Unleashing the Immune System With Checkpoint Inhibitors in Non–Small Cell Lung Cancer: Clinical Review of Adverse Events

SANDRA CUELLAR, PharmD, BCOP

From University of Illinois Hospital and Health Sciences System—Pharmacy Practice, Chicago, Illinois

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Sandra Cuellar, PharmD, BCOP, University of Illinois Hospital and Health Sciences System—Pharmacy Practice, 833 S. Wood Street, MC 886, Chicago, IL 60612-7236. E-mail: scuell1@uic.edu

https://doi.org/10.6004/jadpro.2017.8.5.18

Abstract

Immunotherapy checkpoint inhibitors have dramatically changed our management of metastatic non–small cell lung cancer (NSCLC). Efficacy data have supported immune checkpoint inhibitors as potential first-line options as monotherapy or in combination with chemotherapy. In addition, they are approved as second-line options after a platinum doublet. Their efficacy represents an unprecedented milestone in metastatic NSCLC. In this new age of immunotherapy, health-care professionals are not experienced in the unique side-effect profile that immunotherapy brings to clinical practice. In general, immune checkpoint inhibitors are well tolerated, but fatal adverse events can occur. Therefore, it is imperative that health-care professionals are educated on the monitoring, identification, and management of the immune-related adverse events (irAEs) that can occur with immune checkpoint inhibitors. This article will review the mechanisms of action, incidence, and management of the most common irAEs that occur with the US Food and Drug Administration–approved checkpoint inhibitors in metastatic NSCLC.

J Adv Pract Oncol 2017;8:65–75

Over the past decades and to the present day, non–small cell lung cancer (NSCLC) remains the leading cause of cancer-related death in the United States. Unfortunately, about 80% of patients diagnosed with NSCLC present with advanced disease and are therefore not candidates for surgical resection (Birring & Peake, 2005). So patients are often started on systemic treatment, which, for patients with advanced or stage IV disease, have primarily consisted of cytotoxic platinum-based chemotherapy and targeted therapies. However, in 2015, the introduction of the immuno-oncology agents such as nivolumab (Opdivo) and pembrolizumab (Keytruda)

added to the armamentarium of systemic treatment options for these patients. Their efficacy in the second-line setting (post–platinum doublet) compared with docetaxel has rendered them preferred therapies in the National Comprehensive Cancer Network (NCCN) Guidelines. In addition, recent data with pembrolizumab have demonstrated efficacy in the first-line setting as monotherapy or in combination with chemotherapy (Merck, 2017; Reck et al., 2016). Three US Food and Drug Administration (FDA)–approved immuno-oncology agents have been approved in NSCLC: nivolumab, pembrolizumab, and atezolizumab (Tecentriq). These agents have received category 1 designations compared with other systemic therapy such has docetaxel, pemetrexed (Alimta), gemcitabine, and ramucirumab (Cyramza) plus docetaxel in the 2017 NCCN Guidelines regardless of histology for treatment in the platinum-refractory setting (NCCN, 2017). Pembrolizumab is approved as monotherapy for patients with metastatic NSCLC whose tumors have high programmed cell death ligand 1 (PD-L1) expression. In May 2017, pembrolizumab also received accelerated FDA approval for use in combination with pemetrexed and carboplatin as a first-line treatment option in patients with nonsquamous metastatic NSCLC (Merck, 2017).

Knowledge of the specific toxicity profile and management of these specific immune checkpoint inhibitors are essential to optimize care. Checkpoint inhibitors are biologic agents that modulate the immune system, and therefore, the side-effect profile is different from that typically seen with cytotoxic or targeted therapies. The immune-related adverse events (irAEs) reported with checkpoint inhibitors are generally manageable but can be fatal in some cases. Their appearance may be subclinical, and early diagnosis and management present challenges for clinicians. On February 17, 2017, the American Society of Clinical Oncology (ASCO) and NCCN announced a joint collaboration to develop guidelines for the management of side effects from immunotherapy. In the interim of those published guidelines, this article will summarize the most common irAEs that occur with immune checkpoint inhibitors approved for patients with NSCLC and include recommended monitoring and management strategies that clinicians can implement in their clinical practices.

MECHANISM OF IMMUNE-RELATED ADVERSE EVENTS

To understand the mechanisms of side effects associated with immune checkpoint inhibitors, it is crucial first to outline the mechanism of action. It has been long recognized that the immune system plays a vital role in proactively eliminating abnormal cells, such as cancer cells. The goal of immunotherapy is to amplify and restore the ability of the immune system to detect and subsequently destroy cancer cells (Disis, 2014). Unfortunately, cancer cells have been able to evade the immune system and continue to proliferate and metastasize. The mechanisms of how cancer cells evade the immune system have been under intense research across the past decades, specifically the role of immune checkpoints. Immune checkpoints are one target of the immune system that has led to drug development. Immune checkpoints are inhibitory pathways that the immune system has devised to maintain self-tolerance and homeostasis.

