








# Real-world incidence and impact of pneumonitis in patients with lung cancer treated with immune checkpoint inhibitors: a multi-institutional cohort study

Bruce C Tiu <sup>1,2</sup>, Leyre Zubiri <sup>2</sup>, James Iheke<sup>2</sup>, Vartan Pahalyants <sup>3</sup>, Nicholas Theodosakis<sup>3</sup>, Pearl Ugwu-Dike<sup>3</sup>, Jayhyun Seo<sup>3</sup>, Kimberly Tang<sup>3</sup>, Meghan E Sise<sup>4</sup>, Ryan Sullivan <sup>2</sup>, Jarushka Naidoo <sup>5,6</sup>, Meghan J Mooradian <sup>2</sup>, Yevgeniy R Semenov<sup>3</sup>, Kerry L Reynolds <sup>2</sup>

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YRS and KLR contributed equally.

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For numbered affiliations see end of article.

## Correspondence to

Dr Kerry L Reynolds;  
kreynolds7@partners.org

## ABSTRACT

**Background** Immune checkpoint inhibitors (ICIs) have improved survival and are increasingly used for non-small cell lung cancer. However, use may be limited by immune-related adverse events such as checkpoint-inhibitor pneumonitis (CIP). Literature estimates for CIP incidence are inconsistent. Real-world adherence to guidelines, clinical course, and healthcare utilization in the treatment of CIP has not been described in large cohorts.

**Methods** A combined claims and electronic health record database (TriNetX) was used to identify 13,113 patients with lung cancer treated with programmed cell death receptor/ligand 1 (PD-1/PD-L1) inhibitors, and a propensity score-matched control cohort treated with chemotherapy or targeted therapies. The attributable risk of CIP was calculated in the first 12 months after therapy by comparing the incidence of diagnosis codes for pneumonitis/pneumonia between cohorts. Cases of CIP, identified by the most specific code for drug-induced respiratory conditions, were further analyzed for medication usage, rates of diagnostic bronchoscopy, ICI discontinuation rates, and usage of hospital services compared with patients receiving PD-1/PD-L1 inhibitors who did not develop CIP.

**Results** The attributable risk of pneumonitis to PD-1/PD-L1 inhibitors was 2.49% (95% CI, 1.50% to 3.47%). Median time to onset in the CIP subcohort was 3.9 months (IQR, 2.1–7.3 months). Steroid and antibiotic use increased dramatically after a pneumonitis diagnosis, and 70.2% of patients permanently discontinued ICI therapy. Compared with controls, patients with CIP had more than a threefold increased risk of needing critical care (relative risk 3.59, 95% CI, 2.31 to 5.57) and an increased risk of mortality (HR 2.34, 95% CI, 1.47 to 3.71).

**Conclusions** In a large claims-based analysis, PD-1/PD-L1 inhibitors increase the risk of pneumonitis in patients with lung cancer by 2.49%. Cases of CIP are associated with high healthcare utilization, discontinuation of ICIs, and mortality.

## INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionized the field of oncology and are

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Checkpoint inhibitor pneumonitis (CIP) is an immune-related adverse event (irAE) that occurs after immune checkpoint inhibitor (ICI) therapy, particularly among patients receiving ICIs for lung cancer. However, CIP can resemble pneumonia or chemoradiation-induced pneumonitis, leading to wide-ranging incidence estimates in patients with lung cancer from 3% to 19%.

## WHAT THIS STUDY ADDS

⇒ This large retrospective cohort study of patients with lung cancer from across the USA demonstrates that in the first year after ICI, CIP only marginally increases the risk of pneumonitis and pneumonia-like conditions by 2.49% above the rate caused by chemotherapy or radiation in the first year of therapy. However, patients who develop CIP are very likely to have their ICI therapy discontinued, and have higher rates of critical care admissions and death.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Studies of irAE incidence should be performed with large cohorts and appropriate control groups, as modeled here, to accurately ascertain patients' risk of complications. This study also highlights the need for improved diagnostics for CIP so that patients can be rapidly identified for intervention with immunosuppressive therapy to mitigate the risk of death.

now approved by the Food and Drug Administration (FDA) for over 17 types of cancer, with more than 233,000 patients with cancer in the USA eligible for these treatments yearly.<sup>1</sup> These therapies augment the adaptive immune response by reducing T cell inhibition, promoting the immune-mediated elimination of tumor cells, which leads to

significant and durable anticancer responses in a subset of patients.<sup>2</sup> To date, ICIs that have been approved for clinical use target three different molecules: programmed cell death receptor 1 (PD-1), its ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Unfortunately, increased immune activation from ICIs can result in damage to healthy tissues, as downregulation of checkpoint activity can trigger inflammatory side effects known as immune-related adverse events (irAEs). These toxicities can occur in as many as 70%–90% of patients, and when severe can lead to permanent discontinuation of therapy, increased frequency of hospitalization, and significant healthcare costs.<sup>3–5</sup>

IrAEs can affect nearly every organ system, with incidence varying depending on both type of malignancy and medication class. Checkpoint inhibitor pneumonitis (CIP) manifests most frequently in patients with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC), as well as those treated with PD-1/PD-L1 monotherapy in comparison to CTLA-4 inhibitors, though rates are highest with the anti-PD-1/CTLA-4 combination.<sup>6,7</sup> Symptom severity ranges from asymptomatic (grade 1) to respiratory compromise (grade 4) and can be fatal in more than 10% of cases.<sup>8,9</sup> Recognizing CIP and initiating appropriate treatment is thus a crucial component of drug monitoring in patients with lung cancer on ICIs. Unfortunately, it can be challenging to diagnose CIP as radiographic patterns are non-specific and the differential diagnosis broadly includes disease progression, infection, and chemoradiation-related pneumonitis.<sup>10</sup>

A substantial amount of uncertainty remains regarding the true real-world incidence of CIP. One meta-analysis of clinical trials reported the incidence of CIP in patients with lung cancer treated with PD-1/PD-L1 inhibitors as 4.1% (95% CI, 2.4% to 6.3%).<sup>7</sup> Studies of CIP at single institutions or in real-world large healthcare networks have generally observed a wider range varying from 3% to 11%.<sup>9,11–14</sup> However, two other studies, one mixed trial and real-world study and one claims database analysis, gave estimates up to 19%.<sup>15,16</sup> To date, all published studies have been hampered by limitations such as small sample sizes and a lack of adjustment for baseline rates of pneumonitis or lung comorbidities in cohorts of non-ICI treated patients. Neglecting to compare incidence estimates against chemotherapy and radiation treated patients will overestimate the incidence of pneumonitis, as making the diagnosis of CIP can be imprecise due to difficulty distinguishing it radiographically from pneumonitis of other causes.<sup>10</sup>

To aid practicing oncologists, multiple guidelines for evaluation and treatment have been developed.<sup>5,17–19</sup> These guidelines apply the Common Terminology Criteria for Adverse Events to assign a CIP grade from 1 to 4 depending on the severity of symptoms (ranging from asymptomatic to life-threatening respiratory compromise). All symptomatic patients (grade 2 and above) should have ICI held (or permanently discontinued), receive a broad diagnostic workup including imaging,

and be treated with immunosuppressants. Bronchoscopic evaluation and empiric antibiotics should be considered depending on guideline and grade, although adherence rates by clinicians to these specific recommendations are thus far unknown.

