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Immune-Related Adverse Events in the Setting of PD-1/L1 Inhibitor Combination Therapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

INTRODUCTION

As of November 1, 2018, the U.S. Food and Drug Administration (FDA) had approved six immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1) pathway, including three PD-1 inhibitors (pembrolizumab, nivolumab, and cemiplimab) and three PD-1 ligand (PD-L1) inhibitors (atezolizumab, avelumab, and durvalumab). With indications spanning multiple tumor types [1–47], PD-1 and PD-L1 inhibitors have become the standard of care for many cancers. Because of their mechanism of action, PD-1 and PD-L1 inhibitors can cause a distinct set of inflammatory side effects, known as immune-related adverse events (irAEs). Whereas mild irAEs can generally be treated supportively, severe toxicity requires urgent intervention and, in some cases, may be fatal [48, 49]. The recognition that irAEs may arise in patients receiving PD-1/L1 inhibitors has prompted the coordination of multidisciplinary groups to scrutinize these toxicities [50–61] and the development of consensus guidelines by professional organizations to diagnose and manage them [62–65].

Despite the clinical success of PD-1 and PD-L1 inhibitors for a considerable proportion of patients with cancer, it has become apparent that they do not elicit responses in all tumors or individuals. Thus, efforts are underway to potentiate the activity of these agents by administering them with one or more additional types of therapies (e.g., another immunotherapy, cytotoxic chemotherapy, or targeted therapy), herein referred to as "PD-1/L1 inhibitor combination therapy", and expand the population of patients who may experience clinical benefit. Combining PD-1/L1 inhibitors with a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor has shown promise, as evidenced by the approval of nivolumab in combination with ipilimumab for the treatment of metastatic melanoma, advanced renal cell carcinoma (RCC), and microsatellite instability–high or mismatch repair-deficient colorectal cancer [22, 28, 47]. The combination of pembrolizumab with cytotoxic chemotherapy demonstrated clinical benefit [4, 5] and was FDA approved for first-line treatment of metastatic non-small cell lung cancer (NSCLC) irrespective of PD-L1 expression; because PD-L1 expression is required for pembrolizumab monotherapy in this setting, the combination regimen broadens the eligible patient population. More recently, there were FDA approvals for pembrolizumab or avelumab in combination with axitinib, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, as first-line treatment for advanced RCC, based on two phase III trials [19, 43], and for atezolizumab in combination with chemotherapy for extensive-stage small cell lung cancer [40] and for certain women with advanced triple-negative breast cancer [39].

