STUDY GUIDE

Non-Small Cell Lung Cancer, Version 4.2026, NCCN Clinical Practice Guidelines In Oncology.

National Comprehensive Cancer Network · 2026

Study Guide: Non–Small Cell Lung Cancer (NSCLC) Clinical Practice Guidelines

This study guide provides a comprehensive overview of the treatment recommendations and clinical evidence for advanced or metastatic non-small cell lung cancer (NSCLC) as outlined in the NCCN Clinical Practice Guidelines Version 4.2026.

Key Concepts and Clinical Overview

1. Epidemiology and Survival Trends

- **Disease Prevalence:** In 2026, it is estimated that 229,410 individuals will be diagnosed with lung cancer in the United States, with 124,990 related deaths.
- **NSCLC Classification:** NSCLC accounts for approximately 87% of all lung cancer cases.
- **Survival Rates:** The 5-year overall survival (OS) rate for NSCLC in the United States is approximately 32%. While survival has improved due to increased screening, biomarker testing, and treatment advances, lung cancer remains the leading cause of cancer-related deaths.
- **Prognostic Factors:** Survival is influenced by histology, disease stage, patient age, and the presence of actionable biomarkers.

2. Diagnostic and Pre-treatment Requirements

The NCCN panel emphasizes establishing specific clinical parameters before initiating systemic therapy:

- **Histologic Subtype:** Determination of the specific subtype (e.g., Adenocarcinoma, Large cell, Squamous cell carcinoma) is essential.
- **Biomarker Testing:** Testing must be conducted prior to treatment initiation. Real-world data indicates that having results available before starting therapy is associated with longer OS in patients with advanced nonsquamous NSCLC.

- **Comprehensive Counseling:** Initial evaluation should include smoking cessation counseling and the integration of palliative care.

3. Systemic Therapy Strategies

Three primary classes of therapy are used for advanced or metastatic NSCLC:

1. **Targeted Therapy:** Generally recommended as initial therapy for patients with specific oncogenic drivers, regardless of PD-L1 levels.
2. **Immunotherapy:** Specifically immune checkpoint inhibitors (ICIs).
3. **Chemotherapy:** Often platinum-based regimens.

Rationale for First-Line Targeted Therapy: Targeted therapies are prioritized over ICIs in the first-line setting for patients with actionable biomarkers because they typically offer:

- Higher response rates.
- Better tolerability.
- Superior efficacy for disease involving the central nervous system (CNS).

4. Biomarker Analysis and Testing Methods

The NCCN Guidelines strongly advise the use of **Multigene Panel Testing (MGPT)** to identify rare driver mutations and emerging biomarkers.

Testing Category	Details
Actionable Biomarkers	EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET (exon 14 skipping), RET, ERBB2 (HER2), NRG1.
Testing Priority	PD-L1 testing and MGPT are the initial priorities.
Testing Modalities	Tissue biopsy and/or plasma testing. Concurrent testing (using both simultaneously) is acceptable to improve the speed of results.
Urgent Therapy Protocol	If therapy must start before results are known, clinicians should consider holding immunotherapy for one cycle (using platinum-based chemotherapy instead) to avoid side effects related to the long half-life of ICIs.

Short-Answer Practice Questions

1. **What percentage of lung cancers are classified as non-small cell lung cancer?**
    - Approximately 87%.

2. **Why is it recommended to hold immunotherapy if a patient requires an urgent start to therapy before biomarker results are available?**
    - Due to the long half-life of immune checkpoint inhibitors (ICIs), there is a potential for higher rates of side effects when using certain targeted therapies (such as osimertinib) in combination with or following ICIs.
3. **Which specific mutation is an exception to the rule that targeted therapy is preferred in the first-line setting?**
    - The KRAS G12C mutation; these patients are likely to benefit more from immunotherapy (with or without chemotherapy) as initial treatment.
4. **What is the definition of a Category 1 NCCN recommendation?**
    - An intervention based upon high-level evidence (such as randomized phase 3 trials) with uniform NCCN consensus (at least 85% support) that the intervention is appropriate.
5. **What are the three main histologic categories mentioned for advanced or metastatic disease before biomarker testing?**
    - Adenocarcinoma, Large cell, and Squamous cell carcinoma.
6. **What is the 5-year overall survival rate for patients with NSCLC in the United States according to the 2026 data?**
    - Approximately 32%.
7. **What is the benefit of concurrent tissue and plasma testing?**
    - It can improve the time to receive test results, which is critical for guiding treatment.

Essay Prompts for Deeper Exploration

1. **The Role of Multigene Panel Testing (MGPT) in Precision Oncology:** Discuss the clinical significance of MGPT compared to single-gene testing in the management of NSCLC. Explain how MGPT facilitates the identification of rare driver mutations and why the NCCN panel considers it a "key component" for improving patient care.
2. **Targeted Therapy vs. Immunotherapy in First-Line Settings:** Evaluate the rationale behind preferring targeted therapies over immune checkpoint inhibitors for patients with actionable oncogenic drivers. Consider factors such as response rates, toxicity profiles, and efficacy in the central nervous system.
3. **The Impact of Biomarker Timing on Patient Outcomes:** Analyze the relationship between the timing of biomarker result availability and overall survival in patients with advanced nonsquamous NSCLC. Discuss the clinical implications of starting systemic therapy before results are confirmed.

Glossary of Important Terms

- **Actionable Biomarker:** A specific genetic alteration or protein expression (e.g., EGFR mutation, PD-L1 levels) that can be targeted with a specific therapeutic agent.
- **Category 2A (NCCN):** A recommendation based on lower-level evidence where there is uniform NCCN consensus (≥85%) that the intervention is appropriate.
- **Central Nervous System (CNS) Efficacy:** The ability of a treatment to effectively reach and treat cancer that has spread to the brain or spinal cord.
- **Driver Mutation:** A genetic mutation that actively promotes the growth and survival of cancer cells.
- **Histology:** The study of the microscopic structure of tissues; in NSCLC, this determines the specific subtype of the cancer.
- **Immune Checkpoint Inhibitor (ICI):** A type of immunotherapy that blocks proteins that keep the immune system from attacking cancer cells.
- **Liquid Biopsy (Plasma Testing):** A test performed on a blood sample to look for cancer cells or pieces of DNA from a tumor (circulating tumor DNA).
- **Multigene Panel Testing (MGPT):** Molecular testing that identifies multiple biomarkers simultaneously in either a single assay or a combination of limited assays.
- **Overall Survival (OS):** The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive.
- **Palliative Care:** Specialized medical care focused on providing relief from the symptoms and stress of a serious illness to improve quality of life for the patient and the family.