anti–CTLA-4, anti–PD-1, and anti–PD-L1 can bind CTLA-4, PD-1, and PD-L1 and prevent the PD-1/PD-L1 and CTLA-4/B7 interactions, which restore the antitumor functions of cytotoxic T cells. *MHC*, Major histocompatibility complex; *TCR*, T-cell receptor.

Table I. Major studies investigating ipilimumab (anti–cytotoxic T-lymphocyte-associated protein-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/identifier(s)	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up duration	Common severe (grade 3-5) irAEs
2004-2008	Phase III, MDX-010, NCT00094653	Previously treated, unresectable stage III or IV melanoma, n = 676	Ipilimumab 3 mg/kg + gp100 every 3 weeks, for 4 treatments, n = 403 Ipilimumab 3 mg/kg alone every 3 weeks for 4 treatments, n = 137 gp100 alone every 3 weeks for 4 treatments, n = 136	OS: ipilimumab alone, 10.1 months; ipilimumab + gp100, 10 months; gp100 alone, 6.4 months	Ipilimumab alone, 27.8 months; ipilimumab + gp100, 21 months; gp 100 alone, 17.2 months	Ipilimumab (with or without gp100), 10-15%; gp100 alone, 3%
2008-2011	Phase III, EORTC 18071, NCT00636168	Previously untreated resected stage III cutaneous melanoma, n = 951	Ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 3 months for up to 3 years, n = 475 Placebo every 3 weeks for 4 doses; then every 3 months for up to 3 years, n = 476	RFS: ipilimumab, 26.1 months; placebo, 17.1 months; 3-year RFS: ipilimumab 46.5% and placebo 34.8%	2.74 years	Ipilimumab vs. placebo: gastrointestinal: 16% vs. <1%; hepatic: 11% vs. <1%; endocrine: 8% vs. 0%

EORTC, European Organisation for Research and Treatment of Cancer; *gp100*, glycoprotein 100 peptide vaccine; *OS*, overall survival; *RFS*, recurrence-free survival.

progression-free survival (PFS), and less high-grade toxicity than did ipilimumab (Table II),[29] the US Food and Drug Administration (FDA) expanded the approval to include frontline treatment of patients with advanced melanoma with pembrolizumab regardless of *BRAF* status (Fig 2). In February 2019, after impactful results from the EORTC1325/KEYNOTE-054 phase III trial showing improved RFS of pembrolizumab over placebo (Table II),[30] pembrolizumab was approved for the adjuvant treatment of patients with high-risk stage III melanoma with resected lymph nodes (Fig 2).

Nivolumab: Anti–PD-1 therapy for advanced melanoma

Following the results of the CheckMate-037 phase III trial[31] (Table III), in which nivolumab led to a greater proportion of confirmed objective responses and fewer toxic effects compared with chemotherapy in patients with ipilimumab- and BRAF inhibitor–refractory melanoma, the FDA granted accelerated approval in December 2014[32] (Fig 2). The following year, after a favorable risk/benefit profile associated with significant improvements in OS and PFS (as compared with dacarbazine) was demonstrated by the phase III trial[33] (Table III), nivolumab received additional FDA approval as a first-line single agent treatment of patients with *BRAF* V600 wild-type, unresectable, or metastatic melanoma[34] (Fig 2).

In December 2017, as further improvements in RFS and a lower rate of grade 3 or 4 AEs were seen in the CheckMate-238 phase III trial of 906 patients with resectable high-risk and advanced melanoma[35] (Table III), nivolumab was approved as adjuvant therapy (Fig 2). Since then, long-term favorable efficacy and tolerability perseveres in patients with advanced or recurrent melanoma who were treated with nivolumab, irrespective of melanoma type,[36] with or without BRAF mutations.[37,38]

Nivolumab plus ipilimumab: combination therapy for advanced melanoma

In 2015, the results of the CheckMate-069 phase II trial[39] led to accelerated FDA approval of the first ever immunotherapy combination of nivolumab plus ipilimumab for patients with *BRAF* V600 wild-type, unresectable, or metastatic melanoma (Fig 2). Among 109 patients, the combination had a response rate of 60% compared with 11% for ipilimumab alone, and an acceptable safety profile (Table IV).[39] Afterward, based on longer PFS rates observed with combination immunotherapy as opposed to ipilimumab alone on the CheckMate-067 phase III trial, ipilimumab plus

