

Current Status and Future Directions of the Immune Checkpoint Inhibitors Ipilimumab, Pembrolizumab, and Nivolumab in Oncology

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Abstract

Objective: To provide the clinician with an update and the current status and future direction of approved immune checkpoint inhibitors (ICIs) in oncology. **Data Sources:** A PubMed search from January 1, 1966 to March 13, 2015 was performed using the key terms *ipilimumab*, *pembrolizumab*, *lambrolizumab*, *nivolumab*, *immune checkpoint inhibitor*, *MDX-010*, *MDX-101*, *BMS-734016*, *MK-3475*, *SCH 900475*, *MDX-1106*, *BMS-936558*, *ONO-4538*, *CTLA-4*, *PD-1*, or *PD-L1* and *cancer*, *oncology*, or *neoplasm*. Additional references were identified from the investigators' personal files, recent oncology meetings, review articles, clinical guidelines, and package inserts. **Study Selection and Data Extraction:** All English-language clinical trials assessing the safety and efficacy of ipilimumab, nivolumab, and pembrolizumab in cancer were considered. The PubMed search resulted in 215 trials; 33 met inclusion criteria. A further 28 trials were identified from the above sources; 61 trials from 2005 to 2015 were included. We consolidated and clarified treatment recommendations for the management of immune-related adverse events (irAEs), assessed response criteria, and calculated the clinical utility of leading tumor profiling options. **Data Synthesis:** Ipilimumab and nivolumab, but not pembrolizumab, have an overall survival (OS) advantage over chemotherapy first line in unresectable/metastatic melanoma. Nivolumab has an OS advantage versus chemotherapy in second-line squamous non-small-cell lung cancer. Data in other settings are promising. Nivolumab and pembrolizumab are better tolerated than ipilimumab. Further validation of response criteria is needed. Tumor profiling to predict clinical benefit is premature but promising. **Conclusions:** The treatment landscape in oncology is quickly evolving with the advent of ICIs.

Keywords

ipilimumab, pembrolizumab, nivolumab, CTLA-4, PD-1, immune checkpoint inhibitor

Background

The immune system is important in preventing and controlling cancer.¹ T-cells are a major component of the immune response, and the process is regulated by a series of costimulatory and inhibitory signals that serve as checkpoints. Cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4) and programmed death-1 receptor (PD-1) are 2 of the many checkpoint receptors that regulate the immune response and can be targeted and inhibited (Figure 1).²

Immune checkpoint inhibitors (ICIs) fall into a larger class of molecules, the biological response modifiers (BRMs). BRMs include monoclonal antibodies, autologous cellular immunotherapy, interferons, interleukins, colony stimulating factors, vaccines, and ICIs. When acting directly, BRMs bind to receptors on the tumor cells and impair their function, deliver toxins or radionuclides, and/or promote antibody-dependent cell-mediated cytotoxicity.

ICIs act indirectly by enhancing the immunological response to neoplastic cells.³ Manipulation of the immune system is not a new concept in the treatment of cancer: interferons and hematopoietic stem cell transplantation have been utilized for decades. The novel aspects of the ICIs are the drug targets and their ultimate pharmacodynamic effect to stimulate the immune system.

The purpose of this review is to provide clinicians with a reference for current and future clinical practice with ipilimumab, pembrolizumab, and nivolumab. This review focuses on the literature evaluating the efficacy and safety

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Amgen Exhibit 1066
Amgen v. BMS

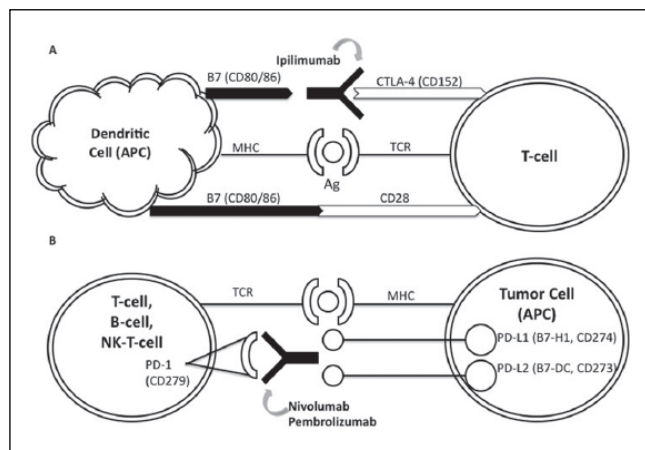


Figure 1. Targets and action of ICIs ipilimumab, nivolumab, and pembrolizumab: A. Ipilimumab binds to the CTLA-4 receptor. CTLA-4 is a coinhibitory cell surface receptor of the CD28 family present on activated CD8⁺ effector T-cells and constitutively present on regulatory T-cells. Both CTLA-4 and CD28 bind to B7; however, CTLA-4 has a higher affinity for the ligand and outcompetes the B7/CD28 stimulating interaction (the second signal of T-cell activation). The CTLA-4/B7 interaction inhibits T-cell proliferation and downregulates expression of IL-2 production in immune cells, inhibiting the third signal of T-cell activation. Blocking CTLA-4 with ipilimumab and, thus, releasing B7 for interaction with CD28 causes activation of T-cells against tumor cells.² B. Nivolumab and pembrolizumab bind to the PD-1 receptor. PD-1 is a coinhibitory cell surface receptor that is a member of the CD28 family of T-cell regulators. PD-1 is expressed on CD4⁺/CD8⁺ thymocytes during thymic development, activated T- and B-cells, natural killer (NK) T-cells, regulatory T-cells, and monocytes after prolonged antigen exposure. When PD-1 binds to its ligands PD-L1 or PD-L2, it serves as a coinhibitory signal to inhibit immune function. The binding inhibits T-cell proliferation and downregulates expression of the antiapoptotic molecule Bcl-xL, cytokine expression, and the mTOR pathway in immune cells. Because PD-1 is also expressed on B-cells, it could amplify antibody production. Binding of nivolumab or pembrolizumab to PD-1 inhibits binding of the receptor to its ligands PD-L1 and PD-L2 on tumor cells, inhibits the coinhibitory signal on T-cells, reverses T-cell suppression, and induces antitumor response.² A coinhibitory interaction has been described that involves binding of PD-L1 on T-cells to B7 on APCs or vice versa, but the clinical impact of this mechanism is currently unknown (not shown in the figure).^{2,52}

Abbreviations: APC, antigen-presenting cell (dendritic cell or tumor cell); CTLA-4 (CD152), cytotoxic T-lymphocyte antigen-4 receptor; ICI, immune checkpoint inhibitor; MHC, major histocompatibility complex; PD-1, programmed cell death-1 receptor (CD279); PD-L1, programmed death ligand-1 (B7-H1, CD274); PD-L2, programmed death ligand-2 (B7-DC, CD273); TCR, T-cell receptor.

of ICIs and combination checkpoint blockade. We also review the pharmacokinetics, pharmacodynamics, and clinical pearls in special populations and include comprehensive tables for the management of immune-related adverse events (irAEs). New response criteria and the utility of tumor profiling are also reviewed.

Data Sources, Study Selection, and Data Extraction

A PubMed search from January 1, 1966 to March 13, 2015 was performed using the key terms *ipilimumab*, *pembrolizumab*, *lambrolizumab*, *nivolumab*, *immune checkpoint inhibitor*, *MDX-010*, *MDX-101*, *BMS-734016*, *MK-3475*, *SCH 900475*, *MDX-1106*, *BMS-936558*, *ONO-4538*, *CTLA-4*, or *PD-1* and *cancer*, *oncology*, or *neoplasm* with limits to English-language clinical trials in humans. The search resulted in 215 studies whose abstracts were reviewed by a single investigator to identify prospective interventional clinical trials assessing the safety and efficacy of ipilimumab, nivolumab, and pembrolizumab in malignant neoplasms. Of the 215 search results, 177 were excluded because they did not fit these criteria (retrospective, news release/commentary, preclinical, alternative drug, primary endpoint not safety/efficacy, safety trials with no correlative clinical efficacy outcomes, case series, nononcological indication, or expanded access program). The remaining 38 trials were reviewed in detail by 2 investigators for inclusion. A third investigator provided input on inclusion if there was disagreement. Trials that fit the inclusion criteria above and were deemed significant and relevant to current or future clinical practice by at least 2 investigators are included in this review ($n = 33$). An additional 28 clinical trials that met the above criteria were identified from the investigators' personal files or the most recent oncology society meetings (European Society of Medical Oncology, American Society of Clinical Oncology, or the American Society of Hematology). Highly impactful clinical trials that led to either FDA approval or category I recommendations are discussed in the text, and other clinical trials are detailed in Tables 1 to 3. Review articles and their citations, clinical guidelines, and package inserts were reviewed and discussed where relevant to provide additional context.

Ipilimumab (Yervoy, MDX-010, MDX-101, BMS-734016)

Ipilimumab is a selective human immunoglobulin G1 (IgG1) κ monoclonal antibody that inhibits CTLA-4 signaling activity (Figure 1).⁴ Ipilimumab was FDA approved in March 2011 as an orphan drug for the treatment of patients with unresectable or metastatic melanoma. Approval was based on overall survival (OS) at a dose of 3 mg/kg intravenous (IV) over 90 minutes Q3W for 4 doses.⁴ A phase III trial in patients with advanced melanoma comparing the safety and efficacy of ipilimumab 3 mg/kg versus 10 mg/kg is under way.⁵ The results may affect ipilimumab dosing. Major dose-limiting toxicities (DLTs) are immune-mediated and detailed in a separate section.⁴

Ipilimumab was evaluated in a multinational, randomized, double-blind, phase III study.⁶ Previously treated patients with unresectable stage III to IV melanoma were

Table 1. Summary of Clinical Trials for Ipilimumab.

