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Current Immunotherapies for Lung Cancer: A Review for Respirologists

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Introduction

Due to revolutionary advancements in treatment, lung cancer has had the largest improvement in mortality of all cancers over the last two decades. Despite this, it remains the type with the highest incidence and mortality of all cancers in Canada, and globally it has the second highest incidence and highest mortality.[1,2]

An important mechanism for cancer cell survival, and one of the hallmarks of cancer, is evasion of destruction by immune cells.[3] Immunotherapy is a class of systemic therapy aimed at activating the cytotoxic activity of immune cells and is one of the major drivers behind the improvement in survival of patients with lung cancer (along with targeted therapies, which will not be covered in this review). Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that disrupt immunosuppressive signaling and result in increased activity of cytotoxic T cells. This article discusses the currently available ICIs and their indications in the treatment of lung cancer, immune-related toxicities and important contraindications to treatment, and a respirology-focused overview of the management of toxicities. This is not a comprehensive review of immunotherapy trials in lung cancer.

How Does Immunotherapy Work?

PD-1/PD-L1 inhibitors

The cell-killing activity of immune cells in the body is carefully modulated to maintain the ability to destroy foreign substances while controlling excessive inflammation and retaining self-tolerance through various "immune checkpoints". Some cancers take advantage of these tolerance mechanisms to evade immune destruction.[4] Programmed cell death protein ligand 1 (PD-L1) is a cell surface protein variably expressed on cancer cells. When it binds to programmed cell death protein 1 (PD-1) on T cells, it inhibits its cytotoxicity towards cancer cells. ICI block the binding of PD-1 to PD-L1, essentially 'releasing the brakes' and allowing T cell killing of the tumour cell. Upregulation of PD-L1 is common in lung cancer and can be reported as a tumor proportion score (TPS) from <1% to 100% via commercially available immunohistochemistry assays.[5] While not a perfect biomarker, higher expression generally predicts better response to immunotherapy. Expression levels ≥50% are considered 'high', levels from 1–49% are 'intermediate', and <1% is low or negative. In tumors with a high PD-L1 expression (≥50%), PD-1/PD-L1 inhibitors can be used as monotherapy.[6-8]

There are several monoclonal antibodies targeting PD-1 or PD-L1 available for cancer treatment, and those with Health Canada-approved indications are summarized in **Table 1**. Where different agents were tested in the same setting, many showed comparable benefit and toxicity profiles. Initially starting as second-line treatment for metastatic non-small cell lung cancer (NSCLC), these have now also shown efficacy as first-line therapy, adjuvant and neoadjuvant therapy for NSCLC, in both limited stage and extensive stage small cell lung cancer (SCLC), and in malignant pleural mesothelioma (MPM).

CTLA-4 Inhibitors

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is another checkpoint inhibitor of T cell activation and plays an important role in preventing immune reactions to self-antigens.[4] An early trial in melanoma that compared CTLA-4 inhibition to PD-1 inhibition versus dual immunotherapy showed that the CTLA-4 monotherapy resulted in significantly worse survival than PD-1 monotherapy, with combination immunotherapy superior to single agent.[9] Subsequently, CTLA-4 inhibitors have

Drug	Brand name	Class	Health Canada-approved indication(s)
pembrolizumab	Keytruda	PD-1	**1st line:** advanced/metastatic NSCLC
			2nd line: advanced/metastatic NSCLC
			Adjuvant: Stage II-III NSCLC after surgical resection
durvalumab	Imfinzi	PD-L1	**Adjuvant:** unresectable Stage III NSCLC, after chemoradiation
			1st line: extensive stage small cell lung cancer, combined with platinum-based chemotherapy
			Adjuvant: limited stage small cell lung cancer, after platinum-based chemoradiation
atezolizumab	Tecentriq	PD-L1	**1st line:** extensive stage small cell lung cancer, combined with platinum-based chemotherapy
			Adjuvant: NSCLC with PD-L1 expression >50%, after surgical resection and followed by platinum-based chemotherapy
			1st line: advanced/metastatic NSCLC
			2nd line: advanced/metastatic NSCLC
nivolumab	Opdivo	PD-1	**2nd line:** advanced/metastatic NSCLC
			1st line: advanced/metastatic NSCLC, in combination with ipilimumab for PD-L1 expression >1%
			1st line: advanced/metastatic NSCLC, in combination with ipilimumab and two cycles of platinum-based chemotherapy
			Neoadjuvant: resectable NSCLC >4cm or node-positive, in combination with platinum-based chemotherapy
cemiplimab	Libtayo	PD-1	**1st line:** advanced/metastatic NSCLC
ipilimumab	Yervoy	CTLA-4	**1st line:** advanced/metastatic NSCLC, in combination with nivolumab for PD-L1 expression >1%
			1st line: advanced/metastatic NSCLC, in combination with nivolumab and two cycles of platinum-based chemotherapy

