

Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers



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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has led to dramatic changes in oncology practice. It is currently unknown whether programmed death 1 (PD-1) blockade therapy affects severity of illness from COVID-19 in patients with cancer. To address this uncertainty, we examined consecutive patients with lung cancers who were diagnosed with COVID-19 and examined severity on the basis of no or prior receipt of PD-1 blockade. Overall, the severity of COVID-19 in patients with lung cancer was high, including need for hospitalization in more than half of patients and death in nearly a quarter. Prior PD-1 blockade was, as expected, associated with smoking status. After adjustment for smoking status, PD-1 blockade exposure was not associated with increased risk of severity of COVID-19. PD-1 blockade does not appear to affect the severity of COVID-19 in patients with lung cancers.

SIGNIFICANCE: A key question in oncology practice amidst the COVID-19 pandemic is whether PD-1 blockade therapy affects COVID-19 severity. Our analysis of patients with lung cancers supports the safety of PD-1 blockade treatment to achieve optimal cancer outcomes.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has led to dramatic changes in treatment decision-making for patients with cancer (1). COVID-19 is associated with varied clinical severity, ranging from minimally symptomatic community transmission (2–5) to respiratory failure and host–virus interactions leading to a proinflammatory state with evidence of local and systemic cytokine storm (6–9). Compared with individuals with COVID-19 without cancer,

early series in individuals with COVID-19 and cancer have been reported to have a higher likelihood of severe disease and mortality (10, 11). Given the risk of severe disease, reports characterizing the presentation and outcomes of COVID-19 in patients with cancer are urgently needed to guide decision-making. This need is especially relevant for patients who are receiving immunotherapy.

Programmed death 1 (PD-1) blockade has improved survival in patients in multiple incurable cancers, but there is uncertainty about the potential impact—harmful, beneficial,

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or neither—of immunotherapy in the context of COVID-19 (12). On one hand, PD-1 blockade might theoretically augment the hyperactive immune phase of COVID-19 and worsen outcomes (13). Alternatively, as PD-1 blockade can enhance immunologic control of viral infections, it could theoretically improve outcomes (14–17). Finally, given the dissipating pharmacodynamic impact of PD-1 blockade following the initial proliferative burst associated with early doses (18–21), it is possible that any interaction of PD-1 blockade, for better or worse, on severity of COVID-19 would be limited to those who recently began therapy.

Some (10, 22–24), but not all (11, 25–27), initial reports of COVID-19 described signals of increased severity associated with immune checkpoint inhibitors (ICI). These conclusions may be confounded by multiple factors, such as lung cancer diagnosis and prior smoking, which are associated with both an increased likelihood of ICI exposure and increased COVID-19 severity. We hypothesized that evaluating the impact of PD-1 blockade on COVID-19 severity within patients with lung cancers permits a more meaningful assessment to guide real-time treatment decisions.

RESULTS

We identified 69 consecutive outpatients with lung cancers seen at a single center who were diagnosed with COVID-19 between March 12, 2020, and April 13, 2020, with information on hospitalization and vital status (Fig. 1A). All cases of COVID-19 were confirmed by RT-PCR; suspected but unconfirmed cases were excluded. The median follow-up from diagnosis of COVID-19 was 14 days. The median age was 69 (range 31–91); 52% (36/69) were female and 80% (55/69) had active or metastatic lung cancer (Table 1). Sixty-four percent (44/69) had at least a 5 pack-year smoking history. The most common presenting symptom that led to testing was cough (77%, 47/61) followed by dyspnea (73%, 43/59) and fever (70%, 42/60; Fig. 1B). Baseline labs within 1 day of the positive swab were notable for low absolute lymphocyte count [median, 0.7; interquartile range (IQR), 0.4–0.9; $n = 34$; Fig. 1C]. Forty percent (27/69) of patients received hydroxychloroquine as treatment for COVID-19. As of this writing, 42 (62%) patients required hospitalization and 16 (24%) patients died (Table 1; Fig. 1D and E).

