

## Original Investigation

# Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

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**IMPORTANCE** Ipilimumab and other immune therapies are effective treatment options for patients with advanced melanoma but cause frequent immune-related toxic effects. Autoimmune diseases are common, and the safety and efficacy of ipilimumab therapy in patients with preexisting autoimmune disorders is not known.

**OBJECTIVE** To determine the safety and efficacy of ipilimumab therapy in patients with advanced melanoma with preexisting autoimmune disorders.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective review of patients with advanced melanoma and preexisting autoimmune disorders who received ipilimumab at 9 academic tertiary referral centers from January 1, 2012, through August 1, 2015. The data analysis was performed on August 24, 2015.

**EXPOSURE** Ipilimumab therapy.

**MAIN OUTCOMES AND MEASURES** Safety, in terms of frequency of autoimmune flares and conventional immune-related adverse events (irAEs), and efficacy, in terms of response rates and overall survival, were evaluated descriptively.

**RESULTS** Of the 30 patients who received ipilimumab (17 [57%] male; median [range] age, 59.5 [30-80] y), 6 had rheumatoid arthritis, 5 had psoriasis, 6 had inflammatory bowel disease, 2 had systemic lupus erythematosus, 2 had multiple sclerosis, 2 had autoimmune thyroiditis, and 7 had other conditions. Thirteen patients (43%) were receiving immunosuppressive therapy at the time of initiation of ipilimumab therapy, most commonly low-dose prednisone or hydroxychloroquine. With ipilimumab treatment, 8 patients (27%) experienced exacerbations of their autoimmune condition necessitating systemic treatment; all were managed with corticosteroids. Conventional grade 3 to 5 irAEs occurred in 10 patients (33%) and were reversible with corticosteroids or with infliximab therapy in 2 cases. One patient with baseline psoriasis died of presumed immune-related colitis after a 1-week delay prior to reporting symptoms. Fifteen patients (50%) had neither autoimmune disease flares nor irAEs. Six patients experienced an objective response (20%), including 1 with a durable complete response.

**CONCLUSIONS AND RELEVANCE** To our knowledge, this is the largest series of patients with preexisting autoimmune disease treated with immune checkpoint inhibitors. Ipilimumab was clinically active and was associated with exacerbations of autoimmune disease and conventional ipilimumab-induced irAEs that were readily manageable with standard therapies when started in a timely fashion. Ipilimumab therapy may be considered in this setting with vigilant clinical monitoring.

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Ipilimumab is a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA-4) that induces antitumor immune responses by removing a key negative regulator of T cell activation. This antibody was the first agent to demonstrate improved overall survival for patients with advanced melanoma and received regulatory approval in 2011.<sup>1,2</sup> Furthermore, durable benefits have been observed, with approximately 20% of patients surviving at least 5 years.<sup>3,4</sup>

Ipilimumab's toxic effects stem from immune dysregulation resulting in aberrant targeting of antigens in normal tissues. Immune-related adverse events (irAEs) include colitis, hepatitis, dermatitis, endocrine disorders (eg, hypophysitis, adrenal insufficiency, and hypothyroidism), neuropathies, and others.<sup>5,6</sup> As such, patients with baseline autoimmune diseases were largely excluded from clinical trials of ipilimumab and other immune checkpoint inhibitors. Between 20 and 50 million individuals in the United States alone have an autoimmune disease,<sup>7,8</sup> ensuring that advanced melanoma and autoimmunity coexist in a substantial number of patients.

Following regulatory approval, there has remained a widespread and understandable reluctance to use ipilimumab in patients with autoimmune conditions due to concerns of exacerbating the underlying autoimmune disorder and/or inducing severe irAEs. This commonly places clinicians and patients in a dilemma because immunotherapies may be the only available treatment options for many patients. Although case reports involving a total of 4 patients have evaluated ipilimumab in patients with preexisting autoimmune diseases,<sup>9-11</sup> the safety and efficacy of ipilimumab in this population is essentially unknown.

In this study, we retrospectively assessed patients with advanced melanoma who received ipilimumab and had preexisting autoimmune diseases, including rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE), inflammatory bowel disease, and others. We captured data from 30 patients treated at 9 large melanoma centers and characterized the safety (incidence and severity of irAEs and autoimmune exacerbations of their underlying disease) and therapeutic efficacy of ipilimumab in this setting.

