Cancer Immunology, Immunotherapy (2019) 68:917–926
https://doi.org/10.1007/s00262-019-02321-z

ORIGINAL ARTICLE

Pre-existing autoimmune disease and the risk of immune-related adverse events among patients receiving checkpoint inhibitors for cancer

Kenneth L. Kehl[1,2] · Shihao Yang[3] · Mark M. Awad[2] · Nathan Palmer[4] · Isaac S. Kohane[4] · Deborah Schrag[1]

Received: 14 October 2018 / Accepted: 4 March 2019 / Published online: 15 March 2019

Abstract

Introduction Patients with pre-existing autoimmune diseases have been excluded from clinical trials of immune checkpoint inhibitors (ICIs) for cancer. Real-world evidence is necessary to understand ICI safety in this population.

Methods Patients treated with ICIs from 2011 to 2017 were identified using data from a large health insurer. Outcomes included time to (1) any hospitalization; (2) any hospitalization with an irAE diagnosis; and (3) outpatient corticosteroid treatment. The key exposure was pre-existing autoimmune disease, ascertained within 12 months before starting ICI treatment, and defined either by strict criteria (one inpatient or two outpatient claims at least 30 days apart) or relaxed criteria only (any claim, without meeting strict criteria).

Results Of 4438 ICI-treated patients, pre-existing autoimmune disease was present among 179 (4%) by strict criteria, and another 283 (6%) by relaxed criteria only. In multivariable models, pre-existing autoimmune disease by strict criteria was not associated with all-cause hospitalization (HR 1.27, 95% CI 0.998–1.62), but it was associated with hospitalization with an irAE diagnosis (HR 1.81, 95% CI 1.21–2.71) and with corticosteroid treatment (HR 1.93, 95% CI 1.35–2.76). Similarly, pre-existing autoimmune disease by relaxed criteria only was not associated with all-cause hospitalization (HR 1.11, 95% CI 0.91–1.34), but was associated with hospitalization with an irAE diagnosis (HR 1.46, 95% CI 1.06–2.01) and corticosteroid treatment (HR 1.46, 95% CI 1.13–1.88).

Conclusion Pre-existing autoimmune disease was not associated with time to any hospitalization after initiating ICI therapy, but it was associated with a modest increase in hospitalizations with irAE diagnoses and with corticosteroid treatment.

Keywords Immunotherapy · Immune-related adverse event · Checkpoint inhibitor · Real-world evidence

Abbreviations

CPT	Current procedural terminology
HCPCS	Healthcare common procedural coding system
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event

Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs) has rapidly changed the therapeutic landscape for patients with cancer. Since initial approval of the anti-CTLA4 antibody ipilimumab in 2011 for metastatic melanoma [1], the anti-PD-1 monoclonal antibodies pembrolizumab and nivolumab and the anti-PD-L1 antibodies atezolizumab, avelumab, and durvalumab have been approved for multiple cancer histologies [2–13]. Pembrolizumab is also approved for patients with microsatellite instability-high tumors, regardless of histology [14]. Hundreds of immunotherapy clinical trials are ongoing [15].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00262-019-02321-z) contains supplementary material, which is available to authorized users.

✉ Kenneth L. Kehl
Kenneth_Kehl@dfci.harvard.edu

1 Division of Population Sciences, Dana-Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215, USA

2 Thoracic Oncology Program, Dana-Farber Cancer Institute, Boston, MA, USA

3 Department of Statistics, Harvard University, Boston, MA, USA

4 Department of Bioinformatics, Harvard Medical School, Boston, MA, USA

Although the overall risk of serious adverse events is lower with single-agent PD-1 inhibition than with chemotherapy, up to 29% of patients in clinical trials of anti-PD-1 therapy experienced an immune-related adverse event (irAE), and up to 10% of patients had a severe (grade 3 or higher) adverse event [11, 12, 16]. In one series of patients treated with combined ipilimumab with nivolumab in a tertiary care center, 91% experienced any significant adverse event, and 36% required hospitalization [17]. IrAEs may include colitis, hepatitis, hypophysitis, dermatitis, pneumonitis, and other inflammatory disorders [17, 18]. IrAEs are generally manageable with prompt corticosteroid treatment, but serious events may require additional immunosuppressive therapy [19].

Data are limited regarding the association between pre-existing autoimmune diseases and the risk of irAEs among patients who receive ICIs. Alterations in the CTLA-4 and PD-1 checkpoints are associated with autoimmune diseases [20–22], raising concerns that checkpoint inhibitors may confer a higher risk of toxicity among patients who have such conditions. Some clinical trials enrolled patients with autoimmune disease if they had not received recent immunosuppressive therapy [16, 23, 24], but most [2, 10–12, 23, 25–28] excluded such patients. These exclusions may have population-level impact, since up to 25% of Medicare patients with newly diagnosed cancer may have pre-existing autoimmune disease [29]. In case series of patients with melanoma with pre-existing autoimmune disease who were treated at academic centers, 50% of those treated with ipilimumab developed a flare of the underlying disease or an irAE [30]; 38% of patients treated with PD-1 inhibitors had flares of underlying disease, and 29% had conventional irAEs [31]. In a recent case series of 56 patients with pre-existing autoimmune disease who received ICIs for lung cancer at academic centers, 55% developed a flare of underlying autoimmune disease or an irAE, although most events were mild [32].

Most adults with cancer are treated outside major academic centers [33]. Little is known regarding the risks and benefits of ICIs for patients with pre-existing autoimmune disease across sites of care. To address this gap and inform the balance of benefits and harms of ICIs among patients with pre-existing autoimmune disease, we analyzed claims data from a large US national private insurer to evaluate the association between pre-existing autoimmune disease and serious irAEs, as measured by hospitalizations and prescriptions for corticosteroids.

