PD-1/PD-L1 Inhibitors for Non–Small Cell Lung Cancer: Incorporating Care Step Pathways for Effective Side-Effect Management

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Abstract

Programmed cell death protein 1 receptor and programmed cell death ligand 1 (PD-L1) inhibitors are immune checkpoint inhibitors (ICIs) that provide a survival benefit for select patients with advanced non–small cell lung cancer (NSCLC). Nivolumab, pembrolizumab, and atezolizumab are second-line therapies for advanced NSCLC after chemotherapy failure. Pembrolizumab and atezolizumab are also approved as first-line treatment for advanced NSCLC, and durvalumab is a PD-L1 inhibitor indicated as consolidation therapy in individuals with locally advanced NSCLC. The novel mechanism of action of these agents provides clear efficacy benefits to many NSCLC patients without good alternatives, but it may also result in unique immune-related adverse events that many health-care providers are unfamiliar with or uncertain about how to diagnosis and manage. Highlighting the resources of the Immuno-Oncology Essentials Initiative, particularly the Care Step Pathways (CSPs), this article addresses the role of the advanced practice provider in administration, side-effect identification and management, and education of patients with advanced NSCLC receiving ICI therapy. The diagnosis and management of pneumonitis, hypophysitis, diabetes mellitus, and arthralgias/myalgias are examined in detail, addressing special considerations in the NSCLC population.

The introduction of immune checkpoint inhibitor (ICI) therapy in non–small cell lung cancer (NSCLC) has been heralded as a major advance in the field. However, ICI therapy is associated with an array of immune-related adverse events (irAEs) that are challenging to manage and quite different from the side effects of the chemotherapeutic and targeted agents used in NSCLC. This article was developed to guide advanced practice providers (APPs)

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in using Immuno-Oncology (IO) Essentials materials to support optimal ICI administration and toxicity management as well as education of patients with NSCLC receiving ICI therapy.

In 2017, the Melanoma Nursing Initiative (MNI) developed a series of APP/nurse–focused educational materials to improve the recognition and management of irAEs in the setting of melanoma (Rubin, 2017). Those materials were quickly adopted by health-care providers (HCPs) working in other tumor types. To address the contextualization of the MNI materials for use in various tumor types, the AIM With Immunotherapy Immuno-Oncology Essentials (IO Essentials) initiative was commissioned. The website for the IO Essentials initiative, aimwithimmunotherapy.org, was launched in October 2018. This article features a review of the use of the IO Essentials materials in NSCLC. Companion articles across tumor types are also included in this supplement, including a pan-tumor article (Wood, 2019) and an article on ICI use in head and neck squamous cell cancer (Fazer, 2019). Finally, this supplement also features a global article on the principles for triaging irAEs via telephone and in the office setting (Hoffner & Rubin, 2019).

RATIONALE FOR ICI USE IN LUNG CANCER

Lung cancer is the second leading cause of death in the United States and worldwide (after cardiovascular disease) and the leading cause of cancer-related death (Cronin et al., 2018; Fitzmaurice et al., 2017; Siegel, Miller, & Jemal, 2018). Each year, more people in the United States die from lung cancer than colorectal, prostate, and breast cancer combined, and approximately 80% to 95% of all lung cancers are NSCLC (American Cancer Society, 2016; Zago, Muller, van den Heuvel, & Baas, 2016). Non–small cell lung cancer is usually diagnosed at an advanced, unresectable stage of disease, and until recently, outcomes were invariably poor with relatively limited treatment options (Brahmer et al., 2018a; Zago et al., 2016).

Targeted therapies are now available to treat the roughly one third of advanced NSCLC patients harboring an identifiable tumor-driving mutation, but the long-term effectiveness of these therapies is limited by the development of resistance (Bui, Cooper, Kao, & Boyer, 2018; Pakkala & Ramalingam, 2018; Recondo, Facchinetti, Olaussen, Besse, & Friboulet, 2018). There was a clear unmet need for other effective therapeutic options.

Immune checkpoints, which may have evolved to prevent autoimmune responses, can be exploited by cancer cells to suppress the immune response to malignant cells (Marshall & Djamgoz, 2018). Immune checkpoints are proteins involved in both self-recognition and dampening immune responses under circumstances when those responses may become harmful (Brahmer et al., 2018b; Postow, Sidlow, & Hellmann, 2018). Therapies designed to inhibit these checkpoints (ICIs) improve tumor-specific immune responses and increase T-cell infiltration into tumors. In NSCLC, ICIs directed to programmed cell death protein 1 (PD-1) and the PD-1 ligand (PD-L1) have been approved. PD-1 and PD-L1 inhibitors reduce NSCLC growth and improve patient survival by preventing binding of PD-L1 ligands with PD-1 receptors expressed on tumor cells and/or tumor-infiltrating cells (McGettigan & Rubin, 2017; Postow et al., 2018; Villanueva & Bazhenova, 2018).

Mechanistic Underpinnings and Range of Immune-Related Adverse Events

The novel mechanism of action of PD-1 and PD-L1 inhibitors involves the enhancement of immune surveillance, which also exposes patients to unique irAEs (Brahmer et al., 2018a). By enhancing the patient's immune system to better battle NSCLC, ICIs also increase the risk of inflammatory side effects (i.e., irAEs; Postow et al., 2018). When immune checkpoint proteins are inhibited, there is a risk the immune system will be released to attack some healthy as well as tumor cells (that is, produce autoimmune reactions or irAEs; Brahmer et al., 2018b; Puzanov et al., 2017).

Immune Checkpoint Inhibitor Use in NSCLC

Immune checkpoint inhibitors have emerged over the past 5 years to significantly alter the treatment landscape for many patients with NSCLCs who are not suited for targeted therapy or who develop resistance to such therapies. These ICIs include two PD-1 inhibitors (nivolumab and pembrolizumab) and two PD-L1 inhibitors (atezolizumab and durvalumab; Brahmer et al., 2018a, 2018b; Villanueva & Bazhenova, 2018).

Table 1 provides a summary of the four PD-1 and PD-L1 inhibitors currently approved for NSCLC treatment, including their indications, how they are used, testing required, and the US Food and Drug Administration (FDA) approval date (Khan et al., 2018; Paz-Ares et al., 2018; Raju, Joseph, & Sehgal, 2018; Villanueva & Bazhenova, 2018). A recent meta-analysis of seven randomized controlled studies of anti–PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab) vs. chemotherapy reported significantly better overall survival, progression-free survival, and overall response rate with anti–PD-1/PD-L1 therapy, together with significantly improved safety (Khan et al., 2018).

