ONCOIMMUNOLOGY
2023, VOL. 12, NO. 1, 2261264
https://doi.org/10.1080/2162402X.2023.2261264

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Safety and effectiveness of combination versus monotherapy with immune checkpoint inhibitors in patients with preexisting autoimmune diseases

Pankti Reid[a*], Sabina Sandigursky[b*], Juhee Song[c], Maria A. Lopez-Olivo[d], Houssein Safa[e], Samuel Cytryn[f], Elizaveta Efuni[f], Maryam Buni[g], Anna Pavlick[h], Michelle Krogsgaard[i], Osama Abu-Shawer[j,k], Mehmet Altan[l], Jeffrey S. Weber[m], Osama E. Rahma[j,n,o], Maria E. Suarez-Almazor[d,g], Adi Diab[e#], and Noha Abdel-Wahab[e,g,p#]

[a]Division of Rheumatology, Department of Medicine, University of Chicago Medical Center, Chicago, IL, USA; [b]Division of Rheumatology, Department of Medicine, NYU Langone Health, New York, NY, USA; [c]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [d]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [e]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [f]Division of Internal Medicine, Department of Medicine, NYU Langone Health, New York, TX, USA; [g]Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [h]Medical Oncology, Weill Cornell Medical Center, New York, NY, USA; [i]Perlmutter Cancer Center, Department of Pathology, NYU Langone Health, New York, NY, USA; [j]Department of Internal Medicine, Harvard Medical School, Boston, MA, USA; [k]Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA; [l]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [m]Perlmutter Cancer Center, Department of Medicine, NYU Langone Health, New York, NY, USA; [n]Department of Oncology, Dana Farber Cancer Institute, Boston, MA, USA; [o]Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA; [p]Department of Rheumatology and Rehabilitation, Faculty of Medicine, Assiut University Hospitals, Assiut, Egypt

ABSTRACT

Patients with preexisting autoimmune disease (pAID) are generally excluded from clinical trials for immune checkpoint inhibitors (ICIs) for cancer due to concern of flaring pAID. In this multi-center, retrospective observational study, we compared safety of ICI combination (two ICI agents) versus monotherapy in cancer patients with pAIDs. The primary outcome was time to AEs (immune-related adverse events (irAEs) and/or pAID flares), with progression-free survival (PFS) and overall survival as secondary outcomes. Sixty-four of 133 patients (48%) received ICI combination and 69 (52%) monotherapy. Most had melanoma (32%) and lung cancer (31%). Most common pAIDs were rheumatic (28%) and dermatologic (23%). Over a median follow-up of 15 months (95%CI, 11-18 mo), the cumulative incidence of any-grade irAEs was higher for combination compared to monotherapy (subdistribution hazard ratio (sHR) 2.27, 95% CI 1.35–3.82). No statistically significant difference was observed in high-grade irAEs (sHR 2.31 (0.95–5.66), $P = .054$) or the cumulative incidence of pAID flares. There was no statistically significant difference for melanoma PFS between combination versus monotherapy (23.2 vs. 17.1mo, $P = .53$). The combination group was more likely to discontinue or hold ICI, but > 50% of the combination group was still able to continue ICI therapy. No treatment-related deaths occurred. In our cohort with pAIDs, patients had a tolerable toxicity profile with ICI combination therapy. Our results support the use of ICI combination if deemed necessary for cancer therapy in patients with pAIDs, since the ICI toxicities were comparable to monotherapy, able to be effectively managed and mostly did not require ICI interruption.

ARTICLE HISTORY
Received 8 June 2023
Revised 14 September 2023
Accepted 17 September 2023

KEYWORDS
Preexisting autoimmune disease; immune-related adverse events; cancer immunotherapy toxicity; autoimmune disease flare; combination immune checkpoint inhibitor

Introduction

Immune checkpoint inhibitor (ICI) treatment targeting inhibitory proteins within the immune system, such as anti-programmed cell death protein 1 and its ligand (PD-[L]1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has considerably advanced our therapeutic options in clinical oncology. Clinical trials for these therapies have yielded promising outcomes for a wide array of malignancies, leading to Food and Drug Administration approval of combination therapy and monotherapy for multiple cancer types.[1–6] Unfortunately, ICI toxicities, known as immune-related adverse events (irAEs), can limit the ability to continue ICI therapy despite encouraging tumor responses. These irAEs can occur at various times after the initiation of ICIs treatment and can affect multiple organ systems, resulting in dermatitis, colitis, pneumonitis, myocarditis, arthritis, hypophysitis, and others.[6–9] Combination ICI therapy (anti-CTLA-4 + anti-PD-1) has been associated with increased response rates and overall survival (OS)[5,6] compared to monotherapy, but also with a higher rate of irAEs (up to 60% ≥ grade 3) leading to treatment discontinuation.[10,11]

CONTACT Noha Abdel-Wahab nahassan@mdanderson.org Department of General Internal Medicine, Unit 3465, The University of Texas MD Anderson Cancer Center, 1400 Bressler, Houston, TX 1400, USA; Pankti Reid pankti.reid@bsd.uchicago.edu Department of Medicine, University of Chicago Medical Center, 5841 South Maryland Avenue, Room DCAM 4C, MC 5841 South Maryland Avenue, Room DCAM 4C, Chicago, IL 60607, USA

*Co-first authors.
#Equally contributed.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/2162402X.2023.2261264

Owing to the phenotypic similarities between irAEs and primary autoimmune diseases, there is concern for an increased toxicity risk when considering ICI treatment for cancer patients with preexisting autoimmune diseases (pAIDs). Patients with pAIDs have generally been excluded from ICI clinical trials due to this concern.[12,13] However, these patients represent a special population at an elevated risk of developing various cancers because of their pAID.[14,15] Moreover, several retrospective cohort studies have shown that these patients could benefit from ICI therapy, and despite the development of de novo irAEs and pAID flares, these adverse events were manageable and did not require ICI discontinuation.[3,16–20]

Given the approval of ICI combination therapy associated with remarkably improved survival in different cancers, clinicians are faced with difficult risk and benefit discussions because of the limited data available to guide ICI combination use in patients with pAIDs.[21] Here, we report the results of a multicenter retrospective cohort study that evaluated the safety and effectiveness of ICI combination therapy compared with single-agent anti-PD-1 therapy in this population of patients with cancer and pAIDs.

Methods

Study design

Cohort selection

After obtaining approval from the Institutional Review Board at the University of Texas MD Anderson Cancer Center, we searched the institutional databases to identify cancer patients who had received ICIs between 3/4/2016 and 7/31/2019. The claims data for the retrieved patients were extracted from 6 months before the first ICI infusion up to the last follow-up or death. Patients with autoimmune diseases were identified using the International Classification of Diseases diagnostic codes 9 and 10 (Table S1). Among the patients with at least one relevant code, those who received a combination of ipilimumab and nivolumab were identified, and their medical records were thoroughly reviewed. Patients were included if they were ≥18 years of age and had pAIDs confirmed by a treating oncologist or organ disease specialist prior to the initiation of ICI combination therapy. Patients were excluded if they did not have established diagnosis of autoimmune disease prior to ICI initiation or did not have sufficient data available regarding their pAID and/or cancer treatments. Eligible patients with pAIDs who were treated with ICI as well as those treated with anti-PD1 monotherapy were also identified from the New York University Langone Health/Laura and Isaac Perlmutter Cancer Center and the Dana Farber Cancer Institute. IRB approval was obtained from each institution.

Data Collection

A universal data collection protocol was established to extract data on patient demographics and baseline characteristics including type of cancer, type of pAIDs (categorized as rheumatic, dermatologic, gastrointestinal, endocrine, neurologic and hematologic), status of pAIDs (defined as active if the patient had active disease manifestations based on documentation in medical record; otherwise, were considered inactive), pAIDs treatment at ICI initiation (systemic corticosteroids and/or disease modifying anti-rheumatic drugs "DMARDs" or other immunosuppressants), occurrence of any adverse events (irAEs and/or pAID flares), time to adverse events since ICI initiation, how adverse events were managed, median duration of follow-up, and tumor response to ICI therapy.

Outcome assessment

The primary outcome was to assess the safety of ICI combination therapy versus anti-PD-1 monotherapy in terms of time to development of de novo irAEs, time to pAID flares, and time to any AEs (de novo irAEs and/or pAID flares) after initiation of ICIs, counting death as a competing event. Patients were deemed to have an irAE if the autoimmune presentation after ICI initiation was clinically different from their preexisting autoimmune disease; irAEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[22] IrAEs of CTCAE grade 3 or higher were considered high-grade irAEs. Patients were deemed to have a pAID flare if they had recurrence or worsening of prior disease manifestations or reported new disease features as determined by treating the clinician based on a medical documentation review. The secondary outcomes were progression-free survival (PFS) and overall survival (OS). PFS was defined as the length of ICI until tumor progression as deemed by clinical annotations or death, and OS was calculated as the time from ICI initiation to the date of death or the most recent follow-up if the date of death was not documented. Subgroup analyses were performed on the patients with melanoma and lung cancer.

Statistical methods

Patient characteristics and management of adverse events were summarized according to the type of immunotherapy agent used, with descriptive statistics, median (range) for continuous variables, and frequency (%) for categorical variables. The two groups of patients treated with ICI combination versus single-agent anti-PD-1 were compared using the two-sample t-test or Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for proportions. The incidence rates (number of events per person year) of any adverse events, any-grade irAEs, high-grade (grade 3–5) irAEs, and pAID flares were estimated according to the type of immunotherapy agent in all patients, melanoma patients, lung cancer patients, and in different subgroups. Univariate and multivariable Fine-Gray hazard models were fitted, considering each time to any adverse event, time to de novo irAE, time to grade 3 or higher irAE, time to pAID flare as a response variable, and death without an event as a competing risk event. The Multivariable Fine-Gray model included the type of ICI and covariates selected by stepwise selection. The Aalen-Johansen method was used to estimate the cumulative incidence, which was plotted over time. Univariate and multivariable Cox models were fitted, considering PFS and OS as response variables for the entire cohort (adjusted for tumor type in the multivariable model), melanoma, and lung cancer patients. The Kaplan-Meier method was used to estimate the survival

curve, and the survival curves were compared between groups using the log-rank test. Statistical significance was set than 0.05. SAS 9.4 (SAS Institute INC, Cary, NC, USA) was used for data analysis.

Ethical considerations

Ethical approval has been obtained from the respective local ethics committees or Institutional Review Boards for University of Texas MD Anderson Cancer Center, New York University Langone Health/Laura and Isaac Perlmutter Cancer Center and the Dana Farber Cancer Institute.

Results

Of the 8423 cancer patients who received ICIs at MD Anderson between March 2016 and July 2019, 41 with pAIDs received ICI combination therapy (Figure S1). An additional 23 patients with pAIDs treated with ICI combination therapy and 69 patients with pAIDs treated with anti-PD-1 monotherapy were identified from other institutions. Therefore, 133 patients were included in our final analysis: 64 (48%) patients who received ICI combination therapy and 69 (52%) who received anti-PD-1 monotherapy.

The patient demographics and baseline characteristics are summarized in Table 1. The median age was 60 years (range, 32–85) in the combination therapy group and 64 (21–91) in the monotherapy group ($p = 0.53$). The sex distribution was similar to that of the female majority in both treatment groups. The most common cancer types were melanoma ($n = 28$ (44%) in the combination group and 15 (22%) in the monotherapy group) and lung cancer ($n = 16$ (25%) in the combination group and 25 (36%) in the monotherapy group). The majority of patients had inactive pAID at ICI initiation ($n = 126$ 133; 95%). There was no significant difference in the proportion of patients receiving baseline corticosteroids or biological DMARDs at ICI initiation; however, there were significantly fewer patients receiving baseline conventional synthetic DMARDs in the ICI combination group than in the monotherapy group (3% vs. 17%, $p = .01$). The median follow-up time since the initiation of ICI therapy was 14.9 months (95% CI, 11.2–17.8) for the entire cohort; 12.9 months (95% CI, 10.8–20.5) for patients treated with ICI combination, and 16 months (95% CI, 8.5–18.2) for those treated with monotherapy. In the total patient cohort, pAIDs included rheumatic ($n = 37$, 133; 28%), dermatologic ($n = 31$; 23%), endocrine ($n = 22$; 17%), gastrointestinal ($n = 16$; 12%), neurologic ($n = 5$; 4%), hematologic ($n = 5$; 4%), and multiple AIDs ($n = 17$; 13%) and were equally distributed between both treatment groups ($p = 0.56$) (detailed information on the types of pAIDs and their frequencies in both treatment groups are shown in Table S2).

Safety

Overall, 84 patients (63%) developed any adverse events (irAEs and/or pAID flares). The incidence rates (number of events per person year) of any adverse events, de novo irAEs, and flares of

Table 1. Patient demographics and baseline clinical characteristics.

Variable		Combination ($n = 64$)	Monotherapy ($n = 69$)	P-value
Age at cancer diagnosis	Median (range)	60 (32–85)	64 (21–91)	.53
Sex	Female	39 (61%)	38 (55%)	.50
	Male	25 (39%)	31 (44%)	
Follow-up since ICI initiation	Median months (95% CI)	12.9 months (10.8–20.5)	16 months (8.5–18.2)	
Cancer type	Gastrointestinal	4(6.3%)	3(4.3%)	.01
	Genitourinary	9(14.1%)	6(8.7%)	
	Lung	16(25%)	25(36.2%)	
	Melanoma	28(43.8%)	15(21.7%)	
	Other	7(10.9%)	20(29%)	
pAID type	Dermatologic	17 (27%)	14 (20%)	.56
	Endocrine	9 (14%)	13 (19%)	
	Gastrointestinal	7 (11%)	9 (13%)	
	Hematologic	4 (6%)	1 (1%)	
	Neurologic	1 (2%)	4 (6%)	
	Rheumatologic	19 (30%)	18 (26%)	
	Multiple PADs	7 (11%)	10 (15%)	
Autoimmune disease status at ICI initiation (Baseline)				
Active vs Inactive PAD	Active	5 (8%)	2 (3%)	.26
	Inactive	59 (92%)	67 (97%)	
Autoimmune disease treatment at ICI initiation (Baseline)				
Baseline Corticosteroids	No	57 (90%)	60 (87%)	.71
	Yes	7 (11%)	9 (13%)	
Baseline DMARDs	No	55 (86%)	50 (73%)	.06
	Yes	9 (14%)	19 (28%)	
Baseline csDMARD	No	62 (97%)	57 (83%)	.01
	Yes	2 (3%)	12 (17%)	
Baseline bDMARD	No	62 (97%)	67 (97%)	1.00
	Yes	2 (3%)	2 (3%)	

ICI = Immune checkpoint inhibitor, AIHA = autoimmune hemolytic anemia, bDMARD= biologic disease modifying anti-rheumatic drug, csDMARD = conventional synthetic disease modifying anti-rheumatic drug, GBS = Guillain-Barre syndrome, ITP = immune thrombocytopenia, PAD= preexisting autoimmune disease, PMR=Polymyalgia rheumatica, RA=rheumatoid arthritis, SLE = Systemic lupus erythematosus, SSc = systemic scleroderma, SD = standard deviation.

Table 2. Incidence rate (number of event per person yrs) and subdistribution hazard ratio (sHR) of AEs for ICI combination compared to anti-PD-1 monotherapy in patients with pAids.