The primary role of immune checkpoints is to protect tissues from damage when the immune system is responding to pathogens and to maintain tolerance to self-antigens. This is accomplished by downregulating T-cell activation. Cancer cells have capitalized on the feature of downregulating T cells by interfering with immune checkpoints, thereby evading the immune system (Disis, 2014). One of the inhibitory pathways of immune checkpoints is mediated by programmed cell death protein 1 (PD-1), which controls immune responses. Programmed cell death protein 1 is expressed on several immune cells such as CD4+ and CD8+ T cells, natural killer cells, B cells, as well as monocytes and dendritic cells in the setting of lymphocyte activation (Eigentler et al., 2016). Therefore, when the ligand PD-L1 binds to PD-1, it limits the activity of T cells. Essentially, the ligand interaction puts the breaks on the T-cell response. Research has demonstrated that several cancer cells have upregulation of PD-L1 on cell surfaces. Upregulation of PD-L1 can negatively interfere with T-cell activity in the tumor microenvironment (Pardoll, 2012).

Immune checkpoint inhibitors approved in NSCLC include two PD-1 monoclonal antibodies, nivolumab and pembrolizumab, and one PD-L1 monoclonal antibody, atezolizumab. These biolog-

ic monoclonal antibodies allow the T cell to attack not only the tumor cells but also normal tissues, leading to autoimmune events. In clinical trials with immune checkpoint inhibitors, patients with known autoimmune disease were excluded because of concern of exacerbations of their autoimmune disease. Review of a medical history of autoimmune disease and current immunosuppressive medications is imperative before initiating immune checkpoint inhibitors. Examples of autoimmune disease include Crohn's disease, psoriasis, lupus, immunologic thrombocytopenic purpura, and multiple sclerosis (Champiat et al., 2016). Patients with a history of autoimmune disease were excluded from clinical trials. The concern with concomitantly taking immunosuppressive agents, such as corticosteroids, is that they may theoretically interfere with the efficacy of immune checkpoint inhibitors. In the event that corticosteroids are clinically indicated, an acceptable dose would not exceed the physiologic equivalent of prednisone at 10 mg daily (O'Kane et al., 2017).

GENERAL CONSIDERATIONS WITH PD-1/PD-L1 IMMUNE CHECKPOINT INHIBITORS

The PD-1 and PD-L1 immune checkpoint inhibitors are generally not associated with infusion-related reactions and do not require any premedication. The incidence of infusion-related reactions across all three agents was less than 2% (Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017). If mild or moderate infusion reactions occur, it is recommended to slow the infusion rate (Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017). The spectrum of reported irAEs associated with the PD-1 and PD-L1 inhibitors is wide; however, the management approach employs systemic corticosteroids in most cases. The irAEs are generally steroid sensitive and reversible (Michot et al., 2016). Moderate to severe irAEs require interruption of therapy as well as systemic corticosteroids.

The onset of irAEs varies and can present insidiously; therefore, it is vital that the patient and/or caregiver receive comprehensive education regarding the early recognition of adverse reactions. As mentioned previously, these agents are well tolerated, but fatal adverse events can occur. Patients experiencing adverse reactions need to inform their health-care providers, especially emergency physicians, they are on immunotherapy agents. Delay in proper identification and management of irAEs can cause significant morbidity and potentially mortality. The most common reported irAEs with nivolumab, pembrolizumab, and atezolizumab monotherapy include diarrhea/colitis, pneumonitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities (O'Kane et al., 2017; Tables 1 to 4). The adverse events with combination checkpoint inhibitors plus chemotherapy have been investigated and the results published. The KEYNOTE-021 study combined pembrolizumab with pemetrexed at 500 mg/m^2 plus carboplatin area under the curve (AUC) 5. The incidence of irAEs in the pembrolizumab plus chemotherapy arm was comparable with that seen with monotherapy pembrolizumab (Langer et al., 2016; Table 2).

IMMUNE-MEDIATED DIARRHEA/COLITIS

Immune-mediated diarrhea or colitis is one of the most common side effects that can occur with PD-1 and PD-L1 immune checkpoint inhibitors. Most of the recommendations regarding management of immune-mediated diarrhea/colitis have occurred with another FDA-approved immune checkpoint inhibitor, ipilimumab (Yervoy). Ipilimumab mediates the immune checkpoint at a different target than PD-1 and PD-L1. It has a similar side-effect profile but higher incidence and severity compared with PD-1 and PD-L1 (Weber, Yang, Atkins, & Disis, 2015). Regardless of the agent, the treatment of immune-mediated diarrhea/colitis is the same across all immune checkpoint inhibitors.

