PD-1 Inhibitors

Safety of use and management of immune-mediated adverse reactions in patients with head and neck cancer

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BACKGROUND: Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with programmed cell death protein 1 (PD-1) inhibitors has been associated with risk of developing immune-mediated adverse reactions (IMARs).

OBJECTIVES: This review provides nurses with an overview of the safety of PD-1 inhibitors approved by the U.S. Food and Drug Administration for recurrent or metastatic SCCHN following platinum chemotherapy, as well as recommendations for assisting with the diagnosis and management of IMARs.

METHODS: PubMed® searches were conducted to identify relevant articles to support this review. Algorithms from drug manufacturers for IMAR management were also reviewed.

FINDINGS: Before treatment with PD-1 inhibitors, nurses should map patients' baseline profiles, which play a key role in aiding the healthcare team in the timely diagnosis and treatment of IMARs. Nurses should educate patients and caregivers on identifying signs and symptoms of IMARs and their progression. Within the interprofessional healthcare team, nurses play an important role in ensuring efficient management of IMARs to minimize withholding or discontinuation of PD-1 immunotherapy.

KEYWORDS
immune-mediated adverse reactions; PD-1 inhibitors; squamous cell carcinoma

DIGITAL OBJECT IDENTIFIER
10.1188/19.CJON.627-638

IMMUNOTHERAPY WITH PROGRAMMED CELL DEATH PROTEIN 1 (PD-1) inhibitors has become the standard of care for numerous malignancies (Constantinidou, Alifieris, & Trafalis, 2019). Nivolumab and pembrolizumab are two PD-1 inhibitors that have been approved by the U.S. Food and Drug Administration (FDA) for use in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) following platinum chemotherapy; both have demonstrated efficacy benefit and have a favorable safety profile compared with standard single-agent chemotherapy (Bristol-Myers Squibb, 2019a; Merck Sharp & Dohme Corp., 2019a). Nivolumab significantly improved overall survival (OS) compared with the investigator's choice of single-agent chemotherapy at primary analysis in a phase 3 trial (CheckMate 141) (Ferris et al., 2016), and OS benefit was maintained at two-year follow-up (Ferris et al., 2018). Pembrolizumab resulted in durable tumor responses in phase 1b (KEYNOTE-012) (Chow et al., 2016; Mehra et al., 2018; Seiwert et al., 2016) and phase 2 (KEYNOTE-055) (Bauml et al., 2017) studies. In addition, OS benefit with pembrolizumab versus standard-of-care, single-agent chemotherapy was noted in a post hoc analysis of a phase 3 study (KEYNOTE-040) (Cohen et al., 2019). In randomized phase 3 studies, nivolumab and pembrolizumab treatment stabilized health-related quality of life, whereas deterioration of health-related quality of life was noted in the chemotherapy arms of the respective studies (Cohen et al., 2018; Harrington et al., 2017). In June 2019, pembrolizumab was also approved by the FDA for first-line treatment of patients with recurrent or metastatic SCCHN in combination with platinum and fluorouracil, and as a single agent in patients with tumors that express programmed cell death-ligand 1 (PD-L1) (combined positive score [the number of PD-L1 staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100] of 1 or greater) (Merck Sharp & Dohme Corp., 2019a).

PD-1 inhibitors demonstrated a more favorable safety profile than chemotherapy, with a lower incidence of grade 3–4 treatment-related adverse events (TRAEs) (Cohen et al., 2019; Ferris et al., 2016, 2018). However, because of their mechanism of action, patients treated with PD-1 inhibitors may experience immune-mediated adverse reactions (IMARs). Tumor cells can upregulate PD-L1 and PD-L2, which bind to PD-1 receptors on T cells, suppressing the immune system and allowing the cancer cells to evade elimination (Topalian, Drake, & Pardoll, 2015). PD-1 inhibitors act by blocking the interaction between PD-1 and PD-L1/PD-L2, preventing checkpoint inhibition on T cells, and enhancing their ability to target tumor cells; this

TABLE 1.
ADVERSE EVENTS (INCIDENCE > 1%) WITH POTENTIAL IMMUNOLOGIC CAUSE IN CTs OF FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

	PD-1 INHIBITORS[a]		CHEMOTHERAPY	
ADVERSE EVENT	**ANY G (%)**	**G 3–4 (%)**	**ANY G (%)**	**G 3–4 (%)**
Endocrine				
Hypothyroidism	4–16	0–< 1	1–4	0
Hyperthyroidism	1–2	0	0–< 1	0
Adrenal insufficiency	3	–	–	–
Gastrointestinal				
Diarrhea	7	0	14	2
Hepatic				
AST increase	1	0	2	0
ALT increase	1	< 1	3	1
Hypersensitivity				
IRR	1–3	0–< 1	2–3	< 1–1
Musculoskeletal				
Myositis	2	0	–	–
Renal				
Acute kidney injury	< 1	0	2	1
Respiratory				
Pneumonitis	2–4	1–2	1	0–1
Skin and SC tissue				
Pruritus	7	0	0	0
Rash	2–8	0–2	5	1
Maculopapular rash	2	0	1	0
Erythema	< 1	0	4	1
PPE syndrome	< 1	0	2	1
Severe skin reaction	3	2	4	3
Dermatitis	0	0	2	0

[a] Nivolumab or pembrolizumab
ALT—alanine transaminase; AST—aspartate transaminase; CT—clinical trial; FDA—U.S. Food and Drug Administration; G—grade; IRR—infusion-related reaction; PD-1—programmed cell death protein 1; PPE—palmar-plantar erythrodysesthesia; R/M—recurrent or metastatic; SC—subcutaneous; SCCHN—squamous cell carcinoma of the head and neck
Note. Based on information from Bauml et al., 2017; Chow et al., 2016; Cohen et al., 2019; Ferris et al., 2016, 2018; Seiwert et al., 2016.

increased immune activity may result in the development of IMARs (Naidoo et al., 2015).

As members of the interprofessional healthcare team, nurses contribute to the diagnosis, monitoring, and management of IMARs. This review of IMARs associated with FDA-approved PD-1 inhibitors for recurrent or metastatic SCCHN provides a foundation for management of IMARs in clinical practice.

Methods

A PubMed® search was conducted to identify safety data from clinical trials of FDA-approved PD-1 inhibitors in recurrent or metastatic SCCHN between January 1, 2015, and April 11, 2019. Relevant abstracts spanning this period were identified from meetings of the American Society of Clinical Oncology, European Society for Medical Oncology, and American Association for Cancer Research. Likewise, a PubMed search was conducted to identify published reports of management guidelines for IMARs associated with PD-1 inhibitors. Relevant references cited in articles identified by the aforementioned searches were also reviewed, as were IMAR management algorithms developed by drug manufacturers.

Overview of Adverse Events

Among patients receiving at least one dose of therapy, TRAEs occurred in 59%–64% of patients in the nivolumab and pembrolizumab arms and in 77%–84% of patients in the investigator's choice and standard-of-care arms in clinical trials of recurrent or metastatic SCCHN (Bauml et al., 2017; Chow et al., 2016; Cohen et al., 2019; Ferris et al., 2016; Seiwert et al., 2016). Grade 3–5 TRAEs were reported in 9%–17% of patients treated with nivolumab or pembrolizumab and in 35%–36% of patients treated with the investigator's choice or standard of care. In clinical trials of recurrent or metastatic SCCHN, the most common TRAEs (with incidence of 5% or greater) associated with nivolumab and pembrolizumab were fatigue, pruritus, hypothyroidism, nausea, decreased appetite, diarrhea, rash, asthenia, anemia, and increased aspartate transaminase. Treatment discontinuation because of TRAEs was reported in 4%–6% of patients (Bauml et al., 2017; Chow et al., 2016; Cohen et al., 2019; Ferris et al., 2018).

Patients with recurrent or metastatic SCCHN can experience TRAEs associated with prior multimodality treatment for locally advanced disease. Fatigue is the most common TRAE associated with PD-1 inhibitors in recurrent or metastatic SCCHN (Bauml et al., 2017; Chow et al., 2016; Cohen et al., 2019; Ferris et al., 2016; Seiwert et al., 2016). The high incidence of fatigue can be attributed, in part, to hypothyroidism, which can result from prior radiation exposure during treatment for locally advanced SCCHN (Chaker, Bianco, Jonklaas, & Peeters, 2017; Cohen et al., 2016). Malnutrition is associated with SCCHN because of the disease itself or treatment (e.g., surgery, radiotherapy) (Gorenc, Kozjek, & Strojan, 2015). Treatment-related facial edema has been reported in a small

proportion of patients receiving pembrolizumab for recurrent or metastatic SCCHN (Mehra et al., 2018). Although its incidence is low, treatment-related facial edema can potentially affect nutrition intake in conjunction with secondary lymphedema, which has been reported as a common late side effect of multimodality treatment received by patients for locally advanced SCCHN (incidence of approximately 75% at three or more months post-treatment) (Deng et al., 2012; Smith & Lewin, 2010).

In clinical trials, treatment-related deaths with nivolumab were attributed to pneumonitis and hypercalcemia; treatment-related deaths with pembrolizumab were attributed to pneumonitis, large intestine perforation, malignant neoplasm progression, Stevens-Johnson syndrome, and an unspecified cause (Bauml et al., 2017; Cohen et al., 2019; Ferris et al., 2016). Treatment-related deaths in the control (chemotherapy) arms occurred in patients with lung infection, pneumonia, and disease progression (Cohen et al., 2019; Ferris et al., 2016).

Treatment with PD-1 inhibitors is associated with the development of IMARs, which can affect almost any organ system (Naidoo et al., 2015). IMARs occurring in more than 1% of patients and reported in clinical trials of nivolumab and pembrolizumab in recurrent or metastatic SCCHN are listed in Table 1; the most common IMARs were skin-related, endocrine, gastrointestinal, or respiratory events. A summary of IMARs reported in less than 10% of patients treated with immune checkpoint inhibitors, including PD-1 inhibitors, is presented in Figure 1.

After initiation of treatment, IMARs can occur at any time, including after stopping treatment (Champiat et al., 2016). For patients with recurrent or metastatic SCCHN treated with nivolumab or pembrolizumab, no data have been reported about the onset of IMARs. In an analysis of 1,994 patients receiving single-agent nivolumab across multiple malignancies, median time to onset was 1.5 months for hyperthyroidism; 2.8–3.5 months for skin-related events, hypothyroidism or thyroiditis, hepatitis, and pneumonitis; and 4.3–5.3 months for adrenal insufficiency, type 1 diabetes mellitus, hypophysitis, and colitis (Bristol-Myers Squibb, 2019b). In an analysis of 2,799 patients receiving single-agent pembrolizumab for melanoma and non-small cell lung cancer, the median time to onset of IMARs was 1.2–1.4 months for hepatitis, thyroiditis, and hyperthyroidism and 3.3–3.7 months for pneumonitis, colitis, hypophysitis, and hypothyroidism (Merck Sharp & Dohme Corp., 2019a).

Diagnosing, Monitoring, and Grading IMARs

Early diagnosis of IMARs is critical for their effective management and reversal (Michot et al., 2016). Timely assessment of IMARs by the interprofessional healthcare team contributes to accurate diagnoses, coordination of care, and prompt referrals; other potential etiologies of symptoms, such as infection or cancer progression, may complicate an accurate IMAR diagnosis (Champiat et al., 2016).

Documentation of a comprehensive baseline profile of the patient prior to initiating treatment with PD-1 inhibitors is key to ensuring that all health-related changes occurring during treatment are correctly assessed and that IMARs are diagnosed appropriately (Champiat et al., 2016). Nurses play a crucial role in this regard. In particular, they must capture any history of chronic or autoimmune diseases and long-term exposure to cortisone, which may affect susceptibility to IMARs. Chronic infections may flare up during treatment because of immune reactivation, leading to a heightened antipathogen response. Therefore, a history of any previous infections should be gathered and risk factors for viral infections, such as viral hepatitis, evaluated. For patients with altered nutritional status because of prior surgical or radiation treatment, IMARs like colitis, enteritis, and thyroiditis may also be of particular concern. Regular medications, such as nonsteroidal anti-inflammatory

FIGURE 1.
IMARs (INCIDENCE < 10%) ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS[a]

ENDOCRINE
Pancreatitis, type 1 diabetes and risk of diabetic ketoacidosis, hypophysitis, acute adrenal insufficiency, hypovolemic shock

GASTROINTESTINAL
Colitis

GENERAL
Infusion reaction, anaphylactic shock

HEPATIC
Hepatitis

NEUROLOGIC
Guillain-Barré syndrome, autoimmune encephalitis, demyelination, myasthenic syndrome

OPHTHALMOLOGIC
Ocular and orbital inflammation, uveitis, retinal and choroidal diseases

RENAL
Acute kidney injury, nephritis

RESPIRATORY
Pneumonitis

RHEUMATOLOGIC
Inflammatory arthritis

SKIN
Severe skin reactions, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), Stevens-Johnson syndrome, toxic epidermal necrolysis

VASCULAR
Myocarditis, cardiac insufficiency

[a] Including anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies
CTLA-4—cytotoxic T-lymphocyte antigen 4; IMAR—immune-mediated adverse reaction; PD-L1—programmed cell death-ligand 1; PD-1; programmed cell death protein 1
Note. Based on information from Champiat et al., 2016; Kumar et al., 2017.

drugs and antibiotics, may interfere with treatment and should also be recorded. Given the high percentage of older adult patients with SCCHN, comorbidities are common (Champiat et al., 2016; Hartmann & Grandis, 2016). For example, patients with recurrent or metastatic SCCHN may have a high incidence of thyroid-related conditions or toxicities because of previous radiation exposure (Bhandare, Kennedy, Malyapa, Morris, & Mendenhall, 2007). As such, physical examination, oxygen saturation levels, laboratory tests, and imaging should be performed before starting immunotherapy with PD-1 inhibitors to provide a reference point for subsequent test results (Champiat et al., 2016; Gordon et al., 2017; Haanen et al., 2017) (see Figure 2).

