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Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies

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Immune checkpoint antibodies that augment the programmed cell death protein 1 (PD-1)/PD-L1 pathway have demonstrated antitumor activity across multiple malignancies, and gained recent regulatory approval as single-agent therapy for the treatment of metastatic malignant melanoma and nonsmall-cell lung cancer. Knowledge of toxicities associated with PD-1/PD-L1 blockade, as well as effective management algorithms for these toxicities, is pivotal in order to optimize clinical efficacy and safety. In this article, we review selected published and presented clinical studies investigating single-agent anti-PD-1/PD-L1 therapy and trials of combination approaches with other standard anticancer therapies, in multiple tumor types. We summarize the key adverse events reported in these studies and their management algorithms.

Key words: immune checkpoint antibody, anti-PD-1, anti-PD-L1, toxicity, adverse event

introduction

Recent regulatory approvals for the anti-programmed cell death protein 1 (PD-1) immune checkpoint monoclonal antibodies (mAbs) nivolumab (BMS-936558) and pembrolizumab (MK-3475, previously lambrolizumab) for metastatic melanoma, and nivolumab for squamous nonsmall-cell lung carcinoma (NSCLC) serve to reinforce that immune-modulating mAbs have joined the list of standard and effective anticancer agents [1–4]. These agents, together with pidilizumab, and two anti-PD-L1 mAbs durvalumab (MEDI4736) and atezolizumab (MPDL3280A) that target the PD-1 ligand PD-L1, have demonstrated antitumor activity in a number of tumor types, including: renal cell carcinoma (RCC) [5], urothelial carcinoma [6], Hodgkin's lymphoma [7], hepatocellular carcinoma (HCC) [8], head and neck carcinoma [9], and mismatch-repair-deficient colorectal cancer (CRC) [10]. These advances create a new set of challenges for clinicians, who must develop a working knowledge of the mode of action of these agents, their unique response kinetics, and importantly how to diagnose and effectively manage their toxicities.

Immune checkpoints are molecules involved in the maintenance of immunologic homeostasis and therefore help to maintain peripheral tolerance to self-molecules. Immune tolerance is critical in preventing excessive autoimmunity throughout life. Generally, tolerance is created through central tolerance in the thymus (during T-cell development) and peripheral tolerance (when self-antigens are encountered outside the thymus) [11]. A number of immune checkpoint molecules exist that may serve to either augment or inhibit an immune response. These include co-inhibitory molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, lymphocyte-activation gene 3, and T-cell immunoglobulin mucin-3, and co-stimulatory molecules such as: glucocorticoid-induced tumor necrosis factor receptor and OX40 (CD134, TNFRSF4, tumor necrosis factor receptor superfamily member 4). Tumor cells can escape from immune system destruction through many mechanisms, including the expression of immune suppressive molecules on their cell surface, secretion of soluble suppressive factors, and the recruitment of other suppressive immune cell populations to the tumor microenvironment [12]. The use of mAbs that block co-inhibitory immune checkpoint molecules, such as CTLA-4 and PD-1, may serve to increase a baseline T-cell-specific immune response that turns the immune system against the tumor [13]. However, a disruption in the functioning of immune checkpoint molecules can lead to imbalances in immunologic tolerance that result in an unchecked immune response. This may clinically manifest with autoimmune-like/inflammatory side-effects, which cause collateral damage to normal organ systems and tissues, including: the skin, gastrointestinal, hepatic, pulmonary, mucocutaneous, and endocrine systems [14]. Such adverse events, termed 'immune-related adverse events' (irAEs), have been the subject of much clinical interest and mechanistic research, and are also thought to be principally T-cell

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mediated [15]. Other immune cells may play a role in the development of irAEs, including B cells that secrete antibodies that may mediate toxicity [16, 17], granulocytes that secrete inflammatory mediators, and cytokines [16, 18]. Standard treatment algorithms for irAEs have been developed that utilize immune-modulating medications including corticosteroids, antihistamines, antitumor necrosis factor medications and calcineurin inhibitors, which may quell the inflammatory response, without eliminating the antitumor immune response [19].

In general, toxicities with anti-PD-1/PD-L1 mAbs appear to be less common and less severe when compared with anti-CTLA-4 mAbs, with reported grade 3–4 AEs ranging from 7% to 12% in patients receiving single-agent anti-PD-1/PD-L1 mAb [1–3], as opposed to 10%–18% of patients who receive single-agent anti-CTLA-4 mAb, in phase III studies [15, 20, 21]. In this review, we summarize the most commonly observed treatment-related irAEs associated with mAbs that target the PD-1/PD-L1 pathway from both single-agent and combination studies with standard anticancer agents, including: other immunotherapeutic agents, chemotherapy, targeted therapy, antiangiogenic agents, and radiation therapy (RT).

general adverse events of anti-PD-1/PD-L1 therapy

fatigue

The most common AE across studies incorporating anti-PD-1/PD-L1 agents is fatigue (Tables 1 and 2). In the first phase I studies published in 2012 of nivolumab and anti-PD-L1 mAb BMS-936559, 16%–24% of patients had treatment-related fatigue, and 1%–2% of these events were grade 3/4 in severity [22, 26]. Fatigue is consistently reported across single-agent studies, with an incidence of 16%–37% with anti-PD-1 agents [3, 25] and 12%–24% with anti-PD-L1 agents from selected studies [6, 33]. Clinical studies that combine anti-PD-1/PD-L1 agents with other immune checkpoint antibodies [23, 34–37], chemotherapy [39, 45], antiangiogenic agents [44–46], and targeted therapies [40–43] have reported slightly higher reported rates of fatigue, ranging from 21% to 71% (Table 2). Fatigue that occurs with other immunotherapeutic agents such as type I interferon therapy [47] may induce fatigue in association with other systemic symptoms such as influenza-like illness, suggestive of cytokine release [15]. In the case of anti-PD-1/PD-L1 agents, fatigue is usually mild and not associated with other systemic symptoms. A specific mechanism by which immune checkpoint antibodies may cause fatigue is currently not known, but this does not appear to be dose-related. A proportion of the patients with treatment-related fatigue may be presenting with early symptoms of hypothyroidism, a known endocrinopathy associated with immune checkpoint blockade therapy (see endocrine toxicities section).

pyrexia, chills, infusion reactions

Fever, chills, and infusion reactions have been described across multiple modalities of immunotherapeutic anticancer agents, including cancer vaccines, adoptive T-cell therapy, chimeric antigen receptor T cells, cytokines, and immune-modulating antibodies [15]. The mechanism underlying the development of these toxicities is postulated to be due to cytokine release and nonspecific activation of an immune response [48]. Fevers and chills may be managed supportively with antipyretics such as acetaminophen or nonsteroidal anti-inflammatory drugs at the time of development of the toxicity, and to prevent the recurrence of infusion reactions, as needed [48]. In cases of grade 3 infusion reactions, patients may also receive antihistamines and corticosteroid medications intravenously at the time of the hypersensitivity reaction as required, in line with prior experience with ipilimumab [49]. Infusion reactions with agents that target the PD-1/PD-L1 pathway are very rare, accounting for <1% of AEs in phase III studies [1–3, 36].

organ-specific adverse events with single-agent anti-PD-1/PD-L1 agents

dermatologic toxicities

Skin rash is the most common irAE associated with immune checkpoint mAb therapy, and typically occurs after the second cycle in the patient's clinical course [14, 15]. A variety of clinical presentations of rash can manifest including: maculopapular, papulopustular, Sweet's syndrome, follicular, or urticarial dermatitis. In a pooled safety analysis of melanoma patients with dermatological AEs such as rash, pruritus, and vitiligo, toxicities were observed in 34% of patients who received nivolumab [50], and 39% of patients who received pembrolizumab [2]. Of note, a direct comparison of pembrolizumab with ipilimumab in the latter study demonstrated a higher incidence of vitiligo of ~10% in pembrolizumab-treated patients versus 2% in ipilimumab-treated patients [2].

With anti-PD-1/PD-L1 mAb, a maculopapular rash is most commonly observed. However, rarer rashes have been described, including lichenoid (e.g. lichenoid dermatitis) [51], and bullous disorders including bullous pemphigoid [52] (correspondence with J. Naidoo et al.), Stevens Johnson syndrome, and toxic epidermal necrolysis [14], which are of special interest due to their severity and potentially life-threatening consequences. It has been postulated in some cases that the underlying mechanism for the development of this toxicity may be due to the effect of blockade of a common antigen, co-expressed on a patient's tumor cells, and those of the dermo-epidermal junction and/or other levels of the skin [53]. Infrequently, cases involving the oral mucosa may be seen with the development of oral lichenoid mucositis (correspondence with M. E. Lacouture et al.). Additional reported mucosal toxicities include: oral mucositis, gingivitis, and sicca syndrome-like symptoms, which can be managed with supportive care.

