The Oncologist®

Melanoma and Cutaneous Malignancies

Ipilimumab and Its Toxicities: A Multidisciplinary Approach

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

Key Words. Ipilimumab • CTLA-4 • Antibody • Melanoma • Immune-mediated toxicity • immune-related adverse events • AEOSI

Abstract

The treatment for metastatic melanoma has evolved significantly in the past few years. Ipilimumab, an immunotherapy, is now in mainstream oncology practice given that it has shown improved overall survival in randomized clinical trials. Other immune modulating agents, such as programmed death receptor-1 and programmed death receptor ligand-1 antibodies, are showing promise in early clinical trials. This manuscript will review ipilimumab and its most common side effects. Immune-related adverse events (irAEs) are important to recognize early, and their presentation, timing of onset, and general recommendations for workup and management will be reviewed. Assembling a multidisciplinary team, as well as thorough education of the patient, is recommended to optimize patient care. ***The Oncologist*** 2013;18:733–743

Implications for Practice: Ipilimumab, an immunotherapy, has shown improved overall survival in randomized clinical trials and is now in mainstream oncology practice. This study reviews ipilimumab and its common side effects, emphasizing the importance of early recognition of immune-related adverse events. Presentation, timing of onset, and recommendations for workup and management of immune-related adverse events are discussed.

Introduction

Melanoma is currently the fifth and sixth most common cancer in men and women, respectively [1]. The incidence continues to rise and it remains a leading disease in terms of loss of expected years of life [1]. Early stage disease is typically curable with surgical excision; however, the prognosis for advanced, unresectable disease is poor, with an estimated median survival of less than 1 year [2]. Traditionally, systemic therapies for advanced disease have had limited activity and benefit [3]. Over the past 2 years, the therapeutic arsenal for metastatic melanoma has evolved dramatically. For the first time, two new agents have demonstrated a survival advantage in the treatment of advanced melanoma. Ipilimumab, an anticytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody, with or without a gp100 vaccine, first demonstrated improved survival compared with gp100 vaccine alone, leading to its approval by the U.S. Food and Drug Administration (FDA) [4]. In another randomized phase III trial, ipilimumab in combination with dacarbazine (DTIC) demonstrated a survival benefit compared with DTIC alone [5]. Vemurafenib, a specific tyrosine kinase inhibitor of V600 mutated BRAF, demonstrated a response rate of approximately 50% and a significant decrease in the relative risk of death compared with DTIC (hazard ratio = 0.37) [6]. Vemurafenib is now FDA-approved, and in patients with V600 mutated BRAF detected on mutational analysis, it is a standard of care treatment.

Ipilimumab is FDA-approved for use in the United States in patients with metastatic or unresectable stage III melanoma and in some other countries for patients who have progressed on previous therapy. The approved schedule is ipilimumab 3 mg per kilogram administered intravenously every 3 weeks for four doses, as was utilized in the randomized phase III study of ipilimumab and gp100 [4]. Maintanence ipilimumab is only being administered in clinical trials at this time. Given its mechanism of action as an immune-modulating agent that affects T-cell function, its side effect profile is distinct from chemotherapies and molecular targeted therapies as well as from other immunotherapies. Bristol-Myers Squibb sponsored a roundtable in November 2010 with a panel of melanoma specialists to discuss the clinical experience with ipilimumab, the evaluation, and management of immune-related adverse events (irAEs), and possible materials and information to facilitate the education of community oncologists as well as patients in light of impending FDA approval. This manuscript is the result of the roundtable, and in it we will review the basic ipilimumab principles of use for the community oncologist, including its mechanism of action and side effect profile, as well as provide data and expert opinion regarding toxicity management and patient selection. The U.S. FDA, in conjunction with Bristol-Myers Squibb, initiated a risk evaluation and mitigation strategy (REMS) optional educational program for ipili-

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http://dx.doi.org/10.1634/theoncologist.2012-0483

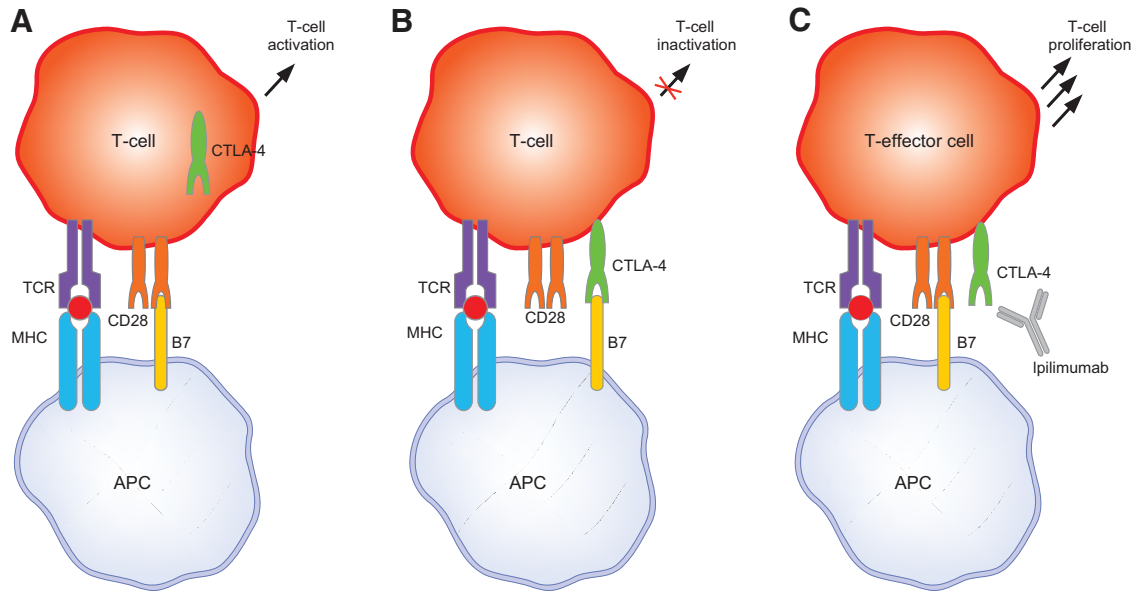


Figure 1. T-cell activation, inactivation, and proliferation. **(A):** T-cell activation occurs via costimulatory binding of B7 to CD28. **(B):** CTLA-4 is upregulated in malignancy and binds B7, thus inhibiting T-cell activation. **(C):** Antagonism of CTLA-4 via ipilimumab promotes T-cell activation/proliferation. (Reprinted with permission [11].)