Materials and methods

Cohort

Our analysis used un-identifiable member claims data from Aetna, a large private national US health insurer. Patients were identified who had any Current Procedural Terminology (CPT)/Healthcare Common Procedural Coding System (HCPCS) code corresponding to administration of an ICI (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab; CPT codes listed in Supplemental Table 1, footnotes) from January 1, 2011 through June 30, 2017. Continuous enrollment in an Aetna medical plan was required for at least 1 year prior to first ICI therapy; patients were censored if they disenrolled from their health plan or reached the end of the follow-up period on June 30, 2017 within 30 days after an ICI dose. For the corticosteroid treatment outcome, we additionally required continuous enrollment in an Aetna prescription (oral) drug benefit plan beginning 60 days before first ICI administration to capture baseline corticosteroid treatment, and we censored patients if they disenrolled from prescription drug coverage or reached the end of the follow-up period on June 30, 2017 within 30 days after an ICI dose (Fig. 1).

Outcomes

The first outcome was time to any-cause hospitalization while receiving ICI therapy, defined by identifying acute care hospital claims with an inpatient place of service. The second outcome was time to any hospitalization with a diagnosis consistent with an irAE; these diagnoses were identified by manually reviewing all diagnosis codes for claims occurring during an inpatient stay ($N = 3678$), separated from individual patient data, to identify codes consistent with probable irAEs [34] (e.g., "toxic gastroenteritis and colitis"); Supplemental Table 2. Classification of these codes was performed blinded to the pre-existing autoimmune disease status of individual patients.

The third outcome was time to first outpatient systemic corticosteroid treatment with prednisone, methylprednisolone, or hydrocortisone after initiating ICI therapy, given the role of steroids in guideline-concordant management of irAEs [19]. Dexamethasone was not included, since guidelines call for prednisone or methylprednisolone as initial management of irAEs [19] or with concurrent chemotherapy [35]; furthermore, in initial exploration of the data set, dexamethasone frequently followed hospitalizations consistent with brain metastases (i.e., diagnoses of cerebral edema) rather than irAEs.

Pre-existing autoimmune disease

The primary independent variable of interest was a pre-existing autoimmune disease during the 12 months prior to initiation of ICI therapy. This was defined by either "strict" criteria, corresponding to an inpatient claim for an autoimmune diagnosis or two outpatient claims 30 days apart [29, 36, 37], or "relaxed" criteria only, corresponding to

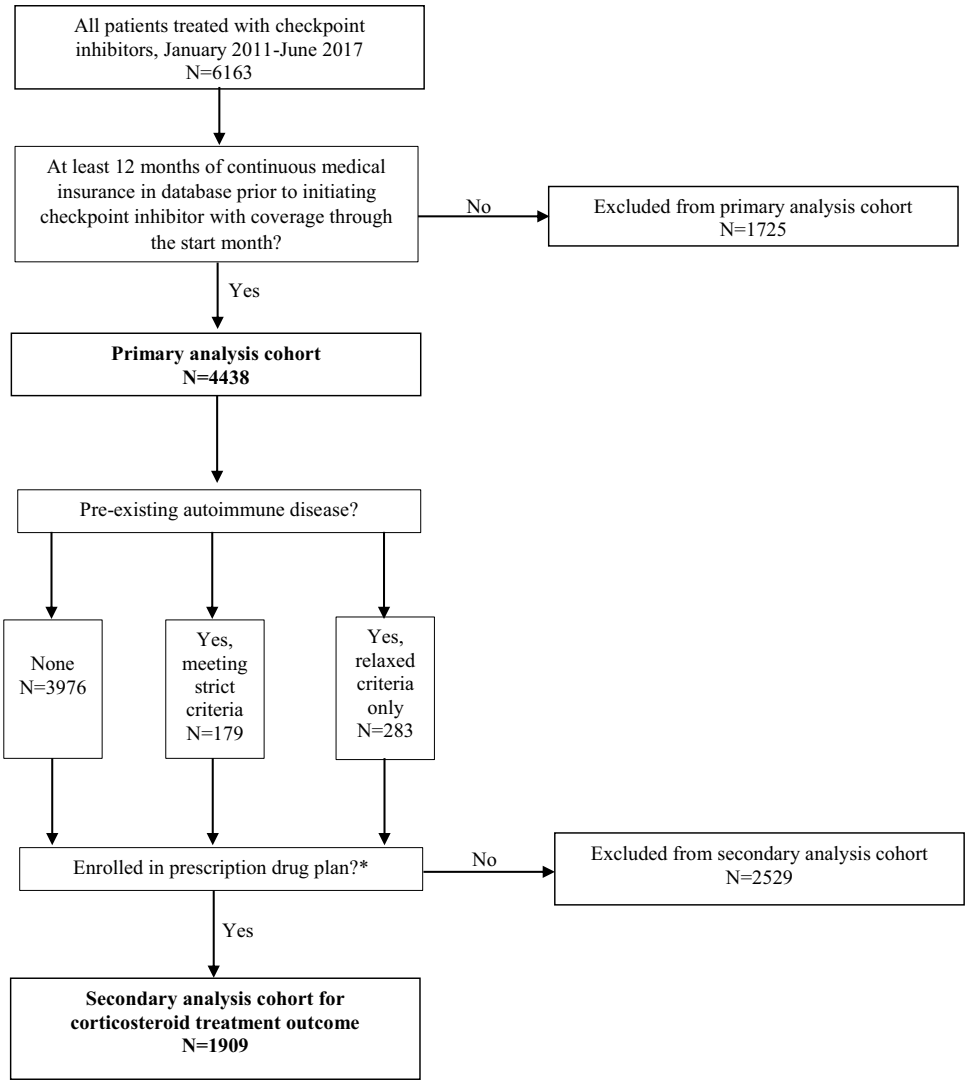

Fig. 1 Derivation of study cohort. Asterisk ICI treatment did not itself require prescription drug coverage, since infusional therapy could be covered under the medical plan

any claim with a diagnosis of pre-existing autoimmune disease, without fulfillment of strict criteria. Categories of pre-existing diseases and specific diagnosis codes are listed in Supplemental Table 3. Endocrine disorders, including diabetes and hypothyroidism, were not considered pre-existing autoimmune diseases for this analysis [32].