The prototypical maculopapular rash seen with anti-PD-1/PD-L1 mAb may be managed successfully with topical or oral corticosteroids, depending on severity, along with oral antipruritic agents (e.g. antihistamines, GABA agonists, NK-1 receptor inhibitors, antidepressants) in patients with pruritus. Early dermatologic evaluation is recommended for any atypical rashes, those that do not improve after interventions, involvement of the oral mucosa, or in patients with grade 3 events. Standard dermatologic evaluation usually involves a clinical assessment with or without a skin biopsy, and laboratory evaluation of kidney and liver function, as well as serum levels of tryptase and immunoglobulin E. Histologic evaluation often reveals an interface, perivascular, and periadnexal lymphocytic dermatitis, with few plasma cells

Table 1. Adverse events in selected single-agent studies with ant-PD-1/PD-L1 antibodies

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
Anti-PD-1 agent							
Nivolumab	Topalian (2012) [22]	I	NSCLC; RCC; CRC; CRPC; melanoma	296	0.1–10 mg/kg every 2 weeks for up to 2 years	Total: 70% (*n* = 207) Fatigue (24%, *n* = 72) Rash (12%, *n* = 36) Pruritus (10%, *n* = 28) Pneumonitis (9%, *n* = 3) Infusion reaction (9%, *n* = 3) Hypothyroidism (2%, *n* = 7)	Total: 7% (*n* = 22) Hypothyroidism (<1%, *n* = 1) Pneumonitis (1%, *n* = 3) Diarrhea (1%, *n* = 3) AST elevation (1%, *n* = 2) ALT elevation (1%, *n* = 2) Rash (1%, *n* = 2) Infusion reaction (<1%, *n* = 1)
	Ansell (2015) [7]	I	Hodgkin's lymphoma	23	3 mg/kg every 2 weeks	Total: 78% (*n* = 18) Rash (22%, *n* = 5) Thrombocytopenia (17%, *n* = 4) Fatigue (13%, *n* = 3) Pyrexia (13%, *n* = 3)	Total: 22% (*n* = 5) Lipase elevation (4%, *n* = 1) Lymphopenia (4%, *n* = 1) MDS[a] (4%, *n* = 1) Pancreatitis (4%, *n* = 1)
	Motzer (2014) [5]	II	RCC	168	0.3, 2, or 10 mg/kg every 2 weeks	Total: 73% (*n* = 122) Fatigue (27%, *n* = 45) Rash (10%, *n* = 17) Pruritus (10%, *n* = 16) Hypothyroidism (12%, *n* = 10) AST elevation (5%, *n* = 8) ALT elevation (4%, *n* = 7) Pneumonitis (3%, *n* = 5)	Total: 11% (*n* = 19) AST elevation (2%, *n* = 3) ALT elevation (2%, *n* = 3) Nausea (1%, *n* = 2) Hypothyroidism (<1%, *n* = 1) Pruritus (<1%, *n* = 1) Arthralgia (<1%, *n* = 1)
	Sampson (2014) [23]	I	GBM	20 (*n* = 10 single-agent arm)	Single-agent arm: 3 mg/kg every 2 weeks	Total: 60% (*n* = 6) Fatigue (30%, *n* = 3) Nausea (30%, *n* = 3)	Total: 0%
	El-Khoueiry (2015) [8]	I/II	HCC	47	0.1–10 mg/kg every 2 weeks	Total = 68% (*n* = 32) AST elevation (19%, *n* = 9) Lipase elevation (17%, *n* = 8) Rash (17%, *n* = 8) Amylase elevation (15%, *n* = 7) ALT elevation (15%, *n* = 7)	Total = 19% (*n* = 9) AST elevation (11%, *n* = 5) ALT elevation (9%, *n* = 4) Lipase elevation (9%, *n* = 4) Fatigue (2%, *n* = 1) Anemia (2%, *n* = 1)
	Gettinger (2015) [24]	I	NSCLC	129	1, 3, or 10 mg/kg every 2 weeks	Total = 71% (*n* = 91) Fatigue (24%, *n* = 31) Decreased appetite (12%, *n* = 16) Diarrhea (10%, *n* = 13) Pyrexia (6%, *n* = 8) Pruritus (9%, *n* = 11) Pneumonitis (6%, *n* = 8)	Total = 14% (*n* = 18) Fatigue (3%, *n* = 4) Pneumonitis (2%, *n* = 3) Low CD-4 cells (2%, *n* = 3) Diarrhea (<1%, *n* = 1)

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Table 1. *Continued*

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
	Rizvi (2015) [25]	II	NSCLC (squamous)	117	3 mg/kg every 2 weeks	Total = 74% (*n* = 87) Fatigue (33%, *n* = 38) Diarrhea (10%, *n* = 12) Rash (11%, *n* = 13) Pneumonitis (5%, *n* = 6)	Total = 17% (*n* = 20) Fatigue (4%, *n* = 5) Diarrhea (3%, *n* = 3) Rash (1%, *n* = 1) Pneumonitis (3%, *n* = 4)
	Weber (2015) [1]	III	Ipilimumab-refractory melanoma	272	3 mg/kg every 2 weeks versus chemotherapy	Total = 67% (*n* = 181) Fatigue (25%, *n* = 67) Pruritus (16%, *n* = 43) Diarrhea (11%, *n* = 30) Nausea (9%, *n* = 25)	Total = 9% (*n* = 24) Lipase elevation (1%, *n* = 3) ALT elevation (1%, *n* = 2) Anemia (1%, *n* = 2) Fatigue (1%, *n* = 2)
	Brahmer [3]	III	NSCLC (squamous)	131	3 mg/kg every 2 weeks versus docetaxel	Total = 58% (*n* = 76) Fatigue (16%, *n* = 21) Low appetite (14%, *n* = 11) Asthenia (10%, *n* = 13) Diarrhea (8% *n* = 10) Pneumonitis (5%, *n* = 6) Hypothyroidism (4%, *n* = 5)	Total = 7% (*n* = 9) Fatigue (<1%, *n* = 1) Low appetite (<1%, *n* = 1) Leucopenia (<1%, *n* = 1) Pneumonitis (<1%, *n* = 1) Colitis (<1%, *n* = 1) Interstitial nephritis (<1%, *n* = 1)
BMS-39886	Brahmer [26]	I	NSCLC; RCC; CRC; melanoma	207	0.3–10 mg/kg every 2 weeks	Total = 61% (*n* = 126)[b] Fatigue (16%, *n* = 33) Infusion reaction (10%, *n* = 21) Diarrhea (9%, *n* = 19) Rash (9%, *n* = 14) Hypothyroidism (3%, *n* = 6) Adrenal insufficiency (2%, *n* = 3)	Total = 5% (*n* = 11) Endocrine (1%, *n* = 2) Fatigue (<1%, *n* = 1) Pyrexia = 1 (<1%, *n* = 1) Diarrhea = 1 (<1%, *n* = 1) Myocarditis = 1 (<1%, *n* = 1) Sarcoidosis = 1 (<1%, *n* = 1)
Pembrolizumab	Hamid (2012) [27]	I	Melanoma	135	2 mg/kg every 3 weeks, or 10 mg/kg every 2 or 3 weeks	Total = 79% (*n* = 107) Fatigue (30%, *n* = 41) Rash (21%, *n* = 28) Pruritus (21%, *n* = 28) Diarrhea (20%, *n* = 27)	Total = 13% (*n* = 17) Rash (2%, *n* = 3) Acute renal failure (1%, *n* = 2) AST elevation (1%, *n* = 2) Fatigue (1%, *n* = 2)
	Le (2015) [10]	I	Metastatic carcinoma with or without mismatch repair deficiency	41	10 mg/kg every 2 weeks	Total = 98% (*n* = 40) Fatigue (32%, *n* = 13) Diarrhea (24%, *n* = 10) Rash/pruritus (24%, *n* = 10) Hypophysitis/thyroiditis/ hypothyroidism (10%, *n* = 6) Pancreatitis (15%, *n* = 4)	Total = 41% (*n* = 17) Lymphopenia (20%, *n* = 8) Hypoalbuminemia (10%, *n* = 4) Anemia (17%, *n* = 7)

