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Knowledge Gaps and Research Priorities in Immune Checkpoint Inhibitor–related Pneumonitis
An Official American Thoracic Society Research Statement: Executive Summary

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Rationale: Immune checkpoint inhibitors (ICIs) have revolutionized cancer care but are associated with unique adverse events, including potentially life-threatening pneumonitis. The diagnosis of ICI-pneumonitis is increasing; however, the biological mechanisms, clinical and radiologic features, and diagnosis and management have not been well defined.

Objectives: To summarize evidence, identify knowledge and research gaps, prioritize topics, and propose methods for future research on ICI-pneumonitis.

Methods: A multidisciplinary group of international clinical researchers reviewed available data on ICI-pneumonitis to develop and refine research questions pertaining to ICI-pneumonitis.

Results: This statement identifies gaps in knowledge and develops potential research questions to further expand knowledge regarding risk, biologic mechanisms, clinical and radiologic presentation, and management of ICI-pneumonitis.

Conclusions: Gaps in knowledge of the basic biological mechanisms of ICI-pneumonitis, coupled with a precipitous increase in the use of ICIs alone or combined with other therapies, highlight the importance in triaging research priorities for ICI-pneumonitis.

Keywords: lung cancer; immunotherapy; interstitial lung disease; NSCLC

Contents

Overview

Immune checkpoint inhibitors (ICIs) have transformed cancer therapy. The steep increase in ICI use in a number of different cancers, both alone and in combination with other cancer therapies, has led to an increase in immune-related adverse side effects (irAEs), including potentially fatal ICI-related pneumonitis (ICI-pneumonitis). Development of irAEs, including ICI-pneumonitis, is sporadic, unpredictable, and relatively uncommon in a single practice or hospital setting, therefore making it difficult to study systematically. This research statement describes and provides a rationale for key questions related to the etiology, diagnosis, and management of ICI-pneumonitis, with the aim to prioritize research that can rapidly improve our diagnosis and management of these patients. Key conclusions of the five research focus sections are detailed below:

Key Topics and Conclusions

- Need for consistent and accurate terminology for describing the features of ICI-pneumonitis
  - Terminology used in the literature to define, diagnose, and describe the radiologic findings of ICI-pneumonitis has been inconsistent.
  - The use of common terminology to describe the characteristic features, particularly the radiologic features, of ICI-pneumonitis is needed.
- Understanding the biological mechanisms underlying ICI-pneumonitis
  - Possible mechanisms for development of ICI-pneumonitis include increased T-cell activity against autoantigens, increased levels of inflammatory cytokines, and enhanced complement-mediated inflammation; however, the key biologic mechanisms remain poorly understood.
  - The paucity of data on the biologic mechanisms of ICI-pneumonitis has resulted in a limited understanding of how best to treat ICI-pneumonitis.
  - It is not known if there is a correlation between the underlying biologic and immunologic mechanisms of ICI-pneumonitis and specific clinical and radiologic manifestations.
  - It is unclear if risk factors, such as preexisting rheumatologic or lung diseases or treatment with other cancer therapies (chemotherapy and radiation therapy), predispose to development of ICI-pneumonitis.
  - Whether steroid-responsive and steroid-refractory ICI-pneumonitis represent disease processes with different biological mechanisms remains uncertain.
- Identifying risk factors and populations at risk for ICI-pneumonitis
  - Because patients with underlying rheumatologic or lung diseases have been underrepresented in clinical trials, it is unknown if comorbid conditions are associated with increased risk for developing ICI-pneumonitis.
  - Whether specific tumor characteristics or treatment with other cancer drugs or radiation therapy increase the incidence of ICI-pneumonitis remains uncertain.
  - How best to risk stratify these patients using baseline physiologic, radiologic, and serologic evaluation is poorly understood and in need of research.
- Optimizing the diagnostic evaluation of ICI-pneumonitis
  - Current recommendations for the diagnostic evaluation of ICI-pneumonitis come without clear evidence that these differentiate between ICI-pneumonitis and infection.
  - The role of physiologic testing (pulmonary function tests) before treatment, for subsequent evaluation of patients with suspected ICI-pneumonitis, or for screening asymptomatic patients on ICIs for early lung injury remains undefined and should be incorporated in research studies.
  - The role and timing of bronchoscopy with BAL in the diagnostic evaluation of ICI-pneumonitis deserves further investigation.
  - Infections pose a major risk for patients who experience irAEs, and the risk is increased when patients are treated with immunosuppressive therapy; however, the incidence, impact, and role infections play in the development and severity of ICI-pneumonitis is unclear. Furthermore, what tests, which patients should be tested, the timing of testing, and the role of bronchoscopy with BAL to diagnose infection is unknown.
- Optimal management of ICI-pneumonitis
  - It is unclear which asymptomatic radiographic changes warrant a change in patient management; whether treatment of symptomatic ICI-pneumonitis changes the course of the disease; what the optimal timing, dose, and duration of treatment with steroids should be; and whether steroid dose and treatment duration impact outcomes. In addition, few data are available to guide clinicians in the diagnostic evaluation of these patients.
  - For patients who do not respond to steroid therapy, the role of steroid-sparing agents should be studied in clinical trials.
  - A major concern raised when steroids are used to treat ICI-pneumonitis is the potential for adverse impact on the ICI antitumor response and the increased risk of infection. Studies evaluating the additive effect of steroid therapy compared with withdrawal of therapy or to steroid-sparing therapies are needed.
- Tables are provided with key topics and proposed research tools to address questions pertaining to the biologic mechanisms, risk factors and populations at risk, diagnosis, and management of ICI-pneumonitis.

