Immunotherapy Use in Patients With Lung Cancer and Comorbidities

Mitchell S. von Itzstein, MD,*† Amrit S. Gonugunta, BSA,‡ Helen G. Mayo, MLS,§ John D. Minna, MD,*† and David E. Gerber, MD*††

Abstract: Immune checkpoint inhibitor (ICI) therapy is now in widespread clinical use for the treatment of lung cancer. Although patients with autoimmune disease and other comorbidities were excluded from initial clinical trials, emerging real-world experience suggests that these promising treatments may be administered safely to individuals with inactive low-risk autoimmune disease such as rheumatoid arthritis or psoriasis, mild to moderate renal and hepatic dysfunction, and certain chronic viral infections. Considerations for ICI in autoimmune disease populations include exacerbations of the underlying autoimmune disease, increased risk of ICI-induced immune-related adverse events, and potential for compromised efficacy if patients are receiving chronic immunosuppression. Immune checkpoint inhibitor use in higher-risk autoimmune conditions, such as myasthenia gravis or multiple sclerosis, requires careful evaluation on a case-by-case basis. Immune checkpoint inhibitor use in individuals with solid organ transplant carries a substantial risk of organ rejection. Ongoing research into the prediction of ICI efficacy and toxicity may help in patient selection, treatment, and monitoring.

Key Words: Autoimmune disease, immune checkpoint inhibitors, immune-related adverse events, immunosuppression, transplant

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APPROPRIATE TO COMORBIDITIES

Based on these observations and experiences, it has become abundantly clear that patient selection and monitoring for ICI differ substantially from those for chemotherapy and molecularly targeted therapy. Nevertheless, which clinical factors truly

and prolonged responses in a majority of patients. In a minority of patients, ICI has complicated the assessment of efficacy, as clinicians may need to distinguish between progression, hyperprogression, and pseudoprogression.

From a clinician’s standpoint, it is the potential for autoimmune toxicity that truly sets ICI apart from chemotherapy and molecularly targeted therapies. So-called immune-related adverse events (irAEs) occur when ICI-induced immune cell activation cross-reacts with normal tissues. Immune-related adverse events may affect almost any organ, including the brain, pituitary, eyes, thyroid, lungs, heart, liver, pancreas, colon, kidneys, adrenal, skin, joints, and muscles. In contrast to the well-characterized onset of classical chemotherapy toxicities—such as alopecia, nausea/vomiting, and myelosuppression—in patients with new clinical or radiographic respiratory findings, lethal cases are exceedingly rare. Similarly, ICI effects on complex physiologic pathways such as the hypothalamic-pituitary-adrenal axis have led to recommendations for routine monitoring of endocrine function and early consultation with relevant experts.

Occasionally, combination therapies have revealed largely unanticipated toxicities. For instance, a study of combined atezolizumab (anti-PDL1) and the epidermal growth factor receptor inhibitor osimertinib demonstrated a pulmonary toxicity rate exceeding 50%, even though each agent independently causes pneumonitis in fewer than 5% of cases. In contrast, certain combinations anticipated to cause substantial toxicity have been surprisingly well tolerated. In a phase III clinical trial, the administration of consolidation durvalumab (anti-PDL1) for up to 1 year after chemoradiation for locally advanced non–small cell lung cancer (NSCLC) led to high-grade pneumonitis in only 3% of patients, comparable to rates seen with chemoradiation alone.

Although ICI has introduced new toxicities, in other areas ICI therapy clearly presents fewer risks than other treatments. The classic toxicities of cytotoxic chemotherapy are alopecia, nausea/vomiting, and myelosuppression leading to cytopenias. These events occur only rarely with ICI. Particularly relevant to patient safety, effects on bone marrow or circulating blood cells occur in well under 5% of individuals.

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influence ICI efficacy and safety remain unclear. We searched clinicaltrials.gov for completed and resulted lung cancer trials using the terms ICIs, checkpoint inhibitors, ICI, nivolumab, ipilimumab, pembrolizumab, atezolizumab, avelumab, and durvalumab. As shown in Table 1 and Supplemental Table 1 (http://links.lww.com/PPO/A35), eligibility criteria vary widely among these trials. We also searched clinicaltrials.gov with the same search terms to identify currently recruiting trials to characterize recent trends in eligibility criteria (Supplemental Table 2, http://links.lww.com/PPO/A35). Over time, we found relatively little change in trial eligibility, with frequent and arbitrary exclusion of autoimmune disease (AID), immunosuppression, organ dysfunction, and chronic viral infections. Although expansion of ICI to these populations represents an area of major interest to researchers and clinicians, we identified only 5 active or forthcoming trials specifically investigating ICI use in patients with comorbidities (NCT 04499053, 04108026, 04473703, 04514484, 03313544).