Table 1. Immune checkpoint inhibitors with Health Canada-approved indications in the treatment of lung cancer as of October 2024; *courtesy of Tsu-Yu Unice Chang, BSc, MD, FRCPC and Paul Wheatley-Price, BSc, MBChB, FRCP (UK), MD*.

Abbreviations: CTLA-4: cytotoxic T lymphocyte-associated protein 4, **NSCLC:** non-small cell lung cancer, **PD-1:** programmed cell death protein 1, **PD-L1**: programmed cell death ligand 1.

only been tested in combination with PD-1/PD-L1 blockade and are no longer in use as single agents.

There is currently one CTLA-4 inhibitor with a Health Canada-approved indication in lung cancer, ipilimumab, given in combination with nivolumab and chemotherapy. This regimen is less commonly used in lung cancer due to the higher risk of immune-related toxicities with dual immunotherapy. However, it represents a good option in those with low tumoral PD-L1 expression, where single agent anti-PD-1/PD-L1 treatment has much lower response rates.[10] Dual immunotherapy is also used in MPM, with particular efficacy in the most aggressive sarcomatoid subtype.[11]

Administration

ICI are typically administered intravenously (IV) as a 30–60-minute infusion, every 2–6 weeks, depending on the specific regimen. Early trials of immunotherapy used weight-based dosing; however, ICIs show similar effects at a large range of concentrations. As both efficacy and risk of toxicity are largely dose-independent, modern clinical trials have switched to flat dosing for ease of administration. Subcutaneous formulations are in development to decrease administration time and increase patient convenience, and are likely to be available within the next couple of years.[12] Infusion reactions are uncommon, and in contrast to chemotherapy, no supportive medications (steroids, anti-emetics) are routinely needed.

Efficacy

Immunotherapy has shown wide-ranging benefits across multiple settings, improving cure rates in early-stage NSCLC and SCLC and prolonging survival in metastatic NSCLC, SCLC, and MPM. Treatment in NSCLC is sometimes stratified by PD-L1 expression, whereas in SCLC, immunotherapy is combined with chemotherapy in all patients. In MPM, benefit of immunotherapy relative to chemotherapy is predicted by non-epithelioid histology rather than PD-L1 expression. Selected survival data from practice-changing trials are included in **Figure 1**.

An encouraging effect of immunotherapy is that, even in the metastatic setting, a significant minority of patients experience long-term disease control even after discontinuation of treatment, unlike chemotherapy and targeted agents, where the expected course is to eventually develop resistant disease.

It should be noted that PD-L1 is not a perfect predictor of response to immunotherapy and special considerations exist in non-smokers, who have a much lower response even with high PD-L1 expression.[13] These patients should be considered for combination chemoimmunotherapy rather than immunotherapy alone. Patients with certain driver mutations associated with non-smoking status, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), are known to have virtually no response and have been excluded from almost all major immunotherapy trials. These patients should not be treated with immunotherapy given the same risk of toxicities, lack of treatment benefit, and the availability of very effective targeted therapies as an alternative.

Immune Toxicities

While ICIs are well tolerated in general, and serious adverse events are less common than with chemotherapy, immune-related adverse events (irAEs) can occur. Use of these drugs is associated with a wide variety of autoimmune reactions that can affect any organ system in the body. Common irAEs include rash, colitis, and hypothyroidism (sometimes preceded by hyperthyroidism). Furthermore, these therapies can also cause other permanent endocrinopathies (e.g. adrenal insufficiency, Type 1 diabetes) as well as life-threatening organ inflammation (e.g. pneumonitis, myocarditis)[14]

Patients with pre-existing autoimmune conditions such as inflammatory bowel disease and rheumatoid arthritis have been excluded from clinical trials, and retrospective data show these patients are at risk of a flare of their autoimmune condition, which can affect as high as 41% of patients with inflammatory bowel disease.[15] Therefore, this therapy may be contraindicated in these patients, but depending on the other therapeutic options available and risk/benefit ratio, can still be considered with careful counselling.