	Robert (2014) [28]	I	Ipilimumab-refractory melanoma	173	2 or 10 mg/kg every 3 weeks	Total = 82% (n = 142) Fatigue (35%, n = 60) Pruritus (23%, n = 39) Rash (18%, n = 31) Diarrhea (13%, n = 22) Pneumonitis (2%, n = 3) Autoimmune hepatitis (<1%, n = 1) Hypothyroidism (4%, n = 7)	Total = 12% (n = 20) Fatigue (3%, n = 5) Diarrhea (<1%, n = 1) Pneumonitis (<1%, n = 1) Hypophysitis (<1%, n = 1) Autoimmune hepatitis (<1%, n = 1)
	Ribas (2015) [29]	II	Melanoma	357	2 or 10 mg/kg every 3 weeks versus standard chemotherapy	Total = 71% (n = 252) Fatigue (26%, n = 92) Pruritus (22%, n = 79) Rash (8%, n = 29) Hypothyroidism (6% n = 22) Pneumonitis (1%, n = 3)	Total = 13% (n = 45) Fatigue (<1%, n = 2) Myalgia (<1%, n = 2) Edema (<1%, n = 2) Colitis (<1%, n = 2) Hypophysitis (<1%, n = 2) Pneumonitis (<1%, n = 2)
	Robert (2015) [2]	III	Untreated melanoma	556	10 mg/kg every 2 or 3 weeks versus ipilimumab	Total = 76% (n = 423) Fatigue (20%, n = 111) Pruritus (14%, n = 79) Rash (14%, n = 77) Hypothyroidism (9%, n = 52) Hyperthyroidism (5%, n = 27) Colitis (3%, n = 15) Hepatitis (1%, n = 8) Pneumonitis (1%, n = 6) Uveitis (<0.1%, n = 4)	Total = 12% (n = 65) Colitis (2%, n = 11) Diarrhea (n = 10) Hepatitis (n = 8) Hypophysitis (n = 2) Pneumonitis (n = 1) Type 1 diabetes (n = 1)
	Garon (2015) [4]	I	NSCLC	495	2 or 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks	Total = 71% (n = 351) Fatigue (19%, n = 96) Pruritus (11%, n = 53) Low appetite (11%, n = 52) Rash (10%, n = 48) Infusion reaction (3%, n = 15) Hypothyroidism (7%, n = 34) Pneumonitis (4%, n = 18)	Total = 10% (n = 47) Dyspnea (4%, n = 19) Pneumonitis (2%, n = 9) Low appetite (1%, n = 5) Fatigue (<1%, n = 4) Infusion reaction (<1%, n = 1)
Pidilizumab	Armand (2013) [30]	II	Lymphoma[c]	72	1.5 mg/kg every 42 days × 3 doses	Total = 96% (n = 69) Neutropenia (26%, n = 19) Fatigue (25%, n = 18) Respiratory infection (19%, n = 14) Diarrhea (17%, n = 12) Thrombocytopenia (14%, n = 10)	Total = 54% (n = 39) Neutropenia (19%, n = 14) Thrombocytopenia (8%, n = 6)

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Table 1. *Continued*

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
Anti-PD-L1 agent							
Durvalumab	Segal [31]	I	Multiple solid tumors[a]	346	10 mg/kg every 2 weeks × 1 year	Total = 39% (*n* = 135) Fatigue (13%, *n* = 45) Rash (9%, *n* = 30) Pneumonitis (1%, *n* = 5) AST/ALT elevation (4%, *n* = 13) Hypothyroidism (2%, *n* = 8)	Total = 6% (*n* = 20) Fatigue (1%, *n* = 2) Rash (<1%, *n* = 1) AST/ALT elevation (1%, *n* = 3) Hypothyroidism (<1%, *n* = 1)
	Rizvi (2015) [32]	I	NSCLC	228	10 mg/kg every 2 weeks × 1 year	Total = 93% (*n* = 213) Fatigue = 18% Low appetite = 9% Nausea = 8% Hyperthyroidism (4%, *n* = 9) Diarrhea (7%, *n* = 15) Rash (8%, *n* = 17) Pneumonitis (1%, *n* = 3)	Total = 53% (*n* = 121) Diarrhea (<1%, *n* = 1) Rash (0%, *n* = 0) Hyperthyroidism (<1%, *n* = 1)
Atezolizumab	Herbst (2014) [33]	I	Multiple solid tumors + hematologic malignancies	277	0.01–20 mg/kg every 3 weeks	Total = 70% (*n* = 194) Fatigue (24%, *n* = 67) Low appetite (12%, *n* = 33) Rash (11%, *n* = 29) Influenza-like illness (6%, *n* = 16) AST/ALT elevation (4%, *n* = 10) Tumor lysis syndrome (<1%, *n* = 2)	Total = 13% (*n* = 35) Fatigue (2%, *n* = 5) Low appetite (0%, *n* = 0) Rash (0%, *n* = 0) Influenza-like illness (<1%, *n* = 1) AST/ALT elevation (2%, *n* = 6) Tumor lysis syndrome (<1%, *n* = 2)
	Powles (2014) [6]	I	Urothelial carcinoma	68	15 mg/kg every 3 weeks × 1 year	Total = 57% (*n* = 39) Low appetite (12%, *n* = 8) Fatigue (12%, *n* = 8) Pyrexia (12%, *n* = 8) Influenza-like illness (4%, *n* = 3) Thrombocytopenia (3%, *n* = 2)	Total = 4% (*n* = 3) Asthenia (1.5%, *n* = 1) Thrombocytopenia (1.5%, *n* = 1) Phosphorus elevation (1.5%, *n* = 1)

[a]MDS, myelodysplastic syndrome.
[b]Investigator-reported adverse events.
[c]Included patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed indolent B-cell lymphoma
NSCLC, nonsmall-cell lung cancer; RCC, renal cell carcinoma; CRC, colorectal carcinoma; CRPC, castration-resistant prostate cancer; HCC, hepatocellular carcinoma; GBM, glioblastoma multiforme.

Table 2. Incidence of adverse events in combination studies with ant-PD-1/PD-L1 antibodies and other therapies, across multiple solid tumors

Agent	Author(s)	Phase	Tumor type	Total patients (*N*)	Treatment schedule	Treatment-related toxicities (grade 1–5)	Grade 3–4 treatment-related toxicities
Immune checkpoint antibodies							
Nivolumab + ipilimumab	Wolchok et al. [34]	I	Melanoma	86 (*n* = 53 concurrent, *n* = 33 sequenced)	Concurrent (N: 0.3–10 mg/kg every 3 weeks) + I (1–10 mg/kg every 3 weeks) then N + I every 3 months × 8	Total = 93% (*n* = 49)[a] Rash (55%, *n* = 29) Pruritus (47%, *n* = 25) Fatigue (38%, *n* = 20) Diarrhea (34%, *n* = 18) Colitis (9%, *n* = 5) AST elevation (23%, *n* = 12) ALT elevation (21%, *n* = 11)	Total = 53%[a] (*n* = 28)[b] Elevated lipase (13%, *n* = 7) AST elevation (13%, *n* = 7) ALT elevation (11%, *n* = 6) Diarrhea (6%, *n* = 3) Colitis (4%, *n* = 2) Rash (4%, *n* = 2)
	Postow et al. [35]	II	Melanoma	142 (*n* = 95 combination arm, *n* = 47 I-alone arm)	N (1 mg/kg every 3 weeks × 4, followed by 3 mg/kg every 2 weeks till progression/ toxicity) + I (3 mg/kg every 3 weeks × 4)	Total = 91% (*n* = 86) Diarrhea (45%, *n* = 42) Rash (41%, *n* = 39) Colitis (23%, *n* = 22) AST elevation (22%, *n* = 21) ALT elevation (21%, *n* = 20) Hypothyroidism (16%, *n* = 15) Hypophysitis (12%, *n* = 11)	Total = 54% (*n* = 51)[b] Colitis (17%, *n* =) Diarrhea (11%, *n* =) AST elevation (11%, *n* = 10) ALT elevation (7%, *n* = 7) Hypophysitis (7%, *n* = 3) Pneumonitis (2%, *n* = 2)
	Larkin et al. [36]	III	Melanoma	945 (N only = 316, N + I = 314, I alone = 315)	N (3 mg/kg every 3 weeks) versus I (3 mg/kg every 3 weeks × 4) versus N + I (N: 1 mg/kg × 4 doses + I then N: 3 mg/kg every 3 weeks × 4, or 3 mg/kg from cycle 3 on every 2 weeks)	Total = 96% (*n* = 299) Diarrhea (44%, *n* = 138) Fatigue (35%, *n* = 110) Pruritus (33%, *n* = 104) Rash (40%, *n* = 126) AST elevation (15%, *n* = 45) ALT elevation (18%, *n* = 55) Hypothyroidism (15%, *n* = 47) Colitis (12%, *n* = 37)	Total = 55% (*n* = 172) Diarrhea (9%, *n* = 29) Fatigue (4%, *n* = 13) Pruritus (2%, *n* = 6) Rash (5%, *n* = 15) AST elevation (6%, *n* = 19) ALT elevation (8%, *n* = 26) Hypothyroidism (<1%, *n* = 1) Colitis (8%, *n* = 24)
	Sampson et al. [23]	I	Glioblastoma multiforme	20 (*n* = 10 combination arm)	Combination arm: N (1 mg/ kg) + I (3 mg/kg every 3 weeks) followed by N (3 mg/kg every 2 weeks)	Total = 100% Fatigue (40%, *n* = 8) Diarrhea (35%, *n* = 7) AST elevation (25%, *n* = 5) High lipase (25%, *n* = 5) Vomiting (20%, *n* = 4) ALT elevation (20%, *n* = 4)	Total = 70% (*n* = 7) Colitis (10%, *n* = 2) Hypothyroidism (10%, *n* = 2) Diarrhea (10%, *n* = 2) ALT elevation (10%, *n* = 2) Cholecystitis (5%, *n* = 1) Diabetic ketoacidosis (5%, *n* = 1) Elevated lipase (5%, *n* = 1)

