

Therapeutic landscape of metastatic non-small-cell lung cancer in Canada in 2020

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ABSTRACT

Lung cancer is the most commonly diagnosed cancer in Canada and remains associated with high mortality. Nevertheless, recent advances in the fields of immuno-oncology and precision medicine have led to significant improvements in clinical outcome in metastatic non-small-cell lung cancer (NSCLC). Those improvements were facilitated by a greater understanding of the biologic classification of NSCLC, which catalyzed discoveries of novel therapies. Here, we present a comprehensive review of the recent avalanche of practice-changing trials in metastatic NSCLC, and we offer an approach to the management of this disease from a Canadian perspective. We begin with an overview of the pathologic and molecular characterization of metastatic NSCLC. Next, we review the indications for currently approved immune checkpoint inhibitors, and we provide an approach to the management of disease with a driver mutation. Finally, we address future avenues in both diagnostics and therapeutics for patients with advanced and metastatic NSCLC.

Key Words Lung cancer, immunotherapy, targeted therapy, chemotherapy, biomarkers

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INTRODUCTION

For the 1 in 2 Canadians who will develop a malignancy during their lifetime, lung cancer remains the most common and the most deadly: each day, 58 Canadians die from lung cancer¹. Despite the implementation of tobacco cessation programs and some access to screening programs in high-risk populations², more than half the patients with non-small-cell lung cancer (NSCLC) are still diagnosed with metastatic disease³. Since about 2010, unprecedented breakthroughs have occurred in the treatment of advanced NSCLC, in part because of the emergence of immune checkpoint inhibition (ICI) and targeted therapy, which provide long-term control in some patients. Indeed, the therapeutic landscape of metastatic NSCLC is becoming increasingly complex, in part because of the use of various biomarkers in many clinical trials and because of new toxicity profiles. Sound knowledge and understanding of that landscape are therefore required for all practitioners involved in the care of the patient with metastatic NSCLC. In this review, we begin with the pathology evaluation of the disease leading to biomarker-driven therapy, followed by a comprehensive evidenced-based approach to current management of advanced or metastatic NSCLC in Canada in 2020. Finally,

we provide a commentary about potential future options for diagnostics and therapeutics that are yet to be approved in Canada.

REVIEW

What Are the Pathology Characterizations of NSCLC and Why Are They Important?

Histologic and Molecular Characterizations of NSCLC
Advanced NSCLC includes patients with either stage IV or stage III disease not eligible for locoregional treatment modalities (according to the 8th version of the TNM classification)⁴. The treatment of such patients relies on systemic therapy tailored to pathologic, histologic, and molecular subtype. A standard pathology evaluation to determine

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histology (adenocarcinoma vs. squamous cell carcinoma vs. other more rare variants) is therefore essential. Defining the histology guides the molecular testing and choice of therapy. For example, pemetrexed, when combined with cisplatin, is associated with improved overall survival (OS) in patients with nonsquamous adenocarcinoma cell histology, and worse OS when used in patients with squamous histology⁵.

Testing for molecular alterations in lung adenocarcinomas amenable to targeted therapy is now considered the standard of care⁶⁻⁸. However, the number of genes approved to be tested according to clinical practice guidelines is not yet homogenous across Canadian institutions, and for rarer actionable mutations, reimbursement of highly active medications is not guaranteed⁸. Patients at higher risk for detection of those molecular alterations include those who have little or no prior smoking history, patients of female sex, younger patients, and patients of Asian descent⁹. Accordingly, based on an expert panel consensus opinion¹⁰, the current recommendation is also to test all tumours with an adenocarcinoma component, non-small-cell carcinoma not otherwise specified, sarcomatoid carcinoma, and squamous cell carcinomas with atypical clinical presentation such as young age (<50 years), nonsmoking or mild smoking habit (<10 pack-years), or presence of a peripheral lesion. National clinical practice consensus recommends that, for those patients, *EGFR* gene mutations, *ALK* gene fusions, *ROS1* rearrangements, and *BRAFV600E* mutations be tested^{8,11,12}. *NTRK* gene fusions, *ERBB2* mutations or *HER2* amplifications, *MET* exon 14 skipping mutations of

whole-gene amplifications, *RET* translocations, and *RAS* mutations are emerging alterations with novel applications in the treatment of NSCLC, although funding and regulatory issues preclude widespread diagnostic testing in Canada at this time⁸. Lastly, it is also recommended that, for all patients with advanced tumours, PD-L1 status be tested (according to “fit-for-purpose” principles¹³) using the Dako 22C3 pharmDx assay on a Dako Autostainer (Dako Corporation, Glostrup, Denmark)¹¹, because the results will affect the choice and sequence of immunotherapy and chemotherapy, as we outline in detail later in this article. Notably, other PD-L1 companion testing such as 28-8, SP-142, SP-263, and 73-10 is not currently reimbursed or recommended.

