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ORIGINAL ARTICLE

Immune checkpoint inhibitor-induced colitis as a predictor of survival in metastatic melanoma

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Abstract

Background Gastrointestinal (GI) immune-related adverse events (irAEs) commonly limit immune checkpoint inhibitors' (ICIs) treatment, which is very effective for metastatic melanoma. The independent impact of GI-irAEs on patients' survival is not well studied. We aimed to assess the impact of GI-irAEs on survival rates of patients with metastatic melanoma using multivariate model.

Methods This is a retrospective study of patients with metastatic melanoma who developed GI-irAEs from 1/2010 through 4/2018. A number of randomized patients who did not have GI-irAEs were included as controls. Kaplan–Meier curves and log-rank test were used to estimate unadjusted survival durations. The Cox proportional hazards model was used to evaluate survival predictors; irAEs were included as time-dependent variables.

Results A total of 346 patients were included, 173 patients had GI-irAEs; 124 (72%) received immunosuppression. In multivariate Cox regression, ECOG 2–3 (HR 2.57, 95%CI 1.44–4.57; $P<0.01$), LDH ≥ 618 IU/L (HR 2.20, 95% CI 1.47–3.29; $P<0.01$), stage M1c (HR 2.21, 95% CI 1.35–3.60; $P<0.01$) were associated with worse OS rates. Any grade GI-irAEs (HR 0.53, 95% CI 0.36–0.78; $P<0.01$) was associated with improved OS rates. Immunosuppressive treatment did not affect OS ($P=0.15$). High-grade diarrhea was associated with improved OS ($P=0.04$). Patients who developed GI-irAEs had longer PFS durations on Cox model (HR 0.56, 95% CI 0.41–0.76; $P<0.01$).

Conclusion GI-irAEs are associated with improved OS and PFS in patients with metastatic melanoma. Furthermore, higher grades of diarrhea are associated with even better patients' OS rates.

Keywords Metastatic melanoma · Colitis · Diarrhea · Immune checkpoint inhibitors · Survival

Abbreviations

CI	Confidence interval
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG PET	Fluorodeoxyglucose positron emission tomography
GI	Gastrointestinal
HQROL	Health-related quality of life
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
iCPD	Confirmed progressive disease
iCR	Immune complete response
IDC	Immune-mediated diarrhea and colitis
imRECIST	Immune-modified response evaluation criteria in solid tumors
iPR	Immune partial response
IQR	Interquartile range
irAE	Immune-related adverse event
iRECIST	Immune-related response evaluation criteria in solid tumors
iSD	Immune stable disease
iUPD	Immune unconfirmed progressive disease
LDH	Lactate dehydrogenase

Adi Diab and Yinghong Wang contributed equally.

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OS	Overall survival
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
SD	Standard deviation

Introduction

Cancer therapy is witnessing a paradigm shift with the advent of immune checkpoint inhibitors (ICIs). By blocking immune checkpoints involved in the downregulation of cytotoxic T-cells, ICIs assist in prolonging cytotoxic T-cells' survival, which subsequently translates into augmented tumor surveillance and antitumor action. Currently available ICIs block programmed death protein-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). These agents have led to improved overall survival (OS) rates in various malignancies, and were first approved by the Food and Drug Administration (FDA) for metastatic melanoma [2–4]. The antitumor efficacy of ICIs is forecasted to encompass more malignancies, and the indications for ICI cancer therapy are expected to grow substantially [5, 6].

Although ICIs represent a promising cancer therapy, they have some drawbacks, the most prominent of which is immune-related adverse events (irAEs). Immune checkpoint blockade does not always result in induction of tumor-antigen specific T-cells and, therefore, ICIs can impact virtually any organ system in the body, resulting in irAEs. Among clinically observed irAEs, those that affect the gastrointestinal tract (GI-irAEs) are the most commonly observed serious irAEs that lead to ICI treatment discontinuation [7–10]. A recent meta-analysis showed that the overall incidence of colitis was 9.1% with CTLA-4 monotherapy, 1.3% with PD-1/PD-L1 therapy, and 13.6% with combination therapy [11].

