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ORIGINAL ARTICLE

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab

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Background: Anti-PD-1 antibodies (anti-PD-1) have clinical activity in a number of malignancies. All clinical trials have excluded patients with significant preexisting autoimmune disorders (ADs) and only one has included patients with immune-related adverse events (irAEs) with ipilimumab. We sought to explore the safety and efficacy of anti-PD-1 in such patients.

Patients and methods: Patients with advanced melanoma and preexisting ADs and/or major immune-related adverse events (irAEs) with ipilimumab (requiring systemic immunosuppression) that were treated with anti-PD-1 between 1 July 2012 and 30 September 2015 were retrospectively identified.

Results: One hundred and nineteen patients from 13 academic tertiary referral centers were treated with anti-PD-1. In patients with preexisting AD ($N = 52$), the response rate was 33%. 20 (38%) patients had a flare of AD requiring immunosuppression, including 7/13 with rheumatoid arthritis, 3/3 with polymyalgia rheumatica, 2/2 with Sjogren's syndrome, 2/2 with immune thrombocytopaenic purpura and 3/8 with psoriasis. No patients with gastrointestinal ($N = 6$) or neurological disorders ($N = 5$) flared. Only 2 (4%) patients discontinued treatment due to flare, but 15 (29%) developed other irAEs and 4 (8%) discontinued treatment. In patients with prior ipilimumab irAEs requiring immunosuppression ($N = 67$) the response rate was 40%. Two (3%) patients had a recurrence of the same ipilimumab irAEs, but 23 (34%) developed new irAEs (14, 21% grade 3–4) and 8 (12%) discontinued treatment. There were no treatment-related deaths.

Conclusions: In melanoma patients with preexisting ADs or major irAEs with ipilimumab, anti-PD-1 induced relatively frequent immune toxicities, but these were often mild, easily managed and did not necessitate discontinuation of therapy, and a significant proportion of patients achieved clinical responses. The results support that anti-PD-1 can be administered safely and can achieve clinical benefit in patients with preexisting ADs or prior major irAEs with ipilimumab.

Key words: PD-1, immunotherapy, autoimmunity, autoimmune disorder, cancer, melanoma

Introduction

Anti-PD-1 antibodies have activity across many cancers, and are now Food and Drug Administration approved for patients with several cancers including melanoma [1–3], lung cancer [4–7], renal cancer [8], and Hodgkin's lymphoma [9], while the combination of nivolumab plus ipilimumab is approved for melanoma [1]. While anti-PD-1 antibodies have a more favorable toxicity profile than most therapies in oncology, infrequently immune-related toxicity can be severe.

All trials of checkpoint immunotherapies to date have excluded patients with significant preexisting autoimmune disorders and only one trial has included a small number of patients with major immune-related adverse events (irAEs) with ipilimumab, and yet the use of immunotherapy is rapidly expanding into a broader, real-world population that includes such patients [10]. Indeed, recently, we reported the safety and activity of ipilimumab in 30 patients with a range of preexisting autoimmune disorders [11]. In this study, ipilimumab was active (20% response rate), despite the fact that 43% of patients were on immunosuppressants at the time of ipilimumab commencement. While 27% of patients experienced a flare of their autoimmune disorder and 33% experienced grade 3–5 irAEs, 50% had no flare or major toxicity, suggesting that ipilimumab can be given to selected patients with autoimmune disorders with reasonable activity, but seemingly greater toxicity.

Anti-PD-1 antibodies are more effective and less toxic than ipilimumab [1, 2]. Thus, these agents may be safer to use in patients who are at high risk for autoimmune complications. However, currently no data exist regarding the safety and efficacy of anti-PD-1 antibodies in patients with preexisting autoimmune disease, who are at increased risk of developing cancer [12], and there are minimal data in those that develop significant toxicity with prior ipilimumab [10]. Herein, we explore the safety and efficacy of anti-PD-1 antibodies in such patients.