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Hodi et al (2010) ⁶ ; phase III	Melanoma: previously treated, unresectable stage III or IV	- Ipilimumab 3 mg/kg IV Q3W + gp100 vaccine Q3W (n = 403) - Ipilimumab 3 mg/kg IV Q3W + placebo Q3W (n = 137) - gp100 vaccine Q3W + placebo Q3W (n = 136)	Median OS - Ipilimumab + gp100: 10 months - gp100: 6.4 months - Ipilimumab: 10.1 months - HR = 0.68, $P < 0.001$; combination vs gp100 - HR = 0.66, $P = 0.003$; ipilimumab vs gp100 - HR = 1.04, $P = 0.76$; combination vs ipilimumab	PFS (WHO) 19% Reduction with ipilimumab + gp100 vs gp100 (HR = 0.81, $P < 0.05$) 36% Reduction with ipilimumab vs gp100 (HR = 0.64, $P < 0.001$) - Less reduction with combination therapy than ipilimumab (HR = 1.25, $P = 0.04$) ORR (WHO) - Ipilimumab + gp100: 5.7% ($P = 0.04$ vs gp100 alone, $P = 0.04$ vs ipilimumab alone) - gp100: 1.5% - Ipilimumab: 10.9% ($P = 0.001$ vs gp100 alone)	Any CTCAE - Ipilimumab + gp100, 98.4%; irAEs, 58.2% - gp100, 97%; irAEs, 31.8% - Ipilimumab, 97%; irAEs, 61.1% CTCAE grade 3-4 - Ipilimumab + gp100, 45.5%; irAEs, 10.2% - gp100, 47%; irAEs, 3% - Ipilimumab, 45.8%; irAEs, 14.5%
Robert et al (2011) ⁸ ; phase III	Melanoma: unresectable stage III or IV, untreated (except adjuvant therapy)	- Ipilimumab 10 mg/kg IV weeks 1, 4, 7, 10 + DTIC 850 mg/m² IV Q3W → DTIC IV Q3W through week 22 (n = 250) - DTIC 850 mg/m² IV Q3W + placebo weeks 1, 4, 7, 10 → DTIC IV Q3W through week 22 (n = 252) - Maintenance in responders with ipilimumab Q12W or placebo	Median OS - Ipilimumab + DTIC: 11.2 months - DTIC: 9.1 months - HR = 0.72; $P < 0.001$	PFS (WHO) 24% Reduction in risk of progression with ipilimumab - HR = 0.76; $P = 0.006$ ORR (WHO) - Ipilimumab + DTIC: 15.2% - DTIC: 10.3% $P = 0.09$ DOR (WHO) - Ipilimumab + DTIC: 19.3 months - DTIC: 8.1 months $P = 0.03$	Any CTCAE - Ipilimumab + DTIC: 98.8%; irAEs, 77.7% - DTIC: 94%; irAEs, 38.2% CTCAE grade 3-4 - Ipilimumab + DTIC: 56.3%; irAEs, 41.7% - DTIC: 27.5%; irAEs, 6%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Attia et al (2005) ¹⁰ ; phase I	Melanoma: stage IV, previously treated	- Ipilimumab 3 mg/kg IV Q3W + 1 mg gp100: 209-217 (210M) peptide (IMDQVPFSV) injected in one extremity and 1 mg of gp100: 280-288(288V) peptide (YLEPGPTV) injected in another extremity (n = 29) - Ipilimumab 3 mg/kg IV x 1 dose followed by 1 mg/kg Q3W + the gp100 peptides as above (n = 27)	ORR (RECIST) - Overall: 13% - Ipilimumab 3 mg/kg: 14% - Ipilimumab 3 → 1 mg/kg: 11% - P = 0.54	ORR (RECIST) - Grade 3-4 irAE: 36%; no grade 3-4 irAE: 5%; P = 0.008 - Grade 1-2 irAE: 29%; no grade 1-2 irAE: 5%; P = 0.022	CTCAE grade 3-4 3 mg/kg Q3W: 31% 3 → 1 mg/kg: 19% - P = 0.22
Maker et al (2005) ¹¹ ; phase I/II	Melanoma: stage IV, heavily pretreated	Phase I - Ipilimumab 0.1 mg/kg IV (n = 3) - Ipilimumab 0.3 mg/kg IV (n = 3) - Ipilimumab 1.0 mg/kg IV (n = 3) - Ipilimumab 2.0 mg/kg IV (n = 3) Phase II - Ipilimumab 3 mg/kg IV + IL-2 720 000 units/kg Q8H up to 15 doses (n = 24)	ORR (RECIST) - Overall: 22% - Phase I: 33% (one in each arm) - Phase II: 21%	Not reported	CTCAE grade 3-4 irAEs Overall: 14%
Weber et al (2008) ¹² ; phase I/II	Melanoma: unresectable stage III-IV, previously treated	- Group A, multiple dose (MD): Transfectoma-derived ipilimumab 2.8 mg/kg x 3 doses, hybridoma-derived ipilimumab 3 mg/kg x 3 doses, or transfectoma-derived ipilimumab 5 mg/kg x 3 doses administered on days 1, 57, and 85 (n = 34) - Group A, single dose (SD): transfectoma-derived ipilimumab at 7.5, 10, 15, or 20 mg/kg (n = 30) - Group B: transfectoma-derived ipilimumab 10 mg/kg on days 1, 22, 43, and 64 (n = 24)	ORR (RECIST) - Overall: 4.6% - Group A, MD: 15% - Group A, SD: 13% - Group B: 39.1%	Not reported	CTCAE grade 3-4 - Group A, MD: 20.6% - Group A, SD: 13.3% - Group B: 25.0%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Weber et al (2009) ¹³ ; phase II	Melanoma: unresectable stage III-IV	- Ipilimumab 10 mg/kg + budesonide 9 mg po daily x 12 weeks (n = 58) - Ipilimumab 10 mg/kg + placebo (n = 57)	Rate of CTCAE Grade 2+ diarrhea - With budesonide: 33% - No budesonide: 35%	ORR (WHO) - With budesonide: 12% - No budesonide: 16% I- And 2-year OS rates - With budesonide: 56%, 40% - No budesonide: 62%, 42% Median OS - With budesonide: 17.7 months - No budesonide: 19.3 months	Any CTCAE - With budesonide: 90% - No budesonide: 95% Any grade irAEs - With budesonide: 81% - No budesonide: 84% CTCAE grade 3-4 irAEs - With budesonide: 41% - No budesonide: 38%
Wolchok et al (2010) ¹⁴ ; phase II	Melanoma; unresectable, stage III-IV, previously treated	- Ipilimumab 10 mg/kg (n = 73) - Ipilimumab 3 mg/kg (n = 72) - Ipilimumab 0.3 mg/kg (n = 72) - Given Q3W x4 (induction) followed by maintenance therapy Q3M	ORR (WHO) 10 mg/kg: 11.1% 3 mg/kg: 4.2% 0.3 mg/kg: 0% - P = 0.0015	Median OS 10 mg/kg: 11.4 months 3 mg/kg: 8.7 months 0.3 mg/kg: 8.6 months - HR = 0.77, 95% CI = 0.52-1.1; 10 mg/kg vs 0.3 mg/kg - HR = 0.875, 95% CI = 0.59-1.29; 10 mg/kg vs 3 mg/kg - HR = 0.879, 95% CI = 0.6-1.27; 3 mg/kg vs 0.3 mg/kg I- And 2-year OS rate 10 mg/kg: 48.6%, 29.8% 3 mg/kg: 39.3%, 24.2% 0.3 mg/kg: 39.6%, 28.4% Median OS - Overall: 10.2 months - I- And 2-year OS rate - Overall: 47.2%, 32.8% Disease control rate - Overall: 27%	Any CTCAE grade irAEs 10 mg/kg: 40% 3 mg/kg: 46% 0.3 mg/kg: 19% CTCAE grade 3-4 irAEs 10 mg/kg: 18% 3 mg/kg: 5% 0.3 mg/kg: 10% Discontinuation because of any drug-related adverse event 10 mg/kg: 11% 3 mg/kg: 5% 0.3 mg/kg: 2%
O'Day SJ, et al (2010) ¹⁵ ; phase II	Melanoma: recurrent and unresectable	Ipilimumab 10mg/kg IV Q3W x4 then maintenance Q12W (n = 155)	ORR (WHO) Overall: 5.8%	Median OS - Overall: 10.2 months - I- And 2-year OS rate - Overall: 47.2%, 32.8% Disease control rate - Overall: 27%	Any CTCAE - Overall: 84% - irAEs: 70% CTAE grade 3-4 - Overall: 28% - irAEs: 22%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Hersh et al (2011) ¹⁶ ; phase II	Melanoma: previously treated, unresectable, metastatic	- Ipilimumab 3 mg/kg IV Q4W x4 doses + DTIC 250 mg/m²/d x5 days Q3W x6 cycles (n = 35) - Ipilimumab 3 mg/kg IV Q4W x4 doses (n = 37). Patients allowed to crossover (n = 13)	ORR (RECIST) - Overall: 9.7% - Ipilimumab + DTIC: 14.3% - Ipilimumab: 5.4% - P not significant	Median OS - Ipilimumab + DTIC: 14.3 months - Ipilimumab: 11.4 months 12-, 24-, And 36-month OS rates - Ipilimumab + DTIC: 62%, 24%, 20% - Ipilimumab: 45%, 21%, 9%	CTCAE grade 3+ - Ipilimumab + DTIC: 22.9%; irAEs: 65.7% - Ipilimumab: 12.8%; irAEs: 53.8% - Crossover: 15.4%; irAEs: 30.8%
Hodi et al (2014) ¹⁷ phase II	Melanoma: previously treated, unresectable, metastatic	- Ipilimumab 10m/kg IV Q3W x4 doses then Q12W + sargramostim 250 µg subcut days 1-14 of 21-day cycles (n = 123) - Ipilimumab 10m/kg IV Q3W x4 doses then Q12W (n = 122)	Median OS - Ipilimumab + sargramostim: 17.5 months - Ipilimumab: 12.7 months - HR = 0.64; 90% CI I-sided, N/A to 0.9, P = 0.01	Median PFS (RECIST) - Ipilimumab + sargramostim: 3.1 months - Ipilimumab: 3.1 months - HR = 0.87; 95% CI = 0.69-1.23; P = 0.37 - ORR (RECIST) - Ipilimumab + sargramostim: 15.5% - Ipilimumab: 14.8% - P = 0.88	CTCAE grade 3+ - Ipilimumab + sargramostim: 44.9% - Ipilimumab: 58.3% - P = 0.04
Eggermont et al (2014) ²⁰ ; phase III	Melanoma: adjuvant treatment, stage III, cutaneous	- Ipilimumab 10 mg/kg IV Q3W x4 doses → maintenance ipilimumab 10 mg/kg IV Q3M up to 3 years (n = 475) - Placebo at above schedule (n = 476)	Median recurrence-free survival - Ipilimumab: 26.1 months - Placebo: 17.1 months - HR = 0.75; 95% CI = 0.64-0.9; P = 0.0013	3-Year recurrence-free survival - Ipilimumab: 46.5% - Placebo: 34.8%	CTCAE grade 3-4 irAEs (ipilimumab vs placebo) - GI: 15.9% vs 0.8% - Hepatic: 10.6% vs 0.2% - Endocrine: 8.5% vs 0% 52% Of ipilimumab patients discontinued trial because of AEs. - There were 5 deaths from ipilimumab.