Budesonide, a long-acting corticosteroid with low systemic bioavailability, was investigated in a clinical trial with the immune checkpoint inhibitor ipilimumab to prevent grade 2 or higher diarrhea/colitis while maintaining efficacy. Approximately 115 patients were randomly assigned to placebo or budesonide at 9 mg daily for 12 weeks. The results were not statistically significant between the groups. The conclusion of the trial was that budesonide should not be used prophylactically (Weber et al., 2009). Therefore, there are no current prophylactic prevention strategies for im-

Table 1. KEYNOTE-001 and KEYNOTE-024 Trials in Non–Small Cell Lung Cancer (Pembrolizumab)

	KEYNOTE-001 (N = 495)		KEYNOTE-024 (N = 154)	
irAEs	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**
Hypothyroidism	34 (6.9)	1 (0.2)	14 (9.1)	0
Hyperthyroidism	NR	NR	12 (7.8)	0
Pneumonitis	18 (3.6)	9 (1.8)	9 (5.8)	4 (2.6)
Dermatologic acneiform	13 (2.6)	0	6 (3.9)	6 (3.9)
Colitis/diarrhea	40 (8.1)	3 (0.6)	3 (1.9)	2 (1.3)
Hypophysitis	NR	NR	1 (0.6)	1 (0.6)
Hepatitis (increase ALT/AST)	26 (5.2)	5 (1.0)	NR	NR
Nephritis	NR	NR	1 (0.6)	1 (0.6)

Note. irAEs = immune-related adverse events; NR = not reported; ALT = alanine aminotransferase; AST = aspartate aminotransferase. Information from Langer et al. (2016).

mune-mediated diarrhea/colitis for patients initiating immune checkpoint inhibitors.

The clinical presentation of immune-mediated diarrhea is similar to non–immune-mediated diarrhea. Patients may present with complaints of watery stools, abdominal pain, abdominal cramping, fever, and rectal bleeding. The incidence of diarrhea among the PD-1 immune checkpoint inhibitors is similar with that of nivolumab and pembrolizumab, ranging from 7% to 8% grade 1/2 and grade 3 diarrhea occurred in less than 1% across NSCLC trials (Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017). The incidence was higher with the PD-L1 inhibitor atezolizumab. In the NSCLC study with atezolizumab, immune-mediated gastrointestinal toxicity was reported with an incidence across all grades of 19.3%. Grade 3 had an incidence of 1.2%. The median time to diarrhea reported in the nivolumab NSCLC trials was 4.7 weeks (range, 0.4–68.6) and 3 weeks (0.1–86.4) with a 1- to 2-week median time to resolution (Eigentler et al., 2016). Median time to onset of immune-mediated gastrointestinal toxicity with pembrolizumab was 3.5 months (range, 10 days–16.2 months), significantly longer compared with nivolumab. The median duration was 1.3 months

Table 2. KEYNOTE-021 Trial in Non–Small Cell Lung Cancer (Pembrolizumab + Pemetrexed + Carboplatin)

	KEYNOTE-021 (N = 59)	
irAEs	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**
Hypothyroidism	34 (6.9)	0
Hyperthyroidism	NR	0
Pneumonitis	18 (3.6)	1 (2)
Severe skin reactions	0	1 (2)
Diarrhea	12 (20)	0
Hypophysitis	NR	NR
Hepatitis (increase ALT/AST)	19 (32)	1 (2)
Acute kidney injury	0	2 (3)

Note. irAEs = immune-related adverse events; NR = not reported; ALT = alanine aminotransferase; AST = aspartate aminotransferase. Information from Langer et al. (2016).

Table 3. CheckMate 017 and 057 Trials in Non–Small Cell Lung Cancer (Nivolumab)

	CheckMate 017 (N = 131)		CheckMate 057 (N = 287)	
irAEs	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**
Hypothyroidism	5 (4)	0	19 (7)	0
Hyperthyroidism	0	0	4 (1)	0
Pneumonitis	6 (5)	1 (1)	8 (3)	3 (1)
Rash	12 (4)	0	36 (13)	1 (< 1)
Diarrhea	1 (1)	1 (1)	45 (16)	3 (1)
Colitis	1 (1)	1 (1)	2 (1)	1 (< 1)
Hypophysitis	0	0	0	0
Hepatitis (increase ALT/AST)	2 (2)	0	1 (< 1)	1 (< 1)
Nephritis	1 (1)	1 (1)	5 (2)	0

Note. irAEs = immune-related adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase. Information from Borghaei et al. (2015); Brahmer et al. (2015).

(range, 1 day to > 8.7 months; Merck, 2017). The median onset of immune-mediated diarrhea/colitis in the atezolizumab arm was 21 days (range, 12 days–3.4 months; Genentech, 2016).

Regardless of the agent used, a step-wise approach for management of immune-mediated diarrhea/colitis is recommended. Determination of etiology and severity of diarrhea will guide management (Table 5). Clinicians should consider ruling out an infectious etiology and complete stool studies in patients who develop diarrhea. For grade 1 diarrhea, supportive care and close monitoring is recommended. Symptomatic management consists of oral hydration, American Dietary Association colitis diet, and electrolyte repletion (Weber, Kahler, & Hauschild, 2012).