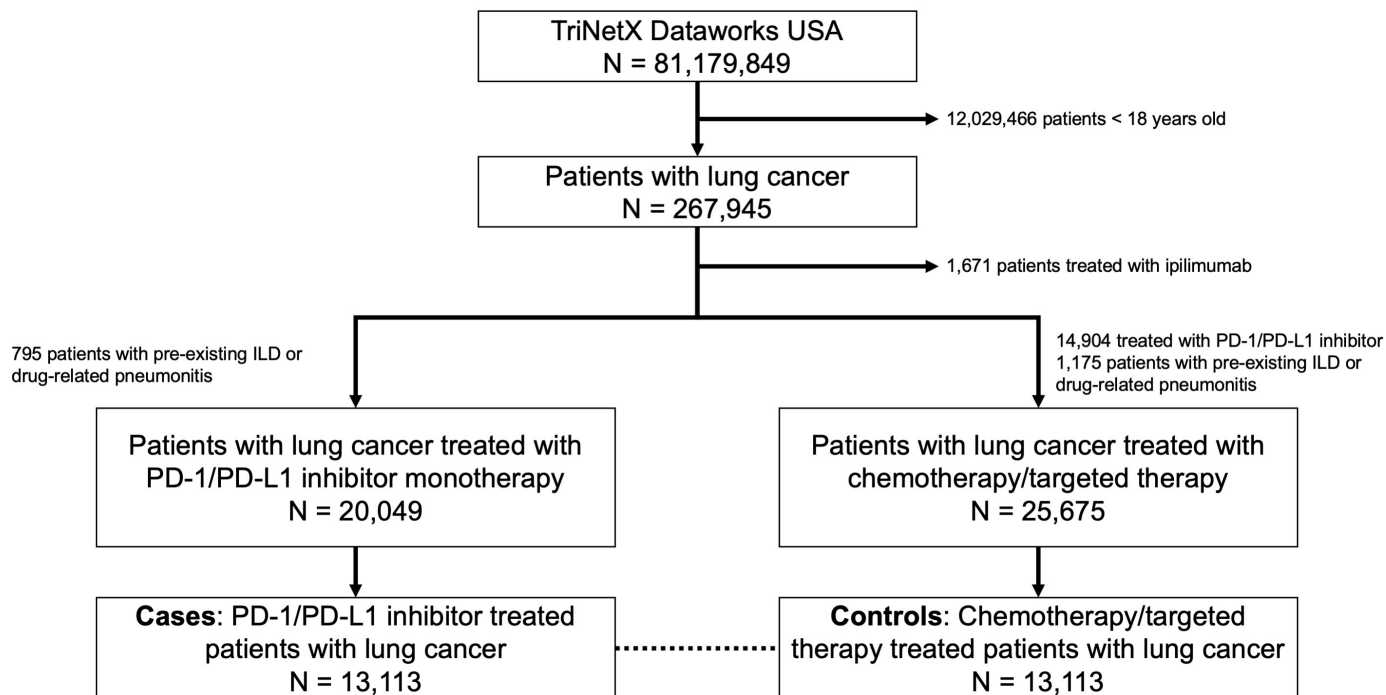
To better understand the real-world incidence of CIP, we analyzed patients with lung cancer from TriNetX, a database network of both claims and electronic health record (EHR) data. This cohort allowed assessment of incidence and adherence to clinical guidelines for diagnosis and management of CIP, as well as the effects of CIP on healthcare utilization, cancer treatment course, and mortality in this large, diverse, geographically widespread patient cohort.

## METHODS

### Patient population

A retrospective cohort study was performed with de-identified data from TriNetX Dataworks, which includes more than 81 million US patients across 49 healthcare organizations. TriNetX (Cambridge, Massachusetts, USA) is a research network containing electronic medical records, which include diagnoses, procedures, medications, and laboratory values, and is compliant with the Health Insurance Portability and Accountability Act.

A search query identified a cohort of patients at risk for CIP by selecting those who had lung cancer and received treatment with PD-1 or PD-L1 inhibitors as any line of therapy during the study period from January 1, 2014, to June 30, 2021 (figure 1). Lung cancer was defined using International Classification of Diseases 10th revision (ICD-10) codes, which capture both patients with NSCLC and small cell lung cancer. The index event for analyses was the initiation of an approved PD-1/PD-L1 inhibitor subsequent to a diagnosis of lung cancer in adult patients 18 years of age and older; agents queried were pembrolizumab, nivolumab, durvalumab, or atezolizumab. A 1:1 propensity score-matched control cohort of contemporaneous patients with lung cancer who were treated with an approved chemotherapy or targeted therapy agent, but without exposure to any ICI at any time, was generated and matched at the time of therapy initiation (online supplemental table S1). Propensity score matching was performed using ‘greedy nearest neighbor matching’ and a caliper of 0.1 pooled SD, with covariates of age, sex, race, smoking status, history of lung conditions (chronic obstructive pulmonary disease, asthma, and pleural conditions), history of radiation therapy or radiation pneumonitis in the 6 months prior, line of therapy for ICI or chemotherapy/targeted therapy, and the presence of ICD-10 codes for regional or distant metastases (ie, ‘secondary malignant neoplasms’). Pulmonary and radiation covariates were selected based on known risk factors for pneumonitis.<sup>20</sup> Exclusion criteria included ipilimumab use (to exclude combination immunotherapy). No limitations were placed on historical or concurrent chemotherapy/targeted therapy use. Similar matched



**Figure 1** Flow chart to select PD-1/PD-L1 inhibitor-treated patients with lung cancer. PD-1/PD-L1 inhibitors included those with FDA approval for lung cancer, namely pembrolizumab, nivolumab, durvalumab, and atezolizumab. Pre-existing ILD or pneumonitis was defined as the presence of a relevant code prior to index event (immune checkpoint inhibitors initiation or advanced lung cancer diagnosis). ILD was defined as the presence of ILD codes J84.11, J84.89, or J84.9, and drug-related pneumonitis was defined as the presence of codes J70.2, 3, 4, 8, or 9. Patients with lung cancer were enrolled between January 1, 2014, and June 30, 2021. FDA, Food and Drug Administration; ILD, interstitial lung disease; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1.

cohorts were generated for renal cell carcinoma, melanoma, and an aggregate group of gastrointestinal cancers based on initiation of approved PD-1/PD-L1 inhibitors for each cancer type.

