Understanding and Managing Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors in Patients With Advanced Melanoma

ALYONA WEINSTEIN,[1] RN, MSN, FNP-BC, RUTH-ANN GORDON,[1] MSN, FNP-BC, OCN®, MARY KATE KASLER,[1] MSN, ACNP-BC, DNP(C), MATTHEW BURKE,[2] MBA, RN, MSN, APRN-BC, SMITA RANJAN,[3] MSN, APRN, JACKIE HODGETTS,[4] MSC, RN, NMP, VANESSA REED,[1] MS, AGPCNP-BC, OCN®, YELENA SHAMES,[1] MSA, ACNP-BC, CNRN, NANA PREMPEH-KETEKU,[1] MS, ANP-BC, and KARLA LINGARD,[5] RNBSC (HONS)

From [1]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [2]Yale University School of Medicine, New Haven, Connecticut, USA; [3]University of Louisville, Louisville, Kentucky, USA; [4]Christie Hospital, Manchester, UK; [5]Royal Marsden Hospital, London, UK

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Correspondence to: Alyona Weinstein, RN, MSN, FNP-BC, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. E-mail: weinsta2@mskcc.org

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Abstract

The immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab represent a substantial improvement in treating advanced melanoma but are associated with adverse events (AEs) likely related to general immunologic enhancement. To ensure that patients receive optimal benefit from these agents, prompt assessment and treatment of AEs are essential. We review the efficacy and safety profiles of these immune checkpoint inhibitors and describe guidelines for managing immune-related AEs. We also present case studies describing the management of toxicities in patients receiving immune checkpoint inhibitor therapy. These cases illustrate the importance of collecting a detailed medical history when administering immunotherapy, as this information is necessary to establish baseline, inform monitoring, and determine the etiology of symptoms. Advanced practice nurses and physician assistants are uniquely positioned to educate patients on the early recognition of AEs and have an important role in establishing appropriate monitoring and open dialogue among services.

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The projected incidence of melanoma within the United States is about 87,110 new cases for 2017, with an estimated 9,730 deaths from the disease in the same year (American Cancer Society, 2017). The lifetime risk of developing melanoma is 2.1%, or 1 out of every 50 men and women (National Cancer Institute [NCI], 2016).

Genetic predisposition and environmental stressors contribute to

the development of melanoma. Ultraviolet (UV) solar radiation promotes melanoma development through direct mutagenic effects on DNA, production of growth factors, decrease of skin immunity, and promotion of reactive oxygen species, which cause DNA damage (Miller & Mihm, 2006). Normally, melanocytes in the skin respond to UV exposure by stimulating the production of melanin, which then absorbs and dissipates UV radiation. In fair-skinned people, susceptibility to melanoma can occur as a result of genetic impairments in the production of melanin. For example, as many as 40% of hereditary melanomas can be linked to germline mutations in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene (Miller & Mihm, 2006).

Although most patients with melanoma are diagnosed in the earlier stages (localized, 84%; regional, 9%; distant metastases, 4%), 5-year survival rates based on data from 2005 to 2011 demonstrate considerably worse prognoses for patients diagnosed with metastatic disease (16.6%) compared with those diagnosed at the localized stage (98.3%; NCI, 2016). Therefore, the use of new agents such as immune checkpoint inhibitors in advanced melanoma has been an area of clinical research.

IMMUNE CHECKPOINT INHIBITION FOR THE TREATMENT OF CANCER

The immune system is able to recognize and mount an immune response against antigenic molecules. However, tumors have developed survival mechanisms for evading immune surveillance, including the use of pathways that normally control immune tolerance (Pardoll, 2012). Two important immune checkpoint pathways are those mediated by cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Once activated, T cells upregulate CTLA-4, which can lead to dampening of the immune response early in the activation phase (Hoos et al., 2010). In contrast, PD-1 functions at the later effector phase, playing a role in moderating T-cell activity in peripheral tissues. Immune checkpoint inhibitors have been developed to exploit these CTLA-4 and PD-1 homeostatic controls, blocking events that suppress T-cell activation and allowing T cells to generate sustained antitumor immune responses (Figure; Rothschild, Thommen, Moersig, Müller, & Zippelius, 2015). The mechanism of action of immune checkpoint inhibitors accounts for their efficacy but also for the immune-related adverse events (irAEs) associated with these therapies.

Currently, three monoclonal antibody immune checkpoint inhibitors have been approved by the US Food and Drug Administration (FDA): the anti–CTLA-4 agent ipilimumab (Yervoy) and the anti–PD-1 agents pembrolizumab (Keytruda) and nivolumab (Opdivo). Ipilimumab was approved in March 2011 for the treatment of unresectable or metastatic melanoma after demonstrating improved overall survival (OS) vs. gp100 peptide vaccine in patients with previously treated metastatic melanoma in a randomized phase III trial (Hodi et al., 2010). Pembrolizumab and nivolumab were initially approved in September and December 2014, respectively, in patients with pretreated unresectable or metastatic melanoma based on tumor response and response duration data in phase I and phase III trials, respectively (Robert et al., 2014; Weber et al., 2015a). More recently, both pembrolizumab and nivolumab received approvals for first-line use in unresectable or metastatic melanoma based on data from phase III trials (Robert et al., 2015a; Robert et al., 2015b). Monotherapy of all three agents is also approved in the European Union. Furthermore, the combination of nivolumab and ipilimumab in the first-line setting is approved by the FDA for the treatment of patients with unresectable or metastatic melanoma based on data from both phase II (Postow et al., 2015) and phase III (Larkin et al., 2015a) trials.

Key efficacy data for these agents as monotherapy and in combination regimens are presented in Table 1. Although ipilimumab is also approved for adjuvant treatment of patients with cutaneous melanoma (Bristol-Myers Squibb, 2015c), and nivolumab and pembrolizumab have indications in metastatic non–small cell lung cancer (Bristol-Myers Squibb, 2016; Merck, 2015a) and renal cell carcinoma (Bristol-Myers Squibb, 2016), our discussion will focus on the use of these agents in advanced melanoma.