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Table 2. *Continued*

Agent	Author(s)	Phase	Tumor type	Total patients (*N*)	Treatment schedule	Treatment-related toxicities (grade 1–5)	Grade 3–4 treatment-related toxicities
Pembrolizumab + ipilimumab	Patnaik et al. [37]	I	NSCLC	18	P (2 or 10 mg/kg every 3 weeks) + I (1 or 3 mg/kg every 3 weeks × 4) + maintenance P	Total = 83% (*n* = 15) Fatigue (33%, *n* = 4) Low appetite (17%, *n* = 2) Pruritus (17%, *n* = 2) Rash (17%, *n* = 2) Myasthenia gravis (6%, *n* = 1) Myocarditis (6%, *n* = 1) Pneumonitis (6%, *n* = 1) Uveitis (6%, *n* = 1)	Total = 17% (*n* = 3) Rash (17%, *n* = 2) Adrenal insufficiency (6%, *n* = 1)
MEDI4736 + tremelimumab	Antonia et al. [38]	Ib	NSCLC	102	M (3–20 mg/kg every 4 weeks or 10 mg/kg every 2 weeks) + T (1–3 mg/kg every 2 or 4 weeks × 6 doses) for 1 year	Total = 93% (*n* = 95) Diarrhea (27%, *n* = 28) Fatigue (26%, *n* = 27) Colitis (12%, *n* = 12) ALT elevation (10%, *n* = 10) AST elevation (6%, *n* = 6) Hypothyroidism (6%, *n* = 6) Pneumonitis (5%, *n* = 5)	Total = 61% (*n* = 60) Diarrhea (8%, *n* = 8) Colitis = (9%, *n* = 9) ALT elevation (3%, *n* = 3) AST elevation (4%, *n* = 4) Myasthenia gravis (*n* = 1) Polymyositis (*n* = 1) Pneumonitis (4%, *n* = 4) Hypothyroidism (1%, *n* = 1)
Chemotherapy							
Nivolumab + platinum-doublet chemotherapy	Antonia et al. [39]	I	NSCLC	56	N (10 mg/kg every 3 weeks or 5 mg/kg every 3 weeks) + chemotherapy × 4) + N alone (10 mg/kg every 3 weeks or 5 mg/kg every 3 weeks)	Total = 93% (*n* = 52) Fatigue (71%, *n* = 40) Nausea (46%, *n* = 26) Low appetite (36%, *n* = 20) Alopecia (30%, *n* = 17) Pneumonitis (13%, *n* = 7)	Total = 45% (*n* = 25) Fatigue (5%, *n* = 3) Anemia (4%, *n* = 2) Rash (4%, *n* = 2) Acute renal failure (5%, *n* = 3) Pneumonitis (7%, *n* = 4)
Targeted therapy							
Durvalumab + AZD9291	Oxnard et al. [40]	Ib	EGFR-mutant T790M-positive NSCLC	14	M (3 or 10 mg/kg every 2 weeks) + A (80 mg daily)	Total: not reported[b] Diarrhea (50%, *n* = 7) Vomiting (50%, *n* = 7) Anemia (45%, *n* = 6) Pneumonitis (21%, *n* = 3)	Total: 1% (*n* = 2)[b] Neutropenia = 2
Durvalumab + gefitinib	Creelan et al. [41]	Ib	NSCLC	10	M (3 or 10 mg/kg every 4 weeks) + G (250 mg daily) × 1 year	Total = 100% (*n* = 10) ALT elevation (50%, *n* = 5) AST elevation (50%, *n* = 5) Diarrhea (50%, *n* = 5)	Total = 30% (*n* = 3) Dyspnea (1%, *n* = 1) Fatigue (1%, *n* = 1) ALT elevation (1%, *n* = 1)

Durvalumab + dabrafenib + trametinib	Ribas et al. [42]	Ib	BRAF-mutant and wild-type melanoma	65	M (3 or 10 mg/kg every 2 weeks) + D (150 mg b.i.d.) + T (2 mg q.d.) or M (10) + T or M (10) + T (× 6 weeks only)	Total = 98% (n = 64) Pyrexia (37%, n = 24) Chills (24%, n = 16) Arthralgia (17%, n = 11) Peripheral edema (17%, n = 11) Folliculitis (18%, n = 12) Pneumonitis (1%, n = 1) AST elevation (12%, n = 8) ALT elevation (10%, n = 7) Low ejection fraction (2%, n = 2)	Total = 46% (n = 30) Pyrexia (2%, n = 2) Chills (3%, n = 1) Peripheral edema (5%, n = 3) AST elevation (8%, n = 2) ALT elevation (4%, n = 1) Low ejection fraction (9%, n = 2) Pneumonitis (0%, n = 0)
Pidilizumab + rituximab	Westin et al. [43]	II	Follicular lymphoma	32	P (3 mg/kg every 4 weeks × 4–12) + R (375 mg/m^2 weekly × 4)	Total = 94% (n = 30) Anemia (47%, n = 14) Fatigue (43%, n = 13) Leucopenia (37%, n = 11)	Total: 0% (n = 0)
Antiangiogenic therapy							
Atezolizumab + bevacizumab	Sznol et al. [44]	Ib	RCC	10	B (15 mg/kg every 3 weeks) + A (20 mg/kg every 3 weeks)	Total: 80% (n = 8) Fatigue (40%, n = 4) Low appetite (30%, n = 3) Diarrhea (30%, n = 3) Arthalgia (20%, n = 2)	Total: 0% (n = 0)
Atezolizumab + bevacizumab	Bendell et al. [45]	Ib	CRC	14 (A + B)	A (20 mg/kg every 3 weeks) + B (15 mg/kg every 3 weeks)	Total = 79% (n = 11) Fatigue (21%, n = 3) Nausea (29% n = 4) Pyrexia (21%, n = 3) Decreased appetite (7%, n = 1)	Total = 7% (n = 1) Neutropenia (7%, n = 1)
Nivolumab + sunitinib or pazopanib	Amin et al. [46]	Ib	RCC	53 (N + S, n = 33, N + P, n = 20)	N (2–5 mg/kg every 3 weeks) + S (50 mg 4 weeks on, 2 weeks off) or P (800 mg daily)	Total: 100% (n = 53) Sunitinib: Fatigue (n = 27) Diarrhea (n = 20) ALT elevation (n = 13) AST elevation (n = 12) Acute renal failure (n = 4) Pneumonitis (n = 2) Pazopanib: Fatigue (n = 12) AST elevation (n = 6) ALT elevation (n = 5)	Total: 77% (n = 41) Sunitinib: ALT elevation (18%, n = 6), AST elevation (9%, n = 3) Autoimmune nephritis (3%, n = 1) Pneumonitis (3%, n = 1) Pazopanib: AST elevation (20%, n = 4) ALT elevation (20%, n = 4) Fatigue (15%, n = 3) Diarrhea (20%, n = 4)

