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Melanoma and Cutaneous Malignancies

Anti-PD1-Induced Immune-Related Adverse Events and Survival Outcomes in Advanced Melanoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Anti-PD-1 • Checkpoint blockade • Immune-related adverse events • Immunotherapy • Melanoma

Abstract

Introduction. Objective response rates (ORR) appear to be higher in melanoma patients who develop immune-related adverse events (irAEs), but whether there is a similar association between irAEs and survival remains unknown.

Materials and Methods. Patients with advanced melanoma treated with single-agent pembrolizumab or nivolumab in the province of Alberta from June 2014 to May 2017 were identified through the provincial pharmacy database. Chart review identified and categorized all irAEs that occurred while on anti–programmed cell death protein 1 (PD-1) checkpoint inhibitors. The primary objective was to compare overall survival (OS) with patients who developed any irAEs versus those who did not. Secondary outcomes included progression-free survival (PFS) and ORR.

Results. Among 186 patients, any-grade and grade ≥3 irAEs occurred in 88 (47%) and 27 (15%) patients, respectively; one patient died of pneumonitis. In a landmark analysis excluding patients who died within the first 12 weeks, the median follow-up was 24 months, 20 months in patients without any irAEs and 26 months in patients with irAEs (p = .006). Median OS was 39 versus 23 months (hazard ratio [HR], 0.46; p = .001) for any irAE and no irAE, respectively, and median OS not reached versus 29 months for grade ≥3 irAEs and no grade ≥3 irAEs, respectively. In multivariate analysis, elevated lactate dehydrogenase correlated with reduced OS (HR, 2.34; p = .001), whereas each additional cycle of treatment received (HR, 0.94; p < .001) and development of grade ≥3 irAEs (HR, 0.29, p = .024) were significantly associated with longer OS.

Conclusion. Anti-PD-1–associated grade ≥3 irAEs in patients with advanced melanoma is associated with better patient outcomes, including overall survival. ***The Oncologist*** 2020;25:438–446

Implications for Practice: Previous prospective randomized clinical trials demonstrate improved response rates in patients with melanoma who develop select adverse events. The current population-based real-world study in advanced melanoma reports an association with anti–programmed cell death protein 1 (PD-1)–induced grade ≥3 immune-related adverse events (irAEs) and better patient outcomes, including overall survival. These results suggest that irAEs may be a manifestation of a patient's ability to mount a systemic immune response from PD-1–directed therapies, which may be associated with therapeutic benefit. The finding of irAEs coinciding with clinical benefit from these therapies supposes that these events are, by and large, unavoidable, and the critical management of irAEs remains essential for optimizing patient outcomes.

Introduction

Immune checkpoint inhibitors have revolutionized the treatment for metastatic melanoma. The programmed cell death protein 1 (PD-1) monoclonal antibodies, pembrolizumab and nivolumab, as single agents have demonstrated superior survival and tolerability compared with ipilimumab, with median overall survivals (OS) approaching 3 years, and are now standard first-line treatment options for patients with advanced melanoma [1–4]. Improved objective response rates (ORR), progression-free survival (PFS), and OS in patients with advanced melanoma with high programmed cell death ligand 1 (PD-L1)–expressing tumors have been demonstrated, yet patients with low expression still derive

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Table 1. Patient characteristics by the development of any irAE

Characteristic	All patients (*n* = 186), *n* (%)	No irAE, (*n* = 98), *n* (%)	Any irAE, (*n* = 88), *n* (%)	*p* value
Age, median (range)	63.5 (55–74)	62 (54–74)	67 (57–75)	.078
Sex, male, *n* (%)	109 (58.6)	62 (63.3)	47 (53.4)	.173
BRAF[a] mutation positive, *n* (%)	51 (27.4)	31 (31.6)	20 (22.7)	.174
ECOG, *n* (%)				.254
0	46 (24.7)	19 (19.4)	27 (30.7)	
1	109 (58.6)	61 (62.2)	48 (54.5)	
2+	26 (14)	16 (16.3)	10 (11.4)	
Unknown	5 (2.7)	2 (2)	3 (3.4)	
M stage,[b] *n* (%)				.098
0/1a	44 (23.7)	22 (22.4)	22 (25)	
1b	39 (21)	15 (15.3)	24 (27.3)	
1c	67 (36)	37 (37.8)	30 (34.1)	
1d	36 (19.4)	24 (24.5)	12 (13.6)	
LDH, *n* (%)				.251
≤ULN	110 (59.1)	53 (54.1)	57 (64.8)	
>ULN	74 (39.8)	44 (44.9)	30 (34.1)	
Unknown	2 (1.1)	1 (1)	1 (1.1)	
Line of anti-PD-1, *n* (%)				.019
1	79 (42.5)	33 (33.7)	46 (52.3)	
2	40 (21.5)	26 (26.5)	14 (15.9)	
3	56 (30.1)	30 (30.6)	26 (29.5)	
≥4	11 (5.9)	9 (9.2)	2 (2.3)	
Median no. of cycles (IQR)	11 (5–20)	8 (4–14)	13 (8–25)	<.001