To diagnose IMARs promptly, nurses are advised to regularly assess and monitor signs and symptoms of inflammation and possible IMARs during treatment (before every treatment session or at least once a month). Nurses should also discuss changes noted on assessments with advanced practice providers to ensure that the appropriate course of action is followed. Patients should continue to be monitored for at least one year after stopping treatment (Champiat et al., 2016).

"Nurses contribute their assessment and monitoring skills so that potential IMARs can be promptly diagnosed and managed."

FIGURE 2.
ASSESSMENT AND MONITORING OF IMMUNE-MEDIATED ADVERSE REACTIONS

LABORATORY TESTS

Types
- Complete blood count
- Liver function
- Renal function
- Electrolytes
- Glucose
- Lactate dehydrogenase
- Erythrocyte sedimentation rate
- Pancreatic
- Hormonal axis

Frequency
- At baseline
- At dosing every 2 weeks (every 2 weeks during the first 12 weeks, every 4 weeks until 3 months after the last dose, and every 3 months thereafter)
- At dosing every 3 weeks (before every infusion until 3 months after the last dose and every 3 months thereafter)

RADIOLOGIC ASSESSMENTS

Types
- CT
- Brain MRI

Frequency
- At baseline
- Every 12 weeks (CT) or when abnormal at baseline (brain MRI)

CT—computed tomography; MRI—magnetic resonance imaging
Note. Based on information from Champiat et al., 2016; Haanen et al., 2017.

To establish the severity of IMARs, providers can use the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2017). However, the CTCAE guidelines were established before the advent of immunotherapies. Therefore, the CTCAE guidelines may not be sufficiently sensitive to grade IMARs without providers also offering their clinical judgment to determine the treatment plan (Kumar et al., 2017). Patient monitoring checklists are available for use by nurses and other healthcare providers to ensure that signs and symptoms of IMARs are accurately captured (Bristol-Myers Squibb, 2019c). During follow-up visits, nurses' use of checklists as a source of accurate data allows advanced practice providers to act on that data to grade IMARs.

Patient Education

Nurses play a pivotal role in educating patients and caregivers about the unique spectrum of IMARs associated with PD-1 inhibitors and in addressing patient questions and concerns. Patients should be encouraged to promptly report apparently general symptoms, such as fatigue or nausea, and avoid self-management because the symptoms may be indicative of IMARs (Champiat et al., 2016) (see Figure 3). When visiting healthcare providers other than their regular doctor, patients should have a card containing information regarding the immunotherapies they are receiving, details of IMARs associated with treatment, and instructions to call their oncologist prior to prescribing any medications, barring instances warranting urgent care (Champiat et al., 2016).

Management of IMARs

Timely treatment of IMARs is crucial to reduce their duration and severity (Champiat et al., 2016). Unlike adverse events associated

with chemotherapy, IMARs with PD-1 inhibitors do not appear to be dose-dependent, and dose reductions are not recommended for their management. Instead, treatment may be withheld or discontinued. Resources for management of IMARs include recommendations provided by the manufacturers of PD-1 inhibitors (Bristol-Myers Squibb, 2019b; Merck Sharp & Dohme Corp., 2019b) that are based on established algorithms used in clinical trials (Bristol-Myers Squibb, 2019b) and guidelines developed by oncology societies that are based on clinical consensus and experience (Brahmer et al., 2018; Haanen et al., 2017; Puzanov et al., 2017). Detailed recommendations for the management of the most common IMARs associated with PD-1 inhibitors, which include skin-related IMARs, endocrinopathies, pneumonitis, gastrointestinal IMARs, and hepatitis, are summarized in Table 2.

Corticosteroids are the primary treatment for IMARs and are administered when there is a need to reduce inflammation (Champiat et al., 2016). Because of their immunosuppressive effects, potential infectious etiologies should be ruled out prior to administration of corticosteroids. Clinical judgment should play an important role, in addition to CTCAE grading, in determining the appropriateness of initiating corticosteroid treatment (Horvat et al., 2015). Prolonged use of corticosteroids may leave the patient vulnerable to opportunistic infections (Postow, Sidlow, & Hellmann, 2018); to prevent this, prophylactic antibiotics may be warranted. Extended corticosteroid use could also be associated with hyperglycemia (Williams, Grauer, Henry, & Rockey, 2017). Nurses should monitor blood sugar levels regularly, particularly in patients with an increased risk of diabetes, such as those with high body mass index and baseline blood glucose levels. Supportive antacid medication may be used to reduce corticosteroid-associated heartburn (Spain, Diem, & Larkin, 2016).

With close monitoring, therapy may continue despite grade 1 IMARs (Brahmer et al., 2018; Bristol-Myers Squibb, 2019b; Champiat et al., 2016; Merck Sharp & Dohme Corp., 2019b). Treatment should be suspended in patients with grade 2 IMARs, with the exception of skin-related and endocrine IMARs, until they improve to grade 1. Grade 1–2 IMARs may be treated in the ambulatory setting, whereas more severe IMARs may require hospitalization. For grade 3 IMARs in any organ category, suspension of treatment is recommended along with a course of corticosteroids, typically administered via IV. Immunosuppressive therapy, such as anti-tumor necrosis factor-α (infliximab) or anti-interleukin-6 (tocilizumab), may be added for some IMARs that have not improved after corticosteroid use. Importantly, the continuation of treatment should be considered only if IMAR severity has reduced to grade 1, if corticosteroid (prednisone) dosage is 10 mg or less per day, and if treatment includes no other immunosuppressive drugs. For grade 4 toxicities, discontinue treatment. An exception to discontinuing treatment is if certain endocrinopathies can be controlled by medical management, such as hormone replacement therapy.

After IMAR severity reduces to grade 1, providers can gradually taper corticosteroids over a period of at least 30 days to avoid relapse or worsening of symptoms (Brahmer et al., 2018). Although most IMARs can be managed and do resolve, endocrine IMARs, such as hypophysitis and diabetes, may require lifelong hormonal treatment (Michot et al., 2016).