The use of anti-diarrheal agents, such as loperamide and diphenoxylate/atropine may also be a consideration. The caution with recommending an antidiarrheal for mild diarrhea is that it may mask the severity of the diarrhea. Therapy with PD-1/PD-L1 can continue; no dose interruption or delay is necessary for grade 1 diarrhea. Management of grade 2 diarrhea involves a similar

Table 4. OAK and POPLAR Trials in Non–Small Cell Lung Cancer (Atezolizumab)

	OAK (N = 609)		POPLAR (N = 131)	
irAEs	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**	**Any grade No. of patients (%)**	**Grade 3–5 No. of patients (%)**
Hypothyroidism	NR	NR	5 (4)	NR
Hyperthyroidism	NR	NR	NR	NR
Pneumonitis	6 (1)	4 (< 1)	NR	NR
Colitis	2 (< 1)	0	NR	NR
Diarrhea	NR	NR	10 (7)	NR
Hypophysitis	NR	NR	NR	NR
Hepatitis (increase ALT)	2 (< 1)	2 (< 1)	3 (2)	NR
Nephritis	NR	NR	NR	NR

Note. irAEs = immune-related adverse events; NR = not reported; ALT = alanine aminotransferase. Information from Fehrenbacher et al. (2016); Rittmeyer et al. (2017).

Table 5. Common Terminology Criteria for Adverse Events Grading

Toxicity	CTCAE grade	Management
Diarrhea/colitis	• Grade 1 diarrhea: increase of < 4 stools/day over baseline; mild increase in ostomy output • Grade 2 colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated	• No dose interruption • Oral hydration • +/- Electrolyte replacement • Antidiarrheal (loperamide)
	• Grade 2 diarrhea: increase of 4 to 6 stools/day over baseline; moderate increase in ostomy output • Grade 2 colitis: abdominal pain; mucus or blood in stool	• Hold therapy temporarily • Oral hydration • ADA diet • Antidiarrheal (diphenoxylate HCL/atropine sulfate QID) • Consider oral budesonide at 9 mg daily • If persists for > 5 days prednisone at 0.5–1 mg/kg day • Consider gastroenterology consult
	• Grade 3 diarrhea: increase of 7 or more stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output, limiting self-care ADL • Grade 3 colitis: severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Discontinue therapy • Intravenous hydration • Electrolyte replacement • Methylprednisolone at 1–2 mg/kg IV • Infliximab at 5 mg/kg if not improvement in 2–3 days of methylprednisolone therapy, may repeat dose in 2 weeks • Gastroenterology consult
	• Grade 4 diarrhea and colitis: life-threatening consequences; urgent intervention indicated	• Same as grade 3 management
Hepatitis	• Grade 1: AST/ALT ULN–3×ULN or bilirubin ULN–1.5×ULN	• Continue therapy and monitor LFTs prior to each dose
	• Grade 2: AST/ALT > 3–5×ULN or bilirubin > 1.5–3×ULN	• HOLD therapy, monitor LFTs every 3 days, if no improvement or worsening consult hepatology
	• Grade 3: AST/ALT > 5–20×ULN or bilirubin > 3–10×ULN	• Discontinue therapy, monitor LFTs daily, methylprednisolone at 1–2 mg/kg IV daily
	• Grade 4: AST/ALT > 20×ULN or bilirubin > 10×ULN	• Discontinue therapy, consult hepatology, methylprednisolone at 1–2 mg/kg IV daily. If no improvement in 48 hours, consider additional immunosuppressive therapy
Pneumonitis	• Grade 1: Radiographic changes/asymptomatic	• Consider delay of therapy, pulmonary, and/or infectious disease consults. Reimage after 3 weeks
	• Grade 2: Mild to moderate symptoms	• HOLD therapy, pulmonary/infectious disease consults, initiate corticosteroids. Monitor daily and consider hospitalization
	• Grade 3: Severe symptoms; limits self-care ADL; oxygen indicated	• Discontinue therapy, admit to hospital, pulmonary/infectious consults, and start high-dose systemic corticosteroids. If no improvement within 48 to 72 hours, consider additional immunosuppressive therapy
	• Grade 4: Life-threatening respiratory compromise	• Discontinue therapy, admit to hospital, pulmonary/infectious consults, and start high-dose systemic corticosteroids. If no improvement within 48 to 72 hours, consider additional immunosuppressive therapy

Note. CTCAE = Common Terminology Criteria for Adverse Events; ADA = American Dietary Association; HCL = hydrochloride; QID = once per day; ADL = activities of daily living; IV = intravenously; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULT = upper limit of normal; LFTs = liver function tests. Information from Howell, Lee, Bowyer, Fusi, and Lorigan (2015); O'Kane et al. (2017); Weber, Kahler, and Hauschild (2012).

approach in terms of ruling out infectious causes and assessment of severity and implementation of supportive care measures. In addition, budesonide can be considered in this setting, although data are lacking. Budesonide is an oral steroid with unique pharmacokinetic features that make it an attractive option for management of immune-mediated diarrhea/colitis. Because it has very low absorption, there is no concern that it will interfere with the efficacy of an immuno-oncology agent (O'Kane et al., 2017; Weber et al., 2012). If the symptoms persist for 5 or more days, initiating systemic corticosteroids with oral prednisone at 0.5 mg/kg/day or equivalent is indicated. The duration of treatment varies but should be continued until the toxicity resolves to grade 1. Steroids generally can be tapered over 2 to 4 weeks. Clinicians can consider a gastroenterology consult for further guidance (Eigentler et al., 2016; O'Kane et al., 2017).

