ORIGINAL ARTICLE

Pneumonitis in Non–Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors

Karthik Suresh, MD,[a,*] Khinh Ranh Voong, MD,[b] Bairavi Shankar, BS,[c] Patrick M. Forde, MD,[c,d] David S. Ettinger, MD,[c] Kristen A. Marrone, MD,[c,d] Ronan J. Kelly, MD,[c,d] Christine L. Hann, MD,[c,d] Benjamin Levy, MD,[c,d] Josephine L. Feliciano, MD,[c,d] Julie R. Brahmer, MD,[c,d] David Feller-Kopman, MD,[a] Andrew D. Lerner, MD,[a] Hans Lee, MD,[a] Lonny Yarmus, DO,[a] Franco D'Alessio, MD,[a] Russell K. Hales, MD,[b] Cheng Ting Lin, MD,[e] Kevin J. Psoter, PhD,[f] Sonye K. Danoff, MD, PhD,[a] Jarushka Naidoo, MBBCh[c,d]

[a]*Division of Pulmonary Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[b]*Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[c]*Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[d]*Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins University, Baltimore, Maryland*
[e]*Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland*
[f]*Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland*

Received 5 July 2018; revised 22 August 2018; accepted 27 August 2018
Available online - 26 September 2018

ABSTRACT

Checkpoint inhibitor pneumonitis (CIP) is an immune-related adverse event that can occur after initiation of anti–programmed death 1/programmed death ligand 1 immune checkpoint inhibitor (ICI) therapy for the treatment of multiple malignancies, including NSCLC. However, the incidence of CIP has not been previously examined in a population that included both trial-enrolled and non–trial-enrolled patients with advanced NSCLC. Furthermore, risk factors and other clinical characteristics associated with CIP severity are not known. In this study, we retrospectively examined clinical characteristics, incidence, and risk factors for CIP in a cohort of 205 patients with NSCLC, all of whom received anti–programmed death 1/programmed death ligand 1 ICIs. Our results demonstrate a higher incidence of CIP (19%) than previously reported in clinical trials (3%–5%). Our data also suggest that tumor histologic type may be a risk factor for CIP development. We observed a wide range of time to onset of CIP (median 82 days), with high morbidity and mortality associated with higher-grade CIP regardless of degree of immunosuppression. Our data provide new insight into the epidemiology and clinical

*Corresponding author.

Disclosure: Dr. Voong reports grants from the Lung Cancer Research Foundation and Radiation Oncology Institute and personal fees from ASCO Advantage outside the submitted work. Dr. Forde reports grants from and service on an advisory board of Bristol-Myers Squibb, grants from and service on an advisory board of AstraZeneca, and grants from Novartis outside the submitted work. Dr. Ettinger reports personal fees from BeyondSpring Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, and Guardant Health and grants from Golden Biotech outside the submitted work. Dr. Marrone reports personal fees from Compugen and Takeda outside the submitted work. Dr. Kelly reports grants from and service on an advisory board of Bristol-Myers Squibb, grants from and service on an advisory board of Eli Lilly and Company, and service on a data monitoring committee and advisory board for Novartis outside the submitted work. Dr. Hann reports personal fees for advisory board participation and compensation to his institution for clinical trial participation from Bristol-Myers Squibb and personal fees for consultation from Genentech outside the submitted work. Dr. Levy reports personal fees from AstraZeneca, Celgene, Eli Lilly and Company, Genentech, and Takeda outside the submitted work. Dr. Brahmer reports an uncompensated advisory board participation and consultation arrangement with Bristol-Myers Squibb, grants from Bristol-Myers Squibb and AstraZeneca/MedImmune, and personal fees from Genentech during conduct of the study, as well as an uncompensated advisory board participation and consultation arrangement with Bristol-Myers Squibb, grants from Bristol-Myers Squibb and AstraZeneca/MedImmune, and personal fees from Genentech outside the submitted work. Dr. Naidoo reports grants and other from AstraZeneca, other from Bristol-Myers Squibb, grants from Merck, and other from Takeda outside the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Karthik Suresh, MD, Johns Hopkins Asthma and Allergy Building, 5501 Hopkins Bayview Circle, Baltimore, MD 21224. E-mail: ksuresh2@jhmi.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.08.2035

characteristics of CIP. Further studies are needed to increase CIP pharmacovigilance, improve risk stratification, and refine diagnostic algorithms for the diagnosis and management of this potential life-threatening complication of ICI therapy.

Keywords: NSCLC; Immunotherapy; Checkpoint inhibitors; Immune-related adverse events; Checkpoint inhibitor pneumonitis

Introduction

Advanced NSCLC is a malignancy with poor prognosis and typically low 1- and 5-year survival rates.[1,2] Despite use of platinum- and paclitaxel-based chemotherapeutic agents and the recent addition of biologics such as vascular endothelial growth factor inhibitors (bevacizumab and ramucirumab), survival outcomes remain poor.[3] Recently, the use of immunotherapy-based treatment regimens has shown great promise in improving overall survival and progression-free survival in NSCLC. These results, along with the poor efficacy of conventional chemotherapy, have led to recent approvals of immune checkpoint inhibitors (ICIs) as first-line therapies in advanced-stage NSCLC. Use of ICIs that target regulatory pathways, which usually suppress antitumor killing by T cells, effectively "release the brakes" on antitumor activity. However, this unique mechanism of action also produces unique toxicities, termed *immune-related adverse events* (irAEs). For instance, colitis, rash, hepatitis, thyroiditis, neuropathy, nephritis, myocarditis, and inflammatory arthritis have all been reported with ICI therapy.[4,5] One particularly worrisome irAE is the development of pneumonitis as a result of ICI therapy, which is termed *checkpoint inhibitor pneumonitis* (CIP).