	Any adverse event (irAE and/or pAID flare)				All-grade Immune-related adverse events				Pre-existing Autoimmune Disease Flares			
	Incidence rate (95% CI)				Incidence rate (95% CI)				Incidence rate (95% CI)			
	Combination	Monotherapy	sHR (95% CI)	P-value	Combination	Monotherapy	sHR (95% CI)	P-value	Combination	Monotherapy	sHR (95% CI)	P-value
Total pAIDs	0.62(0.46–0.83)	0.47(0.34–0.64)	1.15 (0.71–1.86)*	.58*	0.52(0.38–0.72)	0.26(0.17–0.4)	2.27 (1.35–3.82)**	.002**	0.27(0.18–0.43)	0.3(0.2–0.44)	0.91 (0.51–1.63)***	.75***
RHEUMATOLOGIC	0.68(0.4–1.15)	0.39(0.21–0.73)	1.13(0.5–2.52)	.77	0.49(0.26–0.9)	0.16(0.06–0.42)	2.56(0.8–8.17)	.11	0.34(0.16–0.71)	0.31(0.16–0.63)	0.68 (0.26–1.78)	.43
Rheumatoid arthritis	0.63(0.28–1.4)	0.43(0.22–0.82)	0.57(0.22–1.45)	.24	0.42(0.16–1.12)	0.14(0.05–0.44)	1.75(0.41–7.42)	.45	0.32(0.1–0.98)	0.38(0.19–0.76)	0.34(0.1–1.11)	.07
PMR	0.73(0.23–2.25)	–	–	–	0.48(0.12–1.94)	–	–	–	0.48(0.12–1.94)	–	–	–
SLE	0.98(0.14–6.95)	0	–	–	0.98(0.14–6.95)	0	–	–	0	0	–	–
Sarcoidosis	1.45(0.36–5.78)	0	–	–	1.45(0.36–5.78)	0	–	–	0	0	–	–
SSc	0.44(0.11–1.78)	3.23(0.46–22.95)	–	–	0.22(0.03–1.58)	3.23(0.46–22.95)	–	–	0.44(0.11–1.78)	0	–	–
DERMATOLOGIC	0.64(0.37–1.13)	0.49(0.23–1.02)	1.38(0.58–3.29)	.47	0.59(0.33–1.07)	0.14(0.03–0.56)	5.51(1.3–23.47)	.02	0.32(0.14–0.72)	0.35(0.14–0.83)	0.9(0.29–2.78)	.86
Psoriasis ± arthritis	0.64(0.37–1.13)	0.52(0.23–1.15)	1.41(0.55–3.62)	.47	0.59(0.33–1.07)	0.09(0.01–0.61)	9.82(1.22–78.95)	.03	0.32(0.14–0.72)	0.43(0.18–1.03)	0.81(0.26–2.5)	.72
Vitiligo	–	0.36(0.05–2.54)	–	–	–	0.36(0.05–2.54)	–	–	–	0	–	–
GASTROINTESTINAL	0.45(0.17–1.21)	0.42(0.14–1.31)	2.7(0.69–10.63)	.15	0.34(0.11–1.05)	0.42(0.14–1.31)	1.69 (0.39–7.34)	.49	0.34(0.11–1.05)	0	–	–
Crohn's disease	0.58(0.14–2.31)	0	–	–	0.29(0.04–2.05)	0	–	–	0.58(0.14–2.31)	0	–	–
Ulcerative colitis	0.43(0.11–1.73)	0.97(0.24–3.89)	2.56(0.43–15.24)	.30	0.43(0.11–1.73)	0.97(0.24–3.89)	2.56(0.43–15.24)	.30	0.22(0.03–1.53)	0	–	–
Celiac disease	0	0.27(0.04–1.88)	–	–	0	0.27(0.04–1.88)	–	–	0	0	–	–
ENDOCRINE	0.96(0.48–1.93)	0.7(0.33–1.46)	2.21(0.89–5.49)	.09	0.96(0.48–1.93)	0.6(0.27–1.33)	2.82(1.08–7.38)	.03	0.12(0.02–0.85)	0.4(0.15–1.06)	0.3(0.04–2.27)	.25
Graves' disease	0.72(0.23–2.25)	0	–	–	0.72(0.23–2.25)	0	–	–	0.24(0.03–1.71)	0	–	–
Hashimoto's thyroiditis	1.07(0.4–2.85)	0.91(0.43–1.91)	1.83(0.45–7.5)	.40	1.07(0.4–2.85)	0.78(0.35–1.74)	2.39(0.55–10.38)	.25	0	0.52(0.2–1.39)	–	–
Type I diabetes	2.4(0.34–17.06)	–	–	–	2.4(0.34–17.06)	–	–	–	0	–	–	–
NEUROLOGIC	2.2(0.31–15.62)	0.53(0.17–1.64)	–	–	0	0.35(0.09–1.41)	–	–	2.2(0.31–15.62)	0.18(0.02–1.25)	–	–
Multiple Sclerosis	2.2(0.31–15.62)	–	–	–	0	–	–	–	2.2(0.31–15.62)	–	–	–
GBS	–	0.29(0.04–2.06)	–	–	–	0.29(0.04–2.06)	–	–	–	0	–	–
Myasthenia Gravis	–	0.9(0.23–3.61)	–	–	–	0.45(0.06–3.21)	–	–	–	0.45(0.06–3.21)	–	–
HEMATOLOGIC	0.87(0.22–3.49)	0	–	–	0.87(0.22–3.49)	0	–	–	0	0	–	–
AIHA	1.15(0.29–4.59)	–	–	–	1.15(0.29–4.59)	–	–	–	0	–	–	–
ITP	0	0	–	–	0	0	–	–	0	0	–	–
MORE THAN 1 pAID	0.29(0.11–0.78)	0.44(0.23–0.84)	0.36(0.14–0.97)	.04	0.29(0.11–0.78)	0.24(0.1–0.58)	1.13(0.37–3.51)	.83	0.15(0.04–0.58)	0.34(0.16–0.71)	0.3(0.08–1.16)	.08
pAID status and treatment at ICI initiation (Baseline)												
pAID status at ICI initiation												
Inactive	0.61(0.45–0.83)	0.46(0.33–0.63)	1.33(0.87–2.04)	.19	0.51(0.36–0.71)	0.27(0.18–0.41)	2.06(1.22–3.49)	.01	0.27(0.17–0.43)	0.28(0.19–0.43)	0.83(0.45–1.51)	.53
Active	0.71(0.26–1.88)	0.74(0.18–2.95)	0.47(0.13–1.67)	.24	0.71(0.26–1.88)	0	–	–	0.35(0.09–1.41)	0.74(0.18–2.95)	0.23(0.03–1.64)	.14
pAID treatment at ICI initiation												
Off treatment	0.57(0.4–0.82)	0.35(0.21–0.59)	1.67(0.91–3.08)	.10	0.5(0.34–0.73)	0.21(0.11–0.41)	2.61(1.23–5.56)	.01	0.23(0.13–0.4)	0.19(0.09–0.38)	1.05(0.43–2.53)	.92
On treatment	0.73(0.44–1.21)	0.58(0.39–0.87)	1.2(0.66–2.19)	.55	0.59(0.33–1.03)	0.32(0.18–0.54)	1.96(0.94–4.12)	.07	0.39(0.2–0.78)	0.41(0.26–0.66)	0.82(0.37–1.81)	.62
On any DMARDs	0.65(0.29–1.45)	0.57(0.33–0.99)	0.85(0.36–2)	.71	0.33(0.11–1.01)	0.18(0.07–0.47)	1.62(0.41–6.48)	.49	0.54(0.23–1.31)	0.48(0.27–0.88)	0.86(0.34–2.22)	.76

sHRs (95% CI) and p-values presented in this table are those calculated from univariate Fine-Gray models unless specified.

*Adjusted for cancer type. **Adjusted for age at malignancy diagnosis. ***Adjusted for receipt of any immunomodulatory in multivariate Fine-Gray model.

ICI: Immune checkpoint inhibitor, anti-PD-1: Anti- programmed cell death protein 1, pAID: autoimmune disease, irAE: immune-related adverse events, CI: confidence interval, PMR: polymyalgia rheumatica, SLE: Systemic lupus erythematosus, SSc: systemic scleroderma, GBS: Guillain-Barre syndrome, AIHA: autoimmune hemolytic anemia,, ITP: immune thrombocytopenia, DMARD: disease-modifying anti-rheumatic drugs, ICI: immune-checkpoint inhibitor.

pAIDs in patients treated with ICI combination compared to monotherapy and the subdistribution hazard ratios (sHRs) are shown in Table 2. The use of ICI combination therapy was not associated with a significantly increased cumulative incidence of any adverse events compared with anti-PD-1 monotherapy in the overall cohort (incidence rates of 0.62 vs. 0.47, respectively and sHR 1.29 (95% CI 0.86–1.96), $p = .22$) (Figure S2). In a subgroup analysis, patients with melanoma had an incidence rate of any adverse event of 0.61 for the combination therapy group and 0.46 for monotherapy (sHR 0.63 (95% CI 0.32–1.24), $P = .18$). For patients with lung cancer, the incidence rates were 0.71 for combination vs. 0.42 for monotherapy (sHR 1.26 (95% CI 0.52–3.10), $p = .61$) (Figure S2).

Immune-related adverse events

Of 133 patients, 60 (45%) developed irAEs of any grade. The incidence rate of any-grade irAE was 0.52 for patients on combination therapy and 0.26 for those on monotherapy (Table 2). The use of ICI combination therapy was associated with a higher cumulative incidence of any-grade irAEs in the overall cohort (sHR 2.23 (95% CI 1.33–3.74), $p = .002$) (Figure S3), but the results of subgroup analyses by cancer type, although they showed an increase in the sHR, did not reach statistical significance: melanoma (incidence rates 0.42 vs. 0.23, sHR 1.48 (95% CI 0.61–3.56), $P = .39$) and lung cancer patients (incidence rates 0.71 vs. 0.27, sHR 2.17 (95% CI 0.82–5.74), $P = .12$) (Figure S3).