Understanding the efficacy and safety of ICI in diverse patient populations will be critical to realizing the full potential of these therapies. It is estimated that stringent eligibility criteria may exclude up to 70% of patients with lung cancer from ICI clinical trials.14,15 Lung cancer populations may be particularly susceptible to such exclusions. In the United States, the average age at diagnosis is older than 70 years, substantially older than average age for other common malignancies such as breast and colorectal cancer.16 Directly relevant to ICI considerations, incidence of AID increases with age.17 Renal function also decreases with age.18 Separately, more than 80% of individuals with lung cancer are current or former smokers,19 an exposure that conveys risk of both chronic pulmonary conditions and AIDs.20,21

To fill the immense gap between rarefied ICI clinical trial populations and actual lung cancer patients seen in clinical practice, numerous observational studies from real-world settings have emerged. Some of these reveal clear differences with trial reports. For instance, single-agent anti-PD1/PDL1 trials generally report rates of pneumonitis between 3% and 5%.22 However, observational patient series describe incidence closer to 20%.23 Whether this discrepancy reflects characteristics of the treated populations or the inherent challenges of diagnosing and characterizing irAE is not clear. Additionally, retrospective data—particularly for small case series and case reports—may be susceptible to publication bias, with authors and editors choosing to publish events with unexpectedly good or particularly poor outcomes.24

For this review, we identified relevant publications by performing Ovid MEDLINE and Ovid Embase searches of articles published from inception through June 2020 using the terms lung, pulmonary, respiratory, cancer, neoplasm, tumor, malignancy, comorbidity, autoimmune disease, immunotherapy, checkpoint inhibitor, ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, anti-PD1, anti-PDL1, anti-CTLA4, infection, and performance status (PS). Because concerns such as flare of preexisting AID or irAEs do not seem to reflect tumor biology, we included reports of all cancer types. Based on this literature, we provide an overview of the medical comorbidities that have potential clinical relevance to ICI therapy and discuss how these conditions influence trial design, treatment selection, and clinical monitoring.

**AUTOIMMUNE DISEASE**

An estimated 20 to 50 million individuals in the United States have an AID, including up to 14% to 25% of patients with lung cancer.25 While these conditions have not generally represented a major consideration for conventional chemotherapy or molecularly targeted therapies, they are generally restricted or excluded entirely from ICI clinical trials. Some trials have excluded patients with “active” AID (such as those requiring corticosteroids equivalent to prednisone >10 mg daily).26 Some studies have excluded patients with any history of AID.27 Other trials determine eligibility according to the potential morbidity of the AID, allowing enrollment of patients with low-risk AID, such as psoriasis and vitiligo.28

Complicating these considerations is the inherent challenge of diagnosing AID. Establishing a cancer diagnosis is generally a straightforward process relying on pathologic evaluation of biopsy material. By contrast, an AID diagnosis may incorporate clinical history, physical examination findings, laboratory, radiology, and histologic data. Individual diagnostic components may be neither sufficiently sensitive nor specific. For instance, antinuclear antibodies—a characteristic finding of such AID as lupus, scleroderma, Sjögren syndrome, and dermatomyositis/polymyositis—may be observed more frequently in one-quarter of healthy adults.29 The impact of this diagnostic uncertainty is apparent in the wide range of estimated AID cases among the general population and among individuals with cancer.30

Autoimmune disease–related concerns center on potential toxicity, including heightened rates of irAEs and exacerbation of the underlying AID. Autoimmune disease flares represent a wide spectrum of potential clinical severity. Worsening of conditions such as rheumatoid arthritis (RA) and psoriasis are unlikely to be life threatening. However, an acute exacerbation of myasthenia gravis could result in phrenic nerve paresis, diaphragmatic dysfunction, and respiratory failure. Similarly, a flare of multiple sclerosis could have immediate and profound effects on critical functions such as vision.

Given the almost universal exclusion of patients with AID from ICI clinical trials, clinicians have published a number of observational series of patients with AID treated with approved ICI regimens (Table 2). These studies vary in size, cohort characteristics, and outcomes. One study reported occurrence of AID flare in 23% of patients, but no apparent increase in risk of ICI–associated irAE.34 Most AID flares were minor and responded to immunosuppression; none required ICI therapy discontinuation.44 Another series identified increased incidence of grade 1 and 2 irAEs in those with a history of AID (including both “active” and “inactive” cases), but no increased risk of grade 3 and 4 irAE.39 Other observational studies have similarly found increased risk of irAEs in those with preexisting AID.44,45 Patients with an isolated high antinuclear antibody titer without associated clinical features of AID seem to tolerate ICI therapy, although those with titers ≥1:320 may require heightened monitoring due to increased risk of irAE.50