Abbreviations: APC, antigen presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; TCR, T-cell receptor; MHC, major histocompatibility complex.

mumab with management guidelines [7]. The most common ipilimumab-related side effects, irAEs, will be reviewed, including their typical timing of onset as well as recommendations for workup and management. Ipilimumab is generally well-tolerated and irAEs typically are easily managed. Essential to its use is a high level of awareness of potential toxicities as well as frequent and thorough elicitation of symptoms to recognize, diagnose, and manage toxicities promptly. The treating oncologist must be knowledgeable and alert to possible irAEs as well as assemble and collaborate with a team of subspecialists in their management. Subspecialists may include gastroenterologists, hepatologists, endocrinologists, neurologists, ophthalmologists, dermatologists, rheumatologists, infectious disease specialists, and possibly others. Good communication between patient and health care providers also contributes to successful and safe treatment with this drug. It is also advisable to be aware of melanoma specialists in and around your community who may have expertise with ipilimumab. This knowledge may be relevant and applicable to other immunomodulating agents under development.

CTLA-4

CTLA-4 is a surface protein expressed on activated and regulatory T cells and is upregulated in malignancy [8–10]. It functions as a negative regulator of T-cell function, binding to B7.1 and B7.2 on antigen-presenting cells and inducing cell-cycle arrest and T-cell anergy, or tolerance. Its counterpart on T cells, surface protein CD28, is a positive regulator of T-cell function and binds B7 with less affinity (Fig. 1) [11]. The goal of CTLA-4 blockade is to break immune tolerance to a cancer and manifest a prolonged tumor-specific immune attack. However, anti-CTLA-4 antibodies can also break tolerance to other "normal" antigens, which leads to immune attack on normal parts of the body, such as the gastrointestinal (GI) track, the skin, or endocrine glands. Two CTLA-4 antibodies have been developed and investigated in clinical trials, ipilimumab (Yervoy, Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) and tremelimumab (ticilimumab, CP-675,206, Pfizer, New York, NY [now MedImmune, http://www.pfizer.com]). This review will focus on ipilimumab, a fully human, IgG1 monoclonal antagonist antibody to CTLA-4 that is FDA approved and that has demonstrated a survival benefit in randomized clinical trials.

Toxicity

The toxicities of ipilimumab are well studied and described in an extensive clinical trials experience; however, our knowledge continues to evolve as ipilimumab's use increases. Treatment-related adverse events are often mild to moderate, but occur in approximately 70%–88% of patients [4, 12]. Toxicities directly correlate with ipilimumab dose [13]. Common treatment-related adverse events at the time of infusions include fatigue, nausea, vomiting, diarrhea, fever, headache, dizziness, rash, and pruritus. Onset of these side effects can be during the infusion, within 24–72 hours, or later, and treatment is symptomatic with diphenhydramine, antipyretics, antipruritics, and intravenous or oral fluids as needed. Temporary halting and subsequent slowing of the ipilimumab infusion is advised, but typically does not prevent continued treatment. Nonsteroidal premedications are not typically administered but can be added in the event of an infusion reaction. Hypotension and tachycardia can be seen around the time of infusion, but not commonly.

irAEs can occur at any point during treatment with ipilimumab, but often present around the third or fourth dose. The presentations can be subtle, and other causes must be ruled out. Establishing the correct diagnosis promptly, determining severity based on common toxicity criteria grading [14], initiating treatment with steroids, if indicated, and holding further anti-CTLA-4 treatment is essential. irAEs can be severe and life threatening, particularly if diagnosis is delayed.

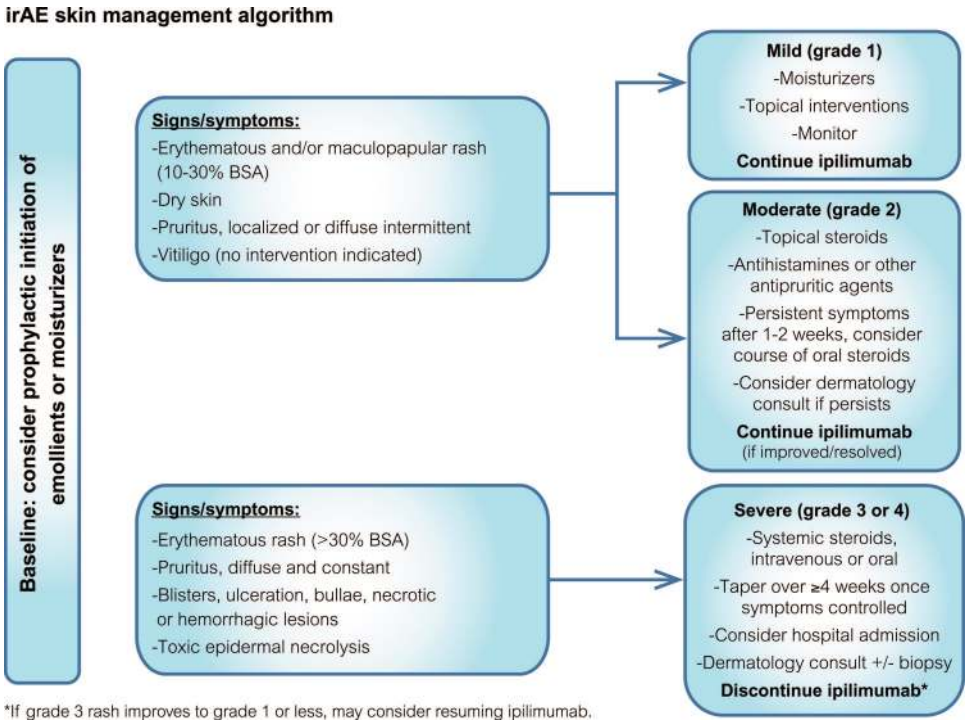


Figure 2. Algorithm for skin irAE management.