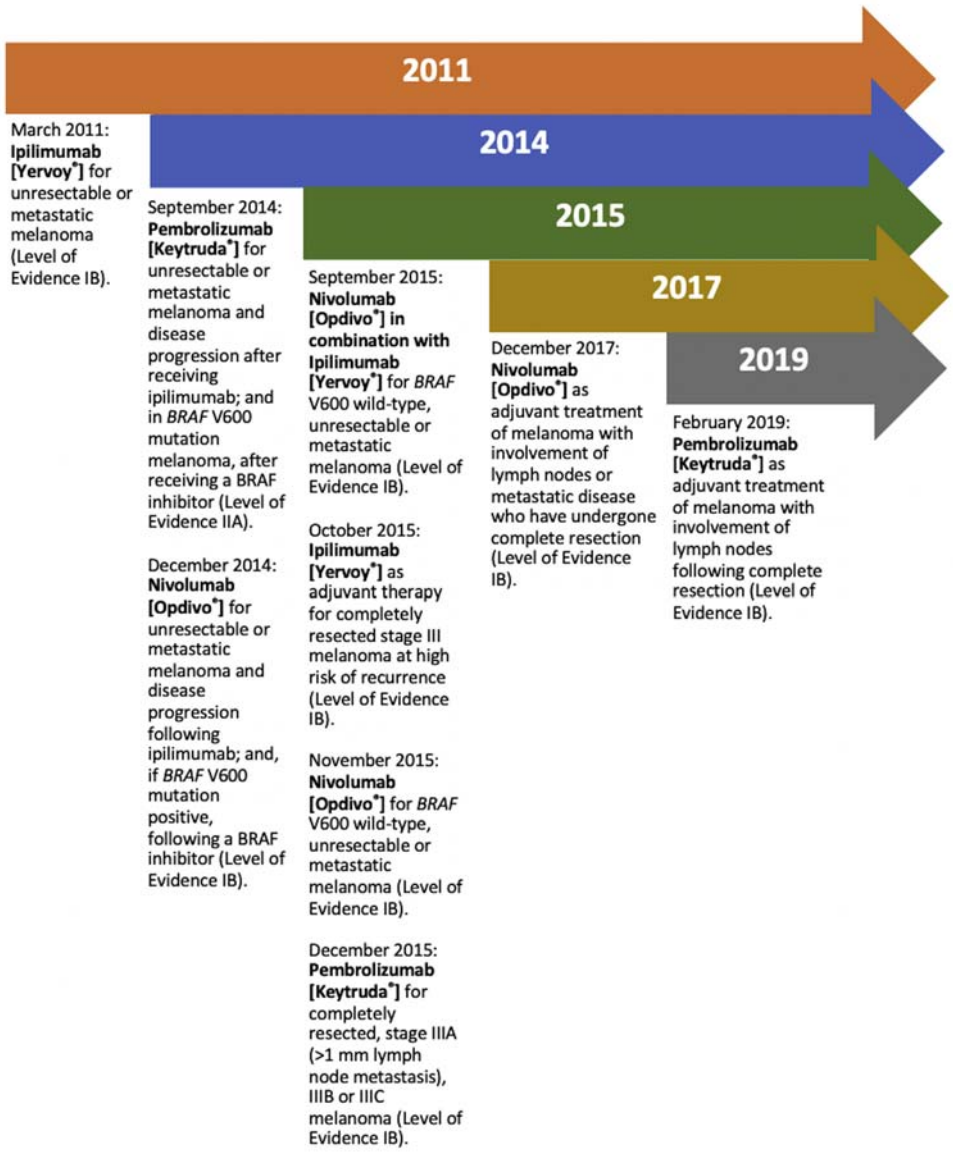

Fig 2. Timeline of approved immune checkpoint inhibitors to treat melanoma. Level IA evidence includes evidence from metaanalysis of randomized controlled trials. Level IB evidence includes evidence from ≥1 randomized controlled trial. Level IIA evidence includes evidence from ≥1 controlled study without randomization. Level IIB evidence includes evidence from ≥1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

nivolumab was granted accelerated approval in January 2016 for patients with *BRAF* V600 mutation−positive unresectable or metastatic melanoma (Fig 2).[40]

Among patients with advanced melanoma, therapy with nivolumab plus ipilimumab or nivolumab alone results in longer PFS and OS than with ipilimumab alone[6,41] (Fig 3); according to the most recently published data, a sunstained long-term OS rate has been observed at 5 years in the nivolumab plus ipilimumab (52%) versus nivolumab (44%) versus ipilimumab group (26%).[6] However, the nivolumab plus ipilimumab combination results in a high degree of side effects; choosing which patients should receive combination immunotherapy and which patients should receive nivolumab or pembrolizumab alone is a major clinical challenge.