Grade 2 diarrhea/colitis does lead to temporary interruption in therapy until diarrhea resolves. In the event grade 3 diarrhea occurs, then interrupt PD-1/PD-L1 therapy and discontinue treatment permanently. Management of severe toxicity generally includes hospitalization and intravenous hydration with electrolyte replacement. Clinicians should consider a gastroenterology consult as well as colonoscopy. In addition, prompt initiation of systemic intravenous methylprednisolone at 1 to 2 mg/kg/day for 3 days, then prednisone at 1 to 2 mg/kg/day until improvement is recommended. Symptom improvement will likely be seen within 1 to 2 weeks with systemic steroid treatment. In addition, once stable, institute a long steroid taper consisting of approximately at least 4 weeks and in some cases up to 8 weeks. Slow taper is recommended to prevent recurrence or worsening of symptoms.

Although corticosteroids frequently resolve the diarrhea/colitis, some patients may have disease that is steroid refractory. The definition of steroid refractory in clinical trials may vary (Eigentler et al., 2016; Howell, Lee, Bowyer, Fusi, & Lorigan, 2015; O'Kane et al., 2017). In clinical practice, the threshold for consideration of other immunosuppressive options in the steroid-refractory settings varies. Clinicians may consider other immunosuppressive options if there is no improvement in 2 to 3 days, whereas others range from 3 to 7 days before consideration of other immunosuppressive options (Eigentler et al., 2016; Spain, Diem, & Larkin, 2016). In the steroid-refractory setting, infliximab (Remicade), a tumor necrosis factor α inhibitor, has been used in immune-mediated diarrhea/colitis among patients treated with immune checkpoint inhibitors (Weber et al., 2012). One dose of infliximab is 5 mg/kg, and it can be repeated in 2 weeks. After resolution or improvement of symptoms, infliximab can be discontinued and a slow steroid taper over 6 to 8 weeks should be instituted (O'Kane et al., 2017; Weber et al., 2012).

IMMUNE-MEDIATED PNEUMONITIS

Immune-mediated pneumonitis is one of the few potentially life-threatening irAEs that can occur with PD-1/PD-L1 immune checkpoint inhibitors. Therefore, prompt recognition and early therapy initiation are vital to prevent poor outcomes. Pneumonitis is a noninfectious lung inflammation with interstitial and alveolar infiltrates (Eigentler et al., 2016; O'Kane et al., 2017). Clinical presentation of immune-mediated pneumonitis in lung cancer can be challenging. Symptoms of shortness of breath and unproductive cough are common in lung cancer, as well as in pneumonitis. The key in clinical presentation is new onset or worsening of shortness of breath, cough, chest pain, fever, and fine inspiratory crackles on lung auscultation. Diagnostic imaging can assist with diagnosis (O'Kane et al., 2017). Five distinct radiologic subtypes have been described in the literature among patients developing pneumonitis from PD-1 immune checkpoint inhibitors in NSCLC. Cryptogenic obstructive pneumonia–like, ground glass opacities, hypersensitivity type, acute interstitial pneumonia/acute respiratory distress syndrome, and pneumonitis not otherwise specified are the distinct radiographic manifestations reported (Naidoo et al., 2015).

The onset of immune-mediated pneumonitis among nivolumab, pembrolizumab, and atezolizumab is wide, with a range of days to more than a year. The incidence of immune-mediated pneumonitis (all grades) among the PD-1/PD-L1 inhibitors was relatively similar: 5% with nivolumab, 4% with pembrolizumab, and 3.7% with atezolizumab. Grade 3 to 5 incidence was 2% or less with all agents. The median onset among all three agents was similar, at approximately 3 months

(Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017).

There are no prospective clinical trials that have defined the optimal treatment approach of immune-mediated pneumonitis. Recommendations are generated by clinical trial experience as well as peer review publications. Grade 1 pneumonitis is clinically asymptomatic, and no intervention is needed. If radiographic changes are seen, consider delay of therapy and pulmonary and infectious disease consults. Grade 2 pneumonitis requires holding PD-1/PD-L1 therapy and starting systemic corticosteroids (prednisone at 1 to 2 mg/kg/day orally or methylprednisone at 1 to 2 mg/kg/day intravenously). Hospitalization may be considered if clinically indicated based on clinician judgment.

Other recommendations are to consider obtaining bronchoscopy, reimage every 1 to 3 days, and specialty consults (pulmonary and infectious disease). If clinical and radiologic improvement is observed, begin a slow steroid taper over 4 weeks. If there is no clinical improvement after 2 weeks of systemic steroids, consider treating as grade 3/4 pneumonitis.