The incidence of grade 3 or higher irAEs is approximately 5%–25% and is dose related [4, 12, 13, 15]. The most common irAEs are dermatitis (pruritus, rash), enterocolitis, endocrinopathies (hypophysitis, thyroiditis), liver abnormalities (elevated serum liver tests, hepatitis), and uveitis, and will be reviewed in detail. irAEs involving the nervous system also have been described: central nervous system (CNS) or peripheral–sensory or motor deficits, as well as irAEs of the cardiovascular system, hematopoietic system, and others. The onset of irAEs can vary from insidious to sudden; severity can range from mild to life threatening, but they uncommonly result in significant morbidity or death. irAEs often mimic other known autoimmune conditions, such as autoimmune hepatitis or inflammatory bowel disease. However, the mechanism of action of the ipilimumab-induced irAEs may be distinct from those analogous autoimmune conditions. At this time, the mechanisms of irAEs appear to be T-cell-mediated phenomena characterized by T-cell-rich inflammatory infiltrates with few reports of circulating antibodies [16, 17].

The primary treatment for most low-grade irAEs is supportive care; high-dose steroids and holding further ipilimumab are indicated for higher grade irAEs. Not all irAEs will require permanent cessation of anti-CTLA-4 therapy. Typically, the majority will respond to steroids, but a longer course with a slow taper over at least 1 month is necessary. Too rapid a taper can lead not only to recurrence of symptoms, but a rebound with worsened severity. The optimal dose, schedule, and course of steroids are still uncertain. If symptoms persist despite high-dose steroids or are refractory to steroid tapering, other immunosuppressive treatment may be necessary [18–20]. Importantly, patients can evolve more than one irAE during the course of their treatment or while on steroids [21]. The development of irAEs appears to be associated with antitumor response in some studies [13, 22, 23]. Continued antitumor activity is seen despite steroid therapy in some patients with irAEs [21, 24, 25]. However, efficacy may be compromised more so in patients on steroids at the time of initiation of ipilimumab [26]. The overriding principle remains: use steroids if needed, but avoid them if not.

The development of irAEs appears to be associated with antitumor response in some studies. Continued antitumor activity is seen despite steroid therapy in some patients with irAEs. However, efficacy may be compromised more so in patients on steroids at the time of initiation of ipilimumab. The overriding principle remains: use steroids if needed, but avoid them if not.

Prior to each and every dose of ipilimumab, ensure that laboratory evaluations, including hepatic panel, basic metabolic panel, complete blood count with differential and thyroid-stimulating hormone (TSH), and free thyroxine (T4) are drawn and reviewed. Evaluation of amylase and lipase levels is also reasonable and recommended. Delayed irAE presentations, weeks to months after treatment, are possible. It is unknown when the risk of irAEs from ipilimumab ends, thus careful patient follow-up is recommended. Self-education as well as the education of office staff and colleagues are key to recognizing and effectively managing the irAEs associated with ipilimumab. Prior to dosing ipilimumab, it is recommended to become familiar with available irAE treatment algorithms. The algorithms presented in this manuscript (Figs. 2, 4–6) are based on the roundtable discussion, as well as influenced by other developed algorithms, including those utilized by BMS in ipilimumab clinical trial protocols and in the package insert [7, 27–29]. Educating patients and maintaining close

communication with them is essential. Assembling a multidisciplinary team prior to treating patients with ipilimumab will foster collaboration and facilitate their future care.

Education

Physician

Medicine is a constantly evolving field and oncology currently has some of the broadest and most rapid drug development pipelines. Molecularly targeted and immune-modulating agents are now standards of care in addition to chemotherapies. Ipilimumab possesses a unique mechanism of action as well as a distinct toxicity profile and management strategy compared with other anticancer therapies. The treating oncologist will need to direct and coordinate the overall care for these patients. Review of the current literature, continuing medical education lectures as well as consultation with colleagues is essential. The FDA, in conjunction with Bristol-Myers Squibb, initiated a REMS optional educational program for ipilimumab. Management guidelines are readily available as well as patient education materials, including a wallet card, at www.yervoy.com/hcp/rems.aspx [7]. There are hotlines available for medical information as well as to report adverse events. In the United States, when a physician places an order for ipilimumab, the company is notified and a representative contacts the prescribing physician within 48 hours to provide and review relevant educational materials and resources.

Patients and Family

Early recognition of symptoms and frequent monitoring is central to irAE management. Patients and families should be counseled concerning signs or symptoms. It is recommended that patients utilize symptom logs and carry wallet cards with drug name, treatment dates, and the treating physician's contact information to facilitate communication and patient care. In an emergency setting, the patient will need to be their own advocate. A unique issue for providers to consider when treating patients with metastatic melanoma is that they may not accurately report side effects for fear of being taken off treatment. Reassurance and education can help. The maxim to call early and to call often to the physicians' office should be reinforced.

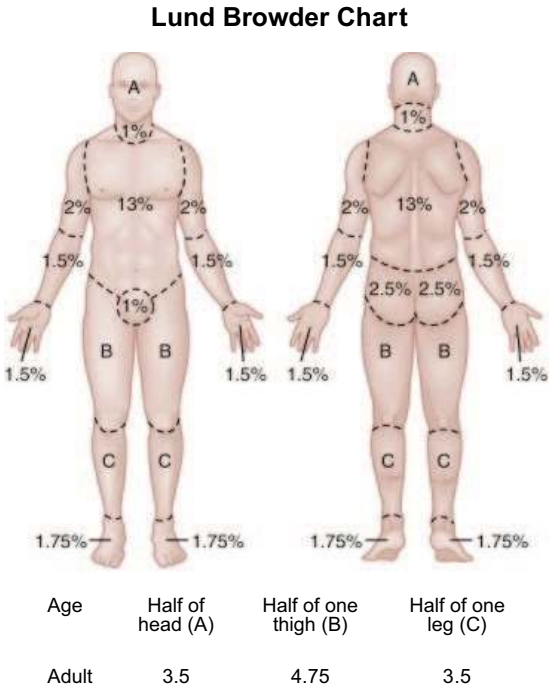
Multidisciplinary Team

Ancillary Staff

Office staff is the first line of defense for recognizing and monitoring toxicities related to ipilimumab. Advanced care practitioners, nurses, and receptionists must be aware of warning signs and symptoms so that patients are triaged appropriately and reassessed in a timely manner. Presentations as well as case-based scenarios and posting of treatment algorithms in the office can be beneficial.

