Guideline Resource Unit
guru@ahs.ca

Advanced Non-Small Cell Lung Cancer: Driver Mutation Positive

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Cancer Care Alberta

Clinical Practice Guideline LU-011 – Version V1
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 Canadian 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

- What is the role for EGFR tyrosine-kinase inhibitors (TKIs) in first-line treatment of patients with stage IV NSCLC?
- What is the role of anaplastic lymphoma kinase (ALK) inhibitors in the treatment of stage IV NSCLC?
- What is the role of palliative radiotherapy (RT) in the management of patients with stage IV NSCLC?
- What is the role of other inhibitors in the treatment of stage IV NSCLC?

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 with actionable alterations.

Recommendations

Diagnosis

Adequate staging is critical for patients with advanced (unresectable stage III and IV) disease to rule out the possibility of extracranial metastasis.[8, 9, 11]

1. Patients with advanced NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest, abdomen and pelvis.

2. Due to elevated risk of brain metastases in driver mutation positive NSCLC, baseline MR Brain (or a CT Head) should be performed to rule out brain metastases.

3. When clinically suspected, a bone scan should be performed to rule out bone metastases.

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

5. PD-L1 immunohistochemistry (IHC) should be determined for all advanced NSCLC.

6. Molecular testing with next-generation sequencing (NGS) should be performed to guide therapeutic decision-making in advanced non-squamous NSCLC. Unusual cases of squamous NSCLC (i.e. patients <50 years with never/minimal smoking history) may also undergo molecular testing. If NGS is unavailable, at minimum, the following molecular tests are recommended: EGFR, ALK, ROS1, BRAF, NTRK, MET, KRAS G12C, HER2, RET rearrangements.

7. RNA-based NGS is preferred for detection of fusion genes.

8. Circulating tumour DNA (or liquid biopsy) can be used to identify oncogenic drivers, but all patients with a negative ctDNA still require a tissue biopsy or cytology.

9. If there is still clinical suspicion for the presence of an actionable genomic alteration, and negative tissue, re-biopsy is recommended, when possible.

Treatment

Biomarker testing is essential to identify subgroups of NSCLC with oncogenic drivers that can be therapeutically targeted. Demonstration of the specific molecular alteration is necessary to tailor treatment with the appropriate targeted therapy.

EGFR-Mutated NSCLC:

EGFR-TKIs have become the standard first-line therapy for patients with common activating EGFR mutations (exon 19 deletion or exon 21 L858R). In the FLAURA[12] double blind phase 3 trial, osimertinib was compared with first generation EGFR-TKIs gefitinib or erlotinib in patients with treatment-naïve advanced NSCLC harbouring a common EGFR mutation. Compared to the comparator group, osimertinib showed higher overall survival (OS=38.6 months versus 31.8 months) and progression free survival (PFS=18.9 months versus 10.2 months).

First line treatment of EGFR-mutated NSCLC:[12]

10. Osimertinib is the preferable first-line treatment option for patients whose NSCLC is harbouring a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R).

11. Osimertinib in combination with platinum-doublet chemotherapy is another first-line option.[13]

12. Erlotinib, gefitinib, and afatinib are other first-line single-agent treatment options in cases of intolerability to osimertinib.

Second- and subsequent-line treatment of EGFR-mutated NSCLC:[8, 9]

13. Patients with minimal or moderate radiologic progression but ongoing clinical benefit may continue with EGFR TKIs. Consider radiation for oligo-progressive disease.

14. Upon development of resistance to first line first- or second-generation EGFR TKIs, patients should undergo testing to look for a potential T790M resistance mutation by ctDNA or tumour re-biopsy. If cDNA is negative, tumour biopsy should be requested. Tumour biopsy of the growing lesion should be performed.

15. Patients with a detected T790M-positive resistance mutation should receive osimertinib as second line therapy following disease progression on a first- or second-generation EGFR TKI.

T790M-negative resistance should be treated with platinum doublet chemotherapy or enrollment in a clinical trial.

16. Patients who develop disease progression on first line osimertinib should receive platinum-pemetrexed second line chemotherapy (unless small cell lung cancer (SCLC) transformation is detected as highlighted in recommendation #16 below), or be enrolled on a clinical trial. Clinical trial enrollment should particularly be encouraged if there is a targetable resistance mutation identified. Up to date information on trials offered in Alberta is available on the Alberta Cancer Clinical Trials website. Tissue or ctDNA testing for identification of the resistance mechanism on progressive disease to osimertinib should be considered, although it is not provincially funded in this context.

17. Third-line and subsequent options include docetaxel and nivolumab. See “Advanced NSCLC: Driver Mutation Negative” guidelines. Consider clinical trial options for fit patients.

18. Single agent immunotherapy may only be considered after progression on EGFR TKIs and platinum-doublet chemotherapy.

19. Antiangiogenic treatment in combination with chemoimmunotherapy (IMpower 150 trial data[14]) is not funded in Alberta.

ALK-Rearranged NSCLC:

First-line recommended tyrosine kinase inhibitor (TKI) treatment options for advanced ALK-positive NSCLC include lorlatinib, alectinib and brigatinib.). The phase III CROWN trial [15] compared 149 patients with ALK-positive NSCLC who received lorlatinib once daily with 147 patients who received crizotinib twice daily, and reported a 5-year PFS of 60% and 8%, respectively. After 5 years of follow-up, the median PFS has yet to be reached in the lorlatinib group, corresponding to the longest PFS reported to date for any single-agent molecular targeted treatment in advanced NCSLC. The phase III ALEX trial compared alectinib to crizotinib in previously untreated patients with advanced ALK-positive NSCLC and reported that median PFS was superior for the alectinib-treated patients (34.8 months vs 10.9 months The phase III ALTA-1L trial[16] compared 137 patients treated with brigatinib once daily to 138 patients treated with crizotinib twice daily. The 3-year PFS was 43% in the brigatinib group versus 19% in the crizotinib group; the median OS was not reached in either group.