Grade 3/4 pneumonitis requires permanent discontinuation of immune checkpoint therapy and hospitalization. Systemic intravenous high-dose steroids are indicated. High-dose steroid recommendation comes from experience in other disease states that have immunogenic etiologies such as diffuse alveolar hemorrhage, which demonstrated improved overall survival. Examples of high-dose steroids include methylprednisolone at 1 g/day intravenous or prednisone at 4 mg/kg/day (Fukuda et al., 2003; Metcalf et al., 1994). If there is no improvement after 48 hours or worsening, consider the administration of additional immunosuppressive therapy such as infliximab, mycophenolate mofetil (CellCept), cyclophosphamide, or intravenous immunoglobulin (Howell et al., 2015; O'Kane et al., 2017). Currently, there are no prospective data with these agents in this setting. Use has been limited to clinical and anecdotal experience (Table 5).

IMMUNE-MEDIATED HEPATITIS

Immune-mediated hepatitis is the term used to describe asymptomatic elevations in liver transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) with or without an increase in bilirubin, as a result of immunotherapy. The occurrence of immune-mediated hepatitis reported in NSCLC trials among nivolumab, pembrolizumab, and atezolizumab was relatively uncommon, up to 3%. Typical onset varies among the agents where it has been reported to occur within days to over a year. Median onset is approximately 1 to 2 months with the PD-1/PD-L1 immune checkpoint inhibitors (Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017).

Monitoring liver function tests (LFTs) at baseline and prior to each dose is recommended because of the possibility of immune-mediated hepatitis. Management of immune-mediated hepatitis depends on the severity of elevations of ALT/AST or total bilirubin. With grade 1 hepatitis, therapy is not interrupted; however, continued monitoring of LFTs is recommended. For grade 2 hepatitis, interrupt therapy and continue to monitor LFTs. If elevations in ALT/AST persist, consider hepatology consult. In the event grade 3 or 4 hepatitis occurs, obtain a hepatology consult, discontinue PD-1/PD-L1, and initiate systemic steroids (methylprednisolone at 1 to 2 mg/kg intravenous daily) and monitor LFTs daily. If no improvement is seen once systemic steroids are initiated, consider treatment with mycophenolate mofetil (Howell et al., 2015).

In non-oncology settings, autoimmune hepatitis refractory to steroids has responded favorably to mycophenolate mofetil at dose ranges from 500 mg to 1 g twice per day (Zachou, Gatselis, Papadamou, Rigopoulou, & Dalekos, 2011). Infliximab is not recommended in immune-mediated hepatitis because of potential hepatotoxicity (Janssen Biotech, 2015).

IMMUNE-MEDIATED HYPOTHYROIDISM AND HYPERTHYROIDISM

Immune-related thyroid disorders are the most common endocrinopathy reported among the PD-1/PD-L1 immune checkpoint inhibitors. Specifically, hypothyroidism is more common compared with hyperthyroidism (Michot et al., 2016). Overt hypothyroidism is defined as increased thyroid-stimulating hormone (TSH) and low T4

or T3. Subclinical hypothyroidism is defined as elevated TSH but normal T3 and T4 (Khandelwal & Tandon, 2012). The incidence across all agents is up to 8% across all grades. The onset of thyroid disorders ranges widely, from 2 weeks to years. Therefore, monitoring TSH at baseline and at regular intervals during therapy is recommended. The package insert does not have specific recommendations, but given the incidence, it is reasonable to monitor at baseline and every other cycle with all three agents.

Although most patients who develop hypothyroidism are asymptomatic, clinicians should be aware of the signs and symptoms of hypothyroidism. They include fatigue, loss of appetite, bradycardia, hair loss, increased sensitivity to cold, dry skin, and constipation (Khandelwal & Tandon, 2012). The mechanism of hypothyroidism is not completely elucidated. It appears to be similar to autoimmune thyroiditis, with immune-mediated destructive effects of the thyroid leading to a temporary, often subclinical hyperthyroidism, followed by a sometimes-permanent hypothyroidism (O'Kane et al., 2017).

In two small retrospective studies reviewing thyroid disorders among patients receiving immune checkpoint inhibitors, investigators have reported antithyroid peroxidase (anti-TPO) as well as antithyroglobulin antibodies, which likely confirm an autoimmune etiology of thyroid disorder. Measurement of antithyroglobulin and anti-TPO antibodies can serve potential value in diagnosis of an immune-mediated thyroid disorder (Michot et al., 2016). Management of subclinical hypothyroidism (TSH 4 to 10 mIU/L) does not require initiation of hormone replacement. In the event a patient has a TSH greater than 10 mIU/L, an assessment of free T4 and T3 is required.

Thyroid hormone replacement should follow general endocrine guidelines. In general, levothyroxine can be instituted at a dose of 1 to 1.5 µg/kg, with a lower dose for elderly patients. Immunotherapy can be continued without interruption of therapy (Spain et al., 2016). In the event of symptomatic hyperthyroidism, pharmacologic agents such as methimazole, beta blockers, and/or steroids can be considered (O'Kane et al., 2017; Spain et al., 2016).