[a]BRAF mutations include V600E/Ec/D/K/R.
[b]American Joint Committee on Cancer 2017 melanoma staging classification. Patients treated for unresectable stage III (M0) were included with M1a for statistical analysis.
Abbreviations: ECOG, Eastern Cooperative Group; IQR, interquartile range; irAE, immune-related adverse event; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; ULN, upper limit of normal.

clinical benefit, and no clinical or biological marker to date has been implemented into practice [5].

The inhibitory checkpoint protein, PD-1, functions as a cellular "rheostat" to regulate the threshold of T cell immune response against infections and cancer, while preventing autoimmune disease toward self-antigens [6, 7]. Consequently, PD-1 axis checkpoint blockade results in distinct toxicity profiles that include autoimmune side effects frequently termed immune-related adverse events (irAEs) that can affect any organ or system [8, 9]. The diverse roles of the PD-1 inhibitory pathway and detailed mechanisms involved in regulating the cellular and humoral immune response are still being characterized, and much remains unknown as to why some patients develop irAEs whereas others do not [7, 10].

In a large single-center retrospective study of 298 patients with melanoma, the development of irAEs from the anti–cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, ipilimumab, did not correlate with any differences in patient outcomes [11]. In contrast, a combined analysis of 5,737 patients receiving various forms of immunotherapy, including interferon alfa, interleukin-2, vaccines, adoptive transfer of tumor-infiltrating lymphocytes, CTLA4, and PD-1 blockade found a survival benefit in those who developed vitiligo [12]. Data relating to irAEs from anti-PD-1 monoclonal antibodies and associated outcomes in melanoma patients are emerging, with some studies suggesting irAEs are predictive of patient outcomes [8, 12–16].

The treatment landscape for melanoma has changed with the development of PD-1–directed checkpoint blockade immunotherapies that have proven survival benefits with favorable side-effect profiles when compared with ipilimumab alone. However, real-world unselected patient data on efficacy, side-effect profiles, and clinical predictors of outcomes are lacking for PD-1 checkpoint inhibitors. In this article, we report a multicenter population-based study for the province of Alberta of patients with advanced melanoma treated with anti-PD-1 checkpoint blockade with either pembrolizumab or nivolumab and investigate the incidence of irAEs and how these relate to patient outcomes.

Subjects, Materials, and Methods

Patients

CancerControl Alberta coordinates all cancer care within the province of Alberta and patients with melanoma are primarily treated at two academic cancer centers, The Cross Cancer Institute in Edmonton and the Tom Baker Cancer Centre in Calgary. We conducted a 3-year retrospective analysis (June 2014 to May 2017) of all adult patients with unresectable

stage III or IV melanoma treated with pembrolizumab (2 mg/kg intravenous every 3 weeks) or nivolumab (3 mg/kg intravenous every 2 weeks) since their introductions into the province of Alberta. The Health Research Ethics Board of Alberta Cancer Committee approved this study. A pharmacy database was used to identify patients who were treated with pembrolizumab or nivolumab for advanced melanoma during the study dates. Baseline patient characteristics, investigations, number of doses of anti-PD-1, occurrence of irAEs (see below), and clinical outcomes were obtained from electronic medical health records. Treatment response was defined by a radiologist as per RECIST version 1.1 [17]. The primary objective was to compare OS between patients who developed any irAE versus those who did not, and secondary outcomes included ORR and PFS. Associations of relevant clinical factors including age at initiation of anti-PD-1 therapy, sex, baseline lactate dehydrogenase (LDH), BRAF mutation status, Eastern Cooperative Oncology Group (ECOG) performance status, M stage (American Joint Committee on Cancer 2017 melanoma staging classification), use of immunomodulatory agents to treat irAEs, line of PD-1 therapy, and number of cycles received with patient outcomes was also conducted.