Two conditions that should be considered absolute contraindications to immunotherapy are pre-existing interstitial lung disease (ILD) and thymoma. Radiologic evidence of ILD is associated with six-fold odds of developing ICI-induced pneumonitis, which has a 25–30% mortality rate.[16,17] Immunotherapy in thymomas is associated with serious or life-threatening toxicity at a rate upwards of 60–70%, with neuromuscular or muscular complications such as myasthenia gravis being particularly prominent.[18]

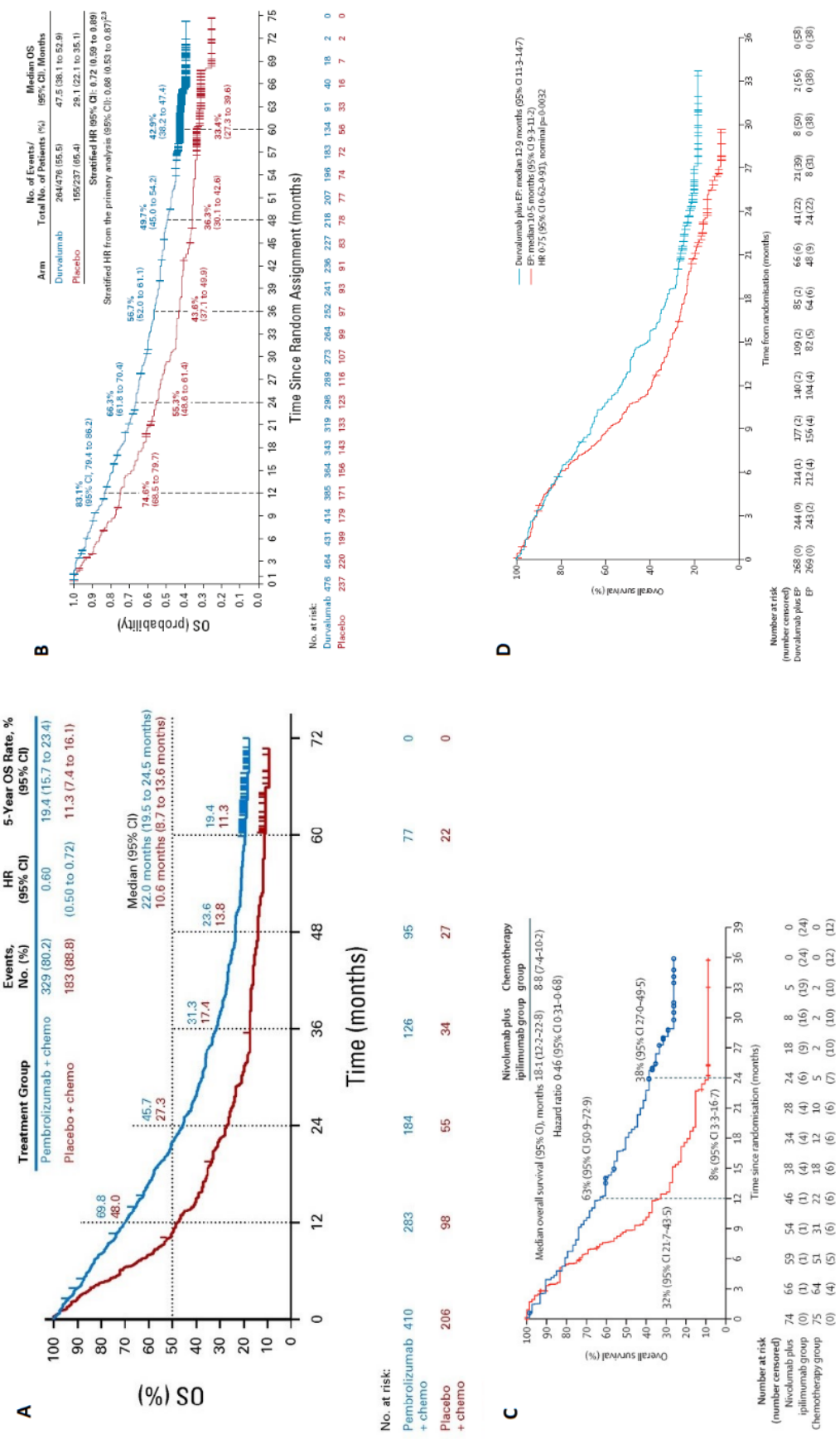

Figure 1. Kaplan-Meier survival curves in several practice-changing clinical trials in lung cancer. **A:** Overall survival in the intention-to-treat population from KEYNOTE-189, metastatic non-small cell lung cancer treated with first-line chemotherapy plus pembrolizumab compared to chemotherapy alone.[13] **B:** Overall survival comparing first-line chemotherapy plus durvalumab versus chemotherapy alone in extensive stage small cell lung cancer from the CASPIAN trial.[21] **C:** Overall survival comparing first-line dual immunotherapy with nivolumab and ipilimumab versus chemotherapy in pleural mesothelioma with non-epithelioid histology from CHECKMATE 743.11 **D:** Overall survival in patients treated with adjuvant durvalumab versus placebo after curative intent chemoradiation for locally advanced, unresectable non-small cell lung cancer from the PACIFIC trial.[22]

Management of Immune Toxicities

irAEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE), in which Grade 1 is mild or asymptomatic, Grade 2 is moderate and warranting local or limited intervention or affecting age appropriate instrumental activities of daily living, Grade 3 is severe and disabling or warranting hospitalization, Grade 4 is life-threatening and warranting urgent intervention, and Grade 5 is causing death.[19]

In general, Grade 1 irAEs can be monitored while continuing immunotherapy. Grade 2 irAEs warrant holding immunotherapy until symptoms improve to Grade 1 or less, with consideration given to initiation of oral prednisone at a dose of 0.5–1 milligrams per kilogram of body weight, tapered over 4–6 weeks. In the case of steroid administration, immunotherapy should be held until it is tapered to a daily prednisone equivalent of ≤10 mg without flare-up of symptoms. Grade 3–4 irAEs warrant hospitalization, with IV methylprednisolone started at a dose of 1–2 mg/kg, switched to oral prednisone and tapered over 6 weeks once improving. Patients who do not improve within 48-72 hours or who experience an inability to taper off prednisone without flare-up should have secondary immunosuppression initiated with other agents, the choice of which is organ dependent and consultation with the relevant organ system specialist and reference to a guideline such as the American Society of Clinical Oncology (ASCO) guideline on irAE is recommended.[20] In general, patients with Grade 3 toxicities can be rechallenged with immunotherapy once the irAEs are resolved to Grade 1 on ≤10 mg of daily prednisone, but those with Grade 4 should permanently discontinue treatment.

