The Advanced Practice Provider Perspective: Treating Patients With Immuno-Oncology Combination Therapy Across Tumor Types

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Abstract

A number of immune checkpoint inhibitors (ICIs) have been approved by the U.S. Food and Drug Administration (FDA) as immuno-oncology (IO) monotherapy for multiple solid and hematologic tumor types across various lines of therapy. Furthermore, evidence shows some patients may derive additional benefit from IO combination therapy. Three IO combination regimens, nivolumab plus ipilimumab, and pembrolizumab or atezolizumab plus chemotherapy, are approved by the FDA as of April 2019. Because peripheral immune surveillance via T-cell activity is increased to attack malignant cells, the antitumor effects of ICIs may be accompanied by immune-mediated adverse reactions (IMARs). Although potentially more efficacious than monotherapy, IO combination therapies are associated with increased incidences of IMARs vs. IO monotherapy. Advanced practice providers (APPs) are uniquely placed within the multidisciplinary team to counsel patients with cancer on their IO treatment and educate them about identifying manifestations of IMARs. Advanced practice providers should be aware of the presentation and time to onset of IMARs, appropriate management to reduce risk of organ dysfunction, and guidelines for treating these patients. This article reviews IO/IO and IO/chemotherapy combination regimens with respect to clinical efficacy and safety, and discusses the role of the APP in managing IMARs associated with IO combination therapy.

Immuno-oncology (IO) is an evolving treatment modality that includes immunotherapies able to directly target and harness the patient's immune system to kill tumor cells (Antonia, Larkin, & Ascierto, 2014). Several IO agents, many of which

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were approved through accelerated regulatory processes (Table 1; U.S. Department of Health and Human Services; U.S. Food and Drug Administration), are available in the United States (US) for the treatment of various types of solid and hematologic malignancies. These include anti–programmed cell death protein 1 (PD-1) antibodies nivolumab (Opdivo), pembrolizumab (Keytruda), and cemiplimab-rwlc (Libtayo); anti–programmed cell death ligand 1 (PD-L1) antibodies atezolizumab (Tecentriq), durvalumab (Imfinzi), and avelumab (Bavencio); and anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody ipilimumab (Yervoy; AstraZeneca UK Limited, 2018; Bristol-Myers Squibb, 2018, 2019; EMD Serono Inc, 2018; Genentech, 2019; Merck & Co Inc, 2019; Regeneron Pharmaceuticals Inc and sanofi-aventis US LLC, 2019).

Immune checkpoint inhibitors (ICIs), a type of IO therapy, target proteins such as CTLA-4, PD-1, and PD-L1 (Kreamer, 2014; Langer, 2015), among other checkpoints. By targeting these proteins, which regulate T-cell immune function, and blocking the interaction with their ligands, ICIs release pathway-mediated inhibition of the antitumor immune response (Kreamer, 2014; Langer, 2015). The mechanisms of action of CTLA-4, PD-L1, and PD-1 ICIs are shown in Figure 1.

Immuno-oncology monotherapy or in combination with another agent have various indications across advanced or metastatic tumor types, as well as in the adjuvant setting (AstraZeneca UK Limited, 2018; Bristol-Myers Squibb, 2018, 2019; EMD Serono Inc, 2018; Genentech, 2019; Merck & Co Inc, 2019; Regeneron Pharmaceuticals Inc and sanofi-aventis US LLC, 2019). Clinical trial data demonstrated that patients with certain types of cancers, such as melanoma, renal cell carcinoma (RCC), microsatellite instability–high or mismatch repair–deficient (MSI-H/dMMR) colorectal cancer (CRC), non–small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), may derive additional benefit from IO/IO or IO/chemotherapy combination therapy (Antonia et al., 2016; Gandhi et al., 2018; Langer et al., 2016; Larkin et al., 2015; Motzer et al., 2018; Overman et al., 2017, 2018; Postow et al., 2015; Wolchok et al., 2017).

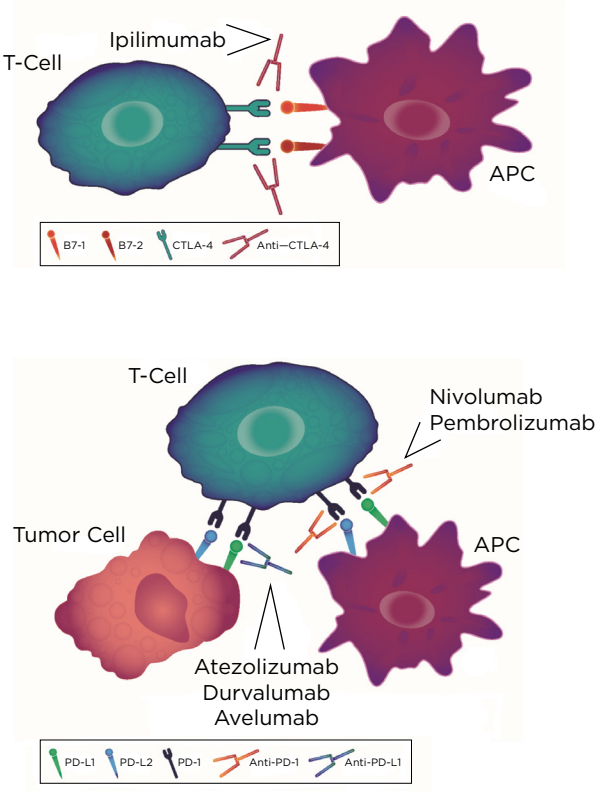

Figure 1. Mechanism of action of CTLA-4, PD-L1, and PD-1 immune checkpoint inhibitors.
APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; PD-1 = programmed cell death protein 1; PD-L1/2 = programmed cell death ligand 1/2. (A) By blocking CTLA-4 from binding to peripheral membrane protein B7, anti–CTLA-4 antibodies (e.g., ipilimumab) allow costimulatory signaling and generation of antitumor T-cell responses. (B) Anti–PD-1 (e.g., nivolumab, pembrolizumab) and anti–PD-L1 antibodies (e.g., atezolizumab, durvalumab, avelumab) inhibit PD-1 from binding to its ligands PD-L1 and PD-L2, thereby restoring antitumor immune response. Figure adapted from Langer (2015).

In animal models, combined anti–PD-1- and anti–CTLA-4-mediated inhibition was shown to enhance T-cell function greater than the effects of either antibody alone (Bristol-Myers Squibb, 2019). In vitro and in vivo evidence from humans and murine models suggest that chemotherapy induces PD-L1 expression on tumor cells and causes immunogenic tumor cell death (Aoto et al., 2018; Grabosch et al., 2015; Peng et al., 2015; Zhang et al., 2016). When combined with immunotherapy, chemotherapy may have an additive effect on the

Table 1. Comparison of FDA Expedited Programs for Serious Conditions

Program	Nature of program	Description	Features	Time for FDA to take action on marketing application	Immuno-oncology examples
Fast Track	Designation	Facilitates the development and expedites the review of drugs to treat serious conditions and fill an unmet medical need	• Increased communication with the FDA • Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met • Rolling Review[a]	Not specified	• Avelumab approved for MCC • Nivolumab approved for NSCLC, RCC, and melanoma • Durvalumab approved for PD-L1+ SCCHN
Priority Review	Designation	Directs overall attention and resources to evaluating drug applications that, if approved, would mean significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions vs. standard applications	• FDA intends to take action (approve/reject) on an application within 6 months (compared with 10 months under standard review)	6 months	• Nivolumab approved for melanoma (adjuvant and metastatic), NSCLC, RCC, UC, SCCHN, SCLC, and cHL • Durvalumab approved for NSCLC • Nivolumab plus ipilimumab approved for RCC and CRC

Note. FDA = U.S. Food and Drug Administration; MCC = Merkel cell carcinoma; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma; PD-L1 = programmed cell death ligand 1; SCCHN = squamous cell carcinoma of the head and neck; UC = urothelial carcinoma; SCLC = small cell lung cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; NSQ = nonsquamous; PMBCL = primary mediastinal large B-cell lymphoma; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient; HCC = hepatocellular carcinoma; GC = gastric cancer; G(EJ)C = gastric or gastroesophageal junction adenocarcinoma; BLA = Biologic License Application; NDA = New Drug Application. Information from AstraZeneca UK Limited (2018); Bristol-Myers Squibb (2018, 2019); Chaudhari (2017); EMD Serono Inc (2018); Genentech (2019); Merck & Co Inc (2019); U.S. Department of Health and Human Services (2014); U.S. Food and Drug Administration (2018a, 2018b).