PD-L1 Testing

As noted in Tables 1 and 2, single-agent pembrolizumab use in either the first-line or second-line setting requires the documentation of PD-L1 expression, with a higher expression (tumor proportion score ≥ 50%) required for the initiation of first-line, single-agent therapy (Wills, Brahmer, & Naidoo, 2018). That is not the case for the other ICIs approved for advanced NSCLC, or for pembrolizumab when used in the first-line setting. In-

Table 1. Indications and US Food and Drug Administration Approvals for Checkpoint Inhibitors in Non–Small Cell Lung Cancer

Drug	Indication(s)	Single agent or combination	First line or second line	FDA approval
Nivolumab	Patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving nivolumab.	Single agent	Second line	October 2015
Pembrolizumab	Patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving pembrolizumab.	Single agent	Second line	October 2015
	First-line treatment of patients with metastatic NSCLC, with PD-L1 expression (TPS ≥ 50%) as determined by FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations	Single agent	First line	October 2016
	Patients with previously untreated metastatic nonsquamous NSCLC, with pemetrexed and carboplatin	Combination	First line	May 2017
	Patients with squamous metastatic NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel	Single agent	First line	October 2018
Atezolizumab	Patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving atezolizumab.	Single agent	Second line	October 2016
	Patients with metastatic nonsquamous NSCLC, combined with bevacizumab, paclitaxel, and carboplatin with no *EGFR* or *ALK* genomic tumor aberrations	Combination	First line	December 2018
Durvalumab	Patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy	Single agent	Consolidation	February 2018

Note. NSCLC = non–small cell lung cancer; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; FDA = US Food and Drug Administration; PD-L1 = programmed cell death ligand 1; TPS = tumor proportion score.

Table 2. PD-L1 Testing Requirements for Checkpoint Inhibitors Used to Treat Advanced NSCLC

Checkpoint inhibitor	Line of therapy	Single/Combination therapy	Testing requirement
Pembrolizumab	First line	Single agent	PD-L1 > 50% tumor proportion score
	Second line	Single agent	PD-L1 > 1% tumor proportion score
	First line	Combination	None required
Nivolumab	Second line	Single agent	None required
Atezolizumab	First line	Combination	None required
	Second line	Single agent	None required
Durvalumab	Consolidation	Single agent following concurrent chemo-RT regimen	None required

Note. PD-L1 = programmed cell death ligand 1; RT = radiotherapy. Information from FDA (2018).

formation on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available from the FDA (Merck & Co., Inc., 2018; US Food and Drug Administration, 2018).

Identifying patients most likely to benefit from ICI therapy is important. At this time, PD-L1 testing is the best predictor of clinical response, particularly for pembrolizumab, where it is required for use as single-agent therapy. PD-L1 testing is sometimes also used with other checkpoint inhibitors as an FDA-approved nonessential complementary test, although that is not required for treatment (Chung, 2018; Kazandjian et al., 2016). The Society for Immunotherapy of Cancer (SITC) consensus statement on immunotherapy for NSCLC indicates that the analysis of PD-L1 expression should be routine for all patients with newly diagnosed advanced NSCLC (Brahmer et al., 2018a).

DOSING AND OTHER PHARMACOLOGIC CONSIDERATIONS

Table 3 highlights the different dosing regimens recommended for nivolumab, pembrolizumab, atezolizumab, or durvalumab as treatment for NSCLC (Bristol-Myers Squibb, 2018; Genentech, Inc., 2018; Merck & Co., Inc., 2018). Unlike the other three therapies, durvalumab is approved as consolidation therapy for patients with unresectable stage III NSCLC following chemoradiation therapy (Antonia et al., 2017; AstraZeneca Pharmaceuticals LP, 2018). It is important that APPs be aware of the sometimes subtle differences in administration and dosing among ICIs used in advanced NSCLC treatment. Nivolumab, pembrolizumab, and atezolizumab are all flat dose (i.e., without regard to body weight), intravenous (IV) infusions. Nivolumab and pembrolizumab are administered over 30 minutes. Atezolizumab is infused over 60 minutes as initial treatment and if tolerated well, infused over 30 minutes for subsequent infusions. Pembrolizumab at 200 mg is infused every 3 weeks and atezolizumab at 1,200 mg every 3 weeks. Nivolumab may be administered IV as either 240 mg every 2 weeks or 480 mg every 4 weeks. (Only the 240 mg every 2 weeks regimen of nivolumab is used for small cell lung cancer treatment.) When pembrolizumab or atezolizumab is given in combination with chemotherapy, each is administered prior to chemotherapy and administered on the same day. Durvalumab is dosed using

Table 3. Dosage and Administration of Nivolumab, Pembrolizumab, and Atezolizumab in Advanced Non–Small Cell Lung Cancer

Checkpoint inhibitor	Dose	Infusion rate	Frequency
Nivolumab	240 mg	30 minutes	Every 2 weeks
	480 mg	30 minutes	Every 4 weeks
Pembrolizumab[a]	200 mg	30 minutes	Every week (weekly)
Atezolizumab	1,200 mg	60 minutes (first infusion) 30 minutes (subsequent infusions)	Every 3 weeks
Durvalumab	10 mg/kg	60 minutes	Every 2 weeks

Note. [a]When used with chemotherapy on the same day, administer prior to chemotherapy.

a weight-based dosing schema via a 1-hour IV infusion every 2 weeks. It should be noted that dosing schedules may vary in other tumor types.

No definitive standard has been established for the duration of ICI therapy in NSCLC (or in other cancers; McGettigan & Rubin, 2017). The prescribing information for pembrolizumab and atezolizumab both recommend continued treatment until disease progression or unacceptable toxicity (Genentech, Inc., 2018; Merck & Co., Inc., 2018). In NSCLC patients receiving first-line pembrolizumab in combination with chemotherapy, standard practice is to continue pembrolizumab (assuming it is well tolerated) for up to 2 years following the termination of chemotherapy. However, institutions and physicians vary in their practices when using ICIs either as first-line or second-line therapy (McGettigan & Rubin, 2017). The durvalumab label recommends the drug be continued until disease progression or unacceptable toxicity for up to 12 months (AstraZeneca Pharmaceuticals LP, 2018).

No premedications are needed when ICIs are used by themselves. Antiemetics are recommended when pembrolizumab is used in combination with chemotherapy. Currently, no definitive evidence indicates whether the concurrent use of corticosteroids for the premedication of ICIs plus chemotherapy negatively impacts the efficacy of ICIs in NSCLC or other cancers. Advanced practice providers should consult with institutional guidelines when managing NSCLC patients on ICI therapy.

Severe or life-threatening infusion-related anaphylactic reactions have been reported with each of the ICIs, albeit rarely (< 1%; AstraZeneca Pharmaceuticals LP, 2018; Bristol-Myers Squibb, 2018; Genentech, Inc., 2018; Merck & Co., Inc., 2018). Patients should be monitored for signs or symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxia, and fever. Grade 3/4 reactions should be managed by infusion termination and treatment discontinuation. Milder reactions may be managed by interrupting or slowing the infusion rate, with consideration of premedication for subsequent doses.

IMMUNE-RELATED ADVERSE EVENTS AND THEIR MANAGEMENT

A wide range of irAEs are associated with ICI therapy. Virtually any organ system may be affected, but those most commonly impacted are the skin, gastrointestinal tract, liver, pituitary and endocrine organs, musculoskeletal organs, and the lungs. Other important but less commonly involved structures or systems include the kidneys, eyes, and nervous and cardiovascular systems. Our group focused on developing 12 Care Step Pathways (CSPs) for notable irAEs, as described below.