Given the immune-mediated activity of ICIs, there has been speculation regarding the prognostic value of irAEs. Some experts consider irAEs to be a projection of the overall immune response to ICI therapy, and hence irAEs could be used to gauge the overall tumor response or drug efficacy. However, studies have shown conflicting results relating to this hypothesis, with some affirming and some negating the prognostic value of irAEs [12–14]. In a study of 198 patients undergoing treatment with ipilimumab, 39 developed enterocolitis and had a significantly higher tumor response rate than those who did not develop a GI-irAE [15]. However, given the lack of stratification by known prognostic serum markers, these findings should be interpreted carefully.

We have previously reported on a cohort of 117 patients who had developed diarrhea as a GI-irAE, in which the diarrhea was revealed to be an independent prognostic marker and was associated with improved OS [16]. However, because patients in this cohort had multiple malignancies, our finding of improved OS in patients who developed diarrhea needed further validation. Herein, we aimed to delineate the prognostic significance of GI-irAEs specifically in a large cohort of patients with metastatic melanoma by performing multivariate Cox hazards proportion analysis.

Methods and materials

Study design and population

This retrospective, single-center study was approved by the Institutional Review Board at MD Anderson Cancer Center. We investigated adult patients with metastatic melanoma who received ICIs and developed GI-irAEs, under a clinical trial protocol or otherwise, at our institution between January 2010 and April 2018. To control for ICI type as a confounding factor, we have conducted a frequency matching regarding ICI treatment options to identify patients without colitis and included equivalent number of them as a control group. Natural language processing was used to identify eligible patients, and then we conducted a comprehensive medical chart review to confirm the diagnosis of immune mediated diarrhea or colitis (IDC) based on the decision of the treating oncologist or gastroenterologist.

Collected data consisted of patient demographics, medical and oncologic history, ICI regimen(s), irAEs related data, and survival data. Recorded comorbidities included coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, hypertension, diabetes mellitus, and dyslipidemia. Performance status scores at the time of ICI initiation was recorded according to the Eastern Cooperative Oncology Group (ECOG) scoring system [17].

Oncologic variables included the following: (1) melanoma stage according to the American Joint Committee on Cancer 7th edition, (2) lactate dehydrogenase (LDH) value, (3) BRAF mutation status, and (4) lymph node status. ICI agents were categorized as monotherapy (CTLA-4 or PD-1/L1) or combination therapy (CTLA-4 and PD-1/L1). Recorded diarrhea or colitis grade at the peak severity was based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03, and was extrapolated as graded in medical charts or from physician's description. Diagnostic modality for colitis was recorded: computed tomography (CT) imaging or endoscopy with histologic evaluation. The treatment for IDC included steroids, infliximab, vedolizumab, and/or antimotility agents.

We collected data pertaining to non-GI adverse events, which involved the liver, pancreas, skin, lung, endocrine system, or others organ systems (hematological,

musculoskeletal, neurological, cardiac, and ophthalmologic). Endocrine toxicities were those that affected the thyroid, pituitary, and adrenal gland.

Radiology assessment of tumor progression

Tumor response was assessed prospectively and was documented in radiological reports. ICI treatment response on CT and/or fluorodeoxyglucose positron emission tomography (FDG PET)/CT images was evaluated on the basis of published criteria [18–22] with consensus among physicians, which combined immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST) [22] and immune-related RECIST 1.1 (iRECIST) [21]. When physician opinion conflicted, the criteria yielding the best response were used. In brief, for each patient, up to two per organ and five total target lesions were measured unidimensionally. Responses of "immune" complete response (iCR), partial response (iPR), stable disease (iSD), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) were assigned using iRECIST. New lesions were added to the total tumor burden along with the sum of the target lesions. All iPD had to be confirmed on the next follow-up scan. Progression in nontarget lesions was not considered iPD. For the analysis of ICI-defined progression free survival (PFS), iPD was considered an event; however, iPD was not considered a PFS event if the response on the next scan ($\geq$4 weeks later) was iSD, iPR, or iCR. An iPD followed by no additional assessments was considered a PFS event.