### Study outcomes

The primary outcome of CIP incidence was the attributable risk of pneumonitis to PD-1/PD-L1 inhibitors, calculated by comparing the incidence of a composite outcome of pneumonitis/pneumonia in patients with lung cancer treated with ICI against those treated with traditional chemotherapy or targeted agents. CIP incidence could not be assessed directly given the absence of an entity-specific ICD-10 code, and so key ICD-10 codes that might be used by clinicians to code for this uncertain diagnosis were identified based on literature review of previous irAE analyses and selected based on author consensus.<sup>16 21</sup> The composite outcome of pneumonitis/pneumonia was defined as presence of a new ICD-10 code for interstitial lung disease (ILD), a drug-induced respiratory condition, or pneumonia within 1 year of index event, with index event defined as therapy initiation (ICI or chemotherapy/targeted therapy) after lung cancer diagnosis. The excess risk of this outcome in patients treated with ICIs represented the attributable risk on top of baseline rates of chemotherapy and targeted therapy-induced pneumonitis and pneumonia in patients not treated with ICIs. Patients with a prior diagnosis of ILD

or drug-induced respiratory conditions were excluded to eliminate potential confounders and increase specificity and accuracy of patient selection. The at-risk observation period of 1 year was selected based on prior reports that the preponderance of CIP occurs within 12 months of ICI start.<sup>9 11 15</sup>

For the secondary analysis of CIP evaluation and management and impact on healthcare utilization, a subset of patients was selected based on the presence of a new code for a drug-induced respiratory condition within 1 year of ICI initiation (herein, the CIP cohort) based on the findings that this code was significantly enriched among ICI-treated patients who developed the composite pneumonitis/pneumonia outcome. Evaluation and management measures in the CIP cohort were compared with their use in the same patients prior to CIP diagnosis. For healthcare utilization outcomes and all-cause mortality, a propensity score-matched control cohort of patients treated with ICIs but without diagnosis codes for drug-induced respiratory conditions or ILD was generated for comparison using the same covariates as before.

All ICD-10, Current Procedural Terminology (CPT), RxNorm concept unique identifier (RXCUI), and TriNetX codes utilized to generate these cohorts are listed in online supplemental table S1. RXCUI codes were used to identify medications used, including ICIs, antibiotics, and immunosuppressive agents. The line of therapy for

ICI was determined using TriNetX-coded values. Bronchoscopy use was recorded from CPT codes. Healthcare utilization outcomes regarding frequency of emergency department (ED) visits, hospitalization, and use of critical care services were assessed using a combination of TriNetX and CPT codes.

### Statistical analysis

Baseline characteristics were reported by count and percentage for categorical variables and means and SD for continuous variables. Risk differences are presented with 95% CIs. P values are uncorrected and based on Z-tests or McNemar's tests. Outcomes affecting less than 10 patients in TriNetX are rounded to 10 for patient anonymity and are used as such in all calculations. To account for lead-time bias during the time to onset of CIP, a landmark analysis at 6 months after ICI initiation was performed, and HRs and log-rank p values are reported from Cox proportional hazards models. Patients were censored at the last recorded data point available. Statistical analyses were performed in real-time using the TriNetX platform.

## RESULTS

### Incidence of CIP

#### Incidence of CIP in lung cancer

267,945 patients with lung cancer from 48 healthcare organizations were identified in the study period. After applying the exclusions shown in [figure 1](#), we identified 20,049 patients with lung cancer who received a PD-1/PD-L1 inhibitor, and 25,675 patients with lung cancer who received chemotherapy/targeted therapy. Following propensity-score matching, a sufficiently close match was found for 13,113 of the 20,049 ICI-treated patients. Baseline characteristics in [table 1](#) demonstrate that most patients analyzed received ICI or chemotherapy/targeted therapy as first-line therapy (71.4% vs 72.7%), and many had metastatic disease at the beginning of the study window (at least 45.9% of each cohort had one of three codes indicating secondary sites of disease). PD-1 inhibitors were used more frequently than PD-L1 inhibitors. The cohorts notably had representation across several racial groups.

The incidence of the composite pneumonitis/pneumonia outcome, which encompassed diagnoses of ILD, drug-induced respiratory conditions, and pneumonia, was 22.0% in the PD-1/PD-L1-treated group and 19.6% in the PD-1/PD-L1-untreated group ([figure 2A,B](#)). The 1-year risk of pneumonitis/pneumonia attributable to PD-1/PD-L1 treatment, in excess of the baseline rate in chemotherapy/targeted therapy-treated patients, was 2.49% (95% CI, 1.50% to 3.47%). Incidence contributions from each component of the pneumonitis/pneumonia definition are shown in online supplemental table S2. At 2 years, the attributable risk increases to 3.49% (95% CI, 2.46% to 4.51%), and sensitivity analyses at further time points demonstrated minimal further increase in the attributable risk.

### Incidence of CIP across tumor types

Attributable risk varied across tumor types. Similar propensity-matched cohorts of patients treated with ICIs or chemotherapy/targeted therapy were generated for three additional cancer types: RCC (N=1845), gastrointestinal cancers (N=4813), and melanoma (N=2427). Patient flow and baseline characteristics for non-lung cancer types are available in online supplemental figure S1 and table S3. At 1 year, patients with RCC had an excess risk comparable to patients with lung cancer at 2.98% (95% CI, 1.03% to 4.93%), while patients with gastrointestinal cancers had a lower excess risk of CIP at 1.64% (95% CI, 0.38% to 2.90%). Use of ICIs in patients with melanoma led to similar rates of pneumonitis/pneumonia as chemotherapy/targeted therapy, with a risk difference of -0.25% (95% CI, -1.86% to 1.36%). ([figure 2C,D](#)).

The aggregate diagnosis codes used for the attributable risk analysis were expected to be non-specific and to capture cases that were not clinically confirmable CIP. To increase specificity, we defined patients with 'CIP' using only diagnosis codes for drug-induced respiratory conditions, capturing 254 patients from 26 healthcare organizations. This code was highly enriched in the ICI-treated group in the incidence analysis (1.3% vs 0.3% in patients not exposed to ICIs,  $p<0.0001$ ) (online supplemental table S2). Median time to onset of CIP in this group was 119 days (IQR 63–223 days), or 3.90 months ([figure 3A](#)).

### Evaluation and management of CIP in lung cancer

Baseline characteristics of the lung cancer cohort that subsequently developed CIP are shown in [table 2](#). A sufficient match was found for all 254 cases of CIP, and baseline demographics, comorbidities, and cancer-related factors were well matched between the two groups.

Glucocorticoids were frequently administered to patients with suspected CIP. The number of patients receiving prednisone doubled from the 30 days prior to CIP diagnosis to the 30 days following, from 92 (36.2%) to 212 (83.5%) of 254 patients,  $p=0.01$  ([figure 3B](#)). Use of methylprednisolone, typically deployed in the inpatient setting for high-grade irAEs, rose from 57 (22.4%) to 145 (57.1%) patients post-diagnosis in the same 30-day intervals ( $p=0.005$ ). One hundred and seventeen (46.1%) patients diagnosed with CIP were admitted to the hospital and treated with methylprednisolone within the first 30 days of diagnosis.