Continued

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Table 2. *Continued*

Agent	Author(s)	Phase	Tumor type	Total patients (*N*)	Treatment schedule	Treatment-related toxicities (grade 1–5)	Grade 3–4 treatment-related toxicities
Antiangiogenic therapy + chemotherapy							
Atezolizumab + bevacizumab + FOLFOX	Bendell et al. [45]	Ib	CRC	30 (A + B + F)	A (14 mg/kg every 2 weeks) + B (10 mg/kg every 2 weeks) + F (standard doses, every 2 weeks)	Total = 100% (n = 30) Fatigue (47%, n = 14) Nausea (27% n = 8) Pyrexia (20%, n = 6) Decreased appetite (20%, n = 6)	Total = 20% (n = 6) Neutropenia (7%, n = 2) AST elevation (7%, n = 2) ALT elevation (3%, n = 1) Diarrhea (3%, n = 1)

[a]Results from concurrent arm only.
[b]All case adverse events.
GBM, glioblastoma multiforme; HNSCC, head and neck squamous cell carcinoma; CRC, colorectal carcinoma; RCC, renal cell carcinoma; EGFR, epidermal growth factor receptor; N, nivolumab, I, ipilimumab; P, pembrolizumab; A, atezolizumab; B, bevacizumab; F, FOLFOX chemotherapy (5-flurouracil bolus and continuous infusion, leucovorin, oxaliplatin).

and eosinophils (correspondence with V. R. Belum et al.). In grade 2 cases with intolerable symptoms, or grade 3 cases, immune checkpoint blockade may be temporarily held until toxicities are grade ≤1 in severity. Permanent discontinuation of therapy due to dermatologic toxicity has been reported in <5% of patients in clinical studies [14]. An algorithm for diagnosis and treatment of checkpoint mAB-induced dermatologic AEs is provided in Figure 1.

diarrhea/colitis

Diarrhea and colitis lie along a clinical spectrum where diarrhea is defined as increased stool frequency, and colitis involves symptoms of abdominal pain and either clinical or radiologic evidence of colonic inflammation [14]. Diarrhea/colitis with CTLA-4 blockade treatment usually occurs 6–8 weeks after commencement of therapy [15], with an incidence of grade 3/4 colitis of ~5% in late phase studies with these agents [21, 54], and 1%–3% in reported studies of anti-PD-1/PD-L1 mAb alone [2, 3, 27, 29, 33]. Pathologic features of ipilimumab-related colitis include both neutrophilic and lymphocytic infiltrates [55], while biopsy-proven colitis with anti-PD-1/PD-L1 therapy has not yet been reported. Mild or grade 1 colitis can be managed with the American Dietary Association's colitis diet and antidiarrheal medications including atropine and oral diphenoxylate hydrochloride [14]. Worsening or persistent diarrhea for more than 3 days should prompt early investigations to rule out an infectious cause, withholding of the anti-CTLA-4 mAb, antidiarrheal medications, intervention with oral corticosteroids, as well as endoscopic or radiologic evaluation to confirm the diagnosis. In clinically severe cases or those that do not respond to the above interventions, patients may be admitted to hospital for intravenous corticosteroids (methylprednisolone 1–2 mg/kg total daily dose) and additional immunosuppression with anti-TNF medicines, such as infliximab, which is administered at a dose of 5 mg/kg [56–58]. Infliximab is typically recommended if intravenous corticosteroids are not effective within approximately the first 3 days, and can be repeated 2 weeks after the initial dose if symptoms persist. The cornerstone of effective colitis management is early intervention, as colitis-related mortality is associated with delayed reporting, noncompliance with an antidiarrheal regimen, and lack of drug withholding [59]. A randomized study of prophylactic budesonide in patients with melanoma treated with ipilimumab did not demonstrate a reduction in the incidence of diarrhea, and is not recommended for use to prevent diarrhea [60]. However, some patients report symptomatic benefit from using budesonide to treat mild diarrhea.

endocrine toxicities

Immune-related toxicities affecting the endocrine glands have been widely described with anti-CTLA-4 mAb, and now to a lesser extent, anti-PD-1/PD-L1 therapy [61, 62]. Typical endocrine irAEs seen with anti-CTLA-4 mAb include: hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency. Establishing a diagnosis of endocrine dysfunction can be clinically challenging, as these AEs may manifest with nonspecific symptoms such as fatigue and headache. Hypophysitis is diagnosed by biochemical testing of the pituitary-hypothalamic (prolactin), pituitary–thyroid (T4, TSH), pituitary–gonadal axes (LH, FSH), and

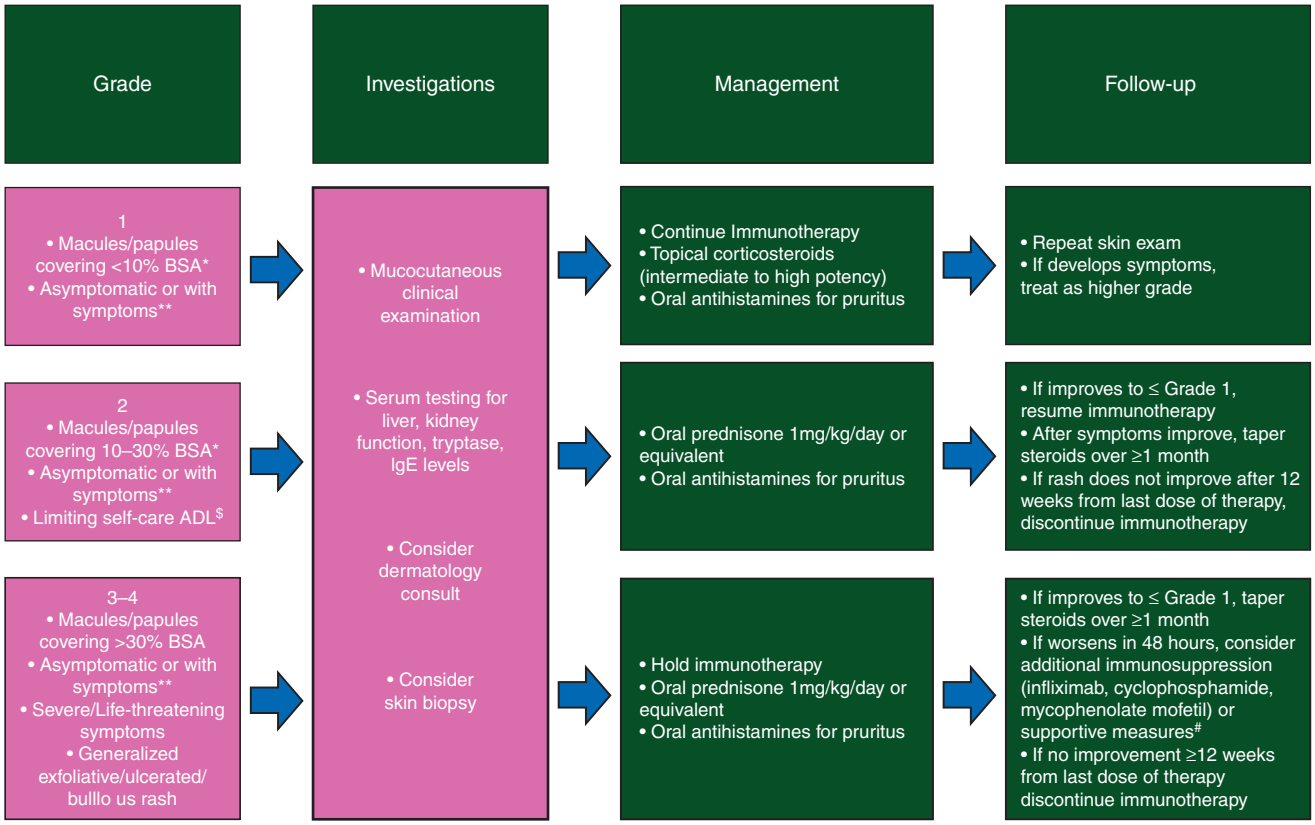

Figure 1. Adapted management algorithm for skin rash with immune checkpoint blockade. *BSA, body surface area, **Symptoms as per CTCAE version 4.0. For example: pruritus, burning and skin tightness. $Additional supportive measures: this denotes the use of, for example, prophylatic antibiotics and management in the burns unit.

pituitary–adrenal axes (ACTH, cortisol), as well as radiologic evidence of pituitary inflammation in selected cases [14]. The incidence of hypophysitis with single-agent anti-PD-1/PD-L1 mAb therapy ranges from 1% to 6% (Table 1) and 2% to 10% in selected combination studies (Table 2). Recovery of endocrine function for the gonadal axis has been reported in 57% of men [63], and recovery of the thyroid axis in 37%–50% of cases in selected studies [64–66]. Primary adrenocortical insufficiency is treated with glucocorticoid replacement, which may be life-long. In rare cases, patients may present with an adrenal crisis that requires hospitalization, endocrinology consultation, intravenous corticosteroid replacement, and aggressive fluid and electrolyte replacement. The immunologic mechanism underlying the development of hypophysitis is postulated to be due to humoral immunity against the pituitary gland, with involvement of the complement system [17].