PFS analysis

For patients who had measurable disease, we measured PFS as the time from ICI initiation to the time of disease progression, time of death, or last staging follow-up (for censored patients). Patients who developed IDC after the progression of disease were excluded from this analysis.

Statistical methods

The distributions of continuous variables were summarized by means, medians, interquartile ranges (IQR), and standard deviations (SD). The distributions of categorical variables were summarized in terms of frequencies and percentages. Kaplan–Meier curves were used to estimate unadjusted OS and PFS time distributions [23]. OS was defined as the time between ICI starting date and death or last follow-up clinical encounter. PFS was defined as the time from ICI initiation until progression, death, or last staging follow-up. To study the effect of immunosuppressive therapy on survival rates, for only patients who had IDC, survival duration was redefined from the date of IDC onset. Log-rank tests were used to compare time-to-event variables between groups. The Cox proportional hazards model was used to evaluate the ability of covariates to predict survival. The Cox model for time-dependent variables was used to assess the effects of IDC or non-GI-irAE on survival, since the onset of IDC or non-GI-irAE changes over the course of survival time [24, 25]. Variables showing a potential effect on survival ($P<0.1$) in the univariate analysis were included in the final multivariable model. Backward model selection was implemented until all remaining predictors had a P value less than 0.05 in multivariable Cox model for overall survival analysis. All tests were two-sided with a significance level of 0.05. All computations were carried out in SAS version 9.4.

Results

Patient characteristics

Out of 1,983 patients with melanoma who received ICI treatment, 173 (8.7%) patients developed IDC (Fig. 1). As a result of the matching, 173 patients without colitis were also included in the final analysis as a control group. Patient characteristics are summarized in Table 1. Most patients were male (222; 64.2%) and white (320; 92.5%), with a mean age of 58.4 years (standard deviation [SD] 15.7 years). An ECOG performance status of 0 or 1 at the time of ICI initiation was reported in 319 patients (92.2%) and 23 patients (6.6%) had an ECOG of 2 or higher. Stage IV M1c melanoma was found in 152 patients (43.9%). A BRAF mutation was identified in 150 patients (43.3%). Anti-CTLA-4 monotherapy was given to 159 (46.0%) patients, whereas combination ICI therapy was administered in 88 (25.4%). The mean duration of ICI treatment was 3.5 months (SD 5.1 months). The median LDH level at the time of ICI

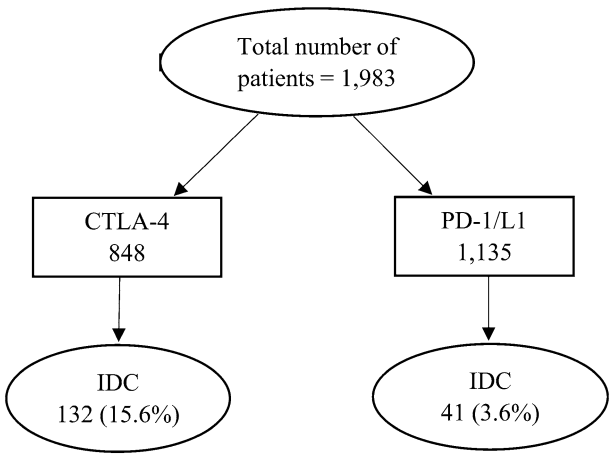

Fig. 1 Incidence of IDC stratified by type of ICI therapy

Table 1 Patient characteristics ($n=346$)

