Target Drug

EGFR
- Erlotinib (approved)
- Gefitinib (approved)
- PF299804
- Afatinib (BIBW2992)

ALK
- Crizotinib (approved)
- LDK378
- AP26113
- AFI02

ROS1
- Crizotinib
- PF299804
- Afatinib (BIBW2992)

HER2
- PF299804
- Afatinib (BIBW2992)

FGFR
- BGJ398
- FP1039 (HGS1036)
- Ponatinib (AP24534)

ALK/FGFR/VEGFR
- BIBF1120
- Pazopanib
- Lenvatinib (E7080)
- Brivanib (BMS-582,864)
- Dovitinib (TKI258)

PDGFRA
- MEDI575
- IMC-3G3

PI3K
- BGJ398
- FP1039 (HGS1036)
- Ponatinib (AP24534)

PDGFRA
- MEDI575
- IMC-3G3

PI3K/MTOR
- GDC-0980
- BEZ235
- SAR245409

MEK
- MEK162
- GDC-0941
- GSK1120212
- MDC1936369B

AKT
- OP851602
- MK2206

Stage | Est. % | General treatment recommendations | 5-year overall survival\(^a\) | clinical stage | path. stage |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>14%</td>
<td>Surgical resection</td>
<td>50%</td>
<td>73%</td>
<td></td>
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<tr>
<td>IB</td>
<td>10%</td>
<td>Surgical resection, can consider adjuvant chemotherapy in selected cases (e.g. tumor size &gt; 4cm)</td>
<td>43%</td>
<td>58%</td>
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<tr>
<td>IIA</td>
<td>6%</td>
<td>Surgical resection followed by adjuvant chemotherapy</td>
<td>36%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>5%</td>
<td>Surgical resection followed by adjuvant chemotherapy</td>
<td>25%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>16%</td>
<td>Multimodality treatment: chemotherapy, radiation, +/- surgery</td>
<td>19%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>8%</td>
<td>Multimodality treatment: chemotherapy and radiation</td>
<td>7%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>41%</td>
<td>Chemotherapy, consider targeted therapies according to driver mutations</td>
<td>2%</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Estimated from SEER validation set of proposed 7th editionIASLC staging.

\(^b\)Overall survival is higher by pathologic stage because clinical stage, which is estimated by clinical characteristics based on CT scan, PET, etc., can underestimate the true stage.

**Mutations in Adenocarcinoma**

- BRAF mutation
- NRAS mutation
- HER2 mutation
- RET translocation
- OTHER

**Mutations in Squamous Cell Carcinoma**

- FGFR1 amplification
- PTEN mutation
- PIK3CA mutation

Mutations in TP53 and STK11/LKB1 are common occurrences, not included in pie chart due to high overlap with other mutations.

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*Denotes proteins commonly mutated in lung cancer.
Proteins in bold are current targets of drug development.
The treatment and diagnosis of non-small cell lung cancer (NSCLC) has been revolutionized by the development of targeted agents for cancers harboring specific genetic mutations. The top table in the adjacent figure summarizes the current clinical landscape of NSCLC. Several somatic “driver” mutations have been described in lung cancer, with the spectra and frequencies of mutations differing between adenocarcinoma and squamous cell carcinoma. The pie charts display the current understanding of the mutation frequencies in these subsets of NSCLC.

Routine genetic testing for somatic mutations from lung cancer biopsies is becoming the standard for providing optimal patient care. Identification of specific mutations such as in EGFR and ALK directs use of FDA-approved targeted therapies that are likely to provide clinical benefit. The identification of other genetic mutations can direct patients and physicians toward appropriate clinical trials with new targeted agents. Many of the therapies currently under development target activated receptor tyrosine kinases (RTKs) or associated downstream signaling pathways, particularly the RAS-RAF-MAPK and PI3K-AKT pathways. The accompanying pathway diagram highlights the proteins that are currently being targeted in NSCLC, and the accompanying table lists the targeted therapies that are FDA approved or currently under active development for treating NSCLC.

There are numerous clinical trials currently underway assessing how to best target specific pathways (alone or in combination) in cancers harboring specific mutations.

### EGFR

Activating EGFR mutations are located in the tyrosine kinase domain and result in constitutive EGFR signaling. Mutant EGFR activates the PI3K-AKT and RAS-MEK-ERK pathways that are central to the growth, survival, and migration of cancer cells. The most common activating mutations are in-frame deletions in exon 19 and a missense mutation at codon 858 that leads to an arginine to leucine substitution (L858R). Lung cancers with EGFR mutations are highly sensitive to EGFR tyrosine kinase inhibitors (TKIs). Currently, genotype screening for mutations in EGFR is often used to select patients with stage IV NSCLC who will receive EGFR TKIs in the first-line setting. Current research is focused on improving the duration of response and finding effective ways to target the resistance mechanisms that develop at the time of progression. The most common resistance mechanism is the EGFR T790M mutation found in ~50% of resistant tumors, but several others, such as MET amplification, PIK3CA mutations, and transformation to SCLC, have also been described.

### ALK

An inversion in chromosome 2 results in a fusion gene combining EML4 and ALK, which encodes a fusion protein with constitutive activation of ALK resulting from ligand-independent dimerization. ALK signaling leads to cellular proliferation and growth through activation of RAS-MEK-ERK, JAK3-STAT3, and PI3K-AKT pathways. ALK translocations in NSCLC are associated with adenocarcinoma histology and signet ring cell morphology and with younger patient age and nonsmoking history. A large phase I study of crizotinib, which inhibits ALK and several other kinases, demonstrated an overall response rate of 57% and disease control rate of 90% in patients whose cancers harbor ALK translocations, leading to FDA approval in this indication. More potent ALK inhibitors and strategies targeting acquired resistance are currently being investigated.

### ROS1

Chromosomal rearrangements involving the ROS1 gene are identified in ~1.5% of lung adenocarcinomas. Similar to ALK-positive cancers, patients with ROS1-positive cancers tