ORIGINAL RESEARCH ARTICLE

Immune-related Adverse Effects Associated with Programmed Death-1 Inhibitor Therapy in the Treatment of Non-Small Cell Lung Cancer: Incidence, Management, and Effect on Outcomes

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ABSTRACT

Background: The programmed death 1 (PD-1) inhibitors may improve survival outcomes of non-small cell lung cancer (NSCLC) patients but are associated with immune-related adverse effects (IRAEs). Management of IRAEs may include immunosuppression (ie, corticosteroids), but there is concern that this may affect efficacy. This study evaluated the influence of IRAEs and immunosuppression for IRAEs on survival outcomes of NSCLC patients treated with PD-1 inhibitors (pembrolizumab and nivolumab).

Methods: We retrospectively examined data from Kaiser Permanente Southern and Northern California members diagnosed with NSCLC who received a PD-1 inhibitor from March 1, 2011 to September 30, 2016. Our primary goal was to evaluate the effects and management of IRAEs on survival with PD-1 inhibitors. Electronic database records were used to identify the occurrence of IRAEs, medication utilization, and death. Cox proportional hazard models were used to evaluate variables for association with increased risk of death.

Results: A total of 662 patients were included in the study (median age = 68 years) (interquartile range 61-74). IRAEs were identified in 18% of patients, of which 62% received immunosuppression. Median overall survival was 10 months (interquartile range = 4 months to not reached). Adjusting for covariates, use of immunosuppression during PD-1 inhibitor treatment was not associated with a significantly higher risk of death (hazard ratio = 1.04, 95% confidence interval = 0.84-1.29), whereas corticosteroid use before initiating PD-1 inhibitor therapy was (hazard ratio = 1.48, 95% confidence interval = 1.14-1.91).

Conclusions: In a large, real-world cohort from an integrated healthcare system, use of corticosteroids prior to PD-1 inhibitors was associated with worse survival outcomes, whereas concomitant treatment was not.

INTRODUCTION

The programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab reduce inhibition of the body's innate immune response to unrecognized antigens including cancer cells, resulting in an anticancer effect.[1] Both have been approved for the treatment of non-small cell lung cancer (NSCLC) due in part to clinical trial data showing significant increases in median overall survival (OS) of 3 to 4 months compared with standard chemotherapy.[2-6]

Unlike traditional cytotoxic chemotherapy, these medications are associated with unique and potentially fatal immune-related adverse effects (IRAEs) as a result of impaired self-tolerance from loss of T-cell inhibtion.[7] Studies of PD-1 inhibitors have shown IRAEs to include colitis, rash, hepatitis, and other immune-mediated manifestations.[2-6] To manage these reactions, protocols have been developed using immunosuppressive agents like corticosteroids in addition to holding or discontinuing PD-1 inhibitor treatment, depending on the severity of the reaction.[8-10] There is, however, a theoretical concern that the use of immunosuppressive management (IM) for IRAEs may reduce the therapeutic effect of PD-1 inhibitors by reducing the inflammatory response associated with both IRAEs and treatment efficacy.

Retrospective data from melanoma patients treated with ipilimumab have suggested that the use of IM may not affect survival outcomes.[11] Conversely, in pooled analyses of melanoma patients treated with ipilimumab or nivolumab, the occurrence of IRAE has had a neutral to positive effect on survival time.[12,13] The influence of IRAEs and IM on the survival outcomes of NSCLC patients treated with nivolumab and pembrolizumab has not been studied in a clinical trial or in a real-world clinical setting.

Thus, the goal of this retrospective cohort study was to evaluate the influence of IRAEs and immunosuppressive treatment of IRAEs on the survival outcomes of NSCLC patients treated with PD-1 inhibitors in an integrated healthcare system based on observational data.

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MATERIALS AND METHODS

Health Plan and Oncology Setting

Study Sample

This study was conducted within Kaiser Permanente Northern and Southern California, a large, integrated healthcare delivery system with over 8 million members. Health plan pharmacy databases and cancer registry data were used to identify histologically defined NSCLC patients administered either of the PD-1 inhibitors pembrolizumab or nivolumab during March 1, 2011 to September 30, 2016. All patients were presumed to have received cancer treatment within Kaiser Permanente due to the Kaiser Permanente's structure as a health maintenance organization. Index date was defined as the first day of PD-1 inhibitor administration, and follow-up continued until patient death; end of Kaiser Permanente Membership; or December 31, 2016; whichever came first. This study was approved by the Kaiser Permanente Northern and Southern California Institutional Review Boards, and a waiver of informed consent was obtained due to the nature of the study.