EFFICACY OF IMMUNE CHECKPOINT INHIBITORS

In advanced melanoma, objective response rates (ORRs) have ranged from 10.9% to 19.0% for ipi-

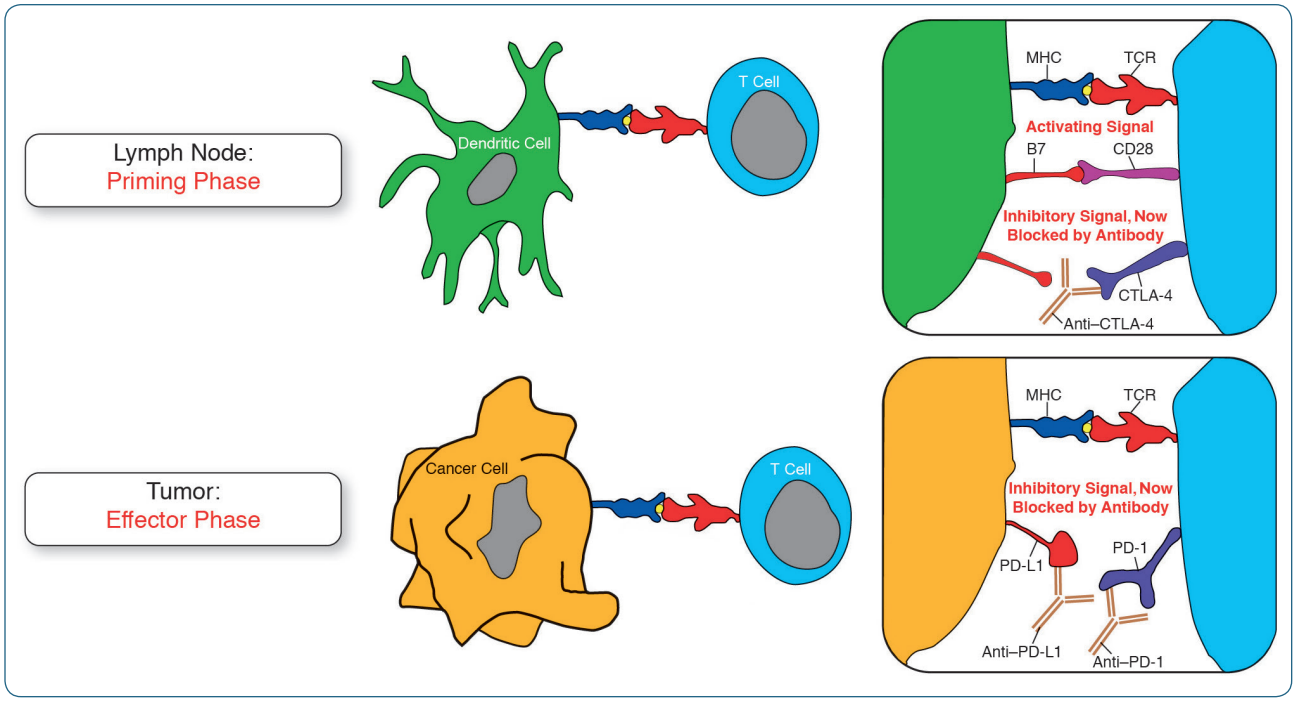

Figure. Immune checkpoint inhibition of CTLA-4 or PD-1 pathways by antitumor immunotherapy. CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; PD-1 = programmed cell death protein 1; MHC = major histocompatibility complex; TCR = T-cell receptor; PD-L1 = programmed cell death ligand 1. Adapted from Rothschild et al. (2015) with permission from EMH Swiss Medical Publishers Ltd.

limumab monotherapy, from 26.0% to 33.7% for pembrolizumab monotherapy, and from 31.7% to 43.7% for nivolumab monotherapy, suggesting higher ORR with PD-1 blockade vs. CTLA-4 blockade (Hodi et al., 2010; Robert et al., 2011; Maio et al., 2015; Robert et al., 2014, 2015a, 2015b; Topalian et al., 2014; Wolchok et al., 2013; Postow et al., 2015; Larkin et al., 2015a; Weber et al., 2015a). For example, the phase III KEYNOTE-006 trial comparing pembrolizumab with ipilimumab found a response rate of 33% to 34% (depending on the regimen) with the anti–PD-1 antibody, vs. 12% with ipilimumab (Robert et al., 2015a). Responses across trials have been durable, with median durations of response not reached in most studies.

A median OS of 10 months was reported for ipilimumab in the registrational phase III study (Hodi et al., 2010), and a pooled analysis of 1,861 patients across ipilimumab studies demonstrated a median OS of 11.4 months, suggesting that the durable responses observed with immune checkpoint inhibitors may translate into a survival benefit (Schadendorf et al., 2015). Although median OS has not been reached in phase III studies of PD-1 agents, KEYNOTE-006 found estimated 12-month OS rates of 68% to 74% with pembrolizumab and 58% with ipilimumab (Robert et al., 2015a). Similarly, in the phase III CheckMate 066 trial, the 12-month OS rate was 73% with nivolumab and 42% with dacarbazine (Robert et al., 2015b).

CTLA-4 and PD-1 have distinct but complementary roles in mediating T-cell immune responses at early and later phases of T-cell activation, respectively (Hoos et al., 2010; Rothschild et al., 2015), and dual blockade results in greater antitumor activity than inhibition of either pathway alone in preclinical models (Curran et al., 2010; Selby et al., 2013). These observations have provided a strong rationale for clinical investigation of dual blockade using combined therapy with anti–CTLA-4 and anti–PD-1 antibodies.

The safety and efficacy of ipilimumab and nivolumab given either concurrently or sequentially have been assessed in the phase I CA209-004 study (Wolchok et al., 2013), whereas concurrent therapy has been compared with ipilimumab alone in the phase II CheckMate 069 study (Postow et al., 2015) and with either ipilimumab or nivolumab monother-

Table 1. Key Efficacy Data in Advanced Melanoma for Immune Checkpoint Inhibitor Therapy