The primary question of our analysis was to examine the impact of PD-1 blockade on severity of COVID-19. A total of 41 (59%) patients previously received PD-1 blockade (median last dose to COVID-19 diagnosis 45 days, range 4–820 days; Table 2). We prespecified four categories of prior PD-1 blockade to characterize the temporal relationship between treatment exposure and diagnosis of COVID-19: ever received PD-1 blockade, most recent dose within 6 months, most recent dose within 6 weeks, and first dose within 3 months. These definitions were selected to examine how recent and more remote exposure to PD-1 blockade might influence COVID-19 severity, cognizant of both the prolonged receptor occupancy that can persist for months (28) as well as the distinct proliferative burst in response to initially starting this therapy (18–21). To characterize the severity of COVID-19, we *a priori* defined rate of hospitalization, a composite of intensive care unit (ICU)/intubation/

transition to do not intubate (DNI) status, and death as outcomes of interest.

Overall, there was no significant difference in severity regardless of PD-1 blockade exposure (Fig. 2A). Within patients who received PD-1 blockade therapy, there were no consistent trends of differences in COVID-19 severity based on increasing proximity of exposure to PD-1 blockade. Peak IL6 level among hospitalized patients was similar based on receipt of PD-1 blockade (no prior PD-1 vs. prior PD-1, median 95 vs. 108 pg/mL; Fig. 2B).

A numerical increase in severity could be seen in some comparisons based on PD-1 blockade exposure (univariate OR, 1.18–1.81 for severity outcomes; Fig. 2C), which may be explained by an expected imbalance in smoking history among the no prior PD-1 compared with prior PD-1 blockade-exposed patients (Table 2). Smoking history significantly associated with severe COVID-19 [OR for death, 5.75; 95% confidence interval (CI), 1.41–39.05; Fig. 2C]. When adjusted for smoking history, the ORs for the impact of PD-1 blockade exposure on hospitalization, ICU/intubation/DNI, and death diminished to 0.95 (95% CI, 0.28–3.01), 0.86 (95% CI, 0.26–2.80), and 1.01 (95% CI, 0.27–3.97), respectively (Fig. 2C). As a sensitivity analysis, we adjusted for both smoking history and gender (the two features that significantly differed between no prior vs. prior PD-1 blockade in this cohort) and found similar results; the ORs for the impact of PD-1 blockade on hospitalization, ICU/intubation/DNI, and death diminished to 1.20 (95% CI, 0.33–4.23), 0.83 (95% CI, 0.24–2.82), and 1.13 (95% CI, 0.25–5.03), respectively.

DISCUSSION

In summary, we found no significant association between receipt of prior PD-1 blockade and COVID-19 severity. To examine the robustness of our results, we tested several prespecified definitions of the proximity of PD-1 blockade exposure to diagnosis of COVID-19 and outcome measures of COVID-19 severity. A numerical increase in severity prompted us to rationally examine confounders by indication. Smoking history unsurprisingly had a strong baseline imbalance ($P < 0.001$ in prior PD-1 vs. no prior PD-1 group) and has high bioplausibility to affect COVID-19 severity (29–33) given the impact on underlying pulmonary dysfunction and association with other relevant comorbidities. After adjusting for smoking status, the adjusted ORs for the impact of PD-1 blockade on hospitalization, ICU/intubation/DNI, and death all diminished to approximately 1. These results support the safety of PD-1 blockade in patients with lung cancers to achieve optimal cancer outcomes.

Notably, we found more than half of our patients with lung cancers and COVID-19 required hospitalization and almost a quarter died. These findings from our patients at a single center in New York add to evidence, supported by reports of outcomes of mostly hospitalized patients with cancer from Hubei province (10, 34), throughout China (35), and a cohort largely from northern Italy (27), that patients with lung cancers are a particularly vulnerable population with high rates of severe COVID-19.

These initial results are promising for the safety of continued use of PD-1 blockade during the COVID-19 pandemic.

