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Immune Checkpoint Inhibitor-Associated Pneumonitis in Patients with Non-Small Cell Lung Cancer and Bladder Cancer in US Community Health Systems

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Abstract

Purpose

Immune checkpoint inhibitor (ICI)-related pneumonitis (ICIP) is an uncommon but high morbidity event. Limited insights exist on its natural history in routine care.

Methods

This retrospective study examined the incidence, management and outcomes of ICIP, curated from electronic health records, of patients with non-small cell lung (NSCLC) or bladder/urothelial (UC) cancers receiving ICI in US community health systems.

Results

120 of 2166 (5%) patients with NSCLC and 3 of 139 (2%) patients with UC exposed to any ICI experienced ICIP of any grade during follow-up, corresponding to a 12-month cumulative incidence of 7% [95% confidence interval (CI): 6-8%] in patients with NSCLC and 3% (95% CI: 1-10%) with UC. For patients

with NSCLC, the median time to ICIP onset was 2.8 months (range: 0-49) and the median duration of ICIP was 2.2 months [95% CI:1.9-2.8]. 84 (70%) of patients with NSCLC who developed ICIP were grade 3+ (inferred severity based on EHR) including 6 ICIP-related deaths. In a final multivariable model adjusted for race, age and stage at initial diagnosis, Black race and stage IV disease were associated with decreased hazard of ICIP; age ≥65 was associated with increased hazard of ICIP in patients with NSCLC. Among the three patients with UC who experienced ICIP, times to ICIP were 1, 4 and 4 months, ICIP durations were 5 days, 1 and 2 months, and grades were 2, 2, and 4.

Conclusion

While small numbers precluded meaningful comparisons with UC; results suggest opportunities for monitoring and improved care of patients with NSCLC.

Introduction

Immune checkpoint inhibitors (ICI) have transformed the treatment of both advanced non-small cell lung cancer (NSCLC) and advanced bladder or urothelial cancer (UC), with many ICIs approved by the United States' (US) Food and Drug Administration (FDA) for the treatment of NSCLC and bladder/urothelial carcinoma (UC).[1-4] In addition to their well-established anticancer effects, ICIs may result in immune-related adverse events like ICI-related pneumonitis (ICIP), a rare but potentially lethal condition, seen in both clinical trials and routine care. ICIP incidence among ICI users with NSCLC ranged from 3% to 12.6% of in clinical trials to between 4% and 19% in real-world reports.[5-11] Among ICI-treated patients with advanced and metastatic UC, trial reported ICIP incidence ranged from 0.5% to 4%;[12-18] data on the real-world incidence are sparse but suggest incidence of 3% to 4%.[9,19] Additional contributing factors to ICIP include radiation therapy in patients with NSCLC or other cancers treated with chemotherapy as well as those treated with ICIs.[20-22] Age, tumor histology, and history of pulmonary disease may also impact the risk of ICIP in patients with NSCLC independent of cancer treatment.[22-25]

Given the non-specific nature of presenting symptoms, ICIP remains a condition difficult to diagnose conclusively.[26] In asymptomatic patients, certain changes detected through radiologic surveillance are considered indicative of ICIP. In addition to these diagnostic complexities, ICIP management is challenging and there is limited evidence on the natural history of ICIP in routine care.[27-31] This study leveraged real-world data (RWD) to determine the incidence of and risk factors for ICIP as well as ICIP treatment patterns in patients with NSCLC or UC treated in the routine care setting. UC was chosen as a comparator to NSCLC due to having fewer confounders for interstitial lung disease, for example less frequent pulmonary involvement with malignancy, and associated surgeries and/or irradiation. While both tumor types are associated with tobacco exposure, UC less so.[33,34]

Patients and Methods

Study Population

This retrospective cohort study of patients in the Syapse Learning Health Network (LHN), includes over 1000 oncologists, and 1.6 million patients with cancer, from 5 not-for-profit health systems, primarily in the MidWest, MidAtlantic, and Southeastern United States, and including patients from urban, suburban, and rural areas. Each of these health systems has centers of excellence for cancer care. Over half of U.S. patients with cancer receive care in the community health setting. Community health systems cover the continuum of care, enabling capture of the comprehensive patient journey. This longitudinal database integrates data from electronic health records (EHR), molecular laboratory and radiology/imaging systems, hospital-based cancer registries, commercial laboratories, and other external sources to capture the patient journey from pre-diagnosis to death. The study included patients with primary NSCLC or UC who first used (*index date*) an ICI between January 1, 2015 and August 31, 2019. Eligible patients were 18 years or older at their initial cancer diagnosis and had more than two documented clinical encounters between the index date and data cut-off (*study end*) on February 29, 2020. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration. This research was determined to be exempt, category 4 (secondary research for which consent is not required) by Advarra IRB.