Table II. Major studies investigating pembrolizumab (anti—programmed cell death-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ identifier	Patients	Randomization/ dosing regimen(s)	Primary end-point(s)/results	Median follow-up duration	Common severe (grade 3-5) irAEs
2012-2013	Phase I, KEYNOTE-001, NCT01295827	Previously treated, ipilimumab-refractory advanced melanoma, n = 173	Pembrolizumab 2 mg/kg every 3 weeks, n = 89; pembrolizumab 10 mg/kg every 3 weeks, n = 84	ORR: pembrolizumab 2 mg/kg 26%; pembrolizumab 10 mg/kg 26%	8 months	Pembrolizumab 2 mg/kg 3%; pembrolizumab 10 mg/kg 0%
2013-2014	Phase III, KEYNOTE-006, NCT01866319	Previously treated and untreated (65.8%) advanced melanoma, n = 834	Pembrolizumab 10 mg/kg every 2 weeks, n = 279; pembrolizumab 10 mg/kg every 3 weeks, n = 277; ipilimumab 3 mg/kg (4 doses) every 3 weeks, n = 278	6 month-PFS, 12-month OS, RR: Pembrolizumab 10 mg/kg every 2 weeks: 47.3%, 74.1%, and 33.7% Pembrolizumab 10 mg/kg every 3 weeks: 46.4%, 68.4%, and 32.9% Ipilimumab 3 mg/kg (4 doses) every 3 weeks: 26.5%, 58.2%, and 11.9%	7.9 months	Pembrolizumab 10 mg/kg every 2 weeks 13.3%; pembrolizumab 10 mg/kg every 3 weeks 10.1%; ipilimumab 3 mg/kg (4 doses) every 3 weeks 19.9%
2015-2016	Phase III, EORTC132, KEYNOTE-054, NCT02362594	Previously treated, completely resected stage III melanoma patients, n = 1019; PD-L1$^+$ subgroup, n = 853	Pembrolizumab 200 mg every 3 weeks for a total of 18 doses (~1 year), n = 514; placebo every 3 weeks for a total of 18 doses (~1 year), n = 505	RFS in overall intention to treat group: Pembrolizumab 75.4% Placebo 61.0% 1-year rate of RFS in PD-L1$^+$ subgroup: Pembrolizumab 77.1% Placebo 62.6%	15 months	Pembrolizumab 14.7%; placebo 3.4%

EORTC, European Organisation for Research and Treatment of Cancer; *irAE*, immune-related adverse event; *ORR*, objective response rate; *OS*, overall survival; *PFS*, progression-free survival; *RFS*, recurrence-free survival; *RR*, response rate.

CUTANEOUS SQUAMOUS CELL CARCINOMA

Key points

- **Cemiplimab is the only approved CPI for cSCC**
- **Pembrolizumab demonstrated antitumor activity against cSCC in a phase II trial**
- **Most patients with cSCC do not respond to immunotherapy**

cSCC is the second most common cutaneous malignancy.[42] Despite excellent prognosis, 4% of cSCCs are unresectable and 1.5% of patients die from the disease.[43] Until recently, there was no accepted standard of care for advanced cSCC. The use of CPIs in cSCC has attracted considerable interest because cSCC has high mutational burden and is more commonly observed in immunosuppressed patients.[18-20]

In 2018, based on the results of the EMPOWER-CSCC-1 and NCT02383212 trials (Table V), cemiplimab, an anti—PD-1 agent, became the first approved CPI for cSCC (Fig 4). The most recent update of the EMPOWER-CSCC-1 phase 2 trial[44] reports a long-

Table III. Major studies investigating nivolumab (anti—programmed cell death-1 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ identifier	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up	Common severe (grade 3-5) irAEs
2012-2014	Phase III, CheckMate 037, NCT01721746	Previously treated, unresectable or metastatic ipilimumab-refractory melanoma; or (if *BRAF* V600 mutation-positive) ipilimumab plus BRAF inhibitor-refractory melanoma, n = 631	Nivolumab 3 mg/kg every 2 weeks, n = 272; chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 combined with carboplatin area under the curve 6 every 3 weeks), n = 133	ORR: nivolumab (n = 120) 37.1%; chemotherapy (n = 47) 10.6%	8.4 months	Nivolumab 5%; chemotherapy 9%
2013-2014	Phase III, Checkmate 066, NCT01721772	Previously untreated melanoma without BRAF mutation, n = 418	Nivolumab 3 mg/kg every 2 weeks and dacarbazine-matched placebo every 3 weeks, n = 210; dacarbazine 1000 mg/m^2 BSA every 3 weeks and nivolumab-matched placebo every 2 weeks, n = 208	1-year OS: nivolumab 72.9%; dacarbazine 42.1%	Nivolumab 8.9 months; dacarbazine 6.8 months	Nivolumab 11.7%; dacarbazine 17.6%
2015	Phase III, Checkmate 238, NCT02388906	Completely resected, advanced (stage IIIb, IIIc, or IV) melanoma patients, n = 906	Nivolumab 3 mg/kg every 2 weeks, n = 453; ipilimumab, 10 mg/kg every 3 weeks for 4 doses; then every 12 weeks, n = 453	RFS in overall intention to treat group: nivolumab 70.5%; ipilimumab 60.8%	18 months	Nivolumab 14.4%; ipilimumab 45.9%