Physicians

A multidisciplinary group of physicians will be necessary for optimal patient care. This team may include a gastroenterologist, hepatologist, endocrinologist, neurologist, ophthalmologist, and dermatologist. Not all subspecialties may be immediately accessible in smaller communities, thus physicians are encouraged to establish a consult network in advance. Experience with ipilimumab may be limited and vary among physicians; subspecialists may have no knowledge of the recommended treatment algorithms for irAEs. Presentations and discussions at tumor boards and staff meetings will facilitate collaboration and patient care. Professional societies and meetings as well as personal interactions also provide opportunities for education. Including emergency department (ED) physicians in the network of physicians is encouraged, as some patients may need evaluation in an ED during or after treatment. Emergency health care professionals often have no experience with ipilimumab or in assessing and managing its associated toxicities. Patients should be able to provide information (e.g., a wallet card) and insist upon direct communication with the treating oncologist. The REMS program and online management guidelines may be helpful [7]. The importance/need for any treating physicians to directly contact the treating oncologist promptly cannot be emphasized enough.



Age	Half of head (A)	Half of one thigh (B)	Half of one leg (C)
Adult	3.5	4.75	3.5

Figure 3. Lund Browder chart for estimating body surface area involved by rash. (Adapted from [30].)

Immune-Related Adverse Events

Dermatologic Toxicities

Dermatologic toxicities are the most common ipilimumab-associated irAEs and are usually the first to manifest, after dose 1 or 2. The most common toxicities are a maculopapular, erythematous rash, or pruritus. The incidence of rash and pruritus is approximately 40%–49% [4, 12] and most often mild. Providers should consider encouraging the use of moisturizers preventatively; other supportive measures such as antipruritic medications or topical steroids may be indicated (Fig. 2). Rare immediate hypersensitivity reactions, such as hives, have been observed during and just after infusions but are not discussed in the literature.

It is uncommon to hold ipilimumab therapy for most dermatologic side effects. Persistent grade 2 toxicities may necessitate a course of oral steroids and prompt a dermatology consult. However, ipilimumab should be held for severe skin rashes (grade 3 or 4), which may require admission to the hos-

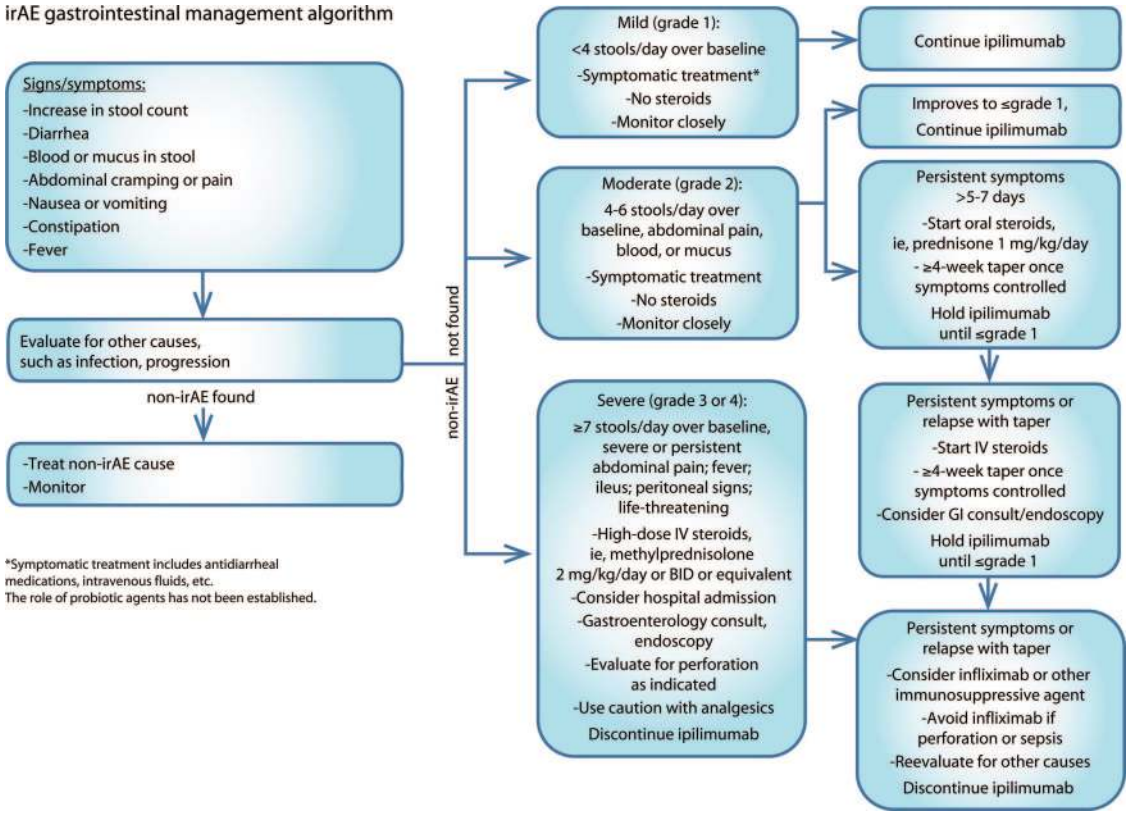


Figure 4. Algorithm for gastrointestinal irAE management.

pital for management and workup in conjunction with a dermatologist as well as treatment with systemic steroids, either intravenous or oral. Blisters are rarely seen, and their presence signals significant toxicity. Life-threatening dermatologic complications such as Steven's Johnson Syndrome or toxic epidermal necrolysis have been seen in fewer than 1% of patients and necessitate emergent treatment and permanent cessation of ipilimumab. It is important to accurately qualify and quantify cutaneous toxicities. The Lund and Browder chart (Fig. 3) [30], for estimation of body surface area involved by burns, is used to assess the surface of involvement of rash for grading. Dermatology referral may be necessary for persistent moderate skin toxicities and is recommended for severe skin rashes. Vitiligo can also be seen and is considered a positive prognostic sign in patients with melanoma as it signals an immune attack on melanocytes. While permanent, this does not require any treatment or necessitate holding ipilimumab, although patients need to be aware that areas of vitiliginous skin are susceptible to severe sun damage.