Use of second-line immunosuppressants was found to be infrequent. Only infliximab was represented in TriNetX, with 17 (6.7%) patients receiving it within 30 days, and 20 (7.9%) patients receiving it within 90 days of pneumonitis diagnosis. Up to 14 (5.5%) patients were treated with intravenous immune globulin within 90 days. TriNetX reported less than 10 patients received either mycophenolate mofetil or cyclophosphamide in the first month after pneumonitis, which did not increase when analysis was extended out to 90 days after pneumonitis diagnosis. Antibiotic use, specifically agents commonly used for respiratory infections such as cephalosporins,

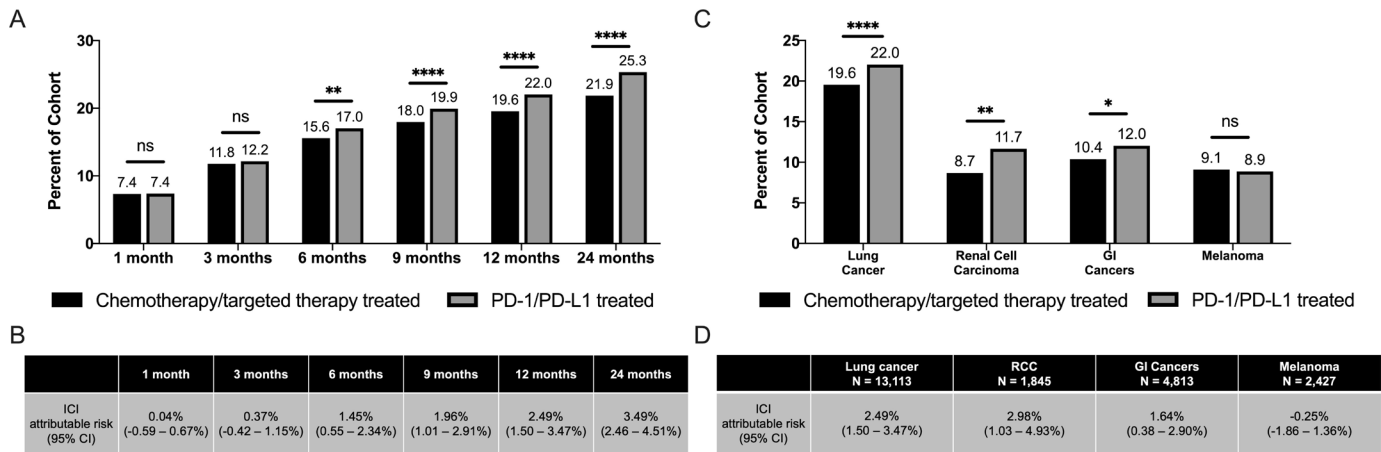
**Table 1** Baseline characteristics of propensity score-matched lung cancer cohort

Characteristic	Unmatched		Matched	
	Chemotherapy/ targeted therapy- treated controls	ICI-treated cases	Chemotherapy/ targeted therapy- treated controls	ICI-treated cases
N	25,675	20,049	13,113	13,113
<b>Demographics</b>				
Age at index*—mean (SD)	65.9 (10.9)	67.0 (10.2)	67.0 (10.5)	67.1 (10.3)
Male sex*—no. (%)	12,362 (48.2)	10,709 (53.4)	6956 (53.0)	6885 (52.5)
Race*—no. (%)				
White	18,308 (71.3)	14,974 (74.7)	9839 (75.0)	9710 (74.0)
Black/African American	3258 (12.7)	2569 (12.8)	1664 (12.7)	1698 (12.9)
Asian	804 (3.1)	377 (1.9)	224 (1.7)	258 (2.0)
American Indian/Native American	72 (0.3)	62 (0.3)	45 (0.3)	42 (0.3)
Native Hawaiian/Pacific Islander	21 (0.1)	≤10 (0.1)	≤10 (0.1)	≤10 (0.1)
Unknown	3212 (12.5)	2057 (10.3)	1336 (10.2)	1397 (10.7)
<b>Cancer</b>				
Secondary malignancy*—no. (%)				
Lymph nodes	5877 (22.9)	5404 (27.0)	3093 (23.6)	3204 (24.4)
Respiratory/digestive	6147 (23.9)	6064 (30.2)	3644 (27.8)	3621 (27.6)
Other	8803 (34.3)	9436 (47.1)	6024 (45.9)	6021 (45.9)
Neuroendocrine tumor	246 (1.2)	246 (1.2)	120 (0.9)	146 (1.1)
Type of therapy				
PD-1	–	15,257 (76.1)	–	10,478 (79.9)
PD-L1	–	4892 (24.4)	–	2720 (20.7)
Chemotherapy	18,789 (73.2)	5205 (46.2)	9707 (74.0)	4851 (37.0)
Targeted therapy	6933 (27.0)	82 (0.4)	3431 (26.2)	72 (0.6)
Line of therapy*—no. (%)				
First line	21,888 (85.3)	6821 (34.0)	9357 (71.4)	9537 (72.7)
Second line	1462 (5.7)	5563 (27.7)	1465 (11.2)	1240 (9.5)
Third and above	466 (1.8)	2160 (10.8)	457 (3.5)	548 (4.2)
<b>Coexisting conditions</b>				
Personal history of nicotine dependence*	7198 (28.0)	6999 (34.9)	4090 (31.2)	4270 (32.6)
Prior encounter for antineoplastic radiation therapy*	1637 (6.4)	2192 (10.9)	934 (7.1)	1073 (8.2)
History of acute radiation pneumonitis*	91 (0.4)	179 (0.9)	66 (0.5)	61 (0.5)
History of prior lung disease				
Chronic obstructive pulmonary disease*	6669 (26.0)	5765 (28.8)	3414 (26.0)	3592 (27.4)
Asthma*	1408 (5.5)	960 (4.8)	534 (4.1)	640 (4.9)
Pleural disease*	6225 (24.2)	4662 (23.3)	2931 (22.4)	2931 (22.4)

Demographic data were obtained from coded TriNetX data. Type of ICI counts patients who received both a PD-1 or PD-L1 inhibitor at any point in both categories. Line of therapy data were not available for every patient.  
 \*Starred variables were used for propensity score matching.  
 ICI, immune checkpoint inhibitors ; PD-1, programmed cell death receptor 1 ; PD-L1, programmed cell death ligand 1 .

macrolides, and piperacillin, increased from the 30-day window preceding diagnosis to the same interval following diagnosis of CIP (figure 3C).

Bronchoscopy was rarely utilized in the workup of patients with lung cancer with suspected CIP. Only 33 (13.0%) patients underwent bronchoscopy in the 30 days



**Figure 2** Incidence of pneumonitis/pneumonia in PD-1/PD-L1 inhibitor-treated patients with cancer. (A) Incidence of pneumonitis/pneumonia in the first year after PD-1/PD-L1 inhibitor or chemotherapy/targeted therapy initiation among patients with lung cancer. (B) Tabulated risk difference of pneumonitis/pneumonia attributable to PD-1/PD-L1 inhibitors compared with chemotherapy/targeted therapy among patients with lung cancer. (C) Incidence of pneumonitis/pneumonia in the first year after PD-1/PD-L1 inhibitor or chemotherapy/targeted therapy initiation across cancer types. (D) Tabulated risk difference of pneumonitis/pneumonia attributable to PD-1/PD-L1 inhibitors compared with or chemotherapy/targeted therapy across cancer types. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ . GI, gastrointestinal; ICI, immune checkpoint inhibitors; RCC, renal cell carcinoma; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1.

following diagnosis, compared with fewer than 10 (3.9%) in the 30 days before,  $p < 0.0001$  (figure 3D). Rates in the 90 days prior and after were numerically similar.

As irAEs can lead to delays in therapy and even discontinuation of ICIs, discontinuation rates of any PD-1/PD-L1 inhibitor were calculated (figure 3E). Of 225 patients who received a PD-1/PD-L1 inhibitor in the 90 days prior to CIP diagnosis, 158 (70.2%) discontinued ICI therapy in the 90 days following. Therapy discontinuation and CIP resulted in substantial mortality, with 83 (32.7%) patients dying within 90 days following CIP.