Immune-Related Adverse Events

PD-1–associated irAEs were graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For statistical analysis, the following categorizations of irAEs and definitions were used (Table 2): vitiligo and poliosis were graded as skin hypopigmentation; diarrhea and enterocolitis were combined; hepatotoxicity was defined as a rise in aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase (within clinical context), or bilirubin; hypothyroid and hyperthyroid were combined; hypophysitis was included with adrenal insufficiency; pneumonitis included any patient with radiographic evidence of pneumonitis as a differential diagnosis in the absence of support for an alternative etiology; and arthritis and arthralgia were combined.

Statistical Analysis

A landmark analysis excluded patients who died within 12 weeks of initiating anti-PD-1 was used to compare outcomes to eliminate bias of poor prognosis patients. OS was defined as the time from initiation of anti-PD-1 to death, and PFS was calculated from time of first dose of anti-PD-1 to progression by RECIST 1.1 or death from any cause. Comparison of subject characteristics between groups with or without irAEs were made using Wilcoxon tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Kaplan-Meier survival analysis of OS and PFS was undertaken and compared across groups using log-rank tests. The Bonferroni correction was applied to adjust for multiple comparisons. A multivariable Cox proportional-hazards regression model of PFS and OS adjusted for underlying differences in subject characteristics.

Results

Patient Characteristics

One hundred eighty-six patients were identified from the pharmacy database over the study period and 2,195 cycles (median, 11; range, 1–60) of anti-PD-1 checkpoint inhibitors with either pembrolizumab or nivolumab were delivered in total. Median age at initiation of anti-PD-1 therapy was 64 years, 109 (59%) patients were male, and 51 (27%) were BRAF mutation positive (Table 1). The majority were cutaneous primaries (n = 153; 82%), including 2 patients with ungual melanoma and 19 with unknown primaries (supplemental online Table 1). Only 79 (43%) patients had single-agent nivolumab or pembrolizumab as first-line therapy for advanced melanoma, with 92 (49%) patients receiving prior ipilimumab, and 43 (23%) had a previous BRAF inhibitor-containing regimen. There were no differences in ECOG performance scores, BRAF mutational status, M stage or baseline LDH levels in patients who developed irAEs versus those who did not (Table 1). Patients who developed any irAEs received on average more cycles of anti-PD-1 (median, 13; interquartile range [IQR], 8–25 vs. median, 8; IQR, 4–14; $p < .001$).

Table 2. irAE by organ system, type, and grade

irAE by system	All patients (n = 186)	
	Any grade, n (%)	Grade ≥3, n (%)
No. of patients with ≥1 irAE[a]	88 (47.3)	27 (14.5)
Skin		
Maculopapular rash	29 (15.6)	5 (2.7)
Hypopigmentation or vitiligo	17 (9.1)	0 (0)
Poliosis	1 (0.5)	0 (0)
Gastrointestinal		
Diarrhea or enterocolitis	27 (14.5)	7 (3.8)
Hepatotoxicity	12 (6.5)	2 (1.1)
Pancreatitis	11 (5.9)	2 (1.1)
Endocrine		
Hypothyroid or hyperthyroid	21 (11.3)	0 (0)
Hypophysitis or adrenal insufficiency	6 (3.2)	3 (1.6)
Hyperglycemia	1 (0.5)	1 (0.5)
Pulmonary		
Pneumonitis	11 (5.9)	8 (4.3)
Rheumatological		
Arthritis or arthralgia	11 (5.9)	3 (1.6)
Myositis	3 (1.6)	1 (0.5)
Renal		
Acute kidney injury	4 (2.2)	1 (0.5)
Ocular		
Uveitis	2 (1.1)	0 (0)

[a]Many patients had more than one irAE. Recurrence of the same irAE on subsequent cycles were not included.
Abbreviation: irAE, immune-related adverse event.

Distribution of irAEs

Any-grade irAEs occurred in 88 (47%) patients and grade ≥3 irAEs occurred in 27 (15%) patients on anti-PD-1 checkpoint blockade (Table 2).