Thyroid dysfunction associated with anti-CTLA-4 mAb occurs typically after two to four infusions, may be transient, but in many cases may be permanent [67]. The timing of onset with anti-PD-1/PD-L1 mAb has not been formally reported. Mechanisms underlying the development of this AE are not fully understood, but may be due to the development of antithyroglobulin or antithyroid peroxidase antibodies [66]. In rare cases, Grave's disease may arise due to the development of anti-TSH-receptor antibodies [68]; however, antibodies do not develop in all cases [61]. Hypothyrodisim is managed with thyroid hormone replacement, and hyperthyroidism is managed with standard antithyroid pharmacotherapy. In cases of thyroiditis, patients may develop initial hyperthyroidism that can be treated with β-blockers in symptomatic cases, followed by hypothyroidism that develops later, and usually requires thyroid hormone replacement [62]. As most endocrinopathies can be treated successfully with hormone replacement, immune checkpoint therapy is not usually discontinued.

hepatic toxicities

Hepatic AEs with immune checkpoint blockade consist mainly of asymptomatic elevations in AST and ALT levels [14]. Anti-CTLA-4 mAbs are associated with elevated AST and ALT levels in 10% of patients or less [20, 21, 54, 69]. With anti-PD-1/PD-L1 mAb, this is 5% or less in reported studies, with grade 3/4 events occurring in 1%–2% of patients [31, 33]. Interestingly, higher rates of AST/ALT elevation of ~20% have been reported with single-agent anti-PD-1 therapy in HCC [8], with the anti-PD-1 and anti-CTLA-4 mAb combination [34], or when anti-CTLA-4 mAb were combined with targeted therapy or chemotherapy [70, 71]. In addition, nivolumab combined with either sunitinib or pazopanib was associated with 9%–20% grade 3/4 AST/ALT elevations in metastatic RCC [46]. Pathologic appearances of immune checkpoint-induced hepatitis with ipilimumab have been reported, with panlobular hepatitis, perivenular infiltrates, or infiltrates surrounding the primary biliary ducts [72]. Radiologic appearances include hepatomegaly, periportal edema, and periportal lymphadenopathy [73]. Hepatitis with anti-CTLA-4 therapy occurs approximately at 8–12 weeks after starting therapy [15]; however, this has not been

reported in the context of anti-PD-1/PD-L1 therapy. An algorithm for the diagnostic investigations and management of suspected immune-related hepatitis adapted from guidelines used across anti-PD-1/PD-L1 studies is depicted in Figure 2. Treatment for immune-related hepatitis involves a corticosteroid taper for a minimum of 3 weeks [14], and occasionally additional immune suppression with mycophenolate mofetil 500–1000 mg b.i.d. or antithymocyte globulin, which has been used successfully in one case [74]. Infliximab should not be used for hepatitis as it confers its own risk of hepatotoxicity.

pneumonitis

Pneumonitis is broadly defined as inflammation of the lung parenchyma, and has been described in <10% of patients receiving anti-PD-1/PD-L1 therapy either alone or in combination, and appears to occur more commonly in patients with lung cancer [3, 4, 24, 32] (Tables 1 and 2). This toxicity led to three treatment-related deaths in an early phase study of nivolumab [22]. Interestingly, this AE was not described in major studies of anti-CTLA-4 mAb alone, where pulmonary toxicities such as sarcoid-like granulomatous reactions [75] and obstructive pneumonia were reported [76]. The incidence of pneumonitis may be higher in studies where anti-PD-1/PD-L1 mAb are combined with other agents also known to carry a risk of pneumonitis, such as standard chemotherapy agents and targeted therapies. Radiologic appearances of pneumonitis have been reported in three cases and were consistent with an acute interstitial pneumonia/acute respiratory distress syndrome-type pattern [77]. Timing of development of pneumonitis appears to exhibit a wide range, with patients in this small series developing pneumonitis between 7.4 and 24.3 months after initiating therapy. Patients with suspected pneumonitis may present with shortness of breath, cough, fever, or chest pain. An algorithm for the diagnostic investigations and management of suspected immune-related pneumonitis adapted from guidelines used across anti-PD-1/PD-L1 studies is depicted in Figure 3. Standard diagnostic algorithms recommend radiologic investigation with a chest computed tomography scan. In cases of grade 2 or higher pneumonitis, consultations from infectious diseases and pulmonology physicians can be considered, in order to to rule out overt infection and malignant lung infiltration, as well as lung function testing and bronchoscopy. Management is guided by clinical symptoms, such that mild cases are managed by withholding therapy, and higher grade cases may be managed with oral or intravenous corticosteroids. Severe cases require hospitalization for intravenous corticosteroids, and other forms of immunosuppression may be used such as infliximab, cyclophosphamide, or mycophenolate mofetil [14].

rare toxicities with anti-PD-1/PD-L1 agents

neurologic syndromes

Isolated cases of myasthenia gravis have been reported in studies combining anti-PD-1/PD-L1 mAb with anti-CTLA-4 mAb [37, 38, 78]. Single-agent ipilimumab therapy was associated with a number of neurologic syndromes such as transverse myelitis

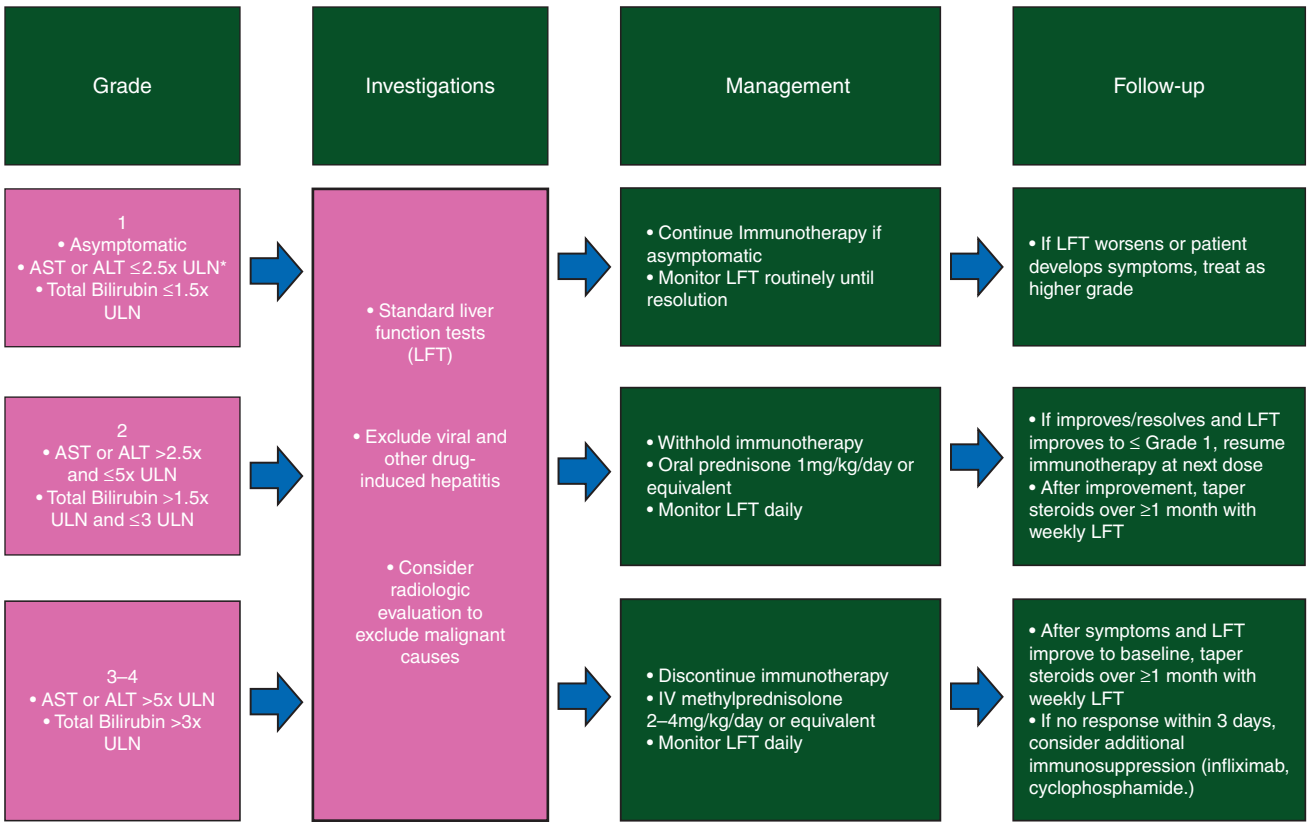

Figure 2. Adapted management algorithm for hepatitis with immune checkpoint blockade. *ULN, upper limit of normal.