ICI Exposure

Reflecting the contemporary treatment landscape, patients with NSCLC treated with atezolizumab, cemiplimab, durvalumab, ipilimumab, nivolumab or pembrolizumab constituted the NSCLC cohort. The UC cohort consisted of patients treated with atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, or pembrolizumab. The lines of therapy (LoT) accounting for all systemic antineoplastic drugs the patient received from cancer diagnosis until the end of study were defined using Syapse's proprietary medication-based algorithm which takes into consideration treatment sequencing, duration, and gaps in administration.[34-36] The LoT algorithm was used to determine whether the index ICI was received in the first, second, or third and later (third+) lines (*index line*) and identify regimen received in the index line.

Outcomes

ICIP incidence, severity, practice patterns and resolution were the primary outcomes of interest. Oncology data specialists (ODS) reviewed patients' EHRs for mention of pneumonitis symptoms (**Appendix A**) or imaging narrative reports for terms describing abnormal pulmonary radiologic findings (**Appendix B**) that were explicitly attributed to the patient's ICI use and medical interventions explicitly for ICIP. If multiple ICIP interventions occurred on the earliest date following ICIP, the intervention corresponding to the higher grade [determined through the Common Terminology Criteria for Adverse Events (CTCAE) version 5 for pneumonitis] was counted as the earliest ICIP intervention. For example, if steroid treatment (grade 2 or higher) and oxygen supplementation (grade 3 or higher) were documented on the same day as the earliest interventions, the oxygen supplementation would be considered as the earliest ICIP intervention, given the latter corresponds to management of a higher grade ICIP. If multiple medical interventions were documented on different days, e.g., treatment with steroids was followed by oxygen supplementation two weeks later, steroids would be considered the earliest ICIP intervention. ICIP resolution required an explicit statement in the physician's note or the completion of planned management. When ICIP grade was not specified in the patient's EHR, it was inferred by mapping the most intensive intervention received or death to severity according to CTCAE. ICIP management tactics were used to assign severity only if the patient's record clearly stated that the patient required the intervention for immune checkpoint inhibitor related pneumonitis. Date of death was determined by a validated mortality score that uses data captured in (1) hospital-based cancer registries; (2) the Social Security Death index; (3) online obituary data; (4) manually abstracted data from physician notes; and (5) health systems' EHR.[37] Time to ICIP onset was calculated from index to the date for first ICIP diagnosis. Patients without ICIP were censored on the earliest of: 60 days after their index ICI was discontinued, death, last contact or study end date. Time to the initiation of ICIP management was calculated from the ICIP onset to start of each management tactic respectively. Patients without evidence of ICIP management were censored on the earliest of: ICIP resolution, death, date of last contact or study end date. Time to ICIP resolution was calculated from the ICIP onset to the date of recorded resolution. Patients with no evidence of ICIP resolution were censored on the earliest of: last contact, death, or study end date. Overall survival time was calculated as the number of months from index date to the date of death; patients without evidence of death were censored on the earlier date of last contact or study end date.

Covariates

Age, race, ethnicity, sex, tumor histology, stage group and smoking status were assessed at initial cancer diagnosis. Eastern Cooperative Oncology Group (ECOG) performance status was measured at initial diagnosis and at index. Lines and regimens of index ICI, indicators of thoracic radiation, systemic therapy or surgery prior to index ICI, the presence of radiation pneumonitis or pneumonia within 3 months prior to the index date were used in analyses. Lung metastasis at the index date was also captured for the BCLA cohort. Demographic data were from hospital registry files and others were curated from EHRs by ODS-certified professionals.

Statistical Analysis

The distributions of patient demographics and clinical characteristics were described for the NSCLC and UC cohorts overall and stratified by the therapy line in which the index ICI was initiated. Categorical variables were summarized as frequencies and percentages (N, %), while continuous variables were reported as mean and standard deviation (SD), median, interquartile range (IQR), minimum and maximum. The Kaplan-Meier Product Limit (KM) estimator was used to assess the distribution of time-to-event outcomes. Time to ICIP onset was also described by the median and range among patients who experienced ICIP. Univariable Cox proportional hazards models were used to assess the association of each demographic and clinical characteristic with ICIP. A "full model" including all covariates assessed in univariable models was built for exploratory purposes, and an indicator for receiving systemic therapy before index ICI (yes or no) was used instead of index ICI line. In addition, a data driven approach was built as follows: all covariates with a p value of <0.25 in univariate models were added to a multivariable model; covariates with $p>0.1$ were dropped from the multivariable model, resulting in a final parsimonious model that only

Table 1: Baseline demographic, clinical characteristics and index ICI therapy among NSCLC and UC cohorts. Index ICI and date: The first ICI therapy and the date of its first administration. Third or later line. Other included: a different ICI drug, a targeted therapy, or a combination of two or more classes of drugs.