Outcomes and Covariables

Medical, laboratory, and pharmacy dispensing data were collected from the Kaiser Permanente California Region electronic database. Baseline characteristics included patient age, sex, ethnicity, comorbidities, and corticosteroid use recorded up to 6 months before index. Corticosteroid use before index was converted to a cumulative prednisone equivalent dose over the period of 6 months before index date. Comorbidities used to calculate Charlson Comorbidity Index included data up to 1 year before index, with the calculation of the Charlson Comorbidity Index performed as described in the medical literature.[14]

Cancer type was identified using histological data from the Kaiser Permanente Northern California Cancer Registry (KPNCCR) and the Kaiser Permanente Southern California Cancer Registry (KPSCCR). KPNCCR and KPSCCR were established in 1994 and 1998, respectively. Both registries manage a database of all Kaiser Permanente California members with a cancer diagnosis. The KPNCCR currently includes cases diagnosed from 1947 to present, and the KPSCCR includes cases diagnosed from 1980 to present. Both registries document invasive and in situ cancer, including all solid tumors (eg, breast and prostate) and systemic malignancies (eg, lymphoma, leukemia, and multiple myeloma). These cases are reported, as mandated, to the California Cancer Registry and the national Surveillance, Epidemiology, and End-Results Program, which prepares an annual report.

IRAEs were identified by International Classification of Diseases, 9th or 10th edition, Clinical Modification (ICD-9 or ICD-10) codes for a variety of different conditions deemed by investigators to be related to IRAEs (Table 1). Certain diagnoses for conditions considered to be chronic were excluded if the patient had a previous diagnosis for the same condition up to 1 year prior to index date. Diagnoses were considered to be related to IRAEs if they occurred after index and up to 180 days after the last PD-1 prescription dose.

IM was defined as the use of any systemic corticosteroid or alternate immunosuppressive medication used up to 30 days after an IRAE. Systemic corticosteroids included oral or injected betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone. Alternate immunosuppressive medications included adalimumab, antithymocyte globulin, cyclophosphamide, cyclosporine, infliximab, mycophenolate, and tacrolimus. IM use in patients without an identified IRAE during PD-1 inhibitor treatment and up to 30 days after the end of PD-1 inhibitor treatment was also recorded and analyzed.

Date of death was determined from Kaiser Permanente Beacon and Kaiser Permanente inpatient records and membership data.

Statistical Analysis

OS was compared between groups defined by IRAE occurrence, IM, and whether subsequent doses of PD-1 inhibitor were administered after the date of IRAE (Figure 1). OS outcomes were compared using Kaplan-Meier estimates, with log rank tests used to compare differences between groups. Cox proportional hazard modeling was used to determine the relative risk of death associated with various baseline and treatment variables. Additional post hoc sensitivity analyses were performed on different criteria for the definition of preindex corticosteroid use by varying the parameters of the variable entered into the model. A p value less than 0.05 was used as the criterion for statistical significance. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

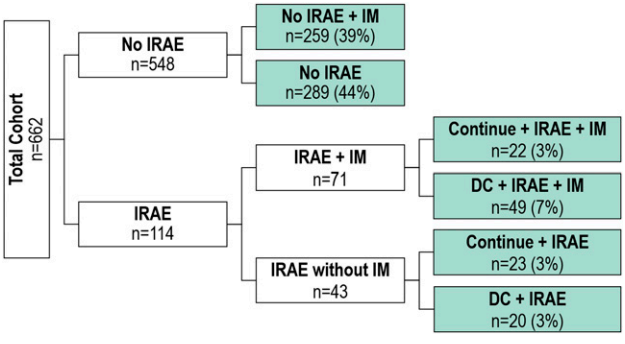

Figure 1. Immunosuppressive management of immune-related adverse effects in non-small cell lung cancer patients treated with programmed death receptor-1 inhibitors. DC = discontinued; IM = immunosuppressive management; IRAE = immune-related adverse effect.