Skin was the most frequently affected organ, with the development of a maculopapular rash occurring in 29 (16%)

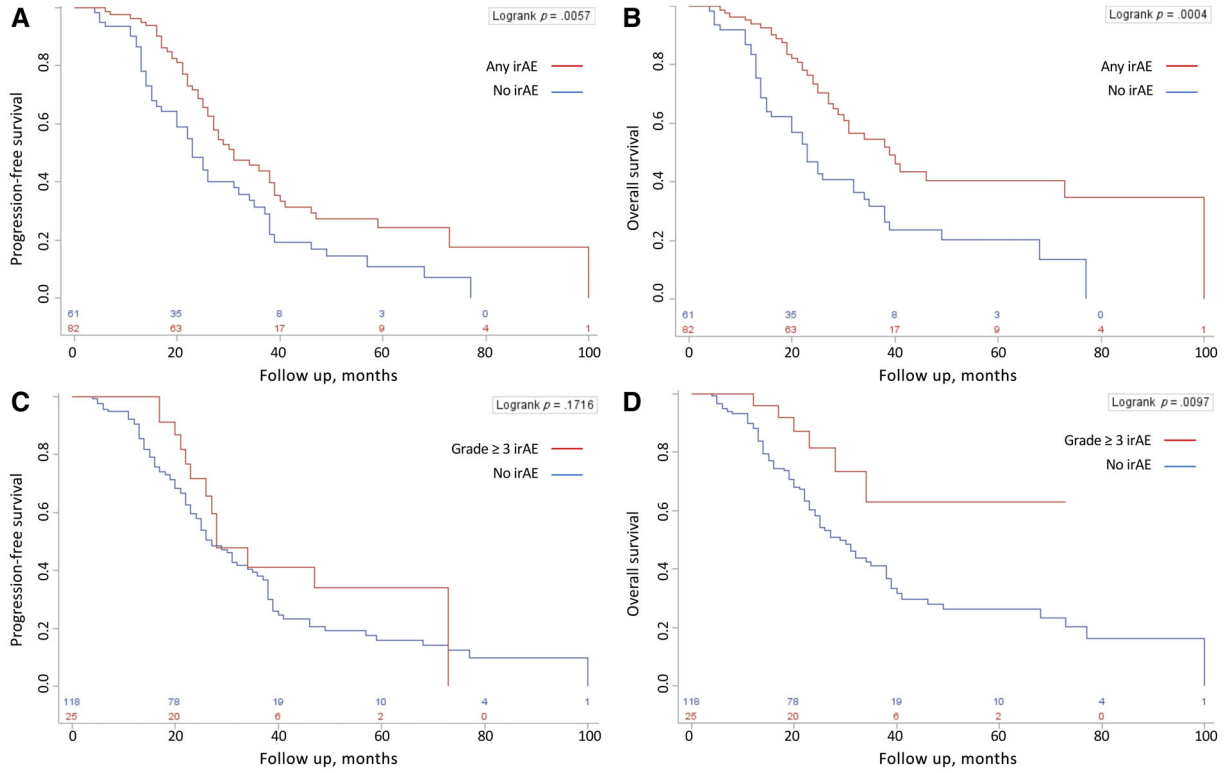

Figure 1 Twelve-week landmark progression-free survival and overall survival Kaplan-Meier survival curves. Any-grade irAEs **(A, B)** and grade ≥3 irAEs **(C, D)**.
Abbreviation: irAE, immune-related adverse event.

and hypopigmentation or vitiligo occurring in 17 (9%) patients. Two patients developed a maculopapular rash resembling psoriasis, and one patient had severe worsening of pre-existing psoriasis requiring temporary discontinuation without exacerbation upon reinitiation of anti-PD-1 treatment.

Twenty (11%) patients had grade 1–2 diarrhea or enterocolitis and another seven (4%) had grade ≥3, including one case of small bowel enteritis with upper gastrointestinal bleed, duodenal ulcers, and both large and small bowel lymphocytic infiltrate on endoscopic biopsy without any prior anti-CTLA4 therapy. The same patient also developed progressive vitiligo over the entire body, erythema marginatum on the lower torso, and grade 1 arthritis with a complete response (CR) of small-volume visceral metastases following 12 cycles of anti-PD-1 checkpoint blockade and is now on surveillance after cycle 18. Any-grade and grade ≥3 hepatotoxicity occurred in 7% and 1% of patients, respectively. Asymptomatic pancreatic enzyme elevation was seen in nine (5%) patients, and only two developed symptomatic pancreatitis.

Changes in thyroid function were common, occurring in 21 (11%) patients, and consistently required levothyroxine replacement at some point during the course of treatment. Grade 1–2 hypophysitis or adrenal insufficiency necessitating steroid supplementation alone occurred in three (2%) patients, and three (2%) others had severe symptoms requiring hospitalization and treatment delays (grade ≥3) in addition to hormone replacement. One patient developed insulin-dependent diabetes resulting in grade 4 hyperglycemia, requiring hospitalization.