The incidence of CIP has been reported to be between 3% and 5% in clinical trial settings,[6,7] but the incidence of CIP in NSCLC in real-world settings is not known. CIP is a serious complication that typically presents with cough, dyspnea, and hypoxia along with pulmonary infiltrates on chest imaging (as illustrated in Fig. 1). CIP is typically responsive to corticosteroid therapy; however, in selected cases, patients may experience development of significant dyspnea and/or need for supplemental oxygen (i.e., Common Toxicity Criteria for Adverse Events [CTCAE] grade 3 or higher [see Supplementary Table 1]), discontinuation of ICI therapy, and possibly initiation of additional immunosuppressives. As described recently by Naidoo et al., though rare, high-grade CIP is associated with very high morbidity and mortality.[8]

Despite this, little is known about the risk factors for CIP and whether incidence differs across patient subgroups. To answer these and other fundamental questions regarding the epidemiology and pathobiology of CIP, we (as part of an irAE initiative) conducted a retrospective study of patients with NSCLC who were receiving ICI in order to better understand factors that may contribute to CIP in this at-risk patient population.

Methods

Study Population

We performed a retrospective study to determine the frequency of CIP and risk factors for its development in patients with advanced NSCLC who were treated with anti–programmed death 1/programmed death ligand 1 ICIs at Johns Hopkins Hospital between 2007 to 2017. All patients received anti–programmed death 1/programmed death ligand 1 ICI therapy either as standard of care treatment or part of a clinical trial. All patients, including those in whom ICI therapy was discontinued (because of development of CIP or for other reasons) were followed over time from the time of initiation of ICI therapy. Follow-up included an inpatient visit or phone call by a member of the research team. Date of last follow-up was identified as either the date of death, last in-person patient visit, or last research phone call. Patients who began undergoing ICI therapy before July 2017 were included in the database. An earlier version of this database was used in a prior report by our group in examining relationships between radiation and pneumonitis outcomes.[9] Onset of CIP was defined as either early (<6 months from initiation of ICI therapy) or late (>6 months after initiation of therapy).

Data Collection

Patient demographics, tumor histologic type, chemotherapy regimen, and outcomes were collected by abstraction from electronic medical records. ICI agent(s) and the presence or absence of combination ICI therapy (for example, concurrent treatment with one of more checkpoint inhibitors) and use of prior chemotherapy was collected. Quantification of radiographic characteristics was performed by a thoracic radiologist (C. T. L.). The database was then locked for addition of new patients (July 2017), and vital status (alive or dead) for these patients was updated through December 2017. The median follow-up for patients was 240 days (range 0–2415 days)

Outcome Definition

The diagnosis of CIP was determined by the treating oncologist (P. F., D. E., K. M., R. K., C. H., B. L., J. F., J. B., or J. N.) and confirmed by a multidisciplinary irAE team