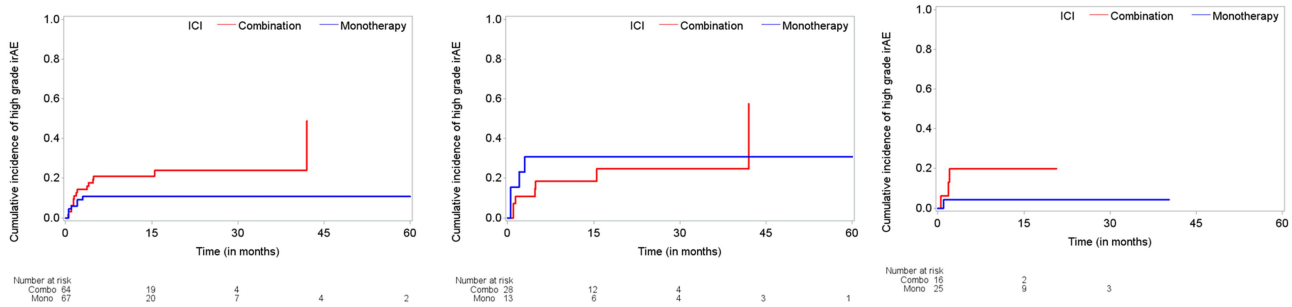
Within the various pAID categories, patients with dermatologic pAIDs had a higher incidence rates of any-grade irAEs when treated with ICI combination compared to monotherapy (0.59 versus 0.14, respectively) with a higher cumulative incidence in combination therapy versus monotherapy (sHR of 5.51 (95% CI 1.3–23.47), $P = .02$). Patients with endocrine pAIDs had a higher cumulative incidence (0.96 in the combination group versus 0.60 in the monotherapy (sHR 2.82 (95% CI 1.08–7.38), $P = .03$). Irrespective of autoimmune disease categories, patients who had inactive pAIDs and those who were not receiving immunomodulatory agents at ICI initiation experienced a significantly higher cumulative incidence of irAEs when treated with ICI combination therapy (incidence rates 0.51 vs. 0.27, sHR 2.06 (95% CI 1.22–3.49), $p = .01$) and (incidence rates 0.50 vs. 0.21, sHR 2.61 (95% CI 1.23–5.56, $p = .01$).

For high-grade irAEs (≥grade 3), regardless of tumor type, there was a higher cumulative incidence in patients treated with ICI combination therapy compared to monotherapy, but this did not reach statistical significance (incidence rates 0.21 vs. 0.09, sHR 2.31 (95% CI 0.95–5.66), $P = .07$). There was no significant difference in high-grade irAEs between combination therapy and monotherapy for patients with melanoma (incidence rates 0.18 vs. 0.14, sHR 0.79 (95% CI 0.23–2.77, $p = .71$) and patients with lung cancer (incidence rates 0.26 vs. 0.04, sHR 4.94 (95% CI 0.52–47.3), $p = .17$), as illustrated in Figure 1.

The distribution of irAE types for all patients and the ICI regimen they received are shown in Table S3. Overall, the most common irAEs were dermatitis and colitis (11.3%) and hepatitis (6.8%), followed by pneumonitis (6%), which was primarily reported in patients treated with ICI combination therapy (10.9% vs. 1.4%, $P = 0.03$). However, there were no significant differences in the frequency of other irAEs between the two treatment groups.

Pre-existing autoimmune disease flares

Of the 133 patients, 45 (34%) experienced a pAID flare. There was no significantly increased cumulative incidence of pAID flares with the use of ICI combination compared to anti-PD-1 monotherapy in the overall cohort (incidence rates 0.27 vs. 0.30, sHR 0.79 (95% CI 0.45–1.4), $p = 0.42$) (Figure S4) or in lung cancer patients (incidence rates 0.18 vs. 0.23, sHR 0.48 (95% CI 0.10–2.35), $p = 0.36$) (Figure S4). The cumulative incidence of developing pAID flares with the use of ICI combination therapy was comparable with the use of ICI combination therapy compared to anti-PD-1 monotherapy in



	All Tumor types (n=131)*†				Melanoma (n=41)*§				Lung cancer (n=41)#			
	Incidence rate (95% CI)		sHR (95% CI)	P-value	Incidence rate (95% CI)		sHR (95% CI)	P-value	Incidence rate (95% CI)		sHR (95% CI)	P-value
	Combination	Monotherapy			Combination	Monotherapy			Combination	Monotherapy		
irAE grade≥3	0.21(0.12-0.34)	0.09(0.04-0.18)	2.31(0.95-5.66)	0.07	0.18(0.09-0.39)	0.14(0.05-0.37)	0.79(0.23-2.77)	0.71	0.26(0.09-0.82)	0.04(0.01-0.27)	4.94(0.52-47.3)	0.17

P-values presented in the tables are based on univariate Fine-Gray model
*Two patients with unknown irAE grade were not included, †15 of 64 patients on combination therapy and 7 of 67 on anti-PD-1 therapy experienced high-grade irAEs, §7 of 28 patients on combination therapy and 4 of 13 on anti-PD-1 therapy experienced high-grade irAEs, #3 of 16patients on combination therapy and 1 of 25 on anti-PD-1 therapy experienced high-grade irAEs
irAE: immune-related adverse event, CTCAE: common terminology for cancer adverse events, ICI: immune checkpoint inhibitor, anti-PD-1: anti-programmed cell death protein 1, pAID: pre-existing autoimmune disease

Figure 1. Depicted here is the Aalen-Johansen estimator of the cumulative incidence function, incidence rate (number of high grade irAE event per person year) and subdistribution hazard ratio (sHR) of high-grade immune-related adverse events (irAes with CTCAE grade ≥ 3) for ICI combination compared to anti-PD-1 monotherapy in patients with pAids. No statistically significant difference was identified in the comparison of high-grade immune-related adverse events (irAes) defined by common Terminology Criteria for adverse events (CTCAE) ≥3 between combination and single-agent immune checkpoint inhibitor (ICI) therapies.

melanoma patients (incidence rates 0.32 vs. 0.33, sHR 0.43 (95% CI 0.19–0.99), $p = .05$). Notably, patients with gastrointestinal pAIDs did not have any disease flares when treated with anti-PD1 monotherapy (incidence rates of 0 vs. 0.34, combination). However, no significant differences were observed in autoimmune disease flares between the two treatment groups in other pAID categories, regardless of the disease status and treatment of pAIDs at ICI initiation.

Management of adverse events

A total of 58 patients (44%) required treatment with systemic immunomodulatory agents; all patients required corticosteroids, 12 (9%) required conventional synthetic DMARDs (methotrexate, hydroxychloroquine, mycophenolate mofetil, cyclosporine), and 7 (5%) required biological DMARDs (infliximab, tocilizumab, rituximab, ustekinumab, vedolizumab) (Table 3). Overall, the need for corticosteroids was significantly higher in the ICI combination group than that in the monotherapy (80% vs. 56%, $p = .02$). However, the use of conventional synthetic DMARDs was significantly higher in the monotherapy group (26% vs. 4%, $p = .006$), and biological DMARDs were used more frequently in the ICI combination group; however, the difference was not statistically significant (13% vs. 3%, $p = .12$). Additionally, management of adverse events required permanent discontinuation of ICI in 22 patients (16.5%), including 15 of 64 patients (23%) in the combination group and 7 of 69 patients (10%) in the monotherapy group ($p = .05$). However, 49 patients (77%) in the combination group and 62 patients (90%) in the monotherapy group were able to continue their ICI treatment course without interruption or after a temporary hold because of adverse events. No treatment-related deaths were observed in either of the groups.

Efficacy

Patients with pAIDs treated with ICI combination had longer therapy PFS compared to those treated with anti-PD-1 monotherapy in the entire cohort (12.3 vs. 7.3 months, $P = .12$) and the melanoma subgroup (23.2 vs. 17.1 months, $P = .53$), however, the differences did not reach statistical significance (Table 4 and Figure 2). Overall, longer PFS was associated with male sex than with female sex (HR 0.58, 95% CI 0.37–0.91, $P = .02$) (Table 4). In contrast, the following variables were associated with significantly shorter PFS: lung cancer compared to melanoma (HR 2.42, 95% CI 1.39–4.21, $P = .002$), hematological pAIDs compared to rheumatologic pAIDs (HR 3.51, 95% CI 1.3–9.44, $P = .01$), and the use of bDMARD for treatment of pAIDs at ICI initiation (HR 3.04, 95% CI 1.1–8.45, $P = .03$). In patients with melanoma, the following variables were associated with shorter PFS: neurologic pAIDs (HR 37.49, 95% CI 2.23–629.31, $P = .01$) and bDMARDs use at ICI onset (HR 4.93, 95% CI 1.04–23.34, $P = .04$). When focusing on patients with lung cancer, shorter PFS was observed in patients who used any immunomodulatory agent (HR 3.9, 95% CI 1.52–10.0, $P = .005$). In the entire cohort, there were no statistically significant differences in OS among patients with pAIDs treated with ICI combination therapy compared to those treated with anti-PD-1 monotherapy (Figure 3). Survival was calculated for patients who received immunosuppression versus those who did not, and the data are presented in the supplementary material (Table S4a for all patients and S4b for patients who experienced ICI AEs).