The baseline profile of patients developed by nurses prior to initiation of PD-1 immunotherapy can be helpful in ensuring

IMPLICATIONS FOR PRACTICE

- Act as the primary point of contact with patients to assist with the diagnosis, monitoring, and management of immune-mediated adverse reactions (IMARs) associated with U.S. Food and Drug Administration–approved programmed cell death protein 1 (PD-1) inhibitors in patients with recurrent or metastatic squamous cell carcinoma of the head and neck following platinum chemotherapy.
- Educate patients and caregivers on the unique spectrum of IMARs associated with PD-1 inhibitors, which is important to ensure prompt diagnosis of new or worsening signs and symptoms.
- Within the interprofessional team of healthcare providers, ensure efficient management of IMARs to minimize withholding or discontinuation of PD-1 immunotherapy.

FIGURE 3.
SIGNS AND SYMPTOMS THAT MAY BE INDICATIVE OF IMARs

ENDOCRINE
Fatigue, headaches, weight changes, dizziness, mood or behavioral changes, feeling cold, nausea, vomiting, thirst or appetite increase, polyuria, hair loss, muscle aches, deepened voice, constipation, increased sweating, rapid heartbeat

GASTROINTESTINAL
Diarrhea, blood or mucus in stool, severe abdominal pain or tenderness

GENERAL
Arthralgia or swelling joints, myalgia, unexplained fever, chest pain

HEPATIC
Yellowing of the skin or whites of the eyes, severe nausea or vomiting, pain on the right side of the abdomen, drowsiness, dark urine, bleeding or bruising more easily than normal, decreased appetite

NEUROLOGIC
Headache, confusion, muscle weakness, numbness, tiredness, sleepiness, hallucinations, forgetfulness, seizures, stiff neck, fever

OPHTHALMOLOGIC
Loss of vision in one or both eyes, change in eyesight

RESPIRATORY
Shortness of breath, coughing, chest pain

SKIN
Extensive rash, severe pruritis, itching, skin blistering, mucosal ulcers

IMAR—immune-mediated adverse reaction
Note. Based on information from Bristol-Myers Squibb, 2019b; Champiat et al., 2016; Merck Sharp & Dohme Corp., 2019b.

TABLE 2.
MANAGEMENT OF COMMON IMARs ASSOCIATED WITH FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

IMAR	NIVOLUMAB TREATMENT	PEMBROLIZUMAB TREATMENT
Adrenal insufficiency		
Grade 2 (moderate symptoms, medical intervention indicated)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Evaluate endocrine function. ■ Consider pituitary scan. ■ Repeat laboratory tests in 1–3 weeks or MRI in 1 month if symptoms persist with normal laboratory values or pituitary scan. ■ Consider endocrinology consultation.	–
Grade 3–4 (grade 3, severe symptoms, hospitalization indicated; grade 4, life-threatening consequences, urgent intervention indicated)	■ Permanently discontinue PD-1 inhibitor. ■ Evaluate endocrine function. ■ Consider pituitary scan. ■ Repeat laboratory tests in 1–3 weeks or MRI in 1 month if symptoms persist with normal laboratory values or pituitary scan. ■ Consider endocrinology consultation. ■ Administer 1–2 mg/kg prednisone or equivalent per day followed by taper over at least 1 month if improvement with or without hormone replacement before resuming treatment.[a] ■ Steroids may need to be continued with mineralocorticoid component. ■ Consider prophylactic antibiotics for opportunistic infections.	–
Diarrhea and colitis		
Grade 1 (diarrhea, increase of less than 4 stools per day over BL; colitis, asymptomatic)	■ Administer symptomatic treatment. ■ Monitor for worsening symptoms. ■ Educate patient to report worsening immediately. ■ Treat as grade 2 or 3–4 if symptoms worsen.	■ Manage with supportive care. ■ Monitor for symptoms.
Grade 2 (diarrhea, increase of 4–6 stools per day over BL, IV fluids less than 24 hours, no interference with ADL; colitis, abdominal pain, blood in stool)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer symptomatic treatment. ■ For colitis of more than 5 days, administer prednisone or equivalent 0.5–1 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 before resuming treatment.[a] ■ Consider prophylactic antibiotics for opportunistic infections. ■ Permanently discontinue PD-1 inhibitor for recurrent colitis. ■ If worsening or no improvement occurs despite initiation of corticosteroids, increase prednisone or equivalent dose to 1–2 mg/kg per day.[a]	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Permanently discontinue PD-1 inhibitor if symptoms do not improve to grade 1 or less within 12 weeks or the corticosteroid dose cannot be reduced to 10 mg or less of prednisone or equivalent per day.
Grade 3 (diarrhea, increase of 7 or more stools per day over BL, incontinence, IV fluids 24 hours or more, interference with ADL; colitis, medical intervention indicated, severe abdominal pain, peritoneal signs)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment.[a] ■ Add prophylactic antibiotics for opportunistic infections. ■ Consider lower gastrointestinal endoscopy. ■ Permanently discontinue PD-1 inhibitor for recurrent colitis. ■ If symptoms persist more than 3–5 days or recur after improvement, add noncorticosteroid immunosuppressive medication.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Permanently discontinue PD-1 inhibitor if symptoms do not improve to grade 1 or less within 12 weeks or the corticosteroid dose cannot be reduced to 10 mg or less of prednisone or equivalent per day.
Grade 4 (colitis, life-threatening, perforation)	■ Permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month before resuming treatment. ■ Add prophylactic antibiotics for opportunistic infections. ■ Consider lower gastrointestinal endoscopy. ■ Permanently discontinue PD-1 inhibitor for recurrent colitis. ■ If symptoms persist more than 3–5 days or recur after improvement, add noncorticosteroid immunosuppressive medication.	■ Permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by tapertaper over at least 1 month if improvement to grade 1 or less.