Enterocolitis

The second most commonly reported irAE is diarrhea, with any grade diarrhea reported in approximately 30%–35% of patients and grade 3–5 diarrhea or enterocolitis in 5%–8% [4, 12, 13]. Mild, intermittent changes in bowel movements are commonly seen. In patients receiving ipilimumab, all diarrhea is suspect and most likely related to ipilimumab. Patient education will ensure that all diarrhea is reported and managed promptly. It can be self-limited; however, ipilimumab-related diarrhea is not typical of drug-induced or idiopathic diarrhea seen with other cancer therapies. It often presents around the second dose of therapy, but its timing of onset can vary and is not predictable. Symptoms can progress rapidly to potentially life-threatening status, if untreated.

Algorithms for the management of diarrhea have been developed and their use is recommended [7, 27–29] (Fig. 4). Initial management for grade 1 diarrhea is symptomatic, without steroids. Grade 2 diarrhea is managed symptomatically as well, but if it persists or worsens, ipilimumab-induced enterocolitis is the most likely diagnosis and treatment with ipilimumab should be held while a workup is pursued. Other causes to be ruled out include gastroenteritis, other medication-induced diarrhea, infectious diarrhea, such as bacterial (*Clostridium difficile*) or viral, or others. It is possible for patients to have a superimposed infection in addition to ipilimumab-induced diarrhea/colitis, and both require treatment. If a diagnosis of ipilimumab-induced colitis is established, treatment should be initiated with oral or intravenous (IV) steroids, depending on the grade of diarrhea. Once an intervention is initiated, reassessment within 24 hours in the office or by telephone is necessary. Frequent reevaluation is recommended as irAE symptoms and course can change rapidly and response to interventions cannot be assumed. Referral to a gastroenterologist for flexible sigmoidoscopy or colonoscopy should be considered for persistent grade 2 diarrhea, or any grade 3–4 diarrhea. Patients presenting with grade 3–4 diarrhea may need hospital admission for workup, monitoring, IV hydration, bowel rest, and high-dose IV steroids. For patients with refractory symptoms despite maximal medical support and treatment with high dose steroids for approximately 5 days, a single dose of infliximab 5 mg/kg has

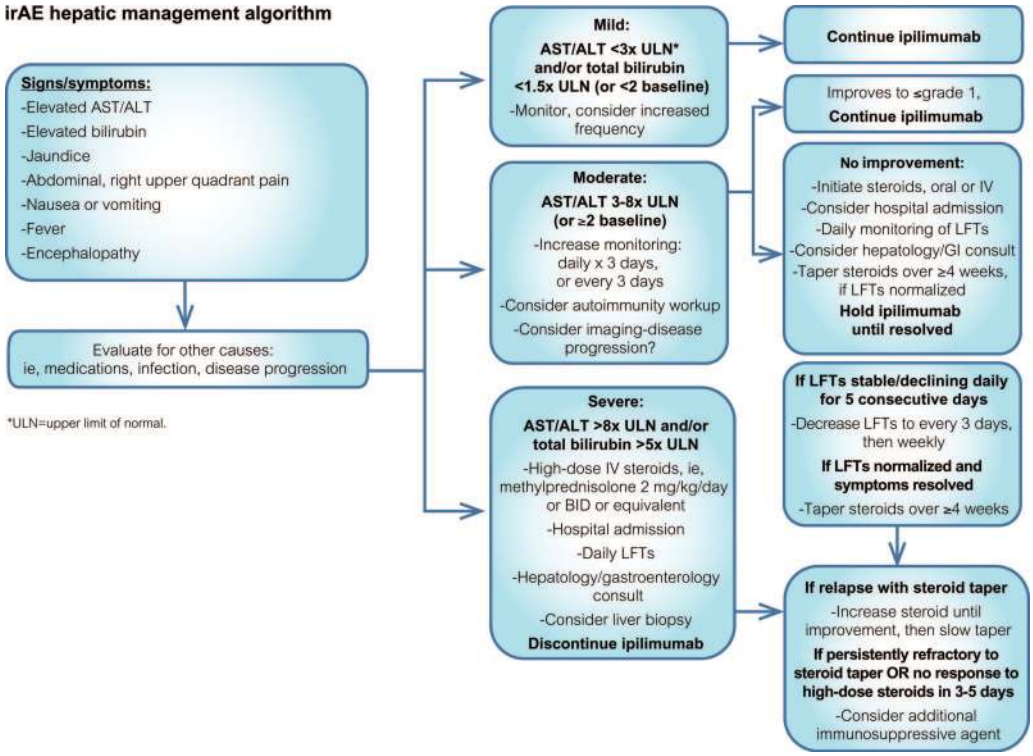


Figure 5. Algorithm for hepatic irAE management.

demonstrated rapid resolution of symptoms and durable efficacy and should be considered [18, 19]. Infliximab may also be considered for persistent grade 2 symptoms that do not resolve despite treatment with steroids. Infliximab can be repeated, but should not be used if there is concern for perforation or sepsis. Consider a surgical consult for patients with severe diarrhea and/or ileus early in the treatment course. If diarrhea persists despite maximal medical and supportive therapy, including the use of total parenteral nutrition, infliximab, and multiple tapering courses of steroids, then a diverting ileostomy or partial/complete colectomy may be indicated as a last resort. Rarely, colitis can progress to intestinal perforation (1%). Permanent cessation of ipilimumab is recommended for grade 3 or 4 colitis, hemorrhage, or perforation. Patients subsequently treated with high-dose interleukin-2 appear to have an increased risk of intestinal perforation [31].

At this time, it is not possible to predict who will develop entercolitis. While metastatic disease involving the GI tract is commonly seen with melanoma, this does not appear to influence or predict ipilimumab-induced GI toxicity. Prophylactic oral budesonide failed to prevent the onset of GI irAEs in patients treated with ipilimumab compared with placebo [24]. Thirty-six percent (21/58) of patients in the budesonide group and 35.1% (20/57) of patients in the placebo group developed grade ≥2 diarrhea and/or grade ≥2 colitis during the first 23 weeks [32]. However, budesonide can be used in the treatment of lower grade enterocolitis.