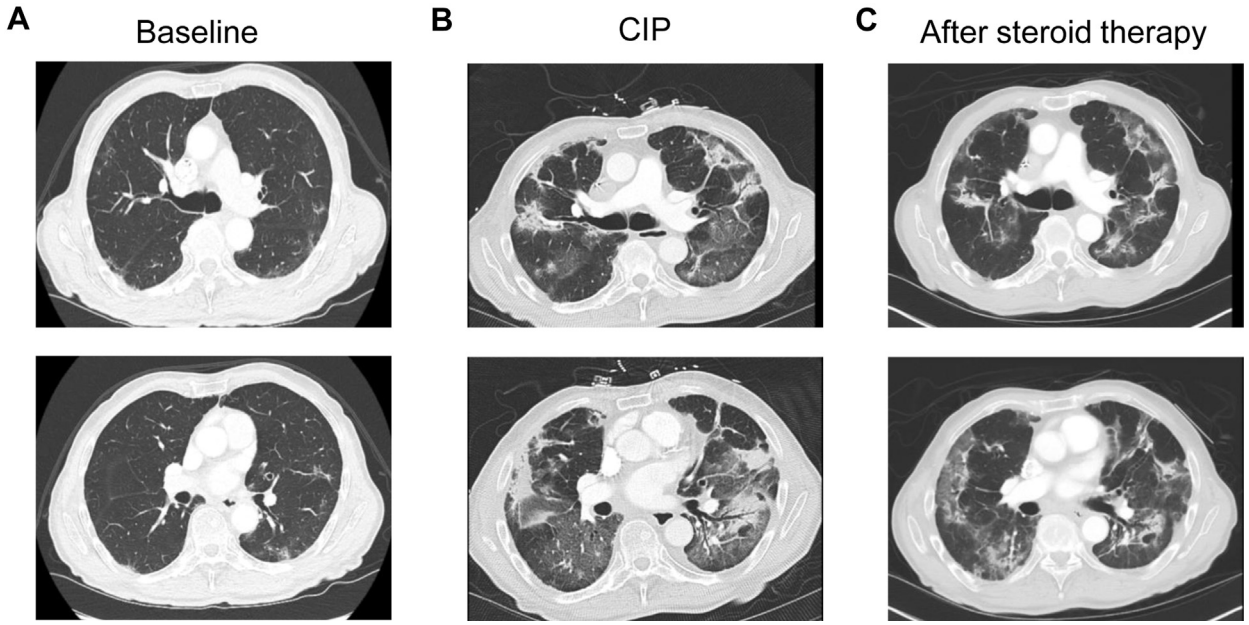


Figure 1. Representative computed tomography images from an immune checkpoint inhibitor–treated patient after initiation of immune checkpoint inhibitor therapy (*A*), at time of checkpoint inhibitor pneumonitis (CIP) diagnosis (*B*), and after 1 week of steroid therapy for CIP (*C*).

consisting of a pulmonologist (S. D. or K. S.), radiologist (C. L.) and a second oncologist (J. N.). Patients with SCLC, confirmed infection, progression of tumor (per the Response Criteria in Solid Tumors criteria), heart failure, or other alternative etiologies were excluded. Specifically, infection was excluded in patients with either (1) bronchoalveolar lavage culture when possible and/or (2) sputum culture and clinical determination of likelihood of infection on the basis of white blood cell count, fever, history, and examination. Furthermore, a diagnosis of CIP was held if clear evidence of tumor progression (based on either radiography, sputum or bronchoalveolar lavage, results of cytopathologic testing, or evidence of cancer spread elsewhere) was noted. For patients who experienced development of CIP, date of CIP diagnosis, maximum CIP grade (as defined by the CTCAE, version 4.0), and clinical outcome of pneumonitis management were also recorded. Improvement was defined as a decrease in oxygen requirement, increase in exercise capacity, or improvement in radiographic infiltrates after commencement of CIP treatment. Conversely, worsening was defined as lack of improvement in oxygen requirement and exercise capacity after 72 hours of steroid therapy.

Statistical Analysis

Demographic and clinical characteristics of patients who experienced development of CIP were compared with those who did not experience development of CIP by using Student's *t* test for continuous variables (age) or the chi-square test (categorical variables). Overall and subgroup-specific CIP incidence rates (IRs) were estimated as the number of observed CIP events divided by the person-time follow-up in years. Person-time was taken as the time from diagnosis to administrative censoring for those who did not experience development of CIP and the time from initiation of ICI therapy to diagnosis of CIP among those who experienced development of CIP. Comparison among the characteristics are reported as IR ratios (IRRs) with corresponding 95% confidence intervals (CIs). To determine whether CIP IRs differed by tumor stage, we repeated the previously described analyses while stratifying by ICI therapy (monotherapy versus combination ICI), smoking status (current/former smoker versus never-smoker and pack-years), presence or absence of antecedent chemotherapy, or tumor histologic type.

Risk factors for time to development of pneumonitis and univariate survival analysis were modeled by using a Cox proportional hazards model. Proportionality assumption and outlier testing for this model were performed, respectively, by (1) visual inspection of Schoenfeld residuals followed by chi-square testing of Cox regression model fit and (2) examination of deviance residuals. Risk of CIP at fixed time points was modeled by using logistic regression. All analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria) statistical environment[10] and Stata software (version 14, StataCorp, College Station, TX).

Results

A total of 205 patients with advanced NSCLC were identified, of whom 39 (19%) experienced development CIP during follow-up. Demographic characteristics were similar between patients who did and did not experienced development of CIP (Table 1). However, the distribution of tumor types among the patients with and without CIP was significantly different; although adenocarcinoma was the predominant NSCLC tumor type in both groups, squamous cell carcinoma comprised a larger proportion of the patients with nonadenocarcinoma) in the group with CIP ($p < 0.05$). Though not significant ($p = 0.07$), the number of patients receiving pembrolizumab was lower in the group with CIP. Approximately 40% of patients were not enrolled in any clinical trials, whereas the remaining 60% of patients were enrolled in various ICI trials.

The median time to pneumonitis development was 82 days (interquartile range 20–183 days [Supplementary Fig. 1 and Supplementary Table 2]). The cumulative incidence of CIP, by grade, is shown in Figure 2. Although most pneumonitis tended to occur early (i.e., <6 months after initiation of ICI treatment) irrespective of grade, 81% of cases of CIP occurring more than 6 months after initiation of therapy (9 of 11) were grade 2 or 3. The cases of high-grade CIP (CTCAE grade ≥3) occurred earlier than lower-grade CIP did; however, the number of high-grade CIP cases was small (n = 7).