Characteristic	IDC $n=173$	No-IDC $n=173$	P value
Mean age (standard deviation)	57.3 (15.9)	59.3 (13.7)	0.394
Male sex	117 (67.6)	105 (60.7)	0.217
White race	166 (96.0)	154 (89.0)	0.023
Comorbidities present	92 (53.2)	83 (48.0)	0.390
History of smoking	70 (40.5)	61 (35.3)	0.375
Eastern Cooperative Oncology Group performance status[a]			0.667
0–1	159 (94.1)	160 (92.5)	
2–3	10 (5.9)	13 (7.5)	
Mean lactate dehydrogenase value (standard deviation)	536 (284)	582 (459)	0.011
Lactate dehydrogenase[b]			0.466
<618 IU/L	148 (85.5)	142 (82.1)	
≥618 IU/L	25 (14.5)	31 (17.9)	
Cancer stage			0.748
III	42 (24.6)	39 (22.5)	
IV			
M1a or M1b	52 (30.4)	59 (34.1)	
M1c	77 (45.0)	75 (43.4)	
Positive BRAF mutation	69 (41.3)	81 (46.8)	0.327
Checkpoint inhibitor type			0.124
CTLA-4	86 (49.7)	73 (42.2)	
PD-1/L1	41 (23.7)	58 (33.5)	
Combination	46 (26.6)	42 (24.3)	

[a]Performance status was available for 342 patients

[b]Lactate dehydrogenase levels were available for 238 patients

initiation was 487 IU/L (SD 702 IU/L). LDH levels were lower than 618 IU/L in most patients.

Adverse events

Overall, 173 patients had IDC (Table 2). The median time to IDC onset from ICI initiation was 1.7 months (IQR 0.1–56.2 months). Regarding IDC severity, 79 of the 173 patients with diarrhea (45.7%) had grade 3–4 diarrhea and 44 of the 140 patients with colitis (31.4%) had grade 3–4 colitis. ICI therapy was discontinued in 115 of the 173 patients who developed IDC (66.5%) owing to toxic effects. Colitis was evident on CT imaging of 48 patients (27.7%), whereas endoscopic features of colitis with histologic confirmation were demonstrated in 76 patients (43.9%). Immunosuppressive therapy for IDC was administered in 124 patients (71.7%). Infliximab was added to corticosteroid treatment in 45 patients (26.6%). In contrast, 49 patients (28.3%) received supportive treatment for IDC without immunosuppressive therapy. The mean duration of corticosteroid treatment was 63.3 days (SD 75.3 days).

OS analyses

The mean follow-up duration of our study was 1.7 years (SD 1.4 years). Univariate Cox regression analysis of patient-related factors are shown in Table 3. High ECOG and high LDH at the time of ICI initiation were associated with decreased OS ($P<0.01$). Advanced stage IV M1c malignancy was associated with poor OS ($P<0.01$). Among treatment-related factors, combination anti-PD-1/L1 and anti-CTLA-4 therapy was not associated with improved OS ($P=0.34$). IDC was associated with improved OS irrespective of symptom severity ($P<0.01$). Significant prolongation of OS was evident when we compared grade 1 with grade 2–4 diarrhea ($P=0.04$). Immunosuppressive therapy did not affect the OS (hazard ratio [HR] 1.5; 95% confidence interval [CI] 0.82–2.74; $P=0.19$, result not shown).

Multivariate Cox regression analysis revealed a statistically significant association between poor OS and the following three factors: high LDH, ECOG score 2–3, and stage IV M1c disease ($P<0.01$) at the time of ICI initiation (Table 4). Conversely, a statistically significant association was found between improved OS and incidence of IDC, irrespective of the grade ($P<0.01$). Furthermore, Kaplan–Meier survival analysis revealed a statistically significant improvement in patients who developed IDC compared with patients who did not ($P<0.001$; Fig. 2a). There was no statistically significant influence from IDC immunosuppressive therapy on OS ($P=0.145$). Grade 2 and higher IDC was associated with improved OS ($P=0.036$; Fig. 2b).

PFS analyses

Kaplan–Meier curve and log-rank test revealed that PFS was better in patients with IDC than in those without ($P=0.0001$; Fig. 2c). Multivariate Cox regression analysis showed that patients who developed IDC had prolonged PFS duration when compared with those who did not (HR 0.56; 95% CI 0.41–0.76; $P<0.01$; Table 5). Among patients who developed IDC, immunosuppressive therapy was associated with longer PFS duration (HR 0.39; 95% CI 0.25–0.63; $P<0.01$, result not shown).