### Healthcare utilization of patients with CIP

To understand the burden of CIP on patients, the use of healthcare services by ICI-treated patients following a CIP diagnosis was compared with use by patients without a suspected CIP diagnosis. Utilization at various time points within the first 12 months from ICI initiation were analyzed, given that the majority of CIP cases occur in the first 2–10 months (figure 3A). Patients who developed CIP visited the ED, were admitted to the hospital, and were admitted to the intensive care unit (ICU) at significantly higher rates than controls (figure 4A). ED visits were more frequent among patients who subsequently developed pneumonitis, with a relative risk of 1.54 (95% CI, 1.20 to 1.96) by 12 months. This representation of ED visits does not overlap with ED visits that led to hospitalization, which are coded separately in TriNetX. By 12 months, 223 (87.8%) ICI-treated patients with pneumonitis had been admitted to the hospital at least once, compared with 131 (51.6%) patients without pneumonitis, with a relative risk of 1.70 (95% CI, 1.50 to 1.93) (figure 4A). Median time from initiation of ICI to first hospitalization was 89 days versus 233 days. Critical care admissions and ICU stays were also significantly more

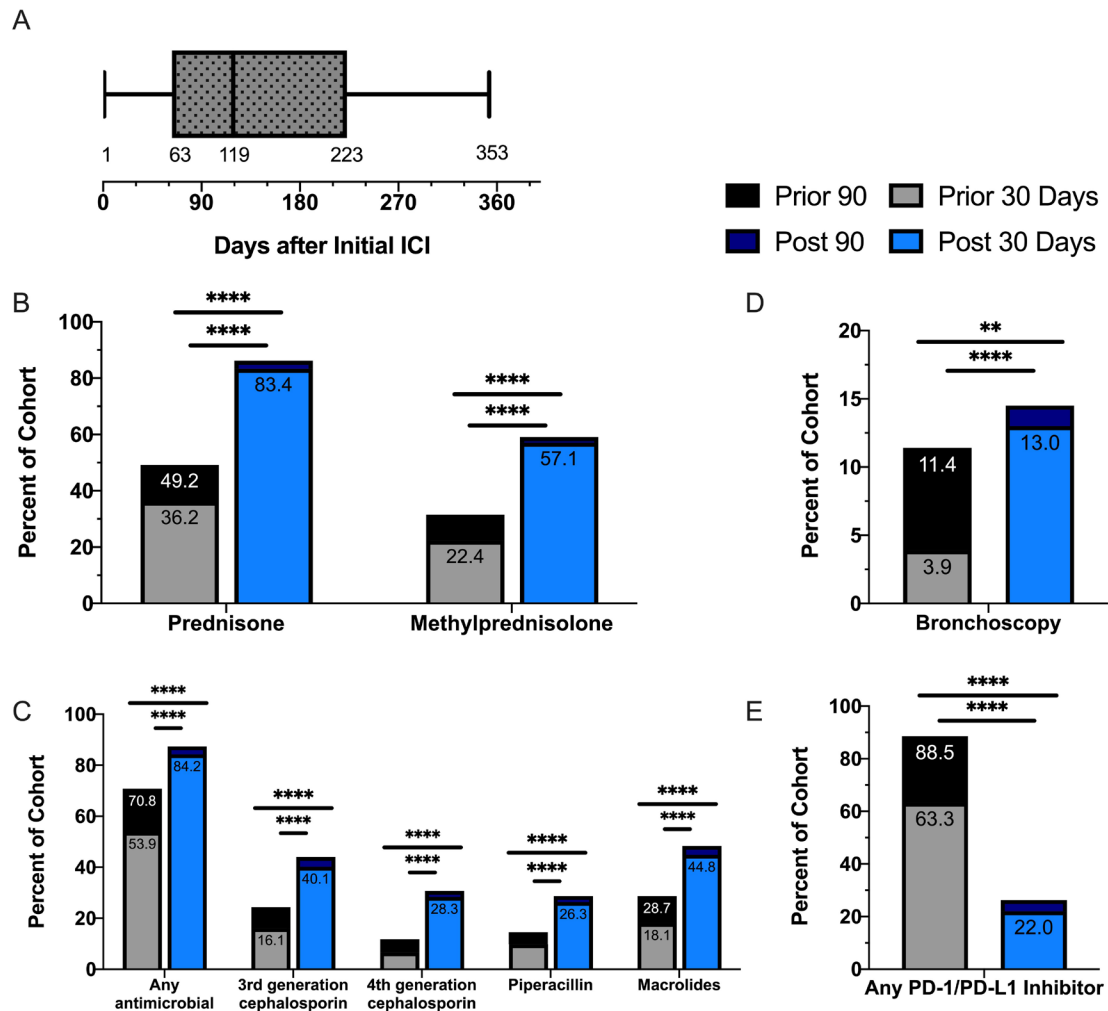
common in patients with pneumonitis, with a relative risk of 3.59 (95% CI, 2.31 to 5.57).

### Outcomes of patients with CIP

A landmark analysis of survival was performed in 102 (40.2%) patients who developed CIP within 6 months of ICI initiation. Kaplan-Meier analysis of those patients surviving from the landmark time onwards demonstrated a HR of 2.34 (95% CI, 1.47 to 3.71) for death, log-rank  $p$  value of 0.0002 (figure 4B). The median survival in the CIP cohort was 428 days (IQR, 312–1184) compared with 1240 days (IQR, 477 – not reached) in the cohort without pneumonitis.

### DISCUSSION

The increasing use of ICIs necessitates careful risk assessment by oncologists and subspecialists to suspect, diagnose, and manage irAEs such as pneumonitis. To our knowledge, this is the largest multi-institutional study to date examining the risk of CIP in real-world practice of patients with lung cancer, analyzing a cohort of over 13,000 patients across 48 healthcare organizations to define a 1-year attributable risk of 2.49%. This may underestimate the absolute incidence, which has been reported between 3% and 11% based on clinical trials and small mixed real-world and single institution studies.<sup>7 12 14 22 23</sup> Our result of 2.49% represents the excess risk above baseline rates of clinically and radiographically similar entities among a control group of patients treated with chemotherapy or targeted therapy. Clinicians should suspect CIP in patients treated with ICI more than in those treated with chemotherapy or radiation, but the incidence of pneumonitis at the population level is only marginally increased.



**Figure 3** Evaluation and management of CIP. (A) Time to onset of CIP in patients with lung cancer treated with PD-1/PD-L1 inhibitors. Annotations indicate the median, IQR, and range. (N=254). (B) Steroid use increases dramatically from before to after a diagnosis of CIP. Longer bars indicate statistical comparisons between prior to post 90 days, while shorter bars depict comparisons between prior to post 30 days. (C) Antibiotics use increases dramatically from before to after a diagnosis of CIP. (D) Bronchoscopy is not utilized significantly in patients with lung cancer with pneumonitis. (E) Utilization of PD-1/PD-L1 inhibitors declines from before to after a diagnosis of CIP. \*\* $P < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ . CIP, checkpoint-inhibitor pneumonitis; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1.

