Guideline Resource Unit
guru@ahs.ca

# Advanced Non-Small Cell Lung Cancer: Driver Mutation Negative

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Cancer Care Alberta

Clinical Practice Guideline LU-012 – Version 1
www.ahs.ca/guru

## Background

Lung cancer is the overall leading cause of cancer mortality in Canadian men and women. By the end of 2024, almost 21,000 Canadians are expected to die of lung cancer.[1, 2] In addition, more Canadian men and women will die from lung cancer as compared to prostate, breast, and colorectal cancers combined. In 2021, the latest year for which Alberta statistics are available, lung cancer was the leading cause of cancer death for both men and women.[3] In males, the incidence of lung cancer began to level off in the mid-1980s and has since been declining, whereas in females, the incidence of lung cancer didn't stop increasing until 2006.[1] Smoking remains the most important risk factor for lung cancer. According to the 2022 Canadian Tobacco and Nicotine Survey, 16.1% of Canadians and 17.4% of Albertans smoke.[4] The differences in lung cancer incidence among males and females likely reflect past changes in tobacco use: in males, a drop in smoking began in the mid-1960s, preceding the drop in lung cancer incidence by almost 20 years. In females, tobacco consumption didn't begin to drop until the mid-1980s, suggesting that lung cancer incidence rates in women should begin to decrease in the next two decades.[4] Despite much research and many clinical advances in lung cancer treatments, the age-standardized five-year survival rate for all types and stages of lung cancer combined is only 17% for Canada overall, and 14% for Alberta.

Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and is categorized using the TNM staging system. Approximately 40% of patients with newly diagnosed NSCLC will have stage IV disease.[5] This group includes patients with locally advanced disease with malignant pleural effusion, as well as patients with distant metastases.[5] Decisions regarding the treatment strategy should take into account the patient's age, performance status (PS), comorbidities, prior therapy, and the presence or absence of EGFR mutations.[6] Patients with a solitary metastasis as the basis for stage IV disease with good PS and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy (RT).[7]

## Guideline Questions

1. What are the recommended criteria for diagnosis of advanced NSCLC?
2. What are the recommended first, second, and third-line therapy options for patients with advanced NSCLC without actionable alterations?
3. What are the recommendations for follow-up of patients with advanced NSCLC without actionable alterations?

## Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2023. The specific search strategy, search results, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following

organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASTRO),[8] European Society for Medical Oncology (ESMO),[9] American Society of Clinical Oncology (ASCO),[10] and the National Comprehensive Cancer Network (NCCN).[11]

## Target Population

The following recommendations apply to adult cancer patients with advanced NSCLC without actionable alterations.

## Recommendations

### Diagnosis

1. Adequate staging is critical for advanced unresectable stage III and IV patients to rule out the possibility of extracranial metastasis.[9, 11]
   - Patients with advanced NSCLC should undergo a diagnostic contrast-enhanced CT scan of the chest, abdomen and pelvis.
   - When clinically suspected, a bone scan should be performed to rule out bone metastases.
   - When clinically suspected, an MR Brain (or a CT Head) should be performed to rule out brain metastases.

2. Adequate tissue material for histological confirmation and molecular testing should be collected.

3. PD-L1 immunohistochemistry (IHC) should be determined for all stage IV NSCLC.

4. Molecular testing with next-generation sequencing (NGS) should be performed to guide therapeutic decision-making.

### Treatment

For patients with a newly diagnosed, metastatic NSCLC without an oncogenic driver, the treatment strategy should take into consideration the tumour histology, tumour genotype, PD-L1 expression, patient performance status (PS), co-morbidities, and the patient's preferences.[8, 9] The type of systemic therapy used for the treatment of patients with advanced NSCLC has been evaluated extensively in randomized controlled trials (RCTs), clinical trials, and meta-analyses. The use of pembrolizumab monotherapy has become the standard treatment for patients with NCSLC and high PD-L1 expression.[12] For patients with PD-L1 expression <50%, combination chemo-immunotherapy may be considered. The KEYNOTE-189 trial[13] showed that pembrolizumab in combination with chemotherapy in first-line treatment of patients with metastatic non-squamous NSCLC significantly prolonged overall survival (OS) (22.0 months, 95% CI 19.5-24) and progression-free survival (PFS) (8.8 months, 95% CI, 7.6-9.2) compared with chemotherapy. The KEYNOTE-407 trial[14] demonstrated the efficacy of combination chemo-immunotherapy in previously untreated squamous cell NSCLC