Patients and methods

Patients

Following institutional review board approval for this study, we extracted data from the medical records across 13 melanoma centers. Patients with advanced melanoma and preexisting autoimmune disorders and/or major irAEs with prior ipilimumab (defined as grade 3–5 and/or requiring systemic immunosuppression) that were treated with anti-PD-1 antibodies between 1 July 2012 and 30 September 2015 were retrospectively identified. Qualifying autoimmune disorders included but were not limited to the following: rheumatologic [rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriatic arthritis, vasculitis, polymyalgia rheumatica (PMR), scleroderma, Sjogren's syndrome], gastrointestinal (Crohn's disease, ulcerative colitis, celiac disease), neurologic [Guillain Barré syndrome (GBS), transverse myelitis, multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy (CIDP)], endocrine (Graves' disease), dermatologic (psoriasis, eczema, erythema nodosum), or other (sarcoidosis, asthma, idiopathic thrombocytopenia) Qualifying ipilimumab irAEs included, but were not limited to, gastrointestinal (colitis, hepatitis), endocrine (hypophysitis, hypoadrenalism, thyroiditis and hyper/hypo-thyroidism), rheumatologic (arthritis, myositis), dermatologic (rash), neurologic (myasthenia gravis, neuropathies), or others (uveitis, neutropenia, pneumonitis).

Study design

Baseline patient characteristics were collected, including age, sex and prognostic factors [7th edition of the American Joint Committee on Cancer (AJCC) pathologic stage [13], presence of brain metastases, serum lactate dehydrogenase level and Eastern Cooperative Oncology Group Performance Status (ECOG PS)]. To characterize the severity of baseline autoimmune disorders, we assessed whether the disorder was active or inactive (deemed by the clinician on clinical grounds), and whether immunosuppressive (IS) therapy was being used for the autoimmune disorder, at time of anti-PD-1 commencement. The severity of prior ipilimumab toxicity was described by assessing the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade [14], the highest level of immunosuppressive treatment required [topical < oral < IV steroids < tumor necrosis factors alpha (TNFα) inhibitors (infliximab), anti-thymocyte globulin (ATG), intravenous immunoglobulin (IVIG), mycophenolate, or colectomy], and the resolution of the toxicity at time of commencement of anti-PD-1 therapy. We assessed the safety of anti-PD-1 antibodies in these patients, as defined by worsening of the autoimmune disorder ('flare') or recurrence of ipilimumab irAE necessitating therapeutic intervention with systemic immune-modifying agents, as well as the incidence of conventional irAEs and their corresponding management. Adverse effects were classified by grade according to the CTCAE grade. We also evaluated the efficacy of anti-PD-1 antibodies in terms of treatment response as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [15], progression-free survival (PFS), duration of response and overall survival (OS).

Statistical analyses

Categorical and continuous variables were summarized using percentages and medians. No formal hypothesis testing was performed with these variables. OS and PFS were estimated using the Kaplan–Meier method; all patients were censored at last available follow-up. PFS was defined as time from treatment start to disease progression (as determined by the treating physician) or death; OS was defined as the time from treatment start to death for any reason. All analyses were performed by IBM SPSS Statistics v22.

Results

Patients and treatment

One hundred and nineteen patients from 13 centers in Australia, USA and Europe that were treated with anti-PD-1 antibodies (109 pembrolizumab, 10 nivolumab) and had either preexisting autoimmune disorders ($N = 52$) or had developed significant toxicity with prior ipilimumab ($N = 67$) were examined. Ninety-five (80%) patients had received ipilimumab prior to anti-PD-1 antibodies. Three patients (2.5%) had uveal melanoma. At the time of analysis, 86 (72%) patients had at least 3 months of follow-up (median 4.7 months). The median PFS was 6.8 months (95% CI 3.6–10.0) and 31 (26%) patients had died (median OS not reached).