There are relatively few data on ICI use in high-risk AID. Immune checkpoint inhibitor administration may induce relapse of multiple sclerosis, in some instances leading to rapid neurological progression and death.51 A case report has described the feasibility of ICI in a patient with granulomatosis with polyangiitis (a form of vasculitis affecting the respiratory and renal systems), although the disease was not clinically active, and the patient was receiving immunosuppression.52

Relevant to ICI administration and monitoring, some cancers predispose patients to autoimmune phenomena. Autoimmune paraneoplastic conditions may affect multiple organ systems, including the nervous system, connective tissue and skin, and blood cells. These events arise from immune cross-reactivity between tumor cells and healthy tissue. For autoimmune paraneoplastic neurologic syndromes (e.g., limbic encephalitis, cerebellar degeneration, and myasthenia gravis), overrepresented cancer types tend to either1 produce neuroendocrine proteins (e.g., small cell lung cancer, neuroblastoma),2 contain neuronal...
<table>
<thead>
<tr>
<th>Trial/NCT#</th>
<th>Reference</th>
<th>Phase Year</th>
<th>Autoimmune Disease</th>
<th>Systemic Immune Suppression</th>
<th>Renal</th>
<th>Liver</th>
<th>Bone Marrow</th>
<th>ILD</th>
<th>Heart Failure</th>
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components (e.g., teratoma),\(^3\) involve immunoregulatory organs (e.g., thymic tumors), or\(^4\) affect immunoglobulin production (e.g., lymphoma, myeloma).\(^5\) The safety profile of ICI in these malignancies varies widely. Despite one of the highest associations with paraneoplastic neurologic syndromes of any cancer, small cell lung cancer treated with ICI has rates of irAEs and other autoimmune phenomena comparable to those of other lung cancer subtypes.\(^54,55\) By contrast, ICI trials in thymic tumors have demonstrated rates of grade \(\geq 3\) irAEs up to 40%,\(^56–58\) suggesting that, independent of a patient's history of AID, these rare malignancies represent at least a relative contraindication to ICI use.

**IMMUNOSUPPRESSION**

Use of immunosuppressive therapies in patients with lung cancer is relatively common. Autoimmune disease and solid organ transplant are common indications for chronic immunosuppression. These regimens may include corticosteroids, calcineurin inhibitors, mammalian target of rapamycin inhibitors, and antimetabolites. Additionally, corticosteroids are frequently used for their anti-inflammatory and antientmetic properties in this population, with specific indications including management of brain metastasis, spinal cord compression, dyspnea, fatigue, decreased appetite, chronic obstructive pulmonary disease (COPD), and prevention of nausea and vomiting.\(^59,60\)

Given the immunosuppressive effects of corticosteroids, in particular negative effects on T-cell function,\(^61,62\) there is concern that concurrent steroid use may reduce the efficacy of ICI. Accordingly, patients taking steroids above specified thresholds (e.g., prednisone equivalent \(\geq 10\) mg/d) are frequently excluded from ICI clinical trials. Early observational studies found statistically significant and clinically meaningful associations between baseline corticosteroid use and worse outcomes in patients receiving ICI therapy, with an overall survival hazard ratio of 1.7 for those receiving baseline steroids (95% confidence interval, 1.3–2.2).\(^63,64\) Subsequent analyses have found that the poor prognosis associated with steroid indications—such as neurologic symptoms or anorexia—may drive these observations, with no difference in progression-free or overall survival between patients receiving less than 10 mg prednisone equivalent per day versus those receiving greater than 10 mg prednisone equivalent per day for non–cancer-related indications.\(^65\) In contrast, treatment of ICI-induced irAEs with corticosteroids does not seem to worsen outcomes.\(^66\) It seems plausible that these findings reflect the clear link between irAEs and ICI benefit, which may counteract the potential negative effects of ICI interruption and corticosteroid administration.

Case reports have described patients with active AID receiving immunosuppression achieving good outcomes with cancer immunotherapy,\(^30,31\) but evidence is limited and subject to publication bias. To optimize ICI efficacy, some experts advocate transitioning from nonselective immunosuppression (e.g., corticosteroids) to targeted agents (such as infliximab and tocilizumab) for specific AIDs prior to ICI initiation,\(^67\) an approach that would require validation in prospective trials.

Immune checkpoint inhibitor use in individuals with solid organ transplants seems to convey substantial clinical risk (Table 3). One review of these cases found that transplant rejection was common (37%) and was the most common cause of death.\(^68\) Nevertheless, there are several reports of ICI administration resulting in antitumor efficacy without inducing graft rejection. However, the potential for reporting and publication bias in these instances seems quite high. Accordingly, ICI use in solid organ transplant recipient should be approached with extreme caution. On a case-by-case basis, some clinicians may distinguish between organ

### Table 1. (Continued)

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<thead>
<tr>
<th>Trial/NCT#/Reference</th>
<th>Phase, Year</th>
<th>Autoimmune Disease</th>
<th>Systemic Immune Suppression</th>
<th>Renal Function</th>
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<tr>
<td><strong>First-Line Nivolumab Versus Investigator’s Choice for Stage IV or Recurrent PDL1+ NSCLC (CheckMate 026)</strong> (NCT02041533)</td>
<td>III 2014</td>
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<tr>
<td>Autoimmune Disease Category</td>
<td>Summary of Findings</td>
<td>Reference</td>
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<td>Gastrointestinal (inflammatory bowel disease)</td>
<td>Case reports including 5 patients (3 CD, 2 UC), multiple cancer and ICI types, concurrent immunosuppression, 2 with AID flare, no irAE, 3 with antitumor response</td>
<td>30-33</td>
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<td></td>
<td>Observational study with 6 patients (3 CD, 3 UC), NSCLC, treated with anti-PD(L)1 therapy, none with AID flare, 3 with irAE. Individual efficacy not reported</td>
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<td></td>
<td>Observational studies with 9 patients (5 UC, 4 CD), melanoma treated with ipilimumab, 2 with AID flare, 2 with irAE, 1 with antitumor response</td>
<td>35,36</td>
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<td></td>
<td>Observational study with 6 patients (3 CD, 2 UC, 1 celiac disease), melanoma treated with anti-PD(L)1 therapy, none with AID flare. Individual efficacy and irAEs not reported</td>
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<td></td>
<td>Observational study with 1 patient with UC, melanoma treated with anti-PD(L)1 therapy, with AID flare, without irAE, with antitumor response</td>
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<td></td>
<td>Observational studies with 17 patients (14 unspecified, 3 CD), multiple cancers treated with multiple ICI therapies, 11 with AID flare, 7 with irAE. Individual efficacy not reported</td>
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<td>Overall: 44 patients, 16 with AID flare, 12 with irAE, 20 with no irAE, 5 with antitumor response, 8 with no antitumor response</td>
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<td>Neurologic</td>
<td>Observational study with 3 patients (2 MS, 1 MG), NSCLC treated with anti-PD(L)1 therapy, none with AID flare, 2 with irAE. Individual efficacy not reported</td>
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<td></td>
<td>Observational studies with 4 patients (3 MS, 1 LETM), melanoma treated with ipilimumab, 1 with AID flare, 2 with irAE, none with antitumor response</td>
<td>35,36</td>
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<td>Observational study with 5 patients (2 GBS, 1 MG, 1 CIDP, 1 Bell palsy), melanoma treated with anti-PD(L)1 therapy, none with AID flare. Individual efficacy and irAEs not reported</td>
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<td></td>
<td>Review of 13 patients with MG, multiple cancer types treated with anti–PD-1 therapy, 11 with AID flare. Individual efficacy and irAEs not reported</td>
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<td>Case reports of 2 patients with MS, melanoma treated with ipilimumab, with AID flare, no irAE, with antitumor response</td>
<td>42,43</td>
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<td></td>
<td>Observational study with 2 patients (1 MS, 1 GBS), melanoma treated with anti-PD(L)1 therapy, none with AID flare, 1 with irAE, none with antitumor response</td>
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<td></td>
<td>Observational studies with 5 patients (3 MS, 2 MG), multiple cancer and ICI types, none with AID flare. Individual efficacy and irAEs not reported</td>
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<td>Observational study with 1 patient with optic neuritis, unspecified cancer and ICI type, with AID flare, with irAE. Individual efficacy not reported</td>
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<td>Overall: 35 patients, 14 with AID flare, 4 with irAE, 7 with no irAE, 1 with antitumor response, 5 with no antitumor response</td>
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<td>Rheumatologic</td>
<td>Observational study with 25 patients (11 RA, 5 PMR, 4 seronegative arthritis, 2 scleroderma, 2 psoriatic arthritis, 1 SLE), NSCLC treated with anti-PD(L)1 therapy, 10 with AID flare, 6 with irAE. Individual efficacy not reported</td>
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<td></td>
<td>Observational studies with 30 patients (20 RA, 4 sarcoidosis, 3 spondylitis, 2 SLE, 1 CREST syndrome) melanoma treated with ipilimumab, 15 with AID flare, 12 with irAE, eight with antitumor response</td>
<td>35,36,45</td>
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<td>Observational study with 27 patients (13 RA, 3 sarcoidosis, 3 PMR, 2 SLE, 2 scleroderma, 2 psoriatic arthritis, 2 SS), melanoma treated with anti-PD(L)1 therapy, 14 with AID flare. Individual efficacy and irAEs not reported</td>
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<td></td>
<td>Case reports with 2 patients with RA, melanoma treated with multiple ICI types, no AID flare, no irAE, 2 with antitumor response</td>
<td>42,46</td>
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<td>Observational study with 7 patients (2 sarcoidosis, 2 spondylitis, 1 RA, 1 PMR, 1 myositis), melanoma treated with anti-PD(L)1 therapy, 5 with AID flare, 2 with irAE, 3 with antitumor response</td>
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<td>Observational study with 7 patients (4 SS, 2 RA, 1 PMR), multiple cancer and ICI types, 1 with AID flare. Individual efficacy and irAEs not reported</td>
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<td>Observational studies with 62 patients (24 RA, 9 PMR, 9 SLE, 5 spondylitis, 4 sarcoidosis, 4 systemic sclerosis, 3 SS, 1 APS, 1 DM, 1 unspecified CTD), multiple cancer and ICI types, 19 with AID flare, 20 with irAE. Individual efficacy not reported</td>
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<td>Observational study with 16 patients (5 RA, 5 PMR, 2 SS, 2 SLE, 1 spondylitis, 1 sarcoidosis), multiple cancer and ICI types, 2 with AID flare, 5 with irAE, 6 with antitumor response</td>
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<td>Overall: 176 patients, 66 with AID flare, 45 with irAE, 97 with no irAE, 19 with antitumor response, 33 with no antitumor response</td>
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### TABLE 2. (Continued)