Care Step Pathways Overview and Development

The CSPs, which debuted in the MNI materials, were designed to assist HCPs in identifying, grading, and managing irAEs in patients receiving ICIs. This article will reference all 12 CSPs featured on the IO Essentials site (see Table 4 for an overview of

Table 4. Care Step Pathways From the IO Essentials Initiative (See Appendix)

irAE category	Toxicity	Appendix location
Most common	Skin toxicities (pruritus, rash, etc.)	Appendix A
	Gastrointestinal toxicities: diarrhea and colitis	Appendix B
	Thyroiditis	Appendix C
	Hepatic toxicities	Appendix D
Less common but serious	Additional endocrinopathies	
	Hypophysitis (pituitary)	Appendix E
	Adrenal insufficiency (adrenalitis)	Appendix F
	Diabetes	Appendix G
	Pneumonitis	Appendix H
Easily overlooked	Arthralgia/arthritis	Appendix I
	Mucositis/xerostomia	Appendix J
	Neuropathy	Appendix K
	Nephritis	Appendix L

Note. irAE = immune-related adverse event.

the Appendix). The 11 CSPs developed by the MNI have been updated here, and a 12th CSP has been added on adrenal insufficiency. In updating these CSPs, the IO Essentials faculty reviewed them with an eye toward relevancy across tumor types. In addition, the CSPs were modified to reflect recently released guidance on irAE management from the Society for Immunotherapy of Cancer (Puzanov et al., 2017), American Society of Clinical Oncology (Brahmer et al., 2018b), and the National Comprehensive Cancer Network (NCCN, 2018).

Overall Approach to Immune-Related Adverse Event Management

Most irAEs are mild to moderate in severity and can be managed without the permanent termination of PD-1/PD-L1 inhibitor therapy. However, rare but serious and even life-threatening irAEs may occur during ICI therapy and require immediate attention to prevent catastrophic outcomes (Brahmer et al., 2018b; Puzanov et al., 2017). Coupled with a variable onset—irAEs may present soon after starting therapy, after extended therapy, or, in some cases, after completion of therapy (Puzanov et al., 2017; Thompson, 2018)—a premium is placed on a heightened suspicion of irAEs to enable early recognition and treatment (Brahmer et al., 2018b; Puzanov et al., 2017).

IN-DEPTH REVIEW OF SELECT IMMUNE-RELATED ADVERSE EVENTS/CARE STEP PATHWAYS

The remainder of this article takes a closer look at the management of pneumonitis, hypophysitis, diabetes mellitus, and arthralgias/myalgias, with a particular focus on NSCLC patients treated with PD-1/PD-L1 inhibitors. All 12 CSPs are discussed in depth across three articles in this supplement. It should be noted that the current CSPs were created at a time when there was little or no information on some of the newer ICIs. Hence, the CSPs here do not discuss all the different ICIs currently approved for NSCLC, although they are generally applicable to newer approved ICIs like atezolizumab and durvalumab.

Pneumonitis (Appendix H)

Pneumonitis is a relatively rare irAE, occurring in approximately 3% to 5% of all patients receiving ICI therapy in clinical trials (Hu et al., 2017; Suresh et al., 2018). However, a higher incidence of 19% has recently been reported in a study that included both trial and nontrial advanced NSCLC patients treated with PD-1/PD-L1 inhibitors (Suresh et al., 2018). The incidence is higher in patients with lung cancer vs. other cancer types because of altered pulmonary integrity (Nishino, Giobbie-Hurder, Hatabu, Ramaiya, & Hodi, 2016), in current or former smokers, and in men compared with women (Naidoo et al., 2017). Prior chest radiation may also elevate the risk. The onset ranges from 9 days to 20 months after treatment start, with a median onset of 2.8 months (Naidoo et al., 2017). The incidence is higher with combination immunotherapy vs. monotherapy (Naidoo et al., 2017; Nishino et al., 2016).

The clinical presentation of pneumonitis includes dyspnea, dry cough, wheezing, tachycardia, and increased oxygen requirements for patients already on oxygen supplementation (Brahmer et al., 2018b; Puzanov et al., 2017). Occasionally, chest pain or discomfort and symptoms indicative of hypoxia may rapidly progress to respiratory failure (Brahmer et al., 2018b). However, approximately a third of patients are asymptomatic and only diagnosed when routine restaging imaging shows ground glass opacities or patchy nodular infiltrates, predominantly in the lower lobes (Brahmer et al., 2018b; Puzanov et al., 2017). The pneumonitis CSP illustrates how to conduct the patient assessment to determine the presence, nature, and quality of pneumonitis in a patient receiving PD-1/PD-L1 inhibitor therapy. The CSP provides examples of how to look (e.g., Does the patient appear uncomfortable? Does the patient appear short of breath?), listen (Has the patient noted any change in breathing? Have the symptoms worsened?), and what to recognize (Is the pulse oximetry low/lower than baseline or last visit? History of lung radiation?).

An evaluation of pneumonitis is a multistep process. Differential diagnosis involves ruling out other potential causes of the symptoms, including infection, pulmonary embolism, pleural effusion, pulmonary fibrosis, sarcoidosis, or even disease progression (Brahmer et al., 2018b; Puzanov et al., 2017). Baseline measures of oxygen saturation should be obtained at rest and then again after

some ambulation (i.e., stress oxygen level) in all patients before beginning treatment and repeated at regular intervals after treatment to evaluate whether there is a change. Often, the first sign of pneumonitis is altered oxygen saturation.

The NCCN recommends a computed tomography (CT) scan with contrast to diagnose pneumonitis. However, a CT scan without contrast might better reveal other causes. Therefore, dual modal imaging with and without contrast is most useful. Radiologic and pathologic features of pneumonitis are diverse (Figure 1; Naidoo et al., 2017). Pneumonitis presentations on a CT scan include cryptogenic organizing pneumonia, ground glass opacities, interstitial infiltrate consolidation, hypersensitivity patterns, and (in some cases) septal inflammation or a mixture of nodular and other subtypes. If infection is suspected, an infection workup should be conducted, including sputum specimen and nasal swab for potential viral pathogens. In some cases, CT scan images may not be definitive, and a bronchoscopy

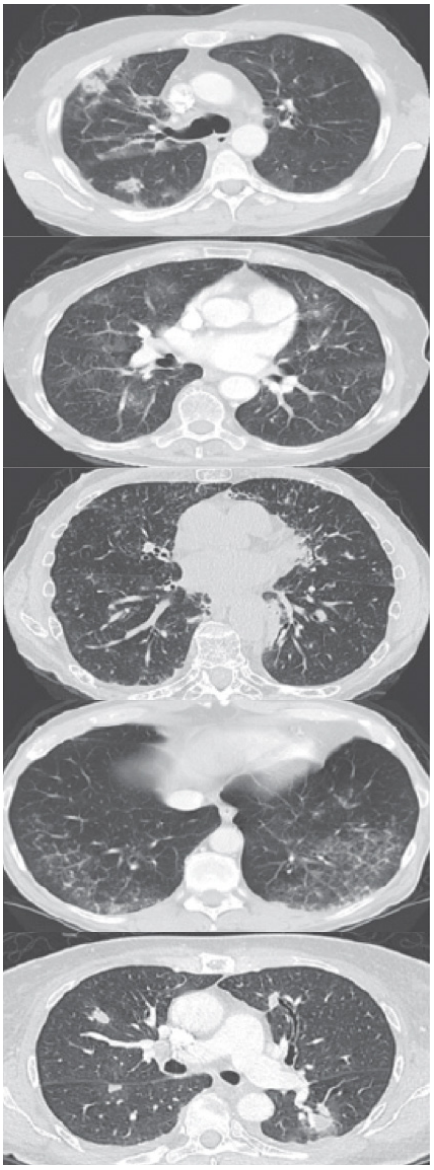
Radiologic subtypes	Representative image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		• Discrete patchy or confluent consolidation with or without air bronchograms • Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		• Discrete focal areas of increased attenuation • Preserved bronchovascular markings
Interstitial (n = 6, 22%)		• Increased interstitial markings, interlobular septal thickening • Peribronchovascular infiltration, subpleural reticulation • Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		• Centrilobular nodules • Bronchiolitis-like appearance • Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		• Mixture of nodular and other subtypes • Not clearly fitting into other subtype classifications

Figure 1. Radiographic features of pneumonitis associated with PD-1/PD-L1 therapy stratified into five distinct phenotypes. Reprinted with permission from Naidoo et al. (2017).

with bronchoalveolar lavage may be used to rule out infection and malignant infiltration (Brahmer et al., 2018b; Puzanov et al., 2017). It is important to recognize that NSCLC patients receiving ICIs could have two lung diagnoses. They may have pneumonitis and an infiltrating pneumonia, in which case both need to be managed. Pulmonary function testing may help demonstrate a restrictive airway pattern.