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TABLE 2. *(CONTINUED)*

MANAGEMENT OF COMMON IMARs ASSOCIATED WITH FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

IMAR	NIVOLUMAB TREATMENT	PEMBROLIZUMAB TREATMENT
Hepatitis with hepatocellular carcinoma		
AST/ALT within normal limits at BL and increases to > 3–5 times ULN; AST/ALT > 1–3 times ULN at BL and increases to > 5–10 times ULN; AST/ALT > 3–5 times ULN at BL and increases to > 8–10 times ULN	■ Withhold PD-1 inhibitor until AST/ALT returns to BL. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper.[a]	–
AST/ALT < 2 times ULN at BL and increases to ≥ 5 times ULN; AST/ALT ≥ 2 or more times ULN at BL and increases to > 3 times BL; total BILI < 1.5 mg/dl at BL and increases to > 2 mg/dl; total BILI increases to > 3 mg/dl regardless of BL levels	–	■ Withhold PD-1 inhibitor until improvement to grade 1 or less or to BL.
AST/ALT increases to > 10 times ULN or total BILI increases to > 3 times ULN	■ Permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper.[a]	–
AST/ALT > 10 times ULN or Child-Pugh score of ≥ 9 points; gastrointestinal bleeding suggestive of portal hypertension; new onset of clinically detectable ascites; encephalopathy	–	■ Permanently discontinue PD-1 inhibitor.
Hepatitis without hepatocellular carcinoma		
Grade 1 (AST/ALT > 1–3 times ULN and/or total BILI > 1–1.5 times ULN)	■ Monitor liver function prior to and periodically during treatment. ■ Treat as grade 2 or grade 3–4 if symptoms worsen.	■ Manage with supportive care. ■ Monitor for symptoms.
Grade 2 (AST/ALT > 3–5 times ULN or total BILI > 1.5–3 times ULN)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Monitor liver function every 3 days. ■ For transaminase elevations, administer prednisone or equivalent 0.5–1 mg/kg followed by taper over at least 1 month if improvement to grade 1 or BL before resuming treatment.[a] ■ Consider adding prophylactic antibiotics. ■ Resume routine liver function monitoring. ■ Treat as grade 3–4 if AST/ALT is > 5 times ULN and/or total BILI is > 3 times ULN.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 0.5–1 mg/kg per day (initial dose) followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment.[b] ■ Permanently discontinue PD-1 inhibitor if symptoms do not improve to grade 1 or less within 12 weeks or the corticosteroid dose cannot be reduced to 10 mg or less of prednisone or equivalent per day.
Grade 3–4 (AST/ALT > 5 times ULN or total BILI > 3 times ULN; for patients with liver metastases who begin treatment with grade 2 AST or ALT, if AST or ALT increases 50% or greater relative to BL and lasts for at least 1 week[c]	■ Permanently discontinue PD-1 inhibitor. ■ Monitor liver function every 1–2 days. ■ Have gastroenterology consultation. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 2.[a] ■ Administer prophylactic antibiotics for opportunistic infections. ■ Add noncorticosteroid immunosuppressive medication if no improvement in 3–5 days or if symptoms worsen or rebound.	■ Permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month before resuming treatment.

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TABLE 2. *(CONTINUED)*

MANAGEMENT OF COMMON IMARs ASSOCIATED WITH FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

IMAR	NIVOLUMAB TREATMENT	PEMBROLIZUMAB TREATMENT
Hyperthyroidism		
Grade 1–2	■ There are no recommended dose modifications. ■ Monitor thyroid function prior to and periodically during treatment. ■ Consider endocrinology consultation. ■ Initiate medical management.	■ Monitor for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. ■ Administer thionamides and beta blockers as appropriate.
Grade 3–4	■ There are no recommended dose modifications. ■ Monitor thyroid function prior to and periodically during treatment. ■ Consider endocrinology consultation. ■ Initiate medical management.	■ Monitor for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. ■ Withhold PD-1 inhibitor until improvement to grade 1 or less, or permanently discontinue PD-1 inhibitor. ■ Administer thionamides and beta blockers as appropriate.
Hypophysitis		
Grade 2 (moderate, minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental ADL)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Evaluate endocrine function. ■ Consider pituitary scan. ■ Repeat laboratory tests in 1–3 weeks or MRI in 1 month if symptoms persist with normal laboratory tests and pituitary scan. ■ Consider endocrinology consultation. ■ Administer prednisone or equivalent 1 mg/kg per day followed by taper over at least 1 month if improvement with or without hormone replacement before resuming treatment.[a] ■ Consider prophylactic antibiotics for opportunistic infections. ■ Administer hormone replacement therapy as clinically indicated.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Administer hormone replacement therapy as clinically indicated.
Grade 3 (severe or medically significant but not immediately life-threatening, hospitalization or prolongation or existing hospitalization indicated, disabling, limiting self-care ADL)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Evaluate endocrine function. ■ Consider pituitary scan. ■ Repeat laboratory tests in 1–3 weeks or MRI in 1 month if symptoms persist with normal laboratory tests and pituitary scan. ■ Consider endocrinology consultation. ■ Administer prednisone or equivalent 1 mg/kg per day followed by taper over at least 1 month if improvement with or without hormone replacement before resuming treatment.[a] ■ Consider prophylactic antibiotics for opportunistic infections. ■ Administer hormone replacement therapy as clinically indicated.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less, or permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Administer hormone replacement therapy as clinically indicated.
Grade 4 (life-threatening consequences, urgent intervention indicated)	■ Permanently discontinue PD-1 inhibitor. ■ Evaluate endocrine function. ■ Consider pituitary scan. ■ Repeat laboratory tests in 1–3 weeks or MRI in 1 month if symptoms persist with normal laboratory tests and pituitary scan. ■ Consider endocrinology consultation. ■ Administer prednisone or equivalent 1 mg/kg per day followed by taper over at least 1 month if improvement with or without hormone replacement.[a] ■ Consider prophylactic antibiotics for opportunistic infections. ■ Administer hormone replacement therapy as clinically indicated.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less, or permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Administer hormone replacement therapy as clinically indicated.
Hypothyroidism		
All presentations	■ There are no recommended dose modifications. ■ Monitor thyroid function prior to and periodically during treatment. ■ Consider endocrinology consultation. ■ Adminster hormone replacement therapy.	■ Monitor for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. ■ Administer replacement hormones.

Continued on the next page

TABLE 2. *(CONTINUED)*

MANAGEMENT OF COMMON IMARs ASSOCIATED WITH FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