Discussion

To our knowledge, this study is the first to compare the safety and effectiveness of ICI combination therapy versus single-agent anti-PD-1 therapy in a cancer population with pAIDs. Our results suggest that the use of ICI combination therapy had twice the cumulative incidence of all-grade irAEs; however, while the cumulative incidence of high-grade irAEs was higher for combination therapy versus monotherapy, the difference was not statistically significant. Notably, more than 90% of our patients had inactive pAID and about 90% had no need for systemic steroids at time of ICI initiation. This was comparable between the monotherapy and combination groups. There was no significant difference between the two cohorts with regard to the pAID flares and most irAEs and flares were successfully managed with corticosteroids and a secondary immunomodulatory agent in some patients. Permanent discontinuation of ICI treatment was rarely required (16.5% of the entire cohort). Although patients on combination therapy were more likely to experience discontinuation or holding of their ICI treatment because of adverse events, more than 50% of those patients were still able to continue their combination therapy. According to our findings, patients with pAIDs treated with ICI combination therapy may have better PFS compared to those treated with anti-PD-1 monotherapy, but the difference was not statistically

Table 3. Details regarding adverse event management for all patients.

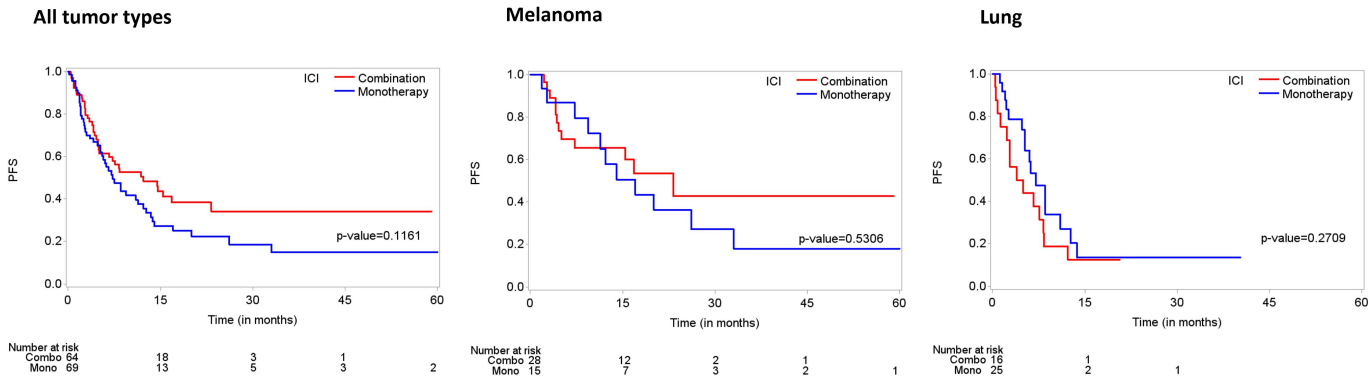
Total patients with any adverse events ($n = 84$)		Combination	Monotherapy	P-value
Treatment of adverse events, N/total (%)	Any systemic immunomodulatory agents	36/45 (80%)	22/39 (56%)	.02
	Corticosteroids	36/45 (80%)	22/39 (56%)	.02
	csDMARDs	2/45 (4%)	10/39 (26%)	.006
	bDMARDs	6/45 (13%)	1/39 (3%)	.12
	Supportive and other treatment	16/45 (36%)	22/39 (56%)	.06
Continuation of ICI therapy	Permanently discontinued due to AEs	15/64 (23%)	7/69 (10%)	.03
	Temporarily withheld ipilimumab due to AEs	15/64 (23%)	11/69 (16%)	
	Continued	34/64 (53%)	51/69 (74%)	
Tumor response to ICI therapy, N/total (%)	Progressed	30/64 (47%)	42/69 (61%)	.11
	Achieved remission/remained stable	34/64 (53%)	27/69 (39%)	

Biologic DMARDs included: infliximab, tocilizumab, rituximab, ustekinumab, vedolizumab.
csDMARDs included: MTX, HCQ, MMF, cyclosporine.
Supportive and other treatment included: naproxen, levothyroxine, topical steroids, vit. D, NB-UVB, plasmapheresis, dialysis, IV hydration.

Table 4. Progression free survival (time to progression or death).

		All cancer types (*N* = 133)		Melanoma cancer (*N* = 43)		Lung cancer (*N* = 41)	
Covariate	Level	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at malignancy dx	In 1 Unit Change	1.00 (0.98–1.01)	.66	1.02 (0.98–1.05)	.37	0.96 (0.92–0.99)	.02
Type of_ICI	Monotherapy	1.00		1.00		1.00	
	Combination	0.71 (0.46–1.09)*	.12	0.77 (0.34–1.76)	.53	1.49 (0.73–3.06)**	.27
Sex	Female	1.00		1.00		1.00	
	Male	0.58 (0.37–0.91)	.02	0.69 (0.30–1.57)	.38	0.77 (0.36–1.65)	.50
Cancer type	Melanoma	1.00					
	Gastrointestinal	0.97 (0.29–3.22)	.96				
	Genitourinary	1.70 (0.78–3.69)	.18				
	Lung	2.42 (1.39–4.21)	.002				
	Others	2.14 (1.15–3.98)	.02				
pAID type	Rheumatologic	1.00		1.00		1.00	
	Dermatologic	0.90 (0.47–1.73)	.76	0.61 (0.18–2.04)	.42	1.40 (0.50–3.91)	.53
	Endocrine	1.91 (0.99–3.68)	.05	1.54 (0.40–5.97)	.53	1.30 (0.34–4.91)	.70
	Gastrointestinal	1.23 (0.58–2.61)	.59	0.94 (0.25–3.59)	.93	1.93 (0.50–7.41)	.34
	Hematologic	3.51 (1.30–9.44)	.01	–		1.81 (0.37–8.76)	.46
	Multiple Aids	0.99 (0.47–2.05)	.97	0.84 (0.25–2.82)	.78	1.43 (0.46–4.42)	.54
	Neurologic	1.75 (0.60–5.13)	.31	37.49 (2.23–629.31)	.01	2.83 (0.56–14.25)	.21
Active versus inactive	Active	1.00		1.00		1.00	
	Inactive	2.09 (0.66–6.63)	.21	1.20 (0.28–5.17)	.81	0.11 (0.01–0.96)	.05
On treatment for pAID at time of ICI initiation	Any immunomodulator	1.60 (0.98–2.61)	.06	1.72 (0.72–4.09)	.22	3.90 (1.52–10.00)	.004
	csDMARD	1.20 (0.62–2.33)	.58	1.11 (0.38–3.27)	.85	3.61 (1.02–12.79)	.05
	bDMARD	3.04 (1.10–8.45)	.03	4.93 (1.04–23.34)	.04	1.63 (0.22–12.29)	.64
	Systemic steroid	0.95 (0.50–1.79)	.87	0.66 (0.20–2.24)	.50	3.27 (1.08–9.92)	.04

HRs (95% CI) and p-values presented in this table are those calculated from univariate cox regression models.
*HR of Combo vs Monotherapy based on a multivariate Cox model, adjusting for sex, malignancy for all cancer types, and any immunomodulatory: 0.87 (95% CI, 0.55–1.38), p = .55
**HR of Combo vs. Monotherapy based on a multivariate Cox model, adjusting for age and any immunomodulatory for lung cancer: 1.69 (95% CI, 0.75–3.77), p = .20.
95% CI: 95% confidence interval, bDMARD: Biologic disease-modifying anti-rheumatic drug, CNS: Central nervous system, csDMARD: Conventional synthetic disease modifying anti-rheumatic drug, Dx: Diagnosis, HR: Hazard ratio, ICI: Immune-checkpoint inhibitor, PAD: Pre-existing autoimmune disease, Tx: Treatment.