[a]Rolling Review: a drug company can submit completed sections of its BLA or NDA for review by the FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA.

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Table 1. Comparison of FDA Expedited Programs for Serious Conditions (cont.)

Program	Nature of program	Description	Features	Time for FDA to take action on marketing application	Immuno-oncology examples
Breakthrough Therapy	Designation	Expedites development and review of drugs intended to treat a serious condition and have preliminary clinical evidence indicating that they may demonstrate substantial improvement over available therapy on clinically significant endpoints	• All Fast Track designation features • Intensive guidance on an efficient drug development program	Not specified	• Nivolumab approved for SCCHN, cHL, melanoma, NSQ NSCLC, RCC, and UC • Pembrolizumab approved for MCC, PMBCL, MSI-H/dMMR solid tumors, UC, cHL, melanoma, and PD-L1+ NSCLC • Nivolumab plus ipilimumab approved for RCC and MSI-H/dMMR CRC • Durvalumab approved for UC and NSCLC • Avelumab approved for MCC • Atezolizumab approved for NSCLC and UC
Accelerated Approval	Approval pathway	Allows drugs for serious conditions that fill an unmet medical need to be approved based on whether a drug has an effect on a surrogate or intermediate clinical endpoint	• Using a surrogate or intermediate clinical endpoint enables the FDA to approve these drugs faster • Additional postmarketing clinical trials may be required to verify and describe the drug's clinical benefit	Not specified	• Nivolumab approved for melanoma, cHL, UC, MSI-H/dMMR CRC, HCC, and SCLC • Nivolumab plus ipilimumab approved for melanoma and MSI-H/dMMR CRC • Pembrolizumab approved for MCC, HCC, PD-L1+ G(EJ)C, MSI-H/dMMR solid tumors, NSQ NSCLC, PD-L1+ NSCLC, melanoma, SCCHN, cHL, PMBCL, UC, and cervical cancer • Pembrolizumab plus chemotherapy approved for NSQ NSCLC • Atezolizumab approved for UC • Durvalumab approved for NSCLC and UC • Avelumab approved for UC and MCC

Note. FDA = U.S. Food and Drug Administration; MCC = Merkel cell carcinoma; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma; PD-L1 = programmed cell death ligand 1; SCCHN = squamous cell carcinoma of the head and neck; UC = urothelial carcinoma; SCLC = small cell lung cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; NSQ = nonsquamous; PMBCL = primary mediastinal large B-cell lymphoma; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient; HCC = hepatocellular carcinoma; GC = gastric cancer; G(EJ)C = gastric or gastroesophageal junction adenocarcinoma; BLA = Biologic License Application; NDA = New Drug Application. Information from AstraZeneca UK Limited (2018); Bristol-Myers Squibb (2018, 2019); Chaudhari (2017); EMD Serono Inc (2018); Genentech (2019); Merck & Co Inc (2019); U.S. Department of Health and Human Services (2014); U.S. Food and Drug Administration (2018a, 2018b).

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antitumor activity of anti–PD-1 and anti–PD-L1 monotherapy (Apetoh, Ladoire, Coukos, & Ghiringhelli, 2015). In clinical trials, the combination of nivolumab plus ipilimumab resulted in improved antitumor responses in metastatic melanoma, advanced RCC, and MSI-H/dMMR metastatic CRC (Bristol-Myers Squibb, 2019; Larkin et al., 2015; Motzer et al., 2018; Overman et al., 2017, 2018; Wolchok et al., 2017); improved antitumor responses also were seen in squamous and nonsquamous NSCLC with pembrolizumab plus chemotherapy (Gandhi et al., 2018; Langer et al., 2016; Paz-Ares et al., 2018). As a result of these studies, the U.S. Food and Drug Administration (FDA) approved nivolumab in combination with ipilimumab for the treatment of melanoma, RCC, and MSI-H/dMMR CRC; and pembrolizumab in combination with pemetrexed and platinum chemotherapy for nonsquamous NSCLC and in combination with carboplatin and either paclitaxel or nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for squamous NSCLC (Bristol-Myers Squibb, 2018, 2019; Merck & Co Inc, 2019). Notably, dosing schedule and infusion duration with nivolumab in combination with ipilimumab vary by indication, underscoring the importance of consulting updated prescribing information (Bristol-Myers Squibb, 2019).

As depicted in Figure 1, ICIs increase T-cell and other effector cell activity to attack malignant cells (Kreamer, 2014; Langer, 2015). However, healthy, nonmalignant cells may also be subject to attack (Postow, Sidlow, & Hellmann, 2018). Therefore, antitumor effects may be accompanied by immune-mediated adverse reactions (IMARs) that can lead to organ dysfunction or death if left untreated (Gandhi et al., 2018; Postow et al., 2018). IO/IO and IO/chemotherapy combination therapies, in particular, are associated with increased incidences of IMARs compared with IO monotherapy (Gandhi et al., 2018; Larkin et al., 2015).

Although a number of resources provide information specifically related to the optimal management of patients receiving IO combination therapy, few focus on the role of advanced practice providers (APPs), including nurse practitioners, physician assistants, and pharmacists (Brahmer et al., 2018; Haanen et al., 2017; Puzanov et al., 2017). Here, we review the clinical efficacy and safety/tolerability of approved IO/IO and IO/chemotherapy combinations and discuss the role of the APP in educating patients about their cancer treatments and managing IMARs associated with IO combination therapy.

CLINICAL EFFICACY OF APPROVED IO COMBINATION THERAPY

In the randomized, double-blind, phase III CheckMate 067 trial of patients with unresectable stage III or IV melanoma, 4-year median progression-free survival (PFS) was significantly longer with both nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg (37%) and nivolumab at 3 mg/kg monotherapy (31%) compared with ipilimumab at 3 mg/kg alone (9%; Hodi et al., 2018). Nivolumab plus ipilimumab and nivolumab monotherapy also both significantly improved overall survival (OS) compared with ipilimumab alone in patients both with and without *BRAF* mutations (53%, 46%, and 30%, respectively; Hodi et al., 2018). In addition, a significantly greater proportion of patients who received combination therapy achieved an objective response (58%) compared with ipilimumab monotherapy (19%; Hodi et al., 2018). Furthermore, a significantly greater proportion of patients treated with nivolumab monotherapy achieved an objective response (45%) compared with ipilimumab alone (19%; Hodi et al., 2018). The median duration of response was 50.1 months with nivolumab plus ipilimumab, not reached with nivolumab monotherapy, and 14.4 months in the ipilimumab group (Hodi et al., 2018).

In the randomized, double-blind, phase II CheckMate 069 study, significantly more patients with *BRAF* wild-type metastatic melanoma who received nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks achieved an objective response (61%) compared to ipilimumab at 3 mg/kg every 3 weeks monotherapy (11%; Postow et al., 2015). Complete responses were reported in 22% of the combination group and no patients in the ipilimumab monotherapy group (Postow et al., 2015). Median PFS was also significantly prolonged in the combination group (Postow et al., 2015). Similar results for response rates were observed in 33 patients with *BRAF* mutation–positive tumors (Postow et al., 2015).