IMMUNE-MEDIATED HYPOPHYSITIS

Immune-mediated hypophysitis is uncommon with the PD-1/PD-L1 checkpoint inhibitors. The incidence of hypophysitis with single-agent PD-1/PD-L1 immune checkpoint inhibitors ranges from 1% to 6% (Bristol-Myers Squibb, 2017; Genentech, 2016; Merck, 2017). Immune-mediated hypophysitis is characterized by cellular infiltration and inflammation of the pituitary gland. Drug-induced hypophysitis by immunotherapy leads to impairment of secretion of anterior and/or posterior pituitary hormones. The secretion of anterior pituitary hormones appears to be impaired in a typical order: TSH and adrenocorticotropic hormone, then gonadotropins, prolactin, and growth hormone secretions (Michot et al., 2016; O'Kane et al., 2017; Spain et al., 2016). Other than routine monitoring of TSH, monitoring of other hormones is generally not indicated because of the low incidence. Levels may be drawn upon differential diagnosis of immune-mediated hypophysitis, and brain magnetic resonance image can also be considered.

Similar to hypothyroidism, it appears that immune-mediated hypophysitis is not universally reversible and may require lifelong hormone replacement (Howell et al., 2015). The clinical presentation of immune-mediated hypophysitis can be nonspecific and potentially underdiagnosed. Examples of symptoms of hypophysitis include fatigue, arthralgia, behavioral changes, loss of libido, visual changes, dizziness, and headaches (Michot et al., 2016). Management of symptomatic hypophysitis includes replacement of hormone deficiency (i.e., hydrocortisone), and systemic steroids (prednisone at 1 to 2 mg/kg/day) would be indicated. In rare cases, patients may present with adrenal crisis and require hospitalization, intravenous steroid replacement, and aggressive fluid and electrolyte replacement. Given the complexity of hormone replacement, an endocrinology consult should be considered. Treatment with immune checkpoint inhibitors can be resumed once the patient recovers if grade 2 or lower (O'Kane et al., 2017; Spain et al., 2016).

IMMUNE-MEDIATED NEPHRITIS

Immune-mediated nephritis manifests as an elevation in serum creatinine. It has a relatively uncommon occurrence of 0% to 4% across NSCLC

trials. Onset is variable and can occur as early as 6 weeks to as late as 30 weeks. Similar to other immune-related toxicities, immune-mediated nephritis is a reversible event (Eigentler et al., 2016). Management includes monitoring serum creatinine at baseline and routinely thereafter. In the event that grade 2 or 3 elevation serum creatinine occurs, treatment should be held until creatinine has improved to at least grade 1. In addition, given the immune-mediated effect, systemic steroids should be employed (Eigentler et al., 2016; Spain et al., 2016; Table 5).

IMMUNE-MEDIATED DERMATOLOGIC TOXICITY

The most common dermatologic toxicity from the PD-1/PD-L1 immune checkpoint inhibitors is a maculopapular rash with or without pruritus. Onset varies from as early as days to as late as more than 1 year after administration. Median onset has been seen at 5 to 7 weeks (O'Kane et al., 2017). Management may include emollient creams, topical steroids, antihistamines, and systemic steroids for severe cases (Spain et al., 2016; Table 5).

CONCLUSION

We have entered a new, exciting era in oncology therapeutics. Immunotherapy offers a new life line for patients diagnosed with advanced/metastatic NSCLC. The PD-1/PD-L1 checkpoint inhibitors are yielding unprecedented improvements in efficacy outcomes in the second-line setting after failure of chemotherapy. Understanding and management of adverse events are essential to optimize care. The irAEs associated with the PD-1/PD-L1 checkpoint inhibitors are generally mild and can be managed in the ambulatory care setting without the need for hospitalization. However, that is not always the case. Clinicians must monitor, identify, and promptly manage the spectrum of irAEs that can occur with these novel agents, as they have the potential for severe life-threatening events.

Disclosure

Dr. Cuellar has received consulting fees or honoraria and served on speakers bureaus for Celgene and Merck.

References

Birring, S., & Peake, M. (2005). Symptoms and the early diagnosis of lung cancer. *Thorax, 60*(4), 268–269. http://dx.doi.org/10.1136/thx.2004.032698

Borghaei, H., Paz-Ares, L., Horn, L., Spigel, D. R., Steins, M., Ready, N. E.,...Brahmer, J. R. (2015). Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine, 373*, 1627–1639. https://doi.org/10.1056/NEJMoa1507643

Brahmer, J., Reckamp, K. L., Baas, P., Crinò, Eberhardt, W. E. E., Poddubskaya, E.,...Spigel, D. R. (2015). Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *New England Journal of Medicine, 373*, 123–135. https://doi.org/10.1056/NEJMoa1504627

Bristol-Myers Squibb. (2017). Opdivo (nivolumab) package insert. Retrieved from https://packageinserts.bms.com/pi/pi_opdivo.pdf

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*(4), 559–574. http://dx.doi.org/10.1093/annonc/mdv623