The occurrence of pneumonitis was high, with any grade occurring in 11 (6%) patients and grade ≥3 occurring in 8 (4%) patients, including one death only 25 days after the first dose of anti-PD-1. Cultures did not reveal an infectious source in this case, and antibiotics were ineffective; intravenous methylprednisolone and infliximab briefly stabilized the patients' condition before the patient and family withdrew care.

Arthritis or arthralgias of any grade were seen in 11 (6%) patients on treatment and grade ≥3 in 3 (2%) patients. Any-grade myositis, acute kidney injury, and uveitis occurred in 1%–2% of patients, whereas grade ≥3 were rare events.

Forty-eight (26%) patients had a total of 65 objective laboratory and radiographic irAEs (hepatotoxicity, pancreatitis, hypo- and hyperthyroid, hypophysitis or adrenal insufficiency, hyperglycemia, pneumonitis, and myositis).

Treatment Outcomes

Using a 12-week landmark analysis to eliminate poor prognosis bias, 43 patients who died within 12 weeks of initiating anti-PD-1 therapy were excluded from the subgroup survival comparison. Median follow-up was 24 months in the landmark patients, 20 months in patients without any irAEs, and 26 months in patients with irAEs (p = .006). The development of any-grade irAEs from anti-PD-1 treatment was associated with an improved median OS of 39 versus 23 months (hazard ratio [HR], 0.46; p = .001), and grade ≥3 irAEs with an improved median OS not reached versus 29 months (HR, 0.35; p = .015; Fig. 1; Table 3). Elevated LDH was associated with a median OS of 22 months versus 38 months for patients with normal LDH levels (HR, 2.25; p < .001). Earlier M stage and objective irAEs were also associated with an improvement in OS. There were no significant differences in survival for age, gender,

Table 3. Median overall survival in 12-week landmark analysis[a] subgroups

Characteristic	Mo (95% CI)	HR (95% CI)	*p* value
Age			
<60 yr	32 (25–49)	Ref	
≥60 yr	31 (24–39)	1.07 (0.68 – 1.68)	.765
Gender			
Male	32 (24–41)	Ref	
Female	35 (25–40)	0.81 (0.51–1.27)	.356
BRAF status[b]			
Wild-type	29 (23–38)	Ref	
Mutant	41 (28–77)	0.63 (0.37–1.08)	.095
LDH			
Normal	38 (31–73)	Ref	
Elevated	22 (17–28)	2.25 (1.43–3.54)	<.001
Primary site[c]			
Cutaneous	34 (25–40)	Ref	
Noncutaneous	27 (22–39)	1.12 (0.68–1.83)	.663
M stage[d]			
0/1a	Not reached	Ref	
1b	30 (20–32)	2.82 (1.4–5.67)	.004
1c	23 (19–39)	2.49 (1.27–4.88)	.008
1d[e]	39 (25–68)	1.72 (0.81–3.69)	.161
Line of anti-PD-1			
1	27 (23–NR)	Ref	
2	27 (20–41)	0.89 (0.49–1.64)	.710
3	38 (26–73)	0.65 (0.37–1.12)	.122
≥4	68 (23–NR)	0.51 (0.19–1.37)	.180
Any irAE			
No	23 (16–32)	Ref	
Yes	39 (30–100)	0.46 (0.3–0.72)	.001
Grade ≥3 irAE			
No	29 (24–38)	Ref	
Yes	Not reached	0.35 (0.15–0.81)	.015
Objective irAE only[f]			
No	25 (22–34)	Ref	
Yes	46 (30–100)	0.45 (0.26–0.77)	.003

[a]A total of 43 patients were excluded from the landmark analysis for dying within 12 weeks of anti-PD-1 checkpoint blockade to eliminate poor prognosis bias.
[b]BRAF mutations include V600E/Ec/D/K/R.
[c]See supplemental online Table 1 for primary site subcategories.
[d]American Joint Committee on Cancer 2017 melanoma staging classification. Five patients had unresectable stage III (M0) and were included with M1a for statistical analysis.
[e]A total of 12 (33%) of patients with brain metastases died before the 12-week landmark and were thus excluded, the most of any M stage group (see supplemental online Table S2).
[f]Includes hepatotoxicity, pancreatitis, hypo- and hyperthyroid, hypophysitis or adrenal insufficiency, hyperglycemia, pneumonitis, and myositis.
Abbreviations: CI, confidence interval; HR, hazard ratio; irAE, immune-related adverse event; LDH, lactate dehydrogenase; NR, not reached; PD-1, programmed cell death protein 1.