BSA, Body surface area; *ICC*, investigator's choice of chemotherapy; *irAE*, immune-related adverse event; *ORR*, objective response rate; *OS*, overall survival; *RFS*, recurrence-free survival.

Table IV. Major studies investigating combination of nivolumab plus ipilimumab (anti—programmed cell death-1 plus anti—cytotoxic T-lymphocyte-associated protein-4 immunotherapy) to treat melanoma

Enrollment period	Trial phase/ identifier	Patients	Randomization/dosing regimen(s)	Primary endpoint(s)/results	Median follow-up	Grade 3-4 irAEs
2013-2014	Phase II, CheckMate-069, NCT01927419	Untreated metastatic melanoma, n = 142	Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg (combination group) once every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 3 weeks for 4 doses or placebo every 2 weeks, n = 95; ipilimumab 3 mg/kg plus placebo, followed by nivolumab 3 mg/kg every 3 weeks for 4 doses or placebo every 2 weeks, n = 47	ORR among patients with *BRAF* V600 wild-type tumors: ipilimumab plus nivolumab (n = 72), 61%; ipilimumab plus placebo (n = 37), 11%	11 months	Combination group 54%; ipilimumab monotherapy 24%
2013-2014	Phase III, CheckMate-067, NCT01844505	Untreated, unresectable stage III or IV melanoma patients, n = 945	Nivolumab alone, n = 316; nivolumab plus ipilimumab, n = 314; ipilimumab alone, n = 315	PFS: nivolumab plus ipilimumab, 11.5 months; nivolumab alone, 6.9 months; ipilimumab alone, 2.9 months	12.2-12.5 months	Nivolumab alone 16.3%; nivolumab plus ipilimumab 55%; ipilimumab alone 27.3%

irAE, Immune-related adverse event; *ORR*, objective response rate; *PFS*, progression-free survival.

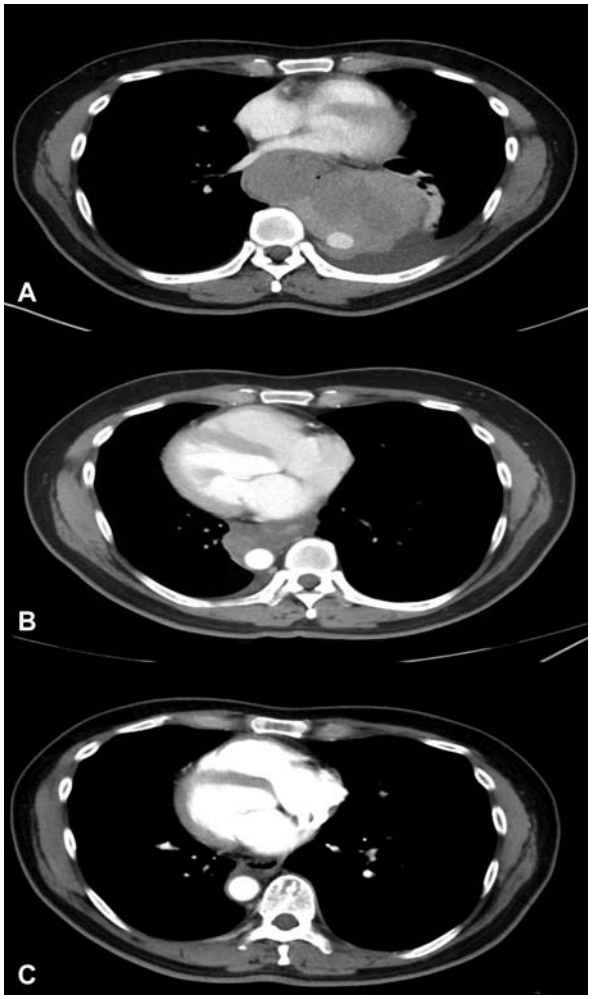

Fig 3. Durable antitumor response after treatment with ipilimumab and nivolumab in a patient with *BRAF* wild-type melanoma, metastatic to the lungs. Computerized tomography scan of metastatic disease in (**A**) February 2016, (**B**) May 2016, and (**C**) January 2018. Adverse events affecting multiple organs were observed and successfully managed with corticosteroids.