Ipilimumab-induced enterocolitis has been likened to inflammatory bowel disease or graft-versus-host disease (GVHD) given its presentation and response to immunosuppressive medications; however, its clinical and histologic findings are quite variable. In addition to inflammatory changes involving the colon, gastritis and small bowel enteritis also have been described [18]. On endoscopy, edema, erythema, ulceration, and exudates may be seen. Endoscopic biopsies have noted mucosal erosion, T-cell rich lymphocytic infiltrates within the lamina propria, and epithelium accompanied by eosinophils and plasma cells, as well as neutrophilic infiltrates with cryptitis and crypt abscesses [18, 32, 33]. Other series have reported rare granulomas [18] and prominent epithelial apoptosis and mucin depletion [33]. The phase II trial evaluating prophylactic budesonide incorporated endoscopy with biopsy 1–2 weeks after the first dose of ipilimumab and endoscopy/biopsy in a few patients after onset of grade ≥2 diarrhea. Immune cell infiltration into the mucosa after the first dose of ipilimumab was suggestive, but not predictive of later onset diarrhea/colitis. Further, the microscopic appearance and location of histologic changes observed after the onset of diarrhea/colitis were distinct from inflammatory bowel disease (absence of granulomas, fissuring ulcers) and from GVHD (absence of prominent epithelial apoptosis). Interestingly, GVHD was not induced or worsened in patients with relapsed malignancies following allogeneic bone marrow transplant when treated with a single dose of ipilimumab [34].

Hepatotoxicity

Liver abnormalities are reported in approximately 2%–9% of patients and include elevation of serum liver transaminases, elevated bilirubin, and inflammatory hepatitis [4, 12, 13]. Ipilimumab-induced hepatitis is rare but can be life threatening. Greater hepatotoxicity was seen when ipilimumab was combined with DTIC and was postulated to be related to hepatic toxicity associated with DTIC alone [5]. Typically, hepatic abnormalities present around the second dose. Current guidelines recommend evaluation of serum markers of hepatic function at baseline and, prior to each dose, and periodically

after completion of therapy. The presence of liver metastases can confound interpretation of serum liver tests; liver metastases can present with either a cholestatic pattern and/or transaminitis. Monitoring and/or minimizing intake of other hepatotoxins such as alcohol or acetaminophen should be stressed to patients [35]. It is reasonable to check baseline viral hepatitis serologies prior to dosing of ipilimumab. All ipilimumab trials excluded patients with hepatitis B or C, and the panel does not recommend treatment with ipilimumab in the setting of active hepatitis B or C outside of a clinical trial.

Serum liver test levels can rapidly increase, fluctuate, and occasionally resolve without intervention. Management algorithms have been developed and are recommended [7, 27, 28] (Fig. 5). If abnormal values for aspartate aminotransferase, alanine transaminase, or total bilirubin greater than or equal to two times the baseline are detected, monitoring should increase with labs repeated every 1–3 days, and workup for autoimmunity should be considered, including serum antinuclear antibody, smooth muscle antibody, antimitochondrial antibodies, antisoluble liver antigen/liver pancreas antibodies, anti-liver–kidney microsomal-1 antibodies, and others as appropriate. Consider imaging to assess for nonautoimmune causes of liver abnormalities. Consultation with a gastroenterologist or hepatologist is reasonable, and a liver biopsy may be considered. There are limited pathologic data regarding changes seen with ipilimumab-induced hepatitis. A few case reports have demonstrated inflammation, necrosis, and rare, if any, fibrosis. These findings more closely resemble those seen with drug-induced acute hepatitis rather than classic autoimmune hepatitis; clinical correlation is essential [36]. An increased frequency of lab monitoring should continue until the liver labs have stabilized or improved then continue with weekly monitoring. Rebound has been described with elevated liver tests as well as with other irAEs. For example, transaminases are abnormal on a follow-up appointment and the ipilimumab dose is skipped. The liver tests then normalize and ipilimumab is resumed with the next planned dose and the liver tests subsequently elevate again. These cases are often difficult to gauge and manage and consideration of consultation with a hepatology specialist is advised. If serum liver tests are greater than eight times the upper limit of normal, further ipilimumab should be held and labs repeated within 24 hours. If no improvement and an irAE is suspected, hospital admission and initiation of high-dose IV steroids and hepatology consult is advised. If there is an inadequate response to high-dose steroids, additional immunosuppressive therapy may be needed [35]. Gastroenterologists will be readily available in most settings, but dedicated hepatologists may not be. Permanent cessation of ipilimumab is indicated for ipilimumab-induced hepatitis that requires treatment with steroids.

Endocrinopathies

Endocrinopathies, other than thyroid dysfunction, are uncommon diagnoses in oncology. Hypothyroidism can be seen with immunotherapies and some molecular therapies and typically follow a subacute presentation. In contrast, the most common endocrinopathy seen with ipilimumab is hypophysitis. Autoimmune hypophysitis, or lymphocytic hypophysitis, is quite rare and often presents in women late in pregnancy or postpartum and is accompanied by altered pituitary function, most commonly of corticotrophin (ACTH) [37]. Hypophysitis related to treatment with ipilimumab typically presents at or after the third infusion, with an incidence of approximately 1.5% (range: 0%–17%) [4, 15, 38]. The presenting symptoms of ipilimumab-induced hypophysitis can be quite vague and require vigilance. Symptoms can include fatigue, headaches, myalgias, loss of appetite, or nausea and vomiting. Patients may also complain of eye pain, diplopia, or other visual changes. Visual changes and/or headaches in patients with metastatic melanoma should also prompt concern for possible CNS or orbital metastases and should be evaluated with a contrasted brain magnetic resonance imaging (MRI). Hypophysitis typically manifests as diffuse enlargement of the pituitary, with or without areas of necrosis, on brain MRI but may also have normal findings [39, 40]. Laboratory evaluations include TSH, free T4, total and free triiodothyronine (T3), cortisol, ACTH, luteinizing hormone, follicle-stimulating hormone, and testosterone (in men). Low levels of ACTH, TSH, and gonadotropins lead to low free T4, cortisol, and testosterone, and establish the diagnosis of hypophysitis with hypopituitarism. Ipilimumab-induced hypophysitis typically involves the anterior pituitary, impacting the thyroid and adrenal axes [40]. Less common presentations include hyponatremia due to the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion or diabetes insipidus [41].

