# Precision Medicine for Lung Cancer

Discover guideline-recommended actionable and emerging biomarkers in NSCLC.

Reading time: **18 min**

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## Biomarker Testing Is Transforming the Management of Lung Cancer

In the US, lung cancer is the leading cause of cancer mortality, causing 20% of cancer deaths.[1] Precision Medicine is improving survival rates for NSCLC through targeted therapies guided by biomarker testing.[2]

**Overall survival doubled** for patients with advanced NSCLC who had biomarker testing, compared with those who did not.[2,a]

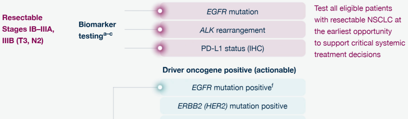
### Footnotes

[a] Results taken from a retrospective analysis including 48,857 patients diagnosed with advanced NSCLC (stage IIIB or IV) between January 1, 2011 and May 31, 2018. 17,555 eligible patients with non-squamous advanced NSCLC were then classified into either patients who had any actionable CDx test for one of the four driver mutations (*ALK*, *BRAF*, *EGFR* or *ROS1* positive or negative) and/or PD-L1 expression (n=14,732) and those who did not have reported evidence of testing (n=2,823). Patients with CDx testing had a longer median survival than those without testing (median overall survival [95% CI], 13.04 [12.62–13.40] months vs 6.01 [5.72–6.24] months).[2]

*ALK*, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene serine/threonine kinase; CDx, companion diagnostic; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

## Lung Cancer Biomarker Testing Recommendations Are Integral to Treatment Decisions

**Precision medicine in NSCLC relies on effective biomarker testing for optimal cancer care. NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend testing for all eligible patients.[3]**



**Resectable Stages IB–IIIA, IIIB (T3, N2)**

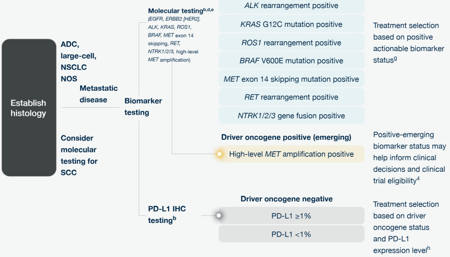
**Biomarker testing[a–c]**

- *EGFR* mutation
- *ALK* rearrangement
- PD-L1 status (IHC)

Test all eligible patients with resectable NSCLC at the earliest opportunity to support critical systemic treatment decisions

**Driver oncogene positive (actionable)**

- *EGFR* mutation positive[f]
- *ERBB2 (HER2)* mutation positive



**Establish histology**

**ADC, large-cell, NSCLC NOS**

**Metastatic disease**

**Consider molecular testing for SCC**

**Biomarker testing**

**Molecular testing**[b,d,e] *(EGFR, ERBB2 [HER2], ALK, KRAS, ROS1, BRAF, MET* exon 14 skipping, *RET, NTRK1/2/3*, high-level *MET* amplification)

*ALK* rearrangement positive

*KRAS* G12C mutation positive

*ROS1* rearrangement positive

*BRAF* V600E mutation positive

*MET* exon 14 skipping mutation positive

*RET* rearrangement positive

*NTRK1/2/3* gene fusion positive

Treatment selection based on positive actionable biomarker status[g]

**Driver oncogene positive (emerging)**

High-level *MET* amplification positive

Positive-emerging biomarker status may help inform clinical decisions and clinical trial eligibility[4]

**PD-L1 IHC testing**[b]

**Driver oncogene negative**

PD-L1 ≥1%

PD-L1 <1%

Treatment selection based on driver oncogene status and PD-L1 expression level[h]

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Testing early, such as at preoperative biopsy, can guide critical systemic treatment decisions, inform potential trial eligibility, and support testing workflow efficiency. In the advanced or mNSCLC setting, when biopsy samples are insufficient or unavailable, consider using plasma ctDNA.[3]

Find more solutions to commonly encountered testing challenges.