Covariates

Additional independent variables included age, sex, cancer type, ICI regimen, and claims for any cytotoxic chemotherapy during the year prior to initiation of ICI therapy, and other comorbidity, measured by modifying the National Cancer Institute comorbidity index [38] to exclude rheumatologic disease, which was instead captured specifically as a pre-existing autoimmune condition. For the outcome of corticosteroid treatment, additional covariates included any prior corticosteroid prescription in the 60 days before, and any claim for chronic obstructive pulmonary disease (COPD) in the year before, starting an ICI.

Analysis

Analyses were conducted in a time-to-event fashion. To depict the distribution of our outcomes over time, cumulative incidence curves were constructed, subject to competing risks of death or cessation of ICI therapy (defined as a gap of 30 days or more following an ICI dose). Our analysis, therefore, focused specifically on irAEs occurring during or immediately after ICI therapy. Landmark analyses were performed after 3 months of ICI treatment.

Univariable and multivariable analyses examined the association between pre-existing autoimmune disorders and the cause-specific hazard of our outcomes [39]. This was accomplished with proportional hazards models in which patients were censored on the date of death, disenrollment

from the health plan, June 30th 2017, or 30 days following an ICI dose, whichever came first.

Sensitivity analysis

A sensitivity analysis was conducted to explore the impact of coding pre-existing autoimmune disease as a continuous independent variable representing the number of days in the prior 12 months with a claim for such a disease—representing the intensity of any medical care required for such a disease—rather than as a categorical variable defined according to "strict" and "relaxed" criteria as above. A second sensitivity analysis was conducted to explore the impact of excluding patients with prescriptions for any systemic corticosteroid in the 60 days prior to initiating ICI therapy on the outcome of subsequent systemic corticosteroid prescriptions.

Results

Cohort

The derivation of the study cohort is illustrated in Fig. 1. Of 4438 patients identified, 179 (4%) had pre-existing autoimmune disease by strict criteria, and 283 (6%) had pre-existing autoimmune disease by relaxed criteria only. The most common categories of pre-existing autoimmune diseases were inflammatory/rheumatoid arthritis and gastrointestinal/inflammatory bowel disease (Supplemental Table 3). Lung cancer was the most common indication for ICI therapy (42% of patients) followed by melanoma (34%). ICI regimens administered included nivolumab (52%), pembrolizumab (20%), atezolizumab (3%), ipilimumab (21%), and ipilimumab + nivolumab (5%). The median duration of ICI treatment was 13.7 weeks (95% CI 13.4–14.4; Supplemental Table 1). Simultaneous cytotoxic chemotherapy (within 7 days of ICI initiation) was administered to 96 patients (2.2%).

Any hospitalization

After 3 months of ICI therapy, the cumulative incidence of all-cause hospitalization in the full cohort was 28.6% (95% CI 27.2–29.9%). Among patients with no pre-existing autoimmune disease, it was 28.0% (95%CI 26.6–29.5%); among patients with pre-existing autoimmune disease by strict criteria, it was 35.0% (95% CI 27.9–42.3); and among patients with pre-existing autoimmune disease by relaxed criteria only, it was 31.7% (95% CI 26.2–37.3%); Table 1; Supplemental Fig. 1.

In multivariable analyses, there was no significant association between pre-existing autoimmune disease as defined by either strict criteria (Hazard ratio, HR, 1.27, 95% CI, 0.998–1.62) or relaxed criteria only (HR 1.11, 95% CI 0.91–1.34) and all-cause hospitalization; Table 1 and Fig. 2. When pre-existing autoimmune disease was coded as a continuous variable corresponding to the number of days in the prior year with a claim for such a diagnosis, there remained no significant association with all-cause hospitalization (HR 1.017, 95% CI 1.000–1.034 per day; $P = 0.053$).

Hospitalization with an irAE diagnosis

After 3 months of ICI therapy, the overall cumulative incidence of hospitalization with a probable irAE diagnosis was 7.8% (95% CI 7.0–8.6%). Among patients with no pre-existing autoimmune disease, it was 7.5% (95% CI 6.7–8.4%). Among patients with pre-existing autoimmune disease by strict criteria, it was 11.1% (95% CI 6.9–16.3%), and among patients with pre-existing autoimmune disease by relaxed criteria only, it was 10.0% (95% CI 6.8–13.9%); Table 2; Supplemental Fig. 2.

In multivariable analyses, pre-existing autoimmune disease by strict criteria and relaxed criteria only were each associated with hospitalization with an irAE diagnosis (HR 1.81, 95% CI 1.21–2.71 and 1.46, 95% CI 1.06–2.01, respectively); Table 2 and Fig. 2. When pre-existing autoimmune disease was coded as a continuous variable corresponding to the number of days in the prior year with a claim for such a diagnosis, there was a significant association with this outcome (adjusted HR 1.05, 95% CI 1.03–1.08 per day; $P < 0.001$).

Systemic corticosteroid treatment

After 3 months of ICI therapy, the cumulative incidence of an outpatient systemic corticosteroid prescription among patients with prescription insurance coverage ($N = 1909$) was 25.1% (95% CI 23.1–27.1%). It was 24.0% (95% CI 21.9–26.1%) among patients without pre-existing autoimmune disease; 40.5% (95% CI 29.5–51.3%) among patients with pre-existing autoimmune disease by strict criteria; and 30.1% (95% CI 21.9–38.6%) among patients with pre-existing autoimmune disease by relaxed criteria only (Table 3; Supplemental Fig. 3).

