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Combination anti-PD1 and ipilimumab therapy in patients with advanced melanoma and pre-existing autoimmune disorders

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ABSTRACT

Background Clinical trials of immunotherapy have excluded patients with pre-existing autoimmune disease. While the safety and efficacy of single agent ipilimumab and anti-PD1 antibodies in patients with autoimmune disease has been examined in retrospective studies, no data are available for combination therapy which has significantly higher toxicity risk. We sought to establish the safety and efficacy of combination immunotherapy for patients with advanced melanoma and pre-existing autoimmune diseases.

Methods We performed a retrospective study of patients with advanced melanoma and pre-existing autoimmune disease who received combination ipilimumab and anti-PD1 at 10 international centers from March 2015 to February 2020. Data regarding the autoimmune disease, treatment, toxicity and outcomes were examined in patients.

Results Of the 55 patients who received ipilimumab and anti-PD1, the median age was 63 years (range 23–83). Forty-six were treated with ipilimumab and nivolumab and nine with ipilimumab and pembrolizumab.

Eighteen patients (33%) had a flare of their autoimmune disease including 4 of 7 with rheumatoid arthritis, 3 of 6 with psoriasis, 5 of 10 with inflammatory bowel disease, 3 of 19 with thyroiditis, 1 of 1 with Sjogren's syndrome, 1 of 1 with polymyalgia and 1 of 1 with Behcet's syndrome and psoriasis. Eight (44%) patients ceased combination therapy due to flare. Thirty-seven patients (67%) had an unrelated immune-related adverse event (irAE), and 20 (36%) ceased combination immunotherapy due to irAEs. There were no treatment-related deaths. Patients on immunosuppression (OR 4.59; p=0.03) had a higher risk of flare.

The overall response rate was 55%, with 77% of responses ongoing. Median progression free survival and overall survival were 10 and 24 months, respectively. Patients on baseline immunosuppression had an overall survival of 11 months (95% CI 3.42 to 18.58) compared with 31 months without (95% CI 20.89 to 41.11, p=0.005).

Conclusions In patients with pre-existing autoimmune disease, not on immunosuppression and advanced melanoma, combination ipilimumab and anti-PD1 has similar efficacy compared with previously reported trials. There is a risk of flare of pre-existing autoimmune disorders, particularly in patients with inflammatory bowel disease and rheumatologic conditions, and patients on baseline immunosuppression.

INTRODUCTION

Combination immunotherapy with ipilimumab, an anti-CTLA4 inhibitor antibody, and anti-PD1 antibodies such as pembrolizumab and nivolumab, have demonstrated efficacy across multiple cancers and are approved first line treatment for BRAF-wild type and mutated melanoma,[1] renal cell carcinoma,[2] non-small lung cancer,[3] mesothelioma,[4] hepatocellular carcinoma[5] and Microsatellite Instability-High (MSI-H) colorectal carcinoma.[6]

CTLA4 and PD1 are fundamental in immune regulation. Immune checkpoint inhibitors targeting these can cause interruption of this homeostasis and lead to immune-related adverse events (irAEs).[7] Clinical trials testing ipilimumab and anti-PD1 alone or in combination have excluded patients with pre-existing autoimmune diseases due to concerns regarding severe irAEs or exacerbation of autoimmune disorders. However, previous retrospective studies suggest the use of single-agent ipilimumab[8] and single-agent anti-PD1[9–12] is safe in patients with pre-existing autoimmune disease.

Two other retrospective studies assessing irAEs in patients with inflammatory bowel disease (IBD)[13] and pre-existing autoimmune diseases[14] included a small number of patients who received combination immunotherapy, 10 patients and 3 patients, respectively. However, these were not powered to assess the safety and efficacy as compared with monotherapy.

Table 1 Baseline patient characteristics

Demographics	No (%)	Detail
Age, median (range), years	63 (23–83)	
Gender		
Male	26 (47)	
Female	29 (53)	
ECOG ≤1	53 (96)	
AJCC stage		
III/M1a/M1b	17 (31)	
M1c	21 (38)	
M1d	17 (31)	
LDH		
Normal	40 (73)	
Elevated	15 (27)	
Mutation status		
BRAF/NRAS wild type	29 (53)	
BRAF	17 (31)	
NRAS	9 (16)	
Autoimmune disorder (AD)*		
Rheumatologic	11 (20)	Rheumatoid arthritis—7, Sjogren's syndrome—1, Behcet's syndrome—1*, polymyalgia—1, uveitis—1*
Gastrointestinal	14 (25)	Ulcerative colitis—7, Crohn's disease—3, Celiac disease—4
Endocrine	21 (38)	Graves' disease—8, Hashimoto's thyroiditis—11*, type I diabetes—2*
Dermatologic	7 (13)	Psoriasis—6, alopecia areata—1*
Neurologic	2 (4)	Multiple sclerosis—2
Hematologic	1 (2)	ITP
Other	2 (4)	Sarcoidosis—2
Activity of AD		
Clinically active	10 (18)	
Not clinically active	45 (82)	
Immunosuppression	13 (24)	
Corticosteroids	5 (9)	
SSA	5 (9)	Sulfasalazine—1, mesalazine—2, plaquenil—1, methotrexate and plaquenil—1
Corticosteroids+SSA	3 (5)	Sulfasalazine, methotrexate, plaquenil
No immunosuppression	42 (76)	

*Three of 55 patients had two concurrent autoimmune diseases.
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Group Performance Status; ITP, immune thrombocytopenic purpura; LDH, lactate dehydrogenase; SSA, steroid-sparing agent.

The safety and efficacy of combination therapy, which is known to have a higher risk of toxicity, has not been assessed in patients with pre-existing autoimmune diseases. As the indications for combination immunotherapy broaden and the use extends to the treatment of other malignancies, the question of safety and efficacy in this population is significant, perhaps more so given the rate of malignancies is higher in patients with a pre-existing autoimmune condition.[15]

We conducted an international, multicenter, retrospective cohort study to assess the safety and efficacy of combination immune checkpoint inhibitors in patients with pre-existing autoimmune disease.

METHODS

Patients

Following approval of institutional review boards, data were extracted from the medical records of patients at 10 international participating centers.

