Lung Cancer Overview

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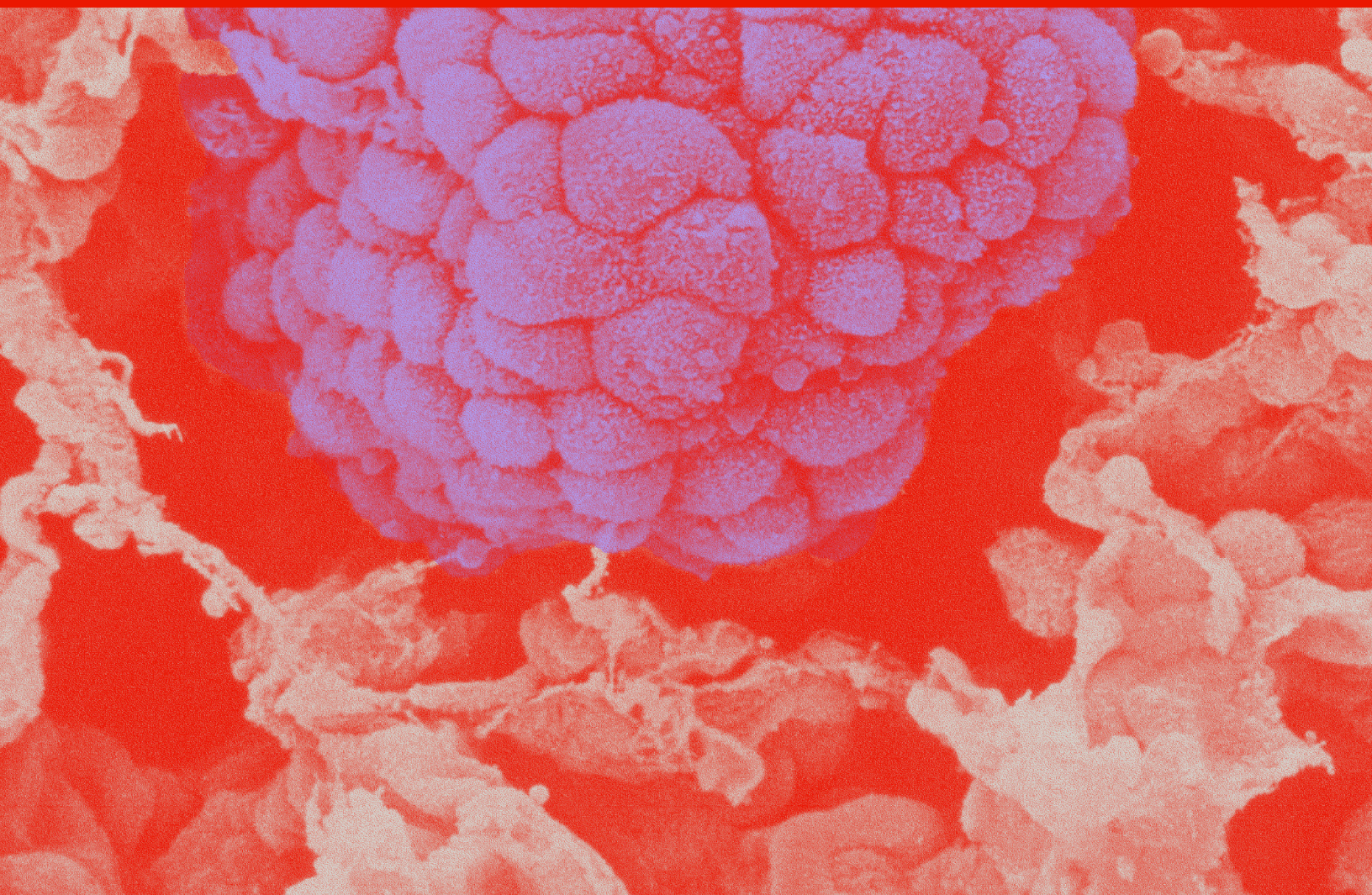


Prevalence, incidence, and risk factors in the United States[1–3]

Prevalence[1]:

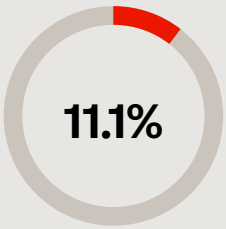
610,816 people
living with lung and bronchus cancer in 2021*