Possible synergies between PD-1/L1 inhibitors and agents with different mechanisms of action [66] are increasingly being investigated in clinical trials [67–69], with one analysis reporting 1,105 studies testing PD-1/L1 inhibitor combinations in 2017 [67], and a recent update identifying 1,716 such trials [69]. Optimistically, the outcomes of these trials may render PD-1/L1 inhibitor combination therapy the dominant treatment strategy for many tumor types. Parenthetically, the sheer number of open combination trials assumes that adding a second agent to PD-1/L1 inhibitors has the potential to offer more than additive benefit and reverse the inactivity of PD-1/L1 inhibitors in some tumor types, a hypothesis that remains largely unproven. Nonetheless, in anticipation of a paradigm shift toward combination therapy, it is crucial to consider how
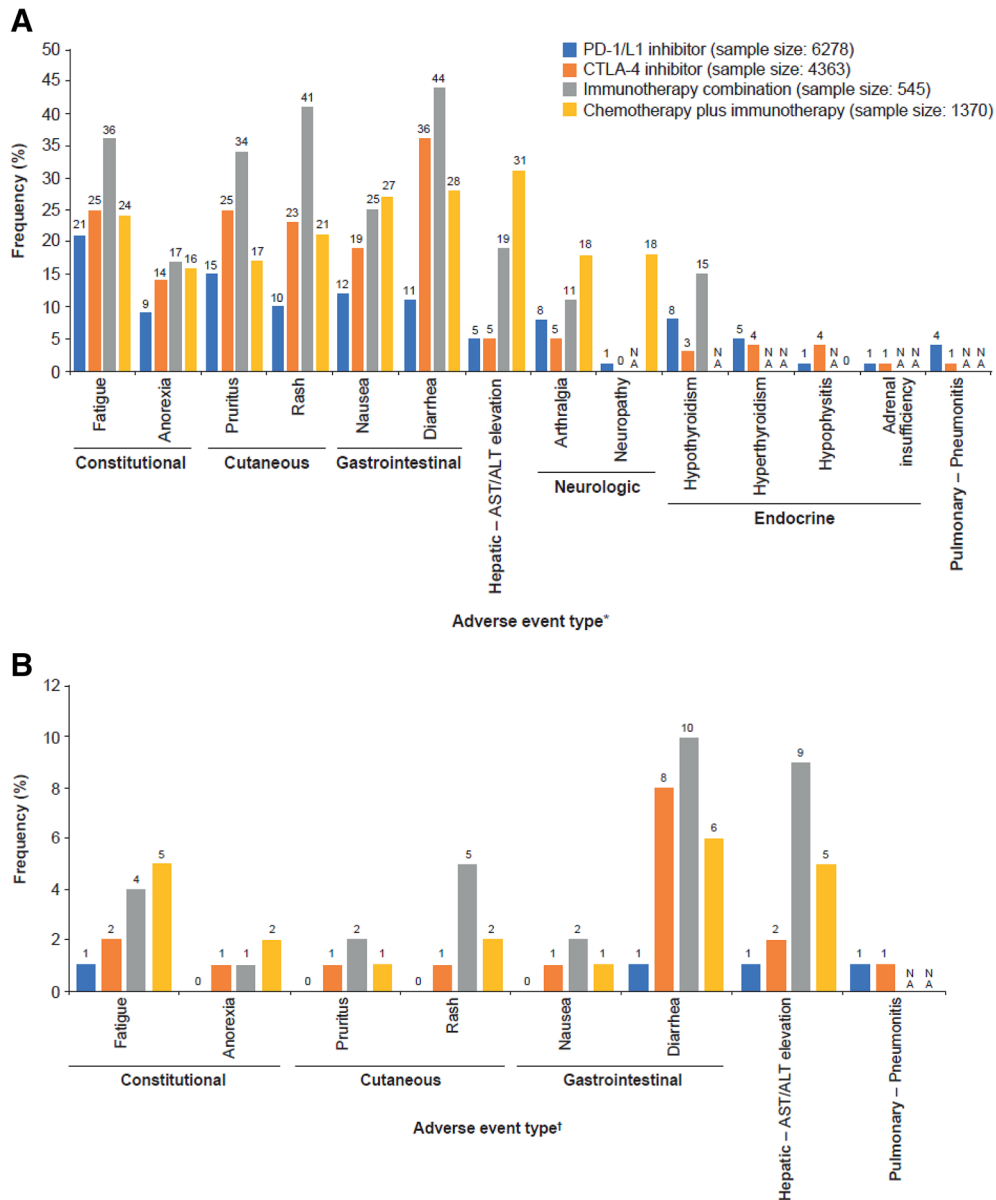
Figure 1. Frequency of **(A)** any grade and **(B)** grade 3/4 adverse events in clinical trials of PD-1/L1 inhibitors, CTLA-4 inhibitors, immunotherapy combinations, and chemotherapy plus immunotherapy combinations [70]. *, Myositis and mucositis not included because these adverse events were NA for all groups except for PD-1/L1 inhibitor. †, Adverse events from panel A with grade 3/4 frequency of 0 or NA in ≥3 groups were excluded.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; NA, not available; PD-1, programmed death-1; PD-L1, PD-1 ligand.

administration of PD-1/L1 inhibitors with other agents may confound the clinical presentation, diagnosis, and management of irAEs, as well as to equip the medical community with sound strategies to identify and treat these side effects. A systematic review of 35 clinical trials showed a different pattern of toxicity regarding frequency and specific organ involvement depending on the type of therapeutic scheme that was administered (i.e., PD-1/L1 inhibitor monotherapy, CTLA-4 monotherapy, immunotherapy combination therapies, or concomitant administration of immunotherapy and chemotherapy; Fig. 1) [70]. The current guidelines for management of irAEs, based largely on toxicities with CTLA-4 and PD-1/L1 monotherapies, will likely require revision as experience with combination therapies

continues to accrue. Guidance and management for irAEs related to administration of different ICIs together will be essential, as well as combination of immunotherapies with chemotherapy and/or targeted therapies, where the resulting toxicity can be challenging to diagnose and treat.