Introduction

Although ICIs have transformed cancer therapy, the pathways targeted by immune checkpoint regulation are essential to maintain immune tolerance and prevent autoimmunity. Consequently, irAEs are common, with ICI-pneumonitis representing a potentially fatal irAE (Table 1) (1–12).

The biological mechanisms of ICI-pneumonitis are poorly understood, rendering diagnosis and clinical management challenging. Existing literature reveals significant gaps related to identification of risk factors, optimal diagnostic approach, and best management of ICI-pneumonitis.

To advance the field, the American Thoracic Society (ATS) convened a multidisciplinary panel to identify and prioritize knowledge gaps and guide basic, translational, and clinical research focused on etiology, diagnosis, and management of ICI-pneumonitis.

Methods

This ATS Thoracic Oncology Assembly project was approved by the ATS Program

Table 1. Immune Checkpoint Inhibitor Pneumonitis at a Glance

General:
ICIs target different receptors on tumor cells, T cells, other immune cells, and/or tumor-associated antigen-presenting cells. They function by downregulating inhibitory pathways on T cells, leading to increased immune system activation and T-cell recognition and attack of tumor cells.

ICIs currently approved for clinical use (by class):
- Anti–PD-1: targets the inhibitory PD-1 receptor on effector T cells and other immune cells
- Anti–PD-L1: targets cancer cells and tumor-infiltrating macrophages expressing PD-L1
- Anti–CTLA-4: targets the primed T-cell inhibitory CTLA receptor

ICI-associated irAEs:
- Can occur in any organ
- Develop in most patients treated with ICIs (70–91%) (1–3)
- Distribution and incidence vary based on type of ICI and underlying malignancy (4–6)

ICI-pneumonitis:
- Most common fatal irAE (accounts for 35% anti–PD-[L]1–related deaths) (12)
- Incidence:
    Clinical trials: 2.5–5% (monotherapy), 7–10% (combination ICI) (8)
    Real world: 7–19% (9, 10)
- Onset: mean 2.8 mo (9 d to 24 mo) (11)

ICI-pneumonitis is likely increased in:
- NSCLC compared with melanoma (4.1% vs. 2.7%) (7)
- Combination ICI inhibitors (especially PD-[L]1 and CTLA-4) (7, 8)
- Radiation to the chest (24)

ICI-pneumonitis is possibly increased by:
- Interstitial lung disease (27)
- Preexisting obstructive lung diseases (asthma and COPD) (24)
- Certain histologies (adenocarcinoma compared to other NSCLC histologic subtypes) (35)
- Treatment in combination with EGFR-TKIs (40–42)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CTLA = cytotoxic T-lymphocyte–associated protein; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; ICI = immune checkpoint inhibitor; irAE = immune-related adverse side effect; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1.

Review Subcommittee. An international multidisciplinary panel with members of multiple disciplines, including pulmonology, medical oncology, thoracic radiology, and pathology, with expertise in lung cancer, drug-related pneumonitis, infectious diseases, and immunology was assembled. Conflicts of interest were disclosed and managed according to ATS policies and procedures.

The Chairs (C.R.S. and M.P.R.) developed an overview of current knowledge and questions in ICI-pneumonitis. Major themes were further defined during a premeeting conference call of the panel.

An in-person meeting, held May 18, 2018 at the ATS International Conference in San Diego, California, consisted of presentations on the biologic and clinical/radiologic characteristics and management of ICI-pneumonitis, breakout sessions to expand discussions of knowledge gaps in pathophysiology, clinical predictors, diagnostic criteria and management of ICI-pneumonitis, and development of the first draft of research questions. A comprehensive summary was compiled by the Chairs and circulated to the writing group (C.R.S., M.P.R., T.P., and J.D.P.). Conference calls focused on refining and prioritizing key research questions. The Chairs drafted a manuscript, which was iteratively revised by the panel before final approval by the ATS Board of Directors.

Results

The results are organized into five sections: *1*) general considerations for research, *2*) biological mechanisms, *3*) individual and population risk factors, *4*) approaches to the diagnosis, and *5*) approaches to the management and follow-up of ICI-pneumonitis.

For sections 2 through 5, research questions were developed and prioritized. The summary of the knowledge, research gaps, and key questions is presented in this statement.

General Considerations for Research in ICI-Pneumonitis

Need for consistent and accurate terminology for describing pulmonary irAEs. The terminology referring to pulmonary irAEs is inconsistently applied in the current literature. We agreed on the term "immune checkpoint inhibitor–related pneumonitis (ICI-pneumonitis)," to align with current nomenclature and because: *1*) it remains unproven whether ICI-pneumonitis represents a true pharmacological side effect of ICIs or a consequence of the effects of ICIs on the immune system, and *2*) to avoid terminology that may implicate a dose–response relationship (such as toxicity), not supported by existing literature (13).