Preexisting autoimmune disorders

The median age of the patients with preexisting autoimmune disorders was 71 years (Table 1). The cohort had a high prevalence of adverse prognostic features (AJCC stage IV M1c disease 85%, brain metastases 31%, elevated serum lactate dehydrogenase level 48%, ECOG PS ≥1 in 56%). Twenty eight (54%) patients had

Table 1. Characteristics of patients with autoimmune disorders

	Number (%) (*N*=52)	Details
Demographics and disease characteristics		
Age, median (range), y	71 (23–88)	
Males	31 (60%)	
AJCC stage M1c	44 (85%)	
Brain metastases	16 (31%)	
Elevated serum LDH	25 (48%)	
ECOG≥1	29 (56%)	
Prior ipilimumab treatment	28 (54%)	
No prior systemic therapy	23 (44%)	
AI disorder[a]		
Rheumatologic	27 (52%)	RA 13, sarcoidosis 3, PMR 3, SLE 2, scleroderma 2, psoriatic arthritis 2, Sjogren's 2
Dermatologic	8 (15%)	psoriasis 6, eczema, erythema nodosum
Gastrointestinal	6 (12%)	CD 3, UC with colectomy 2, celiac disease 1
Neurologic	5 (10%)	GBS 2, CIDP 1, MG 1, Bell's palsy 1
Endocrine	4 (8%)	Graves' disease 4
Respiratory	2 (4%)	Asthma 2 (1 severe on long-term oral steroids)
Hematologic	2 (4%)	ITP 2
Activity of AI disorder at PD1 start		
Not clinically active	37 (71%)	
Clinically active	15 (29%)	11 rheumatologic (RA 5, psoriatic arthritis 2, Sjogrens 2, sarcoidosis 1, PMR 1), 3 psoriasis, 1 severe asthma
Treatment of AI disorder at PD1 start		
No immunosuppresion	32 (62%)	
Corticosteroids	9 (17%)	
Steroid-sparing agent	5 (10%)	Mesalamine 2, leflunomide, hydroxychloroquine, apremilast
Steroids and SSAs	5 (10%)	Sulfasalazine, leflunomide, hydroxychloroquine, methotrexate, ibuprofen
IVIG	1 (2%)	

Data are given as number (percentage) unless otherwise specified.
[a]Total exceeds 52 because 2 patients had 2 disorders.
RA, rheumatoid arthritis; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; CD, Crohn's disease; UC, ulcerative colitis; GBS, Guillain-Barre syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; MG, myasthenia gravis; ITP, immune thrombocytopenia purpura; SSA, steroid-sparing agent.

received prior ipilimumab, and 23 (44%) received 1st line anti-PD-1 therapy. The majority of patients had rheumatologic conditions [total 27 (52%), including 13 with rheumatoid arthritis]. Other conditions included dermatologic (6 patients had psoriasis), gastrointestinal (3 had Crohn's disease, 2 had ulcerative colitis with colectomy) and neurologic conditions (2 had GBS, 1 had CIDP, 1 had myasthenia gravis), among others. Two patients had two autoimmune disorders.

At the time of commencement of anti-PD-1 antibody therapy, 15 (29%) patients had active symptoms of autoimmunity, including 11 (21%) with rheumatologic conditions (5 rheumatoid arthritis), 3 (6%) with psoriasis, and 1 patient with severe asthma. Twenty (38%) patients were on immunosuppressants, including corticosteroids (17%), steroid-sparing agents (SSAs, 10%) or both (10%).