As noted in the Red Flag section of the pneumonitis CSP, delayed diagnosis or misdiagnosis of pneumonitis can have life-threatening consequences when the condition is left unmanaged. The CSP Grading Toxicity section describes how to grade pneumonitis for toxicity, and then proceeds in the Management section to describe the overall strategy of pneumonitis management and toxicity/grade-related management. Immune checkpoint inhibitor therapy needs to be withheld for grade 2 pneumonitis until symptom resolution to grade 0/1 or clearance of pathology on CT scans. Therapy should be discontinued for recurrent or persistent grade 2 events. In our hands, patients may require the supportive care offered by oxygen supplementation and dyspnea management including, in some cases, the use of analgesics to ease the burden of dyspnea. Nebulizers may help in patients with a restrictive airway pattern. As outlined in the CSP, corticosteroids are required for more advanced grade 2 or grade 3/4 pneumonitis. Patients with grade 2 pneumonitis are initiated on lower dosages (prednisone at 1–2 mg/kg/day or equivalent), with dosage elevation for those failing to respond adequately within 24 to 48 hours. High-dose corticosteroids and treatment discontinuation is recommended for grade 3/4 pneumonitis. Infliximab or mycophenolate mofetil may be added for steroid-refractory cases. The section on Administering Corticosteroids provides general guidance on steroid tapering and long-term use of high-dose steroids. Empiric antibiotic therapy may be initiated for patients at risk of infection.

With the increased use of medical cannabis, many individuals will ask the APP about its use to manage cancer symptoms. Requirements vary by state, but where allowed, the delivery system is likely critical, given the risks of marijuana inhalation aggravating pneumonitis. Delivery systems that do not involve inhalation or vaping are preferred—although there is a dearth of clinical data on this at the moment.

Hypophysitis (Appendix E)

Hypophysitis is a rare but very serious endocrinopathy associated with ICI therapy, and is significantly more common with cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors (ipilimumab) than with PD-1/PD-L1 inhibitors (9% vs. <1%; AstraZeneca Pharmaceuticals LP, 2018; Barroso-Sousa et al., 2018; Bristol-Myers Squibb, 2018; Byun, Wolchok, Rosenberg, & Girotra, 2017; Genentech, Inc., 2018; Merck & Co., Inc., 2018; Nishijima, Shachar, Nyrop, & Muss, 2017). Higher rates have been reported with ipilimumab–PD-1 combination therapy (Barroso-Sousa et al., 2018; Byun et al., 2017). Older age and male sex appear to be risk factors for ICI-related hypophysitis (Ntali, Kassi, & Alevizaki, 2017).

Hypophysitis usually appears 5 to 36 weeks after the initiation of ICI therapy, although it has been reported as late as 19 months post treatment start or after treatment termination (Ntali et al., 2017). Diagnosis is complicated because many hypophysitis symptoms are nonspecific and may be attributed to either pituitary dysfunction, underlying illness, or brain metastases (Ntali et al., 2017). Symptoms include headache, fatigue, visual defects or changes, hypotension, nausea, abdominal pain, anorexia, weight loss, temperature intolerance, and loss of libido, among others (Ntali et al., 2017; Puzanov et al., 2017). The CSP anticipates the possibility of these symptoms during assessment and recommends clinicians actively look (Does the patient appear fatigued? Does the patient look listless?), listen (Does the patient report a change in energy or libido, headache, dizziness, nausea/vomiting, altered mental status, visual disturbances, or fever?), and recognize (low levels of pituitary hormones; enhancement and swelling of the pituitary on magnetic resonance imaging [MRI] scans; hypotension) information suggestive or indicative of hypophysitis. Red flags include symptoms of adrenal insufficiency or a new onset of severe headache or vision changes.

Diagnosis is further complicated when a baseline endocrine panel is not obtained before beginning ICI therapy or with early use of corticoste-

roids to manage irAEs, interfering with subsequent endocrine testing (Puzanov et al., 2017). The hypophysitis CSP recommends consideration of an endocrinology consult for all patients undergoing ICI therapy and (ideally) a pretreatment diagnostic workup to monitor levels of morning adrenocorticotropic hormone (ACTH) and cortisol, thyroid stimulating hormone (TSH), free thyroxine (FT4), and electrolytes. Baseline measures for glucose and glycated hemoglobin (HbA1c) should be established before initiating immunotherapy (Brahmer et al., 2018b; Ntali et al., 2017; Puzanov et al., 2017).

When there is a clinical suspicion of hypophysitis due to symptoms and/or laboratory abnormalities, a full endocrine workup is warranted, along with consideration of brain MRI with or without contrast with pituitary/sellar cuts (Brahmer et al., 2018b; Ntali et al., 2017; Puzanov et al., 2017). As discussed in the CSP, an additional workup that includes luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol is advocated for patients exhibiting low libido, mood changes, or fatigue. The differential diagnosis includes the elimination of brain metastases as a cause of symptoms. A brain MRI with sellar cuts is used to rule out brain metastases, identify changes in pituitary features consistent with hypophysitis, and monitor changes during hypophysitis management (Figure 2; Carpenter, Murtagh, Lilienfeld, Weber, & Murtagh, 2009). Pituitary morphology commonly changes during the course of hypophysitis, beginning with mild to moderate enlargement with stalk thickening, followed by atrophy and finally empty sella in the worst cases (Ntali et al., 2017). However, it should be noted that a normal MRI does not necessarily rule out hypophysitis. The patient may be symptomatic with no signs of inflammation. Management should proceed based on clinical presentation and endocrine evaluation.

The Grading Toxicity section of the hypophysitis CSP describes how to grade hypophysitis toxicity, and then proceeds in the Management section to describe the overall strategy for hypophysitis and toxicity/grade-related management. If left undiagnosed and untreated, hypophysitis may lead to permanent endocrine organ dysfunction, including secondary adrenal insufficiency, central hypothyroidism, secondary hypogonadism, and diabetes insipidus (Puzanov et al., 2017). Hypophysitis management involves the replacement of deficient hormones (Brahmer et al., 2018b; Ntali et al., 2017; Puzanov et al., 2017).

Many patients with hypophysitis or other immune-related endocrinopathies will require lifelong hormone replacement, and this should be discussed with the patient. The hypophysitis CSP advocates educating patients regarding the possibility of permanent loss of pituitary or other organ function when receiving ICI therapy and the utility of obtaining a medical alert bracelet.