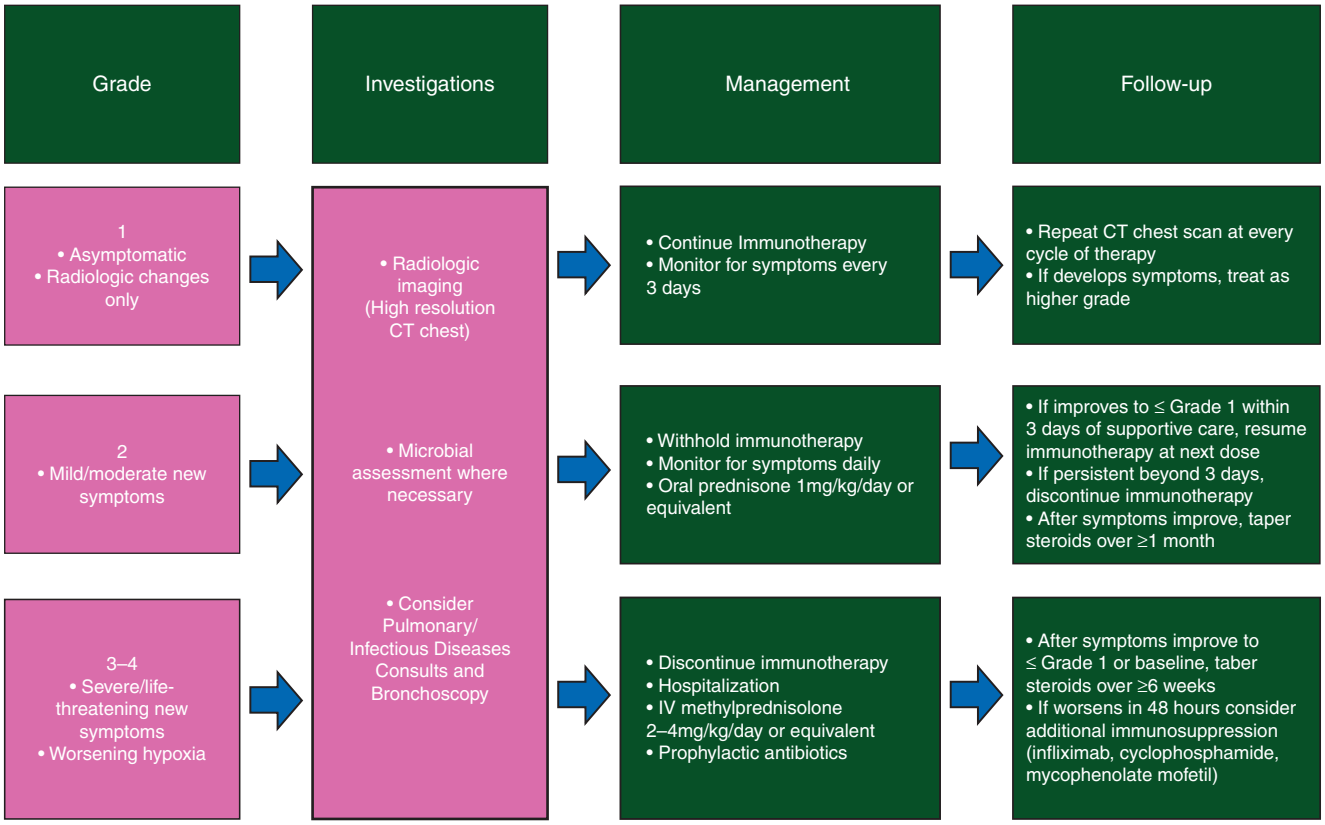

Figure 3. Adapted management algorithm for pneumonitis with immune checkpoint blockade.

[79], enteric neuropathy [80], and aseptic meningitis [81], and a case of Guillain–Barre syndrome that led to treatment-related fatality [82]. Patients should be managed with corticosteroids and neurologic consultation, and intravenous immunoglobulin or plasmapheresis may be of benefit [14].

ocular toxicity

Uveitis has been reported in patients receiving both single-agent [2] and combination therapies with anti-PD-1 and anti-CTLA-4 mAb [37], as well as ipilimumab alone [83]. Patients who develop uveitis are typically managed with topical corticosteroid solutions in consultation with an ophthalmologist, with consideration for oral corticosteroids in grade 3/4 cases [14].

renal toxicity

Isolated cases of interstitial nephritis have been reported with both single-agent anti-PD-1 therapy [27] and the combination of nivolumab and ipilimumab [34]. Pathologic appearances of interstitial nephritis as a result of anti-PD-1/PD-L1 mAb to our knowledge have not been reported; however, ipilimumab-related interstitial nephritis may exhibit pathologic appearances consistent with lupus nephritis [84] or granulomatous nephritis [85, 86]. Three cases of grade 3 acute renal failure were reported in a phase I study of nivolumab plus platinum-doublet chemotherapy in NSCLC and were deemed related to study therapy [39]. The clinical course is usually one of asymptomatic, gradually rising creatinine, and most patients improve with use of corticosteroids.

pancreatic toxicities

Elevations in lipase levels have been reported in studies of both anti-CTLA-4 and anti-PD-1/PD-L1 mAb [1, 7, 8]. These are usually asymptomatic laboratory abnormalities that can be monitored without immunosuppressive therapy. Pancreatitis has been reported infrequently in studies of anti-CTLA-4 [87] and anti-PD-1 agents [7, 10, 28]; therefore, clinical suspicion of pancreatitis should prompt assessment of amylase and lipase. Routine assessment of these enzymes in asymptomatic patients is not required outside of clinical trials and may be detrimental if inappropriate discontinuation of therapy occurs as a result [14].

combinations of anti-PD-1/PD-L1 agents with other anticancer agents

other immunotherapy

Combination studies of anti-PD-1/PD-L1 agents with other immunotherapeutic agents are currently underway in multiple tumor types. The combination of ipilimumab and nivolumab was first studied in a phase I trial of 86 patients with pretreated malignant melanoma and demonstrated a 40% objective response rate by modified World Health Organization criteria, with 30% of patients ($n = 16$) exhibiting responses of >80% in the concurrent arm [34]. These data paved the way for phase II [35] and III studies [36] of this combination in advanced melanoma, and the exploration of similar combinations in other tumor types. While response rates were impressive in these studies, toxicity was notably increased. The majority (83%–89%) of patients in the

combination arm of the melanoma studies required either topical or oral immunosuppressive therapy for irAEs, and these events led to treatment-related drug discontinuation in 36%–47% of all patients on the combination arm [35, 36]. However, 80%–100% of the patients treated with immunosuppressive medications had their irAE completely resolve, or return to baseline. This combination has also been studied in 10 patients with recurrent glioblastoma multiforme (GBM) after standard therapy with surgery, RT, and temozolomide (Table 2) [23]. All patients receiving ipilimumab and nivolumab in this study experienced an AE, and four patients discontinued therapy due to AEs. Similar combinations have been studied in pretreated NSCLC: pembrolizumab plus ipilimumab in 56 patients [37], and durvalumab plus tremelimumab in 102 patients [38]. Preliminary results presented in 2015 demonstrated similar toxicity data, with 83%–93% of patients experiencing treatment-related AEs, and up to 61% of patients experiencing grade 3/4 AEs, with some rarer irAEs reported including polymyositis ($n = 1$), myocarditis ($n = 1$), and myasthenia gravis ($n = 2$) [37, 38].