In multivariable analyses including adjustment for corticosteroid treatment in 60 days before initiating ICI therapy and for pre-existing COPD, pre-existing autoimmune disease by strict criteria and relaxed criteria only were each associated with shorter time to a corticosteroid prescription (HR 1.93, 95% CI 1.35–2.76 and 1.46, 95% CI 1.13–1.88, respectively; Table 3; Fig. 2). These associations persisted when the cohort was restricted to the $N = 1678$ patients who had not received outpatient corticosteroids in the 60 days before starting the ICI (HR 2.20, 95% CI 1.39–3.47 and 1.50, 95% CI 1.10–2.05, respectively).

Table 1 Association between patient characteristics and time to any hospitalization while on immune checkpoint inhibitors

	N	Unadjusted		Adjusted[b]
		Cumulative incidence of hospitalization by 3 months (%, 95% CI)	HR (95% CI)	HR (95% CI)
All ICI-treated patients	4438	28.6 (27.2–29.9)	–	–
Pre-existing autoimmune disease				
No	3976	28.0 (26.6–29.5)	Reference	Reference
Yes, strict criteria[a]	179	35.0 (27.9–42.3)	1.37 (1.07–1.74)	1.27 (0.998–1.62)
Yes, relaxed criteria[a] only	283	31.7 (26.2–37.3)	1.11 (0.92–1.33)	1.11 (0.91–1.34)
Cancer type				
Lung	1855	29.0 (26.9–31.1)	Reference	Reference
Melanoma	1510	29.0 (26.7–31.4)	0.89 (0.80-0.998)	0.84 (0.70–1.02)
Renal	416	26.2 (22.0-30.6)	0.88 (0.74–1.06)	0.97 (0.80–1.18)
Urothelial	157	29.1 (22.0-36.5)	0.98 (0.74–1.31)	0.99 (0.71–1.39)
Head and neck	216	25.8 (20.1–32.0)	0.97 (0.75–1.25)	1.10 (0.84–1.44)
Other	284	27.9 (22.6–33.5)	1.02 (0.81–1.28)	1.05 (0.83–1.34)
Prior chemotherapy in the year before starting ICI treatment				
No	1641	26.9 (24.7–29.1)	Reference	Reference
Yes	2797	29.5 (27.8–31.2)	1.23 (1.11–1.36)	1.21 (1.07–1.36)
ICI regimen				
Nivolumab	2293	28.2 (26.4–30.1)	Reference	Reference
Pembrolizumab	885	23.9 (21.0-26.8)	0.82 (0.71–0.95)	0.93 (0.79–1.09)
Atezolizumab	115	26.9 (19.0-35.5)	1.01 (0.73–1.41)	0.998 (0.67–1.50)
Ipilimumab	945	30.4 (27.4–33.4)	0.99 (0.87–1.12)	1.39 (1.13–1.71)
Ipilimumab + nivolumab	200	43.2 (36.0-50.1)	1.39 (1.11–1.73)	1.81 (1.40–2.33)
Age				
< 40	196	34.5 (27.7–41.4)	1.19 (0.93–1.52)	1.32 (1.02–1.70)
40–49	333	26.8 (22.0-31.8)	0.96 (0.78–1.18)	0.99 (0.80–1.22)
50–59	932	28.9 (25.9–31.9)	1.01 (0.88–1.17)	1.03 (0.90–1.19)
60–69	1349	27.3 (24.9–29.8)	Reference	Reference
70–79	1081	29.1 (26.3–31.8)	1.01 (0.88–1.15)	0.96 (0.84–1.10)
80+	547	29.0 (25.1–32.9)	1.05 (0.90–1.24)	1.4 (0.88–1.23)
Sex				
Male	2634	27.7 (26.0-29.5)	Reference	Reference
Female	1804	29.7 (27.6–31.9)	1.12 (1.01–1.24)	1.13 (1.02–1.25)
Non-autoimmune comorbidity score [38]				
0	1076	23.3 (20.7–25.9)	Reference	Reference
1	1274	26.8 (24.3–29.3)	1.21 (1.05–1.40)	1.23 (1.07–1.43)
2+	2088	32.4 (30.3–34.4)	1.50 (1.32–1.70)	1.57 (1.36–1.80)

[a]Pre-existing autoimmune disease by strict criteria was defined as an inpatient claim for an autoimmune diagnosis or two outpatient claims at least 30 days apart within the 12 months prior to initiating ICI therapy. Pre-existing autoimmune disease by relaxed criteria was defined as any claim for an autoimmune diagnosis within the 12 months prior to initiating ICI therapy

[b]Multivariable Cox model including all variables listed in the table

Discussion

In this observational study of patients receiving commercially available ICIs for cancer, pre-existing autoimmune disease was not significantly associated with all-cause hospitalizations, but it was associated with a modestly increased rate of hospitalization with a diagnosis consistent with irAE. Pre-existing autoimmune disease was also associated with outpatient corticosteroid treatment after initiating ICI therapy, even among patients who had not filled any corticosteroid prescriptions for at least 60 days before starting ICI therapy. These associations were stronger when pre-existing autoimmune disease was defined according to strict criteria or according to the frequency of medical care for such a