Current Management of NSCLC in the First Line

Introduction of ICI in NSCLC

Landmark trials CheckMate 017 and 057 compared nivolumab with docetaxel in previously treated metastatic NSCLC and demonstrated superior OS in the nivolumab group, forever changing the treatment algorithm in both the squamous and nonsquamous histologies. Unlike previous findings in historical chemotherapy trials, ICI provided a sustained response in 20% of patients at 4 years¹⁴. That observation led to the study of ICI in first-line settings, with unprecedented improvements in patient outcomes. As a result, ICI is now a cornerstone in the first-line setting for all eligible patients without a driver mutation, and the choice of regimen depends on PD-L1 status (Figure 1).

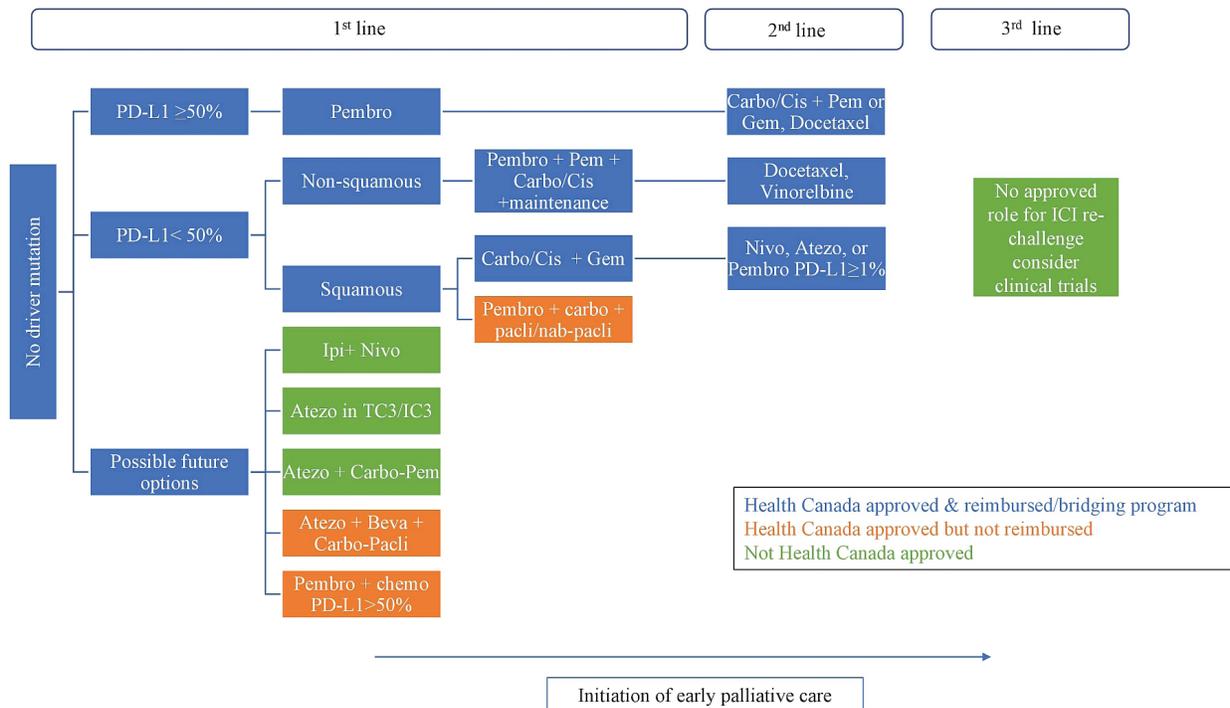


FIGURE 1 Immune checkpoint inhibition in the management of metastatic non-small-cell lung cancer without a driver mutation in January 2020. Pembro = pembrolizumab; Carbo = carboplatin; Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed; Nivo = nivolumab; Atezo = atezolizumab; ICI = immune checkpoint inhibition; Pacli = paclitaxel; Ipi = ipilimumab; Beva = bevacizumab.