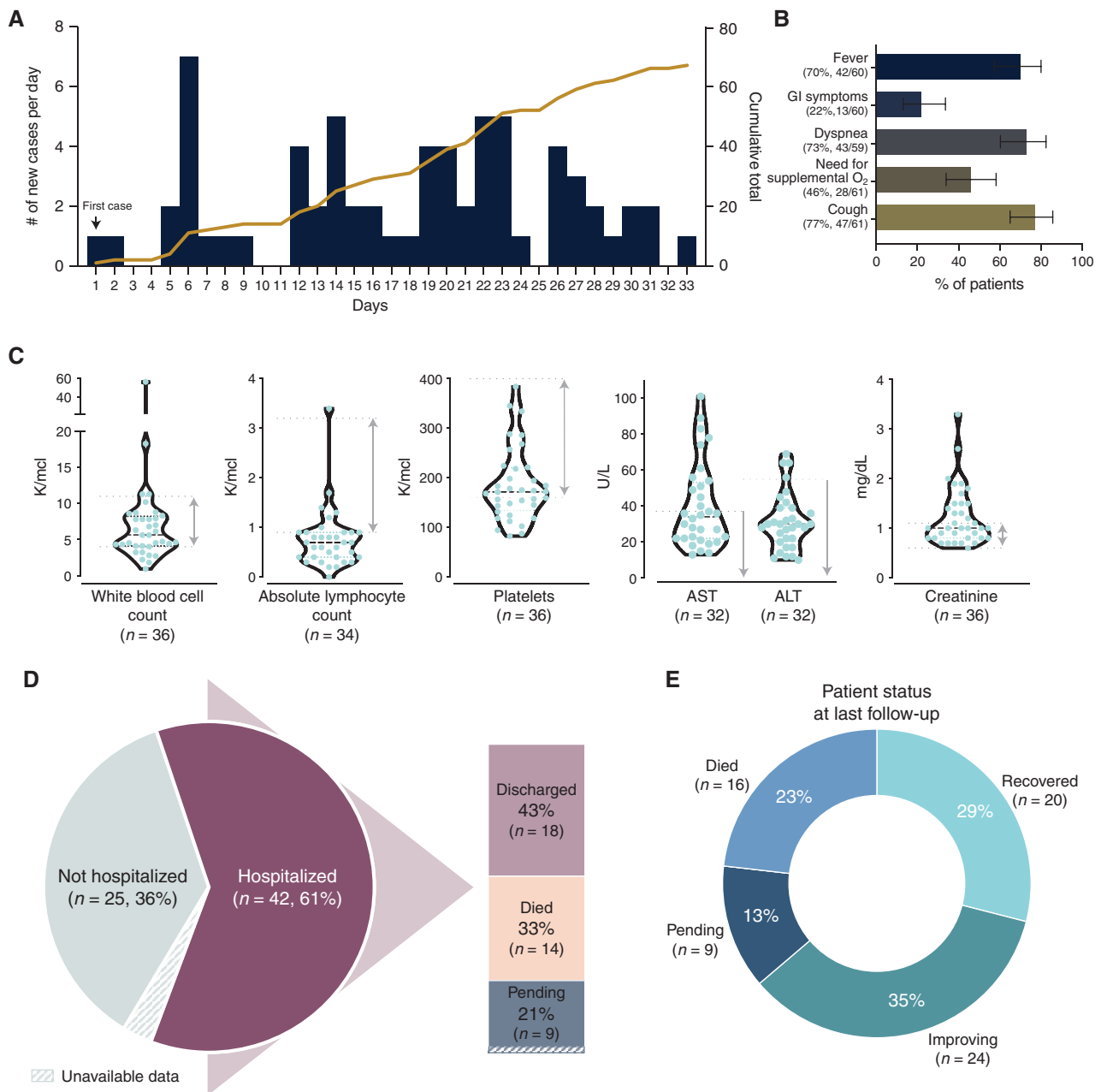


Figure 1. COVID-19 in patients with lung cancers. **A**, Daily cases and cumulative incidence of positive SARS-CoV-2 tests in patients with lung cancer. Date of positive SARS-CoV-2 test was unknown for 2 (3%) patients. **B**, Presenting signs and symptoms of COVID-19 infection in patients with known information. The most common presenting symptom was cough (77%) followed by dyspnea (73%), fever (70%), and need for supplemental oxygen (46%). Gastrointestinal symptoms were least common (22%). Error bars reflect 95% CI estimates of the population proportion. **C**, Baseline white blood cell count (median, 5.6 K/mcl; IQR, 4.1–8.2 K/mcl), absolute lymphocyte count (median, 0.7 K/mcl; IQR, 0.4–0.9 K/mcl), platelet count (median, 172 K/mcl; IQR, 134–220 K/mcl), aspartate aminotransferase (AST; median, 34 U/L; IQR, 22–53 U/L), alanine aminotransferase (ALT; median, 30 U/L; IQR, 21–39 U/L), and serum creatinine (median, 1.0 mg/dL; IQR, 0.8–1.5 mg/dL) in patients at the time of COVID-19 diagnosis. Dots represent individual values. Violin plots show the median and kernel density estimate distributions of each laboratory value. Dashed lines represent median, 25% percentile, and 75% percentile. Dotted lines and arrows in gray represent the normal range of the laboratory value. **D**, Exploded pie chart shows the rate of hospitalization (61%), and the status of patients requiring hospitalization. **E**, Patients were identified starting from the first case on March 12, 2020, through April 13, 2020, and followed until April 17, 2020. Median follow-up was 14 days (IQR, 7–23 days). Donut plot of patient status in regard to COVID-19 diagnosis at the time of last follow-up.

Table 1. Baseline characteristics and clinical course of patients with lung cancers and positive SARS-CoV-2 test

Patients characteristics	Patients (n = 69) no./total no. ^a (%)
Age	
Median (range), year	69 (31–91)
Sex	
Female	36/69 (52%)
Male	33/69 (48%)
Race	
White	40/69 (58%)
Black	12/69 (17%)
Asian	11/69 (16%)
Other	2/69 (3%)
Unknown	4/69 (6%)
Ethnicity	
Hispanic or Latino	8/69 (12%)
Non-Hispanic or Latino	57/69 (82%)
Unknown	4/69 (6%)
Prior smoking history ^b	
<5 pack-years	25/69 (36%)
≥5 pack-years	44/69 (64%)
Lung cancer-specific features	
Non-small cell lung cancer	64/69 (93%)
Small-cell lung cancer	5/69 (7%)
Metastatic or active lung cancer ^c	55/69 (80%)
Prior thoracic surgery or radiotherapy	32/69 (46%)
Comorbid conditions	
COPD ^d	12/69 (17%)
Non-COPD lung disease ^e	14/69 (20%)
Obesity (BMI ≥ 30)	23/69 (33%)
Hypertension	38/69 (55%)
Congestive heart failure ^f	5/69 (7%)
Diabetes mellitus	21/69 (30%)
Clinical course	
Hospitalization	42/67 ^a (63%)
Admission to ICU/receipt of intubation/transition to DNI	24/65 ^a (37%)
Admission to ICU	15/65 ^a (23%)
Receipt of intubation and mechanical ventilation	13/64 ^a (20%)
Transition to do not resuscitate/DNI ^g	10/65 ^a (18%)
Death	16/67 ^a (24%)

Abbreviations: COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association (Class III, IV, etc.).

^aDenominators reflect available data; unless specified, unknowns are not included.

^bFive pack-years was chosen prospectively as a threshold to differentiate those with minor/no tobacco exposure and those with heavy tobacco exposure.

^cMetastatic or active lung cancer was defined as patients with metastatic lung cancer or patients undergoing active treatment for lung cancer (e.g., neoadjuvant or adjuvant therapy).

^dCOPD was defined as anyone with this diagnosis listed as a part of past medical history plus either an abnormal pulmonary function test interpreted as consistent with COPD or had inhalers for COPD listed in the outpatient medication record. Patients with only radiologic evidence of COPD or a note in the medical record that the diagnosis was in question were not included.

^eNon-COPD lung disease was defined as underlying lung disease other than COPD (e.g., reactive airways disease, pneumonitis, abnormal pulmonary function test interpreted as underlying lung disease, etc.).

^fCongestive heart failure was defined as anyone with NYHA functional class I–IV disease. As such, anyone with this diagnosis listed as a part of the past medical history or an abnormal cardiac echocardiogram demonstrating evidence of structural heart disease consistent with this diagnosis was included.