Patients who had received at least one dose of combination ipilimumab and anti-PD1 between 2015 and February 2020 with a concomitant diagnosis of an autoimmune disorder were included. Qualifying autoimmune disorders included but were not limited to the following: rheumatologic (rheumatoid arthritis (RA), systemic lupus erythematosus, psoriatic arthritis, vasculitis, polymyalgia rheumatica, scleroderma, Sjogren's syndrome), gastrointestinal (Crohn's disease, ulcerative colitis, celiac disease), neurologic (Guillain-Barre syndrome (GBS), transverse myelitis, multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy), endocrine (Graves' disease, Hashimoto's thyroiditis, type 1 diabetes mellitus), dermatologic (psoriasis, eczema, erythema nodosum) and other (sarcoidosis, asthma, idiopathic thrombocytopenic purpura). Autoimmune disorders were diagnosed based on each center's standard of diagnosis, for most conditions, a history and serological testing confirmed the diagnosis. For patients with IBD and dermatologic conditions, all had a biopsy confirming the diagnosis.

Study design

Baseline patient demographics were collected including age, gender, Eastern Cooperative Group Performance

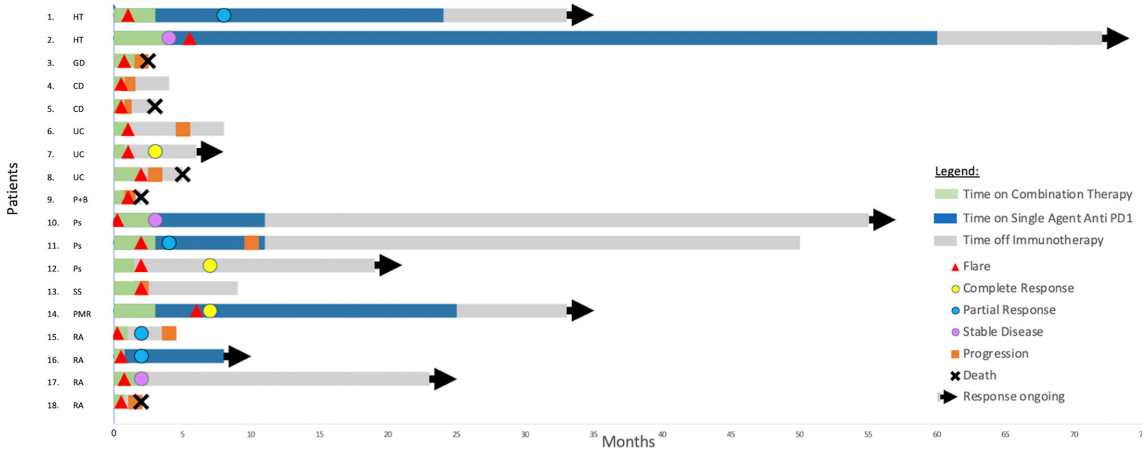

Figure 1 Patients with an autoimmune flare: treatment, response, flare and progression timelines: CD, Crohn's disease; GD, Graves' disease; HT, Hashimoto's thyroiditis; P+B, psoriasis+Behcet's syndrome; PMR, polymyalgia rheumatica; Ps, psoriasis; RA, rheumatoid arthritis; SS, Sjogren's syndrome; UC, ulcerative colitis.

Status (ECOG) and prognostic factors including eighth edition of the American Joint Committee on Cancer pathologic stage, presence of brain and liver metastases and serum lactate dehydrogenase level. Severity of the baseline autoimmune disorder was assessed by clinical activity as deemed by the treating clinician, use of baseline immunosuppression and dose, and recent flare of autoimmune disease.

The safety of combination immunotherapy was assessed by worsening of the autoimmune disorder or flare requiring systemic or immunosuppressive therapy or interruption to immunotherapy as well as the incidence and management of conventional irAE. Flare of autoimmune disease was as diagnosed by the patient's treating oncologist, and where necessary in conjunction with autoimmune disease experts. Severity of irAE and flare was defined by Common Terminology Criteria for Adverse Events criteria.[16] The efficacy of combination immunotherapy in this population was measured either by Response Evaluation Criteria in Solid Tumours V.1.1[17] or by clinical assessment of fluorodeoxyglucose-positron emission tomography (FDG-PET)imaging and assessment of objective response rate, duration of response, progression-free survival (PFS) and overall survival (OS).

Statistical analysis

Categorical and continuous variables are summarized using percentages and medians. No formal hypothesis testing was performed. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test; all patients were censored at last available follow-up. PFS 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. Univariate and multivariable Cox regression analyses served to determine predictive variables. All analyses were performed by IBM SPSS Statistics and R statistics. Data analysis was performed on June 21, 2020.

RESULTS

Patient characteristics

Fifty-five eligible patients were identified. All patients were followed for more than 3 months with a median follow-up time of 14 months. The median age of patients was 63 years (range 23–83), 69% had M1c or d disease.

Pre-existing autoimmune diseases included Crohn's disease (N=3), ulcerative colitis (N=7), Graves' disease (N=8), Hashimoto's thyroiditis (N=11), RA (N=7), psoriasis (N=6), multiple sclerosis (N=2) and others (table 1). Three patients (5%) had more than one autoimmune disease. At commencement of combination immunotherapy, 10 patients (18%) had active symptoms of their autoimmune condition. Thirteen patients (24%) were receiving immunosuppressive therapy (five on corticosteroids, five on steroid-sparing agents and three on both).

Patients received ipilimumab in combination with either nivolumab (N=46) or pembrolizumab (n=9). Forty patients (73%) received an ipilimumab dose of 3mg/kg and nivolumab 1mg/kg 3 weekly for four doses followed by maintenance nivolumab 3mg/kg. Fifteen (27%) had an alternate regimen with a lower dose of ipilimumab of 1mg/kg; six with nivolumab 3mg/kg every 3 weeks for four doses followed by maintenance nivolumab, and nine with pembrolizumab 2mg/kg every 3 weeks for four doses followed by maintenance pembrolizumab. Anti-PD1 monotherapy was given previously to nine patients (16%), resulting in no flares of autoimmune disease and three (33.3%) patients had experienced previous grade 1 or 2 irAEs.