	NSCLC, N = 2166	**UC, N = 139**
Sex, N (%)		
Female	1071 (49)	40 (29)
Male	1095 (51)	99 (71)
Race/ethnicity, N (%)		
Non-hispanic White	1630 (75)	113 (81)
Non-hispanic Black	274 (13)	14 (10)
Hispanic/Latino	79 (4)	4 (3)
Other or Unknown	183 (8)	8 (6)
Age at initial diagnosis, Median (IQR)	67 (59, 73)	67 (58, 76)
Age group at initial diagnosis, N (%)		
<55	274 (13)	22 (16)
55-64	648 (30)	37 (27)
≥65	1244 (57)	80 (58)
Stage at initial diagnosis, N (%)		
<III	240 (11)	62 (45)
III	599 (27)	22 (16)
IV	1258 (58)	52 (37)
Unknown	69 (3)	3 (2)
Histology, N (%)		
Adenocarcinoma	1378 (64)	NA
Squamous cell carcinoma	588 (27)	NA
Urothelial carcinoma	NA	122 (88)
Non-urothelial carcinoma	NA	17 (12)
Other	200 (9)	0
Smoking status		
Never Smoker	181 (8)	35 (25)
Former Smoker	1133 (52)	68 (49)
Current Smoker	842 (39)	36 (26)
Unknown	10 (1)	0
Had thoracic radiation therapy prior to index date, N (%)	832 (38)	0
Had thoracic surgery prior to index date, N (%)	296 (14)	3 (2)
Had radiation pneumonitis within 3 months prior to index date, N (%)	24 (1)	0
Had pneumonia within 3 months prior to index date, N (%)	172 (8)	0
ECOG performance status at index date, N(%)		
0	354 (16)	24 (17)
1	684 (32)	52 (37)
2+	314 (14)	32 (23)
Unknown	814 (38)	31 (22)
Index ICI lines, N (%)		
First	920 (42)	36 (26)
Second	933 (43)	68 (49)
Third+	313 (15)	35 (25)
Index ICI regimen, N (%)		
ICI mono	1553 (72)	127 (91)
ICI + Chemo	583 (27)	9 (7)
ICI + other	30 (1)	3 (2)

ICI: immune checkpoint inhibitor; NSCLC: non-small cell lung cancer; UC: urothelial cancer; ECOG: Eastern Cooperative Oncology Group; Mono: monotherapy; Chemo: chemotherapy; Targeted: targeted therapy.

included factors significantly associated with ICIP. The proportional-hazards assumption was assessed graphically using Schoenfeld residuals. All reported P-values are two-sided with a significance threshold of 0.05, and all statistical analyses were performed in R version 3.6.1.

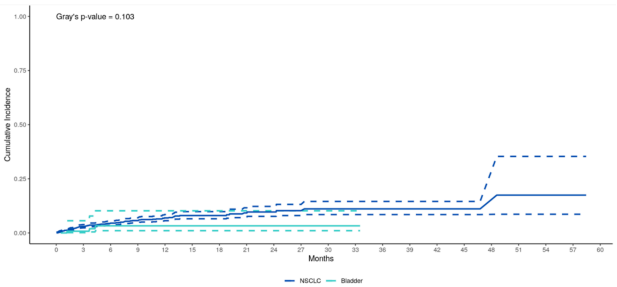
Results

Cohort Characteristics

The NSCLC cohort consisted of 2166 patients who were primarily white (75%, **Table 1**) and had a median age of 67 (IQR: 59, 73) at diagnosis. Most patients had adenocarcinomas (64%). 38% received thoracic radiation and 14% had surgery for NSCLC prior to index. Few patients had pneumonitis (1%) or pneumonia (8%) within three months prior to index. The UC cohort included 139 patients, most of whom had urothelial carcinoma (88%). The age and race distributions were similar between the NSCLC and UC cohorts. The UC cohort had a higher proportion of male patients (71% vs 51%) and patients with ECOG score of 0 or 1 at index (54% vs 48%) than the NSCLC cohort but smaller proportions of patients with *de novo* metastatic disease (37% vs 58%) and patients with a history of smoking (75% vs. 91%). Only three patients with UC had previous thoracic surgery, and none had received thoracic radiation or had pneumonitis or pneumonia prior to index. While similar proportions of patients with NSCLC received the index ICI in the first (42%) and second lines (43%) with fewer in the third+ lines (15%, **Table 1**), patients with UC more often received the index ICI in the second line (49%) than the first (26%) or third+ lines (25%). In both cohorts, patients who received the index ICI in the first line were more likely to have *de novo* metastatic disease than those who received the index ICI in later lines (NSCLC: 80%, UC: 56%, **Supplementary Table 1**) and to be ≥65 years at diagnosis (NSLCL: 61%; UC: 78%). Index ICI was used predominantly as monotherapy in both cohorts (NSCLC: 72%, UC: 91%, **Table 1**).