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Sarnaik et al (2010) ²¹ ; phase II	Melanoma: adjuvant treatment, resected stage IIIc or IV, previously treated or treatment naïve	- Ipilimumab 3 mg/kg IV Q6-8W × 12M (n = 25) - Ipilimumab 10 mg/kg IV Q6-8W × 12M (n = 50) - Each HLA-A*0201 + patient also received 1 mg each of 3 peptide vaccines subcut: tyrosinase, gp100, and MART-1 Q2W × 6, then Q4W × 4, then Q12W × 2	See safety outcomes	Median relapse-free survival (criteria not reported) - Experienced grade 2+ irAE: not reached - Did not experience grade 2+ irAE: 19.7 months - P = 0.03 for comparison Overall, the median relapse-free survival and median overall survival were not reached after a median of 29.5 months of follow-up	CTCAE grade 2-4 irAEs Overall: 37%
Margolin et al (2012) ²² ; phase II	Melanoma: brain metastases with or without concomitant steroids	- Ipilimumab 10 mg/kg IV Q3W × 4 doses (weeks 1, 4, 7, 10) → 10 mg/kg IV Q12W maintenance in clinically stable patients - No steroids, n = 51 - Concomitant steroids, n = 21	12-Week disease control rate (WHO, irRC) - No steroids: 18%, 25% - Steroids: 5%, 10%	ORR (WHO/irRC) - No steroids: 10%/5% - Steroids: 1%/1% Median PFS (WHO, irRC) - No steroids: 1.4, 2.7 months - Steroids: 1.2, 1.3 months Median OS - No steroids: 7 months - Steroids: 3.7 months Interim ORR (irRC) at 5.5 months - Overall: 53.9% Interim Median PFS (irRC) - Not yet reached	CTCAE grade 3-4 (no steroids vs steroids) - Diarrhea: 12% vs 0% - Fatigue: 12% vs 5% - Rash: 2% vs 5% - Nausea: 6% vs 0% - Vomiting: 6% vs 0% - Headache: 4% vs 0%
Rodriguez et al (2014) ²³ ; phase II	Melanoma: metastatic uveal, treatment naïve for uveal disease	Ipilimumab 10 mg/kg IV Q3W × 4 doses → 10 mg/kg IV Q12W maintenance (n = 31)	Interim median OS	Interim ORR (irRC) at 5.5 months - Overall: 53.9% Interim Median PFS (irRC) - Not yet reached	CTCAE grade 3-4 - Grade 3: 32% - Grade 4: 16%
Kwon et al (2014) ²⁴ ; phase III	Prostate: mCRPC with at least 1 bone metastasis, progression after docetaxel	- Bone-directed radiotherapy (8 Gy in one fraction) → ipilimumab 10 mg/kg IV Q3W × 4 doses → maintenance ipilimumab 10 mg/kg IV Q3M (n = 399) - Bone-directed radiotherapy (8 Gy in one fraction) → placebo IV Q3W → maintenance placebo IV Q3M (n = 400)	Median OS - Ipilimumab: 11.2 months - Placebo: 10 months - HR = 0.85; 95% CI = 0.72-1; P = 0.053	Medians PFS (RECIST) - Ipilimumab: 4 months - Placebo: 3.1 months - HR = 0.7; 95% CI = 0.61-0.82; P < 0.0001	CTCAE grade 3-4 - Ipilimumab: 59%, irAEs 26% - Placebo: 41%, irAEs 3% Deaths resulting from adverse events - Ipilimumab: 1.7% - Placebo: 1.1%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Slovin et al (2013) ²⁶ , phase I/II	Prostate: mCRPC, with at least 1 bone metastasis, no more than 1 prior line of chemotherapy	- Ipilimumab 3, 5, or 10 mg/kg IV Q3W ×4 doses (n = 30) - Ipilimumab 3 or 10 mg/kg IV Q3W + bone-directed radiotherapy (8 Gy; n = 41) - Ipilimumab 10 mg/kg IV Q3W + radiation as above (phase II expansion cohort, n = 50)	Maximum tolerated dose: - Not reached in monotherapy - ipilimumab arm	Median OS - Overall: 17.4 months - ORR (RECIST) - Ipilimumab: 7% - Ipilimumab + radiation: 2.4% - Expansion cohort: 2% ≥50% PSA decline - Ipilimumab: 23% - Ipilimumab + radiation: 14.6% - Expansion cohort: 16%	Treatment-related CTCAE grade 3-4 - Ipilimumab: 50% - Ipilimumab + radiation: 39% - Expansion cohort: 32%
Madan et al (2012) ²⁷ , phase I	Prostate: mCRPC, chemotherapy naïve (criteria changed after first 6 patients enrolled who had received chemotherapy)	- Ipilimumab 1 mg/kg IV Q3W (n = 3) - Ipilimumab 3 mg/kg IV Q3W (n = 6) - Ipilimumab 5 mg/kg IV Q3W (n = 6) - Ipilimumab 10 mg/kg IV Q3W (n = 15) - Each patient also received recombinant PSA-Tricom 2 × 10⁸ units subcut day 1 + monthly boosts of 1 × 10⁹ units beginning day 15 + sargramostim subcut ×4 days beginning each day of vaccine	Median PFS (RECIST) - Overall: 3.9 months - P = 0.19 between dose levels - Chemotherapy naïve: 5.9 months - Chemotherapy pretreated: 2.4 months	PSA decline - Any PSA decline: 50% >50% PSA decline: 25% Median OS - Overall: 34.4 months - P = 0.06 between dose levels	CTCAE grade 3-4 1 mg/kg + vaccine: 0% 3 mg/kg + vaccine: 28% 5 mg/kg + vaccine: 53% 10 mg/kg + vaccine: 46%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Fong et al (2009) ²⁸ , phase I	Prostate: mCRPC, chemotherapy naïve	- Ipilimumab 0.5 mg/kg Q4W x4 (n = 3) - Ipilimumab 1.5 mg/kg x1 then 0.5 mg/kg Q4W x3 (n = 6) - Ipilimumab 1.5 mg/kg Q4W x4 (n = 6) - Ipilimumab 3 mg/kg x1 then 1.5 mg/kg Q4W x3 (n = 3) - Ipilimumab 3 mg/kg Q4W x4 (n = 6) - Each patient also received sargramostim 250 µg/m² subcut days 1-14 of each cycle	See safety outcomes	>50% PSA decline - Overall: 12.5% (all in the highest dose cohort) RECIST (ORR) - Overall: 4.2% (observed only in highest dose cohort)	CTCAE grade 3 Overall: 21%
Subudhi et al (2014) ²⁵ ; pilot study	Prostate: hormone-naïve, metastatic	Androgen deprivation therapy x8 months + concurrent ipilimumab 10 mg/kg IV Q4W x4 doses (n = 30)	Rate of undetectable PSA at 7 months Overall: 44%	Median time to PSA progression Overall: 330 days	CTCAE grade 3-4 Overall: 44% leading to study closure
Lynch et al (2012) ²⁹ , phase II	NSCLC: stage IIIB-IV or recurrent disease, free from previous systemic therapy	- Concurrent: paclitaxel + carboplatin + ipilimumab Q3W x4 doses → placebo/paclitaxel/carboplatin x2 (n = 70) - Phased: placebo/paclitaxel/carboplatin Q3W x2 doses → ipilimumab + paclitaxel + carboplatin x4 doses (n = 68) - Control: paclitaxel + carboplatin + placebo Q3W x6 cycles (n = 66) - Doses: paclitaxel, 175 mg/m²; carboplatin AUC6; ipilimumab, 10 mg/kg - Maintenance therapy in responders: ipilimumab or placebo Q3W	Median PFS (irRC) - Concurrent: 5.5 months - Phased: 5.7 months - Control: 4.6 months - HR = 0.87; 95% CI = 0.59-1.28; P = 0.23 for phased vs control; - HR = 0.99; 95% CI = 0.67-1.46; P = 0.48 for concurrent vs control	Median PFS (WHO) - Concurrent: 4.11 months - Phased: 5.13 months - Control: 4.21 months - HR = 0.69; 95% CI = 0.48-1; P = 0.02 for phased vs control - HR = 0.88; 95% CI = 0.61-1.27; P = 0.25 for concurrent vs control Median OS - Concurrent: 9.7 months - Phased: 12.2 months - Control: 8.3 months - P = 0.23; 0.48 for comparisons of phased and concurrent with control, respectively	CTCAE grade 3-4 - Concurrent: 41%, 20% irAEs - Phased: 39%, 15% irAEs - Control: 37%, 6% irAEs Discontinuation as a result of adverse events - Concurrent: 10% - Phased: 6% - Control: 5%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Reck et al (2013) ³⁰ ; phase II	SCLC: treatment naïve, extensive stage (all secondary endpoints of primary study, which included NSCLC)	- Concurrent as above Lynch et al (n = 43) - Phased as above Lynch et al (n = 42) - Control as above Lynch et al (n = 45) - Maintenance therapy in responders: ipilimumab or placebo Q3W	Median PFS (irRC, WHO) - Concurrent: 5.7, 3.9 months - Phased: 6.4, 5.2 months - Control: 5.3, 5.2 months - HR = 0.64; 95% CI = 0.4-1.02; P = 0.03 for phased vs control per irRC - HR = 0.75; 95% CI = 0.48-1.19; P = 0.11 for concurrent vs control per irRC	Median OS - Concurrent: 9.1 months - Phased: 12.5 months - Control: 10.5 months - P = 0.13, 0.41 for comparisons of phased and concurrent with control, respectively - ORR(irRC, WHO) - Concurrent: 49%, 33% - Phased: 71%, 57% - Control: 53%, 49% - P = not significant for all	CTCAE grade 3-4 - Concurrent: 43%, 21% irAEs - Phased: 50%, 17% irAEs - Control: 30%, 9% irAEs Discontinuation as a result of adverse events - Concurrent: 7% - Phased: 5% - Control: 9%
Yang et al (2007) ³¹ ; phase II	Renal cell carcinoma: metastatic, clear cell	- Ipilimumab 3 mg/kg $\times$ 1 $\rightarrow$ 1 mg/kg Q3W (n = 21) - Ipilimumab 3 mg/kg IV Q3W (n = 40)	ORR (RECIST) 3 $\rightarrow$ 1 mg/kg: 4.7% 3 mg/kg: 12.5%	Association of ORR with irAE in 3-mg/kg arm - Responders: 100% - Nonresponders: 0% - P = 0.009 Not reported	CTCAE grade 3+ 3 $\rightarrow$ 1 mg/kg: 14% (all irAEs) 3 mg/kg: 43% CTCAE grade 3-4 irAEs - Overall: 11%
Royal et al (2010) ³² ; phase II	Pancreatic: locally advanced or metastatic ductal adenocarcinoma	Ipilimumab 3 mg/kg IV Q3W $\times$ 4 doses per course, maximum 2 courses (n = 27, 20 metastatic, 7 locally advanced)	ORR (RECIST) Overall: 0%		
Ansell et al (2009) ³³ ; phase I	Non-Hodgkin lymphoma: B-cell, relapsed or refractory	- Ipilimumab 3 mg/kg IV $\times$ 1, then 1 mg/kg IV QM $\times$ 3 (n = 12) - Ipilimumab 3 mg/kg IV QM $\times$ 4 (n = 6)	Maximum tolerated dose 3 mg/kg	ORR (Cheson) Overall: 11%	CTCAE grade 3 Overall: 44%
Davids et al (2014) ³⁴ ; phase I	Hematological malignancy: relapsed after allogeneic stem cell transplant	- Ipilimumab 3 mg/kg IV Q3W $\times$ 4 doses (n = 6) - Ipilimumab 10 mg/kg IV Q3W $\times$ 4 doses (n = 7) - Patients were continued on maintenance dosing Q12W $\times$ 1 year	Maximum tolerated dose Not reached	Incidence of clinical benefit - Overall: 36.4% 6-Month OS - Overall: 65%	Incidence of graft-versus host disease - Acute: 0% - Chronic: 7.7% - Incidence of irAEs - Overall: 15.4%

(continued)

Table 1. (continued)

Study	Patient Population/ Neoplasm	Interventions and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Bashey et al (2009) ³⁵ ; phase I	Relapsed after allogeneic stem cell transplant	- Ipilimumab 0.1 mg/kg IV x1 (n = 4) - Ipilimumab 0.33 mg/kg IV x1 (n = 3) - Ipilimumab 0.66 mg/kg IV x1 (n = 4) - Ipilimumab 1 mg/kg IV x1 (n = 3) - Ipilimumab 3 mg/kg IV x1 (n = 15)	- Maximum tolerated dose - Not reached	- ORR (criteria not reported) - Overall: 10% - Median OS from time of ipilimumab - Overall: 24.7 months 9 Patients received a donor-lymphocyte infusion after progression after 1 dose of ipilimumab	- Incidence of grade 3-4 graft versus host disease - Overall: 0% - Incidence of irAEs - Overall: 14% - CTCAE grade 3-4 - Overall: 28%
Merchant et al (2012) ³⁶ ; phase I	Pediatric: advanced solid tumors (sarcoma, melanoma, neuroblastoma, renal cell carcinoma)	- Ipilimumab 1 mg/kg IV Q3W x4 doses - Ipilimumab 3 mg/kg IV Q3W x4 doses - Ipilimumab 5 mg/kg IV Q3W x4 doses - Ipilimumab 10 mg/kg IV Q3W x4 doses - n = 21, Total - Patients were continued on maintenance Q12W	- Maximum tolerated dose - Ipilimumab 5 mg/kg	- Stable disease - Overall: 23.8%	- CTCAE grade 3-4 5 mg/kg: 16.7% 10 mg/kg: 66%

Abbreviations: AUC, area under the curve; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; DTIC, dacarbazine; HR, hazard ratio; irAEs, immune-related adverse events; IV, intravenous; mCRPC, metastatic castrate resistant prostate cancer; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small-cell lung cancer; WHO, World Health Organization response criteria.

randomized 3:1:1 to receive either an induction course of ipilimumab plus a glycoprotein 100 (gp100) vaccine, ipilimumab plus placebo, or gp100 plus placebo. Ipilimumab was administered as 3 mg/kg Q3W for 4 doses. Patients with other active malignancies, ocular melanoma, previous vaccine or anti-CTLA-4 therapy, autoimmune disease, active brain metastases, or concomitant immunosuppressants were excluded. The original primary endpoint of this trial was overall response rate (ORR) per modified World Health Organization (WHO) criteria but later amended to OS on the basis of evolving phase II data. Key secondary endpoints included a comparison of OS between monotherapy arms and the 2 ipilimumab groups, ORR, the duration of response (DOR), and progression-free survival (PFS). Ipilimumab significantly decreased the risk of disease progression or death compared with gp100, and combination therapy provided no additional benefit (Table 1). Grade 3 to 4 irAEs occurred in 10% to 15% of patients treated with ipilimumab. There were 12 deaths related to the study drugs in the ipilimumab arms, 7 of which were associated with irAEs. Two deaths attributed to the study drug occurred in the gp100 monotherapy arm.⁶ Notably, if patients relapsed after at least 3 months of remission, they were offered reinduction with their initial treatment regimen, of which 68% versus 0% remained stable on ipilimumab therapy versus gp100 monotherapy. This trial showed that ipilimumab at a dose of 3 mg/kg Q3W for 4 doses produced a durable OS, with 60% of patients in the ipilimumab monotherapy group maintaining an objective response for at least 2 years. Additionally, there was a benefit of retreatment in patients who initially benefited from ipilimumab. This benefit was reconfirmed in a follow-up study which showed that 61% of patients retreated with ipilimumab were alive at 2 years.⁷ Some limitations to the trial were the inclusion of previously treated patients only and not reporting post-ipilimumab therapies.