Flare of pre-existing autoimmune disease

Eighteen patients (33%) experienced a flare of their autoimmune disease (figure 1, table 2), most often in rheumatic and gastrointestinal disorders. This included 4 of 7 with RA, 3 of 6 with psoriasis, 3 of 7 patients with ulcerative colitis, (including one of two who had undergone previous subtotal colectomy), 2 of 3 with Crohn's disease, 1 of 8 with Graves' disease, 2 of 11 with Hashimoto's thyroiditis, 1 of 1 with Sjogren's syndrome, 1 of 1

Table 2 Rates of flare of autoimmune disease (AD)

	No (%)	Details
Flare of AD		
No	37 (67)	
Yes	18 (33)	
Time to flare (range) days	19 (4–167)	
Grade of flare of AD		
G1, 2	11 (61)	
G3	5 (28)	Ulcerative colitis—1, Crohn's disease—1, RA—2, psoriasis—1
G4	2 (11)	Ulcerative colitis—2
Flare by AD subtype		
Rheumatologic	7/11 (64)	RA—4/7, Sjogren's syndrome—1/1, Behcet's syndrome and psoriasis —1/1, polymyalgia rheumatica—1/1
Gastrointestinal	5/14 (56)	Ulcerative colitis—3/7, Crohn's disease—2/3
Dermatologic	3/7 (43)	Psoriasis—3/6
Endocrine	3/21 (11)	Hashimoto's thyroiditis—2/11, Graves' disease—1/8
Neurologic	0/2 (0)	
Hematologic	0/1 (0)	
Other	0/2 (0)	
Flare by AD activity at baseline		
Clinically active	5/10 (50)	
Clinically inactive	13/45 (29)	
On immunosuppression	7/13 (54)	
Not on immunosuppression	11/42 (26)	
Immunosuppression for AD flare		
Oral steroids	4 (22)	
Intravenous steroids	3 (17)	
Steroid and SSA*	6 (33)	Ciclosporin—1 for psoriasis, sulfasalazine—2 for ulcerative colitis and polymyalgia, infliximab—2 for ulcerative colitis and Crohn's disease, methotrexate—2 for RA, leflunomide—1 for RA
No immunosuppression	5 (28)	
IO dosing after flare		
Both drugs ceased	5 (28)	IBD—2, Behcet's syndrome—1, RA—1, Sjogren's syndrome—1
Anti-PD1 alone continued	3 (17)	
Both continued	7 (39)	
Ceased due to PD	3 (17)	

*Some patients received two SSAs.
IBD, inflammatory bowel disease; IO, immuno-oncology therapy; PD, progressive disease; RA, rheumatoid arthritis; SSA, steroid-sparing agent.

with polymyalgia rheumatica, and 1 of 1 with concurrent Bechet's syndrome and psoriasis. Flare of autoimmune conditions was based on clinical history and clinician diagnosis. For the patients with RA and Sjogren's syndrome, this was confirmed with serological testing. For patients with a flare of IBD, four of the five patients who experienced a flare underwent a biopsy for histopathological confirmation. The median time to flare was 19 days (range 4–167). The median time to flare for rheumatologic conditions was 16 days and for IBD was 28 days. Sixteen of the 18 (89%) of the flares occurred during combination therapy, and 2 of 18 (11%) occurred on single-agent PD1 maintenance treatment.

Thirteen of the 18 (72%) patients with a flare were managed with corticosteroids and six (33%) required additional immunosuppressive agents which included ciclosporin, sulfasalazine, infliximab, methotrexate and leflunomide. Seven patients (39%) were hospitalized

Table 3 Rates of irAE (unrelated to pre-existing autoimmune disease)

	No (%)	Details
irAE		
No	18 (33)	
Yes	37 (67)	
irAE grade		
G1, 2	16(43)	Colitis—5, hepatitis—2, hypophysitis—4, thyroiditis—2, rash, arthritis, type 1 diabetes
G3	15 (27)	Colitis—7, hepatitis—3, colitis+hepatitis—2*, pneumonitis—2, thyroiditis
G4	6 (15)	Colitis—2, hepatitis—2, Guillain-Barre syndrome, myasthenia gravis
Immunosuppression for irAE		
Oral steroids	7 (19)	
IV steroids	7 (19)	
Steroid and SSA	9 (24)	Colitis—4, hepatitis—3, colitis+hepatitis—2
IVIg	1 (3)	Guillain-Barre syndrome
Plasmapheresis	1 (3)	Myasthenia gravis
IO dosing after irAE		
Both drugs ceased	15 (41)	Colitis—6, hepatitis—3, colitis+hepatitis—2, pneumonitis, Guillain-Barre syndrome, myasthenia gravis, type 1 diabetes mellitus
Anti-PD1 continued alone	2 (5)	
Anti-CTLA4 continued alone	3 (8)	
Both continued	17 (46)	

*Two patients experienced both grade 3 colitis and hepatitis.
irAE, immune-related adverse event; IVIg, intravenous immunoglobulin; SSA, steroid-sparing agent.