IMAR	NIVOLUMAB TREATMENT	PEMBROLIZUMAB TREATMENT
Pneumonitis		
Grade 1 (radiographic changes only)	■ Monitor every 2–3 days. ■ Consider pulmonary and infectious disease consultation. ■ Reimage at least every 3 weeks. ■ Treat as grade 2 or grade 3–4 if symptoms worsen.	■ Manage with supportive care. ■ Monitor for symptoms.
Grade 2 (mild to moderate new symptoms)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Monitor daily. ■ Have pulmonary and infectious disease consultation. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to BL before resuming treatment.[a] ■ Consider adding prophylactic antibiotics. ■ Consider bronchoscopy or lung biopsy. ■ Re-image every 1–3 days. ■ Treat as grade 3–4 if no improvement after 2 weeks or worsening.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Permanently discontinue PD-1 inhibitor if recurrent grade 2 or if symptoms do not improve to grade 1 or less within 12 weeks or the corticosteroid dose cannot be reduced to 10 mg or less of prednisone or equivalent per day.
Grade 3–4 (severe new symptoms, new or worsening hypoxia, life-threatening)	■ Permanently discontinue PD-1 inhibitor. ■ Hospitalize. ■ Have pulmonary and infectious disease consultation. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper if improvement to BL over at least 6 weeks.[a] ■ Have pulmonary and infectious disease consultation. ■ Add prophylactic antibiotics for opportunistic infections. ■ Consider bronchoscopy or lung biopsy. ■ Administer noncorticosteroid immunosuppressive medication if symptoms persist or worsen after 2 days.	■ Permanently discontinue PD-1 inhibitor. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less.
Skin conditions		
Grade 1–2 rash (covering 30% or less BSA)	■ Administer symptomatic treatment (e.g., antihistamines, topical steroids). ■ If symptoms persist more than 1–2 weeks or recur, consider skin biopsy and withhold PD-1 inhibitor. ■ If symptoms worsen, treat as grade 3–4.	■ For rashes, including exfoliative dermatitis and bullous pemphigoid, withhold or permanently discontinue PD-1 inhibitor (based on severity of the adverse reaction). Administer prednisone or equivalent 1–2 mg/kg per day followed by a taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ For suspected SJS or TEN, withhold PD-1 inhibitor and refer the patient to specialized care for assessment and treatment. ■ For confirmed SJS or TEN, permanently discontinue PD-1 inhibitor.
Grade 3 rash or signs or symptoms of SJS or TEN (covering more than 30% BSA, life-threatening consequences)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Have dermatology consultation. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ Add prophylactic antibiotics for opportunistic infections. ■ Consider skin biopsy. ■ For signs or symptoms of SJS or TEN, refer the patient to specialized care for assessment and treatment.	■ For rashes, including exfoliative dermatitis and bullous pemphigoid, withhold or permanently discontinue PD-1 inhibitor (based on severity of the adverse reaction). Administer prednisone or equivalent 1–2 mg/kg per day followed by a taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ For suspected SJS or TEN, withhold PD-1 inhibitor and refer the patient to specialized care for assessment and treatment. ■ For confirmed SJS or TEN, permanently discontinue PD-1 inhibitor.
Grade 4 rash or confirmed SJS or TEN (covering more than 30% BSA, life-threatening consequences)	■ Permanently discontinue PD-1 inhibitor. ■ Have dermatology consultation. ■ Administer prednisone or equivalent 1–2 mg/kg per day followed by taper over at least 1 month if improvement to grade 1 or less before resuming treatment.	■ For rashes, including exfoliative dermatitis and bullous pemphigoid, withhold or permanently discontinue PD-1 inhibitor (based on severity of the adverse reaction). Administer prednisone or equivalent 1–2 mg/kg per day followed by a taper over at least 1 month if improvement to grade 1 or less before resuming treatment. ■ For suspected SJS or TEN, withhold PD-1 inhibitor and refer the patient to specialized care for assessment and treatment.

Continued on the next page

TABLE 2. *(CONTINUED)*
MANAGEMENT OF COMMON IMARs ASSOCIATED WITH FDA-APPROVED PD-1 INHIBITORS IN R/M SCCHN

IMAR	NIVOLUMAB TREATMENT	PEMBROLIZUMAB TREATMENT
Skin conditions *(continued)*		
Grade 4 rash or confirmed SJS or TEN (covering more than 30% BSA, life-threatening consequences)	■ Add prophylactic antibiotics for opportunistic infections. ■ Consider skin biopsy. ■ For signs or symptoms of SJS or TEN, refer the patient to specialized care for assessment and treatment.	■ For confirmed SJS or TEN, permanently discontinue PD-1 inhibitor.
Type 1 diabetes mellitus		
Grade 3 hyperglycemia (fasting glucose value of > 250–500 mg/dl or > 13.9–27.8 mmol/L, hospitalization indicated)	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Monitor for hyperglycemia or other signs and symptoms of type 1 diabetes mellitus. ■ Consider endocrinology consultation.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer insulin for type 1 diabetes mellitus and antihyperglycemics for severe hyperglycemia.
Grade 4 hyperglycemia (fasting glucose value of > 500 mg/dl or > 27.8 mmol/L, life-threatening consequences)	■ Permanently discontinue PD-1 inhibitor. ■ Monitor for hyperglycemia or other signs and symptoms of type 1 diabetes mellitus. ■ Consider endocrinology consultation.	■ Withhold PD-1 inhibitor until improvement to grade 1 or less. ■ Administer insulin for type 1 diabetes mellitus and antihyperglycemics for severe hyperglycemia.

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at the start of tapering or earlier once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
[b] In patients with IMARs that could not be controlled with corticosteroids, administration of other systemic immunosuppressants can be considered (based on limited data from clinical studies).
[c] Included only in the pembrolizumab guidelines
ADL—activities of daily living; ALT—alanine transaminase; AST—aspartate transaminase; BL—baseline; BILI—bilirubin; BSA—body surface area; FDA—U.S. Food and Drug Administration; IMAR—immune-mediated adverse reaction; MRI—magnetic resonance imaging; PD-1—programmed cell death protein 1; R/M—recurrent or metastatic; SCCHN—squamous cell carcinoma of the head and neck; SJS—Stevens-Johnson syndrome; TEN—toxic epidermal necrolysis; ULN—upper limit of normal
Note. Based on information from Bristol-Myers Squibb, 2019b; Merck Sharp & Dohme Corp., 2019b.

that patients are eligible to receive corticosteroids. Nurses play a significant role in the management of IMARs by coordinating care among members of the interprofessional healthcare team, including specialists for the affected organs.

Case Studies

Case Study 1

A White female nonsmoker in her late 50s was initially diagnosed with biopsy-proven, poorly differentiated stage IVA human papillomavirus (HPV)–positive SCC of the left tonsil. No distant metastases were identified by computed tomography (CT) or positron-emission tomography (PET). She underwent left pharyngectomy and node dissection, and was subsequently treated with adjuvant cisplatin (weekly) and radiation therapy, which was well tolerated.

At her six-month follow-up, CT and PET imaging identified the presence of pulmonary nodules and metastatic disease. Biopsy confirmed the diagnosis of metastatic SCC. Treatment with nivolumab (240 mg every two weeks) was started. After eight treatments, she developed grade 2 diarrhea and grade 2 hyponatremia. She was treated with 1 mg/kg prednisone and conventional antidiarrheal agents. She received fluids and underwent comprehensive metabolic panel checks on a weekly basis. Nivolumab treatment was held for six weeks until resolution of hyponatremia and diarrhea and completion of steroid tapering. She has since been treated with nivolumab for three months and has stable disease with no recurrence of diarrhea or worsening of hyponatremia.