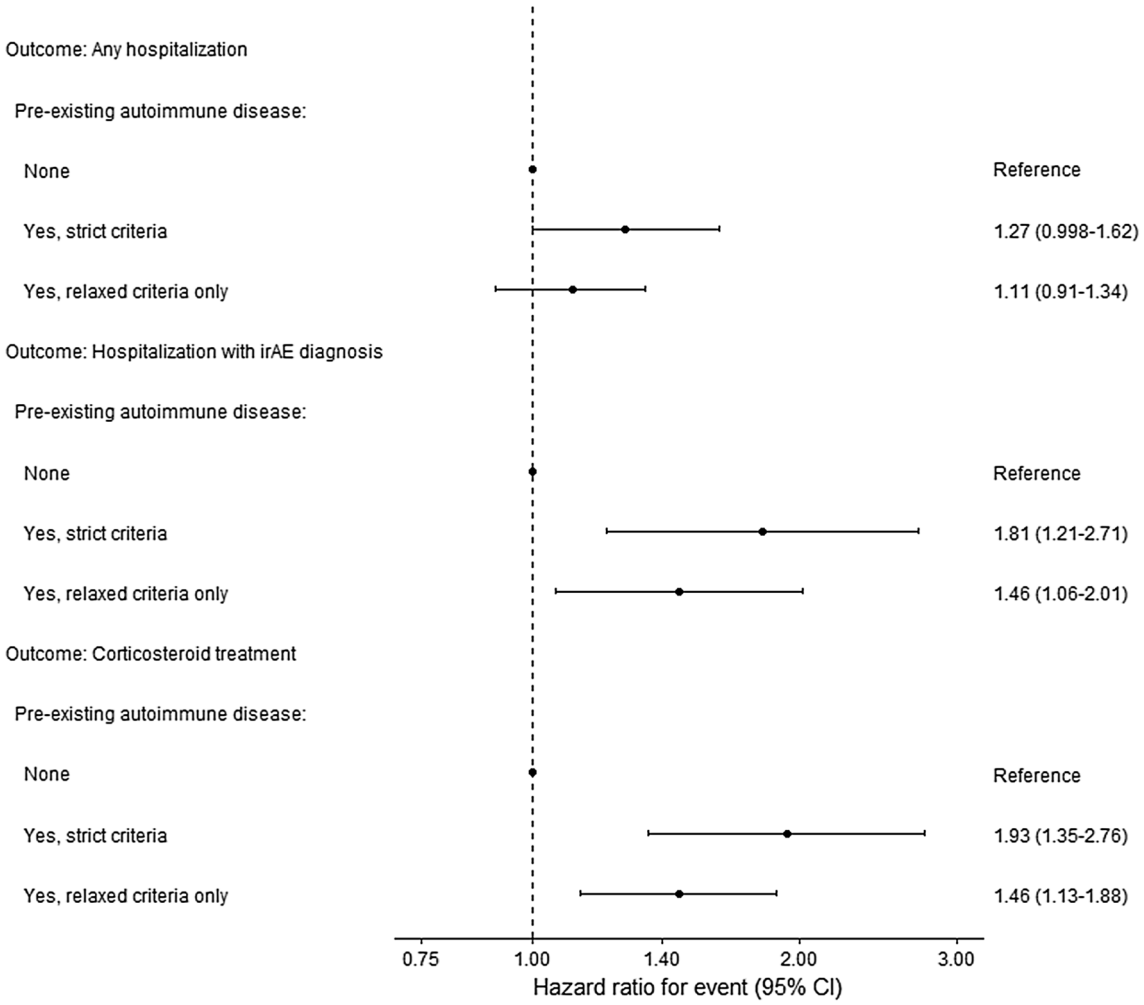

Fig. 2 Associations between measures of underlying autoimmune disease and measures of immune-related adverse events (asterisk results from multivariable time-to-event Cox proportional hazards models with adjustment for cancer type, prior chemotherapy in the year before starting ICI treatment, ICI regimen, age, sex, and non-autoimmune comorbidity score. For the outcome of corticosteroid treatment, the model was additionally adjusted for prior corticosteroid treatment in the 60 days before starting ICI treatment, and for any claim for chronic obstructive pulmonary disease in the 12 months before starting ICI treatment)

diagnosis, suggesting an association between the activity of a pre-existing autoimmune disease and the risk of an irAE. These results provide a broad view of the consequences of ICI therapy for patients across cancer types and care settings, adding important context to case series from academic centers, which have demonstrated similarly modest increases in the risk of an irAE or autoimmune disease flare among patients with pre-existing autoimmune disease [30–32].

Strengths of our analysis included the use of real-world data to understand toxicity patterns among patients not represented in key clinical trials because of pre-existing autoimmune disorders. This provides evidence for practicing clinicians trying to weigh the risks and benefits of immunotherapy for patients with underlying autoimmune disease who are diagnosed with cancer. Unlike some prior reports [30–32], the sample was not restricted to patients treated in academic centers. Still, there are limitations. All patients were privately insured, and generalization to patients who are uninsured or who have Medicaid coverage requires caution. In this claims-based analysis, we analyzed outcomes by examining health services delivered; this represents the best currently available method to address this question at scale across health systems and care settings. Still, our first outcome, all-cause hospitalization, does not readily distinguish between tumor-related symptoms, comorbid illness and ICI toxicity. Many hospitalizations among these patients were likely for complications of cancer and/or progressive disease rather than toxicity. In addition, since our data set consisted specifically of billing claims, further work will be needed to evaluate the utility of hospitalization diagnosis codes for capturing irAEs and cleanly distinguishing between true incident irAEs and flares of pre-existing autoimmune

Table 2 Association between patient characteristics and any hospitalization with a diagnosis consistent with immune-related adverse event while on immune checkpoint inhibitors