^gAn additional 4 patients received intubation and invasive mechanical ventilation and subsequently elected not to receive further necessary intensification of care or interventions.

Table 2. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers

Patient characteristics	No prior PD-1 blockade (N = 28) no. (%)	Prior PD-1 blockade (N = 41) no. (%)	P
Sex			
Female	20 (71%)	16 (39%)	0.01
Male	8 (29%)	25 (61%)	
Age (years)			
<70	17 (61%)	22 (54%)	0.6
≥70	11 (39%)	19 (46%)	
Prior smoking history (pack-years) ^a			
<5	17 (61%)	8 (20%)	<0.001
≥5	11 (39%)	33 (80%)	
Body mass index			
<30	17 (61%)	29 (71%)	0.4
≥30	11 (39%)	12 (29%)	
COPD ^b	3 (9%)	9 (36%)	0.06
Non-COPD lung disease ^c	3 (11%)	11 (27%)	0.1
Hypertension	12 (43%)	26 (63%)	0.1
Congestive heart failure ^d	1 (4%)	4 (10%)	0.6
Diabetes mellitus	5 (18%)	16 (39%)	0.07
Metastatic or active lung cancer ^e	19 (68%)	36 (88%)	0.07
Prior thoracic surgery or radiation therapy	13 (46%)	19 (46%)	1.0

Abbreviation: COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association (Class III, IV, etc.).

^aFive pack-years was chosen prospectively as a threshold to differentiate those with minor/no tobacco exposure vs. heavy tobacco exposure.

^bCOPD was defined as anyone with this diagnosis listed as a part of past medical history plus either an abnormal pulmonary function test interpreted as consistent with COPD or had inhalers for COPD listed in the outpatient medication record. Patients with only radiologic evidence of COPD or a note in the medical record that the diagnosis was in question were not included.

^cNon-COPD lung disease was defined as underlying lung disease other than COPD (e.g., reactive airways disease, pneumonitis, abnormal pulmonary function test interpreted as underlying lung disease, etc.).

^dCongestive heart failure was defined as anyone with NYHA functional class I-IV disease.

^eMetastatic or active lung cancer was defined as patients with metastatic lung cancer or patients undergoing active treatment for lung cancer (e.g., neoadjuvant or adjuvant therapy).

Further follow-up and expanded sample sizes are needed to confirm long-term safety and generalizability of our findings. Universal screening efforts are needed to further determine how PD-1 blockade may affect susceptibility to COVID-19.

METHODS

Ethics Approval

This retrospective study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSK; protocol 20-142), which granted a waiver of informed consent.

Patients

Our study population included all patients with a diagnosis of lung cancers being treated at MSK who had a positive SARS-CoV-2 RT-PCR test between the first case identified on March 12, 2020, through April 13, 2020, followed through April 17, 2020. We did not include patients with suspected but unconfirmed COVID-19. We did not include any patients who were receiving hospice care alone at the time of diagnosis of COVID-19. We employed several data sources to identify patients, including ICD-9 diagnosis codes, pathology reports, institutional databases, and survey

of physicians in the Thoracic Oncology Service at MSK. To minimize selection bias and competing outcomes, patients with known COVID-19 diagnosis were included irrespective of whether COVID-19 was diagnosed at MSK ($n = 45$) or other healthcare facilities ($n = 33$).

We identified 78 patients who fit these criteria. We then excluded an additional 9 patients who did not have any information detailing their history, disposition, or vital status after the positive test. The cohort for this analysis was the remaining 69 patients.

Patient records were manually reviewed to identify demographics, prior smoking history, baseline clinical characteristics, comorbid conditions, pathology characteristics, treatments, symptoms, laboratory values, disease course, and vital status. In particular, smoking history was collected on the basis of a detailed self-reporting survey, including pack-year quantification, provided to all patients with a diagnosis of lung cancer at MSK. Additional details were manually reviewed in the medical history. Molecular testing results were obtained through institutional databases. Medications were obtained through pharmacy records. Baseline laboratory values included complete blood count, serum creatinine, liver function tests, and inflammatory/injury markers obtained on the day of the positive test. If no blood tests were obtained on the date of the SARS-CoV-2 test, we used the value the day before or day after.