Need for common terminology to describe the features of ICI-pneumonitis. A weakness in the current literature is a lack of common terminology to define, diagnose, and describe ICI-pneumonitis. Important therapeutic factors (dose of ICI, time to symptom onset, and duration of symptoms) are inconsistently reported. ICI-pneumonitis presents with a wide spectrum of radiological abnormalities, which may resemble various patterns of interstitial pneumonias implicating yet-unproven pathological correlates and possible risk factors and could guide treatment, further highlighting the importance of using common terminology to report radiologic findings (8, 11, 14). Although we acknowledge potential differences in respective irAEs, for the purposes of this article PD-(L)1 is used when findings have been attributed to both PD-1 (programmed cell death protein 1) and PD-L1 (programmed death ligand 1) inhibitors (6, 15).

Biological Mechanisms of ICI-Pneumonitis

Current evidence and knowledge gaps. Sparse data are available to describe the biologic mechanism of ICI-pneumonitis. This paucity of data limits the development of targeted therapeutic interventions that might decrease reliance on generalized immunosuppression with systemic corticosteroids. On the basis of variability in disease onset, severity, clinical phenotype, histopathology, treatment response, and

chronicity, the biologic mechanisms of ICI-pneumonitis are likely to be heterogeneous, suggesting a potential role for targeted interventions. Several key research questions were developed (Table 2) and further prioritized.

Key research questions.

WHAT ARE THE KEY BIOLOGIC AND IMMUNOLOGIC MECHANISMS DRIVING ICI-PNEUMONITIS? Hypotheses to explain the development of ICI-pneumonitis include increased T-cell activity against autoantigens, increased levels of preexisting autoantibodies and inflammatory cytokines, and enhanced complement-mediated inflammation (16–18). Because the key biological mechanisms underlying ICI-pneumonitis are poorly understood, the diagnostic and therapeutic recommendations for ICI-pneumonitis are largely extrapolated from treatment of other pulmonary drug toxicities.

HOW DO CLINICAL PHENOTYPES OF ICI-PNEUMONITIS CORRELATE TO DIFFERENT BIOLOGICAL AND IMMUNOLOGICAL MECHANISMS OF PATHOGENESIS? It is unknown if the underlying biological mechanism of ICI-pneumonitis is similar regardless of differences in radiologic and clinical manifestations. For instance, patients present with different ICI-pneumonitis severity (clinical grade), both early and late after initiation of ICIs, with variable radiologic patterns and more than one single pathologic entity (9, 16, 19, 20); it is unclear if these observed variations represent distinct phenotypes or a spectrum of the same disease. Translational studies, particularly using serum, BAL, and lung pathologic specimens, may lead to the development of predictive biomarkers and aid in identifying whether biological differences lead to variable clinical presentations and guide the development of phenotype-specific therapeutics.

ARE PHARMACOLOGIC, ACTIVE OR PASSIVE EXPOSURES, OR UNDERLYING COMORBIDITIES INVOLVED IN DEVELOPMENT OF ICI-PNEUMONITIS? A key question remains whether certain risk factors, such as treatment with other cancer therapies (chemotherapeutic drugs, targeted therapies such as epidermal growth factor receptor tyrosine kinase inhibitors [EGFR-TKIs], radiation therapy), other immune-modulating therapies, and comorbidities (collagen vascular diseases [CVD], lung diseases, or low-grade infection) predispose to development of ICI-pneumonitis. These factors may serve as the first of a "two-hit"

model, leading to development of ICI-pneumonitis in some patients (21). Active or passive exposures, such as cigarette smoke, or different cancer histologic types may also impact the development of ICI-pneumonitis (9).

DO BIOLOGICAL MECHANISMS DIFFER BETWEEN STEROID-RESPONSIVE AND STEROID-REFRACTORY ICI-PNEUMONITIS? Most patients (88%) with ICI-pneumonitis will respond to withdrawal of therapy and/or corticosteroid treatment (8). It is unclear if steroid-refractory ICI-pneumonitis represents a different mechanism of disease or simply advanced-stage ICI-pneumonitis, where lung damage is irreversible (diffuse alveolar damage, progression to fibroproliferative disease, or pulmonary fibrosis as observed with other interstitial lung diseases [ILDs]).

Proposed approaches. The use of mechanistic biochemical *in vitro* studies, expanded animal models of disease, and translational research using human specimens may aid research to better understand the biologic mechanisms of ICI-pneumonitis, particularly in the small subset of patients who do not respond to corticosteroid therapy. Existing biological knowledge in lung diseases such as CVD-associated ILD and drug-related pneumonitis can serve as a foundation for investigating specific research questions related to ICI-pneumonitis. Rapid, high-impact advances may be made by prioritizing research on pathways with existing therapies. Multidisciplinary involvement in translational and clinical trials, especially in providing access to clinical research samples (serum, BAL, and lung pathologic specimens), may aid in identifying biological differences that lead to variable clinical presentations and may in turn guide the development of phenotype-specific therapeutics to prevent or treat ICI-pneumonitis. Clear documentation of how research specimens are obtained, processed, and stored will be critical for accurate analyses and comparison studies (Table 3).