lasting antitumor effect and favorable safety profiles in patients with metastatic cSCC.[45] The NCT02383212 phase 1 trial has also demonstrated a positive risk/benefit ratio with durable antitumor response in advanced cSCC (Table V).[46]

Pembrolizumab is being evaluated as first-line therapy in patients with unresectable cSCC in the NCT02883556 trial.[17] Initial results showed a promising objective response rate (ORR) of 38.5% at 15 weeks with a median PFS of 8.4 months. AEs occurred in 67% of patients and caused discontinuation in 10% of patients. Eight percent of patients had severe AEs, including cholestasis and colitis. Retrospective studies and case reports of pembrolizumab for cSCC have shown varying responses.[15,47-52] The use of CPIs in immunosuppressed patients is not well studied.[53] Favorable responses to CPIs have been reported in transplant recipients either with or without graft rejection.[47,48] Optimal immunosuppressive regimens that promote graft preservation without dampening CPI antitumor activity would greatly benefit this group of patients.

Nivolumab for cSCC has only been studied in case reports, showing benefit in recurrent cSCC. AEs include weight loss, nausea, fatigue, hyponatremia, hip pain, and hyperglycemia, with 1 death caused by arrhythmia.[50,51,54,55] Data on ipilimumab for cSCC are limited, with 1 case report showing some efficacy when used in conjunction with radiotherapy in a patient with metastatic cSCC and metastatic melanoma.[56] Chemotherapy and radiotherapy used concurrently with CPIs have shown efficacy in refractory cSCC[55,57] and could be used to further improve the antitumor activities of immunotherapy.

MERKEL CELL CARCINOMA

Key points

- **Avelumab and pembrolizumab are approved for MCC**
- **Nivolumab showed efficacy against MCC with favorable safety profile in an ongoing trial**
- **The NCCN recommends avelumab, pembrolizumab, and nivolumab as first-line therapies for advanced MCC before chemotherapy**

MCC is a rare and aggressive neuroendocrine skin cancer associated with Merkel cell polyomavirus, ultraviolet radiation exposure, immunosuppression, and advanced age.[58] Excision followed by radiotherapy is considered the first-line treatment for primary MCC. Before immunotherapy, chemotherapy was the only systemic treatment available for advanced MCC,[58] which despite a good initial response in nearly 90% of patients, has a short-lived efficacy (approximately 90 days). Currently, CPIs have emerged as front-line therapies for advanced MCC with about 50% of patients demonstrating a durable response, although not without considerable toxicity.

In 2017, on the basis of durable responses and favorable safety profiles observed in the JAVELIN Merkel 200 trial part A, avelumab became the first approved treatment for metastatic MCC (Table V)[59,60]; part B of this trial recently showed good tolerance of the anti—PD-L1 agent as a first-line therapy for metastatic MCC (Table V).[61] In 2018, pembrolizumab was approved for first-line treatment of advanced MCC in the KEYNOTE-017 trial[62]

Table V. Major studies investigating immune checkpoint inhibitors to treat cutaneous malignancy

Type of cutaneous malignancy	Investigating agent/regimen	Trial identifier/ current phase	Patient population	Median follow-up	Efficacy	Adverse event(s)	
						Common	Rare/serious
Cutaneous squamous cell carcinoma	Cemiplimab, 3 mg/kg every 2 weeks	EMPOWER-CSCC-1, NCT02760498/ phase II trial	59 patients with metastatic cSCC	16.5 months	ORR 49.2%; CR 6.8%; PR 42.4%; SD 13.5%; PD 37.3%; PFS 18.4 months	Diarrhea (28.8%), fatigue (25.4%), and nausea (23.7%)	Cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death
	Cemiplimab, 3 mg/kg every 2 weeks	NCT02383212/ phase I trial with expansion cohort	26 patients with locally advanced or metastatic cSCC	11.0 months	ORR 50.0%; CR 0.0%; PR 50.0%; SD 23.0%; PD 27.0%; PFS not reported	Fatigue (26.9%), constipation (15%), decreased appetite (15%), diarrhea (15%), nausea (15%), constipation (15%), hypercalcemia (15%), hypophosphatemia (15%), and urinary tract infection (15%)	Asthenia, maculopapular rash, increased alanine aminotransferase, increased aspartate aminotransferase, adrenal insufficiency, and myalgia
Merkel cell carcinoma	Avelumab, 10 mg/kg every 2 weeks	JAVELIN Merkel 200 NCT02155647/ phase II (part A) trial	88 patients with stage IV MCC that is refractory to chemotherapy	16.4 months	ORR 33.0%; CR 11.4%; PR 21.6%; SD 10.2%; PD 36.4%; PFS 2.7 months	Fatigue (24%), infusion-related reactions (17%), diarrhea (9%), nausea (9%), asthenia, (9%), rash (7%), and decreased appetite (6%)	Lymphopenia (2%), increased serum creatine phosphokinase (1%), aminotransferase (1%), and cholesterol (1%) levels, enterocolitis (1%), chondrocalcinosis (1%), synovitis (1%), and interstitial nephritis (1%)
		JAVELIN Merkel 200 NCT02155647/ phase II (part B) trial	39 patients with metastatic MCC who had not received prior systemic treatment	5.1 months	ORR 62.1%; CR 13.8%; PR 48.3%; SD 10.3%; PD 27.6%; PFS 9.1 months	Infusion-related reactions (23.1%)	Cholangitis, elevated aspartate and alanine aminotransferase levels, paraneoplastic syndrome, gait disturbance, paraneoplastic encephalomyelitis, and polyneuropathy
	Pembrolizumab, 2 mg/kg every 3 weeks	KEYNOTE-017 NCT02267603/ phase II trial	50 patients (26 from original cohort and 24 from expansion cohort) with advanced MCC who had not received systemic treatment	14.9 months	ORR 56.0%; CR 24.0%; PR 32.0%; SD 10.0%; PD 32%; PFS 16.8 months	Fatigue and laboratory abnormalities	Myocarditis, elevated liver enzymes, and death

CR, Complete response; *cSCC*, cutaneous squamous cell carcinoma; *MCC*, Merkel cell carcinoma; *ORR*, objective response rate; *PD*, progressive disease; *PFS*, progression-free survival; *PR*, partial response; *SD*, stable disease.

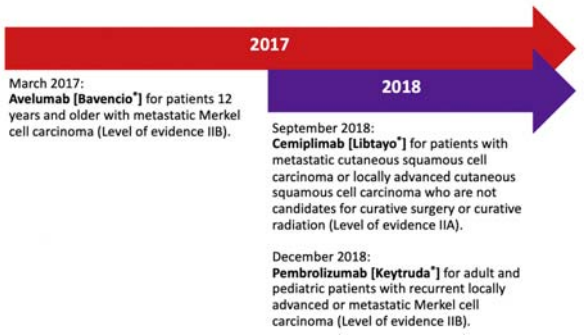

Fig 4. Timeline of approved immune checkpoint inhibitors to treat cutaneous squamous cell carcinoma and Merkel cell carcinoma. Level IA evidence includes evidence from metaanalysis of randomized controlled trials. Level IB evidence includes evidence from ≥1 randomized controlled trial. Level IIA evidence includes evidence from ≥1 controlled study without randomization. Level IIB evidence includes evidence from ≥1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

(Table V), which in addition to positive CPI-associated antitumor efficacy and safety outcomes also showed glucocorticoids having no effect on tumor response among patients with severe AEs.[62] The expanded NCT02267603 trial further strengthened the efficacy of pembrolizumab as first-line treatment for advanced MCC (Fig 5).[63] The CheckMate 358 trial with 25 patients investigated nivolumab for advanced MCC, resulting in a 68% ORR and more than two-thirds with AEs.[64] In the above studies, PD-L1 expression and Merkel cell polyomavirus status did not appear to correlate with clinical responses.[59,60,62,64]

The use of avelumab, pembrolizumab, and nivolumab for advanced metastatic MCC has also been reported in cases studies, with varying responses.[65-74] Serious AEs included central diabetes insipidus,[66] pneumonia, autoimmune hepatitis,[68] cytokine release syndrome,[74] and thrombocytopenia.[75] Ipilimumab has been studied less frequently against MCC, with inconclusive antitumor activity.[76] In addition, ipilimumab did not demonstrate activity as adjuvant therapy for resected MCC.[77] Despite the success of CPIs in treating MCC, many patients do not respond to or develop resistant disease after an initial response; however, the use of combinatorial or sequential CPIs has shown activation of antitumor immunity in a subset of nonresponders,[78] which represents a promising therapeutic approach for patients who do not persistently benefit from CPI treatment in this population.

OTHER CUTANEOUS NEOPLASMS

Key points

- **There is no CPI approved for BCC, cutaneous lymphoma, cutaneous sarcoma, or CAC**
- **In small studies and case reports, anti-PD-1 therapy appears to be efficacious in BCC, certain subsets of cutaneous lymphoma, and cutaneous sarcoma**

Basal cell carcinoma

BCC is the most common human cancer with increasing incidence. A small subset of BCC progresses to locally advanced and metastatic tumors and requires aggressive systemic treatments.[79,80] Immunotherapy is anticipated to be effective in BCC because it bears the highest mutational burden of any human cancer.[81]

Pembrolizumab showed antitumor activity against advanced BCC in a phase Ib trial, in which 9 patients received pembrolizumab monotherapy and 7 patients received pembrolizumab plus vismodegib.[82] The ORRs at 18 weeks were 44% and 29%, and the 1-year PFSs were 62% and 83% for the monotherapy versus dual therapy group, respectively. Thus, the response rate of the dual therapy was not superior to the monotherapy group. Pembrolizumab was well tolerated with dermatitis and fatigue being the most common AEs.[82] The use of pembrolizumab in BCC has also been reported in 5 case reports with clinical responses ranging from disease progression[83] to partial response[16,84,85] and complete response.[83,86] There was only 1 report of subclinical hypothyroidism[84] and sarcoid-like lymph node reaction.[16] Cemiplimab[87] and nivolumab[88,89] have also shown efficacy against advanced BCC without serious AEs.

Cutaneous lymphomas

Cutaneous T cell lymphomas (CTCLs) involve extensive infiltration of malignant T cells into the skin and lack effective treatment for advanced disease.[90] Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common CTCL subtypes, with cells expressing high level of PD-1, PD-L1, and CTLA-4, suggesting a role of CPIs in targeting the disease.[91,92]

As demonstrated by a 15% ORR in 13 patients with MF and 0% ORR in 2 patients with SS in a phase Ib trial, nivolumab has a limited antitumor activity against CTCL.[93] AEs occurred in 65% of patients, with 15% discontinuing treatment because of severe AEs, including pneumonitis, sepsis, and myositis. A phase II study of pembrolizumab for 24 patients with advanced CTCL demonstrated a 38% ORR.[94,95] While

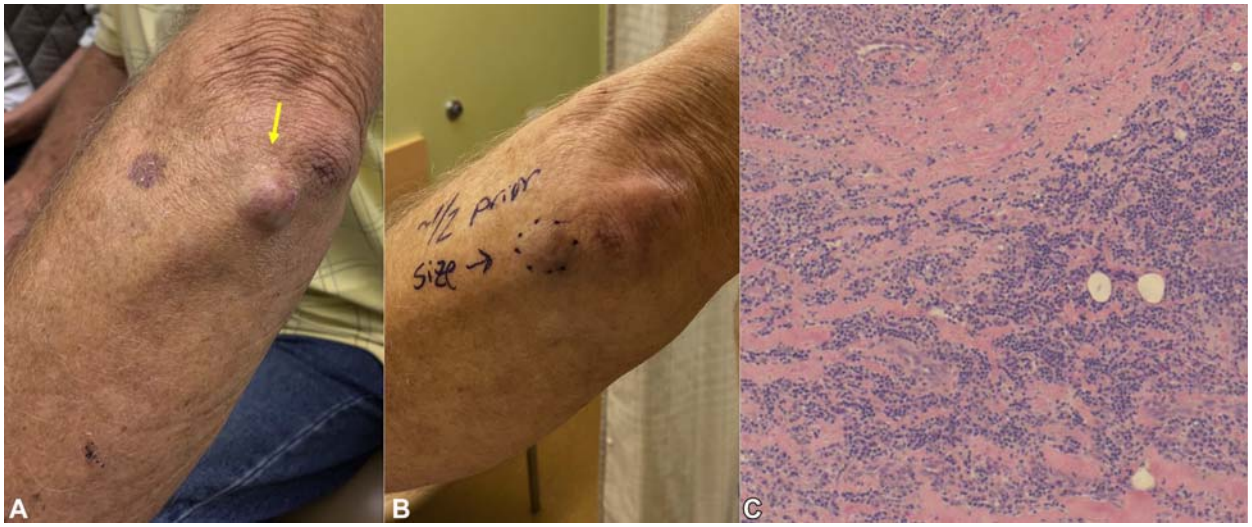

Fig 5. Complete clinicopathologic response in a patient with Merkel cell carcinoma who was treated with pembrolizumab. **A** and **B**, Clinical images of a patient with Merkel cell carcinoma pre-treatment and 3 weeks after the first dose of pembrolizumab. **C**, Findings on histopathology reveal dermal fibrosis and a mixed lymphocytic inflammation with negative synaptophysin and chromogranin stains (not shown), both of which were expressed pre-treatment with pembrolizumab.