Reference	N	Intervention	Key efficacy outcomes
Hodi et al., 2010	676	Ipilimumab (3 mg/kg) + vaccine vs. ipilimumab vs. vaccine in previously treated metastatic melanoma	Median OS: ipilimumab-containing arms 10.0 and 10.1 months vs. vaccine 6.4 months ($p < .001$) ORR: ipilimumab + vaccine 5.7% ($p = .04$)[a] vs. ipilimumab 10.9% ($p = .001$)[b] vs. vaccine 1.5% Median DR: ipilimumab + vaccine 11.5 months vs. ipilimumab NR (median 27.8 months of follow-up) vs. vaccine NR (median 17.2 months of follow-up)
Robert et al., 2011; Maio et al., 2015	502	Ipilimumab (10 mg/kg) plus dacarbazine vs. dacarbazine in previously untreated metastatic melanoma	Median OS: ipilimumab + dacarbazine 11.2 months vs. dacarbazine 9.1 months ($p < .001$) 5-year survival rate: ipilimumab + dacarbazine 18.2% vs. dacarbazine 8.8% ($p = .002$) ORR: ipilimumab + dacarbazine 15.2% vs. dacarbazine 10.3% ($p = .09$) Median DR: ipilimumab + dacarbazine 19.3 months vs. dacarbazine 8.1 months ($p = .03$)
Robert et al., 2014	173	Pembrolizumab (2 mg/kg) vs. pembrolizumab (10 mg/kg) in ipilimumab-refractory advanced melanoma	ORR: 26% in both dose groups ($p = .96$) Median DR: NR (median 8.0 months of follow-up)
Robert et al., 2015a	834	Pembrolizumab (10 mg/kg Q2W or Q3W) vs. ipilimumab (3 mg/kg) in advanced melanoma with ≤ 1 prior therapy	6-month PFS: pembrolizumab Q2W 47.3%/Q3W 46.4% vs. ipilimumab 26.5% ($p < .001$) Estimated 12-month OS: pembrolizumab Q2W 74.1%/Q3W 68.4% vs. ipilimumab 58.2% ($p = .0005$ vs. Q2W and $p = .0036$ vs. Q3W) ORR: pembrolizumab Q2W 33.7%/Q3W 32.9% vs. ipilimumab 11.9% ($p < .001$) Median DR: NR in any group (median 7.9 months of follow-up)
Robert et al., 2015b	418	Nivolumab (3 mg/kg) vs. dacarbazine in previously untreated metastatic melanoma without *BRAF* mutation	1-year OS: nivolumab 72.9% vs. dacarbazine 42.1% ($p < .001$) Median PFS: nivolumab 5.1 months vs. dacarbazine 2.2 months ($p < .001$) ORR: nivolumab 40% vs. dacarbazine 13.9% ($p < .001$) Median DR: nivolumab NR (median 8.9 months of follow-up) vs. dacarbazine 6.0 months
Topalian et al., 2014	107	Nivolumab (0.1–10 mg/kg) in advanced melanoma (outpatient setting)	Median OS: 16.8 months; 1-year OS rate: 62%; 2-year OS rate: 43% Estimated median DR: 24.0 months
Wolchok et al., 2013	86	Concurrent: nivolumab (0.3–10 mg/kg) + ipilimumab (1–10 mg/kg) followed by nivolumab consolidation Sequential: ipilimumab followed by nivolumab (1 mg/kg and 3 mg/kg) in advanced melanoma	ORR concurrent regimen: 40% (53% with nivolumab 1 mg/kg + ipilimumab 3 mg/kg) DR concurrent regimen: 6.1 to 72.1 weeks (median not reported)
Postow et al., 2015	142	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg) or placebo followed by nivolumab consolidation in previously untreated metastatic melanoma	ORR: ipilimumab + nivolumab 61% (CR 22%) vs. ipilimumab 11% and no CR ($p < .001$) Median PFS: ipilimumab + nivolumab NR vs. ipilimumab 4.4 months ($p < .001$) Median DR: NR in either group (minimum 11.0 months of follow-up postrandomization)
Larkin et al., 2015a	945	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg) vs. nivolumab vs. ipilimumab followed by nivolumab or ipilimumab consolidation in previously untreated metastatic melanoma	ORR: ipilimumab + nivolumab 57.6% vs. ipilimumab 19.0% vs. nivolumab 43.7% ($p < .001$ for comparison with ipilimumab alone) Median PFS: ipilimumab + nivolumab 11.5 months vs. ipilimumab 2.9 months vs. nivolumab 6.9 months ($p < .001$ for comparison with ipilimumab alone) Median DR: NR in any group (median 12.2–12.5 months of follow-up)
Weber et al., 2015a	405	Nivolumab (3 mg/kg) vs. chemotherapy[c] in previously treated advanced melanoma	ORR: nivolumab[d] 31.7% vs. chemotherapy[e] 10.6% Median DR: nivolumab NR vs. chemotherapy 3.5 months (median follow-up 8.4 months)

Note. CR = complete response; DR = duration of response; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks.
[a]*p* value vs. vaccine or ipilimumab alone. [b]*p* value vs. vaccine alone. [c]Investigator choice chemotherapy. [d]Per protocol analysis of first 120 patients. [e]First 47 patients.

apy in the phase III CheckMate 067 study (Larkin et al., 2015a). Overall, combination treatment has confirmed preclinical observations and achieved higher ORR (40% to 60%) vs. monotherapy (Table 1).

TREATMENT-RELATED ADVERSE EVENTS WITH IMMUNOLOGIC ETIOLOGY

Much of the insight into irAEs associated with immune checkpoint inhibitor therapy comes from experience with the anti–CTLA-4 antibody ipilimumab. Current evidence indicates that this knowledge can be broadly transferred to inhibitors of the PD-1 pathway, with some differences in incidence and severity (Luke & Ott, 2015; Callahan & Wolchok, 2013). The autoimmune basis of irAEs means that any organ system can be affected, but the most common irAEs are dermatologic (rash, pruritus, vitiligo), gastrointestinal (GI; diarrhea, colitis), and endocrine (hypophysitis, hypothyroidism, thyroiditis, adrenal insufficiency; Callahan & Wolchok, 2013).

