ORIGINAL RESEARCH

An Evaluation of the Use of Corticosteroids for the Management of Immune-Mediated Adverse Events in Cancer Patients Treated With Immune Checkpoint Inhibitors

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Immune checkpoint inhibitors (ICIs) have gained prominence for the treatment of a variety of malignancies. However, they are associated with the development of immune-mediated adverse events (IMAEs). Appropriate management of IMAEs and subsequent rechallenging of patients with ICI therapy remains an important area of research. The primary endpoint of this study was to evaluate the efficacy of current prescribing practices and adherence to guideline recommendations for IMAE management. The incidence of symptom resolution, number of patients reinitiated with ICI therapy, and IMAE recurrence upon ICI therapy reinitiation were explored as secondary endpoints. A retrospective chart review within the Allegheny Health Network was conducted in cancer patients treated with ICI therapy who developed a documented ICI-associated IMAE and subsequently received corticosteroid therapy. IRB approval was obtained for this study. Descriptive statistics were used to analyze both primary and secondary endpoints. The study sample was made up of 81 patients. Overall, 50 out of 81 patient cases (62%) were found to be discordant with guideline recommendations; the primary factors identified were inappropriate starting corticosteroid dosing (64%), initiation of a corticosteroid taper prior to IMAE resolution to at least grade 1 severity, and condensed corticosteroid taper (74%). The main IMAEs identified were colitis (28%), pneumonitis (27%), and skin-related inflammation (12%). 76 out of the 81 patients (94%) achieved IMAE resolution; 41 patients (54%) were rechallenged with ICI therapy, of which 14 patients (34%) developed IMAE recurrence. Future studies may focus on evaluating different immunosuppression strategies to optimize IMAE management.

Cancer cells can suppress the defenses of the immune system through the overexpression of immune regulatory molecules within the tumor microenvironment (Van der Jeught et al., 2015). These molecules include immune checkpoint molecules such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand PD-L1 (Haanen et al., 2017; Puzanov et al., 2017).

A greater understanding of tumor immunology and the role of these molecules has led to the development of targeted immunotherapies that regulate the host immune response to generate clinically enhanced antitumor activity (Emens et al., 2017; McDermott et al., 2014). Immune checkpoint inhibitors (ICIs) enable the immune system to reactivate T lymphocytes to detect and target certain tumor cells (Haanen et al., 2017). There are currently seven ICIs approved by the U.S. Food & Drug Administration for both first-line and palliative therapies: the PD-1 inhibitors nivolumab (Opdivo), pembrolizumab (Keytruda), and cemiplimab (Libtayo); the PD-L1 inhibitors durvalumab (Imfinzi), atezolizumab (Tecentriq), and avelumab (Bavencio); and the CTLA-4 inhibitor ipilimumab (Yervoy; AstraZeneca Pharmaceuticals LP, 2019; Bristol Myers Squibb, 2019a, 2019b; EMD Serono, Inc, 2019; Genentech, 2019; Merck & Co., Inc.; 2019; Regeneron Pharmaceuticals, Inc., 2020).

For patients who respond to ICI therapy, there has been a prolonged survival not previously experienced with traditional cytotoxic and targeted therapies (Ribas et al., 2012; Seidel et al., 2018). Despite these clinical benefits, ICIs are associated with the development of immune-mediated adverse events (IMAEs), which are an inflammatory toxicity affecting any organ system due to the nonspecific activation of the host's immune system (Brahmer et al., 2018; Haanen et al., 2017; Puzanov et al., 2017). Although any organ system in the body can be affected, the skin, colon, lung, endocrine glands, and the liver are commonly affected. Neurologic, ocular, and cardiovascular symptoms occur less frequently (Puzanov et al., 2017). The organ affected and the severity of the IMAE largely varies according to each ICI agent but can also differ across tumor types (Ribas et al., 2012).

Immune-mediated adverse events can occur at any time during and after therapy completion. The onset of IMAEs has been documented to have occurred up to 1 year after discontinuing therapy (Haanen et al., 2017). The overall incidence of all-grade IMAEs has been estimated to occur in approximately 30% of patients receiving CTLA-4 inhibitor therapy and approximately 15% in patients receiving either PD-1 or PD-L1 inhibitor therapy (Seidel et al., 2018). The incidence of IMAEs with combined CTLA-4 inhibitor and PD-1 inhibitor therapy has been reported to occur in upwards of 55% of patients (Seidel et al., 2018; Zhou, et al., 2019). These immune toxicities are largely reversible if treated promptly and appropriately but can lead to treatment-related morbidity and mortality (Wang et al., 2017).