	N	Unadjusted		Adjusted[b]
		Cumulative incidence of hospitalization with irAE by 3 months (%, 95% CI)	HR (95% CI)	HR (95% CI)
All ICI-treated patients	4438	7.8 (7.0-8.6)	–	–
Pre-existing autoimmune disease				
No	4259	7.5 (6.7–8.4)	Reference	Reference
Yes, strict criteria[a]	179	11.1 (6.9–16.3)	1.59 (1.06–2.37)	1.81 (1.21–2.71)
Yes, relaxed criteria[a] only	283	10.0 (6.8–13.9)	1.59 (1.16–2.17)	1.46 (1.06–2.01)
Cancer type				
Lung	1855	5.5 (4.5–6.6)	Reference	Reference
Melanoma	1510	11.9 (10.3–13.7)	1.94 (1.57–2.39)	1.10 (0.76–1.59)
Renal	416	5.7 (3.7–8.3)	1.10 (0.76–1.60)	1.04 (0.71–1.53)
Urothelial	157	8.0 (4.4–13.1)	1.35 (0.80–2.26)	1.82 (1.01–3.27)
Head and neck	216	5.8 (3.2–9.6)	1.03 (0.63–1.71)	1.33 (0.79–2.24)
Other	284	4.6 (2.5–7.6)	1.04 (0.67–1.63)	1.25 (0.78-2.00)
Prior chemotherapy in the year before starting ICI treatment				
No	1641	9.0 (7.7–10.5)	Reference	Reference
Yes	2797	7.1 (6.1–8.1)	0.88 (0.73–1.06)	1.24 (1.00-1.54)
ICI regimen				
Nivolumab	2293	5.7 (4.7–6.7)	Reference	Reference
Pembrolizumab	885	5.3 (3.9-7.0)	0.71 (0.52–0.97)	0.78 (0.55–1.10)
Atezolizumab	115	3.7 (12 − 8.7)	0.50 (0.21–1.21)	0.43 (0.16–1.16)
Ipilimumab	945	12.7 (10.6–14.9)	1.96 (1.59–2.41)	2.10 (1.45–3.06)
Ipilimumab + nivolumab	200	21.6 (16.0-27.8)	3.03 (2.19–4.20)	3.03 (2.00-4.59)
Age				
< 40	196	14.1 (9.5–19.5)	1.66 (1.12–2.44)	1.44 (0.96–2.14)
40–49	333	9.2 (6.4–12.8)	1.19 (0.84–1.69)	0.97 (0.68–1.39)
50–59	932	7.4 (5.8–9.3)	0.99 (0.77–1.29)	0.93 (0.72–1.21)
60–69	1349	7.5 (6.2–9.1)	Reference	Reference
70–79	1081	7.5 (6.0-9.2)	0.87 (0.68–1.13)	0.88 (0.68–1.14)
80+	547	6.5 (4.6–8.9)	0.81 (0.58–1.13)	0.84 (0.60–1.18)
Sex				
Male	2634	7.5 (6.5–8.6)	Reference	Reference
Female	1804	8.2 (7.0-9.6)	1.05 (0.87–1.26)	1.11 (0.91–1.34)
Non-autoimmune comorbidity score [38]				
0	1076	8.2 (6.6–10.0)	Reference	Reference
1	1274	7.7 (6.3–9.3)	0.92 (0.72–1.18)	1.08 (0.84–1.39)
2+	2088	7.6 (6.5–8.9)	0.91 (0.73–1.13)	1.30 (1.01–1.66)

ICI immune checkpoint inhibitor, *HR* hazard ratio

[a]Pre-existing autoimmune disease by strict criteria was defined as an inpatient claim for an autoimmune diagnosis or two outpatient claims at least 30 days apart within the 12 months prior to initiating ICI therapy. Pre-existing autoimmune disease by relaxed criteria was defined as any claim for an autoimmune diagnosis within the 12 months prior to initiating ICI therapy

[b]Multivariable Cox model including all variables listed in the table

disease. Finally, in our analysis of outpatient corticosteroid prescriptions, it is probable that not every prescription for steroids in this cohort reflected an irAE. However, such corticosteroid treatment would still constitute immunosuppression in the context of ICI treatment; furthermore, the results persisted despite adjustment for prior corticosteroid treatment and among patients who did not receive corticosteroids in the 60 days prior to ICI treatment.

Importantly, patients with pre-existing autoimmune disease were only included in our analysis if they received

Table 3 Association between patient characteristics and time to corticosteroid prescriptions while on immune checkpoint inhibitors