The irAEs observed in key registrational studies for immune checkpoint inhibitor therapy are summarized in Table 2. Among monotherapies, rates of all-grade rash have been similar across agents. For example, in the phase III KEYNOTE-006 trial comparing pembrolizumab and ipilimumab (Robert et al., 2015a) and in CheckMate 067, which included ipilimumab and nivolumab arms (Larkin et al., 2015a), rates of all-grade diarrhea or colitis were more frequent with anti–CTLA-4 blockade compared with PD-1 pathway–targeted agents. Hypothyroidism

Table 2. Immune-Related Adverse Events in Key Registrational Trials[a]

	KEYNOTE-006 (Robert et al., 2015a)						CheckMate 067 (Larkin et al., 2015a)					
	Pembro 10 mg/kg[b] Q2W (n = 278)		Pembro 10 mg/kg[b] Q3W (n = 277)		Ipi 3 mg/kg (n = 256)		Nivo 3 mg/kg (n = 313)		Nivo 1 mg/kg + Ipi 3 mg/kg (n = 313)		Ipi 3 mg/kg (n = 311)	
Adverse event	**All**	**Gr. 3/4**	**All**	**Gr. 3/4**	**All**	**Gr. 3/4**	**All**	**Gr. 3/4**	**All**	**Gr. 3/4**	**All**	**Gr. 3/4**
Dermatologic												
Pruritus	14.4	0	14.1	0	25.4	0.4	18.8	0	33.2	1.9	35.4	0.3
Rash	14.7	0	13.4	0	14.5	0.8	21.7	0.3	28.4	2.9	20.9	1.6
Rash maculopapular	3.6	0	2.2	0.4	2.7	0.4	4.2	0.3	11.8	1.9	11.9	0.3
Vitiligo	9.0	0	11.2	0	1.6	0	7.3	0.3	6.7	0	3.9	0
Gastrointestinal												
Diarrhea	16.9	2.5	14.4	1.1	22.7	3.1	19.2	2.2	44.1	9.3	33.1	6.1
Colitis	1.8	1.4	3.6	2.5	8.2	7.0	1.3	0.6	11.8	7.7	11.6	8.7
Endocrine												
Hypothyroidism	10.1	0.4	8.7	0	2.0	0	8.6	0	15.0	0.3	4.2	0
Hyperthyroidism	6.5	0	3.2	0	2.3	0.4	4.2	0	9.9	1.0	1.0	0
Hypophysitis	0.4	0.4	0.7	0.4	2.3	1.6	0.6	0.3	7.7	1.6	3.9	1.9
Hepatic												
Increased ALT	4.3	0	1.4	0.4	3.5	0.8	3.8	1.3	17.6	8.3	3.9	1.6
Increased AST	5.0	0	2.2	0.4	2.3	0.8	3.8	1.0	15.3	6.1	3.5	0.6
Pulmonary												
Pneumonitis	0.4	0	1.8	0.4	0.4	0.4	1.3	0.3	6.4	1.0	1.6	0.3

Note. Pembro = pembrolizumab; Ipi = ipilimumab; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]Most common treatment-related immune-related adverse events and those of particular interest reported; all values shown in table body are percentages.
[b]Not US Food and Drug Administration–approved dose.

appeared more frequently with anti–PD-1 agents vs. ipilimumab (Robert et al., 2015a; Larkin et al., 2015a). The irAEs observed with combination anti–CTLA-4 and anti–PD-1 therapy have generally been similar to those associated with monotherapy, but with a higher frequency (Larkin et al., 2015a).

The time to onset of irAEs differs according to organ system. Median times to onset and resolution are shown in Table 3. With ipilimumab, dermatologic irAEs occur within 2 to 3 weeks of treatment, followed by GI irAEs within 6 to 8 weeks and endocrine irAEs after around 7 weeks (Weber, et al., 2013; Weber, Kähler, & Hauschild, 2012). Similarly, dermatologic irAEs occur within a median of 5 weeks of treatment with nivolumab, followed by GI irAEs (median, 7 weeks), pulmonary irAEs (median, 9 weeks), and endocrine irAEs (median, 10 weeks; Weber et al., 2015b). Timing of irAEs with the nivolumab and ipilimumab combination has been similar to that seen with monotherapy (Larkin et al., 2015a). For pembrolizumab, median time to onset was 6.5 months for colitis, 1.5 to 3.5 months for endocrine irAEs, and 5 months for pneumonitis (Merck, 2015a).

Immune-modulating medications such as corticosteroids and antihistamines are often indicated for the management of irAEs. For example, most patients in the combination arms of CheckMate 069 and 067 required either topical or systemic immune-modulating agents to manage irAEs (89% and 83% of patients, respectively), and most severe irAEs resolved when immune-modulating agents were used, except in the case of endocrinopathies (Postow et al., 2015; Larkin et al., 2015a). In CheckMate 067, resolution rates for grade 3/4 irAEs were between 85% and 100% with the nivolumab and ipilimumab regimen for most organ categories, and the median time to resolution ranged from approximately 2 to 4 weeks (Larkin et al., 2015a).

Immune-modulating medications are believed to quell inflammation without interfering with the antitumor response (Postow, 2015). For example, an analysis of a phase III ipilimumab trial found no difference in response between patients receiving vs. not receiving steroids before response (Baurain et al., 2012). Similarly, a pooled analysis of four nivolumab clinical studies found no impact of the use of systemic immune-modulating medications on objective response (Weber et al., 2015b).

Table 3. Timing of Immune-Related Adverse Events

	Median time to onset, weeks[a]		
Type of irAE	**Ipi**	**Nivo**	**Nivo + Ipi**
Median time to onset, weeks[a]			
Dermatologic	3	5	6
Gastrointestinal	8	7	7
Endocrine	7–20	10	12
Median time from onset to resolution, weeks[b]			
Dermatologic	5	NE	3
Gastrointestinal	4	1	3
Endocrine	NR	4	NE

Note. irAE = immune-related adverse event; Ipi = ipilimumab; Nivo = nivolumab; NE = not evaluable; NR = not reported. Information from Larkin et al. (2015b); Weber et al. (2015b, 2013).
[a]Grade 2 to 5 for ipilimumab; any grade for nivolumab; and grade 3 to 4 for combination therapy.
[b]Grade 2 to 4 for ipilimumab; grade 3 to 4 and managed with immune-modulating medications for nivolumab and combination therapy.

IDENTIFICATION, GRADING, AND MANAGEMENT OF SELECT irAEs

Dermatologic, GI, and Endocrine

Across trials of immune checkpoint inhibitors as either monotherapy or combination therapy, dermatologic, GI, and endocrine irAEs have been observed most frequently. Guidance and recommendations on the management of irAEs associated with FDA-approved immune checkpoint inhibitor therapies emphasize the need for prompt identification and intervention (National Comprehensive Cancer Network [NCCN], 2015; Bristol-Myers Squibb, 2016, 2015c; Merck, 2015a). A Risk Evaluation and Mitigation Strategy (REMS) was originally established for ipilimumab to provide guidance for identification and management of irAEs (Bristol-Myers Squibb, 2012); guidelines are still available, although REMS is no longer required (Bartell et al., 2015).