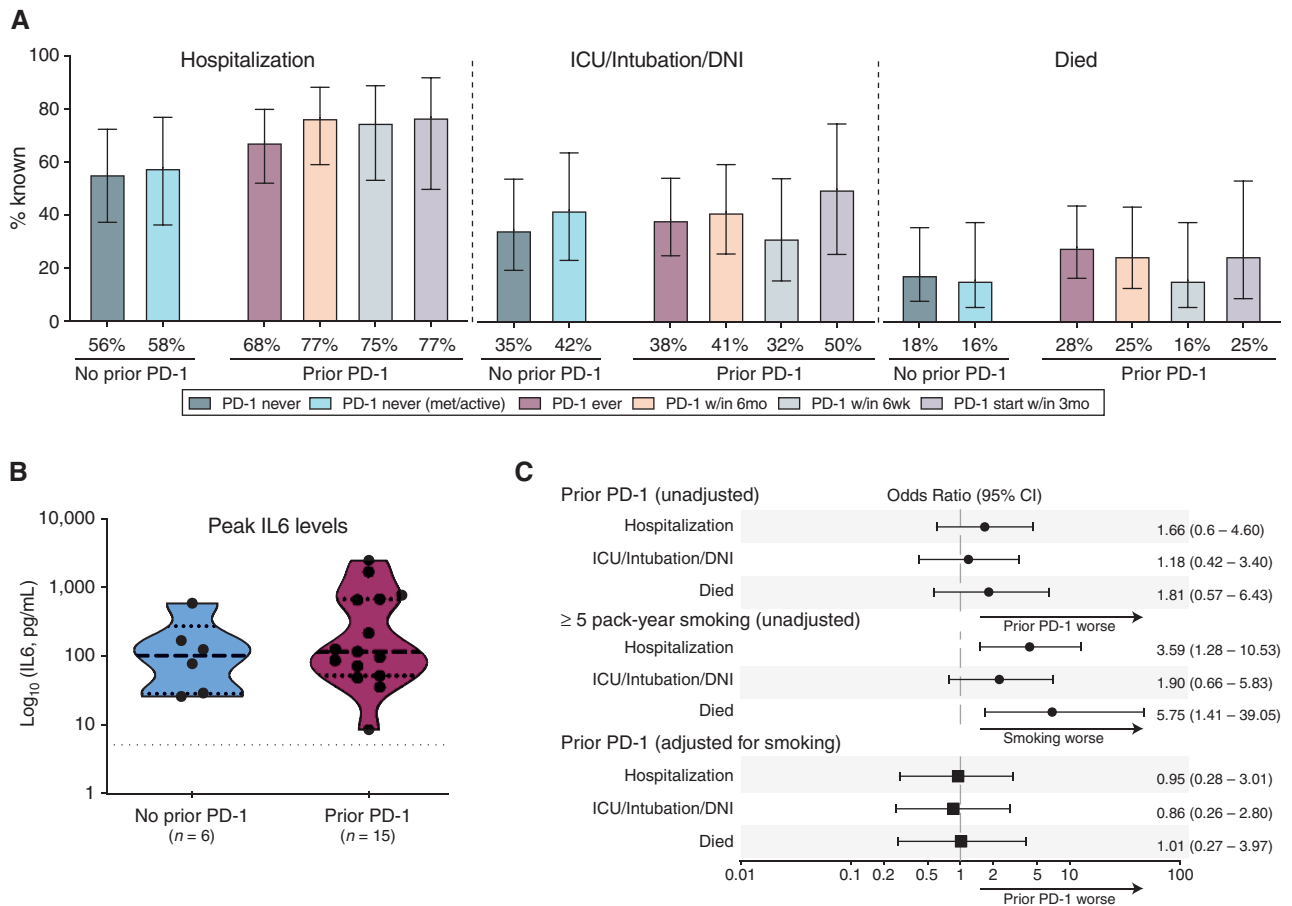


Figure 2. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. **A**, Rate of hospitalization (left), ICU admission, need for intubation, and/or change to DNI status to avoid need for intensification of care (e.g., intubation; middle), or death (right) among patients with lung cancers with no prior PD-1 blockade exposure and those with prior PD-1 blockade exposure. Patients with no prior PD-1 blockade exposure are shown as all patients ($n = 28$), or limited to those with metastatic disease and/or ongoing active treatment for lung cancer ($n = 19$). Patients with prior PD-1 blockade exposure are shown as all patients ($n = 40$), those who had received the most recent dose of PD-1 blockade within 6 months of COVID-19 diagnosis ($n = 30$), those who had received the most recent dose of PD-1 within 6 weeks of COVID-19 diagnosis ($n = 20$), or those who began PD-1 blockade within 3 months of COVID-19 diagnosis ($n = 13$). Histogram represents the rate among patients with known status of the outcome displayed (known hospitalization status = 67/69, known ICU/intubation/DNI status = 65/69, and known died status = 67/69). Percent of cases are below each bar. Error bars represent 95% CIs. **B**, IL6 levels in patients with COVID-19, showing per-patient peak levels in no prior PD-1 blockade treated compared with prior PD-1 blockade treated. Dots represent individual values. Dashed lines represent median, 25% percentile, and 75% percentile. Violin plots show min-max ranges and kernel density estimate distributions of each group. Dotted line represents the upper limit of the normal range, 5 pg/mL. **C**, Forest plot showing unadjusted ORs for the impact of never receiving PD-1 blockade compared with any prior receipt of PD-1 blockade on severity outcomes associated with COVID-19 (hospitalization, ICU/intubation/DNI, and death). Unadjusted ORs for the impact of smoking history (<5 pack-years vs. ≥5 pack-years) on severity outcomes associated with COVID-19 (hospitalization, ICU/intubation/DNI, and death). ORs adjusted for smoking history, for the impact of never receiving PD-1 blockade compared with any prior receipt of PD-1 blockade on severity outcomes associated with COVID-19 (hospitalization, ICU/intubation/DNI, and death). ORs were calculated using univariate and multivariate logistic regression. Error bars represent 95% CIs. The x-axis is on a log scale.