ACTH and TSH deficiency are the most common manifestations of hypophysitis, followed by hypogonadotropic hypogonadism and, more rarely, deficient vasopressin (antidiuretic hormone [ADH]) due to pituitary damage, producing diabetes insipidus (Ntali et al., 2017). When both adrenal insufficiency and hypothyroidism are present, the replacement of corticosteroids should start several days before administering thyroid hor-

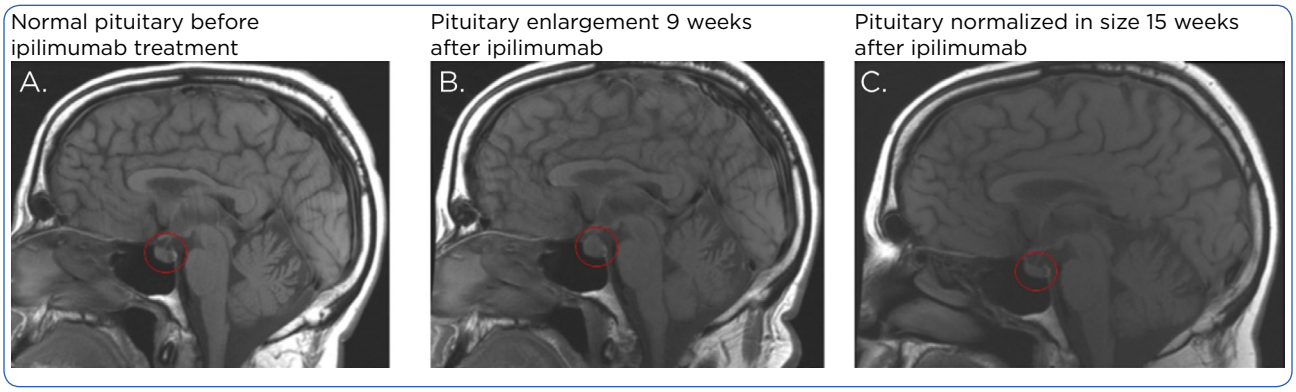


Figure 2. Brain magnetic resonance imaging with sellar cuts for initial and subsequent evaluation of patient with hypophysitis. Reproduced with permission from Min (2016).

mones to prevent precipitating an adrenal crisis (Brahmer et al., 2018b; Puzanov et al., 2017).

As seen in the CSP, grade 1 hypophysitis generally does not require the withholding of ICIs, whereas ICIs should be withheld for grade 2 and/or grade 3 events—with resumption of ICI therapy following stabilization on replacement hormones. The CSP recommends the permanent discontinuation of nivolumab for grade 4 events and of pembrolizumab for grade 3/4 events. Corticosteroids are used to treat grade 3/4 events, beginning with 1 to 2 mg/kg oral prednisone or equivalent and then gradually tapering over at least 1 to 2 weeks. View the Administering Corticosteroids section of the CSP for a guide on how to taper steroid therapy and the use of long-term high-dose steroid therapy, when appropriate. It is also important to instruct patients on the need for hormone dose adjustments (typically doubling) in the time of illness, trauma, or stress ("stress dosing"; Brahmer et al., 2018b).

Diabetes Mellitus (Appendix G)

Diabetes mellitus, and particularly insulin-dependent or type 1 diabetes mellitus (T1DM), is another rare endocrinopathy associated with PD-1/PD-L1 inhibitor therapy (Gauci et al., 2017; Iglesias, 2018; Ntali et al., 2017; Sznol et al., 2017). It sometimes presents as diabetic ketoacidosis (DKA), a life-threatening condition. T1DM has been reported in < 1% of PD-1/PD-L1 inhibitor-treated patients, with lower rates for PD-L1 than PD-1 inhibitors (< 0.1% vs. 0.2%–0.6%; AstraZeneca Pharmaceuticals LP, 2018; Bristol-Myers Squibb, 2018; Genentech, Inc., 2018; Merck & Co., Inc., 2018). Autoimmunity is implicated in the pathogenesis of PD-1/PD-L1 inhibitor-related T1DM, with identification of antibodies against islet cell antigens reported in a number of cases (Gauci et al., 2017; Girotra et al., 2018; Ntali et al., 2017). A rare fulminant subset of T1DM has also been described. It is characterized by extremely rapid pancreatic β-cell destruction and progression of hyperglycemia and ketoacidosis, very high plasma glucose levels, together with a modest rise in HbA1c level and undetectable C-peptide concentrations (Gauci et al., 2017). Fulminant T1DM is usually autoantibody negative.

The onset of T1DM ranges from 1 week to 1 year after initiation of PD-1/PD-L1 inhibitor therapy (median 8.5 weeks). However, there are anecdotal reports of T1DM occurring much later, even many months following the termination of PD-1/PD-L1 inhibitor therapy. As with other irAEs, it is probably best to maintain vigilance and to instruct patients to do so as well. T1DM may occur in patients without a prior history of diabetes or as a compound issue in patients with preexisting disease. Common symptoms of T1DM include polyuria, polydipsia, weight loss, and asthenia/fatigue (DiMeglio, Evans-Molina, & Oram, 2018; Gauci et al., 2017). DKA is a less common presentation. As discussed in the CSP, clinicians should remain vigilant to the emergence of symptoms indicative of T1DM throughout the treatment process and beyond by following the look (Does the patients appear fatigued or dehydrated or have breath that smells sweet or fruity?), listen (Does the patient describe frequent urination or increased thirst, hunger, or fatigue?), and recognize (presence of signs/symptoms of diabetes or infections) suggestions.

Patients should be monitored for hyperglycemia and other signs and symptoms of new or worsening DM at baseline and before every treatment cycle during induction for 12 weeks, and then every 3 to 6 weeks thereafter (Brahmer et al., 2018b). As discussed in the CSP, patients should be further evaluated per institutional guidelines when DKA is suspected, including an assessment of blood pH, basic metabolic panel, urine or serum ketones, and anion gap. An assessment of C-peptide level may be warranted when serum ketones/anion gap is positive. Patients suspected of T1DM should be evaluated for the presence of antibodies against pancreatic β-cells and glutamic acid decarboxylase (GAD), which are highly specific for autoimmune disease (Brahmer et al., 2018b; Ntali et al., 2017).

The CSP recommends clinicians discuss the likely permanent status of T1DM with patients determined to have T1DM after ICI therapy. Those patients should also be educated about signs and symptoms of hyper/hypoglycemia, proper insulin use, and dietary modifications that may be useful. Patients with ICI-related T1DM are closely followed with regular checks on blood glucose levels and for signs of DKA (e.g., fruity breath, confusion, or nausea). The possibility of other endocrine or nonendocrine irAEs should also be discussed.