ICIP Incidence

120/2166 (5%) patients with NSCLC and 3/139 (2%) with UC experienced ICIP during follow-up. The 12-month ICIP cumulative incidence estimates were 7% (95% CI: 6%-8%) and 3% (1%-10%) for NSCLC and UC, respectively (**Figure 1**). Most patients with ICIP (NSCLC: >95%, UC:100) had only one ICIP episode during follow-up (**Table 2**). In the NSCLC cohort, the median time to ICIP onset was 3 months (range: 0-49); the time to ICIP onset for the three patients with UC was 1, 4, and 4 months respectively (**Table 2**). 70% of the first ICIP among patients with NSCLC were grade 3 or higher, with 6 (5% of ICIP patients; 0.3% of the NSCLC cohort) ICIP-related deaths or grade 5 (**Table 2**). Among patients with UC, two cases of ICIP were grade 2, and the other was grade 4.



	3 months	6 months	1 year	5 years
NSCLC	3% (2%, 4%)	5% (4%, 6%)	7% (6%, 8%)	17% (9%, 35%)
UC	1% (0%, 6%)	3% (1%, 10%)	3% (1%, 10%)	Not estimated

Figure 1. Cumulative incidence of immune checkpoint inhibitor (ICI)-related pneumonitis (ICIP) among patients with NSCLC or UC following initiation of index ICI therapy.

ICIP Management

The majority of patients presented with symptomatic first ICIP (NSCLC: 88%, UC: 2/3, **Table 2**). Steroids were typically administered with a high starting dose (NSCLC: 72%, UC: 2/3) defined as greater than 40 mg/day of prednisone, 6 mg/day of dexamethasone, or 32 mg/day of methylprednisolone. At the earliest and most intensive intervention tactic, 14% discontinued the index ICI without further treatment, 28% received steroids without oxygen supplement as outpatients, 3% received oxygen supplement as outpatients, and 49% were treated in hospitals (**Table 2**). Subsequent treatment tactics were intensified for some patients as 92% of patients ever received steroids and 63% were ever hospitalized for ICIP (**Table 3**). Among the patients with UC, one discontinued ICI, one received steroids, and one was hospitalized (**Table 3**).

Time to ICIP-related Events

The median time from first ICIP diagnosis to steroid use was 0 days (95% CI: 0, 0 **Table 3**) for patients with NSCLC, and 1, 9 and 21 days for

Table 2. Characteristics and management of ICIP. High dose cutoffs (v.s. low, mg/day): prednisone ≥ 40, dexamethasone ≥ 6, methylprednisolone ≥32. The most intensive treatment tactic is listed if multiple treatments were given on the same date, e.g. if the patient received steroids and oxygen on the same date, this would be counted as "oxygen supplementation".

	NSCLC, N = 120	**UC, N = 3**
Patients with only one ICIP episode, N (%)	114 (95)	3 (100)
Time to ICIP onset (months), median(range)	3 (0, 49)	4 (1, 4)
Highest severity		
Grade 1	2 (1.7)	0
Grade 2	34 (28)	2 (67)
Grade 3/4	78 (65)	1 (33)
Grade 5	6 (5)	0
Indication for ICIP onset and diagnosis		
Symptom	105 (88)	2 (67)
Imaging (asymptomatic)	15 (12)	1 (33)
Corticosteroids starting dose		
High dosage	86 (72)	2 (67)
Low dosage	14 (12)	1 (33)
Unknown	20 (17)	0
Initial management or clinical course		
ICI stop	17 (14)	1 (33)
Steroids	33 (28)	1 (33)
Oxygen supplementation	4 (3)	0
Hospitalization/intubation	59 (49)	1 (33)
Death due to ICIP	1 (1)	0
Death not due to ICIP	6 (5)	0

the three patients with UC; median time to ICIP-related hospitalization was 0 days (95% CI: 0, 1) for patients with NSCLC. The median was not reached for time to receipt of immunosuppressants, oxygen supplement, or intubation (**Table 3**). ICIP resolution was reported for most of the patients with NSCLC (83%); median duration of the first ICIP episode was 2 months (95% CI: 2, 3). All three patients with UC experienced ICIP resolution and the ICIP duration ranged from <1 to 2 months.

