AMERICAN THORACIC SOCIETY DOCUMENTS

Knowledge Gaps and Research Priorities in Immune Checkpoint Inhibitor–related Pneumonitis

An Official American Thoracic Society Research Statement

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This official Research Statement of the American Thoracic Society was approved September 2019

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 the diagnosis and management have not been well defined.

Objectives: To summarize evidence, identify knowledge and research gaps, and 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

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An Executive Summary of this document is available at http://www.atsjournals.org/doi/suppl/10.1164/rccm.201906-1202ST.

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Am J Respir Crit Care Med Vol 200, Iss 6, pp e31–e43, Sep 15, 2019

DOI: 10.1164/rccm.201906-1202ST
Internet address: www.atsjournals.org

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

The use of ICIs has transformed cancer therapy, on the basis of a more detailed understanding of cancer immune surveillance and the identification of key immunosuppressive pathways within the tumor microenvironment. However, it is important to recognize that the same pathways targeted by immune checkpoint regulation are essential to regulate all normal immune responses, maintain immune tolerance, and prevent autoimmunity. Consequently, it is not surprising that irAEs are common complications of ICIs, occurring in the majority (70–91%) of treated patients (1–3). Recent meta-analyses suggest that the incidence of irAEs varies based on the type of ICI used and the underlying malignancy (4–6). In clinical trials, ICI-pneumonitis (Table 1) is more common in non–small cell lung cancer (NSCLC) than in melanoma (4.1% vs. 2.7%) (7), and it is most frequently reported in patients receiving combination ICI therapy, such as ipilimumab/nivolumab (10%) (8). More recent reports indicate that ICI-pneumonitis will develop in as many as

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) (14)

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 (25)

ICI-pneumonitis is possibly increased by:
- Interstitial lung disease (28)
- Preexisting obstructive lung diseases (asthma and COPD) (25)
- Certain histologies (adenocarcinoma compared to other NSCLC histologic subtypes) (36)
- Treatment in combination with EGFR-TKIs (41–43)

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.

7% to 19% of patients with NSCLC outside of clinical trials (9, 10). Although currently less well characterized than the life-threatening pneumonitis observed with bleomycin (11), ICI-pneumonitis represents the most common fatal irAE from anti–PD-1 (programmed cell death protein 1)/PD-L1 (programmed death ligand 1) monotherapy, accounting for 35% of anti–PD-1/PD-L1–related deaths, further emphasizing the serious consequence of this irAE (12).

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

Methods

This ATS Thoracic Oncology Assembly project was approved by the ATS Program Review Subcommittee. An international multidisciplinary panel including pulmonologists, medical oncologists, thoracic radiologists, and pathologists 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.

At initiation of the project, the Chairs (C.R.S. and M.P.R.) developed an overview of current knowledge and existing knowledge gaps in ICI-pneumonitis. These major themes were further defined during a premeeting conference call of the panel.

An in-person meeting, held on May 18, 2018, at the ATS International Conference in San Diego, California, consisted of presentations on the risk and clinical, radiologic, and biologic findings of ICI-pneumonitis; breakout sessions to expand discussions related to the 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 in ICI-pneumonitis, *2*) biological mechanisms of ICI-pneumonitis, *3*) individual and population risk factors for ICI-pneumonitis, *4*) current approaches to the diagnosis and management of ICI-pneumonitis, and *5*) current approaches to the treatment and follow-up of ICI-pneumonitis.

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

General Considerations for Research in ICI-Pneumonitis

Two key topics emerged as central to developing this research statement.

Need for consistent and accurate terminology for discussing pulmonary irAEs. The terminology referring to pulmonary irAEs is inconsistently applied in the current literature. Three terms were proposed during the meeting: ICI-related pneumonitis, ICI-related lung injury, and ICI-related lung toxicity. All panel members agreed on the term "immune checkpoint inhibitor–related pneumonitis (ICI-pneumonitis)," to align with the most common, current nomenclature. This terminology was believed to be important for additional reasons: *1*) at present, ICI

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).

treatment is "related" to pneumonitis development, and whether it represents a true pharmacological side effect of ICI or a consequence of the effects of the ICI on the immune system remains to be proven; *2*) to avoid terminology that may implicate a dose–response relationship (such as toxicity), which is not supported by existing literature; and *3*) to focus this article on direct lung injury rather than indirect pulmonary complications, such as pulmonary edema and hypercarbic respiratory failure, which may occur as a result of nonpulmonary irAEs such as myocarditis and neuromuscular disease (13).