Immunotherapy agent	Median PFS (95% CI)
Monotherapy	7.3 months (5.2-11.3)
Combination	12.3 months (5.0-23.2)

Immunotherapy agent	Median PFS (95% CI)
Monotherapy	17.1 months (7.3-33.0)
Combination	23.2 months (5.0 – not estimated)

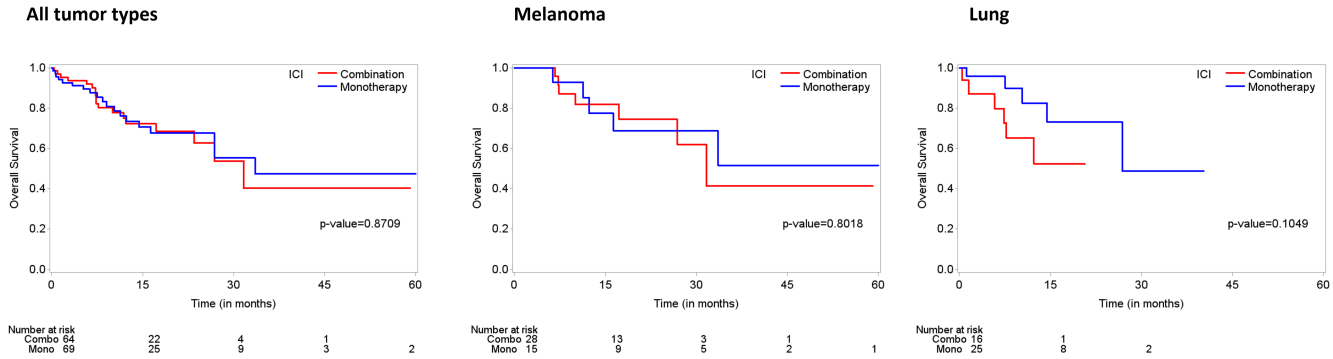
Immunotherapy agent	Median PFS (95% CI)
Monotherapy	7.1 months (5.2-11.0)
Combination	4.4 months (1.3-8.3)

P-values presented in the tables are based on log-rank test.

Figure 2. Depicted here is Kaplan-Meier plot of PFS by type of immunotherapy agent. There was no statistically significant difference regarding progression free survival (PFS) was found between anti-PD-1 monotherapy versus combination immune checkpoint inhibitor therapy. This was true regarding any tumor type, lung/thoracic malignancy or melanoma.

significant. Although larger studies and prospective clinical trials are still needed to assess the safety and efficacy of ICI combination therapy versus monotherapy in patients with pAID, our findings show an expected increase in ICI toxicity with combination therapy, but indicate that most patients, including those in the ICI combination arm, were able to continue ICI therapy without interruption. Importantly, no treatment-related deaths occurred in the entire cohort.

There is mounting evidence that the use of ICI treatment for patients with pAIDs has an acceptable safety profile with a comparable rate of adverse events to what has been reported in trials for patients without pAID, but this is primarily from retrospective studies in patients treated with ICI monotherapy.[3,16–19] It is not surprising that clinicians are more hesitant to use ICI combination treatment in patients with pAIDs because past studies have shown a grade 3 or higher irAE rate of 32% to 60% in patients without pAID.[23,24] Brown et al. reported a series of 55 patients with melanoma and pAIDs treated with ICI combination therapy,[25] and observed de novo irAEs in 67% of patients and flares of the underlying



Immunotherapy agent	Median OS (95% CI)
Monotherapy	33.5 months (26.8- not estimated)
Combination	31.7 months (23.5- not estimated)

Immunotherapy agent	Median OS (95% CI)
Monotherapy	Not reached (12.3- not estimated)
Combination	31.6 months (17.2 – not estimated)

Immunotherapy agent	Median OS (95% CI)
Monotherapy	26.8 months (14.4 – not estimated)
Combination	No reached (5.7- not estimated)

P-values presented in the tables are based on log-rank test.

Figure 3. This figure reflects the Kaplan-Meier curves for OS by type of immunotherapy agent. There was no statistically significant difference regarding overall survival (OS) was found between anti-PD-1 monotherapy versus combination immune checkpoint inhibitor therapy. This was true regarding any tumor type, lung/thoracic malignancy or melanoma.

autoimmunity in 33% (3 of 19 patients with thyroiditis, 5 of 10 with inflammatory bowel disease, 4 of 7 with rheumatoid arthritis, 3 of 6 with psoriasis, 1 of 1 with Behcet's syndrome and psoriasis, 1 of 1 with polymyalgia, and 1 of 1 with Sjogren's syndrome), which led to treatment discontinuation in 51% (20 patients with irAEs and 8 with flares) with no treatment-related deaths. The same study also reported an overall response rate of 55% (similar efficacy to ICI combination trials in melanoma) and observed that patients who were receiving immunosuppression at ICI treatment initiation had a significantly shorter OS than those not receiving baseline immunosuppression (11 vs. 31 months, $p = .005$).[25] The largest cohort to date, which retrospectively evaluated the safety and efficacy of ICI use in patients with melanoma with and without pAIDs enrolled in the Dutch Melanoma Treatment Registry, reported similar rates of grade 3 or higher irAEs in patients with and without pAIDs treated with ICI combination therapy (44% of 34 patients with pAIDs versus 48% of 388 without pAIDs) but did not provide information on pAID flares since only irAEs of grade 3 or higher were registered in their database.[26] The same study also identified a similar objective response rate in patients with and without pAIDs treated with ICI combination therapy (39% vs. 43%) and reported no deaths due to toxicity among patients with pAIDs treated with ICI combination therapy. These data are in accordance with the rates of high-grade irAEs and the effectiveness of ICI combination compared to anti-PD-1 monotherapy we observed in our study, which suggests that having a pAID should not preclude the use of ICI combination therapy if considered necessary, as the increase in toxicity appears to be inherent to combination versus monotherapy per se.[27]

Beyond impact of ICI on pAID, the use of immunosuppressive agents for the treatment of ICI side effects raises concerns regarding the abrogation of ICI effectiveness and subsequent tumor response. Furthermore, patients with pAIDs were more likely to be on baseline immunosuppression at the start of ICI therapy. Contrasting evidence exists with certain retrospective studies reporting attenuation of ICI effectiveness on cancer outcomes with systemic corticosteroid use of ≥10 mg prednisone equivalent, steroid initiation within the first 2 months of ICI therapy, and baseline immunosuppressive therapy, whereas other studies have found no effect on tumor response and overall survival.[6,7,16,17,28–32] Patients with pAIDs, compared to those without, may be at an increased risk of deleterious impact on tumor outcome, as they are more likely to be on baseline immunosuppression for active pAID or potentially to prevent future pAID flares. A 2020 meta-analysis suggested that earlier initiation, higher doses, and longer courses of systemic steroids used to treat irAEs were associated with worse PFS and OS.[33] However, these authors specifically highlighted that this correlation was not statistically significant when systemic corticosteroids were used for ICI adverse event treatment; instead, this correlation was significant only when corticosteroids were used for brain metastases or palliative care.[33] In our cohort, at the time of ICI initiation, most patients (95%) had inactive autoimmune disease and approximately one-fifth (21%) received systemic immunomodulatory treatment. Given that baseline pAID status and/or baseline immunosuppression would have biased clinical decision-making when choosing between ICI combination or monotherapy, this would be a confounder when assessing tumor outcome but could not be accounted for in our findings. More data are required to better understand whether systemic immunosuppression at baseline or used for the treatment of ICI toxicity affects antitumor immunity.

Our results can provide a guide for the development of a randomized controlled clinical trial that identifies the most sensitive patient population with consideration of pAID history and cancer diagnosis to study the safety and efficacy of combination therapy versus single-agent ICI therapy. Within the pAID subgroups, patients with dermatologic or endocrine pAID reflected a significantly higher incidence rate of all-grade irAEs in combination therapy than in monotherapy. For patients with preexisting gastrointestinal autoimmune disease, we saw varying incidences of pAID flares for the combination ICI cohort (0.58 events per person year for

Crohn's disease and 0.22 for Ulcerative colitis), but no patients in the ICI monotherapy group experienced a preexisting autoimmune gastrointestinal disease flare in our cohort. Based on this, patients with preexisting autoimmune dermatologic, gastrointestinal, or endocrine diseases may be more cautious about considering combinations over ICI monotherapy. This increased concern for disease flares after ICIs for patients with preexisting inflammatory bowel disease has been mentioned in prior literature as well.[25] Regarding cancer diagnoses to consider for prospective clinical trials, although not statistically significant, the trend of PFS improvement we found in our analysis could indicate that combination therapy may potentially be of greater benefit in some tumor types compared to ICI monotherapy for patients with pAID. Specifically, our results showed a trend for better PFS with ICI combination therapy for patients with melanoma, but not for patients with lung cancer, so we cannot draw conclusions across cancer diagnoses. This discrepancy between tumor types and the efficacy of combination versus single-agent ICI treatment is in line with what clinical trials have shown for patients without pAIDs.[24,34–36] Future clinical trials assessing the safety and efficacy of ICI combination therapy for patients with pAID should not only consider ICI type and dosing but also the use of empiric or prophylactic immunomodulating therapy with ICI initiation.