Ipilimumab was also studied in treatment-naïve patients with stage III to IV unresectable melanoma in a multinational, randomized, double-blind, phase III study.⁸ Patients were randomized 1:1 to receive either ipilimumab 10 mg/kg plus dacarbazine (DTIC) 850 mg/m² or DTIC 850 mg/m² plus placebo at weeks 1, 4, 7, and 10, each followed by DTIC Q3W through week 22 (induction phase). Patients with stable disease or an objective response, with no DLTs, were allowed to receive additional doses of ipilimumab or placebo Q12W until disease progression, development of toxicities, or the end of the study. Patients were allowed to receive prior adjuvant therapy, but those on concomitant immunosuppressants, with ocular melanoma, or with brain metastases were not allowed. Patients were stratified according to metastatic stage, study site, and performance status. The primary endpoint was OS. Secondary endpoints included PFS and ORR per modified WHO criteria, disease control, time to response, DOR, and safety. Ipilimumab

significantly decreased the risk of disease progression or death and increased response rate and DOR compared with DTIC monotherapy (Table 1). However, the rate of grade 3 to 4 adverse drug events (ADRs) was more than twice as high with combination therapy, but no deaths were reported.⁸ Survival outcomes similar to that in the aforementioned trial with increased toxicity limited the adoption of this treatment strategy. These results were confirmed in a long-term follow-up of patients in this study which showed a 5-year OS rate of 18.2% versus 8.8% (ipilimumab + DTIC vs placebo + DTIC, respectively, $P = 0.002$).⁹ The results from the above phase III trials are similar to results experienced in earlier trials involving melanoma in similar patients.¹⁰⁻¹⁷

A recent meta-analysis of 1861 patients across 12 clinical trials of ipilimumab in melanoma showed a median OS of 11.4 months across all patients (13.5 months in treatment-naïve and 10.7 months in pretreated patients), with a median follow-up of 11 months.¹⁸ The 3-year survival was 22% across all studies. In a secondary analysis of 4864 patients in expanded access programs, including those with brain metastases and noncutaneous melanoma, the median OS was 9.5 months. In both analyses, the Kaplan-Meier OS curve plateaued around year 3 and extended up to 10 years in some patients, indicating a low risk of death in patients who reached this milestone. This meta-analysis confirmed the durable response of ipilimumab in melanoma but did not examine safety outcomes.¹⁸

Ipilimumab revolutionized the treatment landscape in melanoma.¹⁹ It has also been studied in the adjuvant setting,^{20,21} in patients with brain metastases,²² and in metastatic uveal melanoma.²³ Ipilimumab has been evaluated in various other malignancies, including prostate cancer,²⁴⁻²⁸ non-small-cell lung cancer (NSCLC),²⁹ small-cell lung cancer,³⁰ metastatic renal cell carcinoma (mRCC),³¹ pancreatic cancer,³² non-Hodgkin lymphoma,³³ relapse after hematopoietic cell transplantation,^{34,35} and pediatric solid tumors.³⁶ The specifics of these trials are summarized in Table 1.

Pembrolizumab (Keytruda, Lambrolizumab, MK-3475, SCH 900475)

Pembrolizumab (formerly lambrolizumab) is a selective humanized IgG4- κ monoclonal antibody that inhibits PD-1 receptors (Figure 1). It was FDA approved in September 2014 via accelerated approval for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Approval was based on ORR and not survival. The FDA-approved dose is 2 mg/kg IV over 30 minutes Q3W until disease progression or unacceptable toxicity.³⁷ Major DLTs are immune-mediated and detailed in a separate section.

The phase 1 clinical trial, KEYNOTE-001, examined the safety and efficacy of 3 dosing strategies: 10 mg/kg IV Q2W, 10 mg/kg IV Q3W, and 2 mg/kg IV Q3W (Table 2).³⁸ Treatment was continued until disease progression or unacceptable toxicity. The primary outcome of the study was safety. The secondary outcome was ORR as assessed by investigator-reported immune-related response criteria (irRC) and by independent central review per the Response Evaluation Criteria in Solid Tumors (RECIST). Eligible patients were adults with measurable metastatic or locally advanced unresectable melanoma who previously received ipilimumab or no more than 2 lines of therapy regardless of BRAF mutation status. Only 7% of patients previously received a BRAF inhibitor. Patients with ocular melanoma, prior PD-1 or PD-L1 therapy, autoimmune diseases, active infections, or concurrent immunosuppressants were excluded. The ORR was highest in the dose-dense, dose-intense group at the expense of higher incidence of grade 3 to 4 ADRs, although patients stayed on therapy approximately twice as long in this group (40.1 weeks for 10 mg/kg Q2W vs 20.6 weeks for 10 mg/kg Q3W vs 18.1 weeks for 2 mg/kg Q3W). Two patients in the 10 mg/kg Q2W arm experienced grade 3 to 4 kidney failure or rash, constituting the DLTs. Efficacy was not affected by previous treatment.³⁸ In an updated analysis, median PFS was 36 weeks, 6-month OS was 89%, 12-month OS was 81%, and ORR was 41%.³⁹ Median OS and DOR were not reached.³⁹

An open-label, international, multicenter expansion cohort of KEYNOTE-001 was also conducted (Table 2).⁴⁰ Eligible patients included adults with measurable, unresectable or metastatic melanoma who progressed per irRC after treatment with at least 2 doses of ipilimumab and were previously treated with a BRAF and/or MEK inhibitor if BRAF mutation positive. The primary outcome was ORR assessed by investigator-reported irRC and by independent central review per RECIST. Secondary outcomes included DOR, PFS, and OS. Patients with a history of serious or life-threatening irAEs from ipilimumab, prior PD-1 or PD-L1 therapy, autoimmune diseases, active infections, or concurrent immunosuppressants were excluded. Patients were randomized to either pembrolizumab 2 mg/kg IV Q3W or 10 mg/kg IV Q3W. The ORR was similar between groups. The median time to response was 12 weeks. The median DOR was not reached in either group. The median PFS and 1-year OS did not statistically differ between the groups, and the safety profiles were similar. Nearly 82% of patients had a drug-related ADR; however, only 12% were grade 3 to 4. The most common ADRs were fatigue, rash, and pruritus.⁴⁰ The expansion study confirmed that pembrolizumab is beneficial in ipilimumab refractory patients and that the benefit could be seen at a lower dose of pembrolizumab. A further expansion cohort of 244 patients for the KEYNOTE-001 study confirmed earlier findings for the 10 mg/kg Q3W dosing schedule and showed no benefit in dose density with

a 10 mg/kg Q2W dosing schedule.⁴¹ The number of patients exposed to BRAF and/or MEK inhibitors (20%) was higher in this study. Both studies used RECIST and irRC, strengthening their validity, but were limited by their lack of a comparator arm.

Pembrolizumab is being compared against chemotherapy, ipilimumab, and in combination with ipilimumab in melanoma; results of these trials could significantly change the current melanoma treatment landscape.⁵ Pembrolizumab has also been studied in clinical trials in squamous and non-squamous NSCLC,^{42,43} recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction,⁴⁴ classical Hodgkin lymphoma (cHL),⁴⁵ urothelial tract carcinoma,⁴⁶ and head and neck cancer⁴⁷ (Table 2). Though observed response rates are promising, results are premature, and trials are single armed with small numbers.

Nivolumab (Opdivo, MDX-1106, BMS-936558, ONO-4538)

Nivolumab is a human IgG4- κ monoclonal antibody that binds and inhibits PD-1 receptors (Figure 1). It received FDA approval in December 2014 via accelerated approval for patients with unresectable or metastatic melanoma with disease progression after ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive. Approval in melanoma was based on ORR and not survival. It was also approved in March 2015 after fast-track designation by the FDA for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. Approval in squamous NSCLC was based on OS benefit. The FDA-approved dose is 3 mg/kg IV over 60 minutes Q2W until disease progression or unacceptable toxicity. Major ADRs are immune-mediated and detailed in a separate section; however, no DLTs were observed in monotherapy clinical trials.⁴⁸

CheckMate-037 (Table 3), a phase III, open-label trial, examined the safety and efficacy of nivolumab in patients with advanced melanoma whose disease progressed after treatment with ipilimumab and a BRAF inhibitor, if the tumor was BRAF V600 mutation positive.^{48,49} Patients were randomized 2:1 to either nivolumab 3 mg/kg IV Q2W or investigator's choice chemotherapy (ICC). Patients were stratified by PD-L1 expression, BRAF status, and best response to prior anti-CTLA-4 therapy. Treatment continued until disease progression or unacceptable toxicity. Primary endpoints were ORR and OS. Patients with ocular melanoma, autoimmune disease, concurrent systemic immunosuppression, unknown BRAF status, prior PD-1 therapy, active brain metastasis, or a history of grade 3 to 4 ipilimumab-related ADRs that had not resolved or were not controlled within 12 weeks of starting treatment were excluded. A single-arm, noncomparative planned interim analysis evaluated efficacy in the first 120 patients who

Table 2. Summary of Clinical Trials for Pembrolizumab.

Study	Patient Population/ Neoplasm	Intervention and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Hamid et al (2013) ³⁸ ; KEYNOTE-001; phase I	Melanoma: measurable metastatic and locally advanced unresectable	- Pembrolizumab 10 mg/kg IV Q2W (n = 57) - Pembrolizumab 10 mg/ kg IV Q3W (n = 56) - Pembrolizumab 2 mg/ kg IV Q3W (n = 22)	Confirmed ORR (RECIST, irRC) - Overall: 38%, 37% 10 mg/kg IV Q2W: 52%, 56% 10 mg/kg IV Q3W: 27%, 27% 2 mg/kg IV Q3W: 25%, 14%	DOR (months, per RECIST) - Overall: 1.9-10.8 10 mg/kg IV Q2W: 1.9- 10.8 10 mg/kg IV Q3W: 2.6-8.3 2 mg/kg IV Q3W: 2.1-5.5	Any CTCAE - Overall: 79% 10 mg/kg IV Q2W: 91% 10 mg/kg IV Q3W: 73% 2 mg/kg IV Q3W: 64% CTCAE grade 3+ - Overall: 13% 10 mg/kg IV Q2W: 23% 10 mg/kg IV Q3W: 4% 2 mg/kg IV Q3W: 9% Not reported
Daud et al (2014) ³⁹ ; phase I	Melanoma: measurable metastatic and locally advanced unresectable	- Pembrolizumab 10 mg/ kg IV Q2W (n = 57) - Pembrolizumab 10 mg/ kg IV Q3W (n = 56) - Pembrolizumab 2 mg/ kg IV Q3W (n = 22)	Median PFS (RECIST): - Overall: 36 weeks 6-months OS: - Overall: 89% 12-months OS: - Overall: 81% Median OS - Overall: not reached	Median DOR (RECIST): - Overall: not reached. ORR (RECIST): - Overall: 41%	
Robert et al (2014) ⁴⁰ ; KEYNOTE-001 Expansion Cohort; phase I	Melanoma: measurable/ unresectable; prior treatment with ipilimumab	- Pembrolizumab 2 mg/kg IV Q3W (n = 89) - Pembrolizumab 10 mg/kg IV Q3W (n = 84)	ORR (RECIST, irRC) - Overall: 26% 2 mg/kg Q3W: 26%, 27% 10 mg/kg Q3W: 26%, 32% - P = 0.96, 0.46	24-Week PFS (RECIST, irRC): 2 mg/kg Q3W: 45%, 57% 10 mg/kg Q3W: 37%, 57% Median PFS (RECIST) 2 mg/kg Q3W: 22 weeks 10 mg/kg Q3W: 14 weeks - HR = 0.84; 95% CI = 0.57-1.23 Median PFS (irRC) 2 mg/kg Q3W: 31 weeks 10 mg/kg Q3W: 35 weeks - HR = 1.12; 95% CI = 0.73-1.72 1-Year OS 2 mg/kg Q3W: 58% 10 mg/kg Q3W: 63% - HR = 1.09; 95% CI = 0.68-1.75 Median DOR (RECIST) - Not reached in either group	Any CTCAE 2 mg/kg: 82% 10 mg/kg: 82% CTCAE grade 3+ 2 mg/kg: 15% 10 mg/kg: 8%

(continued)

Table 2. (continued)

Study	Patient Population/ Neoplasm	Intervention and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Robert et al (2014) ⁴¹ ; KEYNOTE-001 expansion; phase I	Melanoma: measurable/ unresectable	- Pembrolizumab 10 mg/kg IV Q3W (n = 121) - Pembrolizumab 10 mg/kg IV Q2W (n = 123)	ORR (RECIST) 10 mg/kg IV Q3W: 28% 10 mg/kg IV Q2W: 33% - P = 0.419 - Ipilimumab-naïve: 33% - Ipilimumab-treated: 28%	24-Week PFS rate (RECIST) 10 mg/kg IV Q3W: 43% 10 mg/kg IV Q2W: 47% - HR = 1.19; 95% CI = 0.85-1.66; P = 0.295	CTCAE grade 3-4 10 mg/kg IV Q3W: 12% 10 mg/kg IV Q2W: 15% Discontinuations as a result of any drug-related AE 10 mg/kg IV Q3W: 1% 10 mg/kg IV Q2W: 3% Not reported
Gandhi et al ⁴² ; (2014); KEYNOTE-025; phase I	NSCLC: relapsed	Pembrolizumab 10 mg/kg IV; Q3W (n = 38)	ORR (RECIST/irRC) - Overall: 24% (irRC) - High tumor PD-L1 expression: 57%/67% - Low tumor PD-L1 expression: 5%/0%	6-Month PFS rate (irRC) - High tumor PD-L1 expression: 67% - Low tumor PD-L1 expression: 11% - HR = 0.22; 95% CI = 0.07-0.67; P = 0.004 6-Month OS rate - High tumor PD-L1 expression: 89% - Low tumor PD-L1 expression: 33% - HR = 0.32; 95% CI = 0.1-0.99; P = 0.024	CTCAE grade 3+ Overall: 9% (pneumonitis most common)
Garon et al ⁴³ ; (2014); KEYNOTE-001 Expansion Cohort; phase I	NSCLC: relapsed and treatment naïve	- Pembrolizumab 10 mg/kg IV Q2W (n = 115) - Pembrolizumab 10 mg/kg IV Q3W (n = 141) - Pembrolizumab 2 mg/kg IV Q3W (n = 6)	Not reported	ORR (RECIST, irRC) 10 mg/kg Q2W: 21%, 22% 10 mg/kg Q3W: 21%, 22% 2 mg/kg Q3W: 33%, 67% - Squamous: 18%, 25% - Nonsquamous: 23%, 23% - Treatment naïve: 26%, 47% - Previously treated: 20%, 18%	CTCAE grade 3+ Overall: 9% (pneumonitis most common)
Muro et al (2014) ⁴⁴ ; phase I	Gastric: Recurrent/ metastatic adenocarcinoma of the stomach or gastroesophageal junction	Pembrolizumab 10 mg/kg IV Q2W (n = 39)	ORR (RECIST) - Asia Pacific: 32% - Rest of world: 30%	Median DOR (RECIST) Not reached PD-L1 positivity was positively correlated with improved ORR (P = 0.071) and PFS (P = 0.032) compared with PD-L1 negativity	Any CTCAE - Overall: 26% CTCAE grade 3+ - Overall: 8%

(continued)

Table 2. (continued)

Study	Patient Population/ Neoplasm	Intervention and Arms (n)	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Moskowitz et al (2014) ⁴⁵ ; KEYNOTE-003; phase I	Hodgkin lymphoma: relapsed/refractory	Pembrolizumab 10 mg/kg IV Q2W (n = 15)	ORR (Cheson 2007) Overall: 53% (CR: 20% + PR: 33%)	Not reported	Any CTCAE - Overall: 33% - Respiratory event: 20% - Thyroid: 20% - CTCAE grade 3+ - Overall: 7%
Plimack et al (2014) ⁴⁶ ; phase I	Urothelial: advanced carcinoma of the renal pelvis, ureter, bladder, or urethra	Pembrolizumab 10 mg/kg IV Q2W (n = 33)	ORR (RECIST) Overall: 24%	Median DOR (RECIST) - Not reached Median PFS (RECIST) - Overall: 8.6 weeks	Any CTCAE - Overall: 61% - CTCAE grade 3+ - Overall: 12%
Chow et al (2014) ⁴⁷ ; phase I	Head and neck: HPV+ and HPV–	Pembrolizumab 10 mg/kg IV Q2W (n = 20)	ORR (RECIST) - Overall: 20% - PD-L1 positive: 50% - PD-L1 positivity was positively correlated with improved ORR ($P = 0.018$) and PFS ($P = 0.024$) compared to PD-L1 negativity	Median PFS (RECIST) - Overall: 9.3 weeks - HPV+: 17.2 weeks - HPV–: 8.1 weeks Median OS - Overall: 12.6 months - HPV+: not reached - HPV–: 9.5 months	Any CTCAE - Overall: 58% - CTCAE grade 3+ - Overall: 17%

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; HPV, human papilloma virus; irRC, immune-related response criteria; IV, intravenous;

NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

Table 3. Summary of Clinical Trials for Nivolumab.

Study	Patient Population/ Neoplasm	Intervention	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Weber et al (2015) ⁴⁹ ; CheckMate-037; phase III	Melanoma: relapsed or refractory, advanced	- Nivolumab 3 mg/kg IV Q2W (n = 268, 120 included in this analysis) - ICC: DTIC 1000 mg/m² IV or carboplatin IV AUC6 Q3W + paclitaxel 175 mg/m² IV Q3W (n = 102, 47 included in this analysis)	ORR (RECIST) Nivolumab: 32% vs ICC: 11% OS: not reported	Median PFS (RECIST) - Nivolumab: 4.7 months - ICC: 4.2 months - HR = 0.82, 99.9% CI = 0.32-2.05 Median time to response - Nivolumab: 2.1 months - ICC: 3.5 months DOR - Nivolumab: not reached - ICC: 3.5 months	CTCAE grade 3-4 - Nivolumab: 9% - ICC: 31% Discontinuations as a result of any drug-related adverse event - Nivolumab: 3% - ICC: 7%
Topalian et al (2012, 2014) ^{50,51} ; phase I	Melanoma: relapsed or refractory, advanced	- Nivolumab 0.1 mg/kg IV Q2W (n = 17) - Nivolumab 0.3 mg/kg IV Q2W (n = 18) - Nivolumab 1 mg/kg IV Q2W (n = 35) - Nivolumab 3 mg/kg IV Q2W (n = 17) - Nivolumab 10 mg/kg IV Q2W (n = 20)	ORR (RECIST) - Overall: 30.8% 0.1 mg/kg IV Q2W: 35.3% 0.3 mg/kg IV Q2W: 27.8% 1 mg/kg IV Q2W: 31.4% 3 mg/kg IV Q2W: 41.2% 10 mg/kg IV Q2W: 20%	Median PFS (RECIST) - Overall: 3.7 months Median OS - Overall: 16.8 months I- and 2-Year PFS rate (RECIST) - Overall: 36%, 27% I- and 2-Year OS rate - Overall: 62%, 43% Median DOR - Overall: 2 years	Any CTCAE - Overall: 54% CTCAE grade 3-4 - Overall: 22%
Robert et al ⁵² (2014); CheckMate-066; phase III	Melanoma: treatment-naïve, metastatic	- Nivolumab 3 mg/kg IV Q2W + DTIC-matched placebo IV Q3W (n = 210) - DTIC 1000 mg/m² IV Q3W + nivolumab-matched placebo IV Q2W (n = 208)	Median OS - DTIC: 10.8 months - Nivolumab: not reached - HR = 0.42; 99.79% CI = 0.25-0.73; P < 0.001 I-Year OS - DTIC: 42.1% - Nivolumab: 72.9%	Median PFS (RECIST) - DTIC: 2.2 months - Nivolumab: 5.1 months - HR = 0.43; 95% CI = 0.34-0.56; P < 0.001 ORR (RECIST) - DTIC: 14% - Nivolumab: 40% - OR = 4.06; 95% CI = 2.52-6.54; P < 0.001 OS based on PD-L1 status - No difference	Any CTCAE: - Nivolumab: 74.3% - DTIC: 75.6% CTCAE grade 3-4 - Nivolumab: 11.7% - DTIC: 17.6% Treatment discontinuation as a result of adverse events - Nivolumab: 6.8% - DTIC: 11.7% No deaths were attributed to drug toxicity.

(continued)

Table 3. (continued)

Study	Patient Population/ Neoplasm	Intervention	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Rizvi et al (2015) ⁵³ ; CheckMate-063; phase II	NSCLC: stage IIIB-IV, squamous progression or recurrence after both platinum-doublet and at least 1 additional treatment	Nivolumab 3 mg/kg IV Q2W (n = 117)	ORR (RECIST) 14.5%	6-Month PFS (RECIST) 26% 1-Year PFS (RECIST) 20% Median PFS (RECIST) 1.9 months Median OS 8.2 months 1-year OS 41% ORR (RECIST) per PD-LI status - PD-LI positive: 24% - PD-LI negative: 14% Median time to response 3.3 months	Any CTCAE: - Overall: 74% CTCAE grade 3-4 - Overall: 17% Adverse events that led to discontinuation - Overall: 12% There were 2 treatment-related deaths.
CheckMate-017 ⁴⁸ ; phase III	NSCLC: metastatic, squamous, progressed on or after one platinum-doublet	- Nivolumab 3 mg/kg IV Q2W (n = 135) - Docetaxel 75 mg/m² IV Q3W (n = 137)	Interim median OS - Nivolumab: 9.2 months - Docetaxel: 6 months - HR = 0.59; 95% CI = 0.44-0.79; P = 0.00025	Not reported	Not reported
Getting et al ⁵⁵ (2014); phase I	NSCLC: chemotherapy naïve, advanced, squamous (n = 9) and nonsquamous (n = 11)	Nivolumab 3 mg/kg IV Q2W (n = 20)	ORR (RECIST) - Squamous: 22% - Nonsquamous: 36% Median PFS (RECIST) - Squamous: 15.1 weeks - Nonsquamous: 45.6 weeks	Median DOR - Not reached. ORR per PD-LI status - PD-LI positive: 67% - PD-LI negative: 0% Unknown: 0%	Any CTCAE - Overall: 85% CTCAE grade 3-4 - Overall: 15%
Brahmer et al ⁵⁶ (2014); phase I	NSCLC: previously treated, advanced, squamous (n = 54) and nonsquamous (n = 74)	- Nivolumab 1 mg/kg Q2W (n = 33) - Nivolumab 3 mg/kg Q2W (n = 27) - Nivolumab 10 mg/kg Q2W (n = 59)	Median OS 1 mg/kg Q2W: 9.2 months 3 mg/kg Q2W: 14.9 months 10 mg/kg Q2W: 9.2 months Squamous: 9.2 months	ORR (RECIST) - Overall: 17% Median DOR 17 Months Median PFS (RECIST) and OS per PD-LI status (months) - PD-LI positive: 3.6, 7.8 - PD-LI negative: 1.8, 10.5	CTCAE grade 3-4 Overall: 3%

(continued)

Table 3. (continued)