TABLE I Hazard ratios for overall survival associated with biomarkers in key clinical trials

Marker	KEYNOTE-024 (NSCLC) Pembrolizumab	KEYNOTE-042 (NSCLC) Pembrolizumab	CheckMate 227 (NSCLC) Nivolumab plus ipilimumab	IMpower110 (NSCLC)	IMpower150 (nonsquamous) Atezolizumab plus bevacizumab plus platinum or paclitaxel	KEYNOTE-189 (nonsquamous) Pembrolizumab plus platinum or paclitaxel	IMpower130 (squamous) Atezolizumab plus platinum or nab-paclitaxel	KEYNOTE-407 (squamous) Pembrolizumab plus platinum or paclitaxel or nab-paclitaxel
PD-L1 < 1%	—	—	0.62	—	0.82	0.59	0.81	0.61
Tumour mutational burden								
High	—	—	0.51	—	—	—	—	—
Low	—	—	0.69	—	—	—	—	—
PD-L1 1%–49%	—	0.92	0.94	—	0.80	0.55	0.70	0.57
Tumour mutational burden								
High	—	—	—	—	—	—	—	—
Low	—	—	—	—	—	—	—	—
PD-L1 > 50%	0.63	0.69	0.70	0.59	0.70	0.42	0.84	0.64
Tumour mutational burden								
High	—	—	0.63	—	—	—	—	—
Low	—	—	0.67	—	—	—	—	—
No PD-L1								
Tumour mutational burden								
High	—	0.62	—	—	—	0.64	—	0.74
Low	—	1.09	—	—	—	0.64	—	0.86
Treatment adverse event ^a	26.6%	18%	32.8%	31.8%	57%	67.2%	>50%	69.8%
Treatment discontinuation	5.2%	8%	12.3%	6.3%	34%	11.9%	26%	12.2%

^a Grade 3 or greater.
NSCLC = non-small-cell lung cancer.

Anti-PD-1 and PD-L1 Monotherapy

Single-agent pembrolizumab is indicated in patients with previously untreated advanced NSCLC with a PD-L1 status of 50% or greater. In the phase III KEYNOTE-024 randomized clinical trial, 305 patients with previously untreated NSCLC having no driver mutation were randomized to receive physician's choice of platinum-based chemotherapy or single-agent pembrolizumab¹⁵. Patients treated with single-agent pembrolizumab experienced significantly longer OS [26.6 months vs. 14.2 months; hazard ratio (HR): 0.63; 95% confidence interval (CI): 0.47 to 0.86; $p = 0.002$], and more than 40% of patients in the pembrolizumab arm were still alive at 3 years (Table 1). Patients in the pembrolizumab arm also experienced less-frequent grade III or greater adverse events. Typically, treatment is discontinued after 2 years or at progression, or if serious immune-related adverse events occur.

The greater efficacy of pembrolizumab in patients with a PD-L1 status of 50% or greater was corroborated by KEYNOTE-042. Although pembrolizumab proved to be less toxic than standard chemotherapy in that trial, it was not superior to chemotherapy in patients with PD-L1 expression in the 1%–49% range¹⁶. Conversely, single-agent nivolumab was evaluated in previously untreated patients with a PD-L1 status greater than 5% in the CheckMate 026 trial, where it failed to show superiority¹⁷. In the same vein, the MYSTIC trial failed to show benefit for combination durvalumab–tremelimumab compared with standard chemotherapy¹⁸.