Disis, M. (2014). Mechanism of action of immunotherapy. *Seminars in Oncology, 41*(5), s3–S13. http://dx.doi.org/10.1053/j.seminoncol.2014.09.004

Eigentler, T. K., Hassel, J. C., Berking, C., Aberle, J., Bachmann, O., Grunwald, V.,...Gutzmer, R. (2016). Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treatment Reviews, 45*, 7–18. http://dx.doi.org/10.1016/j.ctrv.2016.02.003

Fehrenbacher, L., Spira, A., Ballinger, M., Kowanetz, M., Vansteenkiste, J., Mazieres, J.,...Rittmeyer, A. (2016). Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. *Lancet, 387*(10030), 1837–1846. http://dx.doi.org/10.1016/S0140-6736(16)00587-0

Fukuda, T., Hackman, R. C., Guthrie, K. A., Sandmaier, B. M., Boeckh, M., Maris, M. B.,...Madtes, D. K. (2003). Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood, 102*(8), 2777–2785. http://dx.doi.org/10.1182/blood-2003-05-1597

Genentech. (2016). Tecentriq (atezolizumab) package insert. Retrieved from https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

Howell, M., Lee, R., Bowyer, S., Fusi, A., & Lorigan, P. (2015). Optimal management of immune-related toxicities associated with checkpoint inhibitors in lung cancer. *Lung Cancer, 88*(2), 117–123. http://dx.doi.org/10.1016/j.lungcan.2015.02.007

Janssen Biotech. (2015). Remicade (infliximab) package insert. Retrieved from https://www.remicade.com/shared/product/remicade/prescribing-information.pdf

Khandelwal, D., & Tandon, N. (2012). Overt and subclinical hypothyroidism: Who to treat and how. *Drugs, 72*(1), 17–33. http://dx.doi.org/10.2165/11598070-000000000-00000

Langer, C. J., Gadgeel, S. M., Borghaei, H., Papadimitrakopoulou, V. A., Patnaik, A., Powell, S. F.,...Gandhi, L. (2016). Carboplatin and pemetrexed with or without pembroli-

zumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncology, 17*(11), 1497–1508. https://doi.org/10.1016/S1470-2045(16)30498-3

Merck. (2017). Keytruda (pembrolizumab) package insert. Retrieved from https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Metcalf, J. P., Rennard, S. I., Reed, E. C., Haire, W. D., Sisson, J. H., Walter, T., & Robbins, R. A. (1994). Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. University of Nebraska Medical Center Bone Marrow Transplant Group. *American Journal of Medicine, 96*(4), 327–334.

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. http://dx.doi.org/10.1016/j.ejca.2015.11.016

Naidoo, J., Cunningham, J., Woo, K. M., Hellmann, M. D., Postow, M. A., Drilon, A. E.,...Wolchok, J. D. (2015). Pneumonitis with anti-PD-1/PD-L1 therapy. *European Journal of Cancer, 21*, S103. http://dx.doi.org/10.1016/S0959-8049(16)30305-7

National Comprehensive Cancer Network (2017). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 4.2017. Retrieved from www.nccn.org

O'Kane, G. M., Labbe, C., Doherty, M. K., Young, K., Albaba, H., & Leighl, N. B. (2017). Monitoring and management of immune-related adverse events associated with programmed cell death protein-1 axis inhibitors in lung cancer. *Oncologist, 22*(1), 70–80. http://dx.doi.org/10.1634/theoncologist.2016-0164

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer, 12*(4), 252–264. http://dx.doi.org/10.1038/nrc3239

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A.,...Brahmer, J. (2016). Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *New England Journal of Medicine, 375*, 1823–1833. https://doi.org/10.1056/NEJMoa1606774

Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., von Pawel, J.,...Gandara, D. R. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. *Lancet, 389*(10066), P255–P365. http://dx.doi.org/10.1016/S0140-6736(16)32517-X

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

Weber, J., Thompson, J. A., Hamid, O., Minor, D., Amin, A., Ron, I.,...O'Day, S. J. (2009). A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clinical Cancer Research, 15*(17), 5591–5598. http://dx.doi.org/10.1158/1078-0432.CCR-09-1024

Weber, J. S., Kahler, K. C., & Hauschild, A. (2012). Management of immune-related adverse events and kinetics of response with ipilimumab. *Journal of Clinical Oncology, 30*(21), 2691–2697. http://dx.doi.org/10.1200/JCO.2012.41.6750

Weber, J. S., Yang, J. C., Atkins, M. B., & Disis, M. L. (2015). Toxicities of immunotherapy for the practitioner. *Journal of Clinical Oncology, 33*(18), 2092–2099. http://dx.doi.org/10.1200/JCO.2014.60.0379

Zachou, K., Gatselis, N., Papadamou, G., Rigopoulou, E. I., & Dalekos, G. N. (2011). Mycophenolate for the treatment of autoimmune hepatitis: Prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naive patients. *Journal of Hepatology, 55*(3), 636–646. http://dx.doi.org/10.1016/j.jhep.2010.12.032