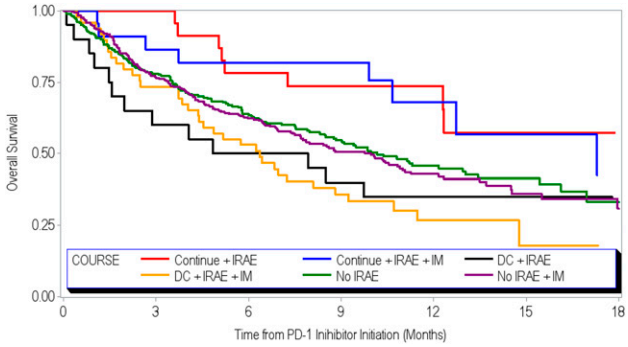

Figure 2. Unadjusted survival outcomes of non-small cell lung cancer patients treated with programmed death receptor-1 inhibitors stratified by occurrence of immune-related adverse effect, immunosuppressive management, and continuation or discontinuation of therapy after immune-related adverse effect. DC = discontinued; IRAE = immune-related adverse effect; IS = immunosuppression.

RESULTS

Cohort Characteristics

A total of 662 patients were included in the study cohort (Table 2). Median follow-up time was 7 months (interquartile range [IQR] = 4-11 months). During the study period, there were 349 deaths, with a median time from drug exposure to death of 10 months (IQR = 4 months to not reached); 93% of patients were treated with nivolumab versus 7% with pembrolizumab, with a median PD-1 exposure time of 3 months (IQR = 2-6 months).

IRAE Incidence

IRAEs were identified in 114 (17%) of patients at a median time to occurrence of 64 days (IQR = 27-126 days) (Figure 1). Dermatologic, gastrointestinal, and pulmonary IRAEs were the most commonly reported at 8%, 3%, and 3%, respectively. Timing and incidence of IRARs were detailed in Table 3.

IRAE Management

Of the 548 patients not identified as having an IRAE, 259 (47%) received IM between index and 30 days after the end of PD-1 inhibitor treatment. Of the 114 patients with identified IRAEs, 71 (62%) received IM within 30 days of the IRAE, but the remaining 43 (38%) did not. Of the 71 patients treated with IM, 49 (69%) did not receive subsequent PD-1 inhibitor doses after IRAE, whereas 20 of 43 (47%) patients who did not receive IM did not receive subsequent PD-1 inhibitor doses after IRAE.

Overall Survival

The median survival time for the cohort was 10 months (IQR = 9-11 months). Median survival time in the groups that continued therapy after the occurrence of an IRAE was numerically higher than in the groups with no IRAE. Conversely, the median survival time for groups that discontinued therapy after IRAE was lower than groups with no IRAE. Groups treated with IM had similar survival times compared with those without IM (Table 4). Kaplan-Meier curve was shown in Figure 2.

Cox proportional hazard modeling of mortality risk showed that IM during PD-1 inhibitor treatment was not associated with a significant increase in mortality risk (hazard ratio [HR] = 1.04, 95% confidence interval [CI] = 0.84-1.29) (Table 5). In contrast, the use of corticosteroids up to 6 months before initiation of PD-1 inhibitor treatment was associated with a significantly increased mortality risk (HR = 1.48, 95% CI = 1.14-1.91). Compared with patients with no IRAE, the occurrence of IRAE followed by continued therapy was associated with a significantly reduced mortality risk (HR = 0.49, 95% CI = 0.30-0.82), whereas an IRAE followed by treatment discontinuation was associated with a significantly higher mortality risk (HR = 1.37, 95% CI = 1.01-1.86). None of the other variables included as part of the Cox model was a significant predictor of mortality, except for Charlson Comorbidity Index equal to or greater than 5 (HR = 1.36, 95% CI = 1.00-1.85).

Sensitivity analyses were performed to further investigate the influence of corticosteroids used before PD-1 inhibitor initiation, which included the effects of different time and dose criteria (Table 6). All criteria for time of corticosteroid use from 2 weeks to 6 months prior produced significantly increased risk of death with corticosteroid exposure before initiation of a PD-1 inhibitor. Variation in dose criteria showed a significantly increased risk of death when no dose criteria were used and with a cumulative prednisone equivalent dose of 1000 mg or greater. Risk of death was numerically higher but not statistically significant with prednisone equivalent doses of 500 mg or greater.