Need for common terminology to describe the features of ICI-pneumonitis. The panel acknowledged that one of the main limitations in the current ICI-pneumonitis literature is the lack of a 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. On imaging, 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. This highlights the need and importance of using common terminology to consistently report radiologic findings (8, 14, 15). Although we acknowledge potential differences in respective irAEs including ICI-pneumonitis, for the purposes of this article PD-(L)1 will be used when findings have been attributed to both PD-1 and PD-L1 inhibitors (16).

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

Key research questions.

WHAT ARE THE KEY BIOLOGIC AND IMMUNOLOGIC MECHANISMS DRIVING ICI-PNEUMONITIS? Animal models of CTLA-4 (cytotoxic T-lymphocyte–associated protein 4) and PD-1 deficiency show inflammatory infiltrative lung disease (17, 18), and hypotheses to explain the development of ICI-pneumonitis include increased overall and/or targeted T-cell activity against autoantigens shared between malignant and benign tissues, increased levels of inflammatory cytokines and preexisting autoantibodies, and enhanced complement-mediated inflammation (19). Because the key biological mechanisms underlying ICI-pneumonitis are poorly understood (Is it caused by perturbations to the local immune response, a hypersensitivity reaction, direct drug effect, or a combination of factors?), the diagnostic and therapeutic recommendations for ICI-pneumonitis are limited and largely

extrapolated from what is known about 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 ICI, and with variable radiologic patterns and more than one single pathologic entity (9, 19–21); it is unclear if these observed variations represent distinct phenotypes or a spectrum of the same disease seen at different points in time. Translational studies, particularly using serum, BAL cells and fluid, 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 may guide the development of phenotype-specific therapeutics.

Are pharmacologic, active, or passive exposures or underlying comorbidities involved in development of ICI-pneumonitis? With little knowledge of the biological mechanisms underlying ICI-pneumonitis, the question remains whether certain risk factors predispose to development of ICI-pneumonitis. Such factors include previous or ongoing treatment with other cancer therapies (chemotherapeutic drugs, targeted therapies such as epidermal growth factor receptor tyrosine kinase inhibitors [EGFR-TKIs], radiation therapy, or rheumatologic/other immune-modulating therapies) as well as comorbid conditions (collagen vascular diseases [CVD], lung diseases, or chronic/low-grade infection). The presence of these factors may serve as the first of a "two-hit" model, leading to development of ICI-pneumonitis in some patients (22). Active or passive exposures, such as cigarette smoke, or different cancer histologic types may impact the development of ICI-pneumonitis as well (9).

Do biological mechanisms differ between steroid-responsive and steroid-refractory ICI-pneumonitis? Most patients (88%) with ICI-pneumonitis, regardless of clinical grade, will respond to withdrawal of therapy and/or corticosteroid treatment (8). In patients who are steroid refractory, it is unclear if this represents a different mechanism of disease or simply the advanced stage of ICI-pneumonitis, at which point damage to the lung is no longer reversible (diffuse alveolar damage, progression to fibroproliferative disease, or pulmonary fibrosis as observed with other interstitial lung disease [ILD]).

Proposed approaches. 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. The use of mechanistic biochemical *in vitro* studies, expanded animal models of disease, and use of human specimens in translational research may aid in answering basic questions that lead to better understanding of the biologic mechanism 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. However, it must be noted that although many drugs cause pneumonitis, including other antitumor drugs such as erlotinib, gefitinib, pemetrexed, and gemcitabine, the mechanism for ICI-pneumonitis may differ, and a common response to systemic corticosteroid therapy, which leads to a number of nonspecific antiinflammatory and immune-suppressive effects, does not necessarily implicate similar causative mechanisms. Multidisciplinary involvement in translational and clinical trials, especially in providing access to clinical research samples (serum, BAL, and lung pathologic specimens) from affected patients, may aid in identifying the biological differences that lead to variable clinical presentations and may in turn guide the development of phenotype-specific targeted therapeutics to prevent or treat ICI-pneumonitis. Clear documentation of how the research specimens are obtained, processed, and stored will be critical for accurate analyses and comparison studies (Table 3). For example, uniformity in collection of BAL specimens would include such documentation as BAL volume (instilled and returned), segment from which BAL was obtained and correlation with radiologic presence of presumed ICI-pneumonitis in that segment, whether the patient was on corticosteroids and/or other steroid-sparing therapies, and how the specimen was processed. Rapid, high-impact advances may be made by prioritizing research on pathways with existing therapies.