Study	Patient Population/ Neoplasm	Intervention	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Gettinger et al ⁵⁷ (2014); phase I	NSCLC: chemotherapy naïve, advanced, squamous, nonsquamous, and mixed histology, and EGFR mutant	- Squamous: nivolumab 10 mg/kg IV Q3W + gemcitabine 1250 mg/m² + cisplatin 75 mg/m² - Nonsquamous: nivolumab 10 mg/kg IV Q3W + pemetrexed 500 mg/m² + cisplatin 75 mg/m² - Mixed: nivolumab 5 or 10 mg/kg IV Q3W + paclitaxel 200 mg/m² + carboplatin AUC6 - n = 56 for platinum-doublet therapy - EGFR mutant: nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg po daily (n = 21)	ORR (RECIST) - Nivolumab + platinum doublet: 33%-47% - Nivolumab + erlotinib: 19%	24-Week PFS rate (RECIST) - Nivolumab + platinum doublet: 38%-71% - Nivolumab + erlotinib: 51% 1-Year OS rate - Nivolumab + platinum doublet: 50%-87%	CTCAE grade 3-4 - Nivolumab + platinum doublet: 45% - Nivolumab + erlotinib: 24%
Hamanishi et al ⁵⁸ (2014); phase II	Ovarian: advanced or relapsed, platinum resistant	- Nivolumab 1 mg/kg IV Q2W (n = 10) - Nivolumab 3 mg/kg IV Q2W (n = 5)	ORR (RECIST) - Overall: 23% 1 mg/kg IV Q2W: 20% 3 mg/kg IV Q2W: 33% Median PFS (RECIST) 0.3 mg/kg IV Q3W: 2.7 months 2 mg/kg IV Q3W: 4 months 10 mg/kg IV Q3W: 4.2 months P = 0.9 No dose response relationship was observed for PFS	Disease control rate - Overall: 54% 1 mg/kg IV Q2W: 50% 3 mg/kg IV Q2W: 67% ORR (irRC) 0.3 mg/kg IV Q3W: 20% 2 mg/kg IV Q3W: 22% 10 mg/kg IV Q3W: 20% - P = 1 Median DOR 0.3 mg/kg: 15.7 months - Not reached for other groups Median OS 0.3 mg/kg: 8.2 months - Not reached for other groups	One patient had a severe adverse drug reaction with fever, disorientation, and gait disturbance Any CTCAE - Overall: 73% CTCAE grade 3-4 0.3 mg/kg IV Q3W: 5% 2 mg/kg IV Q3W: 17% 10 mg/kg IV Q3W: 13% Adverse events that led to discontinuation 0.3 mg/kg IV Q3W: 7% 2 mg/kg IV Q3W: 2% 10 mg/kg IV Q3W: 7%
Motzer et al ⁵⁹ (2014); phase II	Renal cell carcinoma: metastatic, clear cell, refractory to at least 1 line of antiangiogenic therapy in metastatic setting	- Nivolumab 0.3 mg/kg IV Q3W (n = 60) - Nivolumab 2 mg/kg IV Q3W (n = 54) - Nivolumab 10 mg/kg IV Q3W (n = 54)	Median OS 0.3 mg/kg IV Q3W: 4.2 months 2 mg/kg IV Q3W: 4.2 months 10 mg/kg IV Q3W: 4.2 months P = 0.9 No dose response relationship was observed for PFS	Disease control rate - Overall: 54% 1 mg/kg IV Q2W: 50% 3 mg/kg IV Q2W: 67% ORR (irRC) 0.3 mg/kg IV Q3W: 20% 2 mg/kg IV Q3W: 22% 10 mg/kg IV Q3W: 20% - P = 1 Median DOR 0.3 mg/kg: 15.7 months - Not reached for other groups Median OS 0.3 mg/kg: 8.2 months - Not reached for other groups	One patient had a severe adverse drug reaction with fever, disorientation, and gait disturbance Any CTCAE - Overall: 73% CTCAE grade 3-4 0.3 mg/kg IV Q3W: 5% 2 mg/kg IV Q3W: 17% 10 mg/kg IV Q3W: 13% Adverse events that led to discontinuation 0.3 mg/kg IV Q3W: 7% 2 mg/kg IV Q3W: 2% 10 mg/kg IV Q3W: 7%
Drake et al ⁶⁰ (2013); phase I	Renal cell carcinoma: metastatic, previously treated	- Nivolumab 1 mg/kg (n = 18) - Nivolumab 10 mg/kg (n = 16) - For not more than 12 cycles (4 doses/cycle)	Median OS - Overall: not reached. Median DOR 12.9 Months for both doses, with 50% of responders lasting ≥1 year	24-Week PFS rate 1 mg/kg: 50% 10 mg/kg: 67%	CTCAE grade 3-4 - Overall: 21% - Hypophosphatemia: 6% - Respiratory: 6% Adverse events that led to discontinuation - Overall: 6%

(continued)

Table 3. (continued)

Study	Patient Population/ Neoplasm	Intervention	Primary Endpoint Results	Secondary Endpoint Results	Safety Outcomes
Amin et al ⁶¹ (2014); phase I	Renal cell carcinoma: metastatic, previously treated	- Nivolumab + sunitinib 50 mg po daily x4 weeks on, 2 weeks off (n = 33, including expansion) - Nivolumab + pazopanib 800 mg po daily (n = 20) - Starting dose of nivolumab was 2 mg/ kg IV Q3W (N2), with escalation to 5 mg/kg IV Q3W (N5)	Nivolumab + sunitinib - DLT: none observed - MTD: not reached - N5 expanded with 19 additional patients Nivolumab + pazopanib - DLT: elevated AST/ALT (n = 3) at 2 mg/kg; arm closed.	ORR - Nivolumab + sunitinib: 52% - Nivolumab + pazopanib: 45% 24-Week PFS rate - Nivolumab + sunitinib: 79% - Nivolumab + pazopanib: 55%	CTCAE grade 3-4 - Nivolumab + sunitinib: 82% - Nivolumab + pazopanib: 70% CTCAE grade 3-4 adverse events that led to discontinuation - Nivolumab + sunitinib: 30% - Nivolumab + pazopanib: 20%
Ansell et al (2014) ⁶² ; phase I	Classical Hodgkin lymphoma: relapsed or refractory	Nivolumab 1 mg/kg IV, escalated to 3 mg/kg given week 1 and 4, then Q2W until disease progression or CR or 2 years (n = 23)	See safety outcomes	ORR (Cheson 2007) 87% (95% CI = 66-97) 24-Week PFS rate 86% (95% CI = 62-95) Median OS - Not reached	Any drug-related CTCAE - Overall: 78% Drug-related CTCAE: grade 3 - Overall: 22% No drug-related grade 4 or 5 adverse events.
Brahmer et al ⁶³ (2010); phase I	Solid tumors (prostate, metastatic melanoma, NSCLC, colorectal, and renal cell) with progressive, treatment-refractory disease	- Nivolumab 0.3 mg/kg IV (n = 6) - Nivolumab 1 mg/kg IV (n = 6) - Nivolumab 3 mg/kg IV (n = 6) - Nivolumab 10 mg/kg IV (n = 21)	Maximum tolerated dose Not reached	ORR (RECIST) 0.3 mg/kg: 0% 1 mg/kg: 0% 3 mg/kg: 17% 10 mg/kg: 9.5%	Most common CTCAE grade 2+ - Decreased lymphocyte count: 36% - Lymphopenia: 25.6% - Fatigue: 15.4% - Musculoskeletal events: 15.4%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; DLT, dose-limiting toxicity; DTIC, dacarbazine; EGFR, epidermal growth factor receptor; ICC, investigator's choice chemotherapy; irRC, immune-related response criteria; IV, intravenous; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

received nivolumab and 47 patients who received ICC, with a minimum of 6 months of follow-up. The interim analysis per RECIST by central review showed an ORR of 32% in the nivolumab arm versus 11% in the ICC arm, with a median time to response of 2.1 and 3.5 months, respectively. The median DOR was 3.6 months in the ICC arm and was not reached in the nivolumab arm. Grade 3 to 4 ADRs were less frequent and less commonly led to discontinuation with nivolumab than chemotherapy (Table 3). Median time on therapy was 5.3 months in the nivolumab arm and 2 months in the ICC arm.^{48,49} Results confirm earlier phase I findings.^{50,51} Though only interim results were available, and survival data were premature, CheckMate-037 was the landmark trial that led to the FDA approval of nivolumab.

CheckMate-066 was a phase III randomized, placebo-controlled trial that included patients with untreated, unresectable, stage III or IV BRAF wild-type melanoma (Table 3).⁵² Patients were randomized 1:1 to receive either nivolumab 3 mg/kg IV Q2W with DTIC-matched placebo Q3W or DTIC 1000 mg/m² IV Q3W with nivolumab-matched placebo Q2W. Treatment continued until disease progression or unacceptable toxicity. Treatment beyond progression was permissible at the discretion of the investigator. The primary endpoint of the study was OS and secondary endpoints included PFS, ORR per RECIST, and predictability of PD-L1 expression as a biomarker for OS. The main exclusion criteria were active brain metastases, uveal melanoma, and a history of serious autoimmune disease. Results reported were from an unplanned interim analysis by unblinding and crossover to the nivolumab arm. Treatment with nivolumab significantly decreased the risk of disease progression or death, and ORR was higher than DTIC (Table 3). Time to objective response was 2.1 months in both groups. Further reduction in tumor burden of the target lesion was observed in 17 of 54 patients (31%) who were treated beyond progression in the nivolumab group versus 8 of 49 patients (16%) in the DTIC group. Nivolumab was found to extend OS regardless of PD-L1 status. Common ADRs associated with nivolumab included fatigue, pruritus, and nausea. The incidence of ADRs of any grade was similar between nivolumab and DTIC (74.3% and 75.6%, respectively). Grade 3 to 4 ADRs and discontinuation were more frequent with DTIC. Grade 3 to 4 irAEs occurred in 1% of patients, which included diarrhea and elevated alanine aminotransferase levels.⁵² The CheckMate-066 trial was the first fully reported phase III trial that showed a survival benefit with nivolumab over chemotherapy. Both the CheckMate-066 and -037 studies had an advantage over the pembrolizumab trials in melanoma by having a chemotherapy comparator arm, albeit suboptimal with the advent of ipilimumab, but neither used irRC criteria.

CheckMate-063 was a phase II single-arm trial in patients with stage IIIB to IV squamous NSCLC who had progression or recurrence after both a platinum-doublet and at least

1 additional systemic treatment (Table 3).⁵³ Patients received nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity. Treatment beyond progression was permissible at the discretion of the investigator. The primary endpoint of the study was ORR per RECIST by independent review, and secondary/exploratory endpoints included response per investigator review, PFS, OS, and predictability of PD-L1 expression as a biomarker for ORR. Main exclusion criteria were untreated brain metastases, autoimmune disease, previous ICI therapy, disorders requiring systemic immunosuppressive drugs, HIV positivity, and symptomatic lung disease. Results reported were from an interim analysis. Although the ORR was low at 14.5%, there is currently no standard of care in this third-line setting other than clinical trials or best supportive care.⁵⁴ Nivolumab has also been shown to have benefit in the second-line squamous NSCLC population. The phase III trial CheckMate-017 of nivolumab versus docetaxel for metastatic squamous NSCLC after failure of a platinum doublet was terminated early because of superior OS benefit with nivolumab, and the results have yet to be published outside the prescribing information.⁴⁸ Summaries of NSCLC trials with nivolumab^{53,55-57} are provided in Table 3. Nivolumab appears promising in clinical trials in ovarian cancer,⁵⁸ mRCC,⁵⁹⁻⁶¹ cHL,⁶² and other solid tumors⁶³ (Table 3).

Combination Therapy: Dual Checkpoint Blockade

PD-1 predominantly regulates effector T-cell activity within the tumor microenvironment, whereas CTLA-4 globally regulates T-cell activation.² Combination blockade of PD-1 and CTLA-4 was shown to be synergistic in preclinical melanoma mouse models by increasing infiltration of tumors by CD8+ T-cells and CD4+ effector T-cells and increasing the CD8+/regulatory T-cell ratio relative to single blockade.⁶⁴ In the tumor microenvironment, blockade of either CTLA-4 or PD-1 increases the expression of CTLA-4 on CD4+ effector T-cells and CD8+ T-cells and the expression of PD-1 on CD8+ T-cells but decreases receptor expression on regulatory T-cells. Expression of CTLA-4 and PD-1 as well as cytokine production is higher with combination blockade than single. Of note, triplicate blockade by adding a PD-L1 inhibitor further increased these effects. These changes in the tumor microenvironment shift the effect from dominant suppression to an inflammatory environment permissive for immune-mediated tumor rejection.⁶⁴ A review of combination checkpoint blockade and other immuno-oncology combinations has been recently published.⁶⁵

Four clinical trials have studied the efficacy of dual checkpoint blockade. A phase I study of advanced melanoma patients first demonstrated successful dual blockade with ipilimumab and nivolumab either concurrently or sequentially (ipilimumab before nivolumab).⁶⁶ An ORR of

40% per WHO criteria (65% per irRC) was observed across concurrent cohorts, with an ORR of 53% in patients who received maximally tolerated doses of nivolumab 1 mg/kg and ipilimumab 3 mg/kg.⁶⁶ This exceeds the ORR reported with monotherapy.^{6,50,51} Sequential therapy resulted in an ORR of 20% per WHO criteria (43% per irRC).⁶⁶ Dual blockade had a 53% incidence of generally reversible grade 3 to 4 treatment-related ADRs (93% any grade) that were qualitatively similar to those experienced with ICI monotherapy, albeit markedly increased in frequency (monotherapy grade 3 to 4 incidence: 20% with ipilimumab and 15% with nivolumab).^{6,50,51,66} Updated long-term results show 1- and 2-year survival rates of 82% and 75%, respectively.⁶⁷ High ORRs have been reported in phase I trials of mRCC (43%-48%)⁶⁸ and first-line NSCLC (22%).⁶⁹ Head-to-head trials of dual ICI therapy versus ICI monotherapy are under way.⁵ Of note, no trials of pembrolizumab in combination with ipilimumab have been published.