~5.7% of men and women will be diagnosed with lung and bronchus cancer at some point during their lifetimes

Incidence[3]:

226,650 cases
in 2025*

Third most common type of cancer



of all new cancer cases

Risk factors[2,3]

- Cigarette smoking
- Passive smoke inhalation
- Older age
- Radon exposure
- Asbestos exposure
- Family history (genetics)
- Lung damage from inflammation and infection
- Race/ethnicity

While smoking is a major risk factor for lung cancer, **an increasing proportion of patients with lung cancer are never-smokers**[4,5]

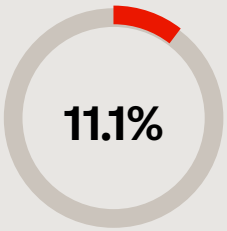
*Estimated.

Survival rates for lung cancer

Deaths in 2025[3]*:

124,730 deaths

Lung and bronchus cancer account for



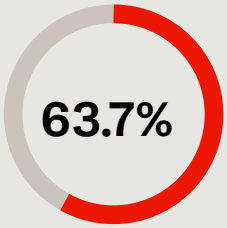
of all new cancer cases

of all cancer deaths

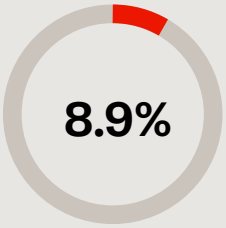
Five-year relative survival rates

(2014–2020)[1]

Overall: 26.7%

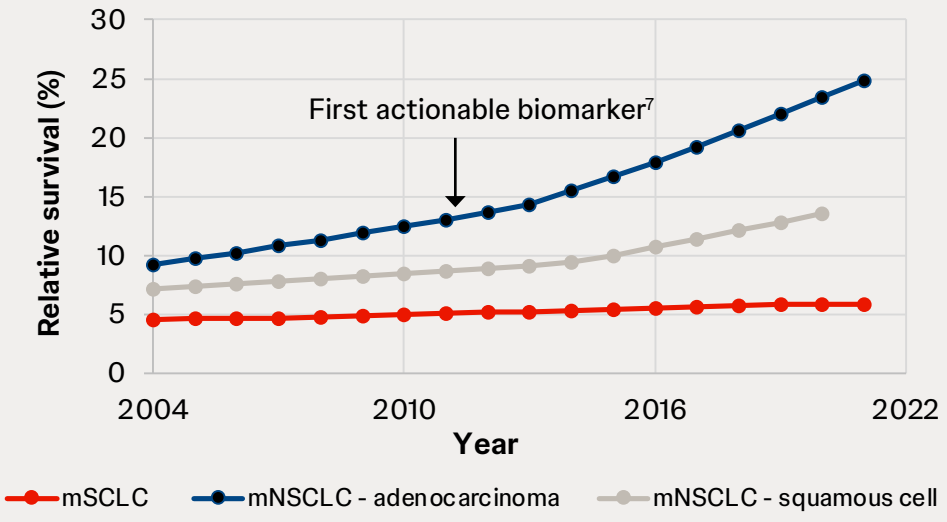


Localized (stage I)



Metastatic (stage IV)

Three-year relative survival in metastatic lung cancer subtypes[6]



Changes in the clinical understanding of lung cancer and the development of new treatment options are positively impacting patient outcomes[3,8]

*Estimated.[3]

Impact of biomarker-informed treatment in NSCLC

Frequency of oncogenic driver alterations in NSCLC (adenocarcinoma)[9,10]

Driver alteration	Frequency (%)
ALK rearrangement	3.8
BRAF V600E mutation	2.1
EGFR exon 19 deletion and exon 21 L858R substitution mutation	16.3
EGFR exon 20 insertion mutation	1.3
Other *EGFR* mutation	1.6
HER2 exon 20 insertion mutation	2.3
KRAS G12C mutation	15.0
Other *KRAS* mutation	10.3
MET exon 14 skipping	3.0
NRG1 gene fusion	0.3
NTRK rearrangement	0.23
RET rearrangement	1.7
ROS1 rearrangement	2.6
No actionable alteration	39.8