Risk Factors and the Populations at Risk for ICI-Pneumonitis

Current evidence and knowledge gaps. Research focused on development and validation of biomarkers predictive of therapeutic responses to ICIs is ongoing. For instance, high PD-L1 immunohistochemical expression levels, presence of local immune cell infiltration in the tumor region, immune cytokines, and a high tumor mutational burden are all being actively investigated as predictive markers for favorable response to therapy and in selected clinical scenarios are already used for patient selection (3, 23, 24). Sparse data are available to identify patients at high risk for development of ICI-pneumonitis (Table 4), although a subgroup analysis of the KEYNOTE-001 trial suggests that a personal history of asthma or chronic obstructive lung disease and prior thoracic radiation may be associated with an increased incidence of ICI-pneumonitis (25). As with most clinical trials, patients enrolled in clinical trials of ICI are highly selected and healthier than the targeted population, which may impact both their response to therapy and development of complications. Clinical trials of ICIs have excluded patients with ILDs or underlying CVD because of the established role of PD-(L)1– and CTLA-4–mediated pathways in CVD, such as rheumatoid arthritis and systemic lupus erythematosus (3). Outside of controlled clinical trials, it is likely that many patients with these conditions will receive ICIs in the absence of definitive knowledge as to whether this patient population is at increased risk for ICI-pneumonitis. Exclusion of these patients may prevent those at lower-than-anticipated risk of ICI-pneumonitis from receiving potentially beneficial therapy (higher benefit-to-risk ratio) (22, 26–28). Although functional and biologic evaluations to screen for preexisting pulmonary or autoimmune diseases have been proposed, it is unclear whether these would aid in prediction of ICI-pneumonitis. Furthermore, the possibility that the potential benefits and irAEs of ICIs may be linked is supported by

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.

studies that have observed improved tumor responses and/or survival after ICIs in those patients who develop irAEs. However, these observations are not specific to ICI-pneumonitis and are potentially limited by small study sizes necessitating pooling of different tumor types, ICIs used, and severity and type of irAEs (29–31).

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 (including underlying lung diseases and CVD) have been underrepresented or completely 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 measures such as pulmonary function tests (PFTs), 6-minute-walk test (6MWT), radiologic assessment of underlying nonmalignant lung disease on chest computed tomography (CT), and baseline serologies for CVD may aid in evaluating whether underlying diseases contribute to or can effectively predict those at higher risk for development of ICI-pneumonitis.

Do specific tumor factors predispose to ICI-pneumonitis? In ICI treatment for NSCLC, a number of factors may portend a higher likelihood of favorable response, such as high PD-L1 expression, high genomic instability, high tumor mutational burden, and possibly chronic obstructive pulmonary disease (32–35). In ICI-pneumonitis, different types of malignancy have higher incidence of ICI-pneumonitis (higher incidence in NSCLC than melanoma and in adenocarcinoma than in other NSCLC histologic subtypes) (7, 36). However, little is known regarding the impact of certain histologic characteristics, oncogenes, tumor suppressors, and other tumor characteristics on development of ICI-pneumonitis.

Do other cancer treatments contribute to the development of ICI-pneumonitis? Use of combined ICIs results in an increased rate of ICI-pneumonitis, with highest rates observed with combined PD-(L)1 and CTLA-4 inhibition (7, 8).

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.

Whether treatment with antineoplastic and/or other drugs (before or concomitant with ICIs) and/or radiation therapy increases the incidence of ICI-pneumonitis is unknown (37). More recently, studies have begun to combine ICIs with chemotherapeutic drugs, EGFR-TKIs, and thoracic radiation. Pneumonitis after thoracic radiation is well described, raising particular concern for increased risk of pneumonitis with either concomitant or sequential ICI and thoracic radiation (38). In a study comparing adjuvant durvalumab (a 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%) compared with placebo (25%) (39). 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 (37, 40). These data are limited by different treatment timing, dosing, and tumor heterogeneity and lower-than-expected irAEs in those treated with ICI alone. Recently, combination of EGFR-TKIs and ICIs has been recognized to increase the risk of pneumonitis (41–43). With combination chemotherapy and ICIs now first-line treatment in many patients with metastatic NSCLC (44, 45), the need to understand potential increased risk of ICI-pneumonitis is even more critical.

Current Approaches to the Diagnostic Evaluation of ICI-Pneumonitis

Current evidence and knowledge gaps. Clinical symptoms of ICI-pneumonitis, such as dyspnea, cough, low oxygen saturation, fever, and, rarely, chest pain, are nonspecific, mirroring other lung diseases, including pneumonia and even progression of malignancy (46). Further complicating matters is the variability in time of onset of ICI-pneumonitis, occurring weeks to many months after initiation of therapy (3, 8). Varying radiographic patterns of ICI-pneumonitis can be categorized according to the classifications of interstitial pneumonias; however, accurate radiologic diagnosis and correlation with pathology can often be challenging and requires expert interpretation and communication between radiologists, oncologists, pulmonologists, and infectious disease specialists (8, 14, 20). Consensus among multidisciplinary investigators is needed regarding the language to describe the different radiologic patterns of ICI-pneumonitis, and interactions between disciplines are important to diagnose irAEs across different organ systems and avoid diagnostic delays. Pulmonary infections, particularly opportunistic infections in those receiving corticosteroids, infliximab, and/or other treatments for irAEs, have been reported (9, 30, 47, 48), and similarities between clinical symptoms and radiologic findings of pulmonary infections and ICI-pneumonitis may further complicate the diagnostic evaluation of ICI-pneumonitis, resulting in harm if an underlying infection is undiagnosed before treatment with immunosuppressive medications (49–51). Furthermore, empiric treatment for suspected pulmonary infection with antibiotics might have unintended consequences, including reduced clinical benefit from ICIs, possibly due to alterations in the gut microbiome (52–54). Diagnostic evaluations, including bronchoscopy 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, 55–58). The precise role of bronchoscopy and the diagnostic value of BAL and/or biopsy and the spectrum of pathologic manifestations have not yet 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 (ASCO/NCCN) for diagnostic evaluation of suspected ICI-pneumonitis include the use of imaging (variably chest X-ray and/or CT), pulse oximetry, and an infectious work-up (including nasal swab, sputum, blood, and urine cultures) (13, 56, 57). 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, it is likely that chest X-ray lacks sensitivity in diagnosing ICI-pneumonitis, as observed with other causes of pneumonitis (8, 59). It is difficult to determine the significance of a clinical severity assessment in those with preexisting chronic pulmonary diseases with underlying symptoms of dyspnea and cough, which are used to differentiate between different grades of ICI-pneumonitis as defined by ASCO/NCCN guidelines (13). Furthermore, the role of pretreatment measures (such as PFTs, pulse oximetry, and 6MWT) and their use in evaluating suspected ICI-pneumonitis are unexplored. In other drug-related lung

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 $\geqslant$ 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.

diseases, bronchoscopy (BAL with or without transbronchial biopsy) plays an important role, not only in diagnosis but also in exclusion of other diseases (60). How pretreatment measures and diagnostic bronchoscopy may aid in the evaluation of patients with ICI-pneumonitis deserves further investigation.

Is there any value in screening asymptomatic patients on ICIs for early lung injury? The frequency with which grade 1 ICI-pneumonitis (patients with asymptomatic 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 radiographic resolution. Whether this approach changes the course of disease is yet unknown, particularly given reports of lack of progression with continued ICI treatment in asymptomatic patients. 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 (61, 62). The utility of serial PFTs (spirometry and diffusing capacity) or home pulse oximetry measurements, useful for diagnosis and management of pulmonary toxicity with bleomycin, has not been extensively studied in ICI-pneumonitis (63, 64).