Find testing solutions

Footnotes ▲

[a] In resectable NSCLC, a preoperative biopsy is recommended for patients with clinical Stage IB or higher who may be candidates for systemic therapy prior to surgery.[3] [b] The NCCN Guidelines® for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific assays or commercial laboratories.[3] [c] Testing is recommended for *EGFR* mutations, *ALK* rearrangements, and PD-L1 status for eligible patients with resectable Stage IB-IIIA, IIIB (T3, N2) NSCLC using a preoperative biopsy or surgical tissue.[3] [d] NCCN Guidelines strongly advise broader molecular profiling for eligible patients with metastatic NSCLC with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all recommended and emerging biomarkers in either a single assay or a combination of a limited number of assays.[3] [e] If there is insufficient tissue to allow testing for all of *EGFR*, *ERBB2* (*HER2*), *ALK*, *KRAS*, *ROS1*, *BRAF*, *MET* exon 14 skipping, *NTRK1/2/3*, and *RET*, consider tissue rebiopsy or ctDNA testing.[3] [f] Includes exon 19 deletions, exon 21 L858R mutation, exon 20 insertion, p.S768I, p.L861Q, and/or p.G719X mutations. Certain patients with *EGFR* exon 20 insertion mutations should receive systemic treatment in 1L; targeted therapies are recommended as 2L treatment options.[3] [g] In patients with metastatic NSCLC, 1L treatment selection is based on driver mutation–positive status except in certain patients whose tumors harbor an *EGFR* exon 20 insertion mutation, a *KRAS* G12C mutation, or an *ERBB2* (*HER2*) mutation as the sole driver mutation. Certain patients with an *EGFR* exon 20 insertion mutation, *KRAS* G12C mutation, or an *ERBB2* mutation should receive systemic treatment in 1L; targeted therapies are recommended as 2L treatment options. Patients with *EGFR* exon 20 insertion mutations and nonsquamous histology can receive targeted therapy in the 1L.[3] [h] In patients with metastatic NSCLC, 1L treatment selection is based on PD-L1 expression level and molecular biomarker status except in certain patients whose tumors harbor an *EGFR* exon 20 insertion mutation, a *KRAS* G12C mutation, or an *ERBB2* (*HER2*) mutation as the sole driver mutation. Certain patients with an *EGFR* exon 20 insertion mutation, a *KRAS* G12C mutation, or an *ERBB2* (*HER2*) mutation should receive systemic treatment in 1L; targeted therapies are recommended as 2L treatment options. Patients with *EGFR* exon 20 insertion mutations and nonsquamous histology can receive targeted therapy in the 1L.[3]

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1L, first-line; 2L, second-line; ADC, adenocarcinoma; *ALK*, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; ctDNA, circulating tumor deoxyribonucleic acid; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-B2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; mNSCLC, metastatic non-small cell lung cancer; N, node; NCCN, National Comprehensive Cancer Network® (NCCN®); NOS, not otherwise specified; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, tyrosine receptor kinase; SCC, squamous cell carcinoma; T, tumor; TAT, test turnaround time.

## Comprehensive Biomarker Testing May Inform Treatment Eligibility[3,5]

NCCN Guidelines strongly advise broad molecular profiling in eligible patients with advanced or mNSCLC with the goal of identifying actionable biomarkers to ensure that the most appropriate treatment can be selected, or to appropriately counsel individuals regarding the availability of clinical trials.[3,a]

NCCN Guidelines recommend the use of tissue and ctDNA specimens.[3,b–d] Testing can be performed concurrently or in a sequence. Consider concurrent testing to help improve turnaround time. If certain clinically actionable biomarkers are identified via either method, biomarker-based therapy may be initiated.[3]

| Setting | Biomarker type | Biomarker | NGS | PCR | ISH/FISH | IHC | Sanger sequencing |
|---|---|---|---|---|---|---|---|
| Resectable | Actionable[3] | *ALK* | ✓ | ✓ | ✓ | ✓ | |
| | | *EGFR* | ✓ | ✓ | | | ✓ |
| | | PD-L1 status | | | | ✓ | |
| Advanced or mNSCLC | Actionable[3] | *ALK* | ✓ | ✓ | ✓ | ✓ | |
| | | *BRAF* | ✓ | ✓ | | | ✓ |