The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) released joint guidelines for the management of IMAEs in February 2018 (Brahmer et al., 2018, Thompson et al., 2020). Prior to the development of these guidelines, the management of IMAEs was largely based on agent-specific protocols. The severity of immune reaction and organ system involved largely dictate the management strategy undertaken, which generally involves discontinuation of the ICI and transient immunosuppression with corticosteroids. Additional supportive therapies may be required to achieve complete symptom resolution. Following symptom resolution, a prolonged corticosteroid taper of at least 4 weeks is generally recommended (Brahmer et al., 2018; Thompson et al., 2020). Based on a patient's clinical response to ICI therapy prior to the onset of IMAE, patients may be rechallenged with further ICI therapy upon IMAE resolution.

Due to the complexity of IMAEs and the potential for differing prescribing practices, there is likely discordance between guideline recommendations and actual clinical practice due to prescriber preference and clinical experiences. Therefore, the primary objective of this study was to evaluate the adherence of current prescribing practices and efficacy of corticosteroid therapy used for the management of IMAEs associated with ICIs within a hospital network system. Secondary objectives included evaluating the incidence of symptom resolution, number of patients reinitiated with ICI therapy, and any IMAE recurrence upon ICI therapy reinitiation.

METHODOLOGY

The study design and research protocol were reviewed and approved for submission by all listed authors for completeness and accuracy. The research protocol was approved by the Allegheny-Singer Research Institute-West Penn Allegheny Health System (ASRI-WPAHS) Institutional Review Board (IRB).

This was a retrospective patient chart review performed using the Epic medical record system within the Allegheny Health Network. Patient charts were reviewed from February 2016 through July 2018. Patients were eligible for inclusion if they were at least 18 years of age or older, had a documented IMAE secondary to receiving ICI therapy, and subsequently received corticosteroid therapy for the management of IMAE. Patients were included if they received either prednisone or methylprednisolone for IMAE management. All corticosteroid dosing was converted to a prednisone-equivalent dose for study evaluation.

Patients were excluded from the study if any of the following criteria were found: there was incomplete chart documentation regarding the IMAE grading and/or medication therapy received, or this information was not accurately determined based upon radiographic imaging, appropriate laboratory parameters, or other pertinent information as determined by the investigators; patients received initial care and/or follow-up outside of the hospital health system; patients had any interruption in IMAE-related corticosteroid therapy due to an adverse event that achieved IMAE resolution; or patients received a corticosteroid dose equivalent of at least 10 mg of prednisone or greater while receiving ICI therapy.

Data variables collected for each patient included baseline characteristics (age, weight, cancer diagnosis, ICI agent received, documented IMAE), overall concordance with guideline-recommended management, incidence of IMAE, corticosteroid dosing (starting and total dose), incidence and duration of steroid therapy until IMAE resolution, additional supportive therapies administered, whether the patient was reinitiated on ICI therapy, and the incidence of IMAE recurrence after restarting ICI therapy.

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics, and primary and secondary outcomes.

RESULTS

A total of 885 patients were screened, of which 81 were evaluated (Table 1). The median age of the patients in the study was 62 years (range: 29–73). The most common cancer diagnoses among patients were melanoma (33%), non–small cell lung cancer (29%), and renal cell carcinoma (19%). Nivolumab and ipilimumab as both monotherapy (56% and 12%, respectively) and combination therapy (15%), and pembrolizumab (14%) were the ICI agents most frequently associated with IMAEs (Table 1).

Primary Objective

An evaluation of the overall concordance of IMAE management with corticosteroid utilization found that 38% of patient cases were concordant with NCCN and ASCO guideline recommendations (Table 2). Of the patient cases that were deemed to have been discordant with guideline recommendations, a large number utilized management strategies that were identified to be discordant due to multiple factors during the course of corticosteroid therapy.