Cancer Treatment following ICIP

Among patients with ICIP, 81% of patients with NSCLC and two out of three patients with UC received ICI monotherapy as their index regimen (**Table 4**). The remainder most often received ICI plus chemotherapy. Following the index ICI regimen, half of the patients (52%) with NSCLC and one of three patients with UC died without receiving any subsequent cancer-directed therapy. Only 8 NSCLC patients (7%) with ICIP and one of the three patients with UC continued ICI-containing regimens in subsequent lines of therapy.

Table 3. The distribution of time to select events following the first ICIP. Time from ICIP onset to ICIP related events. One of the 120 patients was excluded from the analysis due to missing dates associated with listed events. Estimated by the Kaplan-Meier method. –: not applicable or missing; for NSCLC cohort, estimated if events were experienced by at least 50% of patients; for UC, estimated only among patients that had the event.

	NSCLC, N = 119		**UC, N=3**		
	Median (95% CI)	Event n (%)	Patient A	Patient B	Patient C
Time to first steroids in days	0 (0, 0)	109 (92)	1	9	21
Time to hospitalization in days	0 (0, 1)	75 (63)	0	–	–
Time to immunosuppressant in days	–	4 (4)	–	–	–
Time to oxygen supplementation in days	–	55 (46)	–	–	–
Time to intubation in days	–	6 (5)	1	–	–
Time to ICIP resolution (duration of ICIP) in months	2 (2, 3)	99 (83)	0	2	1

Table 4. Subsequent cancer-directed treatment following index ICI receipt for patients experiencing ICIP. Index ICI: The first ICI therapy patients received. Other included: chemotherapy, targeted therapy, a different ICI or combination of more than two classes of drugs. No subsequent treatment data before the study end date.

	NSCLC, N (%)				**UC, N (%)**		
Subsequent line of therapy	ICI mono, N=97	ICI+chemo, N=20	ICI + other, N=3	Total, N=120	ICI mono, N=2	ICI+chemo, N=1	Total, N=3
No, patient died	51 (53)	11 (55)	0	62 (52)	1 (50)	0	1 (33)
No	34 (35)	5 (25)	2 (67)	41 (34)	0	0	0
ICI mono	5 (5)	0	0	5 (4)	0	1 (100)	1 (33)
ICI + Chemo	2 (2)	1 (5.0)	0	3 (3)	0	0	0
Other	5 (5)	3 (15)	1 (33)	9 (8)	1 (50)	0	1 (33)

ICI: immune checkpoint inhibitor; ICIP: ICI-related pneumonitis; Mono: monotherapy; Chemo: chemotherapy.

Risk Factors Associated with ICIP

In a final parsimonious Cox model adjusted for race, age and stage at initial diagnosis (**Figure 2**), Black race [hazard ratio (HR, 95% Confidence Interval [CI] = 0.4 (0.2, 0.9), reference: white] and de novo metastatic disease [HR=0.6 (0.4, 0.8), non-metastatic] were associated with decreased hazard of ICIP; while older age (≥65) at diagnosis was associated with increased hazard [HR=1.6 (0.9, 3.0), <55]. The full exploratory model resulted in similar findings, further suggesting that additional factors may be associated with increased hazard of ICIP (**Supplemental Figure 1**).

Overall Survival

55% of patients with NSCLC and 63% of patients with UC died before the data cut-off. Median overall survival (OS) estimates were 18 (95% CI: 17-20, **Figure 1**) and 10 (95% CI: 7-22) months for the NSCLC and UC cohorts, respectively.

Discussion

This real-world study of patients with NSCLC who were treated with ICIs described the natural history of ICIP and identified important potential factors associated with ICIP risk. While the comparison of incidence, natural history and

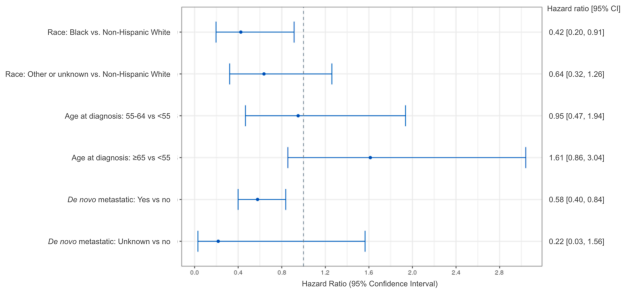


Figure 2. Hazard ratios (95% CI) for ICIP among the NSCLC cohort (N=2166).