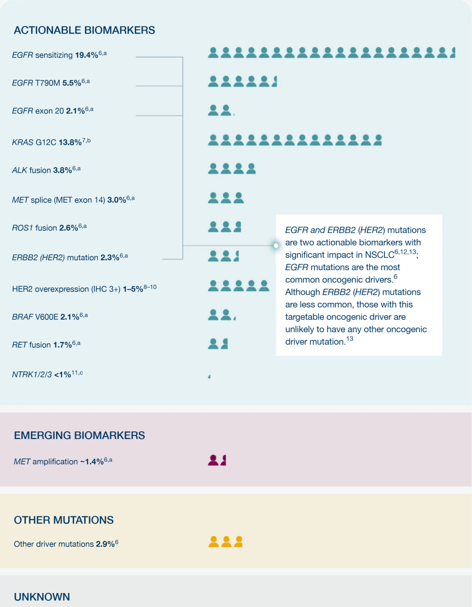
|  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|
|  |  | *EGFR* | ✓ | ✓ |  |  | ✓ |
|  |  | *ERBB2 (HER2)* mutation | ✓ | ✓ |  |  | ✓ |
|  |  | HER2 overexpression |  |  |  | ✓ |  |
|  |  | *KRAS* | ✓ | ✓ |  |  | ✓ |
|  |  | *MET* exon 14 skipping | ✓ |  |  |  |  |
|  |  | *NTRK1/2/3* | ✓ | ✓ | ✓ | ✓ |  |
|  |  | PD-L1 status |  |  |  | ✓ |  |
|  |  | *RET* | ✓ | ✓ | ✓ |  |  |
|  |  | *ROS1* | ✓ | ✓ | ✓ | ✓ |  |
|  | **Emerging**[3,5] | High-level *MET* amplification | ✓ |  | ✓ |  |  |

**Footnotes**

[a] The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories. [b] Plasma ctDNA specimen.[3] [c] ctDNA should not be used to test for PD-L1.[3] [d] ctDNA should not be used in lieu of a histologic tissue diagnosis.[3]

*ALK*, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-B2 receptor tyrosine kinase 2; FISH, fluorescence *in situ* hybridization; *HER2*, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network® (NCCN®); NGS, next-generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, tyrosine receptor kinase.

## Over Half of Patients With NSCLC May Carry an Actionable Mutation, Highlighting the Importance of Accurate Biomarker Testing[6–11]



### ACTIONABLE BIOMARKERS

*EGFR* sensitizing **19.4%**[6,a]

*EGFR* T790M **5.5%**[6,a]

*EGFR* exon 20 **2.1%**[6,a]

*KRAS* G12C **13.8%**[7,b]

*ALK* fusion **3.8%**[6,a]

*MET* splice (MET exon 14) **3.0%**[6,a]

*ROS1* fusion **2.6%**[6,a]

*ERBB2 (HER2)* mutation **2.3%**[6,a]

HER2 overexpression (IHC 3+) **1–5%**[8–10]

*BRAF* V600E **2.1%**[6,a]

*RET* fusion **1.7%**[6,a]

*NTRK1/2/3* **<1%**[11,c]

*EGFR and ERBB2* (*HER2*) mutations are two actionable biomarkers with significant impact in NSCLC[6,12,13]; *EGFR* mutations are the most common oncogenic drivers.[6] Although *ERBB2* (*HER2*) mutations are less common, those with this targetable oncogenic driver are unlikely to have any other oncogenic driver mutation.[13]

### EMERGING BIOMARKERS

*MET* amplification **~1.4%**[6,a]

### OTHER MUTATIONS

Other driver mutations **2.9%**[6]

### UNKNOWN

Unknown mitogenic driver/no driver **~13%**[6,a]