Survival analysis in patients who received anti-CTLA-4 based therapy ($n=247$)

In multivariate Cox regression analysis for OS, poor performance status ($P<0.01$), high LDH ($P=0.02$), and melanoma stage M1c ($P<0.01$) were associated with shorter survival durations (Supplemental Table 1a). By contrary, IDC of any grade ($P<0.01$) and combination regimen of CTLA-4 and

Table 2 Characteristics of patients with IDC ($n=173$)[a]

Adverse event	No. of patients (%)
Mean time to IDC onset (standard deviation)	3.2 months (5.4 months)
Mean duration of diarrhea (standard deviation)	70 days (102 days)
Evidence of colitis among those with diarrhea ($n=173$)	
Computed tomography imaging evaluation	48 (27.7)
Endoscopic/histologic evaluation	76 (43.9)
Diarrhea grade ($n=173$)	
1	45 (26.0)
2	49 (28.3)
3–4	79 (45.7)
Colitis grade ($n=140$)	
1	32 (22.9)
2	64 (45.7)
3–4	44 (31.4)
Treatment for IDC ($n=173$)	
Immunosuppressive	124 (71.7)
Non-immunosuppressive	49 (28.3)
Mean duration of steroid treatment (standard deviation)	63.3 days (75.3 days)
Mean follow-up duration (standard deviation)	1.7 years (1.4 years)

[a]All of these patients had diarrhea and 140 also had colitis

Table 3 Univariate Cox regression analysis for overall survival

Covariate	Hazard ratio	95% confidence interval	*P*
Age	1.01	0.99–1.02	0.09
Comorbidities	1.35	0.96–1.89	0.09
Eastern Cooperative Oncology Group performance status 2–3	2.67	1.56–4.59	< 0.01
Lactate dehydrogenase ≥ 618 IU/L	2.75	1.87–4.06	< 0.01
Cancer stage			
M1a, M1b	1.07	0.62–1.84	0.80
M1c	2.30	1.43–3.72	< 0.01
Positive BRAF mutation	0.79	0.57–1.12	0.19
CTLA-4 monotherapy	1.25	0.83–1.86	0.29
Combination ICI therapy	0.77	0.46–1.31	0.34
Any grade IDC	0.53	0.37–0.76	< 0.01

Table 4 Multivariable Cox regression analysis for overall survival

Covariate	Hazard ratio	95% confidence interval	*P*
Age	1.01	1.00-1.03	0.02
Comorbidities	1.39	0.97-2.00	0.08
Eastern Cooperative Oncology Group performance status 2–3	2.57	1.44–4.57	< 0.01
Lactate dehydrogenase ≥ 618 IU/L	2.20	1.47–3.29	< 0.01
M1c cancer stage	2.21	1.35–3.60	< 0.01
Any grade IDC	0.53	0.36–0.78	< 0.01

PD-1/L1 ($P=0.03$) indicated a better OS rate. Similarly, PFS analysis revealed that any grade IDC ($P<0.01$) and combination regimen of CTLA-4 and PD-1/L1 ($P<0.01$) were indicators of improved survival rates (Supplemental Table 1b). M1c stage was associated with worse survival duration ($P<0.01$).

Survival analysis in patients who received anti-PD-1/L1 monotherapy ($n=99$)

LDH > 618 IU/L was associated with worse OS rates in the multivariate Cox regression model ($P<0.01$; Supplemental Table 2a). Patients who developed IDC of any grade had better OS rates ($P<0.01$). For PFS, high LDH was an indicator of worse outcome ($P<0.01$; Supplemental Table 2b). Any grade IDC was associated with improved PFS ($P=0.03$).