The randomized, open-label, phase III CheckMate 214 trial evaluated patients with International Metastatic RCC Database Consortium (IMDC) intermediate and poor risk who had advanced clear-cell RCC (Motzer et al., 2018). Patients receiving nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks had a significantly higher objective response rate (ORR; 42% vs. 27%), higher complete response rate (9% vs. 1%), longer median PFS (11.6 months vs. 8.4 months), and longer median OS (not reached vs. 26.0 months) vs. sunitinib at 50 mg daily (Motzer et al., 2018). The median duration of response was not reached with combination therapy and was 18.2 months with sunitinib (Motzer et al., 2018). In the intention-to-treat (ITT) population, including IMDC favorable-risk patients, nivolumab plus ipilimumab resulted in a higher ORR and longer OS vs. sunitinib, and survival benefits were observed irrespective of PD-L1 expression (Motzer et al., 2018).

In the open-label, multicohort, phase II CheckMate 142 trial, patients with MSI-H/dMMR metastatic CRC who were treated with nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks showed numerically higher response rates (55%) compared with a similar population of patients receiving nivolumab at 3 mg/kg every 2 weeks alone (31%; Overman et al., 2017, 2018). However, the two treatment groups were not directly compared to evaluate statistical significance. The median duration of response was not reached in either group (Overman et al., 2017, 2018).

In the randomized, double-blind, phase III KEYNOTE-189 study, patients with metastatic nonsquamous NSCLC received pemetrexed at 500 mg/m^2 and carboplatin area under the curve (AUC) 5 mg/mL/min or cisplatin at 75 mg/m^2 with or without pembrolizumab at 200 mg every 3 weeks (Gandhi et al., 2018). At a median follow-up of 10.5 months, median PFS and OS were significantly longer with pembrolizumab plus chemotherapy vs. chemotherapy alone. Survival and PFS benefits were observed with pembrolizumab combination therapy regardless of PD-L1 expression (Gandhi et al., 2018). A significantly higher proportion of patients who received combination therapy achieved an objective response (48%) compared with chemotherapy alone (19%; Gandhi et al., 2018). The median durations of response were 11.2 and 7.8 months, respectively (Gandhi et al., 2018).

In KEYNOTE-021, a randomized, open-label, phase II study of patients with stage IIIB or IV nonsquamous NSCLC, significantly more patients who received pembrolizumab at 200 mg plus carboplatin AUC 5 mg/mL/min and pemetrexed at 500 mg/m^2 every 3 weeks achieved a greater objective response (55%) compared with chemotherapy alone (29%; Langer et al., 2016). The median duration of response was not reached in either group (Langer et al., 2016). Additionally, PFS was significantly longer in the combination group compared with chemotherapy alone (62% vs. 48%); however, no significant difference in OS was observed between groups (Langer et al., 2016).

In the randomized, double-blind, phase III KEYNOTE-407 study, patients with previously untreated metastatic squamous NSCLC received carboplatin AUC 6 mg/mL/min plus either paclitaxel at 200 mg/m^2 or nab-paclitaxel at 100 mg/m^2 with or without pembrolizumab at 200 mg every 3 weeks (Paz-Ares et al., 2018). After a median follow-up of 7.8 months, median PFS (6.4 vs. 4.8 months) and OS (15.9 vs. 11.3 months) were significantly longer with pembrolizumab combination therapy than chemotherapy alone (Paz-Ares et al., 2018). PD-L1 expression had no impact on the survival benefit with combination therapy. Furthermore, a greater proportion of patients who received pembrolizumab plus chemotherapy achieved a greater objective response (58%) compared with chemotherapy alone (38%). The median duration of response was 7.7 months in the pembrolizumab-combination group and 4.8 months in the chemotherapy group (Paz-Ares et al., 2018).

Table 2 summarizes the clinical efficacy of FDA–approved IO combination therapies.

SAFETY PROFILE OF APPROVED IO COMBINATION THERAPY

In CheckMate 067, a similar proportion of patients with melanoma in the nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks, nivolumab at 3 mg/kg every 2 weeks, and ipilimumab at 3 mg/kg every 3 weeks groups experienced any-grade IMARs, defined as select adverse events (AEs; i.e., those with a potential immunologic cause; Wol-

Table 2. Clinical Efficacy of FDA-Approved Immuno-Oncology Combination Therapies

Study	Design	Tumor type	Interventions (N)	Primary endpoints	Key secondary endpoints
CheckMate 067 (Hodi et al., 2018)	Randomized, double-blind, phase III study	Previously untreated unresectable stage III or IV melanoma	NIVO 1 mg/kg (N = 314) + IPI 3 mg/kg vs. NIVO 3 mg/kg (N = 316) vs. IPI 3 mg/kg (N = 315)	PFS NIVO + IPI • Median, 11.5 mo (95% CI = 8.7–19.3) • HR vs. IPI, 0.42 (95% CI = 0.35–0.51; $p < .0001$) NIVO • Median, 6.9 mo (95% CI = 5.1–10.2) • HR vs. IPI, 0.53 (95% CI = 0.44–0.64; $p < .0001$) IPI • Median, 2.9 mo (95% CI = 2.8–3.2) OS NIVO + IPI • Median, NR (95% CI = 38.2–NR) • HR vs. IPI, 0.54 (95% CI = 0.44–0.67; $p < .0001$) NIVO • Median, 36.9 mo (95% CI = 28.3–NR) • HR vs. IPI, 0.65 (95% CI = 0.53–0.79; $p < .0001$) IPI • Median, 19.9 mo (95% CI = 16.9–24.6)	ORR NIVO + IPI • 58% (95% CI = 52.6–63.8) • OR vs. IPI, 6.35 (95% CI = 4.38–9.22; $p < .0001$) NIVO • 45% (95% CI = 39.1–50.3) • OR vs. IPI, 3.54 (95% CI = 2.46–5.10; $p < .0001$) IPI • 19.0% (95% CI = 14.9–23.8)
CheckMate 069 (Postow et al., 2015)	Randomized, double-blind, phase II study	Previously untreated *BRAF* wild-type unresectable stage III or IV melanoma	NIVO 1 mg/kg + IPI 3 mg/kg (N = 72) vs. IPI 3 mg/kg (N = 37)	ORR NIVO + IPI • 61% (95% CI = 49–72) • OR vs. IPI, 12.96 (95% CI = 3.91–54.49; $p < .001$) IPI • 11% (95% CI = 3–25)	PFS NIVO + IPI • Median, NR • HR vs. IPI, 0.40 (95% CI = 0.23–0.68; $p < .001$) IPI • Median, 4.4 mo (95% CI = 2.8–5.7)

Note. FDA = U.S. Food and Drug Administration; NIVO = nivolumab; IPI = ipilimumab; PFS = progression-free survival; CI = confidence interval; HR = hazard ratio; ORR = objective response rate; OR = odds ratio; RCC = renal cell carcinoma; OS = overall survival; NR = not reached; NE = not evaluable; SUN = sunitinib; ITT = intention-to-treat; CRR = complete response rate; MSI-H = microsatellite instability-high; dMMR = mismatch repair; CRC = colorectal cancer; DCR = disease control rate; NSQ = nonsquamous; NSCLC = non–small cell lung cancer; carbo = carboplatin; cis = cisplatin; peme = pemetrexed; pembro = pembrolizumab; chemo = chemotherapy; DoR = duration of response; SQ = squamous; nab-pac = nanoparticle albumin-bound paclitaxel; pac = paclitaxel.

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Table 2. Clinical Efficacy of FDA-Approved Immuno-Oncology Combination Therapies (cont.)