We replicated previously reported estimates from large claims databases studies (19%) by noting a 1-year composite pneumonitis/pneumonia incidence of 22.0%, but highlight that the baseline risk of pneumonitis/pneumonia in the control group was already 19.6% due to high infection risk, chemoradiation exposure, and baseline pulmonary diseases in patients with lung cancer.<sup>15 16</sup> Nineteen per cent grossly overestimates the true risk of CIP by including the incidence of many entities that may appear clinically similar to CIP but are distinct and present in patients not exposed to ICI. These results highlight the essential need for controlled studies in the field of irAE research and indicates that the excess risk of pneumonitis above baseline is tolerable.

A slightly longer time to onset (3.9 months, IQR 2.1–7.3 months) was observed in the CIP subcohort, consistent with more recent studies of CIP after PD-1/PD-L1 monotherapy.<sup>11</sup> This exceeds earlier estimates of 2–3 months,

which may reflect delayed diagnosis in non-clinical trial settings or selection of a subset of patients with a later-onset CIP phenotype.<sup>15</sup> High suspicion should be maintained for CIP, as cases continued to be captured until the 1-year time point. While most irAEs occur early, some late cases may manifest over a year after initiation, necessitating ongoing clinical awareness.<sup>24 25</sup>

Variation of CIP risk across tumor types was consistent with previously described findings in clinical trials.<sup>7</sup> This study demonstrated that CIP occurs more frequently in lung cancer (attributable risk above baseline pneumonitis risk of 2.49%) and RCC (2.98%). Smoking, as a risk factor for underlying lung disease as well as lung cancer and RCC, is one potential contributor to the tumor-specific variation in risk, although was controlled for in this study. This study offers one of the first estimates of real-world CIP risk in gastrointestinal cancers (1.64%). Patients with melanoma had similar pneumonitis risk

**Table 2** Baseline characteristics of propensity score-matched pneumonitis cohort

Characteristic	Unmatched		Matched	
	ICI-treated controls without CIP	ICI-treated cases with CIP	ICI-treated controls without CIP	ICI-treated cases with CIP
N	19,504	254	254	254
<b>Demographics</b>				
Age at index*—mean (SD)	66.9 (10.2)	68.2 (9.7)	69.1 (9.7)	68.2 (9.7)
Male sex*—no. (%)	10,400 (53.3)	157 (61.8)	173 (68.1)	157 (61.8)
Race/ethnicity*—no. (%)				
White	14,570 (74.7)	183 (72.0)	187 (73.6)	183 (72.0)
Black/African American	2506 (12.8)	23 (9.1)	32 (12.6)	23 (9.1)
Asian	368 (1.9)	≤10 (3.9)	≤10 (3.9)	≤10 (3.9)
American Indian/Native American	60 (0.3)	0 (0)	0 (0)	0 (0)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	1990 (10.2)	43 (16.9)	30 (11.8)	43 (16.9)
<b>Cancer</b>				
Secondary malignancy*—no. (%)				
Lymph nodes	5202 (26.7)	104 (40.9)	107 (42.1)	104 (40.9)
Respiratory/digestive	5855 (30.0)	106 (41.7)	100 (3.4)	106 (41.7)
Other	9198 (47.2)	116 (45.7)	115 (45.3)	116 (45.7)
Neuroendocrine tumor	241 (1.2)	≤10 (3.9)	≤10 (3.9)	≤10 (3.9)
Type of ICI*				
PD-1	14,901 (76.4)	186 (73.2)	193 (76.0)	186 (73.2)
PD-L1	4751 (24.4)	71 (28.0)	63 (24.8)	70 (27.6)
ICI line of therapy*—no. (%)				
First line	6648 (34.1)	96 (37.7)	117 (46.1)	96 (37.7)
Second line	5396 (27.7)	70 (27.6)	70 (27.6)	70 (27.6)
Third and above	2105 (10.8)	23 (9.1)	13 (5.1)	23 (9.1)
<b>Coexisting conditions</b>				
Personal history of nicotine dependence*	6737 (34.5)	128 (50.4)	140 (55.1)	128 (50.4)
Prior encounter for antineoplastic radiation therapy*	2109 (10.8)	48 (18.9)	48 (18.9)	48 (18.9)
History of acute radiation pneumonitis*	169 (0.9)	≤10 (3.9)	≤10 (3.9)	≤10 (3.9)
History of prior lung disease				
Chronic obstructive pulmonary disease*	5565 (28.5)	100 (39.4)	85 (33.5)	100 (39.4)
Asthma*	922 (4.7)	17 (6.7)	≤10 (3.9)	17 (6.7)
Pleural disease*	4470 (22.9)	91 (35.8)	84 (33.1)	91 (35.8)

Demographic data were obtained from coded TriNetX data. Type of ICI counts patients who received both a PD-1 or PD-L1 inhibitor at any point in both categories. Line of therapy data were not available for every patient.

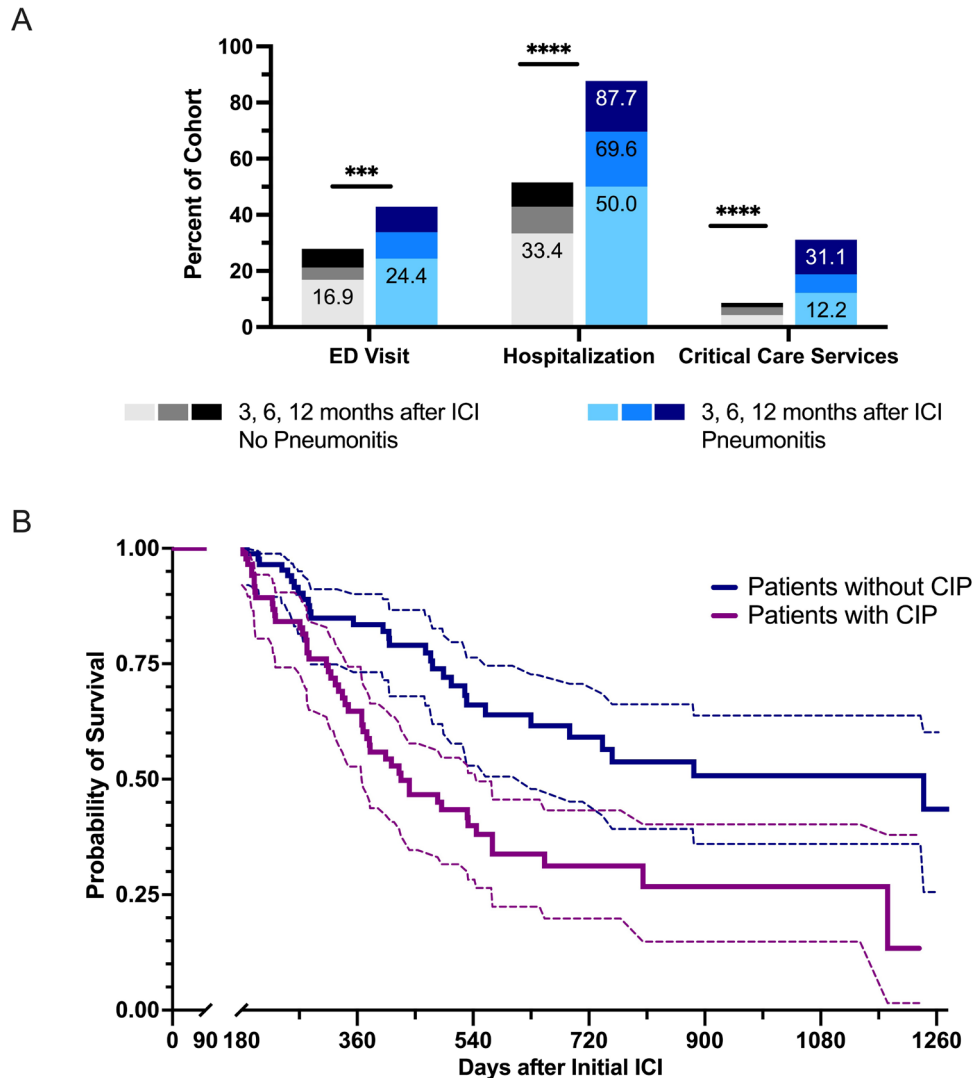
\*Starred variables were used for propensity score matching.