Nonsquamous NSCLC: Anti-PD-1 or PD-L1 in Combination with Chemotherapy

A combination of cytotoxic chemotherapy and pembrolizumab is indicated in previously untreated patients with advanced nonsquamous NSCLC regardless of PD-L1 status and is broadly preferred in patients with less than 50% PD-L1 expression. In the phase III KEYNOTE-189 clinical trial, 616 patients were randomized to receive platinum-based chemotherapy (carboplatin or cisplatin) with pemetrexed, plus either pembrolizumab or placebo for up to 35 cycles, plus pemetrexed maintenance therapy¹⁹. The combination regimen was associated with an improved progression-free survival (PFS) of 8.8 months compared with 4.9 months (HR: 0.52; 95% CI: 0.43 to 0.64; $p < 0.001$) and an improved OS rate (Kaplan–Meier probabilities for proportion of patients alive at 12 months: 69% vs. 49%; HR: 0.49; 95% CI: 0.38 to 0.64; $p < 0.001$; Table 1). Similarly, preliminary data from the IMpower132 trial demonstrated a PFS benefit (median: 7.6 months vs. 5.2 months) with the addition of atezolizumab to pemetrexed-based chemotherapy²⁰. The interim analysis suggested an improvement in OS of 4.7 months with the addition of atezolizumab.

Although cisplatin-based regimens are considered slightly more effective than carboplatin and non-platinum-based regimens, the advantage of cisplatin over carboplatin remains an unanswered question with respect to the chemotherapy–ICI combination¹⁹.

Squamous NSCLC with Less Than 50% PD-L1

In patients with metastatic NSCLC and squamous histology, the KEYNOTE-407 registration trial also assessed the role of ICI

in squamous histology and demonstrated that the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel was associated with improved PFS and OS in patients with previously untreated metastatic disease. Similarly, the IMpower131 study randomized patients into 3 arms (using combinations not currently approved in Canada):

- Arm A: atezolizumab plus carboplatin–paclitaxel
- Arm B: atezolizumab plus carboplatin–nab-paclitaxel
- Arm C: chemotherapy alone (carboplatin–nab-paclitaxel)

The investigators found a benefit for arm B compared with arm C (6.3 months vs. 5.6 months; HR: 0.716; 95% CI: 0.603 to 0.848; $p = 0.0001$)²¹. Interestingly, those findings were independent of PD-L1 status²² (Table 1).

Patterns of Response in NSCLC

What Are the New Patterns of Response in Metastatic NSCLC?

To address the various ways in which tumours respond to ICI compared with standard chemotherapy, the immune Response Evaluation Criteria in Solid Tumors were implemented during the study of immunotherapy agents²³. When using ICI, several unusual responses can be observed, such as durable response (no standard definition currently exists), pseudo-progression (rare, describes regression of tumour index lesions after initial progression), hyper-progression (5%–10% of patients in some studies^{24,25}, with heterogeneous definitions; connotes rapidly progressive disease), and dissociated response (some tumours grow and others regress in a given individual)²³.

Treatment of Older Adults

How Are Special Populations Treated?

The treatment of older adults with standard cytotoxic chemotherapeutic agents is associated with increased toxicity and worse outcomes^{26,27}, a situation that might not be the case with immunotherapy. With immunotherapy, performance status seems to be a more accurate predictor of response, and older adults have outcomes similar to those seen in their younger counterparts. That observation also seems to extend to the overall safety and tolerability of the agents^{28,29}.

Current Management of NSCLC in the Second Line

Cytotoxic chemotherapy is the mainstay for patients who have progressed on standard first-line treatment (aside from patients with targetable mutations who have other options). Regimens are decided as a function of prior therapies, performance status, comorbidities, and organ function. A platinum doublet is typically used after progression on pembrolizumab monotherapy, or docetaxel for patients who have already been exposed to a platinum doublet with pembrolizumab in the first line. Other single-agent regimens such as gemcitabine or vinorelbine can also be used in third- and fourth-line settings^{30,31}. For patients who did not receive ICI in the first-line setting, nivolumab (CheckMate 017 and CheckMate 057), pembrolizumab

(KEYNOTE-010), or atezolizumab (OAK) can be used after progression on chemotherapy^{32–34}.

Current Management of Patients with a Driver Mutation

EGFR

Worldwide, about 20% of all patients with advanced NSCLC are found to have a somatic activating *EGFR* mutation, with the 2 most common mutations being *EGFR*L858R and *EGFR* exon 19 deletion³⁵ (Figure 2). Such mutations are more common in patients of Asian ethnicity or nonsmoking status. In several large randomized clinical trials (LUX-Lung 3 for afatinib, WJTOG3405 for gefitinib, and EURTAC for erlotinib), *EGFR* inhibition with first-generation and second-generation tyrosine kinase inhibitors (TKIs), compared with standard cytotoxic chemotherapy, was associated with improved PFS^{36–38}. In the FLAURA trial, osimertinib, a third-generation TKI, was compared with first-generation TKI and was associated with improved OS and fewer severe adverse events in 556 patients with previously untreated *EGFR*-positive disease. The frequency of disease progression in the central nervous system was also lower in the osimertinib group³⁹.