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<tr>
<th>Autoimmune Disease Category</th>
<th>Summary of Findings</th>
<th>Reference</th>
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<tr>
<td><strong>Endocrine</strong></td>
<td>Observational study with 9 patients (5 Graves thyroiditis, 4 Hashimoto thyroiditis), NSCLC treated with anti-PD(L)1 therapy, 1 with AID flare, 3 with irAE. Individual efficacy not reported</td>
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<td></td>
<td>Observational studies with 17 patients (12 unspecified thyroiditis, 5 Hashimoto thyroiditis), melanoma treated with ipilimumab, 2 with AID flare, 2 with irAE, 1 with antitumor response</td>
<td>35,36</td>
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<td></td>
<td>Observational study with 4 patients with Graves disease, melanoma treated with anti-PD(L)1 therapy, 1 with AID flare. Individual efficacy and irAEs not reported</td>
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<td>Observational study with 6 patients with autoimmune thyroiditis, melanoma treated with anti-PD(L)1 therapy, 1 with AID flare, 1 with irAE, 1 with antitumor response</td>
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<td></td>
<td>Observational studies with 17 patients (8 autoimmune thyroiditis, 4 Graves disease, 3 Hashimoto's thyroiditis, 1 type 1 diabetes, 1 autoimmune hypophysitis), multiple cancer and ICI types, 1 with AID flare. Individual efficacy and irAEs not reported</td>
<td>40,44</td>
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<td></td>
<td>Observational study with 51 patients (10 Graves disease, 41 autoimmune thyroiditis), multiple cancer and ICI types, 22 with AID flare, 19 with irAE. Individual efficacy not reported</td>
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<td></td>
<td>Overall: 104 patients, 28 with AID flare, 29 with irAE, 54 with no irAE, 1 with antitumor response, 22 with no antitumor response</td>
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<td><strong>Dermatologic</strong></td>
<td>Observational study with 16 patients (14 psoriasis, 1 alopecia areata, 1 discoid lupus), NSCLC treated anti-PD(L)1 therapy, 4 with AID flare, 7 with irAE. Individual efficacy not reported</td>
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<td>Observational studies with 14 patients (12 psoriasis, 2 autoimmune urticaria), melanoma treated with ipilimumab, 4 with AID flare, 6 with irAE, 5 with antitumor response</td>
<td>35,36</td>
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<td>Observational study with eight patients (6 psoriasis, 1 eczema, 1 erythema nodosum), melanoma treated with anti-PD(L)1 therapy, 3 with AID flare. Individual efficacy and irAEs not reported</td>
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<td>Case report of patient, melanoma treated with sequential ipilimumab and pembrolizumab, severe AID flare, no irAE, with antitumor response</td>
<td>48</td>
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<tr>
<td></td>
<td>Observational study with 3 patients with psoriasis, melanoma treated with anti-PD(L)1 therapy, 1 with AID flare, none with irAE, none with antitumor response</td>
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<td>Observational study with 33 patients (17 vitiligo, 12 psoriasis, 4 unspecified), multiple cancer and ICI types, eight with AID flare. Individual efficacy and irAEs not reported</td>
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<tr>
<td></td>
<td>Observational study with 45 patients (45 psoriasis), multiple cancer and ICI types, 28 with AID flare, 17 with irAE. Individual efficacy not reported</td>
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<td>Overall: 120 patients, 49 with AID flare, 30 with irAE, 50 with no irAE, 6 with antitumor response, 13 with no antitumor response.</td>
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<td>Overall: 479 patients, 171 with AID flare, 120 with irAE, 228 with no irAE, 32 with antitumor response, 81 with no antitumor response</td>
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APS, antiphospholipid syndrome; CD, Crohn disease; CIDP, chronic inflammatory demyelinating polyneuropathy; CTD, connective tissue disease; DM, dermatomyositis; GBS, Guillain-Barré syndrome; LEM, longitudinal extensive transverse myelitis; MG, myasthenia gravis; MS, multiple sclerosis; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; UC, ulcerative colitis.