CIP, checkpoint-inhibitor pneumonitis ; ICI, immune checkpoint inhibitors ; PD-1, programmed cell death receptor 1 ; PD-L1, programmed cell death ligand 1 .

when treated with ICI compared with chemotherapy or targeted therapies (−0.25%, non-significant), suggesting that patients without tumor or lifestyle factors that predispose to pulmonary injury may be at lower risk of de novo immune-related injury in that tissue. This result aligns with separate estimates of pneumonitis incidence after melanoma therapies, with comparable rates observed

between PD-1/PD-L1 monotherapy (1.6% in melanoma) and chemotherapy/targeted therapy agents used in melanoma such as BRAF and/or MEK inhibitors (1%–3%) and taxanes (1%–5%).<sup>7 26–30</sup> Underlying lung disease and prior radiotherapy, risk factors that predispose to CIP (or indistinguishable entities), were controlled for in this study.<sup>20 31</sup>





**Figure 4** Healthcare utilization and outcomes of patients with CIP. (A) Representation of the per cent of patients in each cohort who were cared for at an emergency department, inpatient unit, or intensive care unit-level unit at 3 months, 6 months, and 12 months after initiating ICI. Patients who are subsequently admitted to the hospital are not coded as having an ED visit. Statistical comparisons depicted are at 12 months after ICI initiation. (N=254) \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ . (B) Kaplan-Meier survival curves comparing outcomes of patients who developed CIP (purple) compared with those who did not (blue) by a landmark time of 6 months. Only a subset of patients who met the landmark criteria (102/254) were analyzed. Patients were censored at death or time of last data point in their record. Survival probability and 95% CI are graphed. CIP, checkpoint-inhibitor pneumonitis; ED, emergency department; ICI, immune checkpoint inhibitors.

A significant limitation of large database studies, including this one, is reliance on billing codes and other coded data to identify events accurately. The codes to identify potential cases of CIP for the incidence analysis were intentionally selected to be sensitive, given that clinicians may bill using one of any number of codes when the diagnosis of CIP is unclear. Previous analyses of CIP have used chart review and adjudication to identify cases, but this traditional approach is also fraught with specificity challenges given that the radiographic hallmarks of CIP can mimic infection, progression of cancer, or unrelated inflammatory disorders.<sup>10</sup> In our study, by selecting cases and controls with a similar extent of disease and at a similar time point in disease course (based on metastatic disease codes and line of therapy), we are able to rely on

the size of the TriNetX cohorts to identify the differential incidence of pneumonitis. While the structure of our incidence analysis did not permit estimation of the absolute risk of CIP, we were able to use the smaller, more stringently defined cohort who developed codes for drug-induced respiratory conditions to profile patients whose characteristics strongly resembled those of true patients with CIP. While the subcohort was unlikely to capture all patients within the database with definitive CIP, the large size of the TriNetX database, as well as integration with EHR data, allowed in-depth evaluation of diagnostic and management practices for a specific irAE at a sample size larger than most previous real-world descriptive studies of CIP.

Future studies of CIP should focus on refining clinical features and optimal diagnostic algorithms, given the lack of a current gold standard for diagnosis. Despite appearing in irAE management guidelines, we demonstrate that bronchoscopy continues to be infrequently used in the diagnostic workup of pneumonitis, as only 3.9% and 13.0% of patients underwent bronchoscopy in the 30 days prior to or following CIP diagnosis.<sup>5 18 19</sup> As diagnostic biomarkers of CIP remain elusive, the main value of invasive bronchoscopy is identification of an alternative etiology (eg, disease progression, infectious pneumonia). Current clinical practice appears to favor empiric respiratory-appropriate antibiotics. However, with increasing data that prior or concurrent use of antibiotics can have a potentially negative impact on ICI responses, improved diagnostics are sorely needed to be able to refine antibiotic use to those with true clinical need.<sup>32–34</sup>

Our data reiterates that glucocorticoids are the backbone of treatment for suspected irAEs and were frequently administered in our CIP subset. We identified that 46.1% of patients with CIP were treated with methylprednisolone in the hospital, which exceeds the reported rate of grade 3 CIP and likely captures a mixture of persistent grade 2 and high grade (grade 3–5) CIP.<sup>7</sup> Unlike glucocorticoids, second-line immunosuppressants were rarely used. We suspect infrequent use could be due to a low incidence of steroid-refractory CIP cases or due to hesitancy to initiate advanced immunosuppression in the absence of a clearly preferred immunosuppressive treatment approach. Conclusions about these questions are not feasible when using large data sets, demonstrating the value of complementary institutional in-depth chart-review level analysis. As refractory pneumonitis is uncommon, future studies of pooled data from multiple institutions or prospective, multicenter trials such as NCT04438382, which compares infliximab to intravenous immunoglobulin in refractory pneumonitis, will be helpful to evaluate which second line immunosuppressants are most effective in the management of pneumonitis and other irAEs.<sup>35</sup>

For most patients who experience CIP, ICIs are often permanently discontinued with low rates of rechallenge. In our cohort, only 29.8% of patients who received PD-1/PD-L1 inhibitors in the 90 days prior to CIP diagnosis continued to receive therapy in the following 90 days. This is consistent with rechallenge rates reported at multiple large academic centers, indicating only a limited number of patients with CIP have benign courses that allow therapy to continue.<sup>9 11 12</sup>

A substantial portion of patients with CIP are admitted to the hospital or an ICU for care, a gap that widens rapidly in the first year after ICI initiation for patients with pneumonitis compared with those without, resulting in increased patient morbidity as well as financial costs. Consistent with other published data, our landmark survival analysis identifies that patients with CIP have substantially worse overall survival than those without.<sup>36 37</sup> Previously, it had been proposed that pulmonary irAEs

associate with increased survival in patients with NSCLC.<sup>38</sup> However, worsened survival is consistent with our findings of a high rate of ICI discontinuation and significant hospitalization burden, which may lead to delays in further disease-directed therapy as well as decline in functional status.