## Methods

### Patients

Following institutional review board approval for all study procedures, we extracted clinical data from the medical records from participating centers. At all sites local institutional review board approval was obtained with waiver of consent due to the retrospective nature of the study. We included all patients who had received at least 1 dose of ipilimumab since 2011 who also had a baseline autoimmune disorder. All patients received ipilimumab as standard of care rather than on clinical trial protocols. Qualifying autoimmune conditions included but were not limited to the following: rheumatologic (rheumatoid arthritis, SLE, psoriatic arthritis, vasculitis), gastrointestinal (inflammatory bowel disease, celiac disease), neurologic (Guillain Barré syndrome, transverse myelitis, multiple sclerosis, myasthenia gravis), endocrine (Graves disease, Hashi-

### At a Glance

- Ipilimumab induces immune-related adverse events (irAEs), so patients with autoimmune disorders are excluded from ipilimumab clinical trials.
- We retrospectively characterized the clinical outcomes of 30 patients with preexisting autoimmune disorders who received ipilimumab.
- We observed that 15 patients (50%) experienced irAEs or flares of their underlying autoimmune disorder, which were generally manageable with standard treatment.
- Six patients (20%) experienced complete or partial responses to therapy; median overall survival was 12.5 (95% CI, 6.3 to not reached) months.
- Ipilimumab appears to be safe and effective for many patients with advanced melanoma and concurrent, preexisting autoimmune disorders; patients should be monitored closely for irAEs and autoimmune flares.

moto thyroiditis), dermatologic (psoriasis), or other (sarcoidosis, rheumatic fever). Asthma and hypothyroidism of unexplained etiology were not included.

### Study Design

We characterized the baseline patient demographic characteristics, including age, sex, and prognostic factors (American Joint Committee on Cancer [AJCC] pathologic stage, serum lactate dehydrogenase level). To characterize the severity of baseline autoimmunity, we assessed the duration, symptoms, ongoing therapies, and prior treatments for each autoimmune condition. We assessed the safety of ipilimumab in these patients, as defined by worsening of the autoimmune disorder necessitating therapeutic intervention with systemic immune-modifying agents, and the incidence of conventional irAEs and corresponding management. We also evaluated the efficacy of ipilimumab in terms of treatment response as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1,<sup>12</sup> progression-free survival (PFS), need for subsequent therapies, and overall survival (OS). Adverse effects were classified by grade according to the Common Terminology Criteria for Adverse Events, version 4.0.<sup>13</sup>

### Statistical Analysis

Categorical and continuous variables were summarized using percentages and means. No formal hypothesis testing was performed with these variables. Overall survival and PFS were estimated using the Kaplan-Meier method; all patients were censored at last available follow-up. Progression-free survival was defined as time of treatment start to disease progression (as determined by the treating clinician); OS was defined as treatment start to death for any reason. All analyses were performed by means of R, version 3.2.2.

## Results

### Patients

We identified 30 patients from 9 centers treated with ipilimumab who had an autoimmune disorder at baseline (**Table 1**).

Table 1. Baseline Demographic and Autoimmune Disorder Characteristics

Characteristic	No. (%) <sup>a</sup> (N = 30)
Age, median (range), y	59.5 (30-80)
Sex	
Male	17 (57)
Female	13 (43)
Stage	
IIIc/M1a/M1b	4 (13)
M1c	26 (87)
Brain metastases	13 (43)
Elevated serum lactate dehydrogenase level	17 (57)
Autoimmune disorder <sup>b</sup>	
Rheumatoid arthritis	6 (20)
Psoriasis	5 (17)
Multiple sclerosis	2 (7)
Crohn disease or ulcerative colitis	6 (20)
Systemic lupus erythematosus	2 (7)
Thyroiditis	3 (10)
Sarcoidosis	2 (7)
Other	7 (23)
Prior systemic therapies for autoimmune disorder	
Any	22 (73)
Corticosteroid	10 (33)
Disease-modifying antirheumatic	13 (43)
Ongoing therapies	
Steroids	6 (20)
Other	7 (23)
Time since autoimmune diagnosis, median (range), y	13.5 (0.25-60)

<sup>a</sup> Data are given as number (percentage) unless otherwise specified.