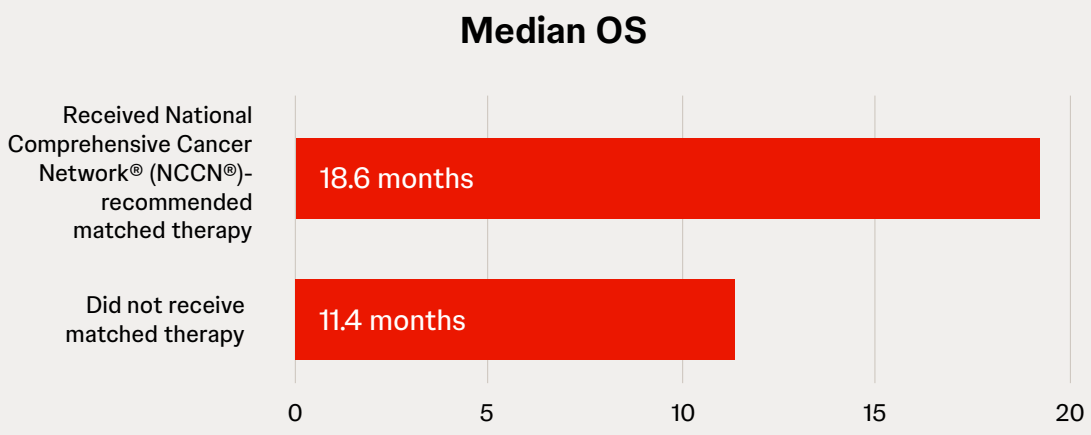
Since 2011, the FDA has approved biomarker-informed therapies for patients with one of[11]*:

11 biomarkers in mNSCLC

3 biomarkers in earlier stages of NSCLC

Real-world, retrospective studies indicate that receipt of biomarker-matched therapy impacts patient outcomes

One study of more than 4000 patients with NSCLC explored associations between tumor genomics and clinical outcomes from 2011 to 2017[12†]



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†Among patients with advanced disease, defined as stage IIIB/IV disease at diagnosis or recurrent/metastatic disease at any stage, who have a mutation in an NCCN-listed gene.[12]

Impact of biomarker testing in NSCLC

Ensuring patients receive biomarker-informed care impacts outcomes[13]

One retrospective study found that patients with a **driver alteration** had different outcomes depending on the **type and timing of treatment given**[13]

28.8-month median overall survival
In patients receiving biomarker-informed treatment

16.5-month median overall survival
In patients receiving treatment* before receiving test results

In another study, the **impact of the biomarker testing panel size** was assessed[14]

With large-panel (>52 genes) testing

32% of patients
had ≥1 actionable biomarker

With small-panel (≤52 genes) testing:

14% of patients
had ≥1 actionable biomarker

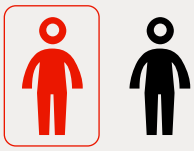
With a larger panel, there was **a higher likelihood of matched therapy** in any line (OR, 3.2 compared with small panel)

Opportunity to optimize

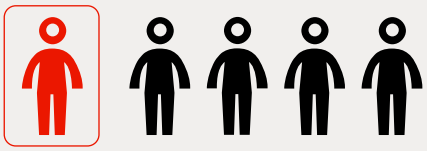
Comprehensive biomarker testing, per guidelines, is critical for optimal therapy selection[13]

*Chemotherapy, ICI, or both.[13]

mNSCLC is defined by molecular drivers, many of which are actionable[9,15]



>1 out of every 2
patients have 1 of the 10 currently actionable driver alterations[9,11,15]*



~1 out of every 5
patients have 1 of the 9 less common actionable driver alterations[9,10,15]†

PD-L1 is also an actionable biomarker in mNSCLC[16,17]

Two retrospective studies demonstrated that patients with driver mutations, may also overexpress PD-L1, reporting that[16,17]:

of patients with *EGFR* mutation

of patients with *ALK* translocation

were also PD-L1+ (TPS ≥1%)[16,17]

>50% of patients with mNSCLC are PD-L1+[16,17]

- PD-L1 is a protein biomarker, not a driver alteration[17]
- PD-L1 may help predict patient response to ICIs[16,17]

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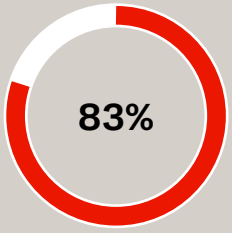
†Less common driver alterations refers to drivers with a prevalence of less than 5%.