CIP IRs and IRRs within demographic subgroups are presented in Figures 3 and 4. The CIP IR was higher in females (0.25/person-year versus 0.19/person-year in males), as well as with combination ICI (0.28/person-year versus 0.18/person-year with monotherapy), though these rates were not statistically significant. Interestingly, squamous or other histologic type (i.e., nonadenocarcinoma and nonsquamous carcinoma) was associated with a significantly higher CIP IR (IRR = 2.29, 95% CI: 1.08–4.83) than other histologic types (IRR = 4.32, 95% CI: 1.24–12.19).

Table 1. Baseline Characteristics

Characteristic	CIP (n = 39)	No CIP (n = 166)	All Patients (N = 205)	*p* Value
Median age, y (IQR)	68 (10.5)	68 (14)	68 (14)	0.38
Female sex, n (%)	18 (47)	73 (44)	91 (44)	0.84
Race, n (%)				0.8
Caucasian	30 (76.9)	132 (79.5)	162 (79)	
African American	7 (17.9)	28 (16.8)	35 (17)	
Other	2 (5.1)	6 (3.6)	8 (3.9)	
Smoking, n (%)				0.72
Current	2 (5)	13 (7.8)	15 (7.3)	
Former	31 (79)	120 (72.2)	151 (73.6)	
Never	6 (15)	33 (19.8)	39 (19)	
Tumor histologic type, n (%)				0.005
Squamous	16 (41)	41 (24.6)	57 (27.8)	
Adenocarcinoma	18 (46)	114 (68.6)	132 (64.3)	
Other[a]	5 (13)	11 (6.6)	16 (7.8)	
Initial cancer stage, n (%)				0.396
I	1 (2.6)	17 (10)	18 (8.7)	
II	5 (12.8)	12 (7.2)	17 (8.3)	
III	13 (33.3)	44 (26.5)	57 (27.8)	
IV	19 (48.7)	90 (54.2)	109 (53.1)	
Unknown	1 (2.6)	3 (1.8)	4 (1.9)	
Prior chemotherapy, n (%)	26 (66)	125 (75)	151 (73.6)	0.52
Prior surgery, n (%)	7 (17.9)	41 (24.6)	48 (23.4)	0.27
ICI agent, n (%)				0.07
Nivolumab	36 (92.3)	124 (74.6)	160 (78.0)	
Pembrolizumab	2 (5.1)	21 (12.6)	23 (11.2)	
Durvalumab	1 (2.5)	10 (6.0)	11 (5.3)	
Combination therapy, n (%)				0.12
CTLA4 therapy	8 (20.5)	11 (6.6)	19 (9.2)	
Other ICI	1 (2.5)	6 (3.6)	7 (3.4)	
Investigational therapy	5 (12.8)	26 (15.6)	31 (15.1)	
Chemotherapy	2 (5.1)	4 (2.4)	6 (2.9)	

[a]Other includes large cell neuroendocrine carcinoma (2), mesothelioma (2), atypical carcinoid (2), and sarcomatoid carcinoma (1).
CIP, checkpoint inhibitor pneumonitis; IQR, interquartile range; CTLA4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor.

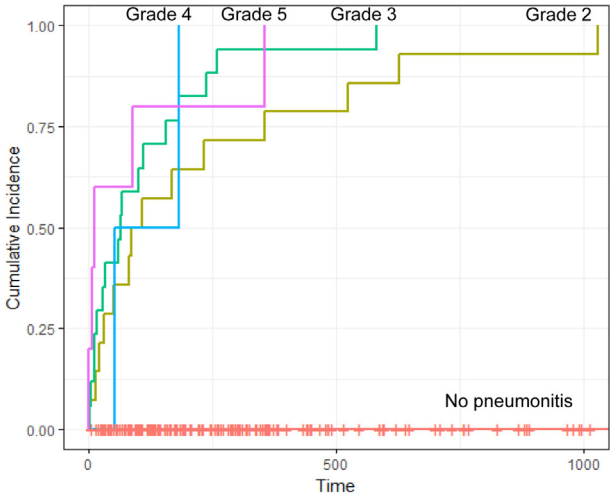


Figure 2. Cumulative incidence curves for development of checkpoint inhibitor pneumonitis (CIP) by grade.

Differences in CIP IR based on type of ICI therapy (monotherapy versus combination ICI), tumor stage, and presence or absence of antecedent chemotherapy were also examined. CIP IR was higher in individuals receiving combination therapy than in those receiving ICI monotherapy for all tumor stages (Supplementary Figs. 2–4).

To determine whether any temporal patterns were present with regard to the time of year during which CIP cases were diagnosed, we determined the number of cases of CIP cases diagnosed per month in our cohort. Interestingly, a higher number of CIP cases were noted in the winter (November–March [Supplementary Fig. 5]), with a peak of six cases in March and a nadir of one case in August.

Because radiographic patterns of CIP can be varied, we examined the patterns of infiltrates noted in computed tomography scans of patients with CIP. As shown in Figure 5, ground glass infiltrates, consolidation, septal thickening, and traction bronchiectasis were observed. Notably, only five of 39 patients presented with pure ground glass infiltrates, and only eight of 39 patients were noted to have a purely consolidative pattern. Infiltrates were peritumoral in 14% of patients.