20. First-line treatment options for patients with advanced ALK-positive NSCLC include lorlatinib, alectinib or brigatinib. There is a lack of randomized data comparing these ALK inhibitor agents. However, many clinicians agree that lorlatinib is the preferred first line agent.

21. Upon disease progression on a first line TKI, other targeted therapy agents are not funded in subsequent lines and can be difficult to access.

22. Patients with minimal or moderate radiologic progression but ongoing clinical benefit may continue with ALK TKIs. Consider radiation for oligo-progressive disease.

23. TKIs that have demonstrated efficacy following crizotinib resistance include alectinib, lorlatinib, brigatinib, and crizotinib.
24. When targeted therapy is no longer available, subsequent treatment options include platinum doublet chemotherapy or enrollment on a clinical trial. See Advanced NSCLC: Driver Mutation Negative guidelines.

25. Antiangiogenic treatment in combination with chemoimmunotherapy (IMpower 150 data[14]) is not funded in Alberta.

26. Single agent immunotherapy is not recommended for ALK positive NSCLC.

ROS1-Rearranged NSCLC:

27. Entrectinib is recommended in the first-line treatment for ROS1-rearranged advanced NSCLC[17].

28. Crizotinib is also an option in the first line setting. However, entrectinib is preferred in patients with brain metastases. Patients who are intolerant of entrectinib may be switched to crizotinib.

29. Patients with minimal or moderate radiologic progression but ongoing clinical benefit may continue with targeted therapy. Consider radiation for oligo-progressive disease.

30. TKIs that have demonstrated efficacy for ROS1+ lung cancer include entrectinib, lorlatinib, repotrectinib and crizotinib, however, targeted therapy is not funded in subsequent lines and can be difficult to access.

31. When targeted therapy is no longer available, subsequent treatment options include platinum doublet chemotherapy or clinical trial. See Advanced NSCLC: Driver Mutation Negative guidelines.

BRAF Mutations:

32. Treatment options for patients with BRAF V600E mutations include BRAF and/or MEK inhibitors, however these are currently not funded in Alberta for NSCLC. Refer to the Advanced NSCLC: Driver Mutation Negative guidelines and consider clinical trial treatment options for fit patients.

RET Fusions:

RET rearrangement occurs in 1-3% of patients with NSCLC. The LIBRETTO-001[18] and ARROW[19] clinical trials showed the clinical benefit of using selpercatinib (LOXO-292) and pralsetinib (BLU-667) as potent and selective inhibitors for the RET fusion positive NSCLC.

33. Treatment with selpercatinib is recommended as first-line therapy for patients with RET fusion-positive NSCLC. Pralsetinib is not funded in Alberta and can be difficult to access.

34. When targeted therapy is no longer available, subsequent treatment options include platinum doublet chemotherapy or clinical trial. See Advanced NSCLC: Driver Mutation Negative guidelines.

Other Oncogenic Targeted Therapy:

35. ***KRAS G12C positive:*** See Advanced NSCLC: Driver Mutation Negative guidelines. Consider clinical trial options for fit patients. KRAS G12C inhibitors are not funded in Alberta and can be difficult to access.

36. ***HER2 activating mutation positive:*** See Advanced NSCLC: Driver Mutation Negative guidelines. Consider clinical trial options for fit patients. HER2 targeted therapy is not funded in Alberta for NSCLC and can be difficult to access.

37. ***MET exon 14 skipping mutation positive:*** See Advanced NSCLC: Driver Mutation Negative guidelines. Consider clinical trial options for fit patients. MET inhibitors are not funded in Alberta for NSCLC and can be difficult to access.

38. ***EGFR Exon20insertion positive:*** See Advanced NSCLC: Driver Mutation Negative guidelines. Amivantamab plus chemotherapy is Health Canada approved for this indication in the first-line context, however access is not universally available. Consider clinical trial options for fit patients. Amivantamab is a potential treatment option for patients have disease progression post first-line combination platinum-based chemotherapy, although this agent is not currently funded in Alberta and can be difficult to access. It is approved Health Canada approved for this indication in patients post platinum exposure.

39. ***NTRK positive:*** See Advanced NSCLC: Driver Mutation Negative guidelines. Larotrectinib or entrectinib are funded treatment options typically after disease progression on prior therapies.

Table 1. Summary of treatment options for metastatic NSCLC with the most common actionable alterations.

EGFR Exon 19del or L858R mutated	
First line management	Osimertinib or osimertinib + platinum based chemotherapy
Second line management	Carboplatin–pemetrexed (if not received in 1L) or clinical trial
ALK-rearranged	
First line management	Alectinib, lorlatinib or brigatinib
Second line management	Carboplatin-pemetrexed or clinical trial
ROS1-rearranged	
First line management	Entrectinib
Second line management	Carboplatin-pemetrexed or clinical trial
RET fusions	
First line management	Selpercatinib

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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, 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

ALK, anaplastic lymphoma kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; MR, magnetic resonance; NGS, next-generation sequencing NSCLC, non-small cell lung cancer; NTRK, neurotropin tyrosine receptor kinase; PFS, progression-free survival; RT, radiotherapy; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor

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 Astra Zeneca, Pfizer, Bristol Myers Squibb, Novartis, and Roche.

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