management, as well as risk factors between NSCLC and UC was a goal of this study, the few cases of ICIP among the patients with UC in this study precluded the comparison between the two groups. Findings from the NSCLC cohort are consistent with previous RWD reports.[8-11] The final multivariable model suggested that *de novo* metastasis was associated with reduced hazard of ICIP among patients with NSCLC, likely since patients with metastasis at initial diagnosis were less likely to receive thoracic radiation than those diagnosed with earlier stage (15% de novo vs. 74% stages I-III), which is expected as radiation is often a part of definitive treatment for stage III. In the full exploratory model (**Supplemental Figure 1**), thoracic radiation was not significantly associated with ICIP after controlling for race, age, smoking history, stage at diagnosis, performance status, history of pneumonitis or pneumonia, prior thoracic surgery or systemic therapy, and index ICI regimen. However, it is possible that any collinearity between thoracic radiation and stage at diagnosis may have limited our ability to detect a significant association. Considering discrepant reports from other studies,[20,22,24,38] further investigation of the relationship between thoracic radiation and ICIP is warranted. Older age at diagnosis was associated with increased hazard of ICIP as older patients were more likely to have lung comorbidities: pre-existing pneumonitis or pneumonia 3 months prior to index date was associated with increased hazard of ICIP (**Supplemental Figure 1**). Additional, unmeasured chronic lung diseases may also contribute to the observed effect of older age. Further, comprehensive assessment of lung comorbidities may be warranted for future studies.

Consistent with prior studies,[8,38-40] most patients experienced ICIP within 6 months of ICI initiation, suggesting the need to closely monitor for signs and symptoms of pneumonitis in the first few months following ICI initiation. As previously reported,[9] a small portion of patients had asymptomatic ICIP onset in this study (12%) resulting from lack of surveillance imaging and other inherent challenges in diagnosing ICIP. The most common initial management for ICIP was hospitalization, high-dose steroid treatment without delay following ICIP onset, reflecting a high alertness of ICIP by US community health providers.

Most patients in this NSCLC cohort were classified as having high-grade ICIP (grade 3 or above), while previous studies reported grades 1 or 2 ICIP as more common.[8,9] This discrepancy may be partially attributed to our definition of ICIP grade: largely missing ICIP grade was inferred based on the most intensive management tactics during its course. Our inferred grade is potentially higher than if it was documented by providers at ICIP diagnosis. Most patients had their ICIP resolved within 3 months of onset without recurrence during follow-up suggesting that ICIP can be efficiently controlled when detected. Most patients experienced interruptions of cancer treatment by ICIP are common, suggesting that management for ICIP needs to be standardized and optimized.

The study has several limitations. Pneumonitis may have incorrectly been attributed by providers to ICI rather than radiation, resulting in biased estimates of ICIP incidence. Furthermore, it is possible that events assumed to be ICIP given their management may have been incorrectly classified. Statistical inference is challenging given the small number of patients with ICIP from both cohorts. Sample size limitations may have contributed to observed incongruence between findings from this study and prior work.[8,24,41] In addition, the assignment of medications into lines of treatment was done algorithmically and may have misclassified the ICI-containing regimen; however, the present LoT algorithm is an approach that has been used extensively in prior work.[34-36] Furthermore, individual immune checkpoint inhibitors were not evaluated. Despite these considerations, RWD provides unique opportunities to study rare events like ICIP in patient populations who may be otherwise underrepresented in clinical trials. The access to both oncology and non-oncology EMR data enables a comprehensive capture of the routine care including the diagnosis and management of ICIP, particularly

for cases with asymptomatic ICIP onset, providing insights that may be more readily turned into actions for improvements.

Conclusion

In this analysis, older age, non-metastatic stage at diagnosis, and white race were significantly associated with the risk of ICIP among patients with NSCLC. This study examined ICIP incidence in a robust sample size of patients with NSCLC receiving cancer care in US community health systems, but the small number of patients with UC who experienced ICIP precluded comparison between the two tumor types. Early and active surveillance of ICI recipients at greater risk of developing ICIP may allow for more effective management of ICIP. The varied treatment approaches following the development of ICIP also suggest an opportunity to optimize and standardize management of patients who developed ICIP in the routine care setting.

Conflict(s) of Interests

YY, KK, HM, CZ, MR, MAI, RB, KM, DH, and WC were Syapse employees and received equity or stocks from Syapse when this work was completed. BT, EP, JH, AC were employees and EH was a consultant working on behalf of AstraZeneca when this work was completed.

Funding Information

This work was supported by AstraZeneca.

Ethical Statements

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. It was reviewed by Advarra IRB and determined to be exempt under category 4 (secondary research for which consent is not required, per 45 CFR 46.104(d)(4)), as it involved retrospective analysis of secondary, de-identified electronic health record data with no direct patient contact. All data were handled in compliance with HIPAA requirements.