The results of unadjusted logistic regression evaluating risk factors for development of pneumonitis at 1 year are presented in Table 2. Interestingly, similar to the incidence data, NSCLC of the adenocarcinoma histologic type was associated with 55% (95% CI: 0.19–0.89) lower odds of development of pneumonitis at 12 months than was NSCLC of the squamous histologic type. This relationship remained significant after adjustment for receipt of prior chemotherapy and combination ICI therapy. The results for development of CIP at 2 years were similar (data not presented).

Finally, we examined the grade and outcomes in patients in whom CIP had been diagnosed. As shown in Table 3, CIP of grade 2 or lower occurred in approximately 35% of patients whereas grade 3 or 4 CIP was observed in 48% of cases and grade 5 CIP was observed in 5%. All patients with CIP received high-dose steroids (at least 1 mg/kg of prednisone) as per the current recommended guidelines.[11] In all, 56% of the patients with CIP (22 of 39) had their CIP improve or completely

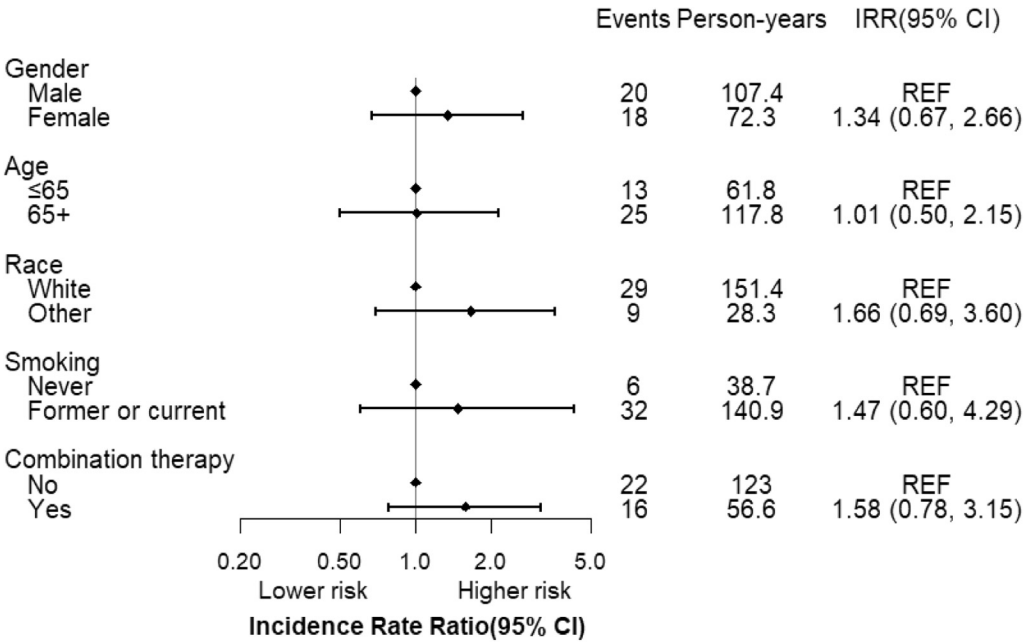


Figure 3. Forest plot showing incidence rate and incidence rate ratios (IRRs) for checkpoint inhibitor pneumonitis (CIP) by demographic factors. CI, confidence interval; REF, reference.

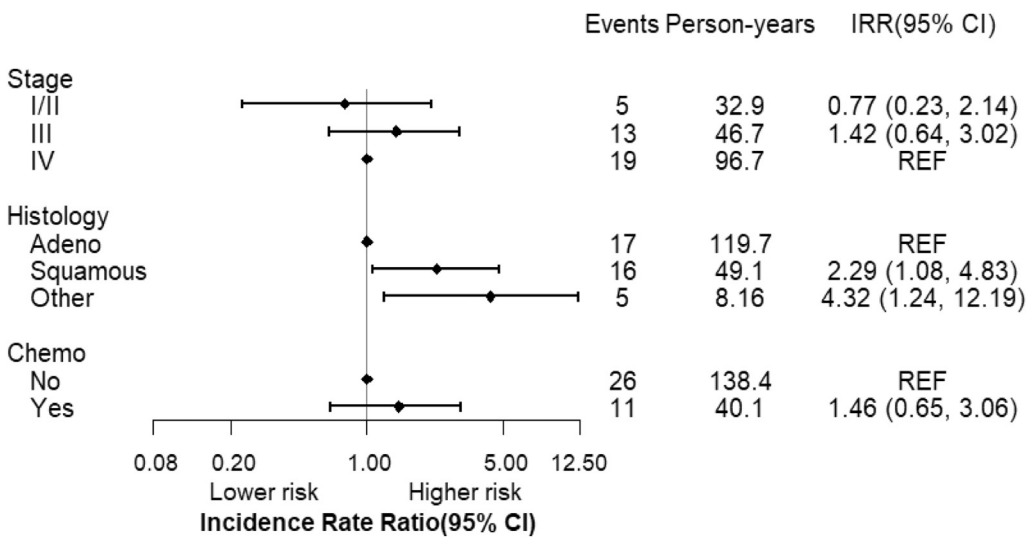


Figure 4. Forest plot showing checkpoint inhibitor pneumonitis (CIP) incidence rate/incidence rate ratio (IRR) by tumor characteristics (stage, histologic type, and antecedent chemotherapy). CI, confidence interval; REF, reference; Adeno, adenocarcinoma; Chemo, chemotherapy.