Risk Factors and the Populations at Risk for ICI-Pneumonitis

Current evidence and knowledge gaps. Biomarkers predictive of favorable therapeutic responses to ICIs (high PD-L1 expression, presence of local immune cell infiltration, immune cytokines, and high tumor mutational burden) are being investigated and used for patient selection in

selected clinical scenarios (3, 22, 23). Sparse data are available to identify patients at high risk for development of ICI-pneumonitis (Table 4), although subgroup analysis suggests that a history of obstructive lung disease and prior thoracic radiation may be associated with an increased incidence (24). Patients enrolled in ICI trials are highly selected and healthier than the targeted population, which may impact both their response to therapy and development of complications. For instance, ICI trials have excluded patients with ILDs or CVDs on the basis of the involvement of PD-(L)1 and cytotoxic T-lymphocyte–associated protein 4–mediated pathways in diseases such as rheumatoid arthritis and systemic lupus erythematosus (3). Outside of clinical trials, it is likely that patients with these conditions will either receive ICIs, potentially increasing the risk for ICI-pneumonitis, or be denied potentially beneficial ICI therapy, particularly if mortality from severe ICI-pneumonitis is lower than anticipated in this population (21, 25–27). The possibility that ICI benefit may be linked to irAE development is supported by studies that have observed improved tumor responses and/or survival after ICIs in patients who develop irAEs (28–30). However, these observations are not specific to ICI-pneumonitis and are potentially limited by small studies necessitating pooling of different tumor types, ICIs used, and severity and type of irAEs (28–30).

Key research questions. Certain demographic groups, particularly black, Hispanic, and older patients, have been grossly underrepresented in ICI clinical trials, leading to a limited understanding of the prevalence and presentation of ICI-pneumonitis.

WHAT COMORBID CONDITIONS PREDISPOSE TO ICI-PNEUMONITIS? Patients with certain comorbidities (lung diseases and CVD) have been underrepresented or excluded from clinical trials of ICIs; whether these diseases impact the development of ICI-pneumonitis remains unknown. It is unclear whether functional and/or radiologically subclinical lung diseases contribute to ICI-pneumonitis. Including pulmonary function tests (PFTs), 6-minute-walk test (6MWT), radiologic assessment of nonmalignant lung disease on chest computed tomography (CT), and baseline serologies for CVD may aid in evaluating whether preexisting diseases contribute to or can predict those at higher risk for development of ICI-pneumonitis.

Table 2. Biological Mechanisms of Immune Checkpoint Inhibitor Pneumonitis

Research Topic in ICI-Pneumonitis	Comments
Immunologic mechanism(s) of development	The role of the immune response in ICI-pneumonitis development is unclear. • What is the role of immune cells (T cells, B cells, NK cells, macrophages, and dendritic cells)? • What are the characteristic antibodies, cytokines, and chemokines? • Is there temporal variation? • Does the immune response vary by grade and/or response to corticosteroids? • Do the mechanisms vary for ICI-pneumonitis occurring early or late after initiation of therapy? In those with persistent ICI-pneumonitis after cessation of therapy? • Is this caused by perturbations to the local immune response, a hypersensitivity reaction, direct drug effect, or a combination of factors?
Role of the microbiome in development	The gut microbiome likely influences efficacy of ICI antitumor effect. • What is the impact of the gut microbiome on ICI-pneumonitis? The role of respiratory and oral microbiomes in ICI-pneumonitis is unknown. • What is the impact of the respiratory/oral microbiomes on ICI-pneumonitis?
Role of underlying lung disease	PD-(L)1 and CTLA-4 are linked to self-tolerance in a number of rheumatologic diseases, including rheumatoid arthritis and systemic lupus erythematosus. Many patients with underlying lung disease (ILD or rheumatologic) were excluded from clinical trials. • Do certain pulmonary diseases, such as pulmonary fibrosis, COPD, and rheumatologic or other ILD, alter the risk of ICI-pneumonitis? • Is there a mechanistic link between ILD and ICI-pneumonitis (i.e., Muc5b polymorphisms)?
Other exposures	Are other exposures needed to develop ICI-pneumonitis (i.e., two-hit model)? Does continued tobacco smoking play a role in the development of ICI-pneumonitis?

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CTLA = cytotoxic T-lymphocyte–associated protein; ICI = immune checkpoint inhibitor; ILD = interstitial lung disease; NK = natural killer; PD-(L)1 = PD-1 (programmed cell death protein 1) and PD-L1 (programmed death ligand 1).

DO SPECIFIC TUMOR FACTORS PREDISPOSE TO ICI-PNEUMONITIS? In ICI treatment for non–small cell lung cancer (NSCLC), high PD-L1 expression, genomic instability, tumor mutational burden, and possibly chronic obstructive lung disease may portend a higher likelihood of favorable response (31–34). Incidence of ICI-pneumonitis varies according to tumor and histologic type (7, 35). However, little is known regarding the impact of other tumor characteristics (molecular changes) on development of ICI-pneumonitis.