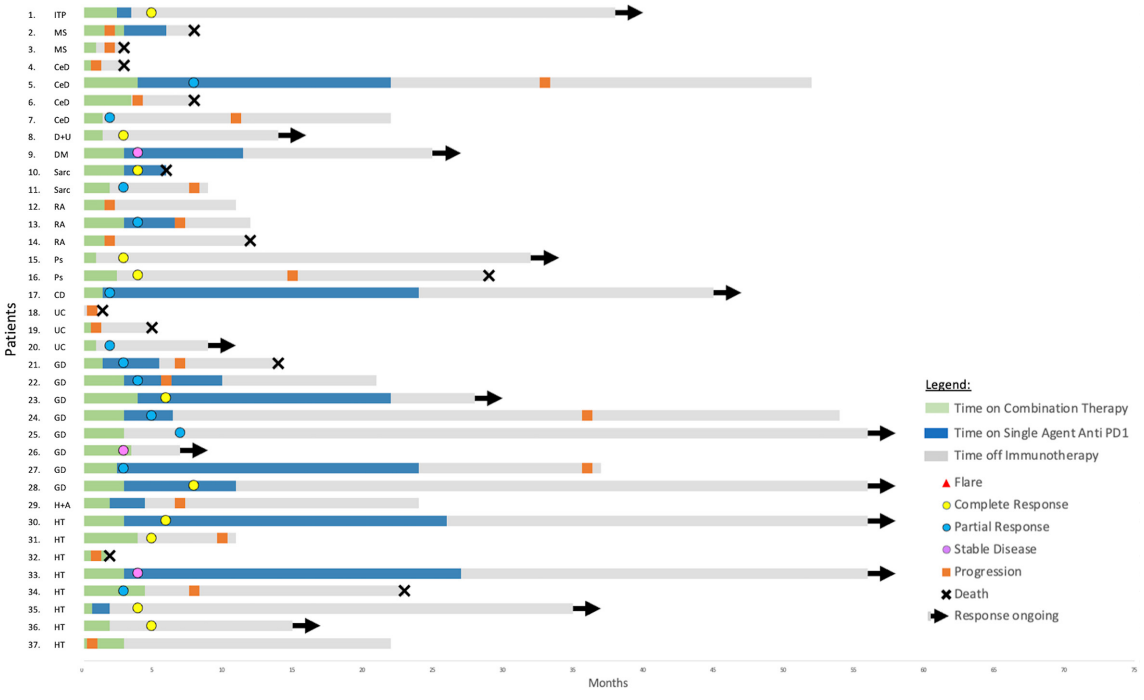

Figure 2 Patients without an autoimmune flare: treatment, response and progression timelines: CD, Crohn's disease; CeD, celiac disease; DM, diabetes mellitus; D+U, diabetes and uveitis; GD, Graves' disease; H+A, Hashimoto's thyroiditis and alopecia areata; HT, Hashimoto's thyroiditis; ITP, immune thrombocytopenic purpura; MS, multiple sclerosis; P+B, psoriasis+Behcet's syndrome; PMR, polymyalgia rheumatica; Ps, psoriasis; RA, rheumatoid arthritis; Sarc, sarcoidosis; SS, Sjogren's syndrome; UC, ulcerative colitis.

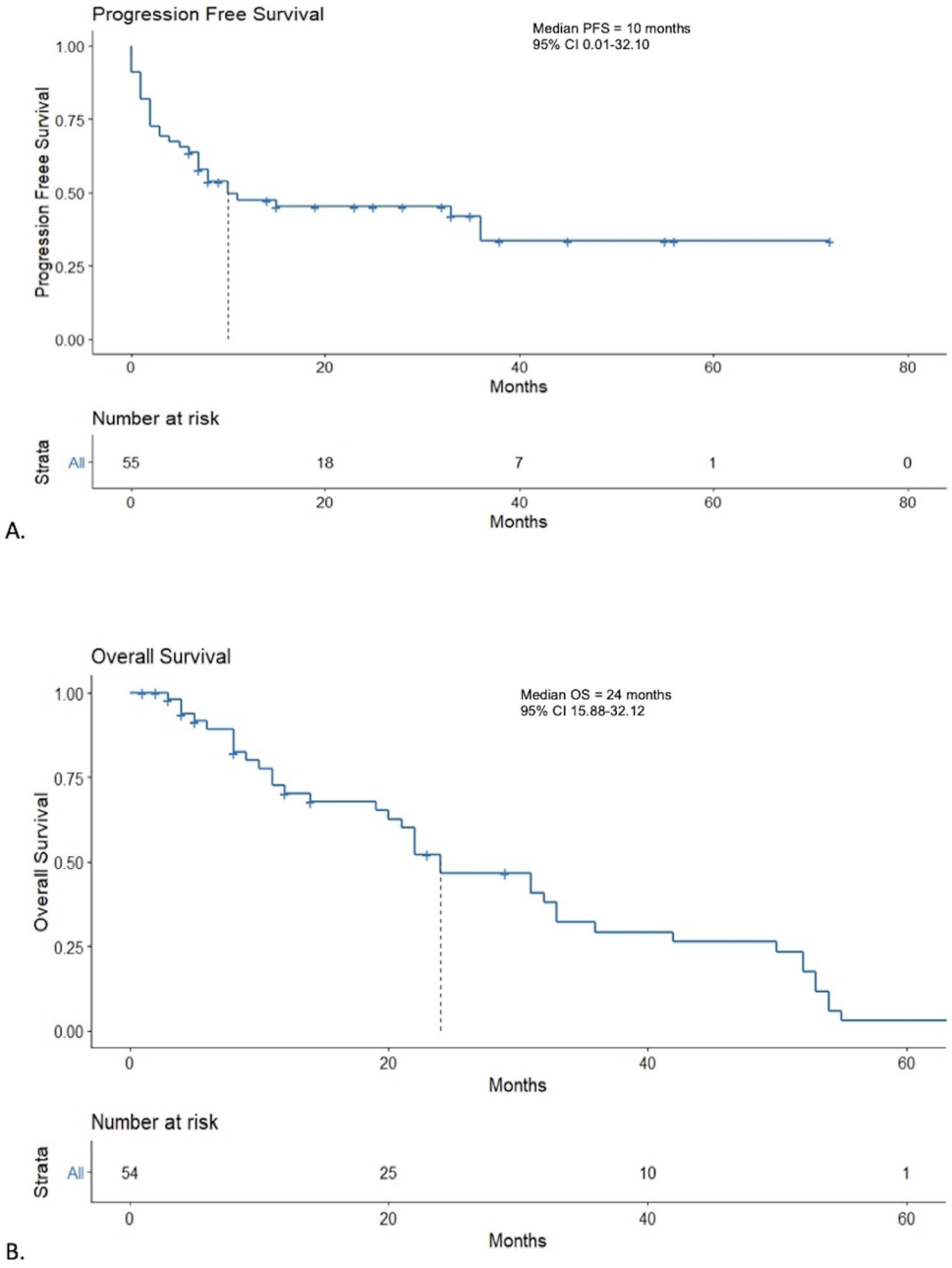

Figure 3 Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS). (A) Kaplan-Meier curves for PFS. (B) Kaplan-Meier curves for OS.

for management of a flare (three with ulcerative colitis, two with Crohn's disease and two with RA). Two patients (11%) required admission to intensive care and vasopressor support for severe flares of ulcerative colitis, which had been quiescent prior to treatment and off immunosuppression. One patient suffered diarrhea and shock and the other a duodenal perforation, both recovered and were responsive to intravenous steroids and sulfonamides. Five patients (28%) permanently ceased both drugs due to the flare (two with IBD, one with RA, one with Behcet's syndrome, one with Graves disease). The median number of doses administered prior to cessation was 1 (range 1–8). Eight of the 18 (44%) patients ceased either both immunotherapy agents or continued on anti-PD1 agent alone due to the flare.