<sup>b</sup> Total exceeds 30 because 2 patients had more than 1 disorder. Other includes transverse myelitis, polymyalgia rheumatica, celiac disease, rheumatic fever, reactive arthritis (Reiter syndrome), and a chronic nonspecific arthritis syndrome that arose during nivolumab therapy.

The median (range) age was 59.5 (30-80) years, and most patients had adverse prognostic features (elevated serum lactate dehydrogenase level in 17 [57%], AJCC stage IV M1c disease in 26 [87%], brain metastases in 13 [43%]). Baseline autoimmune conditions included rheumatoid arthritis in 6 patients, SLE in 2, psoriasis in 5, inflammatory bowel disease in 6, multiple sclerosis in 2, and thyroiditis in 3. The median (range) duration since diagnosis of the autoimmune disease was 13.5 (0.25-60) years, and 22 patients (73%) had received prior systemic immune modulators. At the time of ipilimumab treatment initiation, 13 patients (43%) were actively receiving at least 1 systemic therapy (6 receiving low-dose steroids, 5 hydroxychloroquine sulfate, 1 leflunomide, and 1 methotrexate). The eTable in the Supplement presents detailed clinical information regarding individual patients' autoimmune disorders.

### Safety

Following ipilimumab therapy, 8 patients (27%) had some type of exacerbation of their autoimmune disease that required treatment (Table 2). In general, these were recurrent or increased manifestations of prior symptoms (eg, joint pain with rheumatoid arthritis, worsening plaques in psoriasis) rather

than other less predictable disease manifestations. These disease flares readily resolved with low-dose corticosteroid therapy (5-30 mg prednisone daily) in most cases although did require higher doses (prednisone 1 mg/kg) in 2 instances. One patient with rheumatoid arthritis experienced severe joint pains concurrent with the onset of hypophysitis after 3 doses of ipilimumab and was treated with methylprednisolone 1 mg/kg. Another patient with ulcerative colitis who was already receiving dexamethasone acetate for brain metastases developed diarrhea and then received infliximab. No other patients required additional immune-modifying agents beyond corticosteroids. Notably, the timing of disease exacerbation ranged from 3 days to 7 months following the initiation of ipilimumab therapy but occurred most often at 2 to 3 weeks (n = 3) and at 6 weeks (n = 2). Several patients had concurrent grade 3 to 5 irAEs and autoimmune exacerbations and received higher dose corticosteroids for clinical management.

Conventional ipilimumab-induced irAEs, distinct from exacerbations of the baseline autoimmune disease, were also assessed. Grade 3 to 5 irAEs were experienced by 10 patients (33%) (Table 2). These included colitis (5 patients), hypophysitis (n = 3), thyroiditis (n = 1), and acute glaucoma (n = 1; unclear whether this was a true irAE). Most were well managed with corticosteroids (administered at 1 mg/kg followed by a slow taper). A single patient with an inflammatory arthritis (arising previously during anti-programmed death-1 [anti-PD-1] therapy and improving with hydroxychloroquine therapy) developed colitis during ipilimumab therapy and received corticosteroids and infliximab with subsequent resolution. Among patients with grade 3 or 4 irAEs, the time of onset appeared consistent with other studies, occurring after a median of 3 doses.<sup>6</sup> One patient, a man in his 70s with baseline psoriasis with skin-only involvement and who was not receiving immunosuppressive therapy, died, presumably of ipilimumab-related autoimmune colitis. He developed diarrhea after his third dose of ipilimumab but did not seek medical attention until his symptoms had been ongoing for nearly 1 week. He presented with presumed hypovolemic shock to a different facility from his treating institution and died 2 days later despite corticosteroid administration and volume repletion. It is well known that colitis can be fatal if left untreated for an extended duration, and it was believed that this death was likely related to delays in care and unreported symptoms rather than directly to his psoriasis. No other patients died of irAEs or autoimmune exacerbations. Of note, 15 patients (50%) experienced neither autoimmune flares nor irAEs. Three patients (10%) experienced both an irAE and an autoimmune disease flare.