DO OTHER CANCER TREATMENTS CONTRIBUTE TO THE DEVELOPMENT OF ICI-PNEUMONITIS? Rates of ICI-pneumonitis increase with use of combined ICIs, with highest rates observed with combined PD-(L)1 and cytotoxic T-lymphocyte–associated protein 4 inhibition (7, 8). Whether treatment with other drugs and/or radiation therapy (before or concomitant with ICIs) increases the incidence of ICI-pneumonitis is unknown (36). ICIs are being combined with chemotherapeutic drugs, EGFR-TKIs, and thoracic radiation. Pneumonitis after thoracic radiation is well described, raising particular concern for increased risk of pneumonitis with ICI and thoracic radiation (37). In a study comparing adjuvant durvalumab (PD-L1 inhibitor) to placebo in patients with stage III NSCLC treated with concurrent platinum-based chemotherapy and radiation, pneumonitis was highest in the durvalumab group (34% vs. 25%) (38). Although the risk of pneumonitis is probably increased, retrospective and subgroup analyses so far support a likely favorable risk-to-benefit ratio in patients receiving both ICI and chest radiation (36, 39), although data are limited by different treatment timing, dosing, tumor heterogeneity, and lower-than-expected irAEs in those treated with ICI alone. Combination of EGFR-TKIs and ICIs likely increases the risk of pneumonitis (40–42). With combination chemotherapy and ICIs now first-line treatment in many patients with metastatic NSCLC (43, 44), the need to understand their impact on ICI-pneumonitis is even more critical.

Current Approaches to the Diagnostic Evaluation of ICI-Pneumonitis

Current evidence and knowledge gaps. Nonspecific symptoms of ICI-pneumonitis (dyspnea, cough, fever, and chest pain) mirror other lung diseases, including pneumonia and progression of malignancy (45). Further complicating diagnosis is the variability in onset of ICI-pneumonitis, weeks to months after initiation of therapy (3, 8). Radiographic patterns of ICI-pneumonitis can be categorized according to the classifications of interstitial pneumonias; however, accurate radiologic diagnosis can be challenging, requiring expert interpretation (8, 11, 19). Consensus among multidisciplinary investigators is needed regarding the language to describe different radiologic patterns of ICI-pneumonitis.

Opportunistic infections in those receiving corticosteroids and other drugs for irAEs have been reported (9, 29, 46, 47), and similarities between clinical and radiologic findings of infection and ICI-pneumonitis may further complicate diagnostic evaluation and possibly cause harm if an infection is undiagnosed before treatment with immunosuppressive medications (48–50). Empiric treatment for suspected pulmonary infection with antibiotics might have unintended consequences, including

Table 3. Proposed Reporting of Common Measures and Terminology for Immune Checkpoint Inhibitor Pneumonitis

Research Topic in ICI-Pneumonitis	Proposed Research Reporting Components
Demographics and baseline clinical characteristics	Demographic information (sex, age, and ethnicity) Smoking history (categorical and quantitative [pack-years]) Preexisting conditions (particularly interstitial lung disease, COPD, and systemic autoimmune diseases) Tumor types Prior treatments Type of ICI treatment and regimen, doses, and frequency
Radiologic findings of ICI-pneumonitis	Use of common terminology Routine use of radiologic patterns rather than characteristic findings (examples below) ● COP pattern ● AIP/ARDS pattern ● NSIP pattern ● HP pattern Modality: chest CT
Pathologic findings of ICI-pneumonitis	Use of common terminology: ● Cellular interstitial pneumonia ● Fibrosing interstitial pneumonia ● Usual interstitial pneumonia ● Nonspecific interstitial pneumonia ● Cellular and fibrosing interstitial pneumonia ● Organizing pneumonia ● Bronchiolitis ● Lymphocytic interstitial pneumonia ● Diffuse alveolar damage ● Pleuritis ● Noncaseating granulomas
Clinical findings of ICI-pneumonitis	Document both CTCAE grade and clinical signs and symptoms
Infectious complications	In ICI alone and in combination with corticosteroids and other immunosuppressive medications ● TB and listeria (PD-[L]1) ● *Aspergillus*, CMV, and PJP (CTLA-4) ● Pneumonia (organism[s] when available) ● Sepsis (organism[s] when available) ● Other bacterial, viral, and fungal infections
Additional testing	Patient-reported functional assessments ● Borg scale ● FACT-L questionnaire Pulmonary function testing ● Spirometry and diffusing capacity (corrected for Hb) ● TLC ● Comparison with pretreatment measures 6-min-walk test Bronchoscopy (BAL) ● Volume, location sampled (affected lobe), and protocol for processing ● Cell differential, subsets, and surface markers ● Measures: cytokines, chemokines, and microbiome ● Treatments (pre/post steroids and pre/post antibiotics) ● Correlation with disease severity and temporality Lung biopsy ● Type (TBBx, cryobiopsy, or wedge) and location ● Uniform histologic terminology ● Presence/absence of malignancy and evidence of infection? ● Complications

Definition of abbreviations: AIP = acute interstitial pneumonia; ARDS = acute respiratory distress syndrome; CMV = *Cytomegalovirus*; COP = cryptogenic organizing pneumonia; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTLA = cytotoxic T-lymphocyte–associated protein; FACT-L = Functional Assessment of Cancer Therapy–Lung; HP = hypersensitivity pneumonitis; ICI = immune checkpoint inhibitor; NSIP = nonspecific interstitial pneumonia; PD-(L)1 = PD-1 (programmed cell death protein 1) and PD-L1 (programmed death ligand 1); PJP = *Pneumocystis jiroveci* pneumonia; TB = tuberculosis; TBBx = transbronchial biopsy.

reduced clinical benefit from ICIs, possibly due to alterations in the gut microbiome (51–53). Diagnostic evaluations, including bronchoscopy with BAL and/or biopsy, have been suggested but are variably performed because of inconsistent availability across centers, unfamiliarity with immune-related toxicity, and lack of multidisciplinary collaborations (3, 8, 9, 13, 54–57), and their role and diagnostic value have not been established in ICI-pneumonitis.

Key research questions.

WHAT IS THE OPTIMAL DIAGNOSTIC EVALUATION FOR PATIENTS WITH SUSPECTED ICI-PNEUMONITIS? Expert opinion guidelines from the European Society for Medical Oncology, Society for Immunotherapy of Cancer, and American Society for Clinical Oncology/National Comprehensive Cancer Network for diagnostic evaluation of suspected ICI-pneumonitis include the use of chest X-ray and/or CT, pulse oximetry, and an infectious work-up (viral nasal swab, sputum, blood, and urine cultures) (13, 55, 56). However, these recommendations come without clear evidence that these diagnostic evaluations help to differentiate between ICI-pneumonitis and infection. Because radiologic characterization of ICI-pneumonitis has largely been defined by chest CT findings, chest X-ray likely lacks sensitivity in diagnosing ICI-pneumonitis, as observed with other causes of pneumonia (8, 58). The role of pre-ICI treatment measures (including PFTs, pulse oximetry, and 6MWT) and their use in the diagnosis and severity grading of suspected ICI-pneumonitis in those with preexisting chronic pulmonary diseases with underlying symptoms of dyspnea and cough remain unexplored (13). In other drug-related lung diseases, bronchoscopy (BAL with or without biopsy) plays an important role, chiefly to exclude other diseases (59). How functional measures and diagnostic bronchoscopy may aid in evaluation of patients with ICI-pneumonitis deserves further investigation.

IS THERE ANY VALUE IN SCREENING ASYMPTOMATIC PATIENTS ON ICIs FOR EARLY LUNG INJURY? Whether grade 1 ICI-pneumonitis (asymptomatic with radiological abnormalities, according to Common Terminology Criteria for Adverse Events grades) progresses to higher grades without intervention remains unknown. Expert opinion guidelines recommend withholding ICIs for grade 1 ICI-pneumonitis until

Table 4. Risk Factors and Populations at Risk

Research Topic in ICI-Pneumonitis	Possible Risk Factors
Patient factors	• Age, race/ethnicity, and sex • Underlying lung disease other than malignancy • Preexisting autoimmune disease • Smoking history
Tumor features	• Histology • Microbiome • Tumor biology, mutations, and surface markers
Treatment factors	• Prior treatments (chemotherapy, radiation, and TKIs) • Concurrent and sequential therapy • Concurrent corticosteroids • Adjuvant therapies
Biomarkers and biologic mechanisms	• Cytokines and chemokines • Local and systemic immune response • Immunosuppressive disease or treatment

Definition of abbreviations: ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor.

radiographic resolution, but whether this changes the course of disease is unknown. Examination of lung tissue from patients with subclinical ICI-pneumonitis undergoing surgery after neoadjuvant use of ICIs may aid in our understanding of grade 1 ICI-pneumonitis (60, 61). The utility of serial PFTs, useful for diagnosis and management of pulmonary toxicity with bleomycin, is not extensively studied in ICI-pneumonitis (62, 63).

WHAT IS THE INCIDENCE OF INFECTIONS IN PATIENTS ON ICIs? Infections are relatively common in those who experience ICI irAEs (31%) and even more common when immunosuppressive therapy is required (43.5%) (29). The risk of fatal infections (1–2% of deaths) may increase with the use of corticosteroids, infliximab, and combination ICI therapy (29, 46). This raises several questions regarding the role of infections in ICI-pneumonitis: *1*) Is infection a risk factor for ICI-pneumonitis development (i.e., first or second hit) or a contributor to increased ICI-pneumonitis severity/grade? *2*) Is ICI therapy itself a risk factor for development of infections? *3*) What is the risk of infectious complications with corticosteroid and other agents for the treatment of ICI-pneumonitis? The latter is of particular importance, as opportunistic infections are a serious, sometimes fatal, complication after steroid therapy of ICI-pneumonitis (46).

WHAT IS THE OPTIMAL EVALUATION TO EXCLUDE ALTERNATIVE DIAGNOSES IN SUSPECTED ICI-PNEUMONITIS? When infection cannot be ruled out, symptomatic patients with ICI-pneumonitis are often treated concurrently with antimicrobials and corticosteroids, with or without other immune-suppressing drugs if needed (55). Although current American Society for Clinical Oncology/National Comprehensive Cancer Network recommendations include evaluation for underlying infection (13), what tests, which patients, the timing of testing, and the role of bronchoscopy with BAL to diagnose infection is unknown. Furthermore, understanding the benefit of studies such as CT angiography and echocardiography to rule out other potential mimics to which these patients are at increased risk may be useful.

Proposed approaches. Variability in reported diagnostic findings of ICI-pneumonitis may be due to differences in study design, patient inclusion, or an artifact of reporting methods, in addition to variabilities in the clinical and radiologic manifestations of ICI-pneumonitis itself. Reporting of common measures and terminology may increase the impact of future research in ICI-pneumonitis (Table 3). Routine inclusion of diagnostic testing, particularly bronchoscopic (BAL) evaluation for exclusion of pulmonary infections, may improve ICI-pneumonitis research going forward.

Current Approaches to the Management and Follow-up of ICI-Pneumonitis

Current evidence and knowledge gaps. Treatment recommendations of ICI-pneumonitis, including ICI cessation, systemic corticosteroids, and additional immunosuppressive medications, are based on the clinical grade of pneumonitis and derived from treatment of drug-related hypersensitivity pneumonitis (13, 54, 55, 64–66). Areas of uncertainty include: *1*) optimal dose, duration, and type of immunosuppressive treatment for steroid-refractory ICI-pneumonitis. In addition to rare steroid-refractory cases, a "rebound" effect of worsening pneumonitis has been described in some patients on discontinuation of corticosteroids, with limited guidance for further therapy (11, 67); *2*) the negative impact treatment with corticosteroids may have on tumor response to ICIs (68); *3*) whether permanent discontinuation of ICI therapy is warranted in patients in whom ICI-pneumonitis has improved or resolved, versus rechallenge with the same or an alternative ICI (69); *4*) the impact of corticosteroid treatment on suppression of tumor immune response and risk for opportunistic infections (29, 48–50).

Key research questions.

WHAT IS THE OPTIMAL MANAGEMENT OF GRADE 1 (ASYMPTOMATIC WITH RADIOGRAPHIC FINDINGS) ICI-PNEUMONITIS? Current recommendations include withholding ICIs versus continuing with close monitoring (imaging, frequent clinical evaluation, and possibly PFTs), and treatment with corticosteroids for progressive ICI-pneumonitis (13, 55, 56). However, it is unclear if asymptomatic radiographic changes alone constitute clinically significant ICI-pneumonitis, whether all patients with grade 1 pneumonitis need to have ICIs withheld or warrant any change in therapy, if steroid treatment changes the course of disease, to what degree resolution of radiologic changes constitutes response to therapy, and whether treatment dosage and duration impact these outcomes (68). How these patients should be followed, by what means, and for how long (particularly those with stable ICI-pneumonitis) is also unclear.

WHAT IS THE OPTIMAL MANAGEMENT OF GRADE 2 OR GREATER ICI-PNEUMONITIS, AND HOW SHOULD THESE PATIENTS BE MONITORED? Treatment of symptomatic patients has centered on withholding ICIs, treating with systemic corticosteroids, and, in those with refractory ICI-pneumonitis, adding immunosuppressive medications (13, 55, 56). However, the optimal timing, dose, and duration of corticosteroid therapy are not known. Phenotypic, radiographic, or other

Table 5. Immune Checkpoint Inhibitor Pneumonitis: Key Research Questions and Proposed Approaches

Topic	Key Questions and Proposed Research Approaches
Biological mechanisms	**Key questions:** What are the key biologic and immunologic mechanisms driving ICI-pneumonitis? Do clinical phenotypes of ICI-pneumonitis correlate to different biological and immunological mechanisms of pathogenesis? Are other pharmacologic/environmental exposures or underlying comorbidities involved in development of ICI-pneumonitis? Do biological mechanisms differ between steroid-responsive and -refractory ICI-pneumonitis? **Proposed approaches:** Expanded use of mechanistic biochemical *in vitro* studies, establishment of animal models of disease, and use of human specimens in translational research Basing and testing research hypotheses using existing biological knowledge and techniques established in the study of CVD-associated ILD and drug-related pneumonitis Clear documentation of patient demographics and specimen collection methods, processing, and storage Multidisciplinary involvement in translational and clinical trials to expand clinical, demographic, immunologic, and mechanistic research questions through enhanced access to research samples Prioritization of research focusing on pathways with existing therapies
Risk factors/populations at risk	**Key questions:** What are the comorbid conditions that predispose a patient to ICI-pneumonitis? Do specific tumor factors predispose a patient to ICI-pneumonitis? Do other cancer treatments contribute to the development of ICI-pneumonitis? **Proposed approaches:** Focusing trial design on inclusion of underrepresented demographic groups (including black, Hispanic, and older patients) and preexisting lung disease (including CVD and ILDs) Design of clinical trials to include collection of functional measures, including PFTs, 6MWT, pretreatment chest CT lung radiologic findings (particularly ILD), and baseline serologies for CVD Focus on development of ICI-pneumonitis on the basis of different histologic characteristics, oncogene and tumor suppressor expression, and other routinely collected or molecular biology–based tumor characteristics Detailed documentation of additional immune-modulating, chemotherapeutic, and/or radiation treatments, including timing, dosing, and location of treatment
Diagnostic evaluation	**Key questions:** What is the optimal diagnostic evaluation for patients with suspected ICI-pneumonitis? Is there value in screening asymptomatic patients on ICIs for early lung injury? What is the incidence and effect of infections in patients on ICIs? What is the optimal evaluation to exclude alternative diagnoses, such as infection, in suspected ICI-pneumonitis? **Proposed approaches:** Establishment and use of common diagnostic measures and terminology to facilitate comparing and combining data Routine inclusion of diagnostic testing in all manuscripts, particularly evaluation for and exclusion of pulmonary infections as with BAL Detailed documentation of specific ICIs used as well as additional chemo- and radiation therapies, corticosteroid, immune-modulating therapies, and steroid-sparing drug use, including duration, dose, and time to ICI-pneumonitis development
Management	**Key questions:** What is the optimal management of grade 1 ICI-pneumonitis? What is the optimal management and monitoring of grade ⩾ 2 ICI-pneumonitis? Does treatment with corticosteroids alter ICI-pneumonitis outcomes? Is there a role for steroid-sparing and/or targeted therapy in steroid-refractory or steroid-dependent ICI-pneumonitis? **Proposed approaches:** Maintenance of well-designed, detailed, and accurate registries to study ICI-pneumonitis Inclusion in registries of data on both patients diagnosed with ICI-pneumonitis and ICI-pneumonitis mimics (such as infection, other drug-related ILDs, and progression of malignancy) Careful design of ICI clinical trials to include similar diagnostic and outcomes measures, and diverse ethnic and racial enrollment Prioritization of multiinstitutional studies with diverse, multidisciplinary involvement