Further prospective, high-powered study is needed for patients who suffer from pAID and require ICI treatment for their cancer: to assess if baseline serologies can predict ICI toxicities, if there are empiric medications that can prevent future pAID flares, and how long-term immunosuppression used for pAID treatment may impact tumor outcome. In our cohort, we did not have information regarding serologies at baseline or through the course of ICI therapy. There are a few studies that have looked at the relationship between autoantibodies and that of ICI toxicities, but the results are not conclusive for any particular serologies being able to reliably predict pAID flares or irAEs.[37–41] We also did not have enough detail to evaluate if patients with stable autoimmune diseases were preventively treated with immunosuppressive therapies when starting ICI. Clinical research evaluating the use of DMARDs for *preventing* pAID flares and/or irAEs will be critical and likely only possible via multi-institutional collaboration. Secondary outcomes of this study should evaluate the impact of pre-ICI DMARDs on that of tumor outcome. Certain DMARDs may adjunct the benefit of ICI therapy and while others may abrogate ICI's antitumor immunity. There has been early adoption of infliximab for irAE treatment and multiple studies demonstrate the potential benefits of interleukin 6 receptor antagonists.[42–46] At least one phase 1b study in this area is currently in progress: NCT03816345.

Some limitations of this study should be considered. Our sample size was small, and there may be practice differences between the different institutions that may drive some of the discrepancies observed in the treatment of adverse events between the groups. In addition, the small number of different cancer types precluded further subgroup analysis and given the low number of patients with neurologic or hematologic pAIDs, we caution against broader clinical implication of ICI safety with these pAIDs. This study relied on retrospective chart review. Therefore, some toxicities may not have been documented as thoroughly as those in prospective clinical trials. The retrospective nature of this study is also subject to some selection bias. In particular, patients with active pAID or with high risk of disease flare might not have been selected for combined ICI from the provider. Finally, most patients had inactive autoimmune diseases at ICI initiation, which could potentially underestimate the toxicity rates in our cohort. Finally, many of these patients received ICIs off-label and at late stages of their disease, which may have limited the duration for which they received therapy and may have falsely underestimated PFS and OS. Despite these limitations, our analyses provided important information regarding ICI combination toxicities and their management, which can inform oncologists who care for these complex patients.

Conclusion

Treatment with ICI combination therapy for patients with primary autoimmune disease is currently based on limited data and extrapolation from studies of patients without autoimmune disease who may differ in important respects. This may ultimately lead to withholding ICI treatment or potential under-treatment, either of which could have an impact on patient survival. Our results support the use of ICI combination therapy if deemed necessary for the treatment of cancer in patients with pAIDs, since the reported irAEs and autoimmune disease flares were effectively managed and, in more than half of the cases, did not require ICI treatment interruption or discontinuation. Clinical trials with biomarker analyses focusing on specific cancers and pAID types remain crucial to help understand the pathogenic mechanisms of toxicity, the efficacy of various treatment options, and their impact on underlying autoimmunity in this special cancer population.

Disclosure statement

MK received research support from Merck, Agenus and AgenTus. JW consults for and has received less than $10,000 dollars per annum from Merck, Genentech, Astra Zeneca, GSK, Novartis, Nektar, Medivation, Celldex, Incyte and EMD Serono and $10–25,000 dollars from BMS for membership in Advisory Boards, holds equity in CytoMx, Biond, and Altor, is on a scientific advisory board for Celldex, CytoMx, Incyte, Biond, Protean, CV6, and Sellas, and was named on a patent from the Moffitt Cancer Center on an ipilimumab biomarker and a PD-1 patent from Biodesix.

Dr. Pankti Reid has a patent pending with the University of Chicago for the use of interleukin 6 inhibitors for viral inflammation. Dr. Suarez-Almazor received consultant fees from Bristol Myers Squibb, Pfizer, and Eli Lilly outside the submitted work. Dr. Diab received research funds from Bristol Myers Squibb, Pfizer, Apexigen, Nektar Therapeutics, and Idera Therapeutics. Dr. Abdel-Wahab received consultant fees from ChemoCentryx outside the submitted work. Dr. Abdel-Wahab is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health Award Number K01AI163412 and by the University of Texas MD Anderson Cancer Center Division of Internal Medicine Research and Quality Improvement Development Award, Division of Internal Medicine Bridge Funding Award, Survivorship Seed Money Award, and an Institutional Research Grant. Statistical analysis was supported in part by a Cancer Center Support Grant (NCI Grant P30

CA016672). Dr. Lopez-Olivo was supported by the National Cancer Institute of the National Institutes of Health Award Number K08CA237819.

Funding

The work was supported by the National Institutes of Health.

ORCID

Pankti Reid http://orcid.org/0000-0002-7645-0919

Authors' contributions

Study concept and design: Dr. Reid, Dr. Sandigursky, Dr. Abdel-Wahab
Acquisition of data: Dr. Cytryn, Dr. Efuni, Dr. Safa, Dr. Buni, Dr. Abu-Shawer
Analysis and interpretation of data: Dr. Reid, Dr. Song, Dr. Abdel-Wahab
Quality appraisal: Dr. Reid, Dr. Song, Dr. Abdel-Wahab
Drafting of the manuscript: Dr. Reid, Dr. Sandigursky, Dr. Song, Dr. Abdel-Wahab
Critical revision of the manuscript for important intellectual content: Dr. Lopez-Olivo, Dr. Safa, Dr. Cytryn, Dr. Efuni, Dr. Buni, Dr. Pavlick, Dr. Krogsgaard, Dr. Abu-Shawer, Dr. Altan, Dr. Weber, Dr. Rahma, Dr. Suarez-Almazor, Dr. Diab
Statistical analysis: Dr. Song
Administrative, technical, or material support: Dr. Reid, Dr. Diab, and Dr. Abdel-Wahab
Study supervision: Dr. Reid, Dr. Diab, Dr. Abdel-Wahab

Consent for publication

Informed consent to participate was waived for this study.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

References

1. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, No D, Gobourne A, Littmann E, Huttenhower C, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016;7(1):10391. doi:10.1038/ncomms10391.
2. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. Anticancer Res. 2012;32:1119–1136.
3. Leonardi GC, Gainor JF, Altan M, Kravets S, Dahlberg SE, Gedmintas L, Azimi R, Rizvi H, Riess JW, Hellmann MD, et al. Safety of programmed death–1 pathway inhibitors among patients with non–small-Cell lung cancer and preexisting autoimmune disorders. J Clin Oncol. 2018;36(19):1905–1912. doi:10.1200/Jco.2017.77.0305.
4. Abdel-Wahab N, Safa H, Abudayyeh A, Johnson DH, Trinh VA, Zobniw CM, Lin H, Wong MK, Abdelrahim M, Gaber AO, et al. Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature. J Immunother Cancer. 2019;7(1):106. doi:10.1186/s40425-019-0585-1. [published Online First: 2019/04/18].
5. Peng M, Li X, Lei G, Weng YM, Hu MX, Song QB. The efficacy and safety of immune checkpoint inhibitor combination therapy in lung cancer: a systematic review and meta-analysis. Onco Targets Ther. 2018;11:7369–7383. doi:10.2147/OTT.S177318. [published Online First: 2018/11/15].
6. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, Carvajal RD, Dickson MA, D'Angelo SP, Woo KM, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan Kettering cancer center. J Clin Oncol. 2015;33(28):3193–3198. doi:10.1200/JCO.2015.60.8448. [published Online First: 2015/08/19].
7. Coens C, Suciu S, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol. 2017;18(3):393–403. doi:10.1016/S1470-2045(17)30015-3.
8. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA. Rheumatic and Musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res (Hoboken). 2017;69(11):1751–1763. doi:10.1002/acr.23177. [published Online First: 2016/12/21].
9. Sandigursky S, Mor A. Immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. Curr Rheumatol Rep. 2018;20(10):65. doi:10.1007/s11926-018-0770-0. published Online First: 2018/09/08.
10. El Osta B, Hu F, Sadek R, Chintalapally R, Tang S-C. Not all immune-checkpoint inhibitors are created equal: meta-analysis and systematic review of immune-related adverse events in cancer trials. Crit Rev Oncol Hematol. 2017;119:1–12. doi:10.1016/j.critrevonc.2017.09.002. [published Online First: 2017/10/27].
11. Xing P, Zhang F, Wang G, Xu Y, Li C, Wang S, Guo Y, Cai S, Wang Y, Li J, et al. Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+IPI: a systematic review and meta-analysis. J Immunother Cancer. 2019;7(1):341. doi:10.1186/s40425-019-0779-6.
12. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, et al. Nivolumab versus docetaxel in advanced squamous-Cell non–small-Cell lung cancer. N Engl J Med. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627.
13. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–723. doi:10.1056/NEJMoa1003466.
14. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev. 2017;16(10):1049–1057. doi:10.1016/j.autrev.2017.07.022. [published Online First: 2017/08/06].
15. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. Ann Oncol. 2012;23(4):927–933. doi:10.1093/annonc/mdr333.
16. Abdel-Wahab N, Abudayyeh A, Lei X. Checkpoint inhibitor therapy in solid organ and allogeneic stem Cell transplantation: data mining of the Truven Health marketscan research database. J Immunother Cancer (Suppl). 2018;6(1):115.
17. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, McQuade JL, Shoushtari AN, Tsai KK, Eroglu Z, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017;28(2):368–376. doi:10.1093/annonc/mdw443.
18. Hong D, Infante J, Janku F, Jones S, Nguyen LM, Burris HA, Naing A, Bauer TM, Piha-Paul S, Johnson FM, et al. Phase I study of LY2606368, a checkpoint kinase 1 inhibitor, in patients with advanced cancer. J Clin Oncol. 2016;34(15):1764–1771. doi:10.1200/JCO.2015.64.5788.