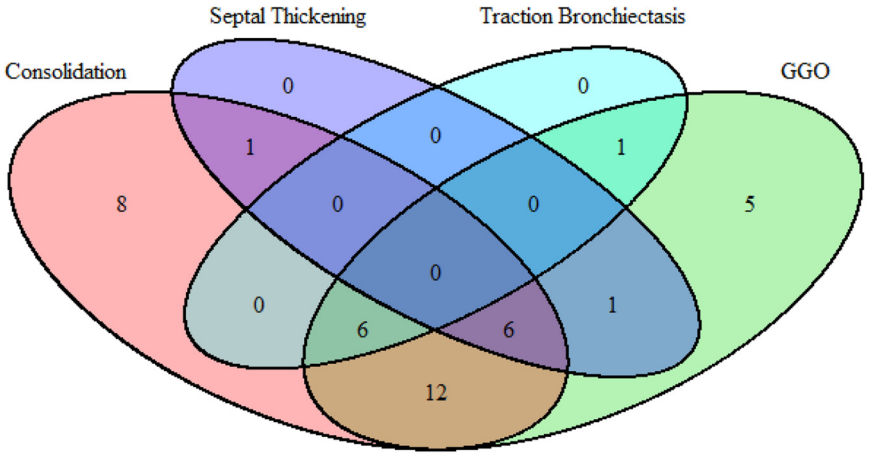
resolve with first-line steroid therapy. Among the 17 patients who did not improve with steroid therapy, CIP was noted to be stable or unchanged in five. Pneumonitis worsened after first-line therapy in nine patients (Table 4), and the outcome was unknown in three patients.

We examined, in closer detail, the clinical characteristics of the 14 patients with CIP whose disease either did not improve or worsened after steroid treatment (see Table 4). The time to CIP onset was fewer than 200 days for 10 of the 14 patients. Three patients received combination ICI therapy. Only two patients whose disease worsened had received antecedent thoracic radiation. Pulmonary function test data from before initiation of ICI therapy were available for three patients; their forced expiratory volume in the first second of expiration ranged from 1.63 to 2.65 (65%–83% predicted), and their diffusion capacity of lung for carbon monoxide level ranged from 54% to 74% predicted. On presentation, their oxygen requirement ranged from room air to 100% (ventilator). Patients received steroid doses of 60 mg of prednisone or 80 to 125 mg of methylprednisolone for 2 to 4 weeks. Arterial blood gas data were available for three of nine patients; the data revealed partial pressure of oxygen–to–fraction of inspired oxygen ratios of 88 to 171 at the time of CIP diagnosis, with an ongoing oxygen requirement despite 72 hours of steroid therapy. In light of this continued deterioration, four of the nine steroid-refractory patients received second-line immunosuppressive agents (either mycophenolate mofetil or infliximab), and three of these four patients improved clinically (two of the three patients who received infliximab improved and one patient who received mycophenolate mofetil also improved). Eight of the 14 patients had died by the end of the follow-up period.

Discussion

Our current study describes the incidence of and risk factors for development of CIP in a cohort of patients with ICI-treated NSCLC. In addition to providing CIP incidence within subgroups of patients receiving ICI, these results suggest that in NSCLC, tumor histologic type and combination ICI therapy may be risk factors associated with development of CIP. The overall incidence of CIP reported by us previously[9] and in this study (19%) is significantly higher than the pneumonitis rates reported in clinical trials.[5,7] The higher observed incidence of CIP may be partially explained by greater awareness of this entity in the past 1 to 2 years, as well as by increased pharmacovigilance with ICI administration. Furthermore, adjudication of CIP cases by a multidisciplinary panel (which is now the standard practice at our institution) likely increased the detection rate. As ICIs have quickly transitioned to becoming first-line medications for advanced-stage NCLC and as maintenance therapy for stage III NSCLC, the burden of CIP in this population is likely to increase. In fact, because we enrolled patients over several years, we examined the yearly incidence of CIP as a proportion of total cases and found that both the total number of patients receiving ICI therapy for NSCLC and the number of patients with documented CIP have increased rapidly since 2015 (see Supplementary Fig. 1).

Our IR and logistic regression analyses (both unadjusted and adjusted) all suggest an association between



	Number (%)
Laterality	9 (2)
Left	12 (2)
Right	19 (45)
Bilateral	
Components of Infiltrate	
Ground-glass	31 (73)
Consolidation	33 (78)
Septal Thickening	8 (19)
Traction Bronchiectasis	7 (16)
Area of pneumonitis	
Peri-tumoral	6 (14)
Away from tumor	36 (86)

Figure 5. Venn diagram and table of radiographic data showing the laterality, infiltrate type, and relationship of infiltrates to primary tumor in patients with checkpoint inhibitor pneumonitis. Abbreviation: GGO, ground glass opacity.

tumor histologic type and development of CIP, with a lower risk of development of CIP in patients with the nonsquamous histologic type. For the logistic regression analyses, we chose to primarily perform univariate analyses to explore relationships between baseline characteristics and development of pneumonitis and restricted our multivariate model to a few key variables because the total number of events (n = 39) was small. Consistent with our data, prior randomized controlled trials[12,13] examining ICI use in squamous and nonsquamous NSCLC reported CIP rates of approximately six of 131 (4.5%) and seven of 287 (2.4%), respectively. However, another possibility for these findings is that tumor histologic type may serve as a marker for some other patient clinical or biologic characteristic (such as performance status or other host characteristics). Interestingly, recent trials focused on nonsquamous NSCLC have reported lower CIP rates[14–16]; our data suggest that some of this decreased incidence may be related to related factors connected with histologic type.