there was no significant association between tumor response and the expression of PD-1, PD-L1, or infiltrating $CD8^+$ T cells, pembrolizumab was well-tolerated; serious AEs included grade 2 pneumonitis and grade 3 diarrhea caused by steroid-refractory duodenitis.[94] Curiously, 53% patients with SS experienced skin flare reactions, characterized by a transient worsening of erythroderma and pruritus.[95] This reaction correlated with PD-1 expression on Sézary cells but did not associate with subsequent clinical responses. The use of ipilimumab for CTCL has been reported in only 2 case reports with conflicting responses and requires additional investigation.[96,97]

Cutaneous sarcomas

Cutaneous sarcomas are a rare and heterogenous group of skin mesenchymal spindle cell tumors with good prognosis for early disease. There is a lack of effective therapy for patients with advanced diseases.[98] In a phase II trial,[99] pembrolizumab did not show benefit in patients with undifferentiated pleomorphic sarcoma. In the NCT01295827 trial with 10 patients with undifferentiated pleomorphic sarcoma, there was 10% complete response, 30% partial response, 30% stable disease, and 30% progressive disease.[100] Among the 10 patients with liposarcoma in the same trial, there was 0% complete response, 2% partial response, 40% stable disease, and 40% progressive disease. The most frequent grade 3 or worse AEs were anemia and other hematologic abnormalities, and 6% of patients discontinued therapy because of toxicity, including nephritis and pneumonitis.

Kaposi sarcoma (KS) is often observed in immunosuppressed patients, suggesting that it might be a good target for CPIs. In a series of 9 HIV-positive patients with KS who received nivolumab (n = 8) or pembrolizumab (n = 1), the ORR was 66%. The most common AEs were fatigue, pruritus, muscle/joint ache, abdominal discomfort, and onycholysis.[101] Pembrolizumab also has antitumor activity against HIV-negative, classic KS.[69,102] Nivolumab is also effective in HIV-negative patients with KS with the only notable AE being hyponatremia because of low cortisol level.[103] Pembrolizumab has also been attempted in 2 separate cases of angiosarcoma in which the patients either achieved a complete response[104] or durable partial response with autoimmune hepatitis that required prednisone treatment.[105] There are no data regarding the efficacy of CPIs against dermatofibrosarcoma protuberans or cutaneous leiomyosarcoma.

Cutaneous adnexal carcinomas

CACs are a heterogenous group of malignant neoplasms that display differentiation toward skin-primary adnexal structures and which currently have limited effective treatment for metastasis.[106] High expression levels of PD-L1 have been reported in sebaceous carcinoma.[73,107] In 2 case reports, the use of pembrolizumab with or without chemotherapy demonstrated clinical efficacy against metastatic sebaceous

carcinoma.[108,109] One patient remained on pembrolizumab despite requiring systemic corticosteroids because of secondary adrenal insufficiency.[108]

FUTURE DIRECTIONS AND CONCLUSIONS

As the field of immunotherapeutics continues to revolutionize the treatment of cutaneous malignancies, blocking antibodies to CTLA-4 and PD-1/PD-L1 have improved survival for many patients. For melanoma, ipilimumab in combination with nivolumab or either nivolumab or pembrolizumab alone are standard front-line treatment options. Several trials are in development to investigate the role of anti—PD-L1 agents in metastatic melanoma,[110,111] including atezolizumab and avelumab.

Cemiplimab is the only approved CPI for cSCC, and there is a critical need for improved therapies that can better target the advanced stage of this cutaneous malignancy. Although pembrolizumab has demonstrated antitumor activity against cSCC in a phase II trial, most patients do not respond to immunotherapy. For MCC, the NCCN guidelines recommend avelumab, pembrolizumab, and nivolumab as first-line therapies, ahead of chemotherapy. Although the data are limited and there is no CPI approved for BCC, cutaneous lymphoma, cutaneous sarcoma, or CACs,[112] evidence from small observational studies and case reports suggest the potential utility of anti—PD-1 therapy in BCC and certain subsets of cutaneous lymphoma and cutaneous sarcoma.

Despite exceptional clinical benefits observed with CPIs in cutaneous malignancies, their associated irAEs require careful monitoring. As such, expanding immunotherapy clinical research efforts can lead to identifying new CPI regimens that improve antitumor responses and reduce the incidence and severity of irAEs. Furthermore, striving to achieve a more concrete understanding of predictive markers of response and mechanisms of resistance to anti—CTLA-4 and anti—PD-1/PD-L1 therapies may help identify subsets of patients who are more likely to respond to therapy with these agents.

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