patients. The study reported an improved OS (15.9 months versus 11.3 months; HR for death=0.64, 95% CI 0.49-0.85; p<0.001) and PFS (6.4 months versus 4.8 months; HR for disease progression or death=0.56, 95% CI 0.45-0.70; p<0.001) with pembrolizumab plus chemotherapy versus placebo plus chemotherapy.

**First Line Management (PD-L1 ≥ 50%)**

5. Systemic therapy should be considered for patients with stage IV NSCLC with an Eastern Cooperative Oncology Group (ECOG) PS of 0-2.

6. Patients with unresectable stage III NSCLC who are not candidates for radical radiation should be treated as stage IV NSCLC.

7. First-line treatment with pembrolizumab monotherapy is recommended as the standard therapy for patients with PD-L1 ≥ 50% and no contraindications to immunotherapy, regardless of squamous or non-squamous histology (KEYNOTE 024). [12]

8. Consider chemo-immunotherapy treatment in NSCLC patients who are never-smokers with PD-L1 ≥ 50%.[15]

9. Dual immunotherapy (nivolumab and ipilimumab) combined with platinum-doublet chemotherapy can also be considered for select patients (CHECKMATE 9LA).[16]

10. Pemetrexed is preferred for non-squamous histology only.

11. Duration of treatment depends on tolerability and clinical efficacy. Platinum chemotherapy is typically stopped after 4-6 cycles. Maintenance pemetrexed should be offered to patients who are fit enough to continue chemotherapy after the initial 4-6 cycles. In Alberta, duration of immunotherapy is 2 years including time on chemotherapy/pembrolizumab.

**First Line Management (PD-L1 1-49%, PD-L1<1%)**

12. First-line treatment with combination chemo-immunotherapy with platinum-doublet chemotherapy and pembrolizumab is recommended as the standard therapy for patients with PD-L1<50% and no contraindications to immunotherapy, as per KEYNOTE 189[13] (non-squamous) and KEYNOTE 407[14] (squamous) clinical trials.

13. Dual immunotherapy (nivolumab and ipilimumab) combined with platinum-doublet chemotherapy for the first two cycles can also be considered for select patients (CHECKMATE 9LA) [16].

14. Pemetrexed should be used for non-squamous histology only.

15. Duration of treatment depends on tolerability and clinical efficacy. Platinum chemotherapy is typically stopped after 4-6 cycles. Maintenance pemetrexed should be offered to patients who are fit enough to continue chemotherapy after the initial 4-6 cycles. In Alberta, duration of immunotherapy is 2 years.

**Second Line Management**

The second-line treatment strategy is heavily influenced by the treatment given in the first line. Systemic therapy should be considered in patients with a PS 0-2 without major comorbidities.

16. Options for second line treatment are docetaxel (any histology and if a taxane was not received in the first line), nivolumab (any histology and if immunotherapy was not received in the first line) or clinical trial. Whenever possible, patients with non-squamous NSCLC should be considered for eligibility in ongoing clinical trials. Up to date information on trials offered in Alberta is available on the Alberta Cancer Clinical Trials website.

17. Other single agent options include vinorelbine or gemcitabine if not received in the first line.

**Third Line Management**

The third line treatment strategy is heavily influenced by the treatment given in earlier lines. Systemic therapy should be considered in patients with a PS 0-2 without major comorbidities.

18. Third-line and subsequent options include docetaxel (if not received in earlier lines) or erlotinib.[17]

19. Whenever possible, patients with non-squamous non-small cell lung cancer (NSCLC) should be considered for eligibility in ongoing clinical trials. Up to date information on trials offered in Alberta is available on the Alberta Cancer Clinical Trials website.