Non-GI adverse events

One hundred thirty-four patients experienced one or more non-GI adverse events (38.7%; Supplemental Table 3). Hepatotoxicity was the most common non-GI adverse event in our cohort ($n=65$; 18.8%). Cox regression analysis for OS revealed that adverse events affecting the endocrine system were associated with improved survival rates (HR 0.58; 95% CI 0.01–0.37; $P<0.01$; Supplemental Table 4a). On the other hand, pancreatic injury was associated with worse overall survival outcomes (HR 2.17; 95%

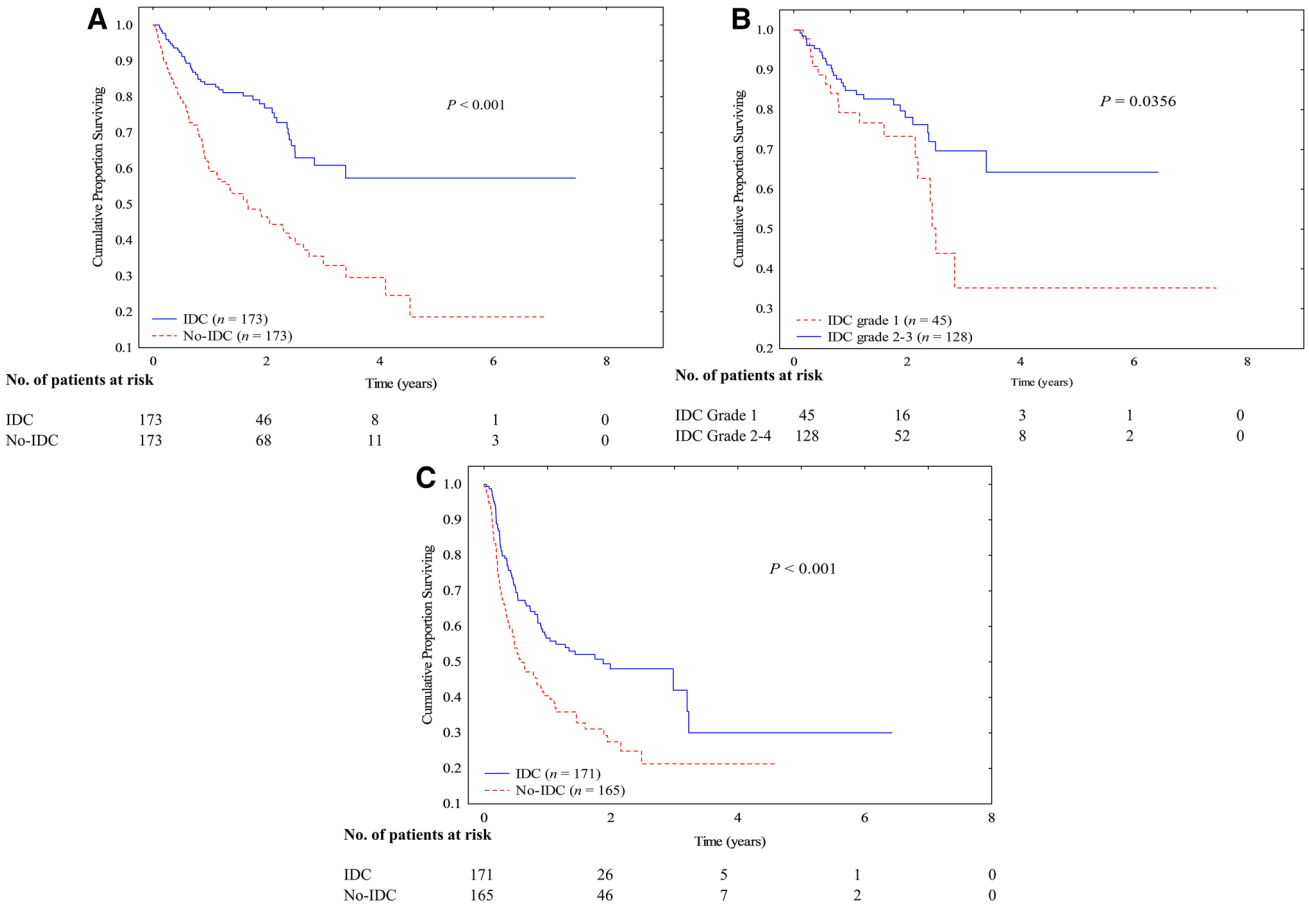

Fig. 2 **a** Kaplan–Meier overall survival curve stratified by IDC status. **b** Kaplan–Meier overall survival curve stratified by diarrhea grade. **c** Kaplan–Meier progression-free survival curve stratified by IDC status