**Footnotes**

[a] Jordan et al (2017) prospectively analyzed a total of 915 tumors from 860 patients with recurrent or metastatic lung adenocarcinoma for mutations using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay, a hybridization capture-based, next-generation sequencing platform.[6] [b] Nassar et al (2021) extracted data from the registry of the American Association for Cancer Research project Genomics Evidence Neoplasia Information Exchange (GENIE) version 8.0 to study the distribution of *KRAS* mutations in 32,138 patients with cancer across race and sex. *KRAS* mutations were identified in 1,867 samples, most frequently in patients with NSCLC (1,443 of 10,444).[7] Stage of disease was not disclosed. [c] Farago et al (2018) examined data on 4,872 patients to determine a frequency of 0.23% (n=11) for *NTRK* gene fusions in NSCLC.[11] [d] Other driver mutations are defined as all mutations excluding actionable, emerging, and unknown driver mutations.

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*ALK*, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-B2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

## Help Inform Clinical Decisions with Biomarker Testing in Eligible Patients

Test for DNA alterations in *EGFR* and *ERBB2* (*HER2*) – as two clinically impactful targetable mutations – to inform eligibility for targeted treatment options.[12]

**Why test for *EGFR* →** **Why test for *ERBB2* (*HER2*) →**

Novel prognostic and predictive biomarkers (e.g., *STK11*, *KEAP1*, and *SMARCA4*) are an evolving area of research and could help better inform treatment planning for patients with newly diagnosed metastatic NSCLC, including for PD-L1 expression <1%.[14–16]

**Explore novel biomarkers in mNSCLC**

DNA, deoxyribonucleic acid; *EGFR*, epidermal growth factor receptor; *ERBB2*, erb-B2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; *KEAP1*, kelch-like ECH-associated protein 1; *NSCLC*, non-small cell lung cancer; PD-L1, programmed death-ligand 1; *SMARCA4*, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; *STK11*, serine/threonine kinase 11.

## Considerations for Your Practice

**Investigate, action, or review multidisciplinary team (MDT) protocols for identifying individuals eligible for biomarker testing,** such as *EGFR* and *ERBB2* (*HER2*):

- Perform biomarker testing as recommended across clinical guidelines in eligible patients with NSCLC to help inform clinical decisions
- Find a testing lab* which can perform biomarker testing
- Standardize biomarker testing protocols with your MDT
- Discover novel biomarkers

*EGFR*, epidermal growth factor receptor; *ERBB2*, erb-B2 receptor tyrosine kinase 2; *HER2*, human epidermal growth factor receptor 2; MDT, multidisciplinary team; NSCLC, non-small cell lung cancer.

*This information is intended as educational and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved.

## Helpful Resources

Check out these featured resources on biomarker testing in lung cancer.

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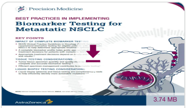

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BEST PRACTICES IN IMPLEMENTING

Biomarker Testing for Metastatic NSCLC

KEY POINTS

AstraZeneca

3.74 MB

FOR HCPS

### Best practices in implementing biomarker testing for metastatic

Read about complete biomarker profiling for informing treatment in metastatic non-small cell lung cancer (mNSCLC), and best practices for performing biomarker testing.

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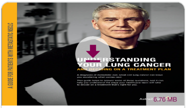

A GUIDE FOR PATIENTS WITH METASTATIC NSCLC

UNDERSTANDING YOUR LUNG CANCER

AND DECIDING ON A TREATMENT PLAN

6.76 MB

FOR PATIENTS

### Understanding your lung cancer

Download this comprehensive guide for your patients to help them navigate through their lung cancer diagnosis and understand what comes next.

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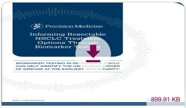

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Informing Resectable NSCLC Treatment Options Through Biomarker Testing

BIOMARKER TESTING IN RESECTABLE NSCLC CAN HELP IDENTIFY THE ONCOGENIC DRIVER OF DISEASE AT THE EARLIEST OPPORTUNITY

899.91 KB

FOR HCPS

### Informing resectable NSCLC treatment options through

View this helpful guide on biomarker testing for patients with non-small cell lung cancer (NSCLC).

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NSCLC, non-small cell lung cancer.

### References

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