Twenty (38%) patients had a flare of their underlying autoimmune disorder at a median of 38 days (range 8–161) after the first dose of anti-PD-1 antibody (Table 2). In general, these were recurrent or increased grade of prior symptoms (e.g. arthralgia with rheumatoid arthritis, worsening plaques with psoriasis) rather than an extension of disease manifestations (e.g. new pulmonary manifestations of RA). Flares occurred more often in those with active symptoms (9/15, 60%) than those with clinically inactive disease (11/37, 30%) ($P=0.039$), and there was a trend for more flares in those on immunosuppressants at start of anti-PD-1 treatment (10/20, 50%) than those not on immunosuppressants (10/32, 31%) ($P>0.05$). Flares occurred in 14/27 (52%) patients with rheumatologic disorders, 3/8 with psoriasis, 1/4 with Graves' disease and 2/2 with immune thrombocytopaenic purpura (Table 1). Notably, no patients with gastrointestinal ($N=6$), neurological ($N=5$) or respiratory ($N=2$) disorders had a flare of their disorder with therapy.

Most flares of autoimmune disorders were mild. Grade 1–2 flares occurred in 17/20 patients (85% of flares, 33% of total

Table 2. Toxicity of anti-PD-1 antibodies in patients with autoimmune disorders

	Number (%) ($N = 52$)	Details
Flare AD on PD1		
No	32 (62%)	
Yes	20 (38%)	
Time to flare, median (range), d	38 (8–161)	
Grade of flare		
G1-2	17 (33%)	
G3	3 (6%)	
G4	0 (0%)	
Flare by AD subtype		
Rheumatologic	14 of 27 (52%)	7/13 RA, 3/3 PMR, 1/2 scleroderma, 2/2 Sjogren's, 1/2 psoriatic arthritis
Dermatologic	3 of 8 (38%)	3/6 psoriasis
Gastrointestinal	0 of 6 (0%)	
Neurologic	0 of 5 (0%)	
Endocrine	1 of 4 (25%)	1/4 Graves
Respiratory	0 of 2 (0%)	
Hematologic	2 of 2 (100%)	2/2 ITP
Flare by AD stability at start of PD1		
Clinically active	9 of 15 (60%)	
Clinically inactive	11 of 37 (30%)	
On immunosuppression	10 of 20 (50%)	
Not on immunosuppression	10 of 32 (31%)	
Immunosuppression required for AD flare		
oral steroids	11 (21%)	
SSA	6 (12%)	
Steroids and SSA	2 (4%)	
IVIG	1 (2%)	
PD1 dosing with AD flare		
Continue	10 (20%)	
Interrupt	8 (15%)	
permanently discontinue	2 (4%)	
Conventional irAE		
No	37 (71%)	
Yes	15 (29%)	
G1-2	10 (20%)	
G3	5 (10%)	2 hepatitis, 1 colitis, pancreatitis and pneumonitis
Immunosuppression required for irAE		
Symptomatic management	8 (15%)	
Oral steroids	4 (8%)	
IV steroids	2 (4%)	
Steroids and SSA	1 (2%)	
PD1 dosing with irAE		
Continue	8 (15%)	
Interrupt	3 (6%)	
Permanently discontinue	4 (8%)	

AD, autoimmune disorder; PD1, anti-PD-1 antibody; irAE, immune-related adverse event; SSA, steroid-sparing agent; IVIG, intravenous immunoglobulin.

cohort). While 8 patients temporarily interrupted therapy, only 2 (10% of flares, 4% of total treated) permanently discontinued therapy due to a flare of autoimmune disorders. Flares were managed with oral steroids and steroid sparing agents (SSAs e.g, methotrexate), and no patient required intravenous steroids or higher levels of immunosuppression (e.g. infliximab, ATG). Conventional irAEs occurred in 15 (29%) patients; 5 (10%) were grade 3 and 4 (8%) permanently discontinued anti-PD-1 therapy due to an irAE. Most irAEs (8/15, 53%) settled with symptomatic/conservative management only. There were no treatment-related deaths.