Table 5 Multivariate Cox regression analysis for progression free survival

Covariate	Hazard ratio	95% confidence interval	*P*
Lactate dehydrogenase ≥ 618 IU/L	1.99	1.36–2.91	< 0.01
Eastern Cooperative Oncology Group performance status 2–3	1.39	0.77–2.51	0.27
M1c cancer stage	1.62	1.08–2.45	0.02
Combination regimen	2.33	0.33–16.7	0.39
Any grade IDC	0.56	0.41–0.76	< 0.01

CI 1.32–3.56; $P < 0.01$). No statistically significant associations were observed with other non-GI adverse events. Similar results were obtained by performing Cox model on PFS (Supplemental Table 4b). Endocrine adverse events were associated with improved PFS rates (HR 0.52; 95% CI 0.29–0.94; $P = 0.03$), whereas, pancreatic adverse events were associated with worse PFS rates (HR 1.71; 95% CI 1.05–2.79; $P = 0.03$).

Discussion

The findings of this retrospective study suggest that the onset of IDC in metastatic melanoma patients receiving ICI therapy could be a harbinger of a favorable cancer response, as evidenced by improved OS and PFS rates. We further found an association between high-grade diarrhea and improved survival, which likely is a projection of the magnitude of immune response, which in turn potentially reflects the antitumor efficacy of ICI therapy. The persistence of the prognostic association between IDC and survival in the multivariate Cox proportional hazards model further strengthens our findings, accounting for known prognostic factors in patients with melanoma. For example, stage IV M1c disease, ECOG of 2 or 3, and abnormal LDH at the time of ICI initiation were associated with poor OS [26–28]. These findings pave the way for the development of a novel prognostic model

that accounts for the development of such irAEs in patients who undergo ICI therapy.

We included patients who did not develop IDC as a control group and we observed a median OS of 11 months, a duration that is adequate for the development of IDC (5–10 weeks) [29]. Likewise, the median PFS was 5 months from the time of ICI initiation, which is suitable for such analysis. The development of irAEs is time-dependent. Therefore, we included irAEs in a statistical model after accounting for the lead-time bias that could arise from such analysis. Moreover, our patient population consisted of patients who received any regimen of ICI agents, which makes our findings applicable to a broader sample of patients. To further validate our findings, we performed separate analysis for patients who received anti-CTLA-4 based therapy and those who received PD-1/L1 monotherapy. This analysis confirmed the finding of improved OS and PFS in patients that developed IDC.

There has been speculation regarding irAEs and their association with improved survival, although the body of evidence relating to this speculation is sparse, and studies have shown conflicting results [12, 13]. The current study adds to the emerging body of evidence on the prognostic value of irAEs induced by ICI therapy. Previously, Hua et al. prospectively studied the prognostic utility of the development of vitiligo in 67 patients receiving pembrolizumab, and they found that vitiligo was associated with a better objective response rate [30]. Most studies on the prognostic significance of autoimmune entities that arise due to cancer immunotherapy have been focused on cutaneous and endocrine autoimmune manifestations [30, 31]. In our study, we found that endocrine adverse events predicted improved OS and PFS rates. In contrast, pancreatic injury was an indicator of worse OS and PFS rates. No impact from other non-GI adverse events was evident. This could be due to a potentially underpowered subgroup, although a sample size of 346 is among the largest studied patient populations to date. Additionally, this could be explained by the selection criteria for our cohort based on the presence of IDC. Still, future studies are needed to validate this finding.