Definition of abbreviations: 6MWT = 6-minute-walk test; CT = computed tomography; CVD = collagen vascular disease; ICI = immune checkpoint inhibitor; ILD = interstitial lung disease; PFT = pulmonary function test.

diagnostic findings (such as BAL differential) may clarify differential response to therapy, and evaluation of their role in guiding treatment should be defined. It is similarly unknown if functional measures such as PFTs or 6MWT in combination with improvement in symptoms would aid in evaluating response to therapy. In those patients who have recovered from ICI-pneumonitis, it is unknown whether certain clinical or physiologic features would identify those at higher risk for recurrence of ICI-pneumonitis after rechallenge with ICIs.

IS THERE A ROLE FOR STEROID-SPARING THERAPY (SUCH AS INFLIXIMAB, CYCLOPHOSPHAMIDE, AND INTRAVENOUS IMMUNOGLOBULIN [IVIG]) IN STEROID-REFRACTORY OR STEROID-DEPENDENT ICI-PNEUMONITIS? The efficacy and timing of steroid-sparing agents, recommended for steroid-refractory disease in multiple consensus statements, remains unknown, with current use extrapolated from treatment of other irAEs and of other drug-induced lung toxicities (13, 55, 70). Whether steroid-sparing therapies, including infliximab, cyclophosphamide, and IVIG, would be useful in relapsing or steroid-dependent disease, and whether these therapies would adversely impact tumor response to ICIs, is similarly unknown (9).

DOES TREATMENT WITH CORTICOSTEROIDS ALTER ICI-PNEUMONITIS OUTCOMES? As the benefit of ICIs is improving a patient's innate immune antitumor response, one could postulate that treatment with steroids may adversely impact the ICI antitumor response, particularly given findings of poorer outcomes in those on corticosteroids before PD-(L)1 therapy (13). Furthermore, steroids increase the risk of infection and may not alter progression to fibrotic lung disease, each of which could worsen patient outcomes (68). The additive effect of steroids compared with withdrawal of therapy alone or targeted, steroid-sparing therapies would help to answer these questions.

Proposed approaches. Well-designed, accurately maintained registry data are critically needed, as currently data from a relatively small number of patients with ICI-pneumonitis, extrapolated from treatment of other pulmonary toxicities and irAEs, are being used to define optimal management of ICI-pneumonitis. These registry data must include both ICI-pneumonitis and its mimics, and data should be curated by a multidisciplinary team (immunology, oncology, pulmonology, infectious disease, pathology, and radiology). Careful design of ICI clinical trials, using similar diagnostic and outcome measures, with an effort to include diverse ethnic and racial enrollment, is essential to draw accurate conclusions on ICI-pneumonitis from pooled data. This includes prioritization of multiinstitutional studies with diverse, multidisciplinary involvement.

Establishing new or increasing the accessibility of existing central databases is needed.

Conclusions

ICIs have revolutionized cancer therapy; their expanded use comes with an increase in irAEs, making essential the accurate identification, characterization, and treatment of potentially severe irAEs, including ICI-pneumonitis. We have identified critical knowledge gaps that must be addressed to ensure progress in research of ICI-pneumonitis and standardized approaches to further study (Table 5). Key challenges in ICI-pneumonitis include further defining and refining the descriptive terminology, identifying the biologic mechanisms, defining risk factors, and determining optimal diagnostic and management strategies. Given the complexity of ICI-pneumonitis, multidisciplinary collaborations will be critical to enhance research and narrow these knowledge gaps. Furthermore, prioritization of multiinstitutional studies and expansion and increased accessibility of large, central databases will improve diversity and impact. It is hoped that this statement will provide a comprehensive framework from which clinical and translational researchers may approach these questions, with the goal of improving the care of patients who develop ICI-pneumonitis. ■

This official research statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Thoracic Oncology.

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