Extracted results were entered into a clinical data form for subsequent analysis.

Data elements extracted from the medical records were predefined by clinicians and researchers J. Luo, H. Rizvi, and M.D. Hellmann after reviewing existing literature on COVID-19. Data were manually abstracted by J. Luo, H. Rizvi, J.V. Egger, I.R. Preeshagul, and M.D. Hellmann, each trained clinicians or researchers skilled at clinical data abstraction. Abstraction results were spot-checked independently by a second individual in the research team for reliability.

Study Outcomes

Outcomes of interest included dates of hospitalization, admission to ICU, intubation and invasive mechanical ventilation, transition to DNI (specifically in place of otherwise urgent need for intensification of care and/or intervention such as intubation for treatment

of hypoxic respiratory failure), death (at home or inpatient), and recovery. Disposition included discharge date. Status of the patient on the date of the datalock (recovered, improving, pending, or died) was determined by clinicians reviewing all available hospital records leading up to the date of the datalock. For patients being treated at MSK who were admitted to outside hospitals for care of COVID-19 ($n = 17$), details of hospital course and severity outcomes were obtained when possible by review of existing outside hospital records and from personal communication with primary oncologists. Patients with unknown status for a given severity outcome were coded as unknown and removed from analysis for that outcome.

Recovered was defined as at least 3 days since resolution of COVID-19 symptoms per CDC guidelines. Improving was defined as existence of a preponderance of evidence in the medical record (dates of disease course, notes, vital signs, and laboratory values) that

the patient was steadily improving with a trajectory toward recovery from COVID-19. The status of all other patients who had not died was categorized as pending.

Statistical Analysis

Our preplanned primary analysis was a comparison of outcomes between individuals who received PD-1 blockade therapy compared with individuals who did not receive PD-1 blockade therapy. This comparison relied on the assumption that in otherwise similar groups of patients, prior or recent PD-1 blockade therapy may directly affect the severity of COVID-19 infection, for better or for worse.