Responses were observed in 17/52 (33%) patients. Median PFS was 6.2 months (95% CI 4.2–8.2) (Figure 1A). Twenty-six (50%) patients remained on treatment at data cut-off, and the median duration of response was not reached (range 2.7–24.6 months). Fourteen (27%) of patients died during the study

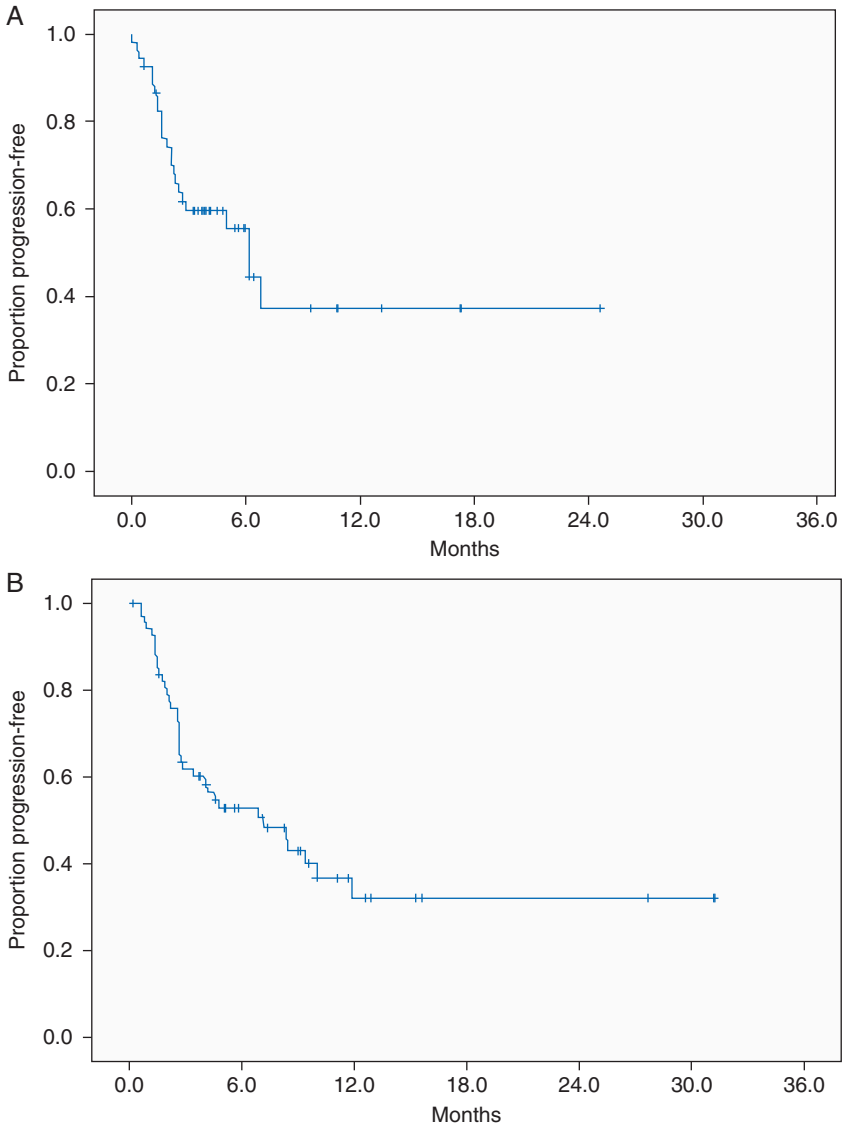

Figure 1. Progression-free survival with anti-PD-1 antibodies (A) patients with autoimmune disease, (B) patients with prior ipilimumab toxicity.

period (median OS not reached). The response rate in those who had a flare of autoimmune disease (7/20, 35%) was similar to those who did not flare (10/32, 31%, $P > 0.05$). The response rate was lower in those on immunosuppressants at start of treatment (3/20, 15%) than those not on immunosuppressants (14/32, 44%) ($P = 0.033$), and this remained significant when adjusting for prognostic factors (AJCC stage, brain metastases, ECOG PS, LDH) ($P = 0.029$). Of note, 2/7 patients on steroids at start of treatment responded, but no patients on steroid-sparing agents (SSAs, $N = 5$), or both steroids and SSAs ($N = 5$) responded. One patient on IVIG responded.

