

# A Multidisciplinary Approach for Patients with Preexisting Lung Diseases and Immune Checkpoint Inhibitor Toxicities

JARUSHKA NAIDOO<sup>a,b</sup>, KARTHIK SURESH<sup>c</sup>

<sup>a</sup>Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, <sup>b</sup>Bloomberg-Kimmel Institute for Cancer Immunotherapy, and

<sup>c</sup>Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

## INTRODUCTION

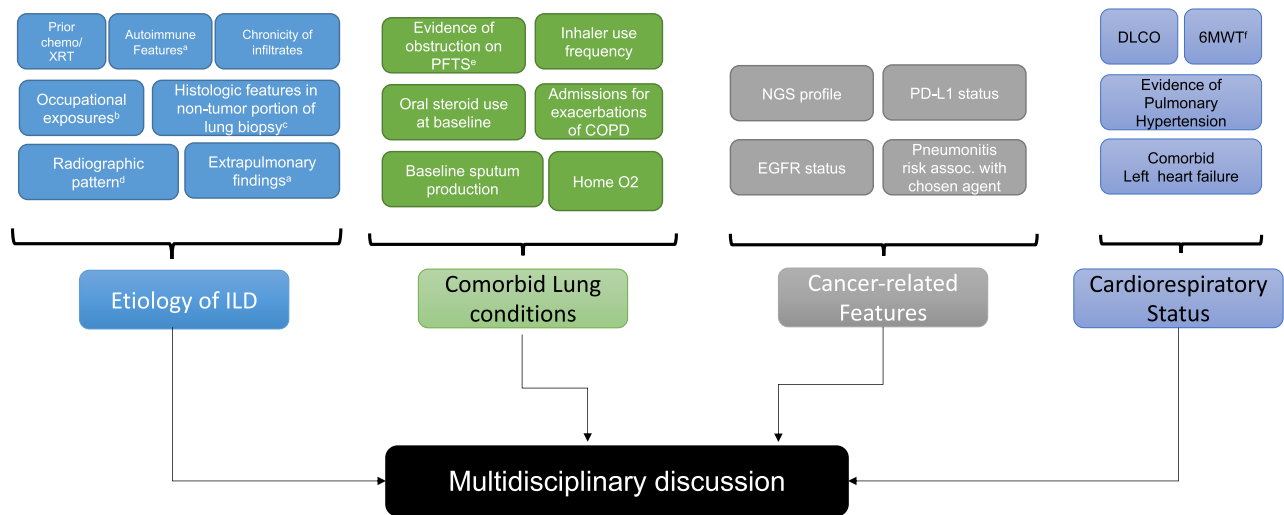
With increasing evidence supporting the efficacy of anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand-1 (PD-L1) immune checkpoint inhibitors (ICIs) across tumor types, the scope of use for these medications has broadened from clinical trials to clinical practice. However, this class of agents is associated with pulmonary toxicities [1–4]. In particular, recent attention has focused on a higher real-world incidence and mortality from ICI-pneumonitis than previously identified in clinical trials [2]. There is also a growing recognition that the prevalence of common pulmonary comorbidities, particularly in patients with non-small cell lung cancer (NSCLC), further complicates the risk assessment for development of ICI-pneumonitis, as well as the management of ICI-pneumonitis once it occurs. Therefore, careful consideration of pneumonitis risk is warranted in patients with preexisting lung disease, prior to initiation of ICIs. In particular, preexisting interstitial lung disease (ILD) poses a significant challenge. Indeed, patients with cancer and antecedent ILD that are due to commence anti-PD-1/PD-L1 ICIs are routinely evaluated at our institution by a multidisciplinary immune-related (IR) toxicity team [5]. Our multidisciplinary team incorporates input from pulmonary medicine, infectious diseases, radiology, pathology, and medical oncology. Patients with known ILD usually require evaluation by pulmonary medicine, oncology, and radiology at a minimum via password-protected electronic referral to relevant members of our institutional IR toxicity team. In the absence of prospective data to guide risk assessment, our team obtains several clinical and radiographic evaluations in these patients, with the goal of (a) providing a means of additional risk stratification regarding worsening known ILD and/or precipitating ICI-pneumonitis in patients with known pulmonary comorbidities and (b) helping to discern between development of ICI-pneumonitis and worsening of a known baseline pulmonary condition, if a patient goes on to develop ICI-pneumonitis. We advocate for completion of these tests at baseline and to facilitate guiding oncology

providers on when to seek a dedicated evaluation by ILD or pulmonary specialists.