There was a numerical trend to flare of autoimmune disease in patients who had clinically active disease more than those who had clinically inactive disease (50% vs 29%, OR 1.59; 95% CI 0.34 to 7.38, p=0.56). There were also more flares in patients on immunosuppression than in those not on immunosuppression for their autoimmune disorders at immunotherapy commencement (39% vs 26%, OR 4.59; 95% CI 1.16 to 18.04, p=0.03). Notably, in the patients with RA with severe flare (defined as severe pain, joint swelling and limiting self-care), all had quiescent symptoms prior to

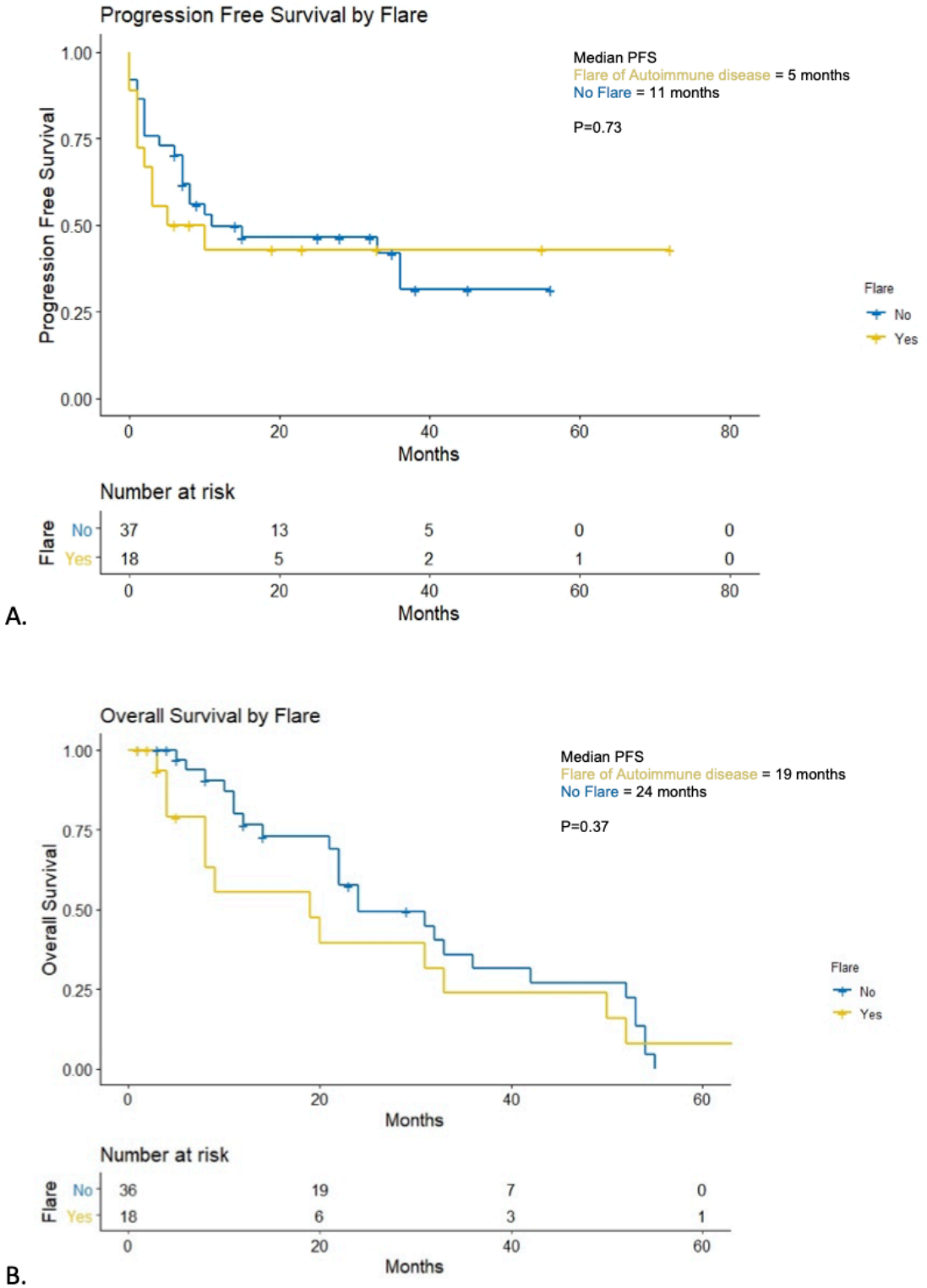

Figure 4 Progression-free survival (PFS) and overall survival (OS) in patients with flare of autoimmune disease. (A) Kaplan-Meier curves for PFS for patients with flare of autoimmune disease versus no flare. (B) Kaplan-Meier curves for OS for patients with flare of autoimmune disease versus no flare.

commencement of therapy. In the four patients with IBD who had a severe flare, none were on immunosuppression and all had been in clinical remission for greater than 24 months prior to commencement of combination immunotherapy.

Immune-related adverse events

Thirty-seven patients (67%) experienced an irAE unrelated to their autoimmune disease (table 3). Twenty-one patients (38%) had grade 3–4 irAEs, these included colitis (N=9), hepatitis (N=5), colitis and hepatitis (N=2),

pneumonitis (N=2), thyroiditis (N=1), myasthenia gravis (N=1) and GBS (N=1). Nine patients (17%) experienced both flare of autoimmune disease and an irAE. All patients with a grade 3 or 4 immune-related colitis underwent diagnostic colonoscopy or flexible sigmoidoscopy and histopathological confirmation.

Twenty-five patients (68%) required immunosuppression for the management of irAE. Seven patients were managed with oral steroids, seven with intravenous steroids, and nine patients were managed with steroids and steroid-sparing agents; one patient with GBS was managed with intravenous immunoglobulin and one patient with myasthenia gravis was treated with plasmapheresis. Both drugs were ceased due to irAE in 15 patients (41%).