A multidisciplinary workshop was held at the Massachusetts General Hospital to discuss challenges in defining, diagnosing, and treating irAEs, including those that occur in patients administered PD-1/L1 inhibitor combination therapy. Here, the workshop participants present a clinical case that illustrates the complexity of irAE diagnosis and management in a patient receiving PD-1/L1 combination therapy, summarize the current state of PD-1/L1 combination therapy based on an analysis of abstracts from the 2018 American

Society of Clinical Oncology (ASCO) Annual Meeting, and discuss challenges and opportunities for the evaluation of irAEs as these combinations become more widely used to treat patients with cancer.

CASE IN POINT: AN IMMUNE-RELATED ADVERSE EVENT WITH PD-1/L1 INHIBITOR COMBINATION THERAPY

Strategies for the diagnosis and management of immune-related colitis in patients receiving PD-1/L1 inhibitor monotherapy or the CTLA-4 inhibitor ipilimumab have been described in detail [62–65, 71, 72]. Briefly, immune-related colitis can generally be diagnosed based on patient symptoms and medical history and following exclusion of infectious colitis, although endoscopy and biopsy may be warranted. Low-grade immune-related colitis may be treated symptomatically, but persistent or higher-grade events typically require administration of systemic corticosteroids. Patients who do not respond to corticosteroids or who have recurring immune-related colitis following a corticosteroid taper may require treatment with the antitumor necrosis factor-α antibody infliximab. As noted above, published guidelines describing irAEs [50–65] are focused on toxicity secondary to CTLA-4 and PD-1/L1 monotherapies or to the concurrent administration of both types of ICIs. Since co-administration of another type of therapy (e.g., chemotherapy with a PD-1/L1 inhibitor) may confound the diagnosis of immune-related colitis and lead to the delay of a suitable remedy, current immunotherapy management guidelines should be applied judiciously.

Here, we describe a 74-year-old man with NSCLC treated with first-line pembrolizumab in combination with pemetrexed and carboplatin. After two cycles of therapy, he developed grade 1 diarrhea, which slowly escalated. One month after symptom onset (following cycle 4 of therapy), he presented with grade 2 diarrhea and rectal bleeding. Outpatient flexible sigmoidoscopy showed significant mucosal inflammation (Fig. 2A), and biopsies revealed neutrophilic cryptitis with dilated, "withered" crypts and without prominent apoptosis, pathology that was not pathognomonic of pembrolizumab-associated inflammation (Fig. 2B and 2C); thus, a chemotherapy-related toxicity was presumed. He was initially treated conservatively using stool-bulking measures (cholestyramine) and antidiarrheal medications (loperamide and diphenoxylate-atropine). After 1 week of supportive management, his diarrhea persisted, and high-dose corticosteroids (oral prednisone 60 mg per day) were initiated. Despite high-dose corticosteroids, diarrhea worsened to grade 3–4 after another week, requiring hospitalization. Repeat flexible sigmoidoscopy showed persistent inflammation (Fig. 2D), and biopsies showed similar characteristics to the prior results but with progressive expansion of the lamina propria and a mixed inflammatory infiltrate more consistent with PD-1 inhibitor-induced colitis [71, 72], in spite of rare apoptotic bodies (Fig. 2E and 2F). *Clostridium difficile* toxin testing of stool cultures and cytomegalovirus stains on the biopsies were negative. Intravenous methylprednisolone was followed by a second-line immunosuppressive agent, infliximab, to treat the refractory diarrhea. Diarrhea symptoms improved to grade 1 within 3 days of the start of infliximab, and the patient was transitioned to oral prednisone (60 mg per day) and discharged. The timely identification and treatment of irAEs is imperative, and in this example, the addition of chemotherapy to a PD-1 inhibitor made the diagnosis even more challenging and led to a delay in appropriate management. This new era of combination therapy requires individuals to be aware of anchor bias and continue to reassess a patient's condition, at times with repeat testing, to avoid diagnostic inaccuracies.

REPORTS OF PD-1/L1 INHIBITOR COMBINATION THERAPY TRIALS AT ASCO 2018

Current trends in PD-1/L1 inhibitor combination therapy were evaluated using the abstract database from the 2018 ASCO Annual Meeting. We identified 359 abstracts that presented information on immuno-oncology agents, of which ICIs are a subset. We excluded abstracts that included unspecified agents, monotherapy, preclinical or health economic and outcomes research studies, or meta-analyses, finally identifying 183 abstracts reporting on clinical trials of PD-1/L1 inhibitors in combination with other agents, representing 51% of the full set of ASCO 2018 abstracts on immuno-oncology agents.