Osimertinib, erlotinib, gefitinib, and afatinib are all approved as first-line therapy for patients with *EGFR*-positive metastatic NSCLC in Canada. Osimertinib is approved for second-line treatment in patients with *EGFR*-positive disease progressing on first- and second-generation TKIs and having *de novo* T790M mutation (AURA3)⁴⁰. The most common side effects seen with *EGFR* TKIs are rash, diarrhea, and cytopenias (lymphopenia, thrombocytopenia).

Over the past few years, the use of liquid biopsy to assess T790M status in patients progressing on an *EGFR*

TKI has also been implemented in some Canadian centres and is under evaluation for reimbursement in several provinces. The technique, which requires a single blood sample, presents notable advantages over invasive sampling. However, given test sensitivity varying from 60%–80%, a negative liquid biopsy result is currently recommended to be complemented with evaluation of a tissue or a cytology specimen, in particular if the native activating mutation is not found⁴¹.

ALK

ALK rearrangements are found in fewer than 5% of patients with metastatic NSCLC. Nevertheless, the therapeutic implications of targeting this driver mutation are important, given that an improved OS is associated with crizotinib (a first-generation TKI targeting *ALK*) compared with standard chemotherapy⁴². The next-generation *ALK* TKIs brigatinib (ALTA-IL)⁴³ and alectinib (ALEX)⁴⁴ have now been shown to be superior to crizotinib. At the time of writing, access to those standard-of-care therapies was variable in Canada. The most important side effect for both brigatinib and alectinib is increased liver enzymes, and brigatinib is also associated with a particular manifestation of pneumonitis (early-onset pulmonary event) and bradycardia.

Rarer Driver Mutations in NSCLC

Targeting of rarer mutations such as *ROS1* with crizotinib, *NTRK* with larotrectinib, *RET* with selpercatinib, and *BRAF*V600E with dabrafenib–trametinib are emerging therapeutic options. If a patient has a rare driver mutation, a second opinion at an academic centre is suggested, as is consideration for a clinical trial.