A further subanalysis was undertaken to compare the outcomes of patients who had a flare of their autoimmune disorder with patients who had an irAE alone or both

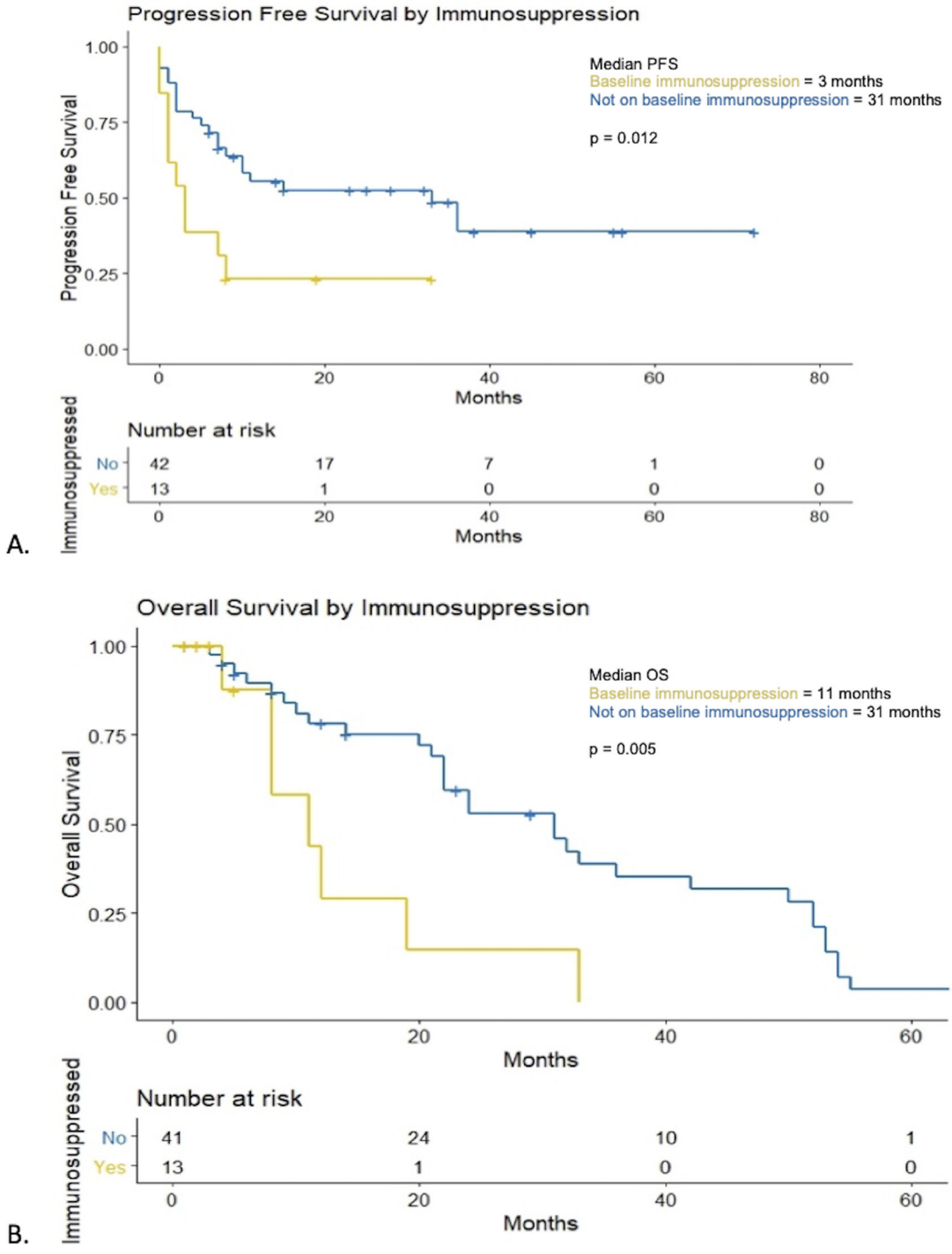

Figure 5 Progression-free survival (PFS) and overall survival (OS) in patients on baseline immunosuppression. (A) Kaplan-Meier curves for PFS for patients on baseline immunosuppression versus no immunosuppression at baseline. (B) Kaplan-Meier curves for OS for patients on baseline immunosuppression versus no immunosuppression at baseline.

an irAE and a flare. Ten patients had no flare or irAE, 27 patients had an irAE alone, 9 patients had a flare of their autoimmune disorder alone, and 9 had both a flare and an irAE (online supplemental table 1). There was a slightly higher use of immunosuppression to manage patients with both a flare and irAE (89%) compared with irAE alone (70%) or flare alone (78%). More patients who experienced both a flare and irAE were alive at the time of analysis (78%) compared with no irAE or flare (60%), irAE alone (70%) and flare alone (67%). Unfortunately the small numbers in this subanalysis limit statistical evaluation.

Patient outcomes

A partial or complete response was observed in 30 patients (55%), 30% partial and 25% complete. Seventy-seven per cent of responses are ongoing, with a median follow-up time of 14 months (figures 1 and 2). The objective response rate was not statistically different in those who had a flare of their autoimmune disease versus those who did not (44% vs 59%, p=0.39) nor in patients who were on baseline immunosuppression versus not (46% vs 57%, p=0.72).

Fourteen patients had a complete response (online supplemental table 2). All of these patients had a performance status of ECOG 0. At commencement of combination immunotherapy, two of the complete responders (14%) had active symptoms of their autoimmune condition and were receiving corticosteroids. Three (21%) of these patients experienced a flare of their autoimmune diseases (one with ulcerative colitis, one with psoriasis, one with polymyalgia). Twelve (86%) patients experienced an irAE with seven of these being grade 3 or 4 (online supplemental table 3). Eleven patients remain in complete response.

The median PFS was 10 months (95% CI 0.01 to 32.10) (figure 3A). Patients with flare of their autoimmune disease had a median PFS of 5 months compared with 11 months in those without a flare (p=0.73) (figure 4A). At 12 months, PFS rates were 33% vs 22% in those with a flare of their autoimmune disease versus no flare, respectively. Patients on baseline immunosuppression had a median PFS of 3 months (95% CI 0.71 to 5.30) compared with 33 months (95% CI 8.38 to 57.62) for patients not on baseline immunosuppression (p=0.012) (figure 5A). At 12 months, PFS rates were 15% vs 48% in those on immunosuppression versus no immunosuppression, respectively.