Study	Design	Tumor type	Interventions (N)	Primary endpoints	Key secondary endpoints
CheckMate 214 (Motzer et al., 2018)	Randomized, open-label, phase III study	Previously untreated intermediate- and poor-risk advanced clear-cell RCC	NIVO 3 mg/kg + IPI 1 mg/kg (N = 425) vs. SUN (N = 422)	OS (intermediate- and poor-risk) NIVO + IPI • Median, NR (95% CI = 28.2–NE) • HR vs. SUN, 0.63 (99.8% CI = 0.44–0.89; $p < .001$) SUN • Median, 26.0 mo (95% CI = 22.1–NE) ORR (intermediate- and poor-risk) NIVO + IPI • 42% (95% CI = 37–47) • vs. SUN, $p < .001$ SUN • 27% (95% CI = 22–31) CRR (intermediate- and poor-risk) NIVO + IPI • 9% • vs. SUN, $p < .001$ SUN • 1% PFS (intermediate- and poor-risk) NIVO + IPI • Median, 11.6 mo (95% CI = 8.7–15.5) • HR vs. SUN, 0.82 (99.1% CI = 0.64–1.05; $p = .03$) SUN • Median, 8.4 mo (95% CI = 7.0–10.8)	OS (ITT) NIVO + IPI • Median, NR • HR vs. SUN, 0.68 (99.8% CI = 0.49–0.95; $p < .001$) SUN • Median, 32.9 mo ORR (ITT) NIVO + IPI • 39% (95% CI = 35–43) • vs. SUN, $p = .02$ SUN • 32% (95% CI = 28–36) CRR (ITT) • CRR not reported for the ITT population PFS (ITT) NIVO + IPI • Median, 12.4 mo (95% CI = 9.9–16.5) • HR vs. SUN, 0.98 (99.1% CI = 0.79–1.23; $p = .85$) SUN • Median, 12.3 mo (95% CI = 9.8–15.2)
CheckMate 142 (Overman et al., 2018)	Open-label, multicohort, phase II study	Previously treated MSI-H/dMMR metastatic CRC	NIVO 3 mg/kg + IPI 1 mg/kg (N = 119)	ORR NIVO + IPI • 55% (95% CI = 45.2–63.8)	DCR (≥ 12 weeks) NIVO + IPI • 80% (95% CI = 71.5–86.6)

Note. FDA = U.S. Food and Drug Administration; NIVO = nivolumab; IPI = ipilimumab; PFS = progression-free survival; CI = confidence interval; HR = hazard ratio; ORR = objective response rate; OR = odds ratio; RCC = renal cell carcinoma; OS = overall survival; NR = not reached; NE = not evaluable; SUN = sunitinib; ITT = intention-to-treat; CRR = complete response rate; MSI-H = microsatellite instability-high; dMMR = mismatch repair; CRC = colorectal cancer; DCR = disease control rate; NSQ = nonsquamous; NSCLC = non–small cell lung cancer; carbo = carboplatin; cis = cisplatin; peme = pemetrexed; pembro = pembrolizumab; chemo = chemotherapy; DoR = duration of response; SQ = squamous; nab-pac = nanoparticle albumin-bound paclitaxel; pac = paclitaxel.

Table 2. Clinical Efficacy of FDA-Approved Immuno-Oncology Combination Therapies (cont.)

Study	Design	Tumor type	Interventions (N)	Primary endpoints	Key secondary endpoints
KEYNOTE-189 (Gandhi et al., 2018)	Randomized, double-blind, phase III study	Previously untreated metastatic NSQ NSCLC	Pembro 200 mg + carbo/cis + peme (N = 410) vs. carbo + peme (N = 206)	OS Pembro + chemo • Median, NR • HR vs. chemo, 0.49 (95% CI = 0.38–0.64; $p < .001$) Chemo • Median, 11.3 mo (95% CI = 8.7–15.1) PFS Pembro + chemo • Median, 8.8 mo (95% CI = 7.6–9.2) • HR vs. chemo, 0.52 (95% CI = 0.43–0.64; $p < .001$) Chemo • Median, 4.9 mo (95% CI = 4.7–5.5)	ORR Pembro + chemo • 47.6% (95% CI = 42.6–52.5) • vs. chemo, $p < .001$ Chemo • 18.9% (95% CI = 13.8–25.0) DoR Pembro + chemo • 11.2 months (range, 1.1+ to 18.0+) Chemo • 7.8 months (range, 2.1+ to 16.4+
KEYNOTE-021 (Langer et al., 2016)	Randomized, open-label, phase II study	Systemic therapy-naive stage IIIB or IV NSQ NSCLC	Pembro 200 mg + carbo + peme (N = 60) vs. carbo + peme (N = 63)	ORR Pembro + chemo • 55% (95% CI = 42–68) • vs. chemo, $p = .0016$ Chemo • 29% (95% CI = 18–41)	PFS Pembro + chemo • Median, 13.0 mo (95% CI = 8.3–NR) • HR vs. chemo, 0.53 (95% CI = 0.31–0.91; $p = .010$) Chemo • Median, 8.9 mo (95% CI = 4.4–10.3)
KEYNOTE-407 (Paz-Ares et al., 2018)	Randomized, double-blind, phase III study	Previously untreated metastatic SQ NSCLC	Pembro 200 mg + carbo + pac/nab-pac (N = 278) vs. pac/nab-pac (N = 281)	OS Pembro + chemo • Median, 15.9 mo (95% CI = 13.2–NR) • HR vs. chemo, 0.64 (95% CI = 0.49–0.85; $p < .001$) Chemo • Median, 11.3 mo (95% CI = 9.5–14.8) PFS Pembro + chemo • Median, 6.4 mo (95% CI = 6.2–8.3) • HR vs. chemo, 0.56 (95% CI = 0.45–0.70; $p < .001$) Chemo • Median, 4.8 mo (95% CI = 4.3–5.7)	ORR Pembro + chemo • 57.9% (95% CI = 51.9–63.8) Chemo • 38.4% (95% CI = 32.7–44.4) DoR Pembro + chemo • 7.7 months (range, 1.1+ to 14.7+) Chemo • 4.8 months (range, 1.3+ to 15.8+)

Note. FDA = U.S. Food and Drug Administration; NIVO = nivolumab; IPI = ipilimumab; PFS = progression-free survival; CI = confidence interval; HR = hazard ratio; ORR = objective response rate; OR = odds ratio; RCC = renal cell carcinoma; OS = overall survival; NR = not reached; NE = not evaluable; SUN = sunitinib; ITT = intention-to-treat; CRR = complete response rate; MSI-H = microsatellite instability-high; dMMR = mismatch repair; CRC = colorectal cancer; DCR = disease control rate; NSQ = nonsquamous; NSCLC = non–small cell lung cancer; carbo = carboplatin; cis = cisplatin; peme = pemetrexed; pembro = pembrolizumab; chemo = chemotherapy; DoR = duration of response; SQ = squamous; nab-pac = nanoparticle albumin-bound paclitaxel; pac = paclitaxel.

chok et al., 2017). Common any-grade IMARs in the combination group included diarrhea (45%), pruritus (36%), rash (30%), increased alanine aminotransferase (ALT; 19%), and hypothyroidism (17%). Grade 3 to 4 skin and subcutaneous, gastrointestinal (GI), endocrine, hepatic, pulmonary, and renal IMARs occurred more frequently with nivolumab plus ipilimumab than either monotherapy group (Wolchok et al., 2017).

In the CheckMate 069 trial of patients with previously untreated advanced melanoma, researchers reported IMARs (defined as select AEs of potentially immune-mediated cause) more frequently with nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks than ipilimumab at 3 mg/kg every 3 weeks alone (Postow et al., 2015). Common any-grade IMARs in patients receiving combination therapy included diarrhea (45%), rash (42%), pruritus (35%), thyroid disorder (23%), colitis (23%), increased ALT (22%), and increased aspartate aminotransferase (AST; 21%), and occurred more frequently than with nivolumab alone. Grade 3 to 5 GI (21%), hepatic (15%), skin (10%), and endocrine (5%) IMARs occurred more frequently with nivolumab plus ipilimumab than nivolumab alone. Immunosuppressants were used in a higher percentage of patients receiving combination therapy (89% vs. 59%). The most commonly used systemic immunosuppressive agents across treatment groups were corticosteroids (82% vs. 50%, respectively), with topical agents used for dermatologic IMARs. Hormone replacement therapy was used to manage endocrine IMARs (Postow et al., 2015).