19. Wu C, Zhong L, Wu Q, Lin S, Xie X. The safety and efficacy of immune-checkpoint inhibitors in patients with cancer and pre-existing autoimmune diseases. Immunotherapy. 2021;13(6):527–539. doi:10.2217/imt-2020-0230.
20. Tang H, Zhou J, Bai C. The efficacy and safety of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease. Front Oncol. 2021;11(53):625872. doi:10.3389/fonc.2021.625872.
21. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob J-J, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, et al. Overall survival with combined Nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377(14):1345–1356. doi:10.1056/NEJMoa1709684. [published Online First: 2017/09/12].
22. Institute NIoHNNC. Common Terminology Criteria for Adverse Events (CTCAE). NIH; 2018.
23. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4(12):1721–1728. doi:10.1001/jamaoncol.2018.3923. [published Online First: 2018/09/23].
24. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, et al. Combined Nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34. doi:10.1056/NEJMoa1504030. [published Online First: 2015/06/02].
25. Brown LJ, Weppler A, Bhave P, Allayous C, Patrinely Jr JR, Ott P, Sandhu S, Haydon A, Lebbe C, Johnson DB, et al. Combination anti-PD1 and ipilimumab therapy in patients with advanced melanoma and pre-existing autoimmune disorders. J Immunother Cancer. 2021;9(5):e002121. doi:10.1136/jitc-2020-002121. published Online First: 2021/05/09.
26. van der Kooij MK, Suijkerbuijk KPM, Aarts MJB, van der Kooij MK, van den Berkmortel FWPJ, Blank CU, Boers-Sonderen MJ, van Breeschoten J, van den Eertwegh AJM, de Groot JWB, et al. Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease: a cohort study. Ann Intern Med. 2021;174(5):641–648. doi:10.7326/M20-3419. [published Online First: 2021/02/16].
27. Bruera S, Suarez-Almazor ME. The effects of glucocorticoids and immunosuppressants on cancer outcomes in checkpoint inhibitor therapy. Front Oncol. 2022;12:928390. doi:10.3389/fonc.2022.928390. [published Online First: 2022/09/10].
28. Postow MA, Sidlow R, Hellmann MD, Longo DL. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–168. doi:10.1056/NEJMra1703481. [published Online First: 2018/01/11].
29. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, Kaneda H, Hasegawa Y, Tanaka K, Takeda M, et al. Association of immune-related adverse events with Nivolumab efficacy in non–small-Cell lung cancer. JAMA Oncol. 2018;4(3):374–378. doi:10.1001/jamaoncol.2017.2925. [published Online First: 2017/10/05].
30. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, Martinez Bernal G, Chaft JE, Ferrara R, Lai WCV, et al. Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC. J Clin Oncol. 2018;36(15):9003–9003. doi:10.1200/JCO.2018.36.15_suppl.9003.
31. Maslov DV, Tawagi K, Kc M, Simenson V, Yuan H, Parent C, Bamnolker A, Goel R, Blake Z, Matrana MR, et al. Timing of steroid initiation and response rates to immune checkpoint inhibitors in metastatic cancer. J Immunother Cancer. 2021;9(7):e002261. doi:10.1136/jitc-2020-002261.
32. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, Cohen J, Sullivan RJ. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer. 2018;124(18):3706–3714. doi:10.1002/cncr.31629. [published Online First: 2018/07/06].
33. Petrelli F, Signorelli D, Ghidini M, Ghidini A, Pizzutilo EG, Ruggieri L, Cabiddu M, Borgonovo K, Dognini G, Brighenti M, et al. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Cancers. 2020;12(3):546. doi:10.3390/cancers12030546.
34. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim S-W, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, et al. Nivolumab plus ipilimumab in advanced non–small-Cell lung cancer. N Engl J Med. 2019;381(21):2020–2031. doi:10.1056/NEJMoa1910231. [published Online First: 2019/09/29].
35. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, et al. Nivolumab versus everolimus in advanced renal-Cell carcinoma. N Engl J Med. 2015;373(19):1803–1813. doi:10.1056/NEJMoa1510665. [published Online First: 2015/09/26].
36. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-Cell carcinoma. N Engl J Med. 2018;378(14):1277–1290. doi:10.1056/NEJMoa1712126. [published Online First: 2018/03/22].
37. Mathias K, Rouhani S, Olson D, Bass AR, Gajewski TF, Reid P. Association between rheumatic autoantibodies and immune-related adverse events. Oncologist. 2023;28(5):440–448. doi:10.1093/oncolo/oyac252. [published Online First: 2023/01/04].
38. Ghosh N, Chan KK, Jivanelli B, Bass AR. Autoantibodies in patients with immune-related adverse events from checkpoint inhibitors: a systematic literature review. J Clin Rheumatol. 2021;28(2):e498–e505. doi:10.1097/rhu.0000000000001777. [published Online First: 2021/08/10].
39. de Moel EC, Rozeman EA, Kapiteijn EH, Verdegaal EME, Grummels A, Bakker JA, Huizinga TWJ, Haanen JB, Toes REM, van der Woude D. Autoantibody development under treatment with immune-checkpoint inhibitors. Cancer Immunol Res. 2019;7(1):6–11. doi:10.1158/2326-6066.CIR-18-0245. [published Online First: 2018/11/15].
40. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, Kawana S, Saito R, Aso M, Tsurumi K, et al. Profiling preexisting antibodies in patients treated with anti–PD-1 therapy for advanced non–small Cell lung cancer. JAMA Oncol. 2019;5(3):376–383. doi:10.1001/jamaoncol.2018.5860. [published Online First: 2018/12/28].
41. Tahir SA, Gao J, Miura Y, Blando J, Tidwell RSS, Zhao H, Subudhi SK, Tawbi H, Keung E, Wargo J, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. Proc Natl Acad Sci U S A. 2019;116(44):22246–22251. doi:10.1073/pnas.1908079116. [published Online First: 2019/10/16].
42. Dimitriou F, Hogan S, Menzies AM, Dummer R, Long GV. Interleukin-6 blockade for prophylaxis and management of immune-related adverse events in cancer immunotherapy. Eur J Cancer. 2021;157:214–224. doi:10.1016/j.ejca.2021.08.031.
43. Hailemichael Y, Johnson DH, Abdel-Wahab N, Foo WC, Bentebibel S-E, Daher M, Haymaker C, Wani K, Saberian C, Ogata D, et al. Interleukin-6 blockade abrogates immunotherapy toxicity and promotes tumor immunity. Cancer Cell. 2022;40(5):509–523.e6. doi:10.1016/j.ccell.2022.04.004. [published Online First: 2022/05/11].
44. Fa'ak F, Buni M, Falohun A, Lu H, Song J, Johnson DH, Zobniw CM, Trinh VA, Awiwi MO, Tahon NH, et al. Selective immune suppression using interleukin-6 receptor inhibitors for management of immune-related adverse events. J Immunother Cancer. 2023;11(6):e006814. doi:10.1136/jitc-2023-006814.
45. Mehmi I, Hamid O, Hodi FS, Vassalo M, Malatyali S, Krishnarajapet S, O'Donnell N, Castrence A, Lim E, Gormley J, et al. Ipilimumab, nivolumab and tocilizumab as first-line therapy for advanced melanoma. J Clin Oncol. 2021;39(15_suppl):PSTPS9589–TPS9589. doi:10.1200/JCO.2021.39.15_suppl.TPS9589.
46. Stroud CR, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, Cherukuri S, Parent T, Hardin J, Walker P, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Oncol Pharm Pract. 2019;25(3):551–557. doi:10.1177/1078155217745144. [published Online First: 2017/12/07].