Table 1. Patient characteristics (N = 81)	
Age, years, median (range)	62.4 (29–73)
Weight, kg, median (range)	88.4 (48–180)
Cancer diagnosis, n (%)	
Melanoma	27 (33)
Non–small cell lung	23 (29)
Renal cell	15 (19)
Gynecologic	6 (7)
Neuroendocrine	4 (5)
Small cell lung	3 (4)
Hepatocellular	2 (2)
Urothelial/bladder	1 (1)
IMAE associated with ICIs, n (%)	
Nivolumab	46 (56)
Ipilimumab	10 (12)
Ipilimumab + nivolumab	12 (15)
Pembrolizumab	11 (14)
Atezolizumab	1 (1)
Durvalumab	1 (1)

Note. IMAE = immune-mediated adverse event; ICI = immune checkpoint inhibitor.

Table 2. Overall IMAE Guideline Adherence and Identified Reasons for Discordance

Overall concordance with guideline-recommended management (n = 81)	n (%)
Yes	31 (38)
No	50 (62)
Type of prescribing deviation (n = 50)	n (%)
Inappropriate starting dose for IMAE severity	32 (64)
Initiation of steroid taper prior to IMAE < grade 1	19 (38)
Condensed steroid taper used	37 (74)
Reinitiation of immunotherapy prior to < 10 mg prednisone-equivalent	4 (8)

Note. IMAE = immune-mediated adverse event.

The predominant factor identified was inappropriate dose upon initiation based on the IMAE severity (64%). Most patients were started on a lower dose of corticosteroids than is recommended in the NCCN and ASCO guidelines. Other reasons included the initiation of a corticosteroid taper prior to the reduction in IMAE severity of at least grade 1 (38%); a condensed corticosteroid taper was used upon IMAE resolution that was less than the recommended 4- to 6-week interval (74%); and, if patients were rechallenged with ICI therapy, patients were reinitiated prior to achieving a corticosteroid taper of less than a prednisone-equivalent dose of 10 mg (8%; Table 2). The IMAEs with the highest incidence documented were colitis (28%), pneumonitis (27%), and skin-related inflammation (12%; Table 3).

Secondary Objectives

Out of 81 patients, 76 (94%) achieved complete IMAE resolution. There were five patients who did not achieve IMAE resolution with corticosteroid therapy: two patients had myalgia, and the other three IMAEs reported were pneumonitis, thyroiditis, and hepatitis. The number of days required to achieve IMAE resolution varied greatly based on the organ affected and severity of IMAE (Table 3). Five patients required additional supportive therapies during corticosteroid therapy; one patient required infliximab, three patients required intravenous immunoglobulin, and one patient required mycophenolate mofetil. All patients who received additional therapies had documented resolution of IMAE symptoms.

Fifty-four percent of patients who developed an IMAE were rechallenged with further ICI therapy (Table 4). Most of these patients had experienced a past IMAE of colitis, pneumonitis, or skin rash. Of note, patients with a documented IMAE associated with the pancreas or cardiovascular system were not rechallenged with repeat ICI therapy. Of the 41 patients restarted on previous ICI therapy, 14 patients (34%) had a recurrence of IMAE symptoms (Table 4); the highest incidences of IMAE recurrence were colitis (54%), hepatitis (50%), nephritis (60%), pneumonitis (25%), and skin rash (25%).

DISCUSSION

As the most prominent class of immunotherapy agents used in the treatment of a wide variety of cancer types, ICIs have been associated with a prolonged objective response and survival in the management of solid tumors. Due to the largely unpredictable onset of immune-mediated toxicity with ICI therapies, early symptom recognition and timely initiation of appropriate corticosteroid immunosuppression is crucial for resolving IMAEs. The primary goal of this study was to compare the management of ICI-associated IMAEs in the Allegheny Health Network with NCCN and ASCO guideline recommendations. Secondary goals evaluated were the efficacy of these prescribing practices in achieving IMAE resolution and assessing the incidence of patients rechallenged with ICI therapy, and any subsequent IMAE recurrence. Of note, the publication of the IMAE management guidelines from NCCN and ASCO in February 2018 occurred during the time period of this retrospective study (February 2016 through July 2018).

There were a wide variety of IMAEs documented among different cancers types, ICI agents used, and organ systems affected, with the most prominent IMAEs being colitis, pneumonitis, and skin-related inflammation. The onset and presentation of IMAEs found in this study varied but did largely reflect similar incidences and within the anticipated time frame reported (De Velasco et al., 2017; Wang et al., 2017). The median time to onset of IMAEs with both PD-1 and PD-L1 inhibitors is typically between 1 to 6 months (Chuzi et al., 2017; Daniels et al., 2019; Friedman et al., 2016).