At the time of analysis, a total of 17 patients (31%) had died. One patient was lost to follow up following progression of disease and was not included in the OS analysis. Median OS was 24 months (95% CI 15.88 to 32.12) (figure 3B). Median OS in patients who had a flare of their autoimmune disease was 19 months vs 24 months in those who did not (p=0.37) (figure 4B). Twelve-month OS rates were 39% in patients who had a flare of autoimmune disease vs 64% in those who did not. Median OS in patients who were on baseline immunosuppression was 11 months (95% CI 3.42 to 18.58) compared with 31 months (95% CI 20.89 to 41.11, p=0.005) (figure 5B). Twelve-month OS rates were 23% in patients on immunosuppression vs 66% in those who were not.

Endocrine autoimmune disorders

Given there were a significant number of patients with an underlying endocrine autoimmune condition, a further subanalysis was performed to assess the difference in outcomes (online supplemental table 4). Endocrine autoimmune disorders were defined as endocrine only disorders and not patients who had an additional autoimmune condition (18 with thyroiditis, 1 with type 1 diabetes mellitus). Patients with an endocrine autoimmune disorder in patients versus patients with non-endocrine autoimmune disorders were less likely to have a flare 16% vs 42% (two-sided Fisher's exact p=0.05). The rates of irAEs were similar across both groups. The median OS was worse in the patients with a non-endocrine autoimmune disorder at 22 months vs 35 months in patients with an endocrine autoimmune disorder (p=0.046).

Subsequent therapies

Nineteen patients (35%) were given subsequent therapy following combination immunotherapy, some of these had multiple lines of therapy. Alternate anti-PD1 therapy was given in 11 patients (58%), BRAF-MEK inhibitors in 8 patients (42%), 1 patient (5%) was treated with chemotherapy and 5 patients (26%) were enrolled on clinical trials. Of the patients given subsequent therapies, 58% had a partial or complete response.

DISCUSSION

Therapy with ipilimumab in combination with anti-PD1 agents is associated with higher rates of irAEs compared with anti-PD1 therapy alone.[1] The safety and efficacy of combination therapy in patients with autoimmune disorders is unknown. To our knowledge, this is the first study to examine this issue. The results of this study suggest that efficacy of combination ipilimumab and anti-PD1 therapy is comparable in patients with autoimmune disorders (not on baseline immunosuppression) with the clinical trial population in patients.[1 18–20]

Flares of pre-existing autoimmune disorders were common, affecting 33% of patients. These events were, for the most part, managed easily by standard treatment protocols. It is known that ipilimumab is associated with increased rates of colitis[21] and anti-PD1 higher rates of arthropathy.[22] Therefore, it is not surprising that in our study, the combination of the two demonstrates an increased risk of flare in both rheumatologic and gastrointestinal autoimmune conditions. In particular, IBD flares seemed to be idiosyncratic and often life-threatening.

Patients with a flare of their autoimmune disease had numerically worse survival outcomes than those without. While this was not statistically significant, a potential explanation for this may be the early cessation of therapy in 44% of patients and the addition of immunosuppression

in 62% contributed to the worse PFS and OS outcomes compared with other patients without flare of their autoimmune disease.

The rate of irAEs otherwise appeared similar to rates observed in clinical trial population.[1 18–20]

Patients on immunosuppression at baseline had similar disease characteristics to patients not on immunosuppression and were noted to have worse outcomes with a lower OS and PFS which have been substantiated in prior studies.[7 9] Although overall response rates were similar, the inferior survival rates may be in part driven by attenuation of the therapeutic T-cell response by concomitant immunosuppressive treatment. Therefore, in patients with pre-existing autoimmune diseases that are not rheumatologic or IBD, weaning or cessation of immunosuppression prior to immunotherapy should be considered in patients without clinically active disease.

The rates of flare were higher in patients with non-endocrine autoimmune conditions versus those with an endocrine autoimmune condition. This is suggestive that perhaps it is safer for patients with endocrine disorders to be on combination immunotherapy. Additionally, patients with non-endocrine autoimmune disorders had worse PFS and OS outcomes perhaps owing to the higher rates of flare leading to discontinuation and/or higher levels of baseline immunosuppression.

A previous study assessing the safety and activity of single-agent ipilimumab in 30 patients with a range of concomitant autoimmune disorders found that 27% of patients experienced a flare of their autoimmune disorder and 33% experienced grade 3–4 irAEs with a 20% response rate.[8] Another retrospective analysis in the same population with anti-PD1 antibodies suggested patients were at risk of mild flare of their autoimmune disorder with 38% of patients experiencing a flare and 10% experiencing grade 3–4 irAEs with a 33% response rate.[9] Both studies concluded there was reasonable activity in patients with baseline autoimmunity, but with greater immune toxicities often of a mild nature. Findings in our study demonstrate a higher rate of flare of autoimmune disease and mirror the higher rates of irAEs in patients who receive combination therapy.

A retrospective assessment of patients specifically assessing IBD has shown relative safety with the use of immunotherapy.[13] There was a higher rate of any grade gastrointestinal adverse events in patients with pre-existing IBD, 41% vs 11%. In this analysis, use of CTLA4 or combination therapy was associated with a higher risk of gastrointestinal adverse events compared with anti-PD1. However, 4 out of 102 patients in t study of immune checkpoint inhibitors in IBD experienced colonic perforation, 3 having previously received anti-PD1 therapy and 1 receiving combination with ipilimumab and anti-PD1 therapy. Comparatively, the rates of flare of IBD in our study were 56% with two of these resulting in intensive care unit admission. Therefore, it is paramount that patients with IBD who develop a suspected gastrointestinal toxicity or flare are thoroughly investigated to ensure appropriate and timely management.

As experience builds in these populations with the use of immunotherapy, management of flares of autoimmune disease will improve. However, recent recommendations have been published for the management of patients with autoimmune diseases.[7] In our study, most patients were managed with corticosteroids, with severe cases of psoriasis, RA and IBD managed with a form of additional immunosuppression to steroids.