DISCUSSION

To our knowledge, the current study is the largest single retrospective study of the outcomes of NSCLC patients treated with PD-1 inhibitors within the United States population. We found IRAE incidence and management rates that were comparable to those seen in clinical trials. Our data also suggest that, although the use of corticosteroids before PD-1 inhibitor treatment initiation and treatment discontinuation after IRAE are associated with worse OS outcomes, the use of IM during PD-1 inhibitor treatment was not.

The rates of IRAE and IRAE management seen in this study are difficult to compare with those found in existing literature due to differences in study methodology. The vast majority of data available on the adverse effect profile of pembrolizumab and nivolumab comes from the clinical

Table 1. International Classification of Diseases Diagnosis Codes for immune-related adverse effects

Category	Excluded if preexisting*	ICD-10	ICD-9	Description
Dermatologic	No	L139	6949	Bullous dermatitis
Dermatologic	No	L27	-	Dermatitis due to substance taken internally
Dermatologic	No	L270	6930	Dermatitis due to substance taken internally
Dermatologic	No	L271	6930	Dermatitis due to substance taken internally
Dermatologic	No	L278	6938	Dermatitis due to substance taken internally
Dermatologic	No	L279	6939	Dermatitis due to substance taken internally
Dermatologic	No	L29	-	Pruritus
Dermatologic	No	L298	6988	Pruritis other
Dermatologic	No	L299	6989	Pruritis NOS
Dermatologic	No	L309	6929	Dermatitis
Dermatologic	No	L309	-	Drug reaction/eruption
Dermatologic	No	L51	-	Erythema multiforme
Dermatologic	No	L511	69,513	SJS
Dermatologic	No	L512	69,515	TEN
Dermatologic	No	L513	69,514	SJS/TEN overlap
Dermatologic	No	L518	69,511	Other erythema multiforme
Dermatologic	No	L518	69,512	Other erythema multiforme
Dermatologic	No	L518	69,519	Other erythema multiforme
Dermatologic	No	L519	69,510	Erythema multiforme unspecified
Dermatologic	No	L80	70,901	Vitiligo
Dermatologic	No	-	6929	Dermatitis
Dermatologic	No	-	9952	Drug reaction/eruption
Dermatologic	No	-	502,164	Dermatitis due to chemotherapy
Dermatologic	No	R21	7821	Rash NOS
Endocrine	No	E032	2443	Hypothyroidism due to medicaments and other exogenous substances
Endocrine	Yes	E038	2448	Other specified hypothyroidism
Endocrine	Yes	E039	2449	Hypothyroidism unspecified
Endocrine	Yes	E0580	24,280	Other thyrotoxicosis
Endocrine	Yes	E0581	24,281	Other thyrotoxicosis
Endocrine	Yes	E0590	24,290	Thyrotoxicosis, unspecified
Endocrine	Yes	E230	2532	Hypopituitarism
Endocrine	Yes	E230	2533	Hypopituitarism
Endocrine	Yes	E230	6281	Hypopituitarism
Endocrine	No	E231	2537	Drug-induced hypopituitarism
Endocrine	Yes	E236	2534	Other disorders of pituitary gland
Endocrine	Yes	E236	2538	Other disorders of pituitary gland
Endocrine	Yes	E237	2539	Disorder of pituitary gland, unspecified
Endocrine	Yes	E271	25,541	Primary adrenocortical insufficiency
Endocrine	No	E273	-	Drug-induced adrenocortical insufficiency
Endocrine	Yes	E2740	25,541	Unspecified adrenocortical insufficiency
Endocrine	Yes	E2749	25,542	Other adrenocortical insufficiency
Endocrine	Yes	E2749	2555	Other adrenocortical insufficiency
Endocrine	Yes	E278	2558	Other specified disorders of adrenal gland
Endocrine	Yes	E279	2559	Disorder of adrenal gland, unspecified
Gastrointestinal	No	K2900	53,500	Acute gastritis
Gastrointestinal	No	K2901	53,501	Acute gastritis