As shown in the CSP, clinicians generally use laboratory value criteria from institutional norms rather than Common Terminology Criteria for Adverse Events (CTCAE) grading due to the shortcomings of the current CTCAE for the grading of the diabetes irAE (US Department of Health and Human Services, 2018). With ICIs, glucose levels can rise quite rapidly and DKA can occur; therefore, an evaluation of any underlying history of type 2 diabetes (T2DM) and DKA suspicion are key (NCCN, 2018). Patients with mild hyperglycemia may continue PD-1/PD-L1 inhibitor therapy with close clinical follow-up, laboratory evaluation, and institution of dietary and other lifestyle modifications (Brahmer et al., 2018b). Oral antihyperglycemic therapy may begin for those with new-onset T2DM. PD-1/PD-L1 inhibitor therapy may be continued in patients with moderate or worse hyperglycemia likely due to T1DM and no DKA, monitoring blood glucose after each dose and providing antihyperglycemic medication per institutional protocol (NCCN, 2018). For patients with moderate or worse hyperglycemia likely due to new-onset T1DM or for any patient with DKA, PD-1/PD-L1 therapy should be immediately withheld and the patient provided with appropriate inpatient care or urgent (same-day) outpatient referral. Insulin should be provided as directed by the inpatient team and/or endocrinologist, and DKA should be managed per institutional guidelines (e.g., IV fluids and insulin, potassium supplementation, hourly glucose, serum ketones, blood pH, and anion gap). The resumption of ICI therapy may be considered once DKA has been corrected and glucose levels have stabilized (NCCN, 2018). See the CSP for the management of "red-flag" and emergency situations.

As the initial presentation of immunotherapy-related diabetes may be frank DKA, patients should be instructed at the onset of ICI therapy about the signs and symptoms of DKA and the importance of immediately reporting them to their HCP or clinic. These symptoms include excess thirst, frequent urination, general weakness, decreased alertness, nausea and vomiting, abdominal pain, dry skin and mouth, increased heart rate, and a fruity odor of the breath. Of note, high-dose corticosteroids used to manage other irAEs may induce or exacerbate hyperglycemia (Williams, Grauer, Henry, & Rockey, 2017). Patients should be instructed about this possibility at the onset of high-dose corticosteroid therapy and educated about the signs and symptoms of DKA and the importance of reporting them. If corticosteroid-induced hyperglycemia is suspected in a previously normoglycemic patient, the risks vs. benefits should be carefully weighed before tapering or proceeding without change.

Arthralgias/Myalgias (Appendix I)

Information on rheumatologic/musculoskeletal irAEs is relatively limited. Musculoskeletal complaints are common in the general population, and it is often difficult to determine if musculoskeletal events in recipients of ICIs are immune related or are caused by the cancer itself or other medical conditions (Abdel-Rahman et al., 2017; Cappelli, Naidoo, Bingham, & Shah, 2017b; Puzanov et al., 2017). Musculoskeletal irAEs most commonly mentioned in clinical trials, observational studies, and case reports include arthralgias (or more specifically, arthritis) and myalgias, including myositis (Cappelli, Gutierrez, Bingham, & Shah, 2017a; Cappelli, Shah, & Bingham, 2017c). A recent systematic review found arthralgia was the most commonly reported musculoskeletal irAE in clinical trials (1%–43%), followed by myalgia (2%–21%) and arthritis (1%–7%; Cappelli et al., 2017a). Arthralgias were reported in 5% to 16% of patients receiving nivolumab in phase III trials (Cappelli et al., 2017c). Similar rates have been observed with ipilimumab monotherapy, and higher rates with nivolumab-ipilimumab combination therapy vs. monotherapy (Cappelli et al., 2017c). A recent report suggests the onset of de novo myositis may occur early following ICI therapy (median 5.4 weeks; range 2.1–17.1 weeks; Shah, Tayar, Abdel-Wahab, & Suarez-Almazor, 2018). There are some reasons to believe musculoskeletal irAEs are generally underreported (Cappelli et al., 2017c; Puzanov et al., 2017).

Early recognition and treatment of musculoskeletal irAEs are important to limit or prevent potential negative long-term consequences and to improve quality of life (Cappelli et al., 2017b; Puzanov et al., 2017). The CSP for arthralgias and arthritis uses the 2017 CTCAE criteria to

grade toxicity. As illustrated in the CSP, clinicians should educate patients that arthralgias/arthritis are the most commonly reported rheumatic and musculoskeletal irAEs with ICIs and that they should immediately report any apparent symptoms. As indicated in the Assessment portion of the CSP, clinicians should be on the lookout for patients who appear uncomfortable, exhibit a disrupted gait, and/or have swollen or deformed joints. Do those patients report symptoms that are worsening, limiting their ability to perform activities of daily living, and/or increasing their fear of falling? If inflammatory arthritis is present, is there an identifiable subtype? Risk of fall due to mobility issues is identified as a red flag.

Differential diagnoses for arthralgias (inflammatory arthritis) include metastases and preexistent autoimmune disease, which can be evaluated with plain x-ray or other imaging and autoimmune blood panel, respectively (Brahmer et al., 2018b; NCCN, 2018). X-rays also provide information about joint damage. A complete rheumatologic history and examination of all peripheral joints can help identify the number of joints affected and the severity of the condition, as well as functional impact (Brahmer et al., 2018b; Puzanov et al., 2017). A laboratory assessment for arthralgias includes antibody screening, and inflammatory markers, erythrocyte sedimentation rate (ESR), and C-reactive protein. Consultation with a rheumatologist may be warranted, especially for advanced cases.

Clinicians should follow new reports of arthralgia after beginning ICI therapy with an eye toward determining whether they are inflammatory (Brahmer et al., 2018b). Per the CSP, patients with grade 1 arthralgia should continue receiving PD-1/PD-L1 inhibitors, be encouraged to engage in physical activity, and be offered low-dose nonsteroidal anti-inflammatory drugs (NSAIDs) when needed. Grade 2 toxicities are managed by withholding PD-1/PD-L1 inhibitors (until grade 0/1) and continuing physical activity with a higher-dose NSAID. If inadequately controlled, low-dose corticosteroids (0.5 mg/kg/day) are recommended, usually for a limited time of 4 to 6 weeks. PD-1/PD-L1 inhibitors are withheld for first-occurrence grade 3/4 arthralgias/arthritis and permanently discontinued if the grade 3/4 event recurs or persists for 12 weeks or longer. High-dose corticosteroids (1–1.5 mg/kg/day) are used for rapid effect on grade 3/4 events. Infliximab or tocilizumab may be considered if there is no improvement within 2 weeks of initiating high-dose corticosteroids. Referral to a rheumatologist is recommended at this point, with anticipation of adjunct treatment with a disease-modifying antirheumatic drug (DMARD). Patients need to be tested for viral hepatitis B and C, as well as undergo latent/active tuberculosis testing before beginning DMARD treatment (Brahmer et al., 2018b). The CSP advocates educating patients that arthralgia/arthritis symptoms may persist beyond treatment completion or discontinuation.

ROLE OF THE ADVANCED PRACTICE PROVIDER

PD-1/PD-L1 inhibitors represent a significant treatment advance for many patients with advanced/metastatic NSCLC. However, these benefits will never be realized if appropriate attention is not focused on identifying and managing irAEs that may arise during the treatment process (Kirkwood & Ribas, 2017). Advanced practice providers are well placed to work with other members of the clinical team and form liaisons between patients and other providers who can help them achieve their treatment goals.

Advanced practice providers are instrumental members of the multidisciplinary team caring for the advanced NSCLC patient. Advanced practice providers may be involved in assessing whether a given patient is suitable for PD-1/PD-L1 therapy. This includes assessing molecular profiling, performing medication reconciliation, and assessing for prior autoimmune conditions. If not already performed upfront, all lung cancer patients should be tested for PD-L1, *EGFR*, *ALK*, *BRAF*, *ROS1*, and *MET*. Depending on the institution, APPs may be the ones ordering this testing. If a patient is referred from another institution and if the first lung biopsy was insufficient, the APP may participate in arranging for a secondary biopsy. When doing medication reconciliation, it is important that the APP not only examine prescribed medications, but also over-the-counter drugs, herbal supplements, and "home-grown,"

out-of-the-country drugs. These drugs may exacerbate developing irAEs.