BRAF mutation status, primary disease site, or line of anti-PD-1 therapy. ORR for the entire cohort was 36%, 17% in patients without any irAEs and 57% and 70% in patients with any-grade and ≥3 irAEs, respectively (Table 4; supplemental online Table 1), whereas PFS had no association with irAEs.

A multivariable Cox proportional-hazards regression model was used to correct for age, sex, LDH, BRAF mutation status, ECOG, M stage, any irAEs, grade ≥3 irAEs, objective irAEs, use of immunomodulatory agents to treat irAEs, line of anti-PD-1, and number of cycles received (Table 4). The development of grade ≥3 irAEs from anti-PD-1 treatment remained significantly associated with an improved overall survival (HR, 0.29; $p = .024$) in the regression analysis, as did normal LDH, earlier M stage, and the number of anti-PD-1 cycles received.

irAEs by Treatment Cycle

A total of 179 irAEs occurred in 88 patients, the majority early in the treatment course, as displayed in Figure 2. Forty-nine percent transpired within the first six cycles, 70% within 12 cycles, and approximately 15% of irAEs still emerged beyond 1 year of treatment. Half of patients with an irAE had more than one event (supplemental online Table 1); however, after complete resolution of an irAE, the same irAE on subsequent cycles occurred only 15 times in the entire cohort. The incidence of irAEs decreases with treatment duration over time where the exposure-adjustment irAE event rate is highest from cycles 4–6 for grade ≥3 irAEs and decreases significantly in later treatment cycles (supplemental online Fig. 2; supplemental online Table 5). The use of immunomodulatory agents for treatment of PD-1–induced irAEs did not affect PFS or OS.

Discussion

We report the first multicenter population-based data outside of a clinical trial of irAEs and survival outcomes from anti-PD-1 checkpoint blockade in advanced melanoma. The landmark KEYNOTE-006 and CHECKMATE-067 studies established improved survival of anti-PD-1 over CTLA-4 checkpoint blockade, with long-term median OS of approximately 3 years with single-agent nivolumab or pembrolizumab [1–4].

The association of better patient outcomes with the development of PD-1–induced irAEs found in our 12-week landmark analysis is substantial, with a median OS of 39 versus 23 months with and without any irAEs, respectively. The median OS for development of grade ≥3 irAEs was not reached and maintained statistical significance in the Cox regression analysis verifying this clinical benefit associated with irAEs. Previous reports support our findings including a recent study of 80 patients who experienced clinically significant irAEs on combined CTLA4 and anti-PD-1 checkpoint blockade in which 70% had either partial or complete responses, similar to 57% in our cohort (supplemental online Table 1) [18]. Weber et al. recently reported a nivolumab-treated pooled analysis of four trials demonstrating an increased ORR with treatment-related select adverse event [13], and Sznol et al. reported on a pooled analysis of ipilimumab with nivolumab combination–treated patients in which an increased ORR was seen in patients who developed irAEs beyond 12 weeks while on single-agent PD-1 compared with patients who developed irAEs less than 12 weeks on combination [14]. A single-center analysis from two phase I cohorts treated with nivolumab and a peptide vaccine showed a survival benefit

Table 4. Twelve-week landmark multivariable Cox proportional-hazards regression model for survival

	PFS		OS	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age				
<60 yr	Reference		Reference	
≥60 yr	1.2 (0.74–1.93)	.465	1.29 (0.76–2.17)	.340
Sex				
Male	Reference		Reference	
Female	1.08 (0.68–1.71)	.746	0.92 (0.55–1.51)	.731
LDH				
Normal	Reference		Reference	
Elevated	1.75 (1.1–2.79)	.019	2.34 (1.4–3.92)	.001
BRAF status				
Normal	Reference		Reference	
Mutant	0.89 (0.51–1.56)	.690	0.53 (0.27–1.03)	.060
ECOG				
0	Reference		Reference	
1	0.77 (0.45–1.3)	.324	0.84 (0.45–1.57)	.592
2+	0.85 (0.34–2.14)	.727	0.54 (0.16–1.84)	.323
M stage				
0/1a	Reference		Reference	
1b	1.15 (0.59–2.25)	.674	2.38 (1.09–5.18)	.029
1c	1.23 (0.68–2.21)	.501	1.71 (0.81–3.59)	.160
1d	0.9 (0.45–1.8)	.773	1.15 (0.49–2.73)	.747
Any irAE				
No	Reference		Reference	
Yes	0.75 (0.41–1.37)	.349	0.81 (0.42–1.56)	.524
Grade ≥3 irAE				
No	Reference		Reference	
Yes	0.73 (0.31–1.74)	.477	0.29 (0.1–0.85)	.024
Objective irAE only				
No	Reference		Reference	
Yes	0.75 (0.4–1.42)	.378	0.58 (0.27–1.23)	.153
Immunomodulatory agent(s) to treat irAE				
No	Reference		Reference	
Yes	0.95 (0.46–1.98)	.899	1.5 (0.67–3.37)	.324
Line of anti-PD-1				
1	Reference		Reference	
2	0.62 (0.33–1.19)	.150	0.79 (0.4–1.55)	.487
3	0.45 (0.25–0.8)	.007	0.62 (0.34–1.14)	.125
≥4	0.3 (0.1–0.94)	.039	0.69 (0.19–2.47)	.566
Each additional cycle	0.96 (0.94–0.98)	<.001	0.94 (0.91–0.97)	<.001