END-ORGAN DYSFUNCTION

For conventional chemotherapy and molecularly targeted therapies, laboratory evidence of end-organ dysfunction (e.g., elevated creatinine, elevated bilirubin, or reduced blood counts indicating renal, hepatic, and bone marrow dysfunction, respectively) may require avoidance or adjustment of certain agents. Specific thresholds are regularly included among clinical trial eligibility criteria. Such guidance reflects the potential for increased toxicity on already compromised organ systems (pharmacodynamic effects) or reduced clearance of the antineoplastic agent (pharmacokinetic effects). For ICI therapies, these pharmacokinetic considerations may not apply, as their clearance is not substantially impacted by renal or hepatic function and instead relies predominantly on nonspecific degradation within plasma and tissues. However, baseline organ function may be relevant to pharmacodynamic concerns.

The most widely used measure of medical comorbidities is the Charlson comorbidity index, which includes conditions such as heart disease and cancer and predicts 1-year mortality.

Pulmonary

Because most patients with lung cancer are current or former smokers, a substantial proportion have comorbid pulmonary disease. A number of retrospective studies have demonstrated that
preexisting interstitial lung disease (ILD) increases risk of immune-mediated pneumonitis in patients receiving ICI.25–27 A single-center series of 102 patients also showed a trend toward increased risk of ICI-associated pneumonitis in patients with preexisting COPD.76 This observation may reflect the inflammatory nature of COPD, which features increased CD8 T-cell numbers and PDL1 expression.77 However, other studies suggest no detrimental effect on pulmonary function or symptoms in patients with COPD receiving ICI.78

Cardiac
Cardiac irAEs are well characterized but quite rare, with myocarditis estimated to occur in fewer than 1% of patients treated with ICI.79 Although 1 case series found myocarditis occurs more frequently in those with underlying cardiovascular risk factors, most patients who develop myocarditis have previously normal cardiac function.79 Unfortunately, further data on the safety of these therapies in individuals with underlying cardiac disease are limited.80 Nevertheless, recommendations for monitoring for these events in this population have emerged, including baseline cardiology evaluation and assessment of cardiac enzymes (including high-sensitivity troponin) every 6 weeks for at least 12 weeks after ICI initiation.81 Although it is not clear whether individuals with reduced ejection fraction at baseline have increased risk of ICI-induced myocarditis, these patients do have less functional reserve should such an event occur.

Liver
Immune checkpoint inhibitor therapy may cause autoimmune hepatitis. While anti-PD1 therapy has been studied in and is now approved for hepatocellular carcinoma, reports of ICI use in patients with underlying liver failure or cirrhosis are extremely limited.82 Immune checkpoint inhibitor use in patients with viral hepatitis is discussed in the infectious disease section below.

Renal
The development of clinically significant ICI-induced nephrotoxicity is relatively rare (approximately 2% of irAEs83), and risk factors for immune-mediated nephritis are poorly understood.83 Furthermore, it is unclear if renal disease impacts the development of other irAE. A study of 78 patients found increased risk of irAEs in those with stage 3 to 4 chronic kidney disease (creatinine clearance [CrCl] <60 mL/min),83 but this finding has not been replicated in other studies. A retrospective analysis of 414 patients found worse baseline renal function and use of proton-pump inhibitors were associated with ICI-induced acute kidney injury.84