What is the incidence of infections in patients on ICIs? Infections are relatively common in those who experience ICI-irAEs and even more common when immunosuppressive therapy is required (31% and 43.5%, respectively) (30). The risk of fatal infections (1–2% of deaths) may increase with the use of corticosteroids, infliximab, and combination ICI therapy (30, 47). This raises several questions regarding the role of infections in ICI-pneumonitis: *1*) Is infection a risk factor for ICI-pneumonitis development (i.e., as the first or second hit) or a contributor to increased severity/grade of ICI-pneumonitis?, *2*) Is ICI therapy itself as risk factor for development of infections?, and *3*) What is the risk of infectious complications with corticosteroid and steroid-sparing agents for the treatment of ICI-pneumonitis?

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-modulating drugs if needed (56). Although current ASCO/NCCN recommendations for the diagnostic evaluation of ICI-pneumonitis include evaluation for infectious causes of disease, including viral nasal swabs, sputum, blood, and urine cultures (13), what tests, which patients should be tested, the timing of testing, and the role of bronchoscopy with BAL to diagnose infection are unknown. Furthermore, understanding the benefit of studies to rule out other potential mimics to which these patients are at increased risk, such as CT angiography for pulmonary embolism and echocardiography for myo- and pericarditis, may be useful as well.

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 of ICI-pneumonitis is based on the clinical grade of the pneumonitis, largely on the basis of expert opinion derived from treatment of drug-related hypersensitivity pneumonitis (13, 55, 65–67). Proposed treatments include ICI cessation, systemic corticosteroids, and variable recommendations for additional immune-suppressive medications (13, 55, 56, 65, 66). This raises several areas of uncertainty. First, the optimal dose, duration, and type of immunosuppressive treatment for steroid-refractory ICI-pneumonitis have not been defined. In addition to rare steroid-refractory cases, a "rebound" or "flare" effect of worsening pneumonitis has been described in some patients on discontinuation of corticosteroids, with limited guidance for further therapy (14, 68). Second, limited retrospective data suggest that treatment with corticosteroids may negatively impact the tumor response to ICI (69). Third, in patients in whom ICI-pneumonitis has improved or resolved, it is not known if permanent discontinuation of ICI therapy is appropriate, given observed durable responses to ICIs in some patients even after discontinuation, versus rechallenge with the same or an alternative ICI agent (70). Finally, treatment with corticosteroids further suppresses the immune response and the risk for opportunistic infections, which have already been described in conjunction with ICI therapy (30, 48–51).

Key research questions.

What is the optimal management of grade 1 (asymptomatic with radiographic findings) ICI-pneumonitis? Current recommendations on management of asymptomatic patients with ICI-pneumonitis includes withholding ICIs versus continuing with close ongoing monitoring (imaging, frequent clinical evaluation, and possibly PFTs), and/or treatment with corticosteroids for progressive ICI-pneumonitis. However, it is unclear which asymptomatic radiographic changes warrant a change in patient management, whether treatment changes the course of disease, and whether treatment dosage and duration impact these outcomes (69). It is unclear if radiologic changes alone constitute clinically significant ICI-pneumonitis; therefore, it is it is not known to what degree resolution of radiologic changes constitutes response to therapy, if it correlates at all. It is similarly unclear whether all patients with grade 1 pneumonitis need to have their ICI withheld. How these patients should be followed, by what means, how frequently, and for how long (particularly those with stable ICI-pneumonitis) is unclear.

What is the optimal management of grade 2 or greater ICI-pneumonitis, and how should these patients be monitored? Treatment of symptomatic ICI-pneumonitis has centered on withholding the ICI agent, treating with systemic corticosteroids over 4 to 6 weeks, and, in those with refractory ICI-pneumonitis, adding immunosuppressive medications (13, 56, 57). However, the optimal timing, dose, and duration of corticosteroid therapy are not known. Phenotypic, radiographic, or other 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 any future ICI.

Is there a role for steroid-sparing therapy (such as infliximab, mycophenolate mofetil, 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 treatment of other drug-induced lung toxicities (13, 56, 71). It is similarly unknown 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 (9).