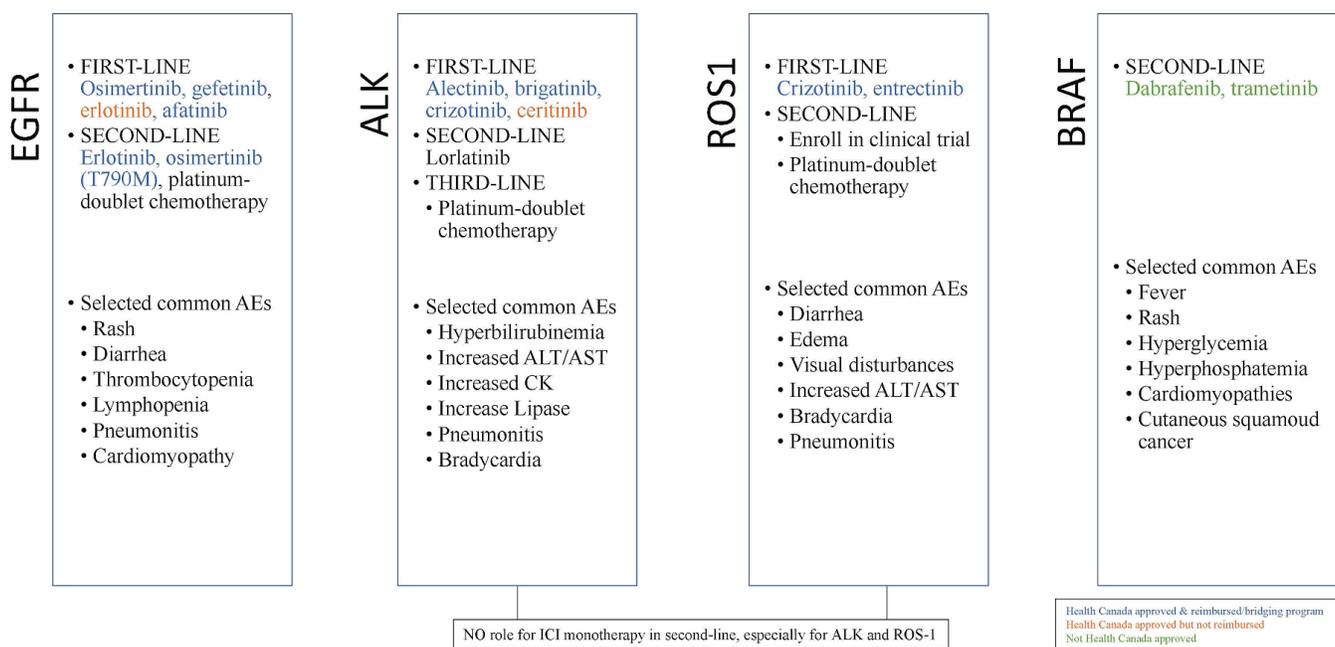


FIGURE 2 Summary of selected targeted agents for the management of metastatic non-small-cell lung cancer with a driver mutation in January 2020. AEs = adverse events; ALT = alanine transaminase; AST = aspartate transaminase; CK = creatine kinase; ICI = immune checkpoint inhibition.

Role of Immunotherapy in Patients with Driver Mutations

A large retrospective study of real-world data for 551 patients with driver mutation–positive disease evaluated the role of ICI in that population. Use of ICI induced a response in a small proportion of patients, with patients having *RET* mutations and *ALK* rearrangements experiencing little to no response. Patients with driver mutation–positive disease should therefore receive standard targeted therapy followed by chemotherapy in the second-line setting⁴⁵. Thus far, the IMpower150 trial is the only study showing a suggestion of clinical activity with ICI (atezolizumab) in a subgroup analysis of patients with *EGFR*-positive disease treated after failure of standard TKIs (when combined with bevacizumab and chemotherapy)⁴⁶. It is important to note that most of the first-line clinical trials excluded participants with driver mutations.

The Importance of Early Palliative Care

Despite the advances already described, metastatic NSCLC is associated with significant morbidity, and most patients will progress on standard treatment. A randomized clinical trial of 151 patients with metastatic NSCLC showed that incorporation of early palliative care with standard oncologic care not only improved quality of life, but also OS⁴⁷. More recently, in a large retrospective cohort of more than 20,000 patients, those with advanced lung cancer who received palliative care within 30–365 days of diagnosis were found to experience improved survival⁴⁸. It is therefore important to integrate palliative approaches early in the management of advanced NSCLC.

Biomarkers of Therapeutic Success

What Are the Biomarkers of Therapeutic Success for Patients Receiving Immunotherapy and What Are the Unanswered Questions After Recent Publications and Presentations at the 2019 Meeting of the European Society for Medical Oncology?

Despite unprecedented—nearly doubled—long-term OS with ICI in metastatic NSCLC, many patients develop resistance to ICI agents. Moreover, the toxicities of those agents, known as immune-related adverse events, can lead to long-term morbidity. (Management of such events is beyond the scope of this review; however, excellent guidelines to aid clinicians in the management of immune-related adverse events are available^{49,50}.) Given those important toxicity profiles, there is an urgent need to find biomarkers for therapeutic success. In a recent multi-omics prediction of the response to PD-1 and PD-L1 inhibitors, CD8+ T cell abundance, tumour mutational burden (TMB), and PD-1 expression were present in 80% of patients who responded to therapy^{51,52}.

Many unanswered questions about interpretation of biomarkers remain, given the multitude of recent studies presented at the 2019 meeting of the European Society for Medical Oncology (Table 1).

PD-L1 50% or Greater Group: In the PD-L1 50% or greater group, efficacies and toxicities are similar with the use

of either pembrolizumab or atezolizumab monotherapy. However, the TC3/IC3 method using the underperforming SP162 antibody is required for testing PD-L1 status in patients receiving atezolizumab, and atezolizumab is not yet available for widespread use in Canada. Again, in the PD-L1 50% or greater subgroup, combination ipilimumab–nivolumab (part of CheckMate 227)⁵³ demonstrated acceptable efficacy (HR: 0.79; 95% CI: 0.65 to 0.96). However, the toxicity associated with ipilimumab–nivolumab compared with anti–PD-1 or PD-L1 monotherapy makes this option less attractive in the absence of a signal for stronger clinical efficacy.