	N	Unadjusted		Adjusted[b]
		Cumulative incidence of prednisone prescription by 3 months (%, 95% CI)	HR (95% CI)	HR (95% CI)
All ICI-treated patients	1909	25.1 (23.1–27.1)	–	–
Pre-existing autoimmune disease				
No	1704	24.0 (21.9–26.1)	Reference	Reference
Yes, strict criteria[a]	82	40.5 (29.5–51.3)	2.09 (1.49–2.94)	1.93 (1.35–2.76)
Yes, relaxed criteria[a] only	123	30.1 (21.9–38.6)	1.56 (1.20–2.02)	1.46 (1.13–1.88)
Cancer type				
Lung	845	24.3 (21.4–27.4)	Reference	Reference
Melanoma	605	33.5 (29.7–37.4)	1.27 (1.07–1.52)	0.99 (0.72–1.38)
Renal	170	19.3 (13.6–25.8)	0.77 (0.56–1.05)	0.92 (0.66–1.28)
Urothelial	69	11.8 (5.5–20.8)	0.47 (0.25–0.87)	0.42 (0.21–0.82)
Head and neck	100	11.7 (6.2–19.2)	0.46 (0.27–0.78)	0.62 (0.36–1.08)
Other	120	13.0 (7.6–19.9)	0.55 (0.33–0.90)	0.58 (0.34-1.00)
Prior chemotherapy in the year before starting ICI treatment				
No	698	26.9 (23.6–30.3)	Reference	Reference
Yes	1211	24.0 (21.6–26.5)	0.96 (0.81–1.14)	1.06 (0.87–1.30)
ICI regimen				
Nivolumab	1002	22.4 (19.8–25.1)	Reference	Reference
Pembrolizumab	396	14.6 (11.2–18.4)	0.68 (0.53–0.87)	0.78 (0.58–1.04)
Atezolizumab	49	12.4 (5.0-23.3)	0.55 (0.25–1.18)	1.00 (0.47–2.13)
Ipilimumab	368	36.0 (31.1–41.0)	1.46 (1.19–1.79)	1.63 (1.15–2.32)
Ipilimumab + nivolumab	94	58.9 (47.7–68.5)	2.63 (1.97–3.49)	2.97 (2.07–4.27)
Age				
< 40	89	37.7 (27.3–47.9)	1.44 (1.00-2.06)	1.32 (0.91–1.92)
40–49	162	26.8 (19.9–34.1)	1.04 (0.78–1.42)	0.98 (0.72–1.34)
50–59	439	27.3 (23.1–31.7)	1.16 (0.93–1.45)	1.11 (0.89–1.40)
60–69	587	23.7 (20.2–27.3)	Reference	Reference
70–79	444	24.1 (20.1–28.2)	1.01 (0.81–1.27)	1.08 (0.86–1.35)
80+	188	19.2 (13.8–25.3)	0.93 (0.69–1.24)	1.00 (0.73–1.38)
Sex				
Male	1144	24.5 (21.9–27.1)	Reference	Reference
Female	765	26.0 (22.9–29.2)	1.16 (0.98–1.36)	1.04 (0.88–1.23)
Non-autoimmune comorbidity score [38]				
0	489	24.4 (20.5–28.4)	Reference	Reference
1	568	26.8 (23.1–30.7)	1.10 (0.88–1.36)	1.06 (0.84–1.33)
2+	852	24.4 (21.5–27.4)	1.07 (0.87–1.30)	0.93 (0.73–1.19)
Prior corticosteroid[c]				
No	1678	21.4 (19.5–23.5)	Reference	Reference
Yes	231	51.7 (44.8–58.1)	3.33 (2.75–4.05)	3.16 (2.56–3.91)
Prior COPD				
No	1218	23.9 (21.5–26.4)	Reference	Reference
Yes	691	27.2 (23.8–30.6)	1.25 (1.06–1.48)	1.19 (0.96–1.47)

ICI immune checkpoint inhibitor, *HR* hazard ratio, *COPD* chronic obstructive pulmonary disease

[a]Pre-existing autoimmune disease by strict criteria was defined as an inpatient claim for an autoimmune diagnosis or two outpatient claims at least 30 days apart within the 12 months prior to initiating ICI therapy. Pre-existing autoimmune disease by relaxed criteria was defined as any claim for an autoimmune diagnosis within the 12 months prior to initiating ICI therapy

[b]Multivariable Cox model including all variables listed in the table

[c]Within 60 days prior to initiating ICI therapy

ICIs anyway. Patients with very active underlying autoimmune disease may never have received immunotherapy. The rates of pre-existing autoimmune disease in our cohort were lower than those described among Medicare patients with lung cancer [29], which could relate in part to exclusion of patients with highly active autoimmune diseases, but may also relate to the derivation of our cohort from a commercially insured population. Still, it would not be appropriate to generalize our results to imply that patients with severe or highly active pre-existing autoimmune disease may receive ICIs with only a modest increase in the risk of irAEs. This consideration is particularly important in light of the association in our analysis between the frequency of claims for such a disease before starting an ICI, which may be a measure of pre-existing autoimmune disease severity, and the risk of hospitalization for an irAE or requiring treatment with a corticosteroid. This dynamic should be considered when interpreting any report of the safety of ICIs for patients with pre-existing autoimmune conditions [30–32].

In conclusion, among commercially insured patients receiving ICIs for cancer, pre-existing autoimmune disease was not associated with the all-cause hospitalization rate, but it was associated with modest increases in hospitalization with a diagnosis of an irAE and initiation of outpatient corticosteroid treatment. Utilization of checkpoint inhibitors for patients with pre-existing autoimmune diseases who have life-threatening malignancies and lack effective alternative treatments may be reasonable, but close monitoring is needed.

Author contributions Conceptualization: KLK. Data curation: KLK, SY, NP, and ISK. Formal analysis: KLK. Writing/original draft: KLK. Review and editing: all authors.

Funding Supported by the National Cancer Institute (K05CA169384; Deborah Schrag).

Compliance with ethical standards

Conflict of interest Dr. Awad reports serving in a consulting or advisory role to Abbvie; ARIAD Pharmaceuticals; AstraZeneca/MedImmune; Boehringer Ingelheim; Bristol-Myers Squibb; Clovis Oncology; Foundation Medicine; Genentech; Merck; Nektar; Novartis; Pfizer; and Syndax. He reports holding research funding from Bristol-Myers Squibb. A portion of Dr. Palmer's salary is supported by Aetna to provide technical support in facilitating access to data used in this analysis; Dr. Palmer also holds research funding from Union Chimique Belge (UCB). Dr. Schrag reports serving as a consultant to Pfizer and Proteus. The other authors report no conflicts of interest.

Ethical approval and ethical standards The Harvard Medical School Institutional Review Board waived the requirement for approval, deeming analysis of the database not to be human subjects' research. The analysis and publication of the results were approved by Aetna, which provided the data.