Major toxicity with prior ipilimumab

The median age of patients with previous irAEs due to ipilimumab was 63 years and the cohort was similarly characterized by a high prevalence of adverse prognostic features (Table 3). Most patients had experienced severe toxicity with ipilimumab (76% grade 3, 10% grade 4), including 42 (63%) patients with grade 3 and 4 colitis (15 were treated with infliximab), 3 (5%) with grade 3 and 4 hepatitis (one of which required ATG), and 12 (18%) with hypophysitis. All irAEs except hypophysitis had resolved at time of commencement of anti-PD-1 antibody therapy, except in 1 patient (Patient A) with ipilimumab-induced seronegative arthritis who remained on prednisone and hydoxychloroquine with mild symptoms. Four other patients were on low doses of immunosuppression (≤10mg prednisone) for prior irAEs at the start of therapy, 3 for colitis and 1 for hepatitis, with no evidence of active inflammation.

Two (3%) patients had a recurrence of ipilimumab irAEs with anti-PD-1 therapy (Table 4). One patient (Patient A) developed a flare of arthritis, managed with an increase in oral prednisone, continuation of hydoxychloroquine, and ongoing dosing of anti-PD-1 therapy. Another patient who had grade 2 colitis with ipilimumab (managed with a brief course of oral prednisone), was similarly managed with another brief course of oral prednisone when colitis recurred and had a temporary interruption of anti-PD1 to treatment. Twenty-three (34%) patients developed new/

Table 3. Characteristics of patients with major ipilimumab toxicity

	Number (%) ($N = 67$)	Details
Demographics and disease characteristics		
Age, median (range), y	63 (30–85)	
Males	46 (69%)	
AJCC stage M1c	58 (87%)	
Brain metastases	18 (27%)	
Elevated serum LDH	27 (40%)	
ECOG ≥1	42 (63%)	
Grade prior ipilimumab irAE		
G2	9 (13%)	
G3	51 (76%)	
G4	7 (10%)	
Prior ipilimumab irAE N (N grade 3+)[b]		
Colitis	47 (42)	5 G2 (3 PO steroids, 2 TNFa), 37 G3 (12 PO steroids, 13 IV, 12 TNFa), 5 G4 (1 PO, 1 IV, 1 TNFa, 2 colectomy)
Endocrine	13 (11)	12 hypophysitis, 1 hypoadrenalism
Dermatologic	4 (4)	4 rash (1 TOP steroid, 3 PO steroids)
Rheumatologic	3 (2)	2 seronegative arthritis (PO steroids, MTX, HCQ), 1 myositis (PO steroids)
Hepatitis	3 (3)	2 G4 (ATG, MMF, IV/PO steroids), 1 G3 (IV steroids)
Neurologic	2 (1)	Myaesthenia gravis (PLEX, IVIG, steroids, mestinon), Bell's palsy (IV steroids)
Ocular	2 (1)	Uvetitis (PO steroids), CSR (PO steroids)
Hematologic	1 (1)	Neutropenia (PO steroids)
Highest immunosuppression used for irAE		
Topical steroid	1 (1%)	
Oral steroid	31 (46%)	
Intravenous steroid	16 (24%)	
TNFa inhibitor	15 (22%)	All for colitis
Intravenous immunoglobulin	1 (1%)	For myesthenia gravis
antithymocyte globulin	1 (1%)	For hepatitis
Colectomy	2 (3%)	For colitis
Ipilimumab irAE resolved at start of PD1[c]		
Yes	66 (99%)	
No	1 (1%)	arthritis
Ongoing immunosuppression at PD1 start		
Yes	5 (7%)	3 for colitis, 1 for hepatitis (all prednisone ≤10mg). 1 for arthritis (Prednisone 10mg and HCQ).
No	62 (93%)	