Pharmacokinetics, Pharmacodynamics, and Considerations for Special Populations Treated With ICIs

Manufacturers do not report specific metabolism and elimination routes for the currently approved ICIs, all of which are IgG κ monoclonal antibodies. It has been suggested that IgG monoclonal antibodies are metabolized via phagocytosis by cells of the reticuloendothelial system.⁷⁰ Patient-specific factors such as antigen concentrations, antigen properties, and protective Fc γ and FcRn receptor expression have been postulated to influence monoclonal antibody pharmacokinetics.⁷⁰ Though direct evidence is lacking, it is possible that phagocytes break down monoclonal antibodies into low-molecular-weight fragments which are renally eliminated.⁷⁰ No clinically important differences in drug clearance were found in patients with renal or mild hepatic impairment, so dose reductions of ICIs are not recommended; however, they have not been studied in patients with moderate to severe hepatic dysfunction.^{4,37,48} Ipilimumab, pembrolizumab, and nivolumab have long half-lives (15.4, 26, and 26.7 days, respectively), with respective clearance rates of 0.4, 0.22, and 0.23 L/d that are unaffected by age or gender.

No formal pharmacokinetic drug-drug interaction studies have been conducted with the ICIs.^{4,37,48} The cytochrome P-450 system is not involved in the direct metabolism of IgG monoclonal antibodies.⁷⁰ However, cytokines may affect CYP450 enzymes.⁷¹ Therefore, caution is advised for CYP450-metabolized drugs with narrow therapeutic indices. Based on the mechanisms of action of ICIs, any drug that could impair T-cell function or impair immune response may negatively affect the efficacy and alter the kinetics of ICIs. For example, immunosuppressants such as methotrexate may

downregulate Fc γ receptors, which protect monoclonal antibodies from phagocyte-mediated metabolism, and potentially affect the clearance of monoclonal antibodies.⁷⁰ Patients on concomitant immunosuppressants, including supraphysiological doses of steroids, were excluded from many of the aforementioned clinical trials.

There are currently no labeled contraindications to ICIs. However, given their mechanism of upregulating the immune system, patients with active autoimmune disease are not optimal candidates for ICI therapy and were excluded from a majority of the aforementioned clinical trials. Patients with a history of solid organ transplant are also not optimal candidates in theory of increased risk of graft rejection with ICI therapy; however, ipilimumab was not associated with increased risk of graft versus host disease after hematopoietic stem cell transplantation.^{34,35} IgG crosses the placenta and is excreted in breast milk; so pregnant or breast-feeding patients are also not optimal candidates for ICI monoclonal antibody therapy.^{4,37,48} Ipilimumab carries a pregnancy category C classification, and pembrolizumab carries a category D.^{4,37} Nivolumab was shown to increase rates of abortion and premature infant death in animal reproduction studies, and women should avoid pregnancy for at least 5 months after the last dose.⁴⁸ The FDA has posted warnings for embryo-fetal toxicity for both PD-1 inhibitors.^{37,48} It is possible that fetal exposure to an anti-PD-1 receptor monoclonal antibody may increase the risk of the fetus developing immune-mediated disorders or of altering the normal immune response.³⁷

Management of IrAEs

IrAEs are the most serious toxicities from ICIs, and the FDA has posted warnings and precautions.^{4,37,48} The frequency, but not the type or quality of irAE, may increase with dose and may vary among different tumor types. The irAEs, which can occur in any organ or tissue, resemble and are treated similarly to graft-versus-host disease in allogeneic stem cell transplant. They are often reversible but can be fatal, and timing of onset varies.^{4,37,48,72} Prompt identification and initiation of effective treatment for irAEs is paramount.⁷³ Counseling patients to immediately report any signs and symptoms of irAEs (Table 4) is important in early detection. Generally, irAEs (except pneumonitis and nephritis) are less frequently observed and less severe in patients treated with nivolumab and pembrolizumab than ipilimumab. In fact, there is an associated Risk Evaluation Mitigation Strategy communication program and black box warning for ipilimumab-related irAEs.⁴ Patients who developed colitis or other irAES had improved response rates and relapse-free survival with ipilimumab.^{8,21,74} However, data from Memorial Sloan Kettering showed that neither the occurrence of irAEs (irrespective of the grade) nor the use

Table 4. Clinical Presentation, Symptomatic Treatment, and Supportive Care Options for Organ-Specific irAEs.^{a,4,37,48,72}

Organ System	Clinical Presentation	Symptomatic Treatment/Supportive Care Options
Gastrointestinal	• Colitis • Diarrhea • Abdominal pain • Blood or mucus in stool • Bowel perforation • Peritoneal signs • Ileus • Liver: abnormal AST, ALT, or total bilirubin • Pancreatitis: increased amylase, lipase, nausea, vomiting, abdominal pain	• Antidiarrheal (loperamide, diphenoxylate/atropine) • Oral hydration • Electrolyte substitution • Budesonide
Integument	• Rash • Pruritus • Psoriasis • Leukocytoclastic vasculitis • Erythema multiforme • Exfoliative dermatitis • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Rash with full thickness dermal ulceration, necrosis, bullous, or hemorrhagic manifestations	• Topical steroids • Urea-containing creams • Antihistamine (diphenhydramine, hydroxyzine hydrochloride)
Nervous	• Neuropathy (motor, sensory) • Unilateral or bilateral weakness • Sensory alterations • Paresthesias • Trouble with ADLs • Meningitis • Encephalitis • Neurosensory hypoacusis • Partial seizures from inflammatory foci • Myasthenic syndrome • Demyelination • Nerve paresis • Guillain-Barré syndrome	Symptom management and supportive care
Endocrine	• Hypophysitis • Hypothyroidism • Hyperthyroidism • Hypopituitarism • Hypogonadism • Autoimmune thyroiditis • Adrenal insufficiency • Fatigue • Headache • Mental status changes • Abdominal pain • Unusual bowel habits • Hypotension • Abnormal serum chemistries • Abnormal thyroid function tests	Hormone replacement/suppressive therapy
Urinary	• Nephritis • Elevated serum creatinine	Symptom management and supportive care

(continued)

Table 4. (continued)

Organ System	Clinical Presentation	Symptomatic Treatment/Supportive Care Options
Ophthalmic	• Blepharitis • Conjunctivitis • Episcleritis • Iritis • Scleritis • Uveitis • Ocular myositis • Optic neuritis • Photophobia • Pain in the eyes • Dryness • Blurred vision	Topical ophthalmic corticosteroids
Respiratory	• Pneumonitis • Interstitial lung disease • Radiographic changes • Difficulty breathing • Cough, dyspnea, persistent fatigue	Symptom management and supportive care
Other (rare)	• Arthritis • Polymyalgia rheumatica • Hemolytic anemia • Angiopathy • Myocarditis • Pericarditis • Temporal arteritis • Vasculitis • Myositis • Polymyositis • Sarcoidosis • Rhabdomyolysis	Treat as serious irAEs with systemic corticosteroids

Abbreviations: ADLs, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; irAEs, immune-related adverse events.

^aThe above options are for treatment of CTCAE grade 1 irAEs and for use in combination with systemic corticosteroids for grade 2 to 4 irAEs.

of systemic corticosteroids to treat irAEs affected OS or time to failure in patients treated with ipilimumab.⁷⁵

Collectively, irAEs are managed the same way for any ICI. Prophylaxis against irAEs is not currently recommended.^{11,72,73} Patients with irAEs should have increased monitoring and referrals as appropriate.^{72,73} No dose reductions are recommended for any ICI. Symptomatic treatment with topical and/or systemic supportive therapy is the front-line option for Common Terminology Criteria for Adverse Events (CTCAE) grade 1 (mild) irAEs (Table 4), and doses of ICI should not be held in such cases.^{4,37,48,76} In addition to symptomatic treatment, ICI therapy is often withheld for grade 2 (moderate) irAEs, and systemic corticosteroids are frequently used if symptoms persist. For grade ≥ 3 irAEs (severe or life threatening), ICI therapy is often permanently discontinued and systemic corticosteroids are initiated. Symptomatic management of irAEs (Table 4) should be used in conjunction with systemic corticosteroid treatment unless contraindicated or no longer necessary.^{4,37,48,77} A detailed CTCAE grade-specific treatment reference for

select irAEs is depicted in Table 5. Where evidence is lacking for specific irAEs for specific ICIs, data may be extrapolated from other ICIs of similar nature and grade. If the irAE resolves to grade 0 to 1, corticosteroids should be tapered over at least 1 month to prevent recurrence or flare.^{4,37,48} Prophylactic antimicrobials against opportunistic infections (ie, *Pneumocystis jirovecii* pneumonia) should be considered in patients who receive prednisone equivalents ≥ 20 mg/d for >4 weeks.⁷⁸

Overall, nivolumab and pembrolizumab appear to be better tolerated than ipilimumab. The irAE profile is slightly different in different malignancies. One speculation is that the irAEs may be linked to the sites of action or sites with the most T-cell concentration.

Pseudoprogression and the irRC

Pseudoprogression is likely caused by either transient activated T-cell infiltration of the tumor environment or continued tumor growth until a sufficient immune response

Table 5. Management of Select irAEs.^{a,4,37,48,76,77}

CTCAE Grade	Grade 2 (Moderate)			Grade 3 (Severe)			Grade 4 (Life Threatening)	
	Ipilimumab ^b	Pembrolizumab ^{c,d}	Nivolumab ^{e,g}	Ipilimumab ^b	Pembrolizumab ^{c,d}	Nivolumab ^{e,g}	Ipilimumab ^b	Nivolumab ^{e,g}
Colitis	Increase of 4-6 stools/d over baseline; abdominal pain; blood or mucus in stool Hold, give supportive care, give steroids if it persists >1 week	Hold and give steroids		Increase of ≥7 stools/d over baseline; incontinence; hospitalization indicated; limiting self-care ADLs; severe or persistent abdominal pain; fever; ileus; peritoneal signs Discontinue and give steroids; consider infliximab if it persists	Hold and give steroids		Life-threatening consequences; urgent intervention indicated Discontinue and give steroids; consider infliximab if it persists	
Hepatitis	AST or ALT >3-5 ×ULN and/or total bilirubin >1.5-3 ×ULN Hold	Hold and give steroids		AST or ALT >5-20 ×ULN and/or total bilirubin >3-10 ×ULN Discontinue and give steroids; consider MMF if it persists	Discontinue and give steroids		AST or ALT >20 ×ULN and/or total bilirubin >10 ×ULN Discontinue and give steroids	
Rash/Dermatitis	Covering 10%-30% of BSA Hold; give supportive care; give steroids if it persists >1 week			Covering >30% of BSA or SJS <10% of BSA Hold (or discontinue if SJS) and give steroids			SJS 10%-30% of BSA, or toxic epidermal necrolysis ≥30% BSA; or rash with dermal ulceration, necrosis, bullous, or hemorrhagic manifestations Discontinue and give steroids	
Motor/Sensory neuropathy	Moderate symptoms; limiting instrumental ADLs Hold			Severe symptoms; limiting self-care ADLs; assistive device indicated Hold and give steroids			Life-threatening consequences; urgent intervention indicated Discontinue and give steroids	
Endocrinopathy	Moderate symptoms; medical intervention indicated; thyroid suppression/replacement indicated; limiting instrumental ADLs Initiate hormone-replacement therapy as indicated; hold ICI and give steroids if symptomatic; grade 2 (unless hypothyroidism only), or requiring hospitalization, urgent medical intervention, or interfering with ADLs; discontinue if life threatening. Do not hold nivolumab for hypothyroidism or hyperthyroidism.			Severe symptoms; hospitalization indicated; limiting self-care ADLs			Life-threatening consequences; urgent intervention indicated	
Pneumonitis	Symptomatic; medical intervention indicated; limiting instrumental ADLs —	Hold and give steroids		Severe symptoms; limiting self-care ADLs; oxygen indicated —	Discontinue and give steroids		Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation) —	Discontinue and give steroids
Nephritis	SCR >1.5-3 ×baseline or ULN —	Hold and give steroids		SCR >3 ×baseline or >3-6 ×ULN —	Discontinue and give steroids	Hold and give steroids	SCR >6 ×ULN —	Discontinue and give steroids

Abbreviations: ADLs, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; MMF, mycophenolate; SCR, serum creatinine; SJS, Stevens-Johnson syndrome; ULN, upper limit of normal.