Key exceptions exist to the general management strategies. Due to the high risk of mortality, even Grade 1 myocarditis should be managed with permanent discontinuation of the ICI and initiation of steroids. For pneumonitis, consideration should be given to holding the ICI even for Grade 1 incidental radiological findings and it should be permanently discontinued for Grade 3 events (requiring oxygen supplementation). Conversely, ICI-induced endocrinopathies are permanent regardless of any treatment and the ICI can be continued with appropriate hormone replacement.

Diagnosis of ICI-induced Pneumonitis

ICI-induced pneumonitis can be difficult to definitively diagnose in patients with lung cancer, as symptoms such as shortness of breath, cough, and hypoxia can also be caused by pneumonia, chronic obstructive pulmonary disease (COPD), or complications of cancer progression, such as lymphangitic carcinomatosis. A variety of appearances may be observed by computed tomography (CT), including ground-glass opacities, organizing pneumonia, and various forms of ILD.[17]

Initial management of such patients usually involves initiation of treatment for all possible causes, including antibiotics for possible pneumonia, inhaler therapy for COPD, and steroids for pneumonitis. It is important that steroids are not delayed while awaiting diagnostic clarification, as this is associated with increased morbidity and mortality.

Respirologists may be consulted to aid in diagnostic clarification, with bronchoscopy and bronchoalveolar lavage being helpful to evaluate for an infectious cause.

Conclusions

ICIs are a class of anti-cancer therapies that have revolutionized the treatment of lung cancer and many other cancers, such as melanoma, renal cell carcinoma, head and neck cancers, triple-negative breast cancer, and certain subtypes of colorectal cancer. These drugs are generally well tolerated but come with the potential for a wide range of autoimmune toxicities. Early identification of irAEs and prompt treatment with immunosuppressive agents is key for minimizing morbidity and mortality. Pneumonitis is a relatively rare complication of immunotherapy but is associated with a higher mortality rate and respirologists may be consulted for help with management and diagnostic clarification in these cases.

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