COVID-19 severity outcomes of interest were defined *a priori* as: hospitalization, death, and a composite metric of severe disease (ICU stay, need for intubation and invasive mechanical ventilation, and/or transition to DNI). These outcomes were chosen because they are well-defined, objective, nontransient, reliably recorded, and reflect increasing severity of COVID-19. The composite metric encompasses reliable measurements that reflect a similar severity of COVID-19.

To test our two-sided hypothesis, we first compared *a priori* defined characteristics of patients who have had no prior exposure to PD-1 blockade therapy to those who had and their COVID-19 outcomes. To identify potential covariates (effect modifiers and confounders by indication), we used literature review, directed acyclic graphs, and backward exclusion of nonsignificant ($P > 0.05$) imbalances in baseline characteristics. We found two significant confounders of severe COVID-19 outcomes in patients with lung cancer: Smoking history had a very strong effect ($P < 0.001$); gender had a weaker effect ($P = 0.01$). We performed unadjusted comparisons of outcomes using a univariate logistic regression model.

Using multivariate logistic regression, we calculated adjusted ORs in which the dependent variable was PD-1 blockade exposure and the independent variable included smoking status as the key covariate of interest, given the statistical imbalance based on PD-1 exposure as well as the biological hypothesis that prior smoking exposure may also affect COVID-19 severity outcomes. As a sensitivity analysis, we adjusted for both smoking history and gender.

As another measurement of robustness, we examined different bioplausible (19–21, 28) definitions to define the proximity of prior PD-1 blockade exposure. This included those who received PD-1 blockade at any time previously, those in whom the most recent dose of PD-1 blockade was within 6 months of COVID-19 diagnosis, those in whom the most recent dose of PD-1 blockade was within 6 weeks of COVID-19 diagnosis, or those who had initiated PD-1 blockade within 3 months of COVID-19 diagnosis.

We performed descriptive statistics characterizing COVID-19 in this patient population. The 95% CI around the estimates reflects an alpha level of 0.025 in each tail. Statistical analyses were performed using Prism 8.4.2 and R statistical software 3.6.2 using glm.

Disclosure of Potential Conflicts of Interest

I.R. Preeshagul has served on an advisory board for Pfizer and AstraZeneca. J.D. Wolchok is a consultant at Astellas, Kyowa Hakko Kirin, Truvax, Sellas, Seramatrix, Surface Oncology, Syndax, Syntalogic, Amgen, Ascentage, Bayer, Boehringer Ingelheim, Merck, Neon Therapeutics, Polynoma, Psioxus, Recepta, Takara, Trieza, and Elucida; reports receiving commercial research grants from Bristol-Myers Squibb, AstraZeneca, and Sephora; and has ownership interest (including patents) in Tizona Therapeutics, Adaptive Biotech, anti-CTLA4 antibodies, anti-GITR antibodies and methods of use thereof, Imvaq, Beigene, Linneaus, Arsenal IO, Apricity, myeloid-derived suppressor cell (MDSC) assay, xenogeneic DNA vaccines, and anti-PD1 antibody. M.D. Hellmann is a consultant at Merck, Bristol-Myers Squibb, Achilles, Arcus, AstraZeneca, Genentech/

Roche, Nektar, Syndax, Mirati, Shattuck Labs, Immunai, and Blueprint Medicines; reports receiving a commercial research grant from Bristol-Myers Squibb; has ownership interest (including patents) in Shattuck Labs, Immunai, Arcus, and PCT/US2015/062208, and has received travel support/honoraria from AstraZeneca, Eli Lilly, and Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J. Luo, I.R. Preeshagul, M.D. Hellmann
Development of methodology: J. Luo, H. Rizvi, M.D. Hellmann
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Luo, H. Rizvi, I.R. Preeshagul, M.D. Hellmann

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Luo, H. Rizvi, I.R. Preeshagul, J.D. Wolchok, M.D. Hellmann

Writing, review, and/or revision of the manuscript: J. Luo, I.R. Preeshagul, J.D. Wolchok, M.D. Hellmann

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Luo, J.V. Egger, M.D. Hellmann

Study supervision: M.D. Hellmann

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