In a pooled analysis of patients with advanced melanoma treated with nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks in CheckMate 067 and 069 and cohort 8 of the phase Ib open-label, dose-escalation CheckMate 004 study, IMARs, defined as AEs with immune-related etiology, were reported by 88% of patients (Sznol et al., 2017). Grade 3 to 4 IMARs occurred in 42% of patients, including hepatic (17%), GI (16%), and skin (7%) IMARs, with resolution rates of at least 79%, with the exception of immune-mediated endocrinopathies, which frequently required lifelong hormone replacement therapy (Sznol et al., 2017).

In CheckMate 214, in patients with previously untreated advanced RCC with a clear-cell component, grade 3 to 4 treatment-related AEs occurred less frequently with nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks (46%) than sunitinib at 50 mg daily (63%; Motzer et al., 2018). Any-grade IMARs, defined as treatment-related select (immune-mediated) AEs, were reported in 80% of patients who received nivolumab plus ipilimumab. Of these, 35% received high-dose corticosteroids (≥ 40 mg of prednisone per day or equivalent; Motzer et al., 2018).

Among patients with MSI-H/dMMR metastatic CRC who received nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks in CheckMate 142, any-grade IMARs, defined as select treatment-related AEs (events with potential immunologic etiology) included skin (29%), endocrine (25%), GI (23%), hepatic (19%) , pulmonary (5%), and renal (5%) IMARs (Overman et al., 2018). Twenty-two percent (GI) to 56% (skin) of patients who experienced IMARs received immunosuppressive medication. Using protocol-specified management algorithms, IMARs resolved in 71% (skin) to 96% (GI) of patients, except for endocrine IMARs, which resolved in only 40% (Overman et al., 2018).

In KEYNOTE-189, 23% of patients with metastatic nonsquamous NSCLC who received pembrolizumab at 200 mg plus pemetrexed at 500 mg/m^2 and carboplatin AUC 5 mg/mL/min or cisplatin at 75 mg/m^2 every 3 weeks experienced IMARs, defined as immune-mediated AEs, vs. 12% of those who received chemotherapy alone (Gandhi et al., 2018). Common any-grade IMARs with combination therapy included hypothyroidism (7%), pneumonitis (4%), hyperthyroidism (4%), infusion reaction (3%), colitis (2%), and severe skin reaction (2%; Gandhi et al., 2018). Grade 3 to 5 IMARs occurred more often with pembrolizumab plus chemotherapy (9%) than chemotherapy alone (5%; Gandhi et al., 2018).

In the KEYNOTE-021 study of patients with advanced nonsquamous NSCLC, IMARs were defined as AEs of interest based on a presumed immunologic mechanism of action (Langer et al., 2016). The incidence of potential IMARs in the pembrolizumab at 200 mg plus pemetrexed at 500 mg/m^2 and carboplatin AUC 5 mg/mL/min every 3 weeks group of the as-treated population (22%) was greater than for chemotherapy alone

(11%; Langer et al., 2016). Similar to KEYNOTE-189, common all-grade IMARs in patients who received pembrolizumab plus chemotherapy included hypothyroidism (15%), hyperthyroidism (8%), pneumonitis (5%), infusion reactions (3%), and severe skin reactions (2%; Langer et al., 2016). As with pembrolizumab plus chemotherapy in patients with NSCLC in KEYNOTE-189, most IMARs were grade 1 or 2 (85%) and manageable without treatment discontinuation (Langer et al., 2016).

In KEYNOTE-407, any-grade IMARs, defined as immune-mediated AEs, occurred in 29% of patients with metastatic squamous NSCLC who received pembrolizumab at 200 mg plus carboplatin AUC 6 mg/mL/min every 3 weeks and paclitaxel at 200 mg/m^2 or nab-paclitaxel at 100 mg/m^2 compared with 9% receiving chemotherapy alone (Paz-Ares et al., 2018). Common any-grade IMARs with combination therapy included hypothyroidism (8%), hyperthyroidism (7%), and pneumonitis (7%). Grade 3 to 5 IMARs were observed in 11% and 3% of patients, respectively, with immune-mediated pneumonitis leading to death in one patient in each group (Paz-Ares et al., 2018).

Table 3 summarizes incidences of any-grade IMARs and common grade 3 to 5 IMARs occurring in clinical trials of approved IO combination therapies, as well as proportions of patients who received immunosuppressive agents to manage IMARs. Although IMARs observed with IO combination therapy are the same as with IO monotherapy, they occur more frequently, earlier, and potentially at a higher grade with IO combination therapy than IO monotherapy (Gandhi et al., 2018; Langer et al., 2016; Larkin et al., 2015; Madden & Hoffner, 2017; Postow et al., 2015; Weinstein et al., 2017; Wolchok et al., 2017).

Monitoring and Management of IMARs With IO Combination Therapy: An APP Perspective

Because IMARs occur at higher rates and severity with IO combination therapy than IO monotherapy, increased vigilance is warranted when managing patients receiving IO combination regimens (Gandhi et al., 2018; Langer et al., 2016; Larkin et al., 2015; Postow et al., 2015; Wolchok et al., 2017). In order to maintain patients on their combination IO treatment, APPs will need to provide sufficient monitoring and early management of IMARs. Advanced practice providers should be diligent in educating patients receiving IO combination therapy about the signs and symptoms of IMARs, whom to alert if they arise, and how they are managed. Early detection and management of IMARs are crucial to optimize clinical outcomes in these patients (Brahmer et al., 2018; Madden & Hoffner, 2017; Puzanov et al., 2017; Weinstein et al., 2017). With prompt recognition and appropriate management, APPs can prevent potentially serious and/or life-threatening IMARs as well as unnecessary treatment discontinuations (Brahmer et al., 2018; Madden & Hoffner, 2017; Puzanov et al., 2017).

Advanced practice providers take on the role of clinicians, educators, and patient advocates, and their skills are most commonly utilized in the active treatment and management of cancer (Reynolds & McCoy, 2016). Nurse practitioners, physician assistants, and pharmacists collaborate with physicians to determine, prescribe, and deliver treatment; oversee care coordination between the patient and the patient's providers; conduct new patient and follow-up visits; and provide treatment and symptom management (Bruinooge et al., 2018; Reynolds & McCoy, 2016). Oncology APPs in particular spend approximately 85% of their time providing direct patient care, with some even conducting genetic counseling and performing procedures (Bruinooge et al., 2018). Thus, oncology APPs are in a unique position to both educate patients with cancer receiving IO therapy to recognize IMARs early, and to appropriately manage IMARs and conduct follow-up care (Weinstein et al., 2017).