Case Study 2

A White male nonsmoker in his late 40s was diagnosed initially with HPV-positive SCC of the base of the tongue; according to the TNM system, which measures tumor (T), lymph node (N), and metastasis (M), his cancer stage was described as T2N2a. He underwent concurrent chemotherapy and radiation therapy with weekly cisplatin for three months. After seven months, he developed lesions within the liver, consistent with biopsy-proven metastatic SCC. He underwent segmental resection and radiofrequency ablation of two liver lesions, which were positive for disease. At that point, he had no detectable disease.

He subsequently developed progressive liver and bone metastases and was treated with the EXTREME regimen (cetuximab with platinum-based chemotherapy and 5-fluorouracil). He responded well and continued on maintenance cetuximab for eight months.

However, progression of liver and bone metastases was diagnosed, as well as new metastases to the neck, peripancreatic, and precaval lymph nodes. He underwent palliative radiation therapy, and treatment with nivolumab at 240 mg was started. He received eight biweekly doses, and imaging data indicated stable disease.

About five months after the initiation of nivolumab treatment, he developed left eye pain, particularly with eye movement, and a small distortion in his central vision, followed by a halo that worsened over a four-day period. Nivolumab treatment was stopped, and he was referred for ophthalmology consultation. Based on a magnetic resonance imaging scan, retrobulbar optic neuritis was diagnosed, and it was attributed to nivolumab. He was initially treated with three doses of 1,000 mg of methylprednisolone and transitioned to prednisone 1 mg/kg in divided doses of 120 mg every 12 hours. His decreased vision resolved over three days. After this, steroids were tapered over a period of at least 30 days. One month after treatment was stopped, he was doing well, with normal vision. Because of his history of optic neuritis, nivolumab treatment was not resumed.

Implications for Practice

The provided case studies serve as examples of IMAR management using the recommendations outlined in this article. Nurses are significantly involved in the early detection and monitoring of IMARs. As members of the interprofessional healthcare team, nurses contribute their assessment and monitoring skills so that potential IMARs can be promptly diagnosed and managed. Nurses hold a pivotal role in educating patients and caregivers in identifying signs and symptoms of IMARs and seeking timely treatment.

Conclusion

PD-1 inhibitors have demonstrated efficacy in patients with recurrent or metastatic SCCHN following platinum chemotherapy and have become an important part of the treatment paradigm for this cancer. Treatment with PD-1 inhibitors is generally associated with a more favorable safety profile compared with chemotherapy. However, because of their mechanism of action, treatment with PD-1 inhibitors may be associated with the development of IMARs. As the primary point of contact for patients treated with PD-1 inhibitors, nurses play an important role in the early detection and monitoring of IMARs. Nurses also aid an interprofessional team of healthcare providers in the efficient management of IMARs by providing the information necessary for timely intervention and treatment. Finally, nurses play a pivotal role in educating patients and caregivers in identifying signs and symptoms of IMARs and seeking timely treatment. This article has summarized recommendations to provide nurses with the tools to efficiently assist with the diagnosis, monitoring, and management of IMARs associated with FDA-approved PD-1 inhibitors and to minimize treatment disruption in patients with recurrent or metastatic SCCHN following platinum chemotherapy.

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The authors take full responsibility for this content. This work was supported by Bristol-Myers Squibb. Miller has previously served on speakers bureaus for AstraZeneca and Genentech. Writing support was provided by Caroline Anderson, PhD, and Meenakshi Subramanian, PhD, CMPP, at Evidence Scientific Solutions. The article has been reviewed by independent peer reviewers to ensure that it is objective and free from bias.

REFERENCES

Bauml, J., Seiwert, T.Y., Pfister, D.G., Worden, F., Liu, S.V., Gilbert, J., . . . Haddad, R. (2017). Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: Results from a single-arm, phase II study. *Journal of Clinical Oncology, 35,* 1542–1549. https://doi.org/10.1200/JCO.2016.70.1524

Bhandare, N., Kennedy, L., Malyapa, R.S., Morris, C.G., & Mendenhall, W.M. (2007). Primary and central hypothyroidism after radiotherapy for head-and-neck tumors. *International Journal of Radiation Oncology, Biology, Physics, 68,* 1131–1139. https://doi.org/10.1016/j.ijrobp.2007.01.029

Brahmer, J.R., Lacchetti, C., Schneider, B.J., Atkins, M.B., Brassil, K.J., Caterino, J.M., . . . Thompson, J.A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 36,* 1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

Bristol-Myers Squibb. (2019a). *Opdivo® (nivolumab)* [Package insert]. Retrieved from https://packageinserts.bms.com/pi/pi_opdivo.pdf

Bristol-Myers Squibb. (2019b). *Opdivo® (nivolumab) immune-mediated adverse reactions management guide.* Retrieved from http://www.opdivohcp.com/servlet/servlet.FileDownload?file=00Pi000000kLoKcEAK

Bristol-Myers Squibb. (2019c). *Opdivo® (nivolumab) patient monitoring checklist.* Retrieved from http://www.opdivohcp.com/servlet/servlet.FileDownload?file=00P1Y00000zAGcxUAG

Chaker, L., Bianco, A.C., Jonklaas, J., & Peeters, R.P. (2017). Hypothyroidism. *Lancet, 390,* 1550–1562. https://doi.org/10.1016/S0140-6736(17)30703-1

Champiat, S., Lambotte, O., Barreau, E., Belkhir, R., Berdelou, A., Carbonnel, F., . . . Marabelle, A. (2016). Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. *Annals of Oncology, 27,* 559–574. https://doi.org/10.1093/annonc/mdv623

Chow, L.Q.M., Haddad, R., Gupta, S., Mahipal, A., Mehra, R., Tahara, M., . . . Seiwert, T.Y. (2016). Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: Results from the phase Ib KEYNOTE-012 expansion cohort. *Journal of Clinical Oncology, 34,* 3838–3845. https://doi.org/10.1200/JCO.2016.68.1478

Cohen, E.E.W., LaMonte, S.J., Erb, N.L., Beckman, K.L., Sadeghi, N., Hutcheson, K.A., . . . Pratt-Chapman, M.L. (2016). American Cancer Society head and neck cancer survivorship care guideline. *CA: A Cancer Journal for Clinicians, 66,* 203–239. https://doi.org/10.3322/caac.21343

Cohen, E.E.W., Soulieres, D., Le Tourneau, C., Dinis, J., Licitra, L.F., Ahn, M.-J., . . . Harrington, K.J. (2018). Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs standard of care (SOC) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) in KEYNOTE-040. *Journal of Clinical Oncology, 36*(Suppl.), 6013. https://doi.org/10.1200/JCO.2018.36.15_suppl.6013