Because ICIs carry out their antitumor activity through an immune-mediated pathway, there is a concern that the immunosuppressive therapy that is traditionally employed for the treatment of severe irAEs could affect the antitumor activity of ICI therapy [13, 32, 33]. We observed comparable OS rates between patients who received immunosuppressive therapy and those who did not. In addition, we found that high-grade diarrhea predicted improved OS. Nevertheless, the finding of longer PFS duration in patients received immunosuppressive therapy could be explained by higher grades of diarrhea, which indicate enhanced effect of ICI, in these patients. Additionally, the enhanced effect of ICI indicated by high-grade diarrhea started earlier than the effect of immunosuppressive therapy, therefore, the favorable PFS. However, on the long term, when the impact of immunosuppressive therapy became evident, the positive effect of ICI indicated by diarrhea was neutralized and the OS became the same for patients who received immunosuppressive therapy and those who did not.

The association of autoimmune events with improved prognosis in the setting of cancer is not a new one, with studies dating back three decades [34]. IDC represents a clinical entity that has yet to be completely characterized in terms of its prognostic value. Moreover, gastrointestinal autoimmune phenomena lack specificity in terms of symptoms. Nonetheless, IDC undoubtedly have a clinical presentation that is highly likely to be reported by the patient, hence paving the way for early recognition of this entity. The potentially positive side of the development of a IDC should be conveyed to the patient, given that IDC indicates more potent ICI response and improved survival rates, unlike infectious causes or graft-versus-host disease [35–37]. As the paradigm of clinical medicine shifts toward a more patient-centered model, it is imperative to keep in mind the impact of interventions, adverse events, and prognosis on patients' health-related quality of life (HQROL). HQROL parameters have been found to be independent prognostic factors in cancer [38]. Informing the patient that an impending adverse event is potentially a herald of a favorable prognosis in terms of their malignancy could significantly decrease the stress and anxiety that may arise with IDC, as well as the inherent stress of a cancer diagnosis. Furthermore, such news has the potential for improving patients' HRQOL and may help them cope with the stress that comes with gastrointestinal dysregulation. Future studies should validate the impact of conveying such news on patients' HQROL through standardized techniques.

Although our study conveys an important finding, it has noteworthy limitations. Although our sample size constitutes one of the largest studies published on this topic to date, it is a modestly underpowered study. The retrospective nature of our study limited our ability to accurately record irAE grade and duration of symptoms, details pertinent to steroid therapy (hence the documentation of steroid therapy duration rather than individual cumulative dose). Not all patients had endoscopic or CT evaluation for IDC, and in some cases the diagnosis of IDC was made on the basis of clinical judgement. We focused on diarrhea and colitis because they are among the most common and debilitating irAEs, and hence all non-GI-irAEs were clumped together into one category to power this subgroup for statistically significant findings. This may have undermined the prognostic value of individual non-GI-irAEs. In terms of malignancy, we clustered all patients with metastatic melanoma, irrespective of disease site, to have an adequately powered sample size. This could have confounded our findings because not all melanomas

behave similarly, and they have variable prognosis. Finally, the decision to administer immunosuppressant therapy was not standardized and was primarily based on the clinician's decision.

In conclusion, we found that IDC is associated with improved OS and PFS in metastatic melanoma. Moreover, high-grade diarrhea, indicated by the requirement for immunosuppressive therapy, is associated with improved survival rates. The onset of IDC should be conveyed to patients as an indicator of a favorable cancer response to ICI as well as improved survival outcome. Such communication may improve their HRQOL, although this should be measured using standardized tools in future studies. Efforts should be made to develop a novel prognostic model that accounts for irAEs in the setting of ICI therapy. Further large prospective studies are required to further validate our findings.

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Author contributions HA-S: conceptualization, data curation, writing-original draft, methodology. FSA: writing-original draft, data curation. WQ: formal analysis, software, review and editing, methodology. YL: conceptualization, writing-review and editing, data curation. SP: conceptualization, writing-review and editing. AD: conceptualization, writing-review and editing, project administration, methodology. YW: conceptualization, writing-review and editing, project administration, methodology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval This retrospective, single-center study was approved by the Institutional Review Board at MD Anderson Cancer Center. Approval number: PA18-0472.

Informed consent This study was granted waiver of consent.

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