GUIDANCE FOR APPs TREATING PATIENTS RECEIVING IO COMBINATION THERAPY

- Advanced practice providers may explain to patients that they could receive IO/IO combination therapy and that although this IO combination approach may improve efficacy, it can also increase the risk for developing IMARs (Gandhi et al., 2018; Langer et al., 2016; Larkin et al., 2015; Postow et al., 2015; Wolchok et al., 2017)
- Advanced practice providers should educate patients to immediately report any

Table 3. Clinical Safety of FDA-Approved Immuno-Oncology Combination Therapy

Study	Tumor type	Interventions (N)	Most common grade 3–5 IMARs in IO combination groups	Proportion of patients who required immunosuppressive agents to manage IMARs[a]
CheckMate 067 (Hodi et al., 2018; Wolchok et al., 2017)	Previously untreated unresectable stage III or IV melanoma	NIVO 1 mg/kg + IPI 3 mg/kg (N = 314) vs. NIVO 3 mg/kg (N = 316) vs. IPI 3 mg/kg (N = 315)	Diarrhea (10%) Increased ALT (9%) Colitis (8%) Increased AST (6%)	Use of immunosuppressive agents not reported
CheckMate 069 (Postow et al., 2015)	Previously untreated *BRAF* wild-type unresectable stage III or IV melanoma	NIVO 1 mg/kg + IPI 3 mg/kg (N = 94) vs. IPI 3 mg/kg (N = 46)	Colitis (17%) Diarrhea (11%) Increased ALT (11%) Increased AST (7%) Rash (5%)	Immunosuppressive agents[b] NIVO + IPI: 89% IPI: 59% Corticosteroids NIVO + IPI: 82% IPI: 50%
CheckMate 214 (Motzer et al., 2018)	Previously untreated intermediate- and poor-risk advanced clear-cell RCC	NIVO 3 mg/kg + IPI 1 mg/kg (N = 547) vs. SUN (N = 535)	Data of IMARs by grade not reported[c]	Corticosteroids[d] NIVO + IPI: 35%
CheckMate 142 (Overman et al., 2018)	Previously treated MSI-H/dMMR metastatic CRC	NIVO 3 mg/kg + IPI 1 mg/kg (N = 119)	Hepatic (11%) Endocrine (5%) Dermatologic (4%) GI (3%)	Use of immunosuppressive agents not reported
KEYNOTE-189 (Gandhi et al., 2018)	Previously untreated metastatic NSQ NSCLC	Pembro 200 mg + carbo/cis + peme (N = 405) vs. carbo + peme (N = 202)	Pneumonitis (3%) Severe skin reaction (2%) Nephritis (1%) Hepatitis (1%)	Use of immunosuppressive agents not reported
KEYNOTE-021 (Langer et al., 2016)	Chemotherapy-naive stage IIIB or IV NSQ NSCLC	Pembro 200 mg + carbo + peme (N = 59) vs. carbo + peme (N = 62)	Pneumonitis (2%) Infusion reactions (2%) Severe skin reaction (2%)	Use of immunosuppressive agents not reported
KEYNOTE-407 (Paz-Ares et al., 2018)	Previously untreated metastatic SQ NSCLC	Pembro 200 mg + carbo + pac/nab-pac (N = 278) vs. pac/nab-pac (N = 281)	Pneumonitis (3%) Colitis (2%) Hepatitis (2%) Infusion reaction (1%) Severe skin reaction (1%)	Use of immunosuppressive agents not reported

Note. Hormone-replacement therapy was used to manage endocrine IMARs. FDA = U.S. Food and Drug Administration; IMAR = immune-mediated adverse reaction; IO = immuno-oncology; NIVO = nivolumab; IPI = ipilimumab; ALT = alanine aminotransferase; AST = aspartate aminotransferase; RCC = renal cell carcinoma; SUN = sunitinib; MSI-H = microsatellite instability-high; dMMR = defective DNA mismatch repair; CRC = colorectal cancer; GI = gastrointestinal; NSQ = nonsquamous; NSCLC = non–small cell lung cancer; pembro = pembrolizumab; carbo = carboplatin; cis = cisplatin; peme = pemetrexed; SQ = squamous; pac = paclitaxel; nab-pac = nanoparticle albumin-bound paclitaxel.
[a]Hormone-replacement therapy in addition to corticosteroids was used to manage endocrine IMARs.
[b]Immunosuppressive agents include systemic, topical steroidal agents, and secondary immunosuppressive medications (e.g., infliximab).
[c]Of the 547 previously untreated patients with advanced clear-cell RCC treated with nivolumab plus ipilimumab in CheckMate 214, 436 (79.7%) patients experienced treatment-related select (immune-mediated) adverse events.
[d]High-dose corticosteroids (≥ 40 mg of prednisone per day or equivalent).

health status changes or AE symptoms and support them throughout the treatment trajectory (Brahmer et al., 2018; Madden & Hoffner, 2017)
- Patient status and potential symptoms should be evaluated regularly (Brahmer et al., 2018; Madden & Hoffner, 2017)
- If an IMAR is suspected, APPs should have a low threshold for obtaining a subspecialty consultation urgently as well as for admitting patients to the hospital for closer monitoring and more intensive treatment if necessary (Brahmer et al., 2018; Puzanov et al., 2017).

IMAR Frequency, Presentation, and Recognition

To provide the most effective support to patients, it is important that oncology APPs understand the differences in IMAR frequencies between monotherapy and combination therapy and between individual ICIs, and their presentation, time to onset, and management (Weinstein et al., 2017).

Immune-mediated adverse reactions are common for all ICIs and across different tumor types: Events of any grade were reported in 11% to 49% of patients treated with anti–PD-1 or anti–PD-L1 monotherapy and 61% to 64% of those receiving anti–CTLA-4 monotherapy (Brahmer et al., 2012; Gulley et al., 2017; Hodi et al., 2010; Pillai et al., 2018; Reck et al., 2016; Tarhini, 2013; Topalian et al., 2012). Immune-mediated adverse reactions were also observed in up to 80% of patients treated with IO/IO combination therapy (Motzer et al., 2018). For combined pembrolizumab/chemotherapy, rates of IMARs ranged from 22% to 32%, compared with 5% to 14% of patients treated with chemotherapy alone (Gandhi et al., 2018; Langer et al., 2016; Nyberg, 2018; Reck et al., 2016; Zhou et al., 2018).

Overall, the most common IMARs associated with IO therapy are those affecting the skin and endocrine, GI (including liver), musculoskeletal, and respiratory systems (Figure 2; Puzanov et al., 2017). However, IMARs can affect any organ system; less common but very impactful IMARs include neurologic, ocular, cardiovascular, hematologic, and renal IMARs (Puzanov et al., 2017). Diverse patterns of IMAR classification and severity exist between IO classes (Khoja, Day, Wei-Wu Chen, Siu, & Hansen, 2017; Puzanov et al., 2017). For example, colitis, hypophysitis, rash, and pruritus IMARs are more commonly associated with anti–CTLA-4 antibodies, whereas pneumonitis, arthralgia, hypothyroidism, and vitiligo are more common with anti–PD-1 antibodies (Khoja et al., 2017). Notably, CTLA-4 inhibitors are more likely than PD-1 inhibitors to induce IMARs (Kartolo, Sattar, Sahai, Baetz, & Lakoff, 2018; Khoja et al., 2017).

Patients receiving IO/IO combinations develop similar types of IMARs as with IO monotherapy, whereas adverse reactions in patients receiving IO/chemotherapy combinations are re-

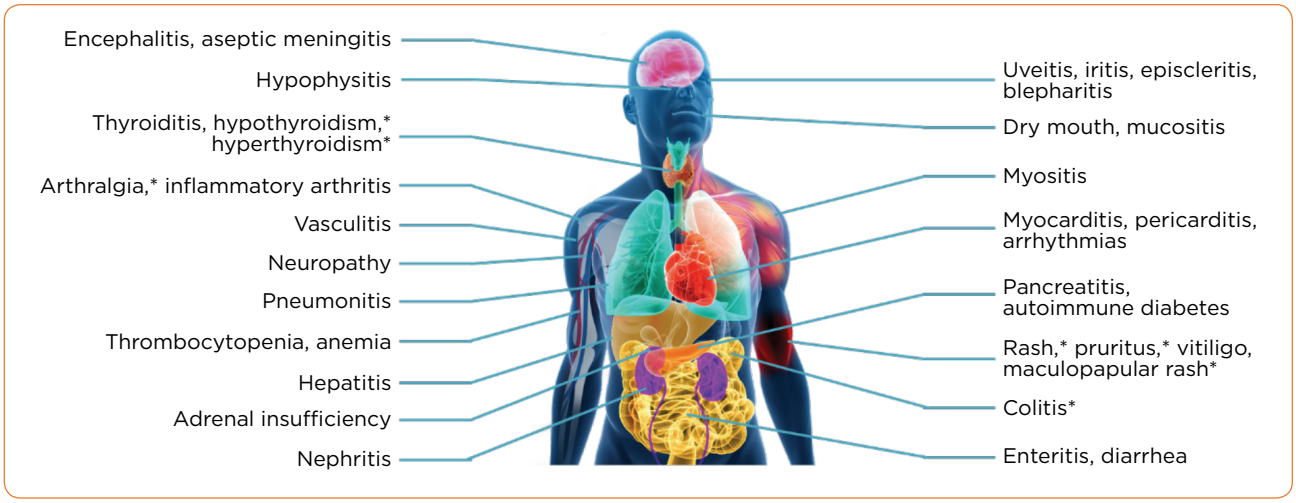

Figure 2. Spectrum of toxicity of immune checkpoint inhibitors. Asterisks denote immune-mediated adverse reactions that may occur frequently with immuno-oncology combination therapy. Information from Brahmer et al. (2018).