^aLower doses of systemic corticosteroids (0.5-1 mg/kg/d prednisone-equivalents) are often used for milder, grade 2 irAEs, whereas higher doses of systemic corticosteroids (1-2 mg/kg/d prednisone-equivalents) are generally used for more severe cases (grade 3-4 irAEs) or for grade 2 irAEs that persist or worsen on lower doses of corticosteroids. Dashes indicate absence of irAEs for particular ICI or lack of recommendations. If observed, the same treatment as for other ICIs for the same grade can be considered.

^bPermanently discontinue ipilimumab for (1) persistent grade 2 adverse reactions; (2) failure to taper steroids to dose of 7.5 mg/d prednisone-equivalents; (3) failure to complete full treatment course within 16 weeks from administration of first dose; (4) select grade 3 to 4 events as above or any other severe or life-threatening events; or (5) severe ocular disease that is unresponsive to corticosteroid eye drops.

^cNivolumab and pembrolizumab should be held for any grade 3 irAE unless otherwise stated above.

^dPermanently discontinue pembrolizumab for (1) persistent grade 2 or 3 adverse reactions that do not recover to grade 0 to 1 within 12 weeks after last dose of pembrolizumab; (2) failure to taper steroids to dose of 10 mg/d or less prednisone-equivalents within 12 weeks of last dose of pembrolizumab; (3) select grade 3 to 4 events as above or any other life-threatening events; or (4) any severe grade 3 reaction that recurs.

^ePermanently discontinue nivolumab for (1) persistent grade 2 or 3 adverse reactions that do not recover to grade 0 to 1 within 12 weeks after last dose of nivolumab; (2) any severe or grade 3 irAE that recurs; (3) failure to taper steroids to a dose of 10 mg/d or less prednisone-equivalents within 12 weeks; or (4) select grade 3 to 4 events as above or any other life-threatening or grade 4 events.

develops.⁷⁹ Patients experience initial tumor flare or new lesions representing pseudoprogression but may subsequently experience a response to ICI therapy. The RECIST or the WHO criteria, used to assess response in solid tumors, do not account for this phenomenon and potentially misclassify patients with pseudoprogression as non-responders, leading to premature discontinuation of ICI therapy (Table A1, available at <http://aop.sagepub.com/content/by/supplemental-data>).^{80,81} Because of possible negative implications on patient outcomes, Wolchok et al⁷⁹ developed the irRC for evaluation of ICI activity in patients with solid tumors based on melanoma patients who received ipilimumab. They found 4 patterns of response: (1) response in baseline lesions; (2) stable disease followed by slow, steady decline in total tumor volume; (3) response after initial increase in total tumor volume; and (4) reduction in total tumor burden after appearance of new lesions. A misclassification rate of 13.2% and 26.6% has been observed using the WHO and RECIST, respectively, instead of the irRC in melanoma.^{79,82}

There are few major differences between the WHO criteria and the irRC (Table A1, online only). First, irRC defines disease progression as a $\geq 25\%$ increase in net tumor burden allowing for new lesions, whereas the WHO criteria (and RECIST) classify any new lesion as progression.⁷⁹⁻⁸¹ Second, progression per the irRC requires confirmation in 2 consecutive observations 4 weeks apart, which is not required by the WHO criteria. This secondary confirmation captures the possible time lag for activated T-cells to infiltrate the tumor, which may cause initial tumor flare or pseudoprogression but subsequent response. The irRC also classifies durable stable disease as a meaningful benefit and therapeutic effect signifying disease control. The categories of the irRC include all patients who would be classified into the parallel categories per the WHO criteria but also include those patients who shift to the irRC categories after WHO-defined progression.⁷⁹

The irRC criteria are currently being used in clinical trials for solid tumors only and in general clinical practice in ICI-treated melanoma patients but are not without limitations. They are limited in their universal applicability because the initial criteria were based on only melanoma patients treated with ipilimumab in a single-arm study, which lacked a chemotherapy control arm, and comparison was only with the WHO criteria and not with RECIST. The irRC has also been studied in NSCLC and other solid malignancies and with pembrolizumab.^{43,83} Further prospective validation and refinement of the irRC is necessary before universal acceptance. Because of the above phenomenon of pseudoprogression and delayed response in some cases, the prescribing information for ipilimumab, but not pembrolizumab or nivolumab, recommends receipt of all 4 doses unless unacceptable toxicity occurs.^{4,37,48}

Current Status of Tumor Profiling for ICI Therapy

Only a minority of patients achieve a durable response with ICI therapy, which can be accompanied by significant ADRs. Ergo, many efforts are under way to identify tumor characteristics that correlate with response. Currently, it is not considered standard of care to select patients for ICI therapy based on tumor profiling. Studies of tumor tissue in ipilimumab-treated melanoma patients have identified several potential biomarkers and genetic profiles that predict clinical benefit.^{84,85} Melanoma patients with a high baseline expression of FoxP3, high baseline expression of indoleamine 2,3-dioxygenase, or an increase in tumor-infiltrating lymphocytes between baseline and 3 weeks posttreatment responded better to ipilimumab than their counterparts.⁸⁴ FoxP3, however, was not found to predict clinical benefit in a separate study.⁸⁵ High mutational load (>100 mutations) observed in whole-exome sequencing of matched tumor and blood samples in melanoma patients treated with ipilimumab was associated with significantly increased long-term clinical benefit and OS. No single gene was universally mutated across studied patients who experienced a sustained clinical benefit. In the same set of patients, a tumor neoantigen landscape of 101 neopeptides was identified and conferred an OS benefit despite mutational load.⁸⁵ With the exception of the 101-neopeptide sequencing, patients who test negative for the aforementioned biomarkers may still respond to therapy, but the 101-neopeptide sequencing is subject to selection bias in the methodology of its development and limited by small numbers. The clinical utility is still limited (Table A2, available at <http://aop.sagepub.com/content/by/supplemental-data>).

PD-L1 expression on tumors has been evaluated as a biomarker for response to anti-PD-1 therapy with pembrolizumab or nivolumab. A high level of PD-L1 expression in tumors of patients treated with pembrolizumab was shown to correlate with improved outcomes in NSCLC,^{42,43} melanoma,³⁹ recurrent/metastatic adenocarcinoma of the stomach or gastroesophageal junction,⁴⁴ and head/neck cancer.⁴⁷ A significantly higher ORR⁵⁰ and a trend toward improved PFS and OS^{86,87} has also been observed in melanoma patients with PD-L1-positive tumors treated with nivolumab, but results were not consistent across trials.⁵² Higher ORRs, PFS, and OS have also been observed in PD-L1-positive mRCC treated with nivolumab.^{34,88}

Many patients whose tumors are PD-L1 negative still respond to anti-PD-1 therapy. Although the threshold for positivity varies between ICIs and tumors, based on the results presented in mRCC, we recommend $\geq 5\%$.⁵⁹ The predictive values, sensitivities, and specificities vary based on ICI, outcomes assessed, and response criteria used. It is important to note differences in response criteria used when

comparing between tumor types and different therapies. Moreover, biomarkers for monotherapy are not necessarily applicable to combination ICI therapy.⁸⁹ There are many variables with PD-L1 testing, such as source of tissue (primary tumor vs metastatic site), fresh versus frozen tissue sample, and assay type, and it is currently unknown which variables are preferred for which tumors. Although tumor profiling is not currently considered standard of care, further refinement may be helpful in identifying patients likely to respond to ICI therapy.

Conclusions

Ipilimumab and nivolumab have category 1 recommendations for treatment of metastatic or unresectable melanoma in the frontline setting based on OS benefit despite BRAF status. This recommendation for nivolumab is not consistent with current labeling, and an OS benefit has yet to be observed with nivolumab in frontline therapy in BRAF mutant patients.¹⁹ Pembrolizumab carries a category 2A recommendation in the frontline setting because of the lack of mature studies.¹⁹ Nivolumab and pembrolizumab have better safety profiles than ipilimumab, which may lead to PD-1 inhibitors replacing ipilimumab as frontline therapy in unresectable stage III or IV melanoma. PD-1 inhibitors are currently preferred over ipilimumab in patients who are expected to clinically deteriorate within 12 weeks because of ipilimumab's suboptimal side effect profile and long time to response, as are the BRAF inhibitors in BRAF mutated patients.¹⁹ However, it is still unclear whether response to PD-1 inhibition is as durable as that for ipilimumab because of shorter follow-up and less clinical experience.

The current FDA indications for nivolumab and pembrolizumab in melanoma after progression following ipilimumab and BRAF inhibitor in V600 mutated patients are lacking in maturity and OS benefit and carry a category 2A recommendation, whereas ipilimumab carries a category 1 recommendation in the second-line setting in patients with a good performance status.^{19,37,48} Ipilimumab, unlike PD-1 inhibitors, has been shown to have clinical activity in melanoma patients with active brain metastases, though clinical trials are currently enrolling in this setting for the PD-1 inhibitors.^{5,6,18,22} All 3 agents have activity in melanoma despite BRAF status.^{6,7,38,40,49,52} Because median time to response is of the order of weeks to months with ICIs, and tumor flare is possible, patients with symptomatic disease who need urgent disease control should be considered for alternative therapies over the ICIs if they exist (ie, in BRAF mutant melanoma). The ICIs have yet to be studied head-to-head against BRAF inhibitors in BRAF mutant patients. The data for combination therapy with ipilimumab and nivolumab are premature, and evidence for combination of ipilimumab and pembrolizumab is nonexistent.

Currently, nivolumab is the only ICI approved for the treatment of squamous NSCLC and carries a grade 2A recommendation for treatment in patients with good performance status after platinum-doublet chemotherapy, based on OS benefit.⁵⁴ The FDA has granted pembrolizumab breakthrough designation for NSCLC. Data are promising for other malignant neoplasms, and nivolumab in particular has been granted fast-track designation by the FDA for mRCC and breakthrough designation for cHL. This systematic review was conducted to provide the current status of and future directions for ICIs in oncology. The data are limited in availability, particularly with pembrolizumab, and many trials presented have yet to be published in full text form. The methodology of review is limited by potential selection bias from the investigators.

Several challenges still exist in the clinical investigation and use of ICIs. The irRC need further refinement, expansion, and validation across all solid and liquid malignancies before clinicians can start using the criteria to assess all patients treated with ICIs. In the meantime, results from clinical trials with ICIs should be examined and compared carefully, taking into account differences in response criteria used and possible implications on rates of reported benefits. Finally, although still premature, there is a growing body of evidence to suggest that a personalized medicine approach for selecting candidates for ICI therapy is on the horizon. Current evidence suggests that neopeptide signature profiling could serve as a promising tool in identifying optimal melanoma candidates for ipilimumab. Existing data suggest that the level of tumor PD-L1 expression seems to be somewhat positively linked to response to anti-PD-1 therapy, but the predictive value of tests among tumors are varied, as are thresholds for defining positivity. To date, no biomarker testing has been implemented as standard of care in ICI therapy.

ICIs deliver promising results in the treatment of patients with melanoma and squamous NSCLC. They are currently being studied across virtually all tumor types as monotherapy and in combination with other ICIs, BRMs, targeted therapies, and chemotherapy.⁵ In addition, several other novel immune checkpoint modulators are currently in development, and novel targets such as LAG-3, TIM-3, CD137, CD40, and ligands CD70, B7-H3, and PD-L1 have been identified.^{2,65,90,91} Despite their drawbacks, ICIs have been the leading breakthrough treatments in cancer in the past decade.

Declaration of Conflicting Interests

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