Colitis is a particularly frequent and potentially life-threatening ipilimumab-induced toxic effect,<sup>1,14-16</sup> and therefore the 6 patients with inflammatory bowel disease (Crohn disease, ulcerative colitis) were of particular clinical interest. Of these, 2 with ulcerative colitis had prior colectomies (including 1 immediately preceding initiation of ipilimumab therapy) and 1 patient with Crohn disease had a partial colectomy. The other 3 patients were receiving aminosalicilate derivatives or topical hydrocortisone at the time of ipilimumab initiation, and all were asymptomatic or minimally sympto-

Table 2. Autoimmune Exacerbations and Grade 3 to 5 Immune-Related Adverse Events

Patient No.	Baseline Condition	Autoimmune Exacerbation	Treatment	Immune-Related Adverse Event	Treatment	Outcome Notes
2	Sarcoidosis	...	...	Glaucoma	Ocular steroids	
3	RA	Joint pain	As for hypophysitis	Hypophysitis	Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg	Durable CR
4	RA	...	...	Thyroiditis	Prednisone 1 mg/kg tapered over 2 wk	
5	Psoriasis	Worsening plaques	As for colitis	Colitis	Methylprednisolone 2 mg/kg tapered over 6 wk	After 1 dose
6	Psoriasis, Graves disease	...	...	Hypophysitis	Prednisone 30 mg ×1 wk, transition to hydrocortisone over 5 d	PR
8	RA, polymyalgia rheumatica	Joint pain, myalgias	Prednisone 30 mg/d tapered over 1 mo	...	...	After 3 d
9	RA	Joint pain	Prednisone 15 mg/d down to 10 mg	...	...	After 7 mo
11	Transverse myelitis	...	...	Colitis	Prednisone 1 mg/kg tapered over 8 wk	
12	Crohn disease	...	...	Colitis	Methylprednisolone 1 mg/kg tapered over 8 wk	After 1 dose
14	Ulcerative colitis	Diarrhea, disease flare	Infliximab, dexamethasone 2 mg daily <sup>a</sup>	...	...	PR
15	Inflammatory arthritis <sup>b</sup>	Joint pain	As for colitis	Colitis	Prednisone 1 mg/kg tapered over 4 wk, infliximab	...
20	Psoriasis	...	...	Hypophysitis	Prednisone 50 mg ×1 dose, then 5 mg daily	...
23	Sarcoidosis	Hypercalcemia, renal insufficiency	Prednisone 25 mg/d, tapered to 20 mg after 4 wk	...	...	Ongoing SD
24	RA	Joint pain	Prednisone 10 mg/d, now receiving 8 mg/d	...	...	Ongoing PR
28	Psoriasis	...	...	Presumed colitis grade 5	Methylprednisolone 1 mg/kg	Patient died

Abbreviations: CR, complete response; ellipses, none; PR, partial response; RA, rheumatoid arthritis; SD, stable disease.

<sup>a</sup> Receiving dexamethasone for brain metastases; infliximab was added with onset of diarrhea.

<sup>b</sup> Patient developed a chronic, inflammatory-appearing arthritis during nivolumab therapy that improved with use of low-dose steroids and hydroxychloroquine.

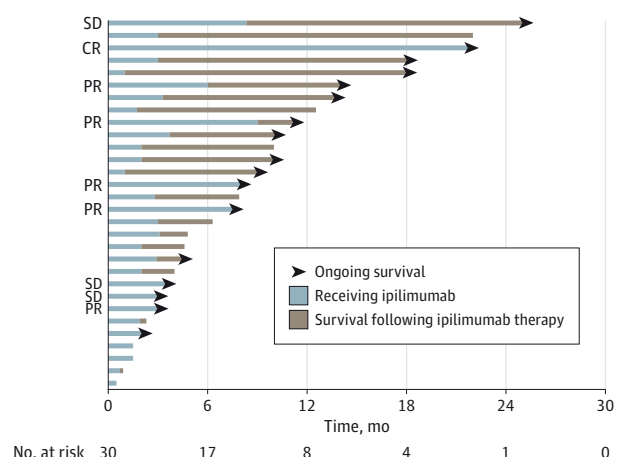
matic. Only 2 of these 6 patients experienced an exacerbation of their disease or ipilimumab-induced colitis during treatment. One patient with ulcerative colitis (with prior colectomy) developed significant diarrhea after her first dose with subsequent resolution after treatment with infliximab. Another patient developed diarrhea after his second dose of ipilimumab; colonoscopy evaluation was more consistent with ipilimumab-induced colitis rather than a Crohn disease flare, and symptoms resolved quickly with methylprednisolone therapy. A third patient had no symptoms but was found to have radiographic evidence of hyperemia and thickening of the rectal stump at the colectomy site on a surveillance computed tomographic scan.