[a]Includes TNF-a inhibitors, mycophenolate mofetil, azathioprine, interleukin-6 inhibitors, methotrexate, or leflunomide.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; irAE, immune-related adverse event; LDH, lactate dehydrogenase; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival.

with cutaneous irAEs [16], and one observational study of 67 patients treated with pembrolizumab for advanced melanoma showed higher ORR with vitiligo [15]. Finally, related retrospective analyses in non-small cell lung cancer have found that patients treated with nivolumab had improved survival with the development of irAEs [19, 20].

Groundwork discovery of high PD-L1 expression on solid tumors correlating with worse prognosis suggested that tumors escape antitumor immunity through engagement of the expressed ligand to PD-1 on effector T cells in the tumor microenvironment (TME) [6, 21, 22]. Successful antitumor activity through PD-1 blockade was thought to require

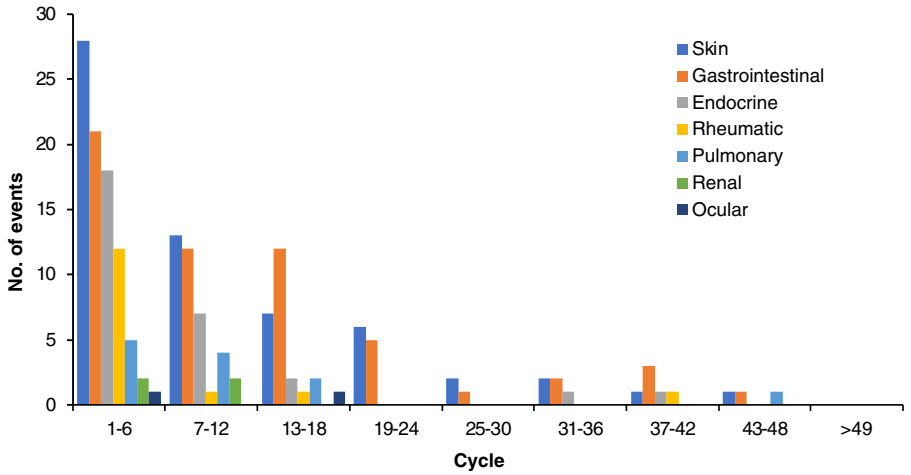

Figure 2 Onset of all immune-related adverse events (irAEs) by treatment cycle. Eighty-eight patients had a total of 179 irAEs of any grade; 16 were recurrences of the same irAE on subsequent cycles after complete resolution.

activation and expansion of T cells within the TME, which has been the basis for the anatomic site-of-action for anti-PD-1 antibodies [22–26]. However, Spitzer et al. recently challenged this notion by demonstrating in a mice model that secondary lymphoid organs were critical sites for T cell generation in PD-1–directed antitumor immune responses, and an expanded population of peripheral CD4 T cells conferred protection to new tumors in responding CTLA-4-treated humans [27]. Moreover, the efficacy of adjuvant anti-PD-1–directed immunotherapy in which the TME is essentially absent provides clinical evidence supporting the systemic immunity hypothesis [28]. The association of the development of irAEs with response and survival does not preclude that PD-1 blockade acts primarily in the TME to stimulate antitumor CD8-positive T cell responses, as a pre-existing T cell response within the TME is likely necessary in mounting an adequate systemic immune response from PD-1 checkpoint inhibitors. Regardless, irAEs from PD-1 checkpoint blockade are manifestations of systemic immune activation that not all patients acquire and are associated with response and survival benefit.