[a]Data are given as number (percentage) unless otherwise specified.
[b]Total exceeds 67 because 7 patients had 2 disorders.
[c]Hypophysitis considered resolved
G, grade; PO, oral; TNFa, tumor necrosis factors alpha inhibitors; IV, intravenous; ATG, antithymocyte globulin; MMF, mycophenolate; PLEX, plasmapheresis; IVIG, intravenous immunoglobulin; CSR, central serous retinopathy; PD1, anti-PD-1 antobody; HCQ, hydroxychloroquine.

different irAEs with anti-PD-1 therapy. Fourteen (21%) patients had grade 3-4 irAEs, and 8 (12%) discontinued therapy due to the development of grade 3 and 4 pneumonitis ($N = 4$), hepatitis ($N = 2$), colitis ($N = 1$) and myasthenia gravis ($N = 1$). There were no treatment related deaths. Of note, of the 12 patients with ipilimumab-induced hypophysitis, only 1 developed an irAE, which was a grade 3 colitis managed successfully with 100mg oral prednisone.

Responses were observed in 27 (40%) of patients. Median PFS was 7.2 months (95% CI 3.1–11.3) (Figure 1B). Thirty (45%) patients remained on treatment at data cut-off, and the median duration of response was not reached (range 2.6–31.2 months). Seventeen (25%) patients died during the study period (median OS not reached). In patients with previous hypophysitis, 4 (33%) responded to anti-PD-1 therapy.

Discussion

Although anti-PD-1 antibodies are now in widespread use in oncology, the safety and efficacy of these drugs in patients with autoimmune disorders is unknown. To our knowledge, this is the

Table 4. Toxicity of anti-PD-1 antibodies in patients with major ipilimumab toxicity

	Number (%) ($N = 67$)	Details
Ipi irAE recurrence on PD1		
No	65 (97%)	
Yes	2 (3%)	Arthritis, colitis
Other irAEs with PD1		
No	44 (66%)	
Yes	23 (34%)	
G1-2	9 (13%)	Colitis 3, hepatitis 1, arthritis 1, rash 2, neuropathy 1, hypothyroidism 1
G3	12 (18%)	Colitis 5, hepatitis 1, arthritis 1, myasthenia 1, pneumonitis 3, DKA 1
G4	2 (3%)	Hepatitis 1, pneumonitis 1
Immunosuppression required for irAE		
Symptomatic management	6 (9%)	
Oral steroids	10 (15%)	
SSA	1 (1%)	
IV steroids	4 (6%)	
Steroids and SSA	2 (3%)	
PD1 dosing with irAE		
Continue	9 (13%)	
Interrupt	6 (9%)	
Permanently discontinue	8 (12%)	Pneumonitis 4, hepatitis 2, colitis 1, myesthenia gravis 1

PD1, anti-PD-1 antobody; ipi, ipilimumab; DKA, diabetic ketoacidosis; SSA, steroid-sparing agent.

first study to examine this issue. The results of this study suggest that anti-PD-1 antibodies have efficacy in metastatic melanoma patients with preexisting autoimmune disorders, and in patients with major irAEs with ipilimumab. Though flares of preexisting autoimmune disorders were common, the rate of 'conventional' irAEs otherwise appeared similar to rates observed in clinical trial populations.

Anti-PD-1 antibodies often exacerbated preexisting autoimmune disorders, particularly rheumatologic conditions. In contrast, flares of gastrointestinal and neurological disorders were not observed in this cohort, although the numbers of patients with these disorders were small. While this discordance may in part be explained by the fact that rheumatologic conditions were more likely to be active at treatment start than other disorders, the pathogenesis of autoimmunity is hetereogeneous, and many disorders do not involve (or heavily rely upon) the PD-1/PD-L1 pathway. For example, GBS is classically a single episode B cell-mediated disease, whereas patients with rheumatoid arthritis and Sjogren's syndrome have progressive chronic inflammation characterized by a PD-1 positive T cell infiltrate [16–18].