There are several limitations of our study. First, the retrospective analysis of patient data adds an inherent selection bias within the cohort reflecting patients who have been deemed suitable for combination ipilimumab and PD-1 therapy by the treating physician. Most of the patients had clinically inactive disease not requiring immunosuppression prior to treatment. Second, the short overall follow-up time of patients may prevent suitable analysis of OS and PFS. Third, we acknowledge patient numbers may have prevented detection of significant differences between groups.

This highlights the importance for this patient population to be considered in further clinical trials so that responses, impacts of immunosuppression and flare management may be evaluated in a prospective manner.[7]

CONCLUSIONS

Combination immunotherapy with ipilimumab and PD1 inhibitors may flare pre-existing autoimmune diseases particularly rheumatologic and gastrointestinal disorders, and those disorders that are clinically active and/or require immunosuppression. Rates of irAE were not increased.

Our results support that combination immunotherapy for patients with pre-existing autoimmune disease is efficacious for patients with advanced melanoma. However, with pre-existing IBD and rheumatologic conditions, the risk of severe flare is significant and these patients should be informed of this risk. Thus, close monitoring and thorough investigation of concerning symptoms are essential in these patients if treated with combination immunotherapy followed by prompt treatment with consultation of irAE management guidelines.

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Supplementary Tables

Supplementary Table 1: Subanalysis of outcomes based on event of flare or irAE

	No flare or irAE n =10 (%)	irAE alone n = 27 (%)	Flare alone n = 9 (%)	Flare and irAE n = 9 (%)
Baseline immunosuppression	1 (10%)	4 (15%)	4 (44%)	4 (44%)
Steroids	1	2	2	1
SSA[#]	0	1	1	1
Steroids + SSA	0	1	1	2
None	9 (90%)	23 (85%)	5 (56%)	5 (56%)
Management of Events during combination IO				
Steroids	0	19 (70%)	7 (78%)	8 (89%)
SSA+Steroids	0	9	5	7
IVIg/Plasmapheresis	0	8	2	1
	0	2	0	0
Number alive at time of analysis	6 (60%)	19 (70%)	6 (67%)	7 (78%)
Number with ongoing response at time of analysis	2 (20%)	12 (44%)	4 (44%)	4 (44%)

[#] SSA = Steroid sparing agent

Supplementary Table 2: Baseline Characteristics and outcomes of Complete Responders

Demographics	No. (%)	Detail
Gender		
Male	6 (43%)	
Female	8 (57%)	
ECOG 0	14 (100%)	
AJCC Stage		
III	3	
M1a/M1b	2	
M1c	4	
M1d	5	
Mutation Status		
BRAF/NRAS Wild Type	2 (14%)	
BRAF	9 (64%)	
NRAS	3 (21%)	
Drugs received		
Ipilimumab 3mg/kg + Nivolumab 1mg/kg	10 (71%)	
Ipilimumab 1mg/kg + Pembrolizumab 2mg/kg	4 (29%)	
Autoimmune disorder (AD)*		
Rheumatologic	1 (7%)	Polymyalgia – 1,
Gastrointestinal	1 (7%)	Ulcerative colitis – 1
Endocrine	7 (50%)	Grave's disease – 2, Hashimoto's thyroiditis – 4, Type I Diabetes – 1
Dermatologic	3 (21%)	Psoriasis – 3
Haematologic	1 (7%)	ITP – 1
Other	1 (7%)	Sarcoidosis – 1
Activity of AD		
Clinically active	2 (14%)	
Not clinically active	12 (86%)	
Immunosuppression	2 (24%)	
Corticosteroids	2 (24%)	
SSA[#]	0 (0%)	
Corticosteroids + SSA[#]	0 (0%)	
No immunosuppression	12 (76%)	
Flare of Autoimmune Disease		
No	11 (79%)	
Yes	3 (21%)	Psoriasis, Polymyalgia, Ulcerative colitis
Immunosuppression for AD flare		
IV steroids	1 (33%)	Ulcerative colitis – 1
Steroids and SSA[#]	2 (67%)	Cyclosporin – 1 for psoriasis, sulfasalazine – 1 for polymyalgia

IO Dosing after flare		
Both drugs ceased	1 (33%)	Ulcerative colitis – 1
PD1 alone continued	0	
Both continued	2 (67%)	Psoriasis – 1, Polymyalgia – 1

[#] SSA = Steroid sparing agent

Supplementary Table 3: irAE outcomes of Complete Responders

Demographics	No. (%)	Detail
irAE		
No	2 (14%)	
Yes	12 (86%)	
irAE Grade		
G1,2	5 (42%)	Colitis, Hepatitis, Hypophysitis, Thyroiditis, T1 Diabetes
G3	4 (33%)	Colitis – 1, Hepatitis – 2, Colitis + Hepatitis – 1 Pneumonitis – 2, Thyroiditis
G4	3 (42%)	Colitis, Hepatitis, Myasthenia Gravis
Immunosuppression for irAE	9 (64%)	
Oral steroids	1 (8%)	Hepatitis
IV steroids	1 (8%)	Hepatitis
Steroid and SSA[#]	6 (67%)	Colitis – 3, Hepatitis – 2, Colitis + Hepatitis – 1
Plasmapheresis	1 (8%)	Myasthenia Gravis

[#] SSA = Steroid sparing agent

Supplementary Table 4: Outcomes of Endocrine Autoimmune Disorders vs. Non-Endocrine Autoimmune disorders

	Endocrine Autoimmune Disorder* n =19	Non-endocrine Autoimmune Disorder n = 36
Total flare events	3/19 (16%)	15/36 (42%)
Flare of autoimmune disorder	2/19 (11%)	7/36 (19%)
Both irAE and flare	1/19 (5%)	8/36 (22%)
Neither	8/19 (42%)	5/36 (14%)
Immune related adverse event	8/19 (42%)	16/36 (44%)
Median OS	35 months (95% CI 21.72 – 48.28)	22 months (95% CI 9.32 – 34.68)
Median PFS	36 months (95% CI 28.36 – 57.87)	7 months (95% 1.94 – 12.06)

*Including endocrine only disorders. Not patients that had an additional autoimmune condition that was not affecting the endocrine system