References

1. Hodi FS, O'Day SJ, McDermott DF et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723. https://doi.org/10.1056/NEJMoa1003466
2. Robert C, Schachter J, Long GV et al (2015) Pembrolizumab versus Ipilimumab in advanced melanoma. N Engl J Med 372:2521–2532. https://doi.org/10.1056/NEJMoa1503093
3. Weber JS, Hodi FS, Wolchok JD et al (2017) Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 35:785–792. https://doi.org/10.1200/JCO.2015.66.1389
4. Rittmeyer A, Barlesi F, Waterkamp D et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265. https://doi.org/10.1016/S0140-6736(16)32517-X
5. Gandhi L, Rodríguez-Abreu D, Gadgeel S et al (2018) Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. https://doi.org/10.1056/NEJMoa1801005 (**NEJMoa1801005**)
6. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803–1813. https://doi.org/10.1056/NEJMoa1510665
7. Ansell SM, Lesokhin AM, Borrello I et al (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372:311–319. https://doi.org/10.1056/NEJMoa1411087
8. Kaufman HL, Russell J, Hamid O et al (2016) Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 17:1374–1385. https://doi.org/10.1016/S1470-2045(16)30364-3
9. Powles T, O'Donnell PH, Massard C et al (2017) Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 3:e172411. https://doi.org/10.1001/jamaoncol.2017.2411
10. Ferris RL, Blumenschein G, Fayette J et al (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375:1856–1867. https://doi.org/10.1056/NEJMoa1602252
11. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135. https://doi.org/10.1056/NEJMoa1504627
12. Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627–1639. https://doi.org/10.1056/NEJMoa1507643
13. Garon EB, Rizvi NA, Hui R et al (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018–2028. https://doi.org/10.1056/NEJMoa1501824
14. Le DT, Durham JN, Smith KN et al (2017) Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409–413. https://doi.org/10.1126/science.aan6733
15. The Lancet Oncology (2017) Calling time on the immunotherapy gold rush. Lancet Oncol 18:981. https://doi.org/10.1016/S1470-2045(17)30521-1
16. Reck M, Rodríguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus Chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:NEJMoa1606774. https://doi.org/10.1056/NEJMoa1606774
17. Shoushtari AN, Friedman CF, Navid-Azarbaijani P et al (2017) Measuring toxic effects and time to treatment failure for

nivolumab plus ipilimumab in melanoma. JAMA Oncol 10065:1–4. https://doi.org/10.1001/jamaoncol.2017.2391
18. Naidoo J, Page DB, Li BT et al (2015) Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol Off J Eur Soc Med Oncol 26:2375–2391. https://doi.org/10.1093/annonc/mdv383
19. Brahmer JR, Lacchetti C, Schneider BJ et al (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. https://doi.org/10.1200/JCO.2017.77.6385
20. Kristiansen OP, Larsen ZM, Pociot F (2000) CTLA-4 in autoimmune diseases—a general susceptibility gene to autoimmunity? Genes Immun 1:170–184. https://doi.org/10.1038/sj.gene.6363655
21. Ueda H, Howson JMM, Esposito L et al (2003) Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 423:506–511. https://doi.org/10.1038/nature01621
22. Okazaki T, Honjo T (2007) PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 19:813–824. https://doi.org/10.1093/intimm/dxm057
23. Herbst RS, Baas P, Kim DW et al (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387:1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7
24. Antonia SJ, López-Martin JA, Bendell J et al (2016) Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 17:883–895. https://doi.org/10.1016/S1470-2045(16)30098-5
25. Wolchok JD, Kluger H, Callahan MK et al (2013) Nivolumab plus Ipilimumab in advanced melanoma. N Engl J Med. https://doi.org/10.1056/NEJMoa1302369
26. Hamid O, Robert C, Daud A et al (2013) Safety and tumor responses with lambrolizumab (Anti–PD-1) in melanoma. N Engl J Med. https://doi.org/10.1056/NEJMoa1305133
27. Hellmann MD, Rizvi NA, Goldman JW et al (2017) Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 18:31–41. https://doi.org/10.1016/S1470-2045(16)30624-6
28. Postow MA, Chesney J, Pavlick AC et al (2015) Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. N Engl J Med 372:2006–2017. https://doi.org/10.1056/NEJMoa1414428
29. Khan SA, Pruitt SL, Xuan L, Gerber DE (2016) Prevalence of autoimmune disease among patients with lung cancer: implications for immunotherapy treatment options. JAMA Oncol 2:1507–1508. https://doi.org/10.1001/jamaoncol.2016.2238
30. Johnson DB, Sullivan RJ, Ott PA et al (2016) Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2:234–240. https://doi.org/10.1001/jamaoncol.2015.4368
31. Menzies AM, Johnson DB, Ramanujam S et al (2017) Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol Off J Eur Soc Med Oncol 28:368–376. https://doi.org/10.1093/annonc/mdw443
32. Leonardi GC, Gainor JF, Altan M et al (2018) Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. J Clin Oncol. https://doi.org/10.1200/JCO.2017.77.0305
33. In H, Neville BA, Lipsitz SR et al (2012) The role of National Cancer Institute-designated cancer center status: observed variation in surgical care depends on the level of evidence. Ann Surg 255:890–895. https://doi.org/10.1097/SLA.0b013e31824deae6
34. Naidoo J, Page DB, Li BT et al (2015) Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 26:2375–2391. https://doi.org/10.1093/annonc/mdv383
35. Vogelzang NJ, Rusthoven JJ, Symanowski J et al (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–2644. https://doi.org/10.1200/JCO.2003.11.136
36. Kim SY, Servi A, Polinski JM et al (2011) Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther 13:R32. https://doi.org/10.1186/ar3260
37. Ng B, Aslam F, Petersen NJ et al (2012) Identification of rheumatoid arthritis patients using an administrative database: a Veterans Affairs study. Arthritis Care Res (Hoboken) 64:1490–1496. https://doi.org/10.1002/acr.21736
38. Stedman M, Doria-Rose P, Warren J et al (2014) Comorbidity technical report: the impact of different SEER-Medicare claims-based comorbidity indexes on predicting non-cancer mortality for cancer patients. https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity-report.html
39. Austin PC, Lee DS, Fine JP (2016) Introduction to the analysis of survival data in the presence of competing risks. Circulation 133:601–609. https://doi.org/10.1161/CIRCULATIONAHA.115.017719