Cohen, E.E.W., Soulières, D., Le Tourneau, C., Dinis, J., Licitra, L., Ahn, M.-J., . . . Harrington, K.J. (2019). Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. *Lancet, 393,* 156–167. https://doi.org/10.1016/S0140-6736(18)31999-8

Constantinidou, A., Alifieris, C., & Trafalis, D.T. (2019). Targeting programmed cell death -1 (PD-1) and ligand (PD-L1): A new era in cancer active immunotherapy. *Pharmacology and Therapeutics, 194,* 84–106. https://doi.org/10.1016/j.pharmthera.2018.09.008

Deng, J., Ridner, S.H., Dietrich, M.S., Wells, N., Wallston, K.A., Sinard, R.J., . . . Murphy, B.A. (2012). Prevalence of secondary lymphedema in patients with head and neck cancer. *Journal of Pain and Symptom Management, 43,* 244–252. https://doi.org/10.1016/j.jpainsymman.2011.03.019

Ferris, R.L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A.D., Licitra, L., . . . Gillison, M.L. (2016). Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *New England Journal of Medicine, 375,* 1856–1867. https://doi.org/10.1056/NEJMoa1602252

Ferris, R.L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A.D., Licitra, L., . . . Gillison, M.L. (2018). Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncology, 81,* 45–51. https://doi.org/10.1016/j.oraloncology.2018.04.008

Gordon, R., Kasler, M.K., Stasi, K., Shames, Y., Errante, M., Ciccolini, K., . . . Fischer-Cartlidge, E. (2017). Checkpoint inhibitors: Common immune-related adverse events and their management. *Clinical Journal of Oncology Nursing, 21*(Suppl.), 45–52. https://doi.org/10.1188/17.CJON.S2.45-52

Gorenc, M., Kozjek, N.R., & Strojan, P. (2015). Malnutrition and cachexia in patients with head and neck cancer treated with (chemo)radiotherapy. *Reports of Practical Oncology and Radiotherapy, 20,* 249–258. https://doi.org/10.1016/j.rpor.2015.03.001

Haanen, J.B.A.G., Carbonnel, F., Robert, C., Kerr, K.M., Peters, S., Larkin, J., & Jordan, K. (2017). Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology, 28*(Suppl. 4), iv119–iv142. https://doi.org/10.1093/annonc/mdx225

Harrington, K.J., Ferris, R.L., Blumenschein, G., Jr., Colevas, A.D., Fayette, J., Licitra, L., . . . Guigay, J. (2017). Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): Health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncology, 18,* 1104–1115. https://doi.org/10.1016/S1470-2045(17)30421-7

Hartmann, S., & Grandis, J.R. (2016). Treatment of head and neck cancer in the elderly. *Expert Opinion on Pharmacotherapy, 17,* 1903–1921. https://doi.org/10.1080/14656566.2016.1220540

Horvat, T.Z., Adel, N.G., Dang, T.-O., Momtaz, P., Postow, M.A., Callahan, M.K., . . . Chapman, P.B. (2015). Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *Journal of Clinical Oncology, 33,* 3193–3198. https://doi.org/10.1200/JCO.2015.60.8448

Kumar, V., Chaudhary, N., Garg, M., Floudas, C.S., Soni, P., & Chandra, A.B. (2017). Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Frontiers in Pharmacology, 8,* 49. https://doi.org/10.3389/fphar.2017.00049

Mehra, R., Seiwert, T.Y., Gupta, S., Weiss, J., Gluck, I., Eder, J.P., . . . Haddad, R. (2018). Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: Pooled analyses after long-term follow-up in KEYNOTE-012. *British Journal of Cancer, 119,* 153–159. https://doi.org/10.1038/s41416-018-0131-9

Merck Sharp & Dohme Corp. (2019a). *Keytruda® (pembrolizumab)* [Package insert]. Retrieved from https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Merck Sharp & Dohme Corp. (2019b). *Keytruda® (pembrolizumab): Give more patients a key: A treatment guide for Keytruda.* Retrieved from https://www.keytruda.com/static/pdf/keytruda-treatment-guide.pdf

Michot, J.M., Bigenwald, C., Champiat, S., Collins, M., Carbonnel, F., Postel-Vinay, S., . . . Lambotte, O. (2016). Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *European Journal of Cancer, 54,* 139–148. https://doi.org/10.1016/j.ejca.2015.11.016

Naidoo, J., Page, D.B., Li, B.T., Connell, L.C., Schindler, K., Lacouture, M.E., . . . Wolchok, J.D. (2015). Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Annals of Oncology, 26,* 2375–2391. https://doi.org/10.1093/annonc/mdv383

National Cancer Institute. (2017). *Common Terminology Criteria for Adverse Events (CTCAE)* [v.5.0]. Retrieved from https://bit.ly/2Nn0LTT

Postow, M.A., Sidlow, R., & Hellmann, M.D. (2018). Immune-related adverse effects associated with immune checkpoint blockade. *New England Journal of Medicine, 378,* 158–168. https://doi.org/10.1056/NEJMra1703481

Puzanov, I., Diab, A., Abdallah, K., Bingham, C.O., III, Brogdon, C., Dadu, R., . . . Ernstoff, M.S. (2017). Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *Journal for ImmunoTherapy of Cancer, 5,* 95. https://doi.org/10.1186/s40425-017-0300-z

Seiwert, T.Y., Burtness, B., Mehra, R., Weiss, J., Berger, R., Eder, J.P., . . . Chow, L.Q. (2016). Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): An open-label, multicentre, phase 1b trial. *Lancet Oncology, 17,* 956–965. https://doi.org/10.1016/S1470-2045(16)30066-3

Smith, B.G., & Lewin, J.S. (2010). The role of lymphedema management in head and neck cancer. *Current Opinion in Otolaryngology and Head and Neck Surgery, 18,* 153–158. https://doi.org/10.1097/MOO.0b013e32833aac21

Spain, L., Diem, S., & Larkin, J. (2016). Management of toxicities of immune checkpoint inhibitors. *Cancer Treatment Reviews, 44,* 51–60. https://doi.org/10.1016/j.ctrv.2016.02.001

Topalian, S.L., Drake, C.G., & Pardoll, D.M. (2015). Immune checkpoint blockade: A common denominator approach to cancer therapy. *Cancer Cell, 27,* 450–461. https://doi.org/10.1016/j.ccell.2015.03.001

Williams, K.J., Grauer, D.W., Henry, D.W., & Rockey, M.L. (2017). Corticosteroids for the management of immune-related adverse events in patients receiving checkpoint inhibitors. *Journal of Oncology Pharmacy Practice, 25,* 544–550. https://doi.org/10.1177/1078155217744872

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