In general, flares were mild, occurred more often in those with active symptoms and those requiring immunosuppressants treatment start, occurred in the first few months of therapy, did not lead to discontinuation of therapy, and were managed with oral steroids or steroid-sparing agents (e.g. methotrexate). Similarly, conventional irAEs were often mild, did not require discontinuation, and most resolved with conservative management. The rate of irAEs in this cohort (29% overall, 10% grade 3) appeared similar to clinical trial cohorts [19, 20], as opposed to patients with autoimmune disorders receiving ipilimumab, who appeared to have greater toxicity with treatment [11]. The response rate in those with flares was similar to those without exacerbations, but the response rate was lower in patients receiving immunosuppressants at treatment start. This result must be viewed with caution given the small numbers of patients involved, the heterogeneous population, and the retrospective nature of this study.

In patients with prior major irAEs with ipilumumab, recurrence of the same irAE was rare (3%). Notably, recurrence of colitis was rare even in patients that had severe colitis requiring TNFα inhibitors. However, new irAEs occurred frequently (34%), and many of these were high grade (21% of patients had grade 3/4 irAEs), required immunosuppression with oral or intravenous steroids, and often led to permanent discontinuation of anti-PD-1 therapy. In contrast, previous trials of anti-PD-1 antibodies have demonstrated that patients who have received prior ipilimumab without significant toxicity [19, 21] have similar rates of toxicity to those who are ipilimumab naïve (approximately 10–15% grade 3/4).[1–3, 19, 20] Taken together, these data suggest that patients with prior ipilimumab toxicity are at increased risk of anti-PD-1 antibody-related toxicities, but such toxicities are generally manageable.

Clinical trials demonstrate response rates with anti-PD-1 antibodies between 33% and 45% in the first-line setting, [1–3, 20] and between 21% and 32% after ipilimumab [21, 22]. Given the high prevalence of adverse prognostic features and prior ipilimumab treatment in this cohort, the response rates to anti-PD-1 antibody therapy (33% in those with autoimmune disorders, 40% in those with ipilimumab irAEs) appear higher than expected. This suggests that patients with a tendency to autoimmunity may be more likely to benefit from anti-PD-1 antibody therapy.

This study has several limitations. First, there was inherent selection bias in both cohorts. The majority of autoimmune disorders

were deemed clinically inactive and not requiring immunosuppression at the start of treatment, and the cohort only reflected a subgroup of patients deemed suitable for anti-PD-1 treatment by their clinicians. Second, the lack of strict classification of activity and severity of autoimmunity beyond clinical grounds and CTCAE grading may bias the results. Third, the relatively short duration of follow-up precludes meaningful survival analyses, and further toxicities may emerge over time. Fourth, in those with major ipilimumab irAEs, the interval between last dose of ipilumumab and anti-PD-1 treatment was not available, however given that all patients required immunosuppression, 86% had grade 3/4 toxicity, and that toxicities had resolved at start of treatment in all but one patient, the interval should have been sufficient to allow for washout of ipilimumab. Thus, larger prospective studies are required to definitively address this issue.

In conclusion, anti-PD-1 antibodies induce relatively frequent immune toxicities in patients with baseline autoimmunity or prior irAEs with ipilimumab, but these immune toxicities are often mild and easily managed, and the patients achieve high rates of clinical response. Anti-PD-1 antibodies may flare preexisting autoimmune disorders, particularly in patients with rheumatologic disorders or requiring active immunosuppression. In patients with prior major irAEs with ipilimumab, recurrence of the same irAE is rare, but new irAEs can occur at high rates. Thus, clinicians may consider anti-PD-1 antibodies for appropriately selected patients with preexisting autoimmune disease or prior severe irAE with ipilimumab, provided there is close monitoring and adherence to standard irAE treatment algorithms, and in discussion with experts in major immunotherapy centers.

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Disclosure

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