(continued on following page)

Table 1. International Classification of Diseases Diagnosis Codes for immune-related adverse effects (continued)

Category	Excluded if preexisting*	ICD-10	ICD-9	Description
Gastrointestinal	No	K2960	53,520	Other gastritis
Gastrointestinal	No	K2961	53,521	Other gastritis
Gastrointestinal	No	K2970	53,550	Gastritis unspecified
Gastrointestinal	No	K2971	53,551	Gastritis unspecified
Gastrointestinal	No	K2980	53560	Duodenitis
Gastrointestinal	No	K2981	53,561	Duodenitis
Gastrointestinal	No	K521	5582	Toxic gastroenteritis and colitis
Gastrointestinal	No	K5289	5589	Noninfective gastroenteritis and colitis
Gastrointestinal	No	K529	5589	Enterocolitis
Gastrointestinal	No	-	78,791	Diarrhea
Gastrointestinal	No	-	53,540	Other gastritis
Gastrointestinal	No	-	53,541	Other gastritis
Gastrointestinal	No	-	5368	Gastritis/dyspepsia
Gastrointestinal	No	R197	-	Diarrhea
Hepatic	Yes	K71	-	Toxic liver disease
Hepatic	Yes	K716	5733	Toxic liver disease
Hepatic	Yes	K72	-	Hepatic failure NOS
Hepatic	Yes	K7200	570	Hepatic failure NOS
Hepatic	Yes	K7210	5728	Hepatic failure NOS
Hepatic	Yes	K7290	5722	Hepatic failure NOS
Hepatic	Yes	K754	57,142	Autoimmune hepatitis
Hepatic	Yes	K759	5733	Inflammatory liver disease NOS
Neurologic	Yes	G7000	35,800	Myasthenia gravis without (acute) exacerbation
Neurologic	Yes	G7001	35,801	Myasthenia gravis with (acute) exacerbation
Neurologic	No	I6783	34,839	Posterior reversible encephalopathy syndrome
Neurologic	No	G0481	32,381	Other encephalitis and encephalomyelitis
Neurologic	No	G0489	32,382	Other myelitis
Neurologic	No	G0489	3239	Encephalitis and encephalomyelitis, unspecified
Neurologic	No	G0491	3239	Myelitis, unspecified
Pancreatic	No	K853	-	Drug induced pancreatitis
Pancreatic	No	K858	-	Other acute pancreatitis
Pancreatic	No	K859	5770	Pancreatitis
Pulmonary	No	J702	-	Acute drug-induced interstitial lung disorders
Pulmonary	Yes	J703	-	Chronic drug-induced interstitial lung disorders
Pulmonary	No	J704	-	Drug-induced interstitial lung disorder, unspecified
Pulmonary	No	J708	5088	Respiratory conditions due to external agents
Pulmonary	No	-	486	Pneumonitis
Renal	Yes	N052	5831	Unspecified nephritic syndrome
Renal	Yes	N055	5832	Unspecified nephritic syndrome
Renal	Yes	N058	58,389	Unspecified nephritic syndrome
Renal	Yes	N059	5830	Unspecified nephritic syndrome
Renal	Yes	N2889	59,389	Unspecified nephritic syndrome
Renal	Yes	N289	5939	Disorder of kidney and ureter, unspecified
Renal	Yes	-	5834	Unspecified nephritic syndrome
Renal	Yes	-	5839	Unspecified nephritic syndrome
Renal	Yes	-	58,381	Nephritis

*Excluded if same diagnosis code was recorded up to 1 y before index.
NOS = not otherwise specified; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Table 2. Baseline characteristics (n = 662)	
Number of patients	662
Median age at treatment initiation, IQR	68 (61-74)
Male, %	51
Ethnicity, %	
White	61
Asian/Pacific Islander	17
African American	12
Hispanic	10
Other	1
Median Charlson comorbidity index[14]	3
Chronic pulmonary disease, %	46
Use of corticosteroids before starting PD-1 inhibitor, %	
Within 6 mo	
Any dose	73
≥ 500 mg prednisone equivalent	17
≥ 1000 mg prednisone equivalent	1
Within 3 mo	56
Within 2 mo	47
Within 1 mo	26
Within 2 wk	13

PD-1 = programmed death 1. mo = month.

Table 3. Incidence and timing of immune-related adverse effects in non-small cell lung cancer patients treated with programmed death receptor-1 inhibitors (n = 662)	
Dermatologic	
%	8
Median days to occurrence, n (IQR)	81 (35-132)
Gastrointestinal	
%	4
Median days to occurrence, n (IQR)	83 (43-154)
Pulmonary	
%	3
Median days to occurrence, n (IQR)	31 (11-65)
Hepatic	
%	2
Median days to occurrence, n (IQR)	102 (52-201)
Renal	
%	1
Median days to occurrence, n (IQR)	55 (28-108)
Pancreatic	
%	0
Median days to occurrence, n (IQR)	52 (13-91)
Endocrine	
%	1
Median days to occurrence, n (IQR)	69 (29-90)
Neurologic	
%	0
Median days to occurrence, n (IQR)	176 (176-176)
Any IRAE	
%	17
Median days to occurrence, n (IQR)	64 (27-126)

Twelve patients (2%) experienced >1 type of immune-related adverse effect.
IQR = interquartile range.

trial setting.[2-6] In this highly regulated and structured environment, the level of adverse effect detection and reporting are likely to be different than what we have seen in our real-world retrospective study. Furthermore, our methodology using ICD codes to identify IRAEs lacks severity information, and thus it is difficult to determine how our IRAE detection compared with clinical trials. Treatment-related adverse effects were reported in clinical trials at rates of 58% to 73%, with rates of grade 3 or higher adverse effects at 7% to 27%.[2-6] Specifically, KEYNOTE-010 and KEYNOTE-024 reported rates of 19% to 29% for investigator-designated immune-mediated adverse effects.[5,6] These numbers are similar to the 17% identified in our current study, although differences in detection undoubtedly exist between our retrospective methodology and the individually assessed adverse effects from clinical trials. Overall, the trends in IRAE incidence seem comparable to our study. Gastrointestinal and dermatologic effects appear to be relatively more common, and the median time to occurrence of IRAE appears to be roughly 1 month to 2 months.

Regarding the use of IM to manage IRAEs, the authors of the CheckMate-017 and CheckMate-057 studies reported steroid use rates of 11% to 83% in NSCLC patients treated with nivolumab depending on the type of IRAE.[2,3] These numbers are in alignment with the overall 62% seen in the current study. It is also interesting to note that almost half of the patients in our study with no identified IRAE required IM for another indication. Preliminary chart review has shown that these indications included chronic obstructive pulmonary disease exacerbations, brain metastases, and procedural preparation; however, these patients warrant further formal investigation.

Treatment discontinuation rates found in previous literature ranged from 3% to 7.1%, whereas the proportion of patients in our study who did not receive subsequent doses of PD-1 inhibitors after an identified IRAE was 10%.[2,3,6] This higher rate may reflect the fact that not all of the patients in our study who "discontinued" therapy did so because of adverse effects. Some may have coincidentally stopped treatment for disease progression or treatment futility at approximately the same time that an adverse effect occurred.

The significant difference in survival outcomes seen between patients who discontinue therapy after an IRAE

Table 4. Unadjusted overall survival outcomes of non-small cell lung cancer patients treated with programmed death receptor-1 inhibitors

IRAE + Continue (n = 23)	
Median months survival	NR
95% CI	12-NR
IRAE + IS + Continue (n = 22)	
Median months survival	17
95% CI	11-NR
IRAE + DC (n = 20)	
Median months survival	6
95% CI	2-NR
IRAE + IS + DC (n = 49)	
Median months survival	6
95% CI	4-9
No IRAE (n = 289)	
Median months survival	10
95% CI	8-13
No IRAE + IS (n = 259)	
Median months survival	10
95% CI	8-11

DC = discontinued; IM = immunosuppressive management; IRAE = immune-related adverse effect; NR = not reached.

versus those who continue therapy is an intriguing finding with two possible explanations. First, patients have discontinued therapy because of declining health and functional status. In such a situation, prescribers may be making a decision to focus on patient quality of life rather than trying to marginally extend OS. The other possibility is that patients with an IRAE who can continue therapy have increased treatment efficacy along with toxicity, as has been suggested by previous data showing better OS outcomes in patients with IRAE.[13]