Hypophysitis with associated adrenal insufficiency/crisis is a potentially life-threatening matter and requires urgent attention (Fig. 6). The hallmarks of adrenal insufficiency are hypotension, dehydration, and electrolyte abnormalities, such as hyponatremia and hyperkalemia. IV high-dose steroids with mineralocorticoid activity such as methylprednisolone should be started after laboratory tests are drawn and while waiting for results and endocrine consult, then discontinued later if another cause is determined. Patients should be evaluated for infections and/or sepsis. If no evidence of adrenal crisis, it is reasonable to wait for laboratory results prior to starting steroids. All patients with hypophysitis require corticosteroids and likely thyroid hormone replacement, as well as testosterone replacement in men. Prednisone 1 mg/kg/day, or the equivalent, is typically recommended as a starting dose, if clinically stable. Steroids can be slowly tapered to a lower physiologic dose once symptoms are controlled. The need for steroids is likely to be permanent in endocrinopathies, as opposed to other irAEs, as this functions as both hormone replacement and immunosuppression. MRI findings of pituitary enlargement and inhomogeneity typically resolve with treatment; thyroid hormone and/or testosterone replacement therapy may not be permanent [40].

Intrinsic thyroid dysfunction can also be seen with ipilimumab and most often presents as autoimmune thyroiditis [16, 21]. Min et al. also reported a case of Graves' ophthalmopathy presenting with eye pain, conjunctivitis, proptosis, and periorbital edema with elevated antithyroid peroxidase and antithyroglobulin antibodies [16]. After an initial response to steroids, the patient relapsed while on a steroid taper and required resumption of IV high-dose steroids. Symptoms and abnormal lab findings persisted for several months. In this case, the patient was treated with a burst of methylprednisolone 1000 mg IV daily for 3–5 days followed by lower doses of IV/oral steroids. A burst of high-dose steroids is reasonable to consider in patients with potentially severe or life-threatening irAEs. Current recommendations include baseline TSH and free T4 and monitoring of this every 3 weeks during ipilimumab treatment and every 2–3 months following comple-

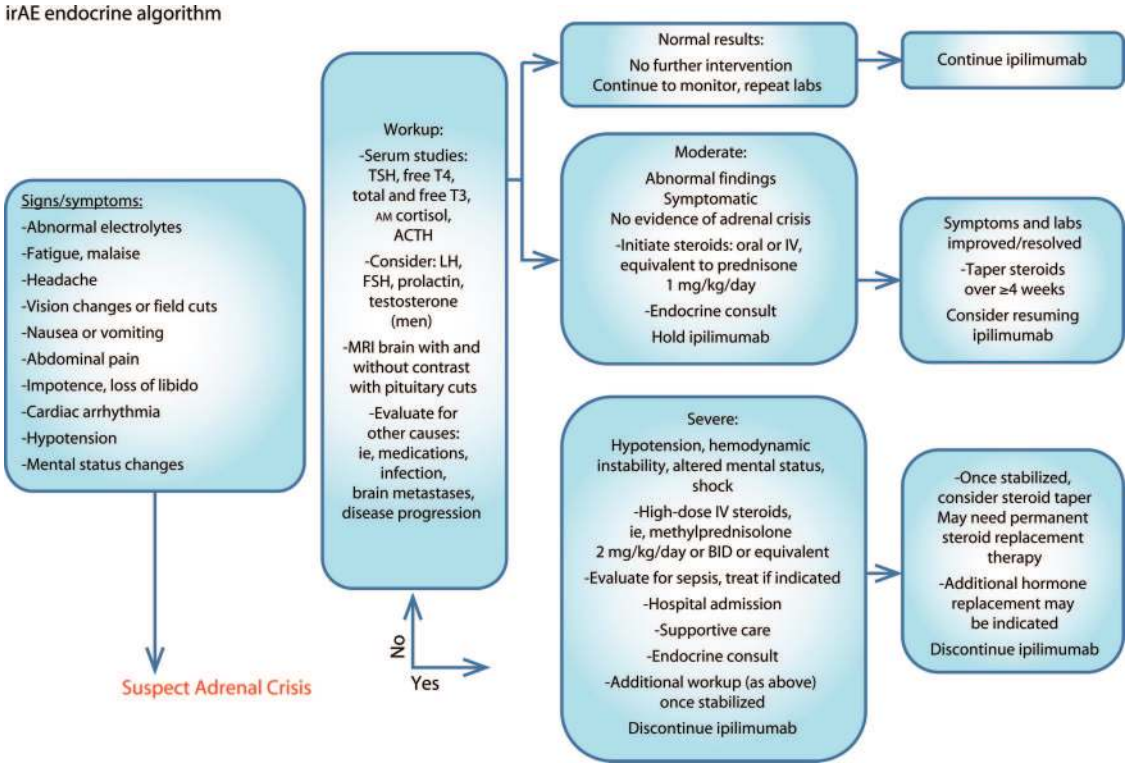


Figure 6. Algorithm for endocrine irAE management.

tion. Baseline early morning cortisol levels during treatment may be considered, but are not required [42]. Ipilimumab should be permanently discontinued in cases of adrenal crisis. However, if a patient is clinically stable at the time of presentation with an endocrinopathy that is controlled with hormone replacement, it may be reasonable to resume ipilimumab. Endocrinologists are a very subspecialized group and may not be readily available in all locales. Establishing contact ahead of time with an endocrinologist, and possibly a pituitary specialist, is recommended.

Neurologic Toxicities

As previously discussed, irAEs can be transient and present with vague symptoms. Neuropathies associated with ipilimumab often fall into this category and have been difficult to assess. Patients with preexisting neuropathies do not appear at greater risk for ipilimumab-induced neuropathy; however, the presence of diabetes mellitus or chemotherapy-associated neuropathies can confound diagnosis and management. The panel felt that a neurology consult for any symptom more severe than general, vague neuropathy should be considered as well as an MRI to evaluate for a disease-related cause. While extremely rare at less than 1%, life-threatening neuropathies, such as Guillain-Barré syndrome, severe motor neuropathy, or myasthenia gravis have been reported [43]. Numbness and tingling of the hands and feet can rapidly progress to loss of sensory and motor function within 48 hours. One patient responded within 48 hours to treatment with high-dose methylprednisolone, after infectious etiologies were ruled out, with significant recovery by 4 weeks. Despite treatment with high dose steroids, the patient did evidence antitumor benefit. Other presentations of neurotoxicity have included enteric neuropathy with severe refractory constipation, inflammatory myopathy, aseptic meningitis, and optic neuritis [18, 44–46]. Any CNS or severe motor or sensory neuropathy necessitates permanent cessation of CTLA-4 therapy.