Although no formal REMS programs were required for anti–PD-1 agents, manufacturers have developed additional guidance on irAE identification and management that generally reflect that given for anti–CTLA-4 therapy (Bristol-Myers Squibb, 2016; Merck, 2015a). Table 4 summarizes the signs and symptoms of dermatologic, GI, and

Table 4. Identification of Dermatologic, Gastrointestinal, and Endocrine irAEs

Site	Adverse event	Signs and symptoms
Dermatologic	Dermatitis (rash, pruritus)	Papules, pustules, burning, or tightness with or without itching. Rare, severe, and fatal inflammation of the skin, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are also possible
Gastrointestinal	Diarrhea, colitis	Colitis: diarrhea (loose stools) or more bowel movements than usual (severe), abdominal pain or tenderness, mucus or blood in stool, fever (may or may not be present) Bowel perforation[a]: peritoneal signs, ileus
Endocrine	Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism	Fatigue or extreme tiredness, headache that will not go away or unusual headaches, weight gain or loss, mental status changes (changes in mood or behavior; e.g., decreased sex drive, irritability, or forgetfulness), abdominal pain, unusual bowel habits, hypotension, dizziness or fainting, hair loss, feeling cold, voice gets deeper, vision changes, rapid heartbeat, muscle aches, increased sweating

Note. irAEs = immune-related adverse events. Information from Bristol-Myers Squibb (2015c, 2015a); Merck (2015b).
[a]Rare event associated with ipilimumab.

endocrine irAEs associated with immune checkpoint blockade (Bristol-Myers Squibb, 2015d, 2015a; Merck, 2015b). The first steps in the management of irAEs are correct identification and grading, and irAEs can be graded according to the Common Terminology Criteria for Adverse Events (CTCAE; Appendix A; NCI, 2009).

Guidelines for the management of dermatologic, GI, and endocrine irAEs are summarized in Appendix B. This includes treatment recommendations for moderate or severe AEs, usually requiring treatment interruption and the use of corticosteroid immunosuppression. Of note, endocrine irAEs such as hypophysitis may require lifelong hormonal replacement. Adrenal insufficiency, which can be primary or occur secondary to hypophysitis, requires intense education on appropriate adjustment of steroids to avoid adrenal crisis.

Recommendations for restarting checkpoint inhibitor therapy and referral points depending on the grade of the irAE are also given. Generally, therapy should be permanently discontinued for severe irAEs, whereas dose is withheld for moderate irAEs (except endocrine AEs) until return to baseline, improvement to mild severity, or complete resolution. Systemic (high-dose) corticosteroids are administered for severe, persistent, or recurring irAEs (Bristol-Myers Squibb, 2015d, 2015a, 2015c, 2016; Merck, 2015b, 2015a). Although rates of irAEs may be numerically higher with combined CTLA-4/PD-1 blockade, no new safety signals have been reported in the phase III CheckMate 067 trial (Larkin et al., 2015a), and management strategies developed for monotherapy remain pertinent in the combination setting. A practical checklist that highlights key issues for nurses involved in caring for patients receiving immune checkpoint inhibitor therapy is presented in Appendix C.

MANAGING PATIENTS WITH irAEs: A PRACTICAL APPROACH

The following case studies illustrate the identification and management of irAEs with immune checkpoint inhibitor therapy and outline the role of advanced care providers, such as nurse practitioners and PAs, in identifying and managing these irAEs.

Case 1: Nephritis and Rash

A 54-year-old male with conjunctival *BRAF* wild-type melanoma metastatic to bilateral lungs and cervical lymph nodes received nivolumab and ipilimumab combination in an expanded-access program. A history of hypertension complicated by retinopathy and a history of seasonal erythematous rash were noted. Before initiation of therapy, the advanced care provider met with the patient and family for an educational session. Potential adverse effects of the regimen were reviewed, and the patient was alerted to symptoms he needed to report. An emergency contact phone number was provided. After the patient received his first dose of therapy, the advanced care provider initiated surveillance phone calls aimed at early detection of toxicities.

The patient developed grade 2 maculopapular rash after the first dose, which was managed by holding the patient's second dose of treatment and same-day referral to dermatology for biopsy. Acute spongiotic and vesicular dermatitis with eosinophils were identified and treatment initiated with clobetasol 0.05% topical cream. Following resolution of an acute cutaneous response, he remained on a reduced dose of prophylactic clobetasol. The role of advanced care providers is essential during dermatologic evaluation and in identifying the need for timely referral to dermatology. After evaluation by dermatology service, the patient continued on close observation during clinic visits and phone surveillance calls for rebound signs and symptoms of rash while on topical steroid treatment.

Before the start of cycle 3, the patient's metoprolol regimen (100 mg daily) for treatment of hypertension was changed to hydrochlorothiazide at 100/25 mg daily, which resulted in mild improvement in hypertension. Following dose 3, grade 2 asymptomatic creatinine elevation occurred (1.4 mg/dL) and was managed by an increase in oral hydration. As the creatinine level increased to 2.1 mg/dL 6 days later, the patient was instructed to begin oral prednisone at 60 mg daily and discontinue the angiotensin-receptor blocker. The patient was also referred to renal services for the evaluation of acute kidney injury. Creatinine returned to near baseline (0.9 mg/dL) within 3 days of prednisone initiation, and prednisone was tapered by 10 mg daily. Urinalysis revealed normal results, and the patient completed the fourth dose of therapy with continued close monitoring of renal function.

Following his first dose of nivolumab monotherapy, he developed grade 2 alanine aminotransferase elevation, which was managed by holding the following dose and treatment with prednisone at 90 mg daily, followed by a 3-week taper schedule. The patient's laboratory evaluation returned to normal values, and repeated imaging revealed an excellent response to treatment, with substantially decreased bilateral pulmonary metastases; decrease in the size of the bilateral hilar, intraparotid, and cervical lymph nodes; and no new adenopathy.

This case demonstrates the importance of collecting a detailed and updated medical history to establish a baseline. The etiology of elevated creatinine in this case may have been due to autoimmune interstitial nephritis or may have been related to the initiation of angiotensin-receptor blocker therapy. A patient's history can assist clinicians with the general direction for monitoring while on immunotherapy, and advanced health care providers such as nurse practitioners and PAs are well positioned to establish a baseline health history and exam and to conduct thorough clinical evaluations at each clinic visit.