Table 3. Incidence and Resolution of IMAE and Starting Corticosteroid Dosing

IMAE	IMAE incidence, n (%)	Corticosteroid starting dose, mg/kg/day, median (range)	IMAE resolution	
			n, (%)	Days, median (range)
Colitis	23 (28)	0.68 (0.24–1.00)	23 (100)	25 (4–91)
Pneumonitis	22 (27)	0.92 (0.36–2.00)	21 (96)	10 (4–42)
Skin	10 (12)	0.7 (0.10–1.00)	10 (100)	10 (2–20)
Hepatitis	8 (10)	1.1 (0.59–1.50)	7 (88)	21 (6–50)
Nephritis	6 (7)	0.52 (0.28–0.73)	6 (100)	11 (7–16)
Thyroid	4 (5)	0.76 (0.41–1.20)	3 (75)	20 (12–38)
Myalgia	4 (5)	0.1 (0.04–0.13)	2 (50)	24 (18–30)
Neurologic	2 (2)	1.1 (0.70–1.50)	2 (100)	10 (7–13)
Pancreas	1 (1)	1	1 (100)	50
Cardiovascular	1 (1)	1	1 (100)	15

Note. IMAE = immune-mediated adverse event.

CTLA-4 inhibitors have been associated with more varying times of IMAE presentation, with dermatologic symptoms typically presenting 2 to 3 weeks into therapy, gastrointestinal and hepatic symptoms reported to occur approximately 6 to 7 weeks into therapy, and some endocrinology complications appearing approximately 7 to 8 weeks after initiating therapy (Weber et al., 2012). Overall, there were a wide variety of steroid strategies identified for IMAE management within the Allegheny Health Network. The major discordance documented with corticosteroid therapy from recommended ASCO and NCCN guidelines was the use of a lower starting dose based upon the organ system and IMAE severity. Most of the initial documentation of a potential IMAE stemmed from patients reporting symptoms to their medical oncologist's offices. From patient chart documentation, the use of a methylprednisolone oral dose pack was a common selection by prescribers as initial corticosteroid therapy presenting with colitis, skin-related inflammation, and myalgia, whereas less common IMAEs, such as pancreatitis and neuropathic- and cardiovascular-related

Table 4. Incidence of ICI Reinitiation and IMAE Recurrence

IMAE	Additional supportive treatments	Time off ICI therapy, days, median (range)	Reinitiation after IMAE resolution, n, (%)	Recurrence after ICI reinitiation, n, (%)
Colitis	1 (infliximab)	83.2 (36–338)	13 (57)	7 (54)
Pneumonitis	–	52.7 (21–144)	8 (38)	2 (25)
Skin	–	22 (14–83)	8 (80)	2 (25)
Hepatitis	3 (2 IVIG, 1 MM)	209 (59–359)	2 (29)	1 (50)
Nephritis	–	37 (22–51)	5 (83)	2 (60)
Thyroid	–	25 (20–30)	2 (67)	0 (0)
Myalgia	–	26 (14–37)	2 (100)	0 (0)
Neurologic	1 (IVIG)	14 (14)	1 (50)	0 (0)
Pancreas	–	–	0 (0)	–
Cardiovascular	–	–	0 (0)	–

Note. ICI = immune checkpoint inhibitor; IMAE = immune-mediated adverse event; MM = mycophenolate mofetil; IVIG = intravenous immunoglobulin.

inflammation were associated with higher initial doses of prednisone therapy. The less commonly observed toxicities may have been considered more life threatening and therefore resulted in a higher dose of corticosteroid therapy. The use of an abbreviated corticosteroid taper upon IMAE symptom resolution was another major discordance documented; although not presented in this study, the median corticosteroid taper time chosen seemed to vary based upon the organ system affected and the initial severity of IMAE symptoms, and was largely at the prescriber's discretion.