Hypophysitis is another common and stereotypical irAE that may complicate ipilimumab therapy. In our experience, 3 patients (10%) experienced this complication; 1 was treated with a high-dose regimen (prednisone 1 mg/kg), and the others received a lower dose followed by replacement dosing (Table 2). As in other studies, clinical outcomes following corticosteroid therapy were excellent although all patients required ongoing corticosteroid replacement therapy.<sup>17,18</sup>

### Efficacy

Of 30 patients who received ipilimumab, 6 experienced a partial or complete response (20%) (Figure 1). One patient (with

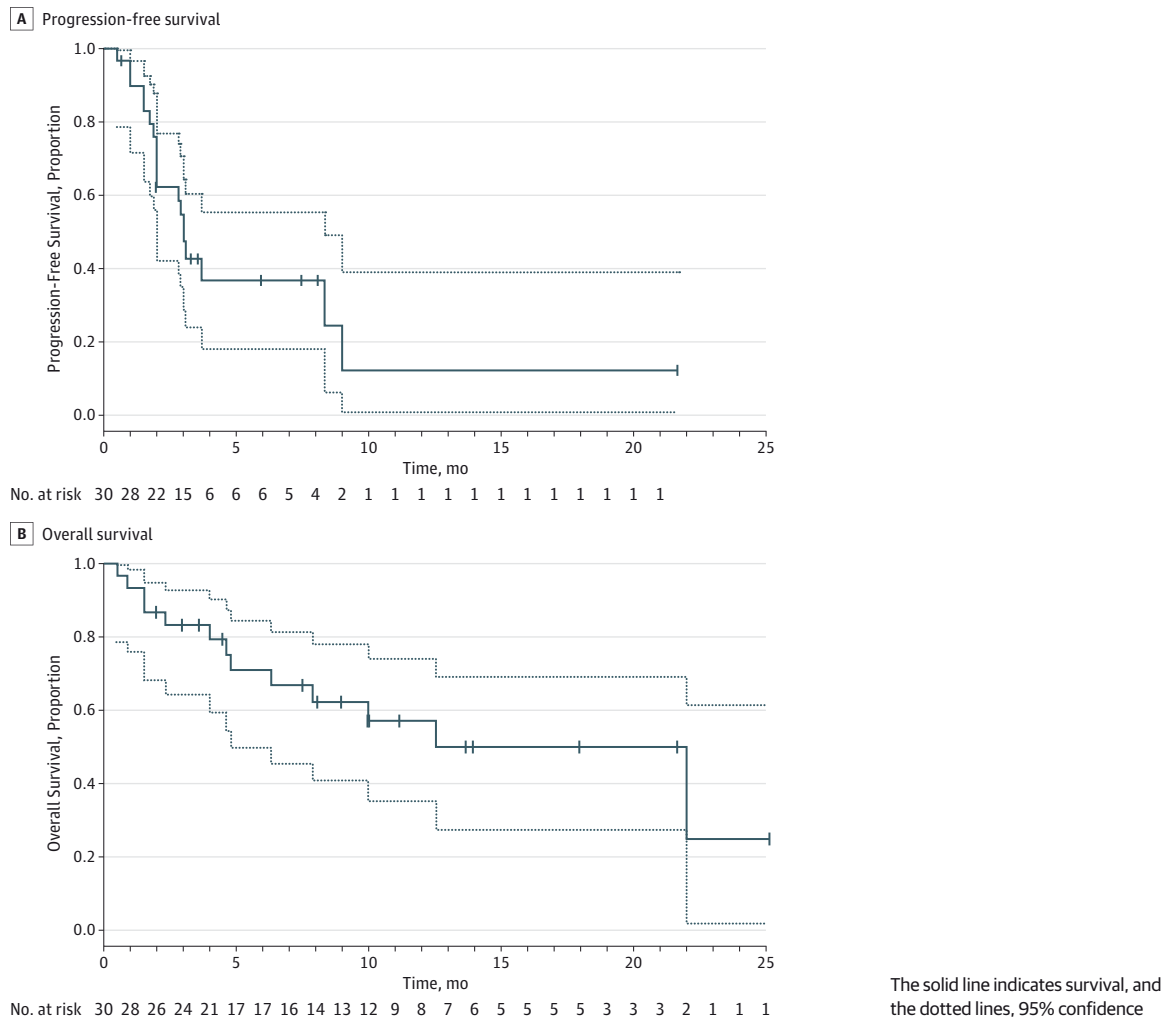
Figure 1. Response, Duration of Ipilimumab Therapy, and Survival