Upon development of irAEs, referral to specialists (e.g., dermatology and renal service in this case) for early evaluation and intervention can assist in the initiation of therapy that will target symptoms and minimize compromise of patient safety. Although immune-related phenomena of cutaneous toxicities caused by immunotherapy are well known, autoimmune conditions such as nephritis are relatively rare and complex. Advanced health care providers play a critical role in educating and guiding patients in the recognition of AEs and in facilitating timely referrals to specialty services.

Case 2: Hypothyroidism, Pneumonitis, and Hemolytic Anemia

A 71-year-old female with *BRAF* mutation–positive melanoma presented with metastases to the lungs, spleen, abdominal lymph nodes, sternum, right lateral sixth rib, and right ilium subsequent to disease progression on vemurafenib (Zelboraf). In a phase I study, she received 4 doses of combination nivolumab and ipilimumab over 12 weeks, followed by nivolumab monotherapy every 2 weeks. She experienced no toxicities and a partial response, with a 69% decrease in tumor burden after 12 weeks of combination therapy.

Grade 2, asymptomatic hypothyroidism (onset at day 15 of nivolumab monotherapy) was initially treated with levothyroxine at 25 µg while continuing nivolumab; the patient was later referred to endocrinology, and levothyroxine was increased to 100 µg. Grade 1 periorbital edema relating to hypothyroidism was noted on day 15 of monotherapy cycle 3, shortly after the increased dose of levothyroxine, and was closely observed without further adjustment in levothyroxine.

At the start of cycle 4, imaging revealed a continuing partial response, with an 85% decrease in tumor burden and grade 1 pleural effusions. A transthoracic echocardiogram ruled out potential cardi-

ac etiology, and nivolumab monotherapy was withheld. Two weeks later, the patient had developed grade 1 nonproductive cough and a chest CT scan found bilateral pleural effusions and new ground-glass opacities demonstrating grade 1 pneumonitis. Nivolumab continued to be withheld, and the patient was referred for thoracic consultation. Surveillance with serial imaging was recommended.

On day 29 of cycle 5, the patient presented with a total bilirubin of 1.7 mg/dL, hemoglobin of 8.7 g/dL, rising lactate dehydrogenase of 1,208 U/L, grade 1 fatigue, and jaundice. She was referred for inpatient admission, and further workup was consistent with pernicious anemia. Treatment was initiated with intramuscular injection of vitamin B12 (1,000 µg daily) for 1 week, followed by successive weekly injections, and the patient was discharged.

At the start of cycle 7, the patient had multiple new and enlarging pulmonary nodules but resolution of pleural effusions. She was referred to interventional radiology for lung biopsy, and treatment with nivolumab was resumed. The biopsy revealed nondiagnostic parts of lung parenchyma with areas of chronic inflammation. Furthermore, the patient experienced a decline in hemoglobin, escalation of bilirubin and lactate dehydrogenase, and a positive super Coombs test. Nivolumab was withheld, and a course of prednisone was implemented.

The patient was tapered off prednisone during cycle 9 and found to have complete resolution of hemolytic anemia. Cycle 10 assessment imaging revealed resolution of grade 1 pneumonitis; however, dominant splenic lesion measurements increased. Monotherapy was resumed at the start of cycle 11, and the patient received her last nivolumab infusion on day 29 of cycle 11. An assessment scan on day 43 of cycle 11 revealed stability of the splenic lesion, but the patient experienced early signs of resumption of hemolytic anemia and underwent surgical resection and splenectomy. Response was a 94% decrease in tumor burden before surgical resection, with no evidence of disease after surgery.

This case demonstrates that collaboration among a multidisciplinary team is essential for the care of patients being treated with immunotherapy. The complexity of this case and development of numerous side effects while on therapy reveal the importance of vigilant monitoring, and advanced care providers are uniquely positioned to help establish an appropriate timeframe for AE monitoring and open communication among services.

Recommendations for identification and management of immune-related pneumonitis seen primarily with PD-1 blockade deserve special mention. Signs and symptoms include radiographic changes, new or worsening cough, chest pain, and shortness of breath (Bristol-Myers Squibb, 2015a). Patients should be monitored for signs and symptoms and evaluated with radiographic imaging for suspected pneumonitis. Corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for grade 2 or greater pneumonitis, followed by a corticosteroid taper. Anti–PD-1 therapy should be permanently discontinued for severe (grade 3) or life-threatening (grade 4) pneumonitis and withheld until resolution for moderate (grade 2) pneumonitis (Bristol-Myers Squibb, 2016; Merck, 2015a).

Special considerations in the management of irAEs relate to certain patient populations. The safety of immune checkpoint inhibition in patients with underlying autoimmune disorders has not been evaluated in clinical trials, as patients with autoimmune conditions are typically excluded. Expert recommendations highlight the need for a careful risk/benefit analysis in such patients (Postow, 2015). Registrational trials of ipilimumab, nivolumab, and pembrolizumab monotherapy included sufficiently high numbers of elderly patients (aged ≥ 65 years) to indicate no overall differences in safety or efficacy, suggesting these patients may be treated as the general population (Bristol-Myers Squibb, 2015c, 2016; Merck, 2015a). Based on CheckMate 069 and 067, data also suggest similar outcomes for nivolumab and ipilimumab combination therapy in elderly patients (Postow et al., 2015; Larkin et al., 2015a).

SUMMARY

Immune checkpoint blockade has emerged as a promising new treatment strategy, with three immune checkpoint inhibitor antibodies currently approved by the FDA for the treatment of metastatic melanoma as monotherapy (ipilimumab, pembrolizumab, and nivolumab) as well as in combination (nivolumab and ipilimumab). A clear understanding of the distinct immune-

mediated safety profile of these agents is critical to their safe and appropriate use. The irAEs are well known, and several management algorithms, practical checklists, and tools have been established to aid patient management. Clinical data suggest that appropriate immunosuppressive treatment does not impair therapeutic efficacy, and most irAEs resolve with the use of immunomodulatory medications.

These novel therapies have opened a new avenue for antitumor response. However, we must recognize that patients who have been treated with immune checkpoint inhibitors may develop immune-related patterns of response that may deviate from Response Evaluation Criteria in Solid Tumors as a result of immune infiltration at tumor sites. Clinical and radiographic evaluation is imperative in determination of clinical benefit, and advanced health-care providers such as nurse practitioners and PAs are ideally placed to monitor, educate, and liaise with patients and the multidisciplinary team to facilitate early identification and intervention should irAEs occur, ensuring optimal management and patient outcome.