Informed Consent

Not applicable. This study used retrospective, de-identified electronic health record data with no direct or indirect patient contact; the IRB's exemption determination (category 4) confirmed that informed consent was not required.

Data Availability Statement

We will adhere to the ethical obligations for responsible sharing of data. The data that support the findings of this study are not publicly available due to patient privacy and legal restrictions. Requests for access to the de-identified data can be submitted to Research@syapse.com for review and approval.

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Declaration of AI Use in Scientific Writing

AI tools were not used to generate scientific content, interpret data, or influence the conclusions of this review.

Author Contributions

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All authors (YY, KK, HM, CZ, MR, RB, KM, DSH, BT, ERH, ECP, JTH, AC, MAI) approved the final version of the manuscript and agree to be accountable for all aspects of the work, in accordance with the International Committee of Medical Journal Editors criteria.

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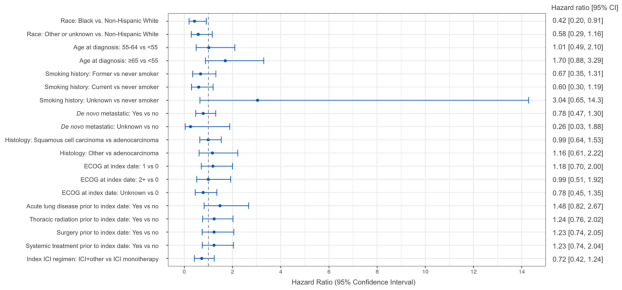
Supplementary Materials

Appendix A: Symptoms related to pneumonitis

Shortness of breath (increasing)
Dry cough/cough
Weakness
Fatigue

Appendix B: Terms describing abnormal radiologic findings in patients' lung imaging narrative reports

Acute interstitial pneumonitis
Acute respiratory distress syndrome
Acute respiratory failure
Air-space consolidation
Allergic eosinophilia
Alveolar lung disease
Alveolar proteinosis
Alveolitis
Alveolitis allergic
Alveolitis necrotizing
Architectural distortion
Autoimmune lung disease
Bronchiolitis
Combined pulmonary fibrosis and emphysema
Diffuse alveolar damage
Drug-induced interstitial lung disorder
Eosinophilia myalgia syndrome
Eosinophilic granulomatosis with polyangiitis
Eosinophilic pneumonia
Eosinophilic pneumonia acute
Eosinophilic pneumonia chronic
Granulomatous pneumonitis
Ground-glass attenuation
Ground-glass opacities
Idiopathic interstitial pneumonia
Idiopathic pneumonia syndrome
Idiopathic Pulmonary Fibrosis
Interlobular septal thickening
Interstitial lung disease (ILD)
Interstitial opacities
interstitial pneumonia
Interstitial pulmonary disease
Intralobular reticular opacity
Lung infiltration
Necrotising bronchiolitis
Nodular opacities
Non-septal linear opacity
Obliterative bronchiolitis
Obstructive lung disease
Organising pneumonia
Pleural effusion
Pneumonia
Pneumonitis
Previous tuberculosis
Progressive massive fibrosis
Pulmonary emphysema
Pulmonary fibrosis
Pulmonary necrosis
Pulmonary radiation injury
Pulmonary toxicity
Pulmonary vasculitis
Radiation alveolitis
Radiation fibrosis - lung
Radiation pneumonitis
Respiratory failure
Restrictive pulmonary disease
Rheumatoid lung
Scarring or inflammation of interstitium
Small airways disease
Thickening of bronchovascular bundles
Traction bronchiectasis



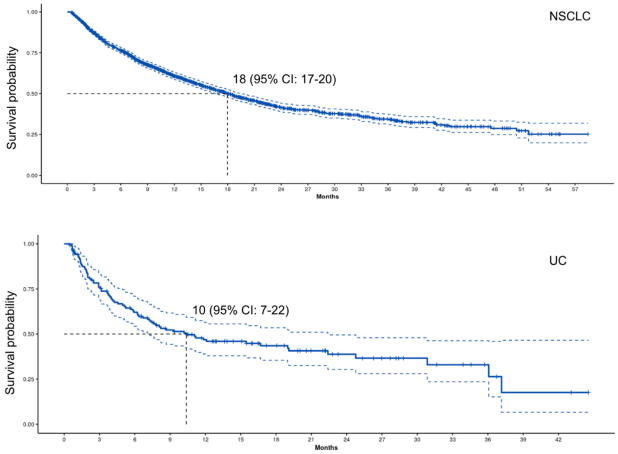
Supplemental Figure 1: Forest plot showing hazard ratios and 95% confidence intervals for association between covariates and ICIP in the exploratory cox model among the NSCLC cohort. Explanatory variables included: race, age, smoking history, metastasis at diagnosis (de novo), histology, ECOG performance score at index date, acute lung disease (pneumonia or pneumonitis) 3 months prior to index date, thoracic radiation prior to index date, surgery prior to index date, systemic treatment prior to index date, index ICI regimen.