CR indicates complete response; PR, partial response; and SD, stable disease.

rheumatoid arthritis) had a complete response, which remains ongoing nearly 2 years after starting therapy. This patient had a mild exacerbation of joint pain as well as hypophysitis after the third dose of ipilimumab, which symptomatically

Figure 2. Progression-Free Survival and Overall Survival for All Patients



resolved with corticosteroid therapy. Five other patients had partial responses. Two responses lasted 6 and 9 months, respectively; 3 others have ongoing responses at 3, 8, and 8 months. These responding patients had rheumatoid arthritis (n = 3), psoriasis, ulcerative colitis, and reactive arthritis, respectively. Seven patients (23%) experienced rapid disease progression with less than 6-month OS. Temporary disease stabilization was observed in 3 (10%) others. The median PFS was 3.0 (95% CI, 2.0-8.3) months, and the median OS was 12.5 months (95% CI, 6.3 months to upper limit not applicable) (Figure 2).

## Discussion

Ipilimumab is an immune checkpoint inhibitor that has demonstrated improved survival in patients with advanced melanoma but causes frequent immune-related toxic effects. Patients with autoimmune disease were excluded from many of the early trials, leaving clinicians with minimal safety and efficacy data for these patients. In this study, we found that 50%

of patients with advanced melanoma and baseline autoimmune disease experienced either autoimmune exacerbations or irAEs when treated with ipilimumab. These events, however, were easily managed by standard treatment algorithms in nearly all cases and did not preclude clinical benefit. Moreover, the incidence of irAEs did not exceed that observed in large clinical trials.<sup>1,19-21</sup> We conclude, therefore, that ipilimumab therapy can be carefully considered in many patients with baseline autoimmunity after an informed discussion and with close monitoring.

Autoimmune disorders comprise more than 80 distinct diseases and cause substantial morbidity in some cases. Certain autoimmune conditions may confer a decreased life expectancy. For example, older observational series suggest that patients with rheumatoid arthritis may have a 3- to 10-year shorter lifespan compared with age-matched controls.<sup>22,23</sup> Despite the importance of efforts to counter this increased mortality, clinicians should also note that untreated advanced melanoma is associated with a median survival of only 6 to 9 months, with similar survival for patients who receive only cytotoxic chemotherapy.<sup>24</sup> We conclude, therefore, that



treatment of melanoma should be prioritized in most cases, particularly in view of the relative safety observed in our series. Important exceptions may exist, such as in patients with life-threatening conditions such as Guillain-Barré syndrome requiring respiratory support or active and/or uncontrolled inflammatory bowel disease. These situations were not directly addressed in this study.

We did observe frequent immune-mediated toxic effects, including autoimmune exacerbations, and irAEs that are classically associated with ipilimumab use. Most irAEs occurred in standard, well-described time frames following the onset of ipilimumab treatment and were easily managed by corticosteroid treatment. In some cases, augmentation of baseline immune-modulating drug regimens, used to treat the baseline autoimmune disease, was necessary. One patient experienced a fatal presumed irAE (colitis); this death appeared to be more related to delays in seeking treatment rather than to the preexisting autoimmune condition (psoriasis). An underlying, overly responsive immune system cannot be completely excluded, although initial clinical trials of ipilimumab therapy in patients without baseline autoimmune disorders reported a drug-related mortality rate of up to 2%.<sup>1</sup>

Cytotoxic T-lymphocyte antigen 4 plays a critical role in maintaining tolerance to peripheral self-antigens, as evidenced by a lethal, multiorgan autoimmunity in CTLA-4 knockout mice, and the irAE profile associated with CTLA-4 blockade.<sup>1,25</sup> However, the specific role of CTLA-4 and other immune checkpoints (eg, PD-1) in many autoimmune disorders has not been thoroughly elucidated. A number of studies have variably correlated CTLA-4 gene polymorphisms with the development of various autoimmune disorders.<sup>26</sup> Moreover, agents that promote CTLA-4 signaling have demonstrated efficacy in autoimmune disease. Abatacept, a fusion protein comprising the extracellular domain of CTLA-4, competes with CD28-CD80 pathway signaling and improves outcomes in rheumatoid arthritis.<sup>27</sup> In parallel, a number of studies have also suggested that ipilimumab use is largely

safe following solid-organ or hematopoietic stem cell transplants.<sup>28-31</sup> Our experience potentially corroborates these studies, suggesting frequent but readily manageable exacerbations of baseline autoimmunity with CTLA-4 blockade.