Despite the utilization of different corticosteroid strategies for IMAE management, the majority of patients were able to achieve resolution of their IMAE symptoms. This highlights the importance of early IMAE recognition with appropriate triage, evaluation, and therapy initiation with appropriate follow-up in either the inpatient or outpatient setting (Daniels et al., 2019; Sosa et al., 2018). Due to the commonality of certain IMAE-associated presentations, other potential etiologies, including infection, effect of concurrent medications, and malignancy need to be systematically assessed and ruled out (Brahmer et al., 2018; Daniels et al., 2019; Thompson et al., 2020). Certain ICI-related IMAEs may present very similarly to adverse effects caused by anticancer therapies; therefore, educating nononcology providers who may encounter these patients at the time of IMAE onset on the appropriate triaging strategies to investigate relevant past courses of therapy, diagnostic procedures, and initiating supportive care is critical to ensure timely and appropriate management of ICI-related IMAEs (Weber et al., 2012).

The publication of NCCN and ASCO guidelines for IMAE management occurred during the time period of this retrospective study. Although there were patient cases identified as receiving discordant IMAE management when compared with current NCCN and ASCO guideline recommendations, IMAE management prior to the publication of the consensus guidelines may not have necessarily been inappropriate based on the prescribing practice at the time. Moreover, prior to the development of consensus guidelines, the management of IMAEs was largely based on agent-specific protocols, medication labeling, and practitioner experience. However, the accessibility of NCCN and ASCO guideline recommendations for ICI-associated IMAE management likely contributed to more appropriate immunosuppression strategies utilized. Although not specifically reported in this study, data for both primary and secondary study outcomes largely reflected greater conformance to NCCN and ASCO guideline recommendations, particularly for patients managed after February 2018. Greater practitioner experience with ICI therapy and managing IMAE symptoms, in addition with guideline publication, likely also contributed to the improvements in conforming to guideline recommendations.

There were a significant number of patients who were restarted on ICI therapy upon IMAE resolution. The reinitiation of ICI therapy upon IMAE resolution remains controversial in oncology practice, and there are limited prospective studies investigating the efficacy and safety of rechallenging patients after an IMAE. A study by Simonaggio and colleagues (2019) assessed the safety of rechallenging patients with a PD-1 or PD-L1 inhibitor after resolution of a grade 2 or higher IMAE. In the study, 93 patients were included, of which 43% were rechallenged with the same PD-1 or PD-L1 inhibitor prior to the onset of IMAE symptoms. At a median follow-up of 14 months, 55% of patients rechallenged developed another IMAE; arthralgia (27%), skin toxicity (18%), colitis (14%), and hepatitis (14%) were the most commonly encountered IMAE-related toxicities after ICI reinitiation. The authors noted that a shorter time to the development of the first IMAE was linked to the occurrence of a second IMAE, but the second IMAE was not found to be more severe than the first IMAE (Simonaggio et al., 2019).

A study by Abu-Sbeih and colleauges (2019) also evaluated the recurrence of IMAE after restarting either a CTLA-4 inhibitor or PD-1/PD-L1 inhibitor. Of the 167 patients assessed, 34% of patients overall (44% on CTLA-4 inhibitor and 32% on PD-1/PD-L1 inhibitor) had an IMAE recurrence after a median of 53 days after resuming ICI therapy. The majority of patients with IMAE recurrence experienced grade 2 diarrhea (70%) and grade 1 colitis (54%). Although most IMAEs were deemed mild in severity, 81% of these patients required immunosuppressive therapy (corticoste-

roids), with 12% of patients receiving additional infliximab or vedolizumab therapy. Regression analysis found that patients were at greater risk of recurrence if they required immunosuppression for an initial IMAE or had a longer duration of symptoms during the initial IMAE episode (Abu-Sbeih et al., 2019). A comparable percentage of patients (34%) were reinitiated on ICI therapy upon successful IMAE resolution in this study. The influence of prior ICI therapy on IMAE recurrence and symptom management, and patient follow-up afterwards were not investigated in this study. There was a similar percentage of patients in this retrospective study who were both rechallenged and developed IMAE recurrence. Although not investigated, the use of a condensed steroid taper upon IMAE resolution may have contributed to the increased number of IMAE recurrences upon ICI reinitiation, particularly the development of colitis symptoms.