Table 5. Cox-proportional hazard model of risk associated with various baseline and treatment factors in non-small cell lung cancer patients treated with programmed death receptor-1 inhibitors

	Overall survival		
Factor	HR	95% CI	p value
IM during PD-1 inhibitor treatment: yes vs no	1.04	0.84-1.29	0.71
PD-1 after IRAE occurrence: yes vs no IRAE	0.49	0.30-0.82	<0.01
PD-1 after IRAE occurrence: no vs no IRAE	1.37	1.01-1.86	0.05
Corticosteroid use before PD-1 inhibitor treatment: yes vs no	1.48	1.14-1.91	<0.01
Charlson Comorbidity Index: 5 vs 1-2	1.36	1.00-1.85	0.05
Charlson Comorbidity Index: 3-4 vs 1-2	1.29	1.00-1.67	0.05
PD-1 inhibitor: pembrolizumab vs nivolumab	1.25	0.83-1.88	0.29
Ethnicity: white vs non-white	1.09	0.87-1.37	0.44
Sex: male vs female	0.98	0.79-1.21	0.82
Age: ≥65 y vs <65 y	0.84	0.66-1.06	0.13

CI = confidence interval; HR = hazard ratio; IRAE = immune-related adverse effect; PD-1 = programmed death 1.

Table 6. Sensitivity analysis of altering parameters of corticosteroid use before programmed death receptor-1 inhibitor initiation

Time (any dose)	
6 mo	
HR	1.48
95% CI	1.14-1.19
3 mo	
HR	1.39
95% CI	1.12-1.73
2 mo	
HR	1.43
95% CI	1.16-1.77
1 mo	
HR	1.37
95% CI	1.09-1.73
2 wk	
HR	1.87
95% CI	1.41-2.49
Dose (over 6 mo)	
Any dose	
HR	1.48
95% CI	1.14-1.91
500 mg cumulative prednisone equivalent	
HR	1.3
95% CI	0.99-1.69
1000 mg cumulative prednisone equivalent	
HR	2.38
95% CI	1.08-5.21

CI = confidence interval; HR = hazard ratio. mo = month.

The fact that IM during PD-1 inhibitor treatment does not produce worse treatment outcomes supports a growing body of literature that suggests the same. Two pooled analyses of clinical trial data from metastatic melanoma patients have suggested that response rates are not affected by corticosteroid use during treatment, and an additional retrospective study of 298 metastatic melanoma patients suggests that OS is also not affected.[11,15,16] Thus, this study provides data from a larger sample to support the hypothesis that the same patterns seen in melanoma patients may be similar in NSCLC.

In contrast, data from this study suggest that the use of corticosteroids before the initiation of PD-1 therapy may be correlated with worse survival outcomes. In general, patients in clinical trials were required to be free from corticosteroids, with few exceptions, in the period immediately before

the initiation of therapy for a period of 3 to 14 days.[2-6] Beyond the period of time immediately before the initiation of therapy, the numbers of patients exposed to corticosteroids were not reported. Our data suggest that, either due to interference with the therapeutic effect of PD-1 inhibitors or identification of higher risk patients, this factor may help to identify patients who may have shorter expected survival when treated with PD-1 inhibitors. This effect also seems relatively stable regardless of the time frame used up to 6 months prior to first exposure or the cumulative dose of corticosteroid used. Similar results have been observed in a recent study by Arbour et al[17].

As a retrospective study based on database variables, there are a number of potential limitations to this study. One limitation is that our methodology for identifying IRAEs relies on ICD diagnosis codes. Although this allowed us to analyze a large amount of data, it is also subject to the subjective evaluation of different healthcare professionals. Additionally, as a study within Kaiser Permanente, our results are not necessarily generalizable to outside healthcare systems that may not have the level of integration present at Kaiser Permanente. Finally, there is the potential for selection bias because treatment decisions were made based upon clinician judgement rather than on randomization. Regardless, this study provides intriguing data suggesting that the use of corticosteroids may influence or predict survival outcomes when used outside the realm of IRAE management.