The majority (n = 134; 72%) of combination regimens presented at ASCO 2018 used pembrolizumab or nivolumab as the backbone (Fig. 3A), as expected, given the timing of FDA approvals. PD-1/L1 inhibitors are being combined with a multitude of other therapies (Fig. 3B), most frequently within the categories of immunotherapy (n = 60; 31%), targeted therapy (n = 53; 27%), or cytotoxic chemotherapy (n = 37; 19%). Although most combinations (n = 173; 88%) consisted of a PD-1/L1 inhibitor plus one other category of therapy, there were also studies of a PD-1/L1 inhibitor administered with two additional types of therapies (e.g., chemotherapy plus targeted therapy).

Consistent with the current indications for PD-1/L1 inhibitor monotherapy [1–3, 6–18, 20, 21, 23–27, 29–38, 41, 42, 44–46], combination regimens were most commonly being studied for the treatment of lung cancer, genitourinary cancer, gastrointestinal cancer, and melanoma (Fig. 3C). Tumor types thought to be less susceptible to ICIs were also under study, as well as trials with multiple tumor types. Combination regimens were most frequently being tested as second-line or later treatment (n = 71; 39% overall). Nevertheless, it is notable that 22 (12%) abstracts described first-line or subsequent therapy, 40 (22%) focused on first-line treatment only, and 23 (13%) analyzed neoadjuvant and/or adjuvant therapy. The proportion of trials testing first-line or neoadjuvant and/or adjuvant PD-1/L1 inhibitor combination therapy is noteworthy, given that the majority of monotherapy approvals to date are for second-line or later treatment, and approved indications of PD-1/L1 inhibitors in an adjuvant setting are scarce (e.g., for nivolumab in patients with melanoma [23] and durvalumab in patients with unresectable stage III NSCLC following chemoradiotherapy [45]).

Furthermore, our analysis indicated that PD-1/L1 inhibitor combination regimens are predominantly in early stages of clinical development, with 41 (22%) abstracts reporting on phase I trials, 41 (22%) on phase I–II trials, 61 (33%) on phase II trials, and only 29 (16%) on phase III trials; the trial
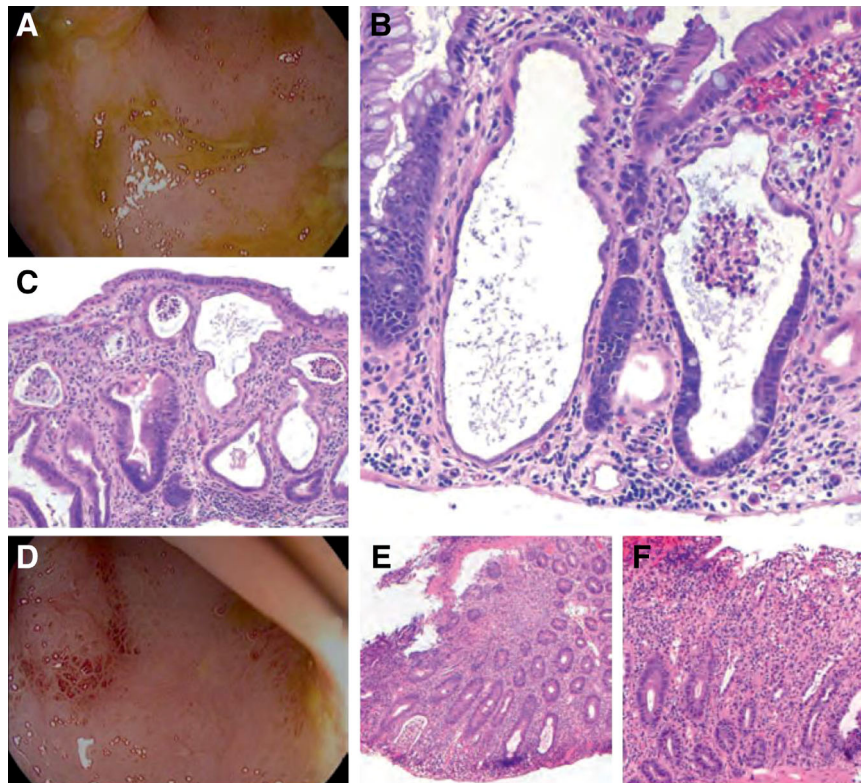
Figure 2. Colitis following treatment with a programmed death-1 inhibitor (pembrolizumab) plus chemotherapy (pemetrexed and carboplatin). Images are following **(A–C)** onset of symptoms and **(D–F)** treatment with corticosteroids; symptoms subsided following treatment with intravenous methylprednisolone and infliximab. Initial biopsies **(B–C)** show prominent neutrophilic cryptitis with crypt epithelial injury, loss of goblet cells, and rare apoptotic bodies and lymphocytes. Subsequent biopsies **(E–F)** show similar features but also with expansion of the lamina propria by a mixed inflammatory infiltrate. Original magnification ×100 **(C** and **E)** and ×200 **(B** and **F)**.