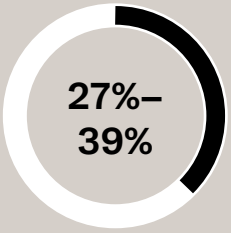
Targeted therapy or immunotherapy?

In clinical practice, patients are sometimes started on immunotherapy before receiving full biomarker testing results due to the relative speed of obtaining PD-L1 results.[13] However:

In clinical trials:

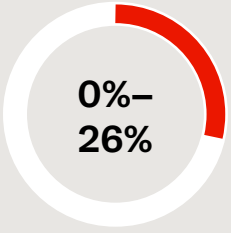


ORR* in patients receiving **matched, targeted therapy** can be as high as 83%[18,19]



Response rates* reported in **ICI monotherapy trials** ranged from 27%–39%[20,21]

Real-world data:



In a study involving patients **with driver alterations** receiving **ICI as monotherapy**, ORR ranged from 0%–26%, depending on the alteration[22]

Real-world data indicate that **patients with driver alterations may have lower response rates to immunotherapy**[13,22]

Studies have reported that **concurrent treatment** or treatment with t**argeted therapy following ICI can lead to SAEs, including higher risk of**[23–27]**:**

- **Pneumonitis** (grades 3–5)
- **Interstitial lung disease** (grades 3–4)
- **Hepatotoxicity** (grades 3–4)

ASCO guidelines state:

"In cases where patients must start therapy for immediate symptom control or to avoid risk of imminent deterioration, initial treatment with chemotherapy without immunotherapy is appropriate if a driver alteration is suspected.

Treatment can be adjusted when biomarker testing results are available."[24]

Opportunity to optimize

Wait for full biomarker testing results prior to initiating 1L therapy, if clinically feasible[11†]

*ORR was not a primary endpoint in these clinical trials.[18–20]

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Complete biomarker testing requires testing for different biomarker types

Driver alterations:
Can be the result of a number of different types of genetic alterations[28,29]

Protein biomarker

CNV[28]	Fusion/ rearrangement[28]	INDEL[28]	SNV[28]	
A deletion or insertion of a larger segment of DNA[28]	A chromosome breaks and the fragmented pieces re-attach to different chromosomes[28]	Addition or deletion of ≥1 nucleotides into a segment of DNA[28]	Substitution of 1 nucleotide for another[28]	A protein found on cells in tissue or bodily fluids[29]
MET amplifications are an emerging biomarker in NSCLC[28,30]	*ALK, NTRK, RET, ROS1*[28,30]	*EGFR, HER2, MET*ex14[28,30]	*BRAF, EGFR, HER2, KRAS*[28,30]	PD-L1[30]
	Actionable biomarkers in mNSCLC[28,30]			

Testing capabilities differ by methodology

Oncogenes can have multiple actionable driver alterations or alteration types

For example:

Driver gene	Driver alteration	Alteration type
EGFR[31]	Exon 19	Deletion
	Exon 20	Insertion*
	Exon 21	SNV (L858R)
MET[32]	*MET*ex14	2- to 193-bp deletion, SNV
RET[33]	*RET* fusion	Wide range of fusions†

Options for detecting these alterations include

PCR	NGS
Tests for individual, known alterations[34,35]	**Sequences DNA samples and identifies alteration by comparing with a normal/control sample[34,36]**

There are many sequence options for insertions, deletions (if more than a point deletion), and fusions. **NGS is the optimal test that can detect multiple driver alterations simultaneously[34]**

*There may be >100 insertion options in *EGFR* exon 20.[31]
†In a recent study, 61 novel *RET* fusions were identified across solid tumor types.[33]