In summary, the use of corticosteroids before treatment initiation may be associated with treatment outcomes, whereas the use of IM during treatment may not. This may suggest that, although the use of IM to suppress IRAEs should be performed routinely, the use of corticosteroids before treatment may be more problematic. With further prospective research, we may be able to identify specific criteria regarding the dose, timing, and indication of corticosteroid use to separate out patients that are better suited to immunotherapy with PD-1 inhibitors. ❖

Disclosure Statement

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Authors' Contributions

Timothy Chiu, PharmD, BCPS; Christopher Yamamoto, PharmD, BCPS, BCPS; Fang Niu, MS; and Rita Hui, PharmD, MS, participated in study conception and design, with assistance from Helen Moon, MD; Thach-Giao Truong, MD; and Robert Cooper, MD. Rita Hui, PharmD, MS, and Fang Niu, MS, participated in data collection. Christopher Yamamoto, PharmD, BCPS, BCPS; Rita Hui, PharmD, MS; Fang Niu, MS; Timothy Chiu, PharmD, BCPS; Helen Moon, MD; Thach-Giao Truong, MD; and Robert Cooper, MD, interpreted the data. Christopher Yamamoto, PharmD, BCPS, BCPS; Timothy Chiu, PharmD, BCPS; and Rita Hui, PharmD, MS wrote the manuscript. Helen Moon, MD; Thach-Giao Truong, MD; and Robert Cooper, MD, critically reviewed the manuscript. All authors performed the final approval of the version to be published.

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References

1. Pardoll, DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012 Mar;12(4):252-64. DOI: https://doi.org/10.1038/nrc3239, PMID:22437870
2. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015 Jul;373 (2):123-35. DOI: https://doi.org/10.1056/NEJMoa1504627, PMID:26028407
3. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015 Oct;373 (17):1627-39. DOI: https://doi.org/10.1056/NEJMoa1507643, PMID:26412456
4. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015 May;372 (21):2018-28. DOI: https://doi.org/10.1056/NEJMoa1501824, PMID:25891174
5. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet 2016 Apr;387 (10027):1540-50. DOI: https://doi.org/10.1016/S0140-6736(15)01281-7, PMID:26712084
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chrmotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016 Nov;375(19):1823-33. DOI: https://doi.org/10.1056/NEJMoa1606774, PMID:27718847
7. Fetcher LA, Agarwala SS, Hodi FS, et al. Ipilimumab and its toxicities: a multidisciplinary approach. Oncologist 2013 Jun;18:733-43. DOI: https://doi.org/10.1634/theoncologist.2012-0483
8. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015 May;372(21):2006-17. DOI: https://doi.org/10.1056/NEJMoa1414428, PMID:25891304
9. Keytruda [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2016.
10. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
11. Horvat TZ, Adel NG, Dang TO, 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 Oct;33(28):3193-8. DOI: https://doi.org/10.1200/JCO.2015.60.8448, PMID:26282644
12. Ascierto PA, Simeone E, Sileni VC, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. J Transl Med 2014 May;12:116. DOI: https://doi.org/10.1186/1479-5876-12-116, PMID:24885479
13. Freeman-Keller M, Kim Y, Cronin H, et al. Nivolumab in resected and unresected metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016 Feb;22(4):886-94. DOI: https://doi.org/10.1158/1078-0432.CCR-15-1136, PMID:26446948
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987 Jan; 40(5):373-83. DOI: https://doi.org/10.1016/0021-9681(87)90171-8, PMID:3558716
15. Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 2007 Nov;13(22 Pt 1):6681-8. DOI: https://doi.org/10.1158/1078-0432.CCR-07-0187, PMID:17982122
16. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017 Mar;35(7):785-92. DOI: https://doi.org/10.1200/JCO.2015.66.1389, PMID:28068177
17. Arbour KC, Mezquita L, Long N et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol 2018 Oct;36(28):2872. DOI: https://doi.org/10.1200/JCO.2018.79.0006, PMID:30125216
18. Eggermont AMM, Kicinski M, Blank CU et al. Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: a secondary analysis of a randomized clinical trial. JAMA Oncol 2020 Apr;6(4):519-27. DOI: https://doi.org/10.1001/jamaoncol.2019.5570.