lated to both IO and chemotherapy agents (Gandhi et al., 2018; Paz-Ares et al., 2018; Wolchok et al., 2017). In patients receiving IO/chemotherapy combinations, IMARs related to ICIs may present similarly to those with chemotherapy (e.g., diarrhea and colitis) but may have very different causes and, therefore, require different diagnostic procedures, additional workup, and distinct management. As a result of pharmacodynamic differences, IMARs may present later and last longer than AEs related to chemotherapy (Puzanov et al., 2017).

Immune-mediated adverse reactions related to IO therapy can affect any organ system, and because more than one organ may be affected, APPs need to consider all organs in their differential IMAR diagnosis (Madden & Hoffner, 2017; Puzanov et al., 2017). The signs and symptoms of IMARs, such as immune-mediated pneumonitis, hepatitis, and hematologic AEs, may present similarly to cancer progression (Champiat et al., 2016; Puzanov et al., 2017).

IMAR Time to Onset

Although IMARs most often occur within 3 to 6 months of IO initiation, some IMARs occur earlier (e.g., after one infusion) or later, even after treatment has been discontinued (Champiat et al., 2016; Madden & Hoffner, 2017; Michot et al., 2016). Importantly, IMARs associated with IO combination therapies tend to have an earlier onset and are more severe compared with IO monotherapy (Madden & Hoffner, 2017). For instance, grade 3 to 4 GI IMARs in patients receiving nivolumab plus ipilimumab occur at a median of 7.4 weeks (range, 1.0–48.9) after initiation of IO combination therapy compared to a median of 26.3 weeks (range, 13.1–57.0) in patients receiving nivolumab monotherapy (Haanen et al., 2017).

IMAR Management

The American Society of Clinical Oncology (ASCO), in collaboration with the National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer (SITC) have published multidisciplinary guidelines and treatment algorithms that are available to APPs to assist in recognizing and managing IMARs (Brahmer et al., 2018; Puzanov et al., 2017). These guidelines focus on the recognition and management of a wide array of IMARs by organ system, including asymptomatic or mild cases in addition to less frequent toxicities not discussed in this review. They also provide recommendations for additional evaluations, interrupting or permanently discontinuing ICI treatment, dosing of corticosteroid therapy, and alternative immunosuppressive therapies (Brahmer et al., 2018; Puzanov et al., 2017).

ASCO/NCCN guidelines are summarized in Table 4 (Brahmer et al., 2018). The management of IMARs relies heavily on early intervention with corticosteroids and other immunomodulatory agents, such as infliximab, which should be considered secondary to corticosteroids in order to reduce the potential for short- and long-term complications (Puzanov et al., 2017). Patients who experience immune-mediated endocrinopathies, such as adrenal insufficiency, hypothyroidism, and type 1 diabetes mellitus, commonly require lifelong hormonal replacement or antidiabetic medication, as immune-mediated endocrinopathies are typically irreversible (Brahmer et al., 2018; Champiat et al., 2016; Puzanov et al., 2017). Advanced practice providers should advise all patients who experience adrenal insufficiency to obtain and carry a medical alert bracelet (Puzanov et al., 2017).

With the exception of some neurologic, hematologic, and cardiac toxicities, ASCO/NCCN guidelines generally recommend ICI therapy be continued with careful monitoring for grade 1 toxicities (Brahmer et al., 2018). In contrast, ICIs should be withheld for most grade 2 toxicities, and patients may receive corticosteroids (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent; Brahmer et al., 2018). Advanced practice providers should consider resuming ICI therapy withheld for grade 2 toxicities when symptoms and/or laboratory values revert to grade 1 or less (on daily prednisone equivalents of ≤ 10 mg; Brahmer et al., 2018).

Immune checkpoint inhibitors should also be withheld for patients with grade 3 IMARs, who should receive high-dose corticosteroids (prednisone at 1 to 2 mg/kg/day or methylprednisolone IV at 1 to 2 mg/kg/day; Brahmer et al., 2018). ASCO/NCCN guidelines recommend tapering corticosteroids over the course of at least 4 to 6

Table 4. American Society of Clinical Oncology/National Comprehensive Cancer Network General Recommendations for the Management of Immune-Mediated Adverse Reactions in Patients Treated With Immune Checkpoint Inhibitor Therapy

IMAR grade	Recommendation
1	In general, continue ICIs with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities
2	Hold ICIs for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to ≤ grade 1 Corticosteroids (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) may be administered
3	Hold ICIs for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone IV 1 to 2 mg/kg/day) Taper corticosteroids over the course of at least 4 to 6 weeks If symptoms do not improve within 48 to 72 hours of high-dose corticosteroids, infliximab may be offered for some toxicities
4	In general, permanently discontinue ICIs for grade 4 toxicities (with the exception of endocrinopathies that have been controlled by hormone replacement)

Note. ICI = immune checkpoint inhibitor. Information from Brahmer et al. (2018).

weeks (Brahmer et al., 2018). If symptoms do not improve with 48 to 72 hours of high-dose corticosteroids, secondary immune-modulating treatment with infliximab, mycophenolate mofetil, azathioprine, or cyclophosphamide may be offered for some toxicities (Brahmer et al., 2018). Vedolizumab may be considered in patients experiencing immune-mediated colitis refractory to infliximab and/or contraindicated to tumor necrosis factor alpha (TNFα) inhibitors (Brahmer et al., 2018). Advanced practice providers should be aware that infliximab may cause liver failure and might not be appropriate for patients experiencing immune-mediated hepatitis (Brahmer et al., 2018; Janssen Biotech, 2017). Infliximab has also been associated with heart failure, and should be avoided in patients with moderate-to-severe heart failure (Page et al., 2016).

When symptoms and/or laboratory values of grade 3 toxicities revert to grade 1 or less in patients initially receiving IO/IO combination therapy, resuming IO therapy may be offered to the patient, most commonly as anti–PD-(L)1 monotherapy. However, APPs should use caution when rechallenging patients, especially those who developed early-onset IMARs during initial ICI therapy (Brahmer et al., 2018). Dose adjustments, such as lowering the dose of ICI treatment, are not recommended (AstraZeneca UK Limited, 2018; Brahmer et al., 2018; Bristol-Myers Squibb, 2018, 2019; EMD Serono Inc, 2018; Genentech, 2019; Merck & Co Inc, 2019; Regeneron Pharmaceuticals Inc and sanofi-aventis US LLC, 2019), and in general, ICI therapy should be permanently discontinued for grade 4 IMARs with the exception of endocrinopathies controlled by hormone replacement therapy (Brahmer et al., 2018). Because dose modifications (i.e., withholding or permanently discontinuing ICI therapy) vary by IMAR, grade of severity, and drug, APPs should refer to up-to-date prescribing information for each ICI and/or multidisciplinary guidelines for appropriate dose modifications (AstraZeneca UK Limited, 2018; Brahmer et al., 2018; Bristol-Myers Squibb, 2018, 2019; EMD Serono Inc, 2018; Genentech, 2019; Haanen et al., 2017; Merck & Co Inc, 2019; Puzanov et al., 2017; Regeneron Pharmaceuticals Inc and sanofi-aventis US LLC, 2019).