Our finding of a higher (IRR = 1.34; 95% CI: 0.67–2.66) CIP incidence in females is intriguing. Though not significant, this datum requires further investigation; factors intrinsic to sex variability may contribute to the pathobiology of this disease, and thus, consideration of investigation in preclinical models of ICI-treated lung cancer using male and female animals may be warranted.

Our finding of a seasonal pattern (an increased number of cases in the winter) raises several interesting possibilities regarding the relationship between ICI treatment, viral infection, and CIP. One caveat to these data is that patient travel during summer months could also have artificially decreased the number of incident cases. That said, one interesting explanation for our findings is that a seasonally occurring viral infection that is not detected by a standard viral panel may be contributing to CIP development.

Our radiographic data are largely consistent with prior reports noting a variety of radiographic patterns in

Table 2. Risk Factors for Development of CIP at 1 Year

Risk Factor	OR	CI	*p* Value
Univariate analysis			
Demographics			
Female Sex	1.12	(0.53-2.35)	0.75
Smoking	0.86	(0.41-1.82)	0.70
Age	1	(0.96-1.04)	0.69
Race (vs. white)			
Black	1.08	(0.37-2.72)	0.87
Asian/other	2.09	(0.28-10.2)	0.39
Tumor characteristics			
Adenocarcinoma	0.42	(0.19-0.89)	0.02
Initial stage (vs. stage IV)			
I	0.33	(0.01-1.83)	0.30
II	1.24	(0.26-4.39)	0.74
III	1.44	(0.62-3.26)	0.38
Therapy-related factors			
Chemotherapy	0.86	(0.38- 2.0)	0.72
Surgery	0.53	(0.17-1.37)	0.22
ICI therapy (vs. nivolumab therapy)			
Pembrolizumab	0.39	(0.06-1.44)	0.22
Other	0.19	(0.01-1.00)	0.11
Combination ICI	1.72	(0.80-3.67)	0.16
Multivariate analysis[a]			
Adenocarcinoma	0.38	(0.17-0.82)	0.01

[a]Adjusted for prior chemotherapy and combination ICI therapy.
CIP, checkpoint inhibitor pneumonitis; OR, odds ratio; CI, confidence interval; ICI: immune checkpoint inhibitor.

CIP, ranging from organizing pneumonia to primarily ground glass or interstitial patterns.[17–19] Also in accordance with prior studies[5] is our observation of increased risk for CIP with combination ICI therapy, although the increase was not statistically significant in this cohort. Interestingly, though smoking was associated with increased CIP risk in a large retrospective cohort comprising multiple tumor types,[5] we did not observe this relationship in our data set, presumably because nonsmokers were underrepresented in our data owing to the cancer type under study. We also examined both CIP IR in current, former, and never-smokers according to tumor histologic type and did not observe any significant differences, nor did we note any baseline differences in numbers of patients in each smoking classification based on tumor histologic type (data not shown).

We hypothesized that chemotherapy may increase CIP incidence; however, the rate of CIP was not significantly different in patients who had received antecedent chemotherapy than in chemonaive patients. In contrast, we observed an inverse relationship between cancer stage and CIP incidence in patients who received combination ICI therapy (i.e., a higher rate of CIP at a lower cancer stage in patients receiving combination ICI therapy). This is an intriguing finding, suggesting that earlier-stage tumors, perhaps owing to differential effects on the lung inflammatory milieu, may contribute more toward "priming" the lung for CIP after ICI treatment.

Our time-to-onset analysis and case series of patients with refractory CIP suggest that there may be two different phenotypes of disease: early-onset CIP, which is characterized by high grade and early mortality, and late-onset CIP, which is predominantly of lower grade. There may be important implications for patients who have had good tumor response to ICI treatment, in whom low-grade CIP is diagnosed several months (or years) into therapy. Though we observed a mortality of 57% (eight of 14 patients) in steroid-unresponsive/steroid-refractory CIP cases, further work is needed to determine whether CIP specifically contributed to increased mortality in this subgroup.

As discussed earlier, our data were collected over a period of 10 years during which the use of ICI in NSCLC steadily increased. To our knowledge, outside of meta-analyses, this is the largest study reporting patient-level data on CIP cases in NSCLC. Grade 1 CIP was not recorded in this data set, as these patients were by definition asymptomatic and did not undergo further evaluation for infiltrates that were noted on routine screening imaging. Demographically, certain subgroups such as Asian patients are underrepresented in this cohort. Lastly, the epidemiology and risk factors associated with CIP may continue to evolve as patients previously thought to be ICI unresponsive start receiving an ICI as part of newer chemotherapeutic strategies aimed at expanding the envelope of ICI-eligible patients with NSCLC.