Supplementary Table 1: Baseline demographic, clinical characteristics among NSCLC and UC cohorts, stratified by line of index ICI. Index ICI and date: The first ICI therapy and the date of its first administration. Third or later line. NA: Not applicable. ICI: immune checkpoint inhibitor; NSCLC: non-small cell lung cancer; UC: urothelial cancer; ECOG: Eastern Cooperative Oncology Group.

	NSCLC, N= 2166			**UC, N=139**		
	First, N = 920	Second, N = 933	Third+, N = 313	First, N = 36	Second, N = 68	Third+, N = 35
Sex						
Female	463 (50)	441 (47)	167 (53)	14 (39)	15 (22)	11 (31)
Male	457 (50)	492 (53)	146 (47)	22 (61)	53 (78)	24 (69)
Race/ethnicity						
White	708 (77)	719 (77)	203 (65)	31 (86)	51 (75)	31 (89)
Black	118 (13)	115 (12)	41 (13)	3 (8.3)	9 (13)	2 (5.7)
Hispanic/Latino	44 (4.8)	22 (2.4)	13 (4.2)	1 (2.8)	3 (4.4)	0 (0)
Other or Unknown	50 (5.4)	77 (8.3)	56 (18)	1 (2.8)	5 (7.4)	2 (5.7)
Age group at diagnosis						
<55	101 (11)	97 (10)	76 (24)	3 (8.3)	13 (19)	6 (17)
55-64	252 (27)	296 (32)	100 (32)	5 (14)	17 (25)	15 (43)
≥65	567 (61)	540 (58)	137 (44)	28 (78)	38 (56)	14 (40)
Stage at initial diagnosis, N (%)						
<III	78 (8.5)	111 (12)	51 (16)	9 (25)	30 (44)	23 (66)
III	68 (7.5)	416 (44)	115 (37)	6 (17)	11 (16)	5 (14)
IV	739 (80)	379 (41)	140 (45)	20 (56)	25 (37)	7 (20)
Unknown	35 (3.8)	27 (2.9)	7 (2.2)	1 (2.8)	2 (2.9)	0 (0)
Histology, N (%)						
Adenocarcinoma	653 (71)	515 (55)	210 (67)	NA	NA	NA
Squamous cell carcinoma	171 (19)	337 (36)	80 (26)	NA	NA	NA
Urothelial carcinoma	NA	NA	NA	30 (83)	58 (85)	34 (97)
Non-urothelial carcinoma	NA	NA	NA	6 (17)	10 (15)	1 (2.9)
Other	96 (10)	81 (8.7)	23 (7.3)	0	0	0
Smoking status						
Never Smoker	78 (8.5)	58 (6.2)	45 (14)	8 (22)	17 (25)	10 (29)
Former Smoker	502 (55)	484 (52)	147 (47)	21 (58)	33 (49)	14 (40)
Current Smoker	339 (37)	386 (41)	117 (37)	7 (19)	18 (26)	11 (31)
Unknown	1 (0.1)	5 (0.5)	4 (1.3)	0	0	0
Had thoracic radiation therapy prior to index date, N (%)	108 (12)	537 (58)	187 (60)	0	0	0
Had thoracic surgery	71 (7.7)	140 (15)	85 (27)	0	2 (2.9)	1 (2.9)

prior to index date, N (%)						
Had radiation pneumonitis within 3 months prior to index date, N (%)	2 (0.2)	17 (1.8)	5 (1.6)	0	0	0
Had pneumonia within 3 months prior to index date, N (%)	97 (11)	61 (6.5)	14 (4.5)	0	0	0
ECOG performance status at index date, N(%)						
0	163 (18)	144 (15)	47 (15)	2 (5.6)	14 (21)	8 (23)
1	282 (31)	286 (31)	116 (37)	9 (25)	28 (41)	15 (43)
2+	129 (14)	136 (15)	49 (16)	10 (28)	13 (19)	9 (26)
Unknown	346 (38)	367 (39)	101 (32)	15 (42)	13 (19)	3 (8.6)

Supplementary Figure 2



Supplementary Figure 2. Overall survival for immune checkpoint inhibitors (ICI) treated NSCLC (upper) and UC (lower) patients in this study. Median times and 95% confidence intervals (CI) were indicated.

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