Immune-mediated adverse reaction treatment should be tailored to each patient's medical history; comorbidities; underlying disease status; type, number, and severity of AEs; ICI administered; and ability to tolerate corticosteroids (Puzanov et al., 2017). Treating IMARs in patients with existing comorbidities can be challenging because practice guidelines and established guidelines often utilize evidence from clinical trials in which patients with multiple chronic conditions, including those with autoimmune disorders and transplant recipients, may be excluded (Brahmer et al., 2018). Advanced practice providers must take into account the complexity and uncertainty created

by the presence of comorbidities when developing any treatment plan. Advanced practice providers should review all chronic conditions present in the patient and take them into account when formulating management and follow-up plans for patients who develop IMARs on IO therapy (Brahmer et al., 2018; Puzanov et al., 2017). Before initiating IO therapies in transplant recipients or patients with comorbid autoimmune disorders, APPs should thoroughly discuss potential risks and benefits with the patient (Boils, Aljadir, & Cantafio, 2016; Brahmer et al., 2018).

Best practice lessons related to IO combination therapy management may be transferable between tumor types. The IO landscape is changing rapidly, with many new agents in development for multiple tumor types (Tang, Shalabi, & Hubbard-Lucey, 2018). The recognition and appropriate management of IMARs are similar regardless of tumor type (AstraZeneca UK Limited, 2018; Bristol-Myers Squibb, 2018, 2019; EMD Serono Inc, 2018; Genentech, 2019; Merck & Co Inc, 2019; Regeneron Pharmaceuticals Inc and sanofi-aventis US LLC, 2019). As research in immune-system activation and suppression advances and more data are made available, APPs need to stay abreast of these developments to enrich their understanding and appropriate management of IMARs as they evolve (Bertrand, Kostine, Barnetche, Truchetet, & Schaeverbeke, 2015; Khoja et al., 2017; Puzanov et al., 2017).

CLINICAL VIGNETTE

Patient LL (weight, 60 kg) was diagnosed with *BRAF* wild-type stage IV metastatic melanoma. (This clinical vignette was developed based on clinical practice and not approved indications.) Her medical oncologist prescribed IO combination therapy, consisting of nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for four doses or until unacceptable toxicity, followed by nivolumab at 480 mg every 4 weeks.

At week 6, patient LL reported having five large-volume watery stools (baseline one bowel movement per day) and was evaluated by her APP. Upon physical examination, a stat chemistry panel, complete blood count, and a stool evaluation for *Campylobacter*, *Salmonella*, *Clostridium difficile*, ova, and parasites were obtained. Nivolumab and ipilimumab were withheld per ASCO/NCCN guidelines because of suspected grade 2 immune-mediated colitis, and patient LL was monitored closely by the APP (Brahmer et al., 2018).

Patient LL was given an initial 30-mg dose of IV methylprednisolone and started on prednisone at 30 mg twice daily (1 mg/kg/day), to be taken with food, until symptoms resolved to grade 1, and was given the option to start an H_2-receptor antagonist or a proton pump inhibitor to minimize the risk for heartburn, GI bleeding, and ulcerations associated with steroid use. The APP educated patient LL on the side effects of corticosteroids, including irritability, increased appetite, and difficulty sleeping. A prednisone taper over the course of 6 weeks was planned upon resolution of symptoms to grade 0 or 1. A low fiber, low residual diet and an oral hydration plan were recommended. Education concerning IO–induced colitis and IO untoward side effects were again provided to patient LL and the approved caregiver. Both the patient and caregiver were counseled to be aware of and inform the APP if abdominal pain, nausea, cramping, blood or mucus in the stool, changes in bowel habits, fever, abdominal distention, obstipation, or constipation occurred, and they were urged to report a worsening of any untoward side effect immediately. The patient and caregiver understood the instructions and were able to correctly repeat them back to the APP.

Patient LL was monitored closely with daily telephone calls by the APP for assessment of diarrhea symptoms, as well as overall health status. All stool cultures were negative when patient LL returned 3 days later for further examination. However, diarrheal symptoms had not improved, with bowel movements increasing to eight times per day. The patient was admitted to the hospital and corticosteroid treatment changed to IV methylprednisolone at 60 mg twice daily (2 mg/kg/day).

Diarrheal symptoms persisted 48 hours after initiating IV corticosteroids. IV infliximab at 300 mg (5 mg/kg) was therefore administered as a single dose, and the patient was monitored for hypersensitivity reaction, liver enzyme elevation, infections, and cytopenia. Diarrheal symptoms subsided over the following week and recovered to grade 1. Per ASCO/NCCN guidelines, ipilimumab was permanently discontinued and nivolu-

mab monotherapy was initiated at 480 mg every 4 weeks (Brahmer et al., 2018). The APP followed patient LL closely for potential IMARs during nivolumab monotherapy; colitis did not recur.

FUTURE DIRECTIONS

New ICI combination therapies are being evaluated in clinical trials and have demonstrated clinical activity and tolerability in multiple tumor types. The clinical activity and safety/tolerability of nivolumab, an anti–PD-1 antibody, in combination with relatlimab, an anti–lymphocyte-activation gene 3 (LAG-3) antibody, are being assessed in a cohort of patients with metastatic and/or unresectable melanoma who received prior IO therapy in a phase I/IIa study (Ascierto et al., 2017). Of 48 evaluable patients, 13% achieved a response and approximately 31% had a reduction in tumor burden from baseline at a median follow-up of 14 weeks (Ascierto et al., 2017). The safety profile of relatlimab plus nivolumab was comparable to that of nivolumab monotherapy (Ascierto et al., 2017). In the prior IO melanoma cohort (n = 55), the most common any-grade AEs were diarrhea and nausea (in 5% each; Ascierto et al., 2017).

The anti–PD-1 antibody durvalumab is being evaluated in combination with the anti–CTLA-4 antibody tremelimumab in various advanced tumor types, including NSCLC, urothelial carcinoma, and squamous cell carcinoma of the head and neck (Antonia et al., 2016; Balar et al., 2018; Siu et al., 2018). In a phase Ib study that evaluated durvalumab plus tremelimumab in patients with locally advanced or metastatic NSCLC who had no prior immunotherapy, the authors concluded that frequencies of AEs, as well as proportions of patients receiving immunomodulatory agents (e.g., topical steroids) and immunosuppressive agents (e.g., infliximab) were broadly comparable with those in a phase III trial of previously untreated patients with advanced melanoma who received nivolumab plus ipilimumab (Antonia et al., 2016; Larkin et al., 2015).

CONCLUSION

As meaningful partners on a multidisciplinary cancer-care team, APPs play a vital role in treating patients with cancer, especially those receiving IO combination therapy with ICIs. Because IMARs frequently occur with IO/IO and IO/chemotherapy combination therapies, APPs have a unique opportunity to appropriately educate patients. Recipients of these therapies need to learn from their APPs about the possibility of IMARs, and how to identify and manage them in order to reduce the risk of short- and long-term complications; remain on IO therapy; and ultimately experience improved clinical outcomes.

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Ms. Hoffner has served on the advisory board for Bristol-Myers Squibb and Merck. Ms. Vaughn has no conflicts of interest to disclose. Ms. Reed has served on speakers bureaus and advisory boards for Array BioPharma and Bristol-Myers Squibb, the advisory board for Pfizer, and speakers bureaus for Genentech, Merck, Novartis, and Taiho. Ms. Weber has served as a speaker for Bristol-Myers Squibb.

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