**Special Populations**

20. ***ECOG≥2:*** Platinum doublet chemotherapy can be considered for ECOG 2 patients. Immunotherapy can also be considered although limited data are available on its use in this population. [8]

21. ***Patients with multiple comorbidities:*** Treatment recommendations for patients with adequate organ function and good PS are similar to the general population. Carboplatin is the preferred option in elderly patients due to toxicity of cisplatin. Single agent chemotherapy may be used for patients ineligible for doublet chemotherapy.

22. ***Patients with contraindication to immunotherapy:*** Platinum doublet chemotherapy should be considered in patients with no other comorbidities and good performance status. [8, 9]

### Role of Palliative RT in Stage IV Disease

23. Palliative RT can achieve symptom control in cases of oligoprogression, hemoptysis, symptomatic airway obstruction, painful chest wall disease, bone metastases, superior vena cava syndrome, soft tissue or neural invasion or spinal cord compression.

### Follow up

24. Follow up imaging and assessment can be carried out every 6-12 weeks if receiving ongoing treatment.[9, 11]

25. Patients who have completed their 2 years of immunotherapy with no evidence of disease progression may be followed up with CT scans every 3-4 months. This interval can be increased for patients who have been off systemic therapy for 5 years or more.

26. Smoking cessation should be encouraged. For further information, refer to the clinical practice guideline on Tobacco Cessation and Treatment for Adult Cancer Patients.

**Table 1.** Summary of treatment options for metastatic NSCLC without actionable alterations.

| **Non-squamous** | |
|---|---|
| First line management | PD-L1 ≥ 50%:<br>• Pembrolizumab monotherapy or can consider carboplatin, pemetrexed and pembrolizumab.<br>• Can consider nivolumab/ipilimumab in select patients.<br><br>PD-L1 < 50%:<br>• Carboplatin, pemetrexed and pembrolizumab.<br>• Can consider nivolumab/ipilimumab in select patients. |
| Second line management | Docetaxel, vinorelbine, gemcitabine, paclitaxel, or pemetrexed |
| Third line management | Docetaxel or erlotinib depending on treatments received in the earlier lines. |
| **Squamous** | |
| First line management | PD-L1 ≥ 50%:<br>• Pembrolizumab monotherapy or can consider platinum-doublet chemotherapy with either platinum/docetaxel or platinum/gemcitabine.<br>• Can consider nivolumab/ipilimumab in select patients.<br><br>PD-L1 < 50%:<br>• Platinum-doublet chemotherapy with either platinum/docetaxel or platinum/gemcitabine.<br>Can consider nivolumab/ipilimumab in select patients. |
| Second line management | Docetaxel |

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## Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Lung Tumour Team. Members include medical oncologists, radiation oncologists, surgeons, radiologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Lung Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2024.

## Levels of Evidence

| | |
|---|---|
| **I** | Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity |
| **II** | Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| **III** | Prospective cohort studies |
| **IV** | Retrospective cohort studies or case-control studies |
| **V** | Studies without control group, case reports, expert opinion |

## Strength of Recommendations

| | |
|---|---|
| **A** | Strong evidence for efficacy with a substantial clinical benefit; strongly recommended |
| **B** | Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended |
| **C** | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional |
| **D** | Moderate evidence against efficacy or for adverse outcome; generally not recommended |
| **E** | Strong evidence against efficacy or for adverse outcome; never recommended |

## Maintenance

A formal review of the guideline will be conducted in 2028. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; MR, magnetic resonance; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized clinical trial; RT, radiotherapy

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Lung Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.




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## Conflict of Interest Statements

Dr. Doreen Ezeife reports receiving honoraria from Pfizer, Bristol Myers Squibb, and Novartis, and is a member of the advisory board for Pfizer and Novartis.

Dr. Vishal Navani reports receiving consulting fees from Novotech Pty, Pfizer, Sanofi, Astra Zeneca, EMD Serono, Oncology Education, Sanofi, Janssen, Roche, MSD, Bristol Myers Squibb, and Takeda, and speaking fees from Ipsen, Astra Zeneca, MSD, and Bristol Myers Squibb. Dr. Navani reports receiving research support from Astra Zeneca (Inst) and Janssen (Inst), and travel support from EMD Serono, Pfizer, and Sanofi.

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