Does treatment with corticosteroids alter ICI-pneumonitis outcomes? As the beneficial impact of ICIs is by 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, long-term steroids increase the risk of infection and may not affect progression to fibrotic lung disease, each of which could worsen patient outcomes (69). The additive effect of steroids compared with withdrawal of therapy alone or compared with targeted, steroid-sparing therapies would help to answer these questions.

Proposed approaches. Well-designed, accurately maintained, and accessible registry data are critically needed, as data from a relatively small number of patients with ICI-pneumonitis and extrapolated from treatment of other pulmonary toxicities and IRAEs are currently being used to define optimal treatment strategies for ICI-pneumonitis. In creating these registry data, care must be taken to include both ICI-pneumonitis and ICI-pneumonitis mimics, and data should be curated by a multidisciplinary team that includes at a minimum representation from 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 multi-institutional studies with diverse, multidisciplinary involvement. Establishing new or increasing the accessibility of existing central databases (such as that maintained by the Oncology Cooperative group) is needed.

Conclusions

ICIs have revolutionized cancer therapy, and their expanded use comes with a numeric increase in irAEs, making essential the accurate identification, characterization, and treatment of potentially severe irAEs, including ICI-pneumonitis. In this article, an expert multidisciplinary panel has identified critical knowledge gaps that must be addressed to ensure progress in the field of ICI-pneumonitis and proposed standardized approaches to further study (Table 5). The panel identified key challenges in this field, including the need to further define and refine the terminology used to describe ICI-pneumonitis, identify the biologic mechanisms of ICI-pneumonitis, define risk factors, and determine the optimal diagnostic and management strategies for ICI-pneumonitis. Given the complexity of ICI-pneumonitis, multidisciplinary collaborations will be critical to enhance the research and narrow these knowledge gaps. Furthermore, prioritization of multi-institutional 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 teams 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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Author Disclosures: C.R.S. served on an advisory committee for Biodesix; and received research support from the American Cancer Society and the Bristol-Myers Squibb Foundation. M.P.R. served on an advisory committee for Abbvie Technologies, bioAffinity

Technologies, and Biodesix. P.C. served as a speaker for Boehringer Ingelheim; and owns stocks or options in Roche. M.G. served on an advisory committee for Nucleix; received research support from AstraZeneca, Boehringer Ingelheim, Elpen, Menarini, and Novartis; and received personal fees from AstraZeneca, Bristol-Myers Squibb, Chiesi, MSD, and Pharmaten. E.B.G. served as a consultant for Dracen and EMD Serono; received research support from AstraZeneca, Bristol-Myers Squibb, Dynavax, Eli Lily, Genentech, Iovance, Merck, Mirati, Neon, and Novartis; and received payment for manuscript preparation from Pfizer. M.K.G. received research support from Medial EarlySign; and received royalties from UpToDate for authoring chapters on lung cancer diagnosis and staging. P.R.M. received research support from ResMed. J.N. served as a consultant for AstraZeneca, Bristol-Myers Squibb, and Genentech/Roche; and received research support from Merck and AstraZeneca. M.N. served as a consultant for Daiichi Sankyo; and received research support from AstraZeneca, Canon Medical Systems, Merck, and Toshiba Medical Systems. S.P.P. received research support from AstraZeneca/MedImmune, Bristol-Myers Squibb, Eli Lilly, Fate Therapeutics, Genocea, Incyte, Iovance, Merck, Pfizer, Roche/Genentech, and Xcovery; and served on an advisory committee for AstraZeneca, Bristol-Myers Squibb, Illumina, Nektar, and Tempus. T.P. served on an advisory committee for AstraZeneca and Novocure. A.H.L., J.D.P., and W.D.T. reported no relevant commercial relationships.

Acknowledgment: The chairs thank Dr. Claudia Onofrei for her input to initial discussions, the members of the American Thoracic Society Assembly on Thoracic Oncology for their support in creating this research policy statement, and American Thoracic Society staff members John Harmon and Kimberly Lawrence for their help in organizing the in-person meeting and conference calls. The authors thank the members of the Documents Development and Implementation Committee for their help in reviewing drafts of this report.

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