Another important responsibility of the APP is to educate the patient with NSCLC and his or her family/caregivers about what to expect during the treatment process, including what types of irAEs to be on alert for when receiving PD-1/PD-L1 therapy. Patients should be instructed to report to the team all unusual events arising during therapy (no matter how subtle or seemingly insignificant) so that they may be promptly evaluated and managed if necessary (McGettigan & Rubin, 2017). Patients should also be informed that irAEs can arise at any time during therapy, even long after treatment has stopped. They should be educated about the importance of carrying an immunotherapy wallet card with them at all times (even after discontinuing therapy; McGettigan & Rubin, 2017). This helps inform emergency department staff or other HCPs not involved in their usual care about the immunotherapy regimen they are receiving (or have received) and the irAEs associated with them, thereby facilitating better care. The Patient Action plans on the IO Essentials site are specifically designed to support individualized patient education and instruction (see aimwithimmunotherapy.org/patient-resourcesaction-plans).

In addition to aiding in diagnosis, assessing severity, discussing lifestyle changes, and monitoring treatment effectiveness, APPs may also play an important role in reassuring patients who are concerned they will lose the antitumor benefits of a PD-1/PD-L1 inhibitor when treatment is withheld to deal with an irAE. Studies show no difference in overall or progression-free survival between patients in whom therapy is temporarily withheld and those without a treatment hold (Thompson, 2018). Other patients will need to be informed they will require lifelong hormone replacement therapy to manage the permanent endocrinopathy that arose during treatment. Likewise, they can be reassured that this need not significantly impair their quality of life. Beyond establishing a strong therapeutic relationship, the APP can educate and support the patient with NSCLC through the longer-term cancer journey afforded by the recent therapeutic advances.

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References

Abdel-Rahman, O., Eltobgy, M., Oweira, H., Giryes, A., Tekbas, A., & Decker, M. (2017). Immune-related musculoskeletal toxicities among cancer patients treated with immune checkpoint inhibitors: A systematic review. *Immunotherapy, 9*(14), 1175–1183. https://doi.org/10.2217/imt-2017-0108

American Cancer Society. (2016). What is non-small cell lung cancer? Retrieved from https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html

Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R.,...Özgüroğlu, M. (2017). Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *New England Journal of Medicine, 377*, 1919–1929. https://doi.org/10.1056/NEJMoa1709937

AstraZeneca Pharmaceuticals LP. (2018). Imfinzi (durvalumab) package insert. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf

Barroso-Sousa, R., Barry, W. T., Garrido-Castro, A. C., Hodi, F. S., Min, L., Krop, I. E.,...Tolaney, S. M. (2018). Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncology, 4*(2), 173–182. https://doi.org/10.1001/jamaoncol.2017.3064

Brahmer, J. R., Govindan, R., Anders, R. A., Antonia, S. J., Sagorsky, S., Davies, M. J.,...Herbst, R. S. (2018a). The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *Journal for ImmunoTherapy of Cancer, 6*, 75. https://doi.org/10.1186/s40425-018-0382-2

Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M.,...Thompson, J. A. (2018b). 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*(17), 1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

Bristol-Myers Squibb. (2018). Opdivo (nivolumab) package insert. Retrieved from http://www.opdivoyervoyhcp.com

Bui, K. T., Cooper, W. A., Kao, S., & Boyer, M. (2018). Targeted molecular treatments in non-small cell lung cancer: A clinical guide for oncologists. *Journal of Clinical Medicine, 7*(8), E192. https://doi.org/10.3390/jcm7080192

Byun, D. J., Wolchok, J. D., Rosenberg, L. M., & Girotra, M. (2017). Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. *Nature Re-*

views Endocrinology, 13, 195–207. https://doi.org/10.1038/nrendo.2016.205

Cappelli, L. C., Gutierrez, A. K., Bingham, C. O., 3rd, & Shah, A. A. (2017a). Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature. *Arthritis Care and Research (Hoboken), 69*(11), 1751–1763. https://doi.org/10.1002/acr.23177

Cappelli, L. C., Naidoo, J., Bingham, C. O., 3rd, & Shah, A. A. (2017b). Inflammatory arthritis due to immune checkpoint inhibitors: Challenges in diagnosis and treatment. *Immunotherapy, 9*(1), 5–8. https://doi.org/10.2217/imt-2016-0117

Cappelli, L. C., Shah, A. A., & Bingham, C. O., 3rd. (2017c). Immune-related adverse effects of cancer immunotherapy—Implications for rheumatology. *Rheumatic Diseases Clinics of North America, 43*, 65–78. https://doi.org/10.1016/j.rdc.2016.09.007

Carpenter, K. J., Murtagh, R. D., Lilienfeld, H., Weber, J., & Murtagh, F. R. (2009). Ipilimumab-induced hypophysitis: MR imaging findings. *American Journal of Neuroradiology, 30*(9), 1751–1753. https://doi.org/10.3174/ajnr.A1623

Chung, C. (2018). To do or not to do: A concise update of current clinical controversies in immune checkpoint blockade. *Journal of Oncology Pharmacy Practice*. Advance online publication. https://doi.org/10.1177/1078155218786365

Cronin, K. A., Lake, A. J., Scott, S., Sherman, R. L., Noone, A. M., Howlader, N.,...Jemal, A. (2018). Annual report to the nation on the status of cancer, part I: National Cancer Statistics. *Cancer, 124*(13), 2785–2800. https://doi.org/10.1002/cncr.31551

DiMeglio, L. A., Evans-Molina, C., & Oram, R. A. (2018). Type 1 diabetes. *Lancet, 391*(10138), 2449–2462. https://doi.org/10.1016/S0140-6736(18)31320-5

Fazer, C. (2019). Checkpoint inhibitor immunotherapy for head and neck cancer: Incorporating Care Step Pathways for effective side-effect management. *Journal of the Advanced Practitioner in Oncology, 10*(suppl 2), 37–46. https://doi.org/10.6004/jadpro.2019.10.2.12

Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H.,...Naghavi, M. (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the Global Burden of Disease Study. *JAMA Oncology, 3*(4), 524–548. https://doi.org/10.1001/jamaoncol.2016.5688

Gauci, M. L., Laly, P., Vidal-Trecan, T., Baroudjian, B., Gottlieb, J., Madjlessi-Ezra, N.,...Gautier, J-F. (2017). Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: A case report and literature review. *Cancer Immunology, Immunotherapy, 66*(11), 1399–1410. https://doi.org/10.1007/s00262-017-2033-8

Genentech, Inc. (2018). Tecentriq (atezolizumab) package insert. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s010lbl.pdf

Girotra, M., Hansen, A., Farooki, A., Byun, D. J., Min, L., Creelan, B. C.,...Gravell, A. E. (2018). The current understanding of the endocrine effects from immune checkpoint inhibitors and recommendations for management. *JNCI Cancer Spectrum, 2*(3), pky021. https://doi.org/10.1093/jncics/pky021

Hoffner, B., & Rubin, K. (2019). Meeting the challenge of immune-related adverse events with optimized telephone triage and dedicated oncology acute care. *Journal of the Advanced Practitioner in Oncology, 10*(suppl 2), 9–20. https://doi.org/10.6004/jadpro.2019.10.2.10