**PERFORMANCE STATUS/AGE**

Historically, patients with poor PS (Eastern Cooperative Oncology Group [ECOG] ≥2) and elderly patients have been excluded from or underrepresented in clinical trials, even though these individuals account for more than 50% of the overall lung cancer population.85 Although early ICI clinical trials restricted enrollment to ECOG 0–1 PS, more recent studies have included patients with worse functional status. The phase II CheckMate 171 trial of nivolumab in advanced squamous NSCLC reported no difference in treatment-related adverse events in ECOG 2 patients compared with the ECOG 0–1 population; however, ECOG 2 patients had inferior overall survival (median, 5.4 months in ECOG PS 2 cohort vs. 9.9 months in total cohort),86 consistent with historical data in this population.87 Comparable findings were reported in the phase III/IV CheckMate 153 study of nivolumab for previously treated advanced NSCLC.88 A meta-analysis across cancer types found no difference in outcomes between patients with ECOG 0 and ECOG 1–2, although there were relatively few patients in the ECOG 2 category.89 Other observational studies reported no safety concerns in patients with worse PS, but again identified inferior survival.90–95 However, 1 single retrospective evaluation of 190 patients identified an increased risk of high-grade irAEs in those with ECOG PS 2 to 3.96 There are clearly substantial challenges to determining the benefit of ICI therapy in patients with poor functional status, as they tend to have inherently poor prognosis independent of treatment.71,97 The phase III eNERGY trial (NCT 03351361) comparing first-line combination ICI therapy with cytotoxic therapy in elderly patients and those with poor PS has completed enrollment and will provide more insights into these understudied populations.

A single-center study of 75 patients found that older patients (age ≥70 years) tolerated ICI therapy without an increased safety signal and that the poor overall survival in this group was driven by poor PS (median survival, 13.7 months for ECOG 0 to 1, compared with 3.8 months for ECOG ≥2).98 A larger study of 245 patients found no increased risk of toxicity with age, although patients older than 80 years had substantially lower overall survival (median, 3.6 months) compared with those 70 to 79 years old (median, 12.9 months).99 Additional observational evidence found no new safety signals in older patients receiving ICI therapy.100,101 Furthermore, 2 meta-analyses of ICI clinical trials found that patients 65 years or older derive similar clinical benefit to younger patients and actually may have a lower incidence of grade 3 and 4 irAE.102,103 These findings suggest that advanced age alone should not be considered a contraindication to ICI therapy.

**INFECTIOUS DISEASE**

A number of studies have evaluated ICI use in individuals with human immunodeficiency virus (HIV) infection. Hypothetically, administration of immunotherapy to a population with suppressed and dysregulated immunity raises both efficacy and safety concerns. Nevertheless, a growing body of evidence supports the safety and efficacy of ICI therapy in patients infected with HIV104–106 Specifically, ICI responses have been documented in patients with low CD4+ counts.107 While a single study identified a heightened risk of irAE, particularly pneumonitis (24%), in patients with HIV,108

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<th>TABLE 3. Summary of Evidence for ICI Use in Organ Transplant</th>
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Adapted from Fisher et al.84

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other studies have not replicated this observation. Ongoing clinical trials are evaluating ICI use in this population prospectively.

To date, relatively little information is available on ICI use in chronic viral hepatitis. Limited case series have demonstrated ICI safety and efficacy in patients with hepatitis B and hepatitis C viruses.

Historically, acute infections have been considered relative contraindications to the administration of chemotherapy due to concerns that myelosuppression could worsen severity and prolong duration of the infection. For ICI, there have been few studies addressing this clinical question. It has been observed that concurrent diagnosis of lung cancer and respiratory tract infection is associated with worse ICI outcomes, although may be due to reduced treatment exposure. Recent or ongoing infection may also influence efficacy of ICI through possible alteration of host microbiome and immune system. Additionally, there are be a link between antibiotic exposure and ICI outcomes. The underlying mechanism seems to be dysregulation of the fecal microbiome, which may persist for months after antibiotic use. Microbiome changes seem not only to influence ICI efficacy, but may also increase the risk or irAE, in particular colitis.

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic has implications on ICI therapy for patients with lung cancer. Patients with lung cancer are at particular risk of coronavirus disease 2019 (COVID-19) given their underlying malignancy and frequent comorbidities. Diagnosis of COVID-19 in lung cancer patients receiving ICI is particularly difficult, as its nonspecific symptoms of dyspnea, cough, and fever could also represent tumor progression, pulmonary embolism, exacerbation of respiratory comorbidities such as COPD, or immune-mediated pneumonitis (which may have similar radiographic features as COVID-19). Immune checkpoint inhibitor administration raises hypothetical concerns about increasing COVID-19 severity, as morbidity and death may result from cytokine storm. Indeed, tocilizumab (an interleukin-6 receptor antagonist occasionally used to treat severe ICI-induced irAEs) has been investigated as a potential treatment for COVID-19. At this time, there is limited clinical evidence of the safety and efficacy of ICI therapy in patients with COVID-19 infection. For patients currently on ICI therapy without COVID-19 infection, it may be reasonable to continue therapy, with consideration of increasing the dosing interval (such as pembrolizumab 400 mg every 6 weeks) to minimize exposure risk. Some experts have recommended ICI treatment breaks for patients with long-term disease control during the COVID-19 pandemic. Nevertheless, recent observations suggest that patients with lung cancer and recent COVID-19 infection treated with ICI had outcomes comparable to similar patients receiving other therapies. In newly diagnosed, treatment-naïve patients with history of COVID-19 infection, the optimal therapeutic approach is even less clear. Based on the hypothetical risk of cytokine storm, some authors have suggested initially withholding ICI therapy in favor of cytotoxic chemotherapy.