## INTERSTITIAL LUNG DISEASE

ILD comprises a heterogeneous group of diseases affecting the pulmonary interstitium, characterized by active inflammation that, in many cases, progresses to chronic fibrosis. Overall, these changes result in reduced pulmonary compliance and gas exchange. In patients with ILD, selected chemotherapies may induce more frequent or severe exacerbations of known ILD or chemotherapy-induced pneumonitis. A number of features of the antecedent ILD are associated with these outcomes, including baseline lung function (vital capacity) [6], radiologic pattern of ILD [7], and extent of ground-glass opacities on computed tomography (CT) imaging [8]. Even though the mechanisms underlying interstitial damage may be different, baseline lung function [9] and extent of radiologic changes on CT [10] are also associated with development of pneumonitis from systemic cytotoxic agents (e.g., bleomycin [9]) and radiation pneumonitis [10]. In pneumonitis that occurs from anti-PD-1/PD-L1 ICIs, 26 patients with known ILD were treated with nivolumab in a retrospective series, demonstrating nearly three times the rate of ICI-pneumonitis versus those without ILD (31% vs. 12% [11]). In contrast, in a pilot trial of six patients with preexisting ILD, nivolumab did not precipitate any ICI-pneumonitis events [12]. Taken together, there are insufficient data to truly inform an evidence-based risk stratification approach for ILD exacerbations or de novo ICI-pneumonitis from ICIs in patients with known ILD. Despite this, many patients with a variety of ILD etiologies and severity are currently receiving ICIs for NSCLC. We have begun applying a standardized approach, based on current evaluation paradigms for ILD patients without cancer, to inform a comprehensive clinical, radiologic, and functional assessment of the chronicity and severity of preexisting ILD in patients with

Correspondence: Jarushka Naidoo, M.H.S., Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Suite 4500, 301 Mason Lord Drive, Baltimore, Maryland 21224, USA. Telephone: 410-550-2646; e-mail: jnaidoo1@jhmi.edu Received April 2, 2020; accepted for publication July 6, 2020; published Online First on September 14, 2020. <http://dx.doi.org/10.1634/theoncologist.2020-0266>  
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**Figure 1.** Clinical considerations for patients with preexisting lung conditions due to commence anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1(PD-L1) therapy. Clinical, radiologic, and functional assessment in patients with preexisting lung conditions due to receive anti-PD-1/PD-L1 immune checkpoint inhibitors. a, Rashes (Gottron's papules, Heliotrope rash), evidence of synovitis, family history of rheumatoid arthritis or systemic lupus erythematosus, history of dry eyes or mouth, Raynaud's phenomenon. b, Steelworkers, farmers, exposures to heavy metals, organic fumes, dusts, and birds. c, such as poorly formed granulomas and lymphocytic aggregates. d, NSIP vs. UIP-pattern, evidence of air trapping, lobar dominance; e, may present as complex obstruction ( $TLC_{pp} - FVC_{pp} > 15$ ); f, may present as complex obstruction ( $TLC_{pp} - FV_{pp} > 15$ ).

Abbreviations: 6MWT, 6-minute walk test; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; EGFR, epidermal growth factor receptor; FV<sub>pp</sub>, Forced vital capacity percent predicted; ILD, interstitial lung disease; NGS, next-generation sequencing; NSIP, non-specific interstitial pneumonia; PFT, pulmonary function test; TLC<sub>pp</sub>, total lung capacity percent predicted; UIP, usual interstitial pneumonia; XRT, radiotherapy.

cancer. We have consistently used this framework to assess ILD exacerbation and ICI-pneumonitis risk (Fig. 1).

### ETIOLOGY OF ILD

Although a full description of the evaluation of ILD is beyond the scope of this commentary, it is important to identify patients with a clinical history suggestive of ILD prior to starting anti-PD-1/PD-L1 ICIs. For instance, clinical stigmata of known autoimmune diseases could suggest a connective tissue ILD. However, presence of mechanic's hands or Gottron's papules should prompt further assessment for antibodies associated with inflammatory myositis related ILD, and dysphagia, Raynaud's phenomenon, or significant arthritis raises concern for comorbid rheumatic disease (e.g., scleroderma, rheumatoid arthritis, and systemic lupus erythematosus) as an etiology for ILD. History of work in farming, mining, steel-working, or exposure to organic fumes or moldy dusts should also be assessed, as well as nonoccupational exposures such as birds and hot tubs. Presence of these exposures should prompt further evaluation for occupational ILD and hypersensitivity pneumonitis. If identified, ongoing exposure to these offending antigens can be mitigated. Evaluation of the radiographic pattern of ILD on CT imaging (e.g., usual interstitial pneumonitis vs. nonspecific interstitial pneumonitis pattern) can point to the underlying etiology of ILD, with serial images ideally assessed together with a radiologist in a multidisciplinary fashion. ILD severity can also be evaluated by pulmonary function tests (PFTs), through assessment of diffusing capacity of the lung for carbon monoxide (DLCO), forced expiratory volume at 1 second (FEV<sub>1</sub>), and forced vital capacity (FVC). Correlation of pre-ICI PFTs with prior PFTs can also provide valuable insight into ILD chronicity and severity.

### PRESENCE OF COMORBID NON-ILD LUNG DISEASE

Patients with NSCLC in particular have a high prevalence of chronic obstructive pulmonary disease (COPD). Acute exacerbations of COPD may be frequent and complicate a diagnosis of ICI-pneumonitis. The severity of COPD at baseline in patients pre-ICI may help to identify those at greater risk for exacerbations. At particular risk are those COPD patients with frequent inhaler or nebulizer use, recent hospitalizations, and frequent corticosteroid prescriptions. Patients may also have signs of lung obstruction due to tumor-mediated compression, and selected case reports have shown early ICI-pneumonitis development in these patients [13]. In these cases, the need to differentiate pulmonary infection (especially distal to the obstruction) from ICI-pneumonitis is paramount. Patients with cancer suitable for receipt of ICI may also have a higher risk of aspiration, such as those with head and neck cancers, pulmonary resection, or recurrent laryngeal nerve palsies [14]. These patients may exhibit resultant interstitial lung changes that complicate the diagnosis of ICI-pneumonitis. Presence of brain metastases, prior cerebrovascular accident, patulous esophagus on imaging, or asymmetric (right middle and lower lobe-predominant) infiltrates raise concerns for underlying aspiration. These patients may benefit from a formal swallow assessment, or equivalent study, prior to ICI.

### CANCER-RELATED FEATURES

Specific features of a patient's cancer have also been found to be relevant in terms of ICI-pneumonitis risk. Recently, patients with stage III NSCLC treated with durvalumab were shown to be at a higher risk for ICI-pneumonitis if their tumor possessed an activating *EGFR* mutation or *ALK* alteration [15]. In stage IV

NSCLC however, these patients do not appear to benefit from PD-1/PD-L1 monotherapy [16], but may benefit from selected PD-1/PD-L1-based combinations [17]. Additionally, retrospective data has shown that sequential EGFR tyrosine kinase inhibitor (TKI) therapy with osimertinib followed by anti-PD-1/PD-L1 therapy, results in severe pneumonitis [18]. However, no pneumonitis was seen when osimertinib preceded anti-PD-1/PD-L1 therapy, or other EGFR TKIs were used. Other biomarkers that are used to select patients for anti-PD-1/PD-L1 therapy, do not seem to imply ICI-pneumonitis risk. For example, tumoral PD-L1 immunohistochemical expression is used to select patients with NSCLC, platinum-ineligible urothelial carcinoma, and triple negative breast cancer for PD-1/PD-L1 monotherapy or chemotherapy-PD-1/PD-L1 combinations, but does not appear to associate with ICI-pneumonitis risk. We therefore advocate for ensuring that assessment for relevant tumor biomarkers of ICI response/nonresponse are completed prior to ICI treatment selection, in order to (a) provide the treatment most likely to generate an ICI response and (b) minimize ICI-pneumonitis risk.

### CARDIAC FACTORS

The diagnosis of ICI-pneumonitis can also be complicated by comorbid cardiorespiratory conditions such as congestive heart failure or pulmonary hypertension. These conditions may result in a clinical presentation of pulmonary edema, which can cause sudden interstitial lung changes, mimicking ICI-pneumonitis. In this context, it may be prudent for patients with these conditions to undergo baseline cardiac clinical evaluation (S3, raised jugulovenous pressure, lower extremity edema), echocardiogram to quantify left and right heart function and valvular disease, and CT imaging and pulmonary function testing. Specifically, a reduction in DLCO that is disproportionate to the FEV1 and FVC, especially when observed with clinical evidence of volume overload, should raise concerns for underlying pulmonary hypertension.

### CONCLUSION

The presence of preexisting lung conditions such as ILD, COPD, aspiration, and cardiorespiratory disorders is prevalent

in patients with cancer, and particularly NSCLC. The evaluation and management of these conditions while safely delivering anticancer therapy has been a long-standing challenge for medical oncologists. In the era of immunotherapy for cancer, new challenges in managing the pulmonary toxicities of ICIs in these patient populations now exist.

While awaiting prospective data and validated risk stratification tools, we propose a multidisciplinary approach to perform comprehensive clinical, radiologic, and lung functional assessment in patients with known ILD pre-ICI. Although no specific thresholds for determining safety of ICI administration in ILD currently exist, consideration of the abovementioned factors may provide preliminary guidance regarding suitability for ICIs and a baseline from which to monitor patients after they start ICIs. Indeed, because patients with NSCLC have a higher incidence of ICI-pneumonitis [19], the role for a multidisciplinary assessment pre-ICI is a thought-provoking research question. However, in the absence of known risk assessment tools, this is currently not a standard approach at our institution or others.

Challenges and areas for additional research at present include (a) feasibility of completing the above assessments in a timely fashion pre-ICI, (b) interpreting values without clearly defined cut-off values that associate with increased risk, and (c) designing prospective studies to validate these approaches. Importantly, prospective risk assessment studies will require coordination between interested pulmonologists and medical oncologists that work in concert, or in the context of a multidisciplinary IR-toxicity team. However, the era of immunotherapy is upon us, and we will need to tailor our approach to these patients today while waiting for prospectively validated data.

### DISCLOSURES

**Jarushka Naidoo:** Merck, AstraZeneca (RF), Bristol Myers-Squibb, AstraZeneca, Roche/Genentech (C/A), Merck, AstraZeneca, Bristol Myers-Squibb (H). **Karthik Suresh** indicated no financial relationships.

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