phase was not identified in 11 (6%) of the abstracts. Nearly half (*n* = 81; 44%) of the abstracts reported trials in progress, an indication that an abundance of PD-1/L1 inhibitor combination data will be forthcoming. The number of trials in early development, in progress, or both, signals that we are still at the beginning of the era of PD-1/L1 inhibitor combination therapy.

Immune-Related Adverse Events with PD-1/L1 Inhibitor Combination Therapy: Challenges and Opportunities

Toxicities associated with PD-1/L1 inhibitor combination therapy come with an additional layer of complexity, as ICI use may magnify or alter the presentation of adverse events typically seen with traditional cancer therapies and may produce challenges in identifying the etiology. As illustrated in the case above, presentations of PD-1/L1 inhibitor–associated colitis in the setting of combination treatment may be atypical. Both the endoscopic appearance and the pathology of the colitis seen in this case did not fall into established patterns, which typically demonstrate colonic edema, erythema, and, in severe cases, superficial ulcerations with pathology showing an acute colitis with prominent epithelial apoptosis. Because presentations may differ from established patterns, maintaining a high level of vigilance for potentially atypical presentations and failure of initial supportive therapy, as well as the ability to provide additional diagnostics to guide second-line therapeutics, are essential for prompt diagnosis and treatment of irAEs in

the setting of PD-1/L1 inhibitor combination therapy. Moreover, this case illustrates the wide morphologic spectrum that may be seen on biopsy in bona fide cases of irAEs, which is increasingly recognized to be broader than that reported in initial case series. Delay or deferral of appropriate diagnostics may lead to inaccurate diagnoses, and empiric therapy may obscure distinctions between true irAEs and non-irAEs. Downstream consequences could include unnecessary use of corticosteroids, which carries the possibility of immunosuppression that may increase the risk of infection and alter wound healing, and/or the delay or even discontinuation of additional courses of potentially life-saving ICI treatment.