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☞ *See Appendices A through C on the following pages.*

Appendix A Grading of irAEs: Common Terminology Criteria for Adverse Events for Dermatologic, Gastrointestinal, and Endocrine irAEs

Dermatologic adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	–	–
Rash acneiform	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10% to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any percentage of BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Rash maculopapular	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10% to 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL	–	–

Gastrointestinal adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Endocrine adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Note. ADL = activities of daily living (instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.; self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden); BSA = body surface area; IV = intravenous; irAEs = immune-related adverse events. Information from NCI (2009).

Appendix B Management of Dermatologic, Gastrointestinal, and Endocrine irAEs

Dermatologic adverse events

Ipilimumab		Nivolumab	Pembrolizumab
Gr. 1	• Continue ipilimumab and administer symptomatic treatment • Continue ipilimumab on resolution of symptoms • Symptoms persist > 1 week: continue ipilimumab; administer topical or systemic steroids (0.5–1 mg or equivalent); once controlled, taper steroids over at least 1 month	**General guidance** • Suspected irAE: confirm etiology, exclude other causes • Based on the severity of the adverse reaction, withhold nivolumab, administer high-dose corticosteroids • Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event • Permanently discontinue nivolumab for any life-threatening or grade 4 AE; any severe or grade 3 treatment-related AE that recurs; inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks; persistent grade 2 or 3 AEs that do not recover to grade 0–1 within 12 weeks after last dose	**General guidance** • Suspected irAE: confirm etiology, exclude other causes • Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids • Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Restart pembrolizumab if the adverse reaction remains at grade 1 or less • Permanently discontinue pembrolizumab for any adverse reaction that does not improve to grade 0–1 within 12 weeks after last dose or for which corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, any severe or grade 3 immune-mediated adverse reaction that recurs, and for any life-threatening immune-mediated adverse reaction
Gr. 2	• Withhold ipilimumab and administer symptomatic treatment • Resume ipilimumab until administration of all 4 planned doses, or 16 weeks from the first dose • Symptoms persist > 1 week: administer topical or systemic steroids (0.5–1 mg or equivalent); once controlled, taper steroids over at least 1 month		
Gr. 3/4	• Withhold treatment. Permanently discontinue ipilimumab in patients with SJS, TEN, or rash complicated by full-thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations • Dermatology consultation/referral • Administer 1–2 mg/kg/day of prednisone or equivalent • Symptoms resolve or return to grade 1: taper steroids over at least 1 month; resume ipilimumab when steroid dose is ≤ 7.5 mg prednisone or equivalent until administration of all 4 planned doses, or 16 weeks from the first dose		

Gastrointestinal adverse events

Ipilimumab		Nivolumab	Pembrolizumab
Gr. 1	• Continue ipilimumab and administer antidiarrheal treatment • Employ close monitoring for worsening symptoms and educate patient to report worsening immediately	**Gr. 1** • Continue nivolumab and administer antidiarrheal treatment • Employ close monitoring for worsening symptoms and educate patient to report worsening immediately	**Gr. 1** • Supportive care • Continue pembrolizumab and monitor
Gr. 2	• Withhold ipilimumab and administer antidiarrheal treatment • If symptoms persist > 1 week, worsen, or recur: administer 0.5 mg/kg/day prednisone or equivalent • If symptoms improve to grade 1 or resolve: resume ipilimumab • If steroids have been administered: taper steroids over at least 1 month; resume ipilimumab when steroid dose is ≤ 7.5 mg prednisone or equivalent per day until administration of all 4 planned doses, or 16 weeks from the first dose • If symptoms worsen: treat as grade 3/4	**Gr. 2** • Withhold nivolumab and administer antidiarrheal treatment • If symptoms persist > 5 days, or recur: administer 0.5 to 1.0 mg/kg/day prednisone equivalents • If improved: resume nivolumab; if steroids have been administered, taper steroids over at least 1 month before resuming nivolumab • If symptoms worsen or persist > 3 to 5 days with oral steroids: treat as grade 3/4	**Gr. 2/3** • Withhold pembrolizumab • Administer corticosteroids • Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Restart pembrolizumab if the adverse reaction remains at grade 1 or less • Permanently discontinue pembrolizumab for any adverse reaction that does not improve to grade 0/1 within 12 weeks after last dose, for which corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, or for any severe or grade 3 immune-mediated adverse reaction that recurs
Gr. 3/4	• Permanently discontinue ipilimumab • Rule out bowel perforation; administer 1 to 2 mg/kg/day of prednisone or equivalent • Consider endoscopic evaluation/referral • If improved from grade 3: continue steroids at the same dose until grade 1; upon improvement to grade 1 or less, initiate steroid taper over at least 1 month • If symptoms worsen or persist 3 to 5 days, or recur after improvement: add noncorticosteroid immunosuppressive medication	**Gr. 3/4** • Grade 3: withhold nivolumab until grade 1 • Grade 3 persists or worsens, or grade 4: permanently discontinue nivolumab • Administer 1 to 2 mg/kg/day prednisone equivalents • Consider lower-GI endocscopy/referral • If improved from grade 3: when at grade 1, taper steroids over at least 1 month before resuming nivolumab • If improved from persistent grade 3 or grade 4: continue steroids until grade 1, then taper over at least 1 month • If symptoms persist > 3 to 5 days, or recur after improvement: add noncorticosteroid immunosuppressive medication	**Gr. 4** • Permanently discontinue pembrolizumab

☞ *Appendix B continued on next page.*

Appendix B Management of Dermatologic, Gastrointestinal, and Endocrine irAEs (cont.)