Guideline recommendations for biomarker testing in NSCLC

Biomarker	NCCN[11]*	CAP/IASLC/AMP[37]	ASCO[38,39]	Testing technology[10,30]
ALK	●	●	●	NGS, FISH (historical standard), IHC (validated against FISH)
BRAF	●	●	●	Any appropriate, validated technology, subject to external quality assurance
EGFR	●	●	●	Any appropriate, validated technology, subject to external quality assurance
ERBB2/HER2	●	●	●	NGS
KRAS	●	●	●	NGS, RT-PCR, pyrosequencing
MET	●	●	●	NGS, IHC, FISH
NRG1	●	●	●	NGS
NTRK	●	●	●	NGS, IHC, FISH, RT-PCR
PD-L1	●	●	●	IHC
RET	●	●	●	NGS, FISH, RT-PCR
ROS1	●	●	●	NGS, FISH (trial-validated standard), IHC to select for confirmatory FISH

● Testing recommended ● Expanded panel testing recommended ● No guideline recommendations to date

Guidelines from multiple US organizations recommend testing for all actionable biomarkers in mNSCLC, often via expanded panel testing[11,37–39]*

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Biomarkers are integral to the treatment of NSCLC

The lung cancer treatment landscape continues to evolve with approaches focused on biomarker-informed treatment[40–42]

Patient outcomes are linked to comprehensive biomarker testing for targeted therapies[13,14]

Guideline-recommended treatment for lung cancer is comprehensive broad-based testing[11,37,39,43]*

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ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CAP, College of American Pathologists; CNV, copy number variant; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2; FDA, U.S. Food and Drug Administration; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; INDEL, insertion or deletion; KRAS, Kristen rat sarcoma virus; MET, mesenchymal epithelial transition; mNSCLC, metastatic non-small cell lung cancer; mSCLC, metastatic small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; OR, odds ratio; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; RET, receptor tyrosine kinase; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; RT-PCR, reverse transcription polymerase chain reaction; SAE, serious adverse event; SNV, single-nucleotide variant; TPS, tumor proportion score.

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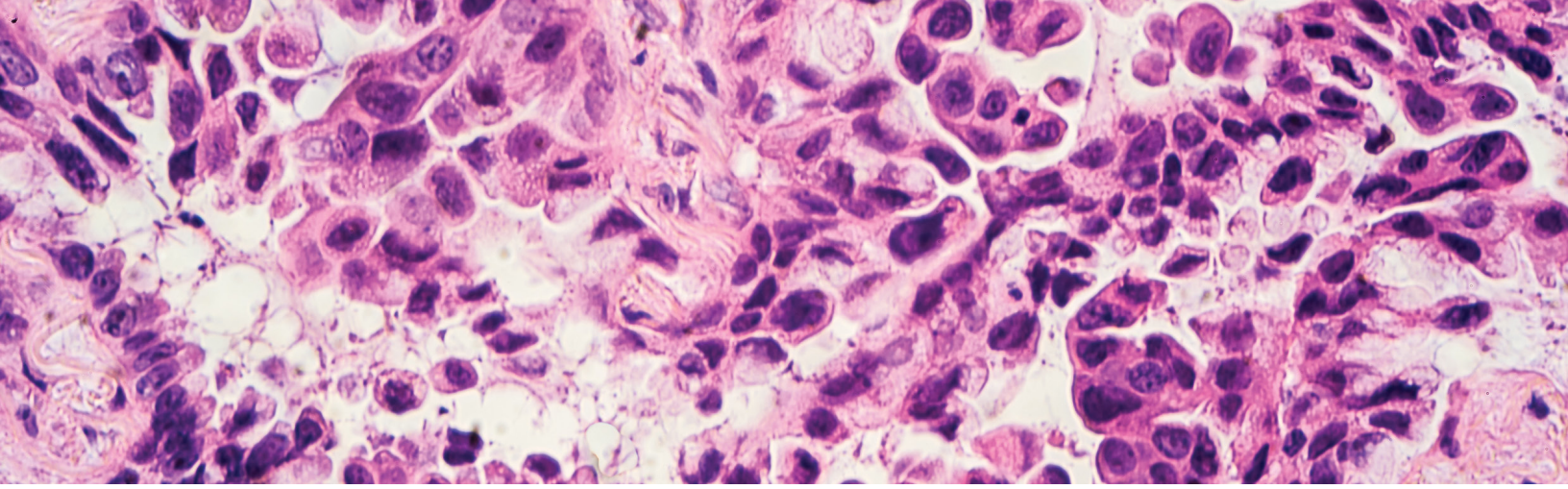

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