Other Toxicities

As previously stated, ipilimumab may prompt a T-cell–mediated immune attack on any part of the body. Ophthalmic toxicities are important to recognize, with uveitis being the most common [47]. While rare (1% or less), patients with visual changes need to be seen and evaluated by an ophthalmologist promptly and may require treatment with steroid eye drops and/or systemic steroids if an irAE is confirmed or highly suspect. Again, evaluation for CNS or orbital metastases should be considered. There may be an association between ipilimumab-induced enterocolitis and uveitis [47]. Case reports have described glomerulonephritis presenting with proteinuria and positive anti-double stranded DNA antibodies [48]: pneumonitis [34], temporal arteritis [40], as well as sarcoidosis [49, 50]. Additionally, hematologic toxicities including neutropenia [51], thrombocytopenia [52], red cell aplasia [53], and clotting dysfunction [17] have been described. Vigilance and a high level of suspicion for possible irAEs on the part of the treating oncologist are essential to the use of ipilimumab.

Toxicities of Immunosuppression

High-dose steroids are indispensable for the treatment of moderate to severe irAEs. However, with high doses and prolonged courses as well as the possibility for additional immunosuppressive agents, these medications carry toxicities as well. Direct side effects of steroids include activation, depression, insomnia, psychosis (rarely), appetite stimulation, myopathy, and hyperglycemia, as well as other issues. Deconditioning can be exacerbated with frequent hospitalizations and erratic oral intake. Further, prolonged steroids and other immunosuppressives carry an in-

creased risk of infection. Common bacterial infections can occur; however, viral and fungal infections as well as opportunistic infections, less commonly seen in the solid oncology realm, are important to recognize. Consideration should be given to prophylactic antimicrobials against pneumocystis jiroveci pneumonia (formerly pneumocystis carinii), herpes simplex virus, and fungal organisms in some patients [20]. Tuberculosis (TB) testing to evaluate for latent TB is recommended prior to initiation of infliximab or other anti-tumor necrosis factor alpha antagonists [54]. An infectious disease specialist may need to be a member of an oncologist's multidisciplinary team.

Selection of Patients

Ipilimumab therapy is not right for every melanoma patient, yet selection criteria for ipilimumab are still uncertain and there remain significant gaps in knowledge. Currently, no predictive markers are available to guide which patients will get therapeutic benefit from ipilimumab. One factor to consider is the pace of a patient's melanoma. In patients with rapidly progressive disease, they may not be able to survive the time needed to manifest a response to immunotherapy [55]. Treatment with an agent with a shorter time to possible response may be preferable. Thus, patient selection for ipilimumab presently centers on factors that may predict unacceptable toxicity. Age does not appear to impact tolerance or efficacy and ipilimumab has been administered safely to patients in their 80s. While no contraindications to treatment are listed in the FDA-approved package insert, it is crucial to elicit a history of any prior autoimmune diseases, such as Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, etc. All clinical trials with ipilimumab excluded subjects with prior autoimmune disease given the concern for exacerbation that could lead to significant morbidity or mortality. The panel did not recommend ipilimumab therapy in patients with systemic autoimmune conditions such as the ones previously listed outside of a clinical trial. However, it is unclear if patients with type I diabetes, severe psoriasis, or other conditions can be safely treated with ipilimumab, and no consensus on these conditions was reached. In the setting of autoimmune hypothyroidism or vitiligo that can be easily managed and are not considered life threatening, treatment with ipilimumab is reasonable. Patients with conditions of unclear etiology that may have an autoimmune component, such as sarcoidosis, are also challenging. There are very limited, if any, data regarding ipilimumab in these patient subsets, and there is no consensus regarding such patients at this time. Others excluded from clinical trials with CTLA-4 blocking agents included patients with hepatitis B or C, human immunodeficiency virus, or those on chronic immunosuppression, including organ transplant patients. Over time, case reports and anecdotal data are becoming available [56, W.H. Sharfman, personal communication].

Currently, no predictive markers are available to guide which patients will get therapeutic benefit from ipilimumab. One factor to consider is the pace of a patient's melanoma. In patients with rapidly progressive disease, they may not be able to survive the time needed to manifest a response to immunotherapy. Treatment with an agent with a shorter time to possible response may be preferable.

Prior to treatment with ipilimumab, there should be an analysis of the possible benefits and risks and a discussion with the patient and family. The current status of any underlying autoimmune (or other immune-mediated) condition, possibility of exacerbation (which may be persistent), and potential for response to treatment (if exacerbated) must be considered and discussed. In metastatic melanoma, no systemic treatments are considered curative and that must be weighed against potential toxicities, which could lead to significant morbidity or death. If the decision is made to treat with ipilimumab, close monitoring and aggressive education for ancillary staff as well as for patients and their families is recommended.

Conclusion

Ipilimumab is a definite advance in the treatment of metastatic melanoma, demonstrating improved survival and durability of response in randomized trials. Continued investigations will inform us about its optimal schedule and dose. Often well tolerated, including in the elderly, ipilimumab-induced irAEs can occur and are not typical of other anticancer agents. irAEs may follow an unpredictable course and, if untreated, can be severe and life threatening. Vigilance and suspicion are needed in treating patients with ipilimumab so that an irAE, if manifest, can be diagnosed and managed promptly. Most are controlled with high-dose steroids followed by a slow taper. In some cases, additional immunosuppression may be necessary. Steroids should be avoided if not needed; however, if an irAE develops, they should be used without hesitation, as they do not impair antitumor benefits of ipilimumab. Assembling and educating a multidisciplinary team of physicians and ancillary staff will facilitate the care and management of these patients.

Acknowledgments

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise. The authors also wish to acknowledge Jennifer Wietzke, Ph.D., and Rebecca Goldstein, Ph.D., from StemScientific, funded by Bristol-Myers Squibb, for providing editorial support. Neither Bristol-Myers Squibb nor StemScientific influenced the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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EDITOR'S NOTE: See the accompanying commentary on pages 658–660.