Endocrine adverse events

Ipilimumab		Nivolumab		Pembrolizumab	
Asymptomatic	• Continue ipilimumab • Monitor: If TSH < 0.5x LLN, or TSH > 2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated • Consult: consider endocrinology • Follow-up: continue standard monitoring	**Asymptomatic**	• Continue nivolumab • Monitor: If TSH < 0.5x LLN, or TSH > 2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated • Consult: consider endocrinology • Follow-up: continue standard monitoring	**Asymptomatic or grade 1**	• Supportive care • Continue pembrolizumab and monitor
Symptomatic	• Withhold ipilimumab • Monitor: Evaluate endocrine function. Consider pituitary scan. Repeat labs in 1 to 3 weeks/MRI in 1 month if symptoms persist but normal lab/pituitary scan • Consult: consider endocrinology • Administer 1 to 2 mg/kg/day prednisone or equivalent, if symptomatic with abnormal lab/pituitary scan • Hormone replacement: initiate if symptomatic with abnormal lab/pituitary scan (long-term replacement therapy may be needed) • Follow-up: If improved (with or without hormone therapy): resume ipilimumab when steroid dose is ≤ 7.5 mg prednisone or equivalent until administration of all 4 planned doses, or 16 weeks from the first dose; taper steroids over at least 1 month; continue standard monitoring • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component	**Symptomatic**	• Continue nivolumab for hypothyroidism or hyperthyroidism; withhold nivolumab for other endocrinopathies with abnormal lab/pituitary scan • Monitor: Evaluate endocrine function. Consider pituitary scan. Repeat labs in 1 to 3 weeks/MRI in 1 month if symptoms persist but normal lab/pituitary scan • Consult: consider endocrinology • Hormone replacement: initiate if symptomatic with abnormal lab/pituitary scan • Follow up: if improved (with or without hormone replacement) then resume nivolumab; continue standard monitoring • Patients with adrenal insufficiency may need to continue steroids with mineral-ocorticoid component	**Symptomatic or grade 3**	• Continue pembrolizumab for isolated hypothyroidism and manage using replacement therapy • Administer insulin for type 1 diabetes; withhold pembro-lizumab in cases of severe hyperglycemia until metabolic control if achieved • Withhold pembrolizumab for other endocrinopathies and administer corticosteroids: - Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month - Restart pembrolizumab if the adverse reaction remains at grade 1 or less - Permanently discontinue pembrolizumab for any adverse reaction for which corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks or for any severe or grade 3 immune-mediated adverse reaction that recurs
Suspected adrenal crisis[a]	• Discontinue ipilimumab • Monitor: rule out sepsis • Consult: endocrinology • Administer stress dose of IV steroids with mineral-ocorticoid activity and IV fluids • When adrenal crisis ruled out: treat as symptomatic endocrinopathy	**Suspected adrenal crisis[a]**	• Withhold nivolumab • Monitor: rule out sepsis • Consult: endocrinology • Administer stress dose of IV steroids with mineralocorticoid activity and IV fluids • When adrenal crisis ruled out: treat as symptomatic endocrinopathy	**Grade 4**	• Permanently discontinue pembrolizumab

Note. AE = adverse event; GI = gastrointestinal; IV = intravenous; irAEs = immune-related adverse events; LLN = lower limit of normal; MRI = magnetic resonance imaging; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TSH = thyroid-stimulating hormone; ULN = upper limit of normal. Information from Bristol-Myers Squibb (2015d, 2015a); Merck (2015b).
[a]For example, severe dehydration, hypotension, shock out of proportion to current illness.

Appendix C Nurse's Checklist for Immune Checkpoint Inhibitor Therapy[a]

QUESTIONS	RESPONSE		NOTES
GENERAL			
Are you having difficulty performing your normal activities?	Yes ☐	No ☐	
Have you had constant or unusual headaches?	Yes ☐	No ☐	
Have you felt drowsy or extremely tired?	Yes ☐	No ☐	
Have you felt dizzy or fainted?	Yes ☐	No ☐	
Have you had changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness?	Yes ☐	No ☐	
Have you felt cold?	Yes ☐	No ☐	
Have you gained or lost weight?	Yes ☐	No ☐	
Have you had hair loss?	Yes ☐	No ☐	
Has your voice gotten deeper?	Yes ☐	No ☐	
Are you urinating less often than usual?	Yes ☐	No ☐	
Do you have swelling in your ankles?	Yes ☐	No ☐	
Have you had severe or constant muscle or joint pain?	Yes ☐	No ☐	
Have you had muscle weakness?	Yes ☐	No ☐	
Have you been running a fever?	Yes ☐	No ☐	
Have you had changes in your eyesight?	Yes ☐	No ☐	
Have you had eye pain or redness?	Yes ☐	No ☐	
Are you having numbness or tingling in your hands or feet?	Yes ☐	No ☐	
Are you having unusual weakness of legs, arms, or face?	Yes ☐	No ☐	
Have you started taking any new medications (prescription, nonprescription, or herbal)? If yes, which and how often?	Yes ☐	No ☐	
SKIN			
Does your skin itch?	Yes ☐	No ☐	
Have you had a rash?	Yes ☐	No ☐	
Has your skin blistered and/or peeled?	Yes ☐	No ☐	
Do you have sores in your mouth?	Yes ☐	No ☐	
GASTROINTESTINAL			
Are you severely nauseous and/or vomiting?	Yes ☐	No ☐	
Do you have a loss of appetite or have you felt less hungry than usual?	Yes ☐	No ☐	
How many bowel movements are you having each day?	Yes ☐	No ☐	
• Is this different than normal? If yes, how?	Yes ☐	No ☐	
• Are your stools loose or watery, or do they have a foul smell?	Yes ☐	No ☐	
• Have you seen blood or mucus in your stools?	Yes ☐	No ☐	
• Are your stools dark, tarry, or sticky?	Yes ☐	No ☐	
Are you having painful bowel movements?	Yes ☐	No ☐	
Are you having pain or tenderness around your belly? If yes, where?	Yes ☐	No ☐	
HEPATIC			
Is your urine bloody, dark, or tea-colored?	Yes ☐	No ☐	
Do you bleed or bruise more easily than normal?	Yes ☐	No ☐	
Have you noticed your skin or the whites of your eyes are turning yellow?	Yes ☐	No ☐	
PULMONARY			
Do you have a new cough or one that has worsened?	Yes ☐	No ☐	
Are you having chest pain?	Yes ☐	No ☐	
Are you having trouble breathing or shortness of breath?	Yes ☐	No ☐	
NEUROLOGIC			
Have you experienced any periods of confusion?	Yes ☐	No ☐	
Have you lost consciousness at any point?	Yes ☐	No ☐	
Have you had any stiffness in your neck?	Yes ☐	No ☐	
Have you had any seizures?	Yes ☐	No ☐	
Have you had any sudden changes in your mood, perception, judgment, or memory?	Yes ☐	No ☐	

[a]Information from Bristol-Myers Squibb (2015b, 2015e).