A retrospective analysis of patients with melanoma who were treated with the CTLA-4 inhibitor ipilimumab at Massachusetts General Hospital and experienced hypophysitis found that use of higher doses of glucocorticoids to treat this irAE was associated with reduced survival and earlier time to treatment failure [73], and another retrospective analysis of patients with NSCLC treated with PD-1/L1 inhibitors found that corticosteroid use at baseline was associated with inferior outcomes [74]. These contrast with an earlier retrospective study that clearly demonstrated that patients receiving immunotherapy who are treated with corticosteroids can have durable antitumor responses [75]. Although further study is needed, recent reports highlight the potential detrimental effect on anticancer response of high-dose steroids at the onset or during PD-1/L1 inhibitor treatment [73, 74] and thus the need to continue to refine treatment algorithms for irAEs based on available evidence.
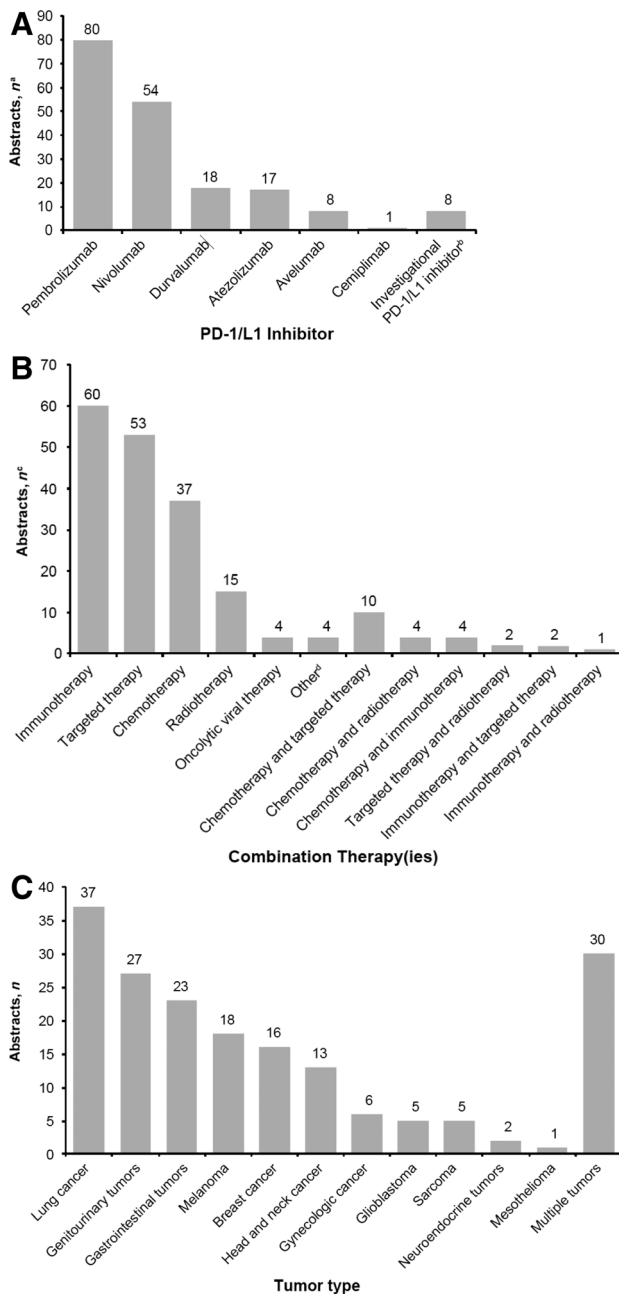
Figure 3. Analyses of programmed death-1 (PD-1) and PD-1 ligand (PD-L1) inhibitor combination trials at American Society of Clinical Oncology 2018. Analysis according to **(A)** PD-1/L1 inhibitor tested, **(B)** type of combination therapy(ies) tested, and **(C)** cancer type.
[a]Some trials had >1 PD-1/L1 inhibitor arm (n = 186).
[b]Investigational PD-1/L1 inhibitors were spartalizumab (n = 2) and BGBA333, CX-072, JS001, M7824, MGA012, and SHR-1210 (n = 1 each).
[c]Some trials had >1 combination agent arm (n = 196).
[d]Other agents were paricalcitol, ADI-PEG 20, metformin, and LTX-315 (n = 1 each).

Similar to the approach used for PD-1/L1 inhibitor monotherapy [50–61], the diagnosis and management of irAEs in patients receiving combination therapy will require an integrated team of oncologists and specialists.

The benefit of combining PD-1/L1 inhibitors with other types of therapies has already been demonstrated with the approvals of nivolumab plus ipilimumab for melanoma, RCC, and colorectal cancer [22, 28, 47]; the approval of pembrolizumab plus chemotherapy for NSCLC [4, 5]; and the approvals of pembrolizumab [19] or avelumab [43] plus axitinib for advanced RCC. Our review of the 2018 ASCO abstracts, as well as analyses of clinical trials [67, 69], point to a likely rapid transition to combination therapy for additional cancers. Current management approaches for irAEs rely heavily on empiric treatment, with diagnostic testing typically playing a role only in the most severe clinical scenarios. It is critical that action is taken now to gather and evaluate information on irAEs in the context of PD-1/L1 inhibitor combination therapy and to update guidelines for diagnosis and management accordingly in order to circumvent incorrect diagnoses, which may limit the use of these promising treatments, and empirical administration of steroids, which may diminish anticancer efficacy [73, 74].

The large quantity of PD-1/L1 inhibitor combination data on the horizon will provide an opportunity to gain valuable insights into the management of irAEs. A collaborative approach involving academia, industry, and regulatory agencies will enable the formulation of appropriate irAE definitions and reporting, biomarker development, and monitoring and management algorithms. Moreover, this advanced strategy may aid in the selection of the most appropriate immunotherapy treatment for individual patients, in terms of possible toxicity and predicted outcomes.

AUTHOR CONTRIBUTIONS

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