Hu, Y. B., Zhang, Q., Li, H. J., Michot, J. M., Liu, H. B., Zhan, P., & Song, Y. (2017). Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: A meta-analysis. *Translational Lung Cancer Research, 6*(suppl 1), S8–S20. https://doi.org/10.21037/tlcr.2017.12.10

Iglesias, P. (2018). Cancer immunotherapy-induced endocrinopathies: Clinical behavior and therapeutic approach. *European Journal of Internal Medicine, 47,* 6–13. https://doi.org/10.1016/j.ejim.2017.08.019

Kazandjian, D., Suzman, D. L., Blumenthal, G., Mushti, S., He, K., Libeg, M., & Pazdur, R. (2016). FDA approval summary: Nivolumab for the treatment of metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. *The Oncologist, 21*(5), 634–642. https://doi.org/10.1634/theoncologist.2015-0507

Khan, M., Lin, J., Liao, G., Tian, Y., Liang, Y., Li, R.,...Yuan, Y. (2018). Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. *Medicine (Baltimore), 97*(33), e11936. https://doi.org/10.1097/MD.0000000000011936

Kirkwood, J. M., & Ribas, A. (2017). Collaborative care in melanoma: The essential role of the nurse. *Clinical Journal of Oncology Nursing, 21*(4 suppl), 4–6. https://doi.org/10.1188/17.CJON.S4.4-6

Marshall, H. T., & Djamgoz, B. A. (2018). Immuno-oncology: Emerging targets and combination therapies. *Frontiers in Oncology, 8*, 315. https://dx.doi.org/10.3389%2Ffonc.2018.00315

McGettigan, S., & Rubin, K. M. (2017). PD-1 inhibitor therapy: Consensus statement from the faculty of the Melanoma Nursing Initiative on managing adverse events. *Clinical Journal of Oncology Nursing, 21*(4 suppl), 42–51. https://doi.org/10.1188/17.CJON.S4.42-51

Merck & Co., Inc. (2018). Keytruda (pembrolizumab) package insert. Retrieved from http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Min, L. (2016). Immune-related endocrine disorders in novel immune checkpoint inhibition therapy. *Genes & Diseases, 3*(4), 252–256. https://doi.org/10.1016/j.gendis.2016.10.002

Naidoo, J., Wang, X., Woo, K. M., Iyriboz, T., Halpenny, D., Cunningham, J.,...Hellmann, M. D. (2017). Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *Journal of Clinical Oncology, 35*(7), 709–717. https://doi.org/10.1200/JCO.2016.68.2005

National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Management of immunotherapy-related toxicities. v1.2018. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Nishijima, T. F., Shachar, S. S., Nyrop, K. A., & Muss, H. B. (2017). Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: A meta-analysis. *The Oncologist, 22*(4), 470–479. https://doi.org/10.1634/theoncologist.2016-0419

Nishino, M., Giobbie-Hurder, A., Hatabu, H., Ramaiya, N. H.,

& Hodi, F. S. (2016). Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: A systematic review and meta-analysis. *JAMA Oncology, 2*(12), 1607–1616. https://doi.org/10.1001/jamaoncol.2016.2453

Ntali, G., Kassi, E., & Alevizaki, M. (2017). Endocrine sequelae of immune checkpoint inhibitors. *Hormones (Athens), 16*(4), 341–350. https://doi.org/10.14310/horm.2002.1754

Pakkala, S., & Ramalingam, S. S. (2018). Personalized therapy for lung cancer: Striking a moving target. *JCI Insight, 3*(15), e120858. https://doi.org/10.1172/jci.insight.120858

Paz-Ares, L., Luft, A., Vicente, D., Tafreshi, A., Gümüş, M., Mazières, J.,...Wilson, J. (2018). Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *New England Journal of Medicine, 379*(21), 2040–2051. https://doi.org/10.1056/NEJMoa1810865

Postow, M. A., Sidlow, R., & Hellmann, M. D. (2018). Immune-related adverse events 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., 3rd, Brogdon, C., Dadu, R.,...Emstoff, 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

Raju, S., Joseph, R., & Sehgal, S. (2018). Review of checkpoint immunotherapy for the management of non-small cell lung cancer. *ImmunoTargets and Therapy, 7,* 63–75. https://doi.org/10.2147/ITT.S125070

Recondo, G., Facchinetti, F., Olaussen, K. A., Besse, B., & Friboulet, L. (2018). Making the first move in EGFR-driven or ALK-driven NSCLC: First-generation or next-generation TKI? *Nature Reviews Clinical Oncology, 15,* 694–708. https://doi.org/10.1038/s41571-018-0081-4

Rubin, K. M. (2017). Advances in melanoma: The rationale for the Melanoma Nursing Initiative. *Clinical Journal of Oncology Nursing, 21*(4), 7–10. https://doi.org/10.1188/17.CJON.S4.7-10

Shah, M., Tayar, J. H., Abdel-Wahab, N., & Suarez-Almazor, M. E. (2018). Myositis as an adverse event of immune checkpoint blockade for cancer therapy. *Seminars in Arthritis and Rheumatism*. Advance online publication. https://doi.org/10.1016/j.semarthrit.2018.05.006

Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians, 68*(1), 7–30. https://doi.org/10.3322/caac.21442

Suresh, K., Voong, K. R., Shankar, B., Forde, P. M., Ettinger, D. S., Marrone, K. A.,...Naidoo, J. (2018). Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: Incidence and risk factors. *Journal of Thoracic Oncology, 13*(12), 1930–1939. https://doi.org/10.1016/j.jtho.2018.08.2035

Sznol, M., Raju, M. A., Davies, M. J., Pavlick, A. C., Plimack, E. R., Shaheen, M.,...Robert, C. (2017). Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. *Cancer Treatment Reviews, 58,* 70–76. https://doi.org/10.1016/j.ctrv.2017.06.002

Thompson, J. A. (2018). New NCCN guidelines: Recognition and management of immunotherapy-related toxicity. *Journal of the National Comprehensive Cancer Network, 16*(5S), 594–596. https://doi.org/10.6004/jnccn.2018.0047

US Department of Health and Human Services. (2018). Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

US Food and Drug Administration. (2018). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Retrieved from https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm

Villanueva, N., & Bazhenova, L. (2018). New strategies in immunotherapy for lung cancer: Beyond PD-1/PD-L1. *Therapeutic Advances in Respiratory Disease, 12,* 1–29. https://doi.org/10.1177/1753466618794133

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*. Advance online publication. https://doi.org/10.1177/1078155217744872

Wills, B., Brahmer, J. R., & Naidoo, J. (2018). Treatment of complications from immune checkpoint inhibition in patients with lung cancer. *Current Treatment Options in Oncology, 19,* 46. https://doi.org/10.1007/s11864-018-0562-9

Wood, L. S. (2019). Immune-related adverse events from immunotherapy: Incorporating Care Step Pathways to improve management across tumor types. *Journal of the Advanced Practitioner in Oncology, 10*(suppl 2), 47–62. https://doi.org/10.6004/jadpro.2019.10.2.13

Zago, G., Muller, M., van den Heuvel, M., & Baas, P. (2016). New targeted treatments for non-small-cell lung cancer - role of nivolumab. *Biologics, 10,* 103–117. https://doi.org/10.2147/BTT.S87878