This study has several limitations. First, severe cases of autoimmune disease may have been underrepresented. This series reflects only patients whom clinicians were willing to treat, but did include patients with inflammatory bowel disease and other clinically active autoimmune diseases. Second, a generally less toxic class of immune therapies are now available (anti-PD-1) and will likely be the first choice for most patients with underlying autoimmunity. Preclinical models support a less immunogenic role of anti-PD-1; while CTLA-4 knockout mice develop a lethal autoimmune phenotype, PD-1 knockout mice experience substantial but less severe autoimmunity.<sup>32</sup> Furthermore, delayed toxic effects unmasked by subsequent immune therapies (such as anti-PD-1) should be assessed in the subset of patients whose ipilimumab treatment failed. Finally, a relatively small number of patients were included, although this study represents a substantially greater sample size compared with all other previous studies combined, and combines the experience of 9 large melanoma centers.<sup>9-11</sup>

## Conclusions

Ipilimumab use caused immune events in some patients with baseline autoimmunity. Nevertheless, patients were easily treated with appropriate treatment algorithms and sustained durable therapeutic benefits in some cases. Therefore, clinicians may judiciously consider ipilimumab therapy in patients with advanced melanoma and baseline autoimmunity with close monitoring and adherence to irAE treatment algorithms. These insights are also important for other T-cell checkpoint inhibitors, which are now achieving regulatory approval in melanoma and other types of cancer.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Johnson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Johnson, Sullivan, Puzanov, Kaufman, Mehnert, Sosman.

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**Conflict of Interest Disclosures:** Dr Johnson has consulted for Genoptix and Bristol-Myers Squibb. Dr Ott has consulted for and received honoraria from Bristol-Myers Squibb and Amgen. Dr Carlino has received honoraria from Novartis; consulted for Bristol-Myers Squibb, Merck, and Amgen; and received travel reimbursement from GlaxoSmithKline. Dr Khushalani has consulted for Genentech, Provectus, and Amgen; has been a member of the speaker's bureau for Prometheus;

and has received research funding from Merck, Pfizer, Bristol-Myers Squibb, Threshold, Eisai, and Amgen. Dr Guminski receives honoraria/consulting fees from Roche, Novartis, and Bristol-Myers Squibb, all less than \$3000. Dr Puzanov has consulted for Amgen and Roche and received travel reimbursement from Amgen. Dr Kaufman serves as a consultant for Alkermes, Amgen, EMD Serono, Prometheus, and Sanofi, has received research funding from Bristol-Myers Squibb, and serves on the speaker's bureau for Merck. Dr Menzies has received honoraria from Bristol-Myers Squibb and Merck and travel reimbursement from Bristol-Myers Squibb. Dr Hassel has received honoraria from Bristol-Myers Squibb, Roche, MSD, Amgen, and GlaxoSmithKline; has consulted for GlaxoSmithKline and Amgen; and has received travel reimbursement from Bristol-Myers Squibb and Amgen. Dr Mehnert has consulted for Amgen and received research funding from Merck, Sanofi, Novartis, and Polynoma. Dr Sosman has consulted for Merck and received research funding from Bristol-Myers Squibb and Novartis. Dr Long has consulted for GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Roche/Genentech, Amgen, Merck, and Provectus and received travel reimbursement from Roche/Genentech. Dr Clark has received honoraria from Bristol-Myers Squibb, Prometheus, Argos, Pfizer, and Novartis; has consulted for Prometheus, Argos, and Novartis; has been a member of the speaker's bureau for Prometheus, Bristol-Myers Squibb, Pfizer, and Novartis; and received research funding from Bristol-Myers Squibb and Prometheus. No other disclosures are reported.

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