Immune-related AE occurred more frequently in patients with normal LDH than those with elevated LDH levels (65% vs. 34%), although this difference was not statistically significant. Elevated LDH was also independently associated with worse survival as seen on the multivariate analysis, consistent with previous studies. A recent analysis in patients from KEYNOTE-001 also found that elevated LDH correlated with increased tumor size and lower rates of CR [29]. When all considered together, this supports aspects of the "cancer immunogram" framework that a patient's immune system may be overwhelmed or perhaps even suppressed by a larger tumor burden, possibly from inhibitory tumor metabolism [30]. The independent associations for poorer outcomes in patients with high LDH levels and without the development of any irAEs may also indicate that inhibitory tumor metabolism itself, or some other unknown marker of cellular interference, could have the ability to impact the general immune status on a more systemic level.

It is noteworthy that rates of pneumonitis in the current study are high in comparison with previous clinical trial reports [1, 2, 23], although comparable to other institutional reported outcomes [31]. The diagnosis of pneumonitis remains one of exclusion with variable clinical presentations, radiographic changes, and pathologic findings, whereas confirmatory bronchoscopy and tissue biopsies are not always practical, especially for asymptomatic patients. Naidoo et al. demonstrated that a simple treatment delay often results in radiographic resolution of grade 1 pneumonitis with the risk of recurrent pneumonitis in future cycles. Nevertheless, grade ≥3 pneumonitis can progress despite immunosuppressive therapy and fatalities do occur, reflecting the clinical significance of this irAE that requires judicious management.

It is worth noting that there are no clinical data in melanoma to suggest that longer duration of therapy is superior in responding patients. Treatment length is a reflection of physician practice styles, patient preferences, patient tolerance to treatment, and clinical benefit. More therapy is not necessarily better for every patient despite the multivariable analysis suggesting that more cycles result in improved outcomes. Additionally, there are strong data to suggest that stopping treatment after a complete response is safe [29].

Finally, this study carries limitations, including the retrospective nature, which cannot exclude selection bias. It is limited by patient reporting and physician documentation of adverse events, and the low rates of grade 1–2 irAEs in our study may represent underreporting. This low rate of grade 1–2 irAEs reporting may have also contributed to the lack of statistical significance of all irAEs and objective irAEs after multivariate analyses. This limitation of potential underreporting and misattribution of grade 1–2 irAEs is inherent to all real-world evidence or observational studies. The potential for lead time bias is also noted, in which patients with longer survival are more likely to receive longer treatment exposure and thus more likely to experience irAEs. IrAEs are also more common in early treatment cycles and decrease with exposure over time (supplemental online Fig. 2; supplemental online Table 5). Moreover, a recent study in patients with urothelial cancer treated with immunotherapy has shown an association of irAEs with improved outcomes that was not attributed to increased drug exposure [32]. Although, PD-L1 expression status is a known predictive biomarker for anti-PD-1

checkpoint inhibitors, particularly in non-small cell lung cancer, this was not evaluated in comparison to irAEs in our study. PD-L1 expression is not required for drug eligibility in advanced melanoma and thus was not completed on our patient population. However, this should be sought in future studies, particularly in other tumor types in which the predictive and prognostic role of PD-L1 expression impacts management decisions.

Conclusion

These results suggest that host-specific factors may impact a patient's ability to mount a systemic immune response from PD-1–directed therapies, perhaps more significantly than previously considered. Further research identifying strategies aimed at monitoring, and conceivably augmenting, the systemic immune response may improve outcomes for nonresponding patients. Nevertheless, the finding of irAEs coinciding with clinical benefit from these therapies supposes that these events are, by and large, unavoidable, at least for the time being, and the critical management of irAEs remains essential for optimizing patient outcomes.

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The Health Research Ethics Board of Alberta Cancer Committee approved this study. This was a retrospective chart review; individual patient consent was not required. This study did not involve animal or human tissue.

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Disclosures

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For Further Reading:
Adil Daud, Katy Tsai. Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma. ***The Oncologist*** 2017:22;823–833.

Implications for Practice:
Targeted therapy with BRAF plus MEK inhibitors has become the standard of care for patients with advanced-stage *BRAF* V600–mutant metastatic melanoma. To provide optimal therapeutic benefit to patients, clinicians need a keen understanding of the toxicity profiles of these drugs. Prompt identification and an understanding of which adverse events are most likely BRAF or MEK inhibitor associated provide a rationale for appropriate therapy adjustments. Practical recommendations derived from clinical experience are provided for management of key drug-related toxicities.