chemotherapy

A number of multiarm phase I studies are currently underway in NSCLC and other solid tumors, aimed at investigating the safety and tolerability of combining anti-PD-1/PD-L1 mAb with standard chemotherapeutic agents (NCT01454102, NCT02039674, NCT01633970). In NSCLC, a four-arm study examined the combination of single-agent nivolumab with one of three possible platinum-doublet chemotherapy regimens at standard doses (cisplatin/gemcitabine, cisplatin/pemetrexed, and carboplatin/paclitaxel) [39]. High rates of all AEs (93%) and grade 3/4 AEs (43%) were seen, where the treatment arm with the highest rate of toxicity was nivolumab 10 mg/kg with carboplatin/paclitaxel ($n = 11/15$, 73%) [39]. Eleven patients discontinued treatment due to AEs, of which eight (17%) were grade 3/4 (pneumonitis: $n = 3$, 15%; acute renal failure: $n = 3$, 15%) [39]. Certain cytotoxic chemotherapeutic agents are thought to have immunogenic properties, such as 5-flurouracil which may decrease myeloid-derived suppressor cells (MDSC) [88] and increase effector T cells at the tumor microenvironment [89], and oxaliplatin which induces immunogenic cell death [90]. These effects form the basis of a phase I study of the combination of FOLFOX chemotherapy, bevacizumab, and atezolizumab in metastatic CRC [45]. Preliminary results of this study demonstrate that 80% of patients ($n = 24/30$) receiving the three-drug combination experienced a treatment-related AE, 20% of which ($n = 6/30$) were grade 3/4 in severity.

targeted therapy

The majority of patients treated with targeted therapies eventually develop acquired resistance to these agents through a number of mechanisms [91–93], one of which is postulated to be immune escape via the PD-1/PD-L1 and other immune checkpoint pathways [94]. In patients with epidermal growth factor receptor (*EGFR*)-mutant NSCLC with confirmed positivity of the T790M resistance mutation, the combination of an oral irreversible selective EGFR tyrosine kinase inhibitor (TKI) AZD9291 with durvalumab was investigated in 14 patients [40]. Toxicities with the combination included: diarrhea (50%), vomiting (50%), anemia (45%), and three cases of pneumonitis (21%). A similar study examined the combination of durvalumab and nonselective EGFR-TKI gefitinib in heavily pretreated patients, regardless of *EGFR* mutation status. This study demonstrated promising clinical activity with the combination, with mild treatment-related AEs in all patients, most commonly AST/ALT elevation (50%, $n = 5$ each) [41]. In melanoma, a three-arm study of durvalumab with the *BRAF*-inhibitor dabrafenib and MEK-inhibitor trametinib either concomitantly or sequentially with trametinib alone is under investigation in BRAF-mutant and wild-type melanoma [42]. Toxicities associated with dabrafenib (pyrexia, chills, arthralgia) or trametinib (peripheral edema and acneiform rash) did not appear to be increased with the addition of the anti-PD-L1 agent (Table 2). Lastly, the anti-PD-1 mAb pidilizumab has been studied as a single agent in a phase II study in lymphoma [30], and in combination with anti-CD20 mAb rituximab in a phase II study in follicular lymphoma [43]. In the combination study, the majority of patients had grade 1–2 AEs (94%), including anemia, fatigue, and leukopenia. Overall, combination approaches with anti-PD-1/PD-L1 mAb and targeted agents appear to have increased rates of toxicity, depending on the targeted agents used. Specific anti-PD-1/PD-L1 toxicities do not appear to be increased; however, our experience with these combinations is early and limited.

antiangiogenic agents

Antiangiogenic agents including mAb aimed at vascular endothelial growth factor (VEGF), such as bevacizumab, and multitargeted TKIs have been combined with anti-PD-1/PD-L1 mAb in early phase clinical studies. In metastatic RCC, nivolumab has been combined with both sunitinib ($n = 33$) and pazopanib ($n = 20$) in a phase I study [46]. Grade 3/4 treatment-related AEs were reported in 73% ($n = 24/33$) of patients who received nivolumab plus sunitinib and 60% ($n = 12/20$) patients who received nivolumab plus pazopanib. These led to treatment discontinuation in 24% ($n = 8/33$) of the sunitinib patients and 20% ($n = 4/20$) of the pazopanib patients. In addition to antiangiogenic effects, blockade of VEGF has been reported to possess immunomodulatory effects such as promoting increased effector T-cell trafficking [95, 96], and reducing MDSCs, T-regulatory cells, and suppressive cytokines at the tumor microenvironment [97]. The combination of bevacizumab and atezolizumab has been studied in metastatic clear-cell RCC and metastatic CRC, without any exacerbation of known bevacizumab AEs [44, 45]. This combination is currently being studied in the phase II setting in RCC (NCT01984242).

radiation therapy

Ionizing radiation is known to lead to immunogenic death of cancer cells in the tumor microenvironment [98], which can in turn result in proimmunogenic effects such as increased antigen presentation by tumor cells, increased chemokine release, and recruitment of effector T cells to the tumor microenvironment; as well as less favorable immunologic effects, such as impaired dendritic cell function [99, 100], increases in tumor-associated macrophages and T-regulatory cells [101, 102]. Combining RT and immunotherapy may create opportunities to synergize these effects, as well as generate an antitumor effect outside the irradiated field, termed the abscopal effect [103, 104]. This

phenomenon is postulated to be mediated by cross-priming of cytotoxic T cells [103]. The combination of 8 Gy of external-beam RT delivered to one to three osseous metastases plus ipilimumab was investigated in metastatic castration-resistant prostate cancer, and deemed to be safe and tolerable [105]. In this study, ipilimumab 3–10 mg/kg demonstrated similar rates of toxicity with or without the addition of RT. In the 10 mg/kg ipilimumab ± RT expansion cohort, toxicities included diarrhea (54%), colitis (22%), rash (32%), and pruritus (20%); and grade 3/4 irAEs included colitis (16%) and hepatitis (10%) [105]. Studies aimed at determining the safety and efficacy of RT combined with anti-PD-1/PD-L1 mAb are currently underway, with no reported toxicity data.

anti-PD-1/PD-L1 therapy in patients with pre-existing autoimmune or infectious diseases

Typical exclusion criteria for treatment with immune checkpoint mAb in clinical trials include autoimmune conditions that require immune suppression above a certain daily dosage. This is based on murine models where fatal autoimmune conditions were unmasked during anti-CTLA-4 therapy [106, 107]. A select number of patients with known autoimmune diseases have received ipilimumab safely outside of clinical studies [108, 109], including patients with prior organ transplant [110, 111]. However, general conclusions regarding treatment with immune checkpoint mAb in large numbers of such patients is unknown. In addition, patients with hepatitis B and C infection have not been suitable candidates for these therapies in the past, due to a theoretical concern for worsening viral infection. However, comparable rates of toxicity have been reported in a single-agent nivolumab study in HCC, which included patients with hepatitis B and C infection [8]. Furthermore, ongoing studies are evaluating the role of checkpoint blockade in HIV-associated malignancies such as HPV-associated squamous cell carcinomas (NCT2408861, NCT02255097).

conclusion

Three immune checkpoint antibodies are now FDA-approved for the treatment of metastatic melanoma (ipilimumab, pembrolizumab, and nivolumab) and lung cancer (nivolumab), and a clear knowledge of the toxicities of these agents is vital to achieving their safe delivery outside of clinical trials. Anti-PD-1/PD-L1 mAb appears to be generally less toxic compared with anti-CTLA-4 mAb, with a slightly different toxicity profile that includes organ-specific inflammatory conditions such as pneumonitis rather than colitis. With increasing use of these agents and an awareness of what toxicities to expect and how to manage them, morbidity as well as mortality associated with severe irAEs, appear to be waning. However, use of these agents in new tumor types and combination approaches with standard anticancer agents that carry their own toxicities may result in an increase in the incidence of AEs and facilitate the emergence of new irAEs. As our familiarity with these agents grows, we may expand the patient population we deem acceptable to receive these treatments and learn more about their effects on different patient populations. Further research is required to advance our understanding of the mechanisms underlying the development of these toxicities, why they occur in particular patients, and improve upon current management strategies.

disclosure

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