For patients who achieve successful ICI-associated IMAE resolution, identifying patients who are appropriate candidates for restarting ICI therapy remains a challenge for providers. Patients who develop IMAEs have reported improved rates of response to ICI therapy. The ASCO and NCCN guidelines advise against rechallenging patients who have achieved either a complete or partial response to ICI therapy due to the greater likelihood of IMAE toxicity recurrence. The organ system affected, severity of IMAE, and ICI agent involved all factor into determining whether a patient should be rechallenged or if ICI therapy should be permanently discontinued. Immune checkpoint inhibitor therapy should not be reattempted in patients with life-threatening, severe (grade 3 to 4), or select moderate-intensity IMAEs (e.g., encephalitis, myocarditis) induced by the same class as the ICI agent previously used (e.g., PD-1, PD-L1, CTLA-4 inhibitors). For patients with moderate-intensity (grade 2) IMAEs, most may be considered for restarting ICI therapy upon IMAE resolution to at least grade 1, adequate management of symptoms, or correction in laboratory abnormalities. Management of central nervous system (CNS)-associated toxicities differ from general recommendations. Patients with aseptic meningitis may be considered for ICI resumption if symptoms resolve to grade 0. Immune check-

point inhibitor therapy should be permanently discontinued for patients with any evidence of Guillain-Barré syndrome or transverse myelitis of any grade.

The recurrence of IMAE toxicities after ICI reinitiation is grounds for permanently discontinuing the class of immunotherapy. An organ-specific specialist should be consulted during the management of IMAEs and when considering the reinitiation of ICI therapy following IMAE resolution. In addition to close monitoring and follow-up, discussions on goals of care should be addressed to align treatment goals with patient objectives and quality of life (Brahmer et al., 2018; Thompson et al., 2020).

Study Limitations

There were a number of study limitations identified with this research study. The retrospective cohort, single-center study with a small patient population for analysis limits the external validity and applicability of the study results. With provider subjectivity and the effects on practice experience, prescribing practice, and resource utilization, these factors could have largely influenced the clinical approach taken by providers in IMAE management. Another limitation with this study was patient adherence to corticosteroid therapy and provider instructions during initial therapy and follow-up were largely unknown. Documentation from provider notes, prescription details, and patient follow-up were all utilized to the best of the investigators' abilities to estimate the approximate dose and total duration of corticosteroid therapy and IMAE response. Whether patients were completely adherent to these corticosteroid strategies or had additional worsening of clinical symptoms in between provider follow-up or chart documentation was difficult to determine from patient medical records, and likely could have affected the patient's clinical response and progress during management.

The publication of NCCN and ASCO guidelines during the retrospective study period likely positively influenced study outcomes, although it is unclear of the true magnitude of IMAE management and guideline discordance, particularly for patients treated prior to the publication of the NCCN and ASCO consensus guidelines. Providers

were likely to have conformed to recommended guideline strategies for IMAE management based on the organ and severity of IMAE encountered. Due to the limited clinical data published, it is unknown whether NCCN and ASCO guideline recommendations played a significant role in guiding health-care providers on selecting appropriate patients to be rechallenged with ICI therapy in this study.

CONCLUSION

As ICIs continue to be a major treatment option for a variety of different cancers, prompt identification and management of symptoms associated with IMAEs with appropriate immunosuppression are paramount. A retrospective review within the Allegheny Health Network found that the management of approximately two thirds of patients treated with corticosteroid therapy was discordant with published NCCN and ASCO guideline recommendations. However, greater conformance to appropriate immunosuppression strategies utilized after the publication of NCCN and ASCO guidelines for ICI-associated IMAE management likely improved study outcome results. The majority of patients were found to have been started on a lower-than-recommended corticosteroid dose and were placed on abbreviated corticosteroid tapers upon IMAE resolution. There was a large percentage of patients who achieved IMAE symptom resolution in the study, with a number of patients reinitiated on ICI therapy.

Future prospective studies may focus on comparing different treatment strategies to optimize the management of IMAEs in patients treated with ICIs. Furthermore, for patients rechallenged with an ICI upon IMAE resolution, additional research may be beneficial to identify potential factors that may facilitate the risk of IMAE recurrence, including in patients who had clinical response to ICI therapy and may continue to derive an immunogenic response in their tumor without additional ICI therapy. ●

Disclosure

Dr. Julius has served on an advisory board for Bristol Myers Squibb and on the speakers bureaus for AstraZeneca and Bristol Myers Squibb. The remaining authors have no conflicts of interest to disclose.

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