Combining pembrolizumab with chemotherapy in patients with PD-L1 50% or greater remains a conundrum, especially given the latest evidence that patients with a low TMB do not respond to pembrolizumab alone, but they do respond to pembrolizumab plus chemotherapy. Indeed, pembrolizumab plus chemotherapy is efficacious regardless of TMB status. In contrast, a subgroup analysis from the MYSTIC trial showed that TMB was not a significant biomarker in the chemotherapy arm compared with the durvalumab arm. In the chemotherapy arm compared with the durvalumab–tremelimumab arm, no correlation between PD-L1 and TMB was observed, but TMB measured in blood was found to be a significant biomarker, validating the studies already described⁵⁴.

To add another layer of complexity, the first published CheckMate 227 paper suggested that only patients with a high TMB (10 or more mutations per megabase) responded to ipilimumab–nivolumab. However, the latest results from that group showed that TMB was not actually predictive of response. Despite TMB serving as an important prognostic factor, its widespread use in Canada remains controversial and requires further validation in prospective trials given its high cost and a lack of standardization in technique and cut-off values.

PD-L1 1%–49% Group: In the PD-L1 1%–49% group (and keeping in mind that the treatments were never compared head-to-head), pembrolizumab plus chemotherapy seems to be the best option (HR: 0.55; 95% CI: 0.34 to 0.90); combination nivolumab–ipilimumab does not seem to be as efficacious (HR: 0.94; 95% CI: 0.75 to 1.18). In addition, several options combining atezolizumab with chemotherapy represent interesting new alternatives.

Finally, in the PD-L1 less than 1% group, chemotherapy plus pembrolizumab is the preferred option in Canada. Recent results from CheckMate 227 showing efficacy in terms of an OS similar to that found with chemotherapy plus pembrolizumab might challenge that standard. Although the toxicities in the two groups were never compared head-to-head, a higher incidence of grade 3 or greater events was observed in the chemotherapy plus pembrolizumab group.

Other Biomarkers

Lastly, the unforeseen role of the gut microbiome is also emerging as a major predictor of immunotherapy response⁵⁵. Indeed, a recent systematic review demonstrated the independent negative predictive effect of antibiotics in patients receiving immunotherapy^{56,57}, and novel clinical trials are under way to advantageously modify the

gut microbiome so as to improve the response to immunotherapy. Finally, other concomitant medications—such as baseline corticosteroids at doses greater than 10 mg daily—have been associated with negative outcomes in patients with metastatic NSCLC.⁵⁸

Future Directions

What Are the Future Directions in the Management of Metastatic NSCLC?

Overall, the therapeutic landscape of metastatic lung cancer has been revolutionized in recent years. Nevertheless, further advances are needed to overcome resistance in both ICI and targeted therapy, and much work is currently dedicated to that concern. Moreover, the discovery of new therapeutic targets⁵⁹ through next-generation sequencing (high throughput) are under way. Finally, advances in liquid biopsy analysis of circulating biomarkers in peripheral blood⁶⁰, such as circulating tumour cells and circulating tumour DNA are paving the way to more personalized approaches.

SUMMARY

Advances in the molecular biology and genomics of lung cancer have drastically improved patient outcomes. In the current era, patients are treated using a multidisciplinary approach, receiving either immunotherapy, immunotherapy and chemotherapy combinations, or targeted therapy depending on their PD-L1, *EGFR*, *ALK*, *ROS1*, *BRAF*, and *NTRK* statuses. Continued research innovations in the field of lung cancer are eagerly awaited.

Key Points

- Treatment of advanced or metastatic NSCLC is becoming increasingly complex because of a recent avalanche of clinical studies involving ICI, ICI and chemotherapy combinations, and targeted therapy
- It is essential that adequate histologic and molecular evaluation be performed for patients with metastatic NSCLC, specifically looking for PD-L1 expression and driver mutation status.
- The correct interpretation of biomarkers of success in clinical trials is essential when choosing therapies for patients with metastatic NSCLC.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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