A limitation of our study and others from the TriNetX database is the lack of granularity regarding individual patient courses, such as pneumonitis grade, steroid responsiveness, or imaging findings. Combining data from many healthcare organizations may capture inaccurate coding due to diverse institutional coding practices. Nevertheless, these results allow for representation of practices across the USA rather than single-institution experiences. Another weakness of using diagnosis codes is that timing of pneumonitis codes in the record may not align with the onset of symptoms. Still, accounting for this would only strengthen the management results, as steroid and antibiotic treatments that precede the official chart code are counted in the baseline steroid/antibiotic rates presented here. Coded data around pneumonitis is further limited by the fact that pneumonitis is a difficult clinical diagnosis to distinguish from pneumonia or other respiratory processes.

This work demonstrates proof of concept that irAE incidence and impact can feasibly be studied in a controlled fashion using large integrated claims and EHR databases. Additionally, single irAEs can be isolated and profiled, depending on the availability of specific diagnosis codes. Standardization of diagnostic definitions for CIP would aid in uniformity of recognition and management. The generation of specific ICD-10 diagnostic codes for irAEs would also greatly aid in increasing specificity in large data sets. This study adds to the existing literature by providing an additional estimate of CIP incidence in patients with lung cancer and identifying common management strategies and healthcare utilization patterns.

#### Author affiliations

<sup>1</sup>Harvard Medical School, Boston, Massachusetts, USA

<sup>2</sup>Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

<sup>3</sup>Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts, USA

<sup>4</sup>Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

<sup>5</sup>The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<sup>6</sup>Beaumont RCSI Cancer Centre, Beaumont Hospital and the RCSI University of Health Sciences, Dublin, Ireland

**Twitter** Bruce C Tiu @BTiu, Jarushka Naidoo @DrJNaidoo, Yevgeniy R Semenov @EugeneSemenovMD and Kerry L Reynolds @kreynoldsMD

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**Patient consent for publication** Not applicable.

**Ethics approval** As per TriNetX's website, any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval.

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**Data availability statement** Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Raw data may be obtained from a third party (TriNetX) and are not publicly available. TriNetX is a live network and subsequent queries may return results with mild variability.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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#### ORCID iDs

Bruce C Tiu <http://orcid.org/0000-0002-2815-5579>

Leyre Zubiri <http://orcid.org/0000-0003-4226-7443>

Vartan Pahalyants <http://orcid.org/0000-0003-4671-620X>

Ryan Sullivan <http://orcid.org/0000-0001-5344-6645>

Jarushka Naidoo <http://orcid.org/0000-0002-3470-8686>

Meghan J Mooradian <http://orcid.org/0000-0002-8289-8015>

Kerry L Reynolds <http://orcid.org/0000-0002-7793-654X>

#### REFERENCES

- Haslam A, Gill J, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for immune checkpoint inhibitor drugs. *JAMA Netw Open* 2020;3:e200423.
- Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018;8:1069–86.
- Arnaud-Coffin P, Maillet D, Gan HK, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. *Int J Cancer* 2019;145:639–48.
- George S, Bell EJ, Zheng Y, et al. The impact of adverse events on health care resource utilization, costs, and mortality among patients treated with immune checkpoint inhibitors. *Oncologist* 2021;26:e1205–15.
- Haanen JBAG, Carbone F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28:iv119–42.
- Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol* 2017;28:2377–85.
- Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol* 2016;2:1607–16.
- Wang DY, Salem J-E, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 2018;4:1721–8.
- Delaunay M, Cadranet J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J* 2017;50:1700050. doi:10.1183/13993003.00050-2017
- Kalisz KR, Ramaiya NH, Laukamp KR, et al. Immune checkpoint inhibitor therapy-related pneumonitis: patterns and management. *Radiographics* 2019;39:1923–37.
- Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol* 2017;35:709–17.
- Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res* 2016;22:6051–60.
- Atchley WT, Alvarez C, Saxena-Beem S, et al. Immune checkpoint inhibitor-related pneumonitis in lung cancer. *Chest* 2021;160:731–42.
- Hindocha S, Campbell D, Ahmed M, et al. Immune checkpoint inhibitor and radiotherapy-related pneumonitis: an informatics approach to determine real-world incidence, severity, management, and resource implications. *Front Med* 2021;8:764563.
- Suresh K, Voong KR, Shankar B, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. *J Thorac Oncol* 2018;13:1930–9.
- Cathcart-Rake EJ, Sangaralingham LR, Henk HJ, et al. A population-based study of immunotherapy-related toxicities in lung cancer. *Clin Lung Cancer* 2020;21:421–7.
- Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer* 2021;9:e002435.
- National Comprehensive Cancer Network. *Management of immunotherapy-related toxicities (version 4.2021)*, 2021.
- Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 2021;39:4073–126.
- Cui P, Liu Z, Wang G, et al. Risk factors for pneumonitis in patients treated with anti-programmed death-1 therapy: a case-control study. *Cancer Med* 2018;7:4115–20.
- Chiu T, Yamamoto C, Niu F, et al. 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. *Pern J* 2020;25:1.
- Bjørnhart B, Hansen KH, Jørgensen TL, et al. Efficacy and safety of immune checkpoint inhibitors in a Danish real life non-small cell lung cancer population: a retrospective cohort study. *Acta Oncol* 2019;58:953–61.
- Fujimoto D, Yoshioka H, Kataoka Y, et al. Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study. *Lung Cancer* 2018;119:14–20.
- Martins F, Sofiya L, Sykietis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019;16:563–80.
- Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691–7.
- Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med* 2012;367:107–14.
- Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012;367:1694–703.
- Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17:1248–60.
- Dimopoulou I, Bamias A, Lyberopoulos P, et al. Pulmonary toxicity from novel antineoplastic agents. *Ann Oncol* 2006;17:372–9.
- Graziano SL, Herndon JE, Socinski MA, et al. Phase II trial of weekly dose-dense paclitaxel in extensive-stage small cell lung cancer: cancer and leukemia group B study 39901. *J Thorac Oncol* 2008;3:158–62.
- Zhai X, Zhang J, Tian Y, et al. The mechanism and risk factors for immune checkpoint inhibitor pneumonitis in non-small cell lung cancer patients. *Cancer Biol Med* 2020;17:599–611.
- Derosa L, Hellmann MD, Spaziano M, et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. *Ann Oncol* 2018;29:1437–44.
- Pinato DJ, Howlett S, Ottaviani D, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. *JAMA Oncol* 2019;5:1774–8.



- 34 Tinsley N, Zhou C, Tan G, *et al.* Cumulative antibiotic use significantly decreases efficacy of checkpoint inhibitors in patients with advanced cancer. *Oncologist* 2020;25:55–63.
- 35 National Library of Medicine (US). Clinicaltrials.Gov. identifier NCT04438382: infliximab and intravenous immunoglobulin therapy in treating patients with Steroid-Refractory pneumonitis, 2020. Available: <https://clinicaltrials.gov/ct2/show/NCT04438382> [Accessed 31 Dec 2020].
- 36 Fukihara J, Sakamoto K, Koyama J, *et al.* Prognostic impact and risk factors of immune-related pneumonitis in patients with non-small-cell lung cancer who received programmed death 1 inhibitors. *Clin Lung Cancer* 2019;20:442–50.
- 37 Suresh K, Naidoo J. Lower survival in patients who develop pneumonitis following immunotherapy for lung cancer. *Clin Lung Cancer* 2020;21:e169–70.
- 38 Ricciuti B, Genova C, De Giglio A, *et al.* Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol* 2019;145:479–85.