In conclusion, CIP is a complication of ICI therapy that may be occurring at a higher rate than previously reported in patients with ICI-treated NSCLC. Risk factors for development of CIP, such as age, tumor histologic type, and use of combination ICI, warrant further study. Study of CIP subtypes based on time to onset and initial CIP grade may provide more insight into the biology of this very relevant disease of increasing prevalence.

Table 3. CIP Grade and Outcomes

Outcome	n (%)
All pneumonitis	39 of 205 (19)
Grade	
2	14 (35.8)
3	17 (43.5)
4	2 (5.1)
5	5 (12.8)
Unknown	1 (2.5)
Clinical outcome	
Completely resolved	2 (5.1)
Improved	20 (51.2)
Stable/unchanged	5 (12.8)
Worsened	9 (17.9)
Unknown	3 (10.2)

CIP, checkpoint inhibitor pneumonitis.

Table 4. Clinical Characteristics of Those Who Did not Improve after Initial Steroid Therapy for CIP

Demographics					Tumor Characteristics and Treatment						CIP Characteristics and Outcome				
Age	Sex	Race	Smoking Pack-years	Alive	Histologic Type	Initial Stage	Radiation	Chemo	ICI	Second Agent	CIP Grade	Time to Onset, d	CIP Outcome	Second-Line Agent	Improvement with Second-Line Drug
73	M	B	55	Alive	Sq	III	Yes	Yes	Nivo		3	239	Stable/unchanged	MMF	Yes
67	F	W	42	Alive	AC	IV	No	Yes	Nivo		4	53	Stable/unchanged		
62	M	B	56	Deceased	AC	III	Yes	Yes	Nivo		2	15	Stable/unchanged		
60	F	W	11	Alive	AC	IV	No	Yes	Nivo		3	67	Worsened		
78	M	W	26	Deceased	Sq	III	Yes	Yes	Nivo		5	91	Worsened		
68	F	W	49	Alive	AC	II	Yes	Yes	Nivo	Ipi	3	183	Worsened	Infliximab	Yes
76	F	W	24	Alive	Sq	IV	No	No	Nivo	Ipi	3	582	Worsened	MMF	Yes
69	M	W	20	Deceased	AC	IV	No	Yes	Nivo		5	9	Worsened	IVIG, Infliximab	No
57	M	W	49	Deceased	Sq	IV	No	Yes	Nivo		5	12	Worsened		
65	F	W	47	Deceased	Sq	IV	No	Yes	Nivo		5	0	Worsened	Infliximab	Yes
59	F	B	41	Deceased	AC	I	No	No	Nivo	Azacitidine + entinostat	3	69	Worsened		
63	F	W	15	Deceased	AC	III	Yes	Yes	Durva		2	23	Stable/unchanged		
75	M	B	24	Alive	Sq	IV	No	Yes	Nivo		3	29	Stable/unchanged		
77	M	W	54	Deceased	Sq	III	Yes	Yes	Nivo		5	357	Worsened		

CIP, checkpoint inhibitor pneumonitis; Chemo, chemotherapy; ICI, immune checkpoint inhibitor; M, male; F, female; B, black; W, white; MMF, mycophenolate mofetil; AC, adenocarcinoma; Sq, squamous cell carcinoma; nivo, nivolumab; Ipi, ipilumimab; IVIG, intravenous immunoglobulin; Durva, durvalumab.

Acknowledgment

Support for this study was provided by the National Heart, Lung and Blood Institute Grant K08HL132055 (KS).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.08.2035.

References

1. Assi HI, Kamphorst AO, Moukalled NM, Ramalingam SS. Immune checkpoint inhibitors in advanced non-small cell lung cancer. *Cancer*. 2018;124:248–261.
2. Morgensztern D, Herbst RS. Nivolumab and pembrolizumab for non-small cell lung cancer. *Clin Cancer Res*. 2016;22:3713–3717.
3. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542–2550.
4. Brahmer JR, Lacchetti C, Schneider BJ, et al. 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*. 2018:17141768.
5. 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;35:709–717.
6. De Velasco G, Je Y, Bosse D, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res*. 2017;5:312–318.
7. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest*. 2017;152:271–281.
8. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375–2391.
9. Voong KR, Hazell S, Hu C, et al. MA 09.08 Receipt of chest radiation and immune-related pneumonitis in patients with NSCLC treated with anti-PD-1/PD-L1. *J Thorac Oncol*. 12:S1837.
10. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018.
11. Weber JS. Practical management of immune-related adverse events from immune checkpoint protein antibodies for the oncologist. *Am Soc Clin Oncol Educ Book*. 2012:174–177.
12. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
13. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
14. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
15. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
16. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
17. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic profiling of immune-related adverse events in advanced melanoma patients treated with ipilimumab. *Cancer Immunol Res*. 2015;3:1185–1192.
18. Nishino M, Hatabu H. Programmed death-1/programmed death ligand-1 inhibitor-related pneumonitis and radiographic patterns. *J Clin Oncol*. 2017;35:1628–1629.
19. 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;22:6051–6060.