PUBLISHED GUIDELINE RECOMMENDATIONS

While oncology society guidelines infrequently address specific comorbidities, treatment recommendations routinely incorporate functional status. In many cases, this guidance reflects the data available from clinical trials. The most recent European Society for Medical Oncology guidelines recommend first-line ICI therapy for ECOG 0–1 patients, but they extend ICI recommendations to those with ECOG 2 in the second-line setting. Likewise, the latest American Society of Clinical Oncology guidelines endorse first-line ICI therapy for ECOG 0–1 patients, but do not comment on those with worse PS. The European Society for Medical Oncology and American Society of Clinical Oncology guidelines do not address specific comorbidities.

The National Comprehensive Cancer Network (NCCN) guidelines consider AID, use of immunosuppression, or presence of a driver oncogene (which may correlate with lack of therapeutic benefit from ICI) as potential contraindications to ICI therapy. The NCCN does not specify a PS threshold for single-agent ICI therapy in those with tumor PD-L1 expression ≥50%, but does restrict recommendations for combination ICI and chemotherapy to ECOG 0 to 1 patients. For patients with squamous NSCLC and ECOG 2, the NCCN recommends cytotoxic chemotherapy rather than ICI therapy.

DISCUSSION AND RECOMMENDATIONS

Although ICI therapy has been in widespread use for lung cancer and other malignancies for several years, relatively little is known about the use of these agents in patients with comorbidities. Based on the available evidence, we have developed a suggested approach to ICI therapy in this population (Fig. 1).

In considering the relevance of medical comorbidities to ICI administration, it is important to note clear differences between these agents and conventional chemotherapy and targeted therapies: (1) the clearance of ICIs does not depend on renal and hepatic function to the extent that other treatments do; (2) ICIs almost never cause cytopenias, substantial nausea and vomiting, or alopecia—the classic triad of chemotherapy toxicities; (3) ICIs have a unique mechanism of action, relying on the patient’s own immune system to induce cancer cell death; (4) they have also introduced novel toxicities, namely, irAEs; and (5) there is no option for dose modification of ICI; these drugs are either given at full dose, temporary withheld, or permanently discontinued.

An important consideration in the use of ICI is the role of clinical monitoring. Currently, recommended laboratory assessments include renal, hepatic, thyroid, pituitary, and adrenal function. Radiographic surveillance for pulmonary toxicities is not routinely performed, so regular thoracic imaging may only occur if indicated for assessment of response to therapy. Nor is routine monitoring for cardiac or intestinal toxicities undertaken. As clinicians consider administering ICI to patients at higher risk of toxicities, adjusting the components and frequency of monitoring may mitigate potential risk. Additionally, biomarkers for the prediction of irAEs represent an area of ongoing investigation.

Perhaps more so than for other cancer treatments, comorbidities may affect the efficacy of ICI, as well as safety. Conditions requiring chronic immunosuppression may render an individual less likely to benefit from immune checkpoint inhibition. Similarly, antibiotic exposure may reduce ICI efficacy through modification of the microbiome. Understanding the influence of these clinical factors is important because lung cancer patients who progress on an initially selected therapy may not be able to receive subsequent treatment if they decline clinically at the time of progression. Additionally, ICIs are costly therapies that may lead to substantial financial burden on patients and their families. Indeed, some economic analyses suggest that many of these agents are not cost-effective for their standard-of-care indications.

In conclusion, at this point in the clinical development of ICI for lung cancer treatment, there are few prospective studies evaluating the safety and efficacy of these therapies in patients with comorbidities. While trials in selected populations such as certain AID are currently underway, clinicians must make real-world decisions now about which patients to offer these promising but potentially toxic treatments. Retrospective, observational studies suggest that ICI administration may be feasible in the elderly,
FIGURE 1. Algorithm for treating lung cancer with ICI in patients with comorbidities. *In rare cases, potential exception for kidney transplant (see text). †Receiving prednisone ≥10 mg daily or other immunosuppressive agents. ‡Eg, myasthenia gravis, multiple sclerosis. §Eg, psoriasis, rheumatoid arthritis.
individuals with HIV and hepatitis B and C virus infection, and patients with low-risk and inactive AID. Use of ICIs in transplant recipients and patients with high-risk AID (such as myasthenia gravis and multiple sclerosis) seems to convey substantial morbidity, is unlikely to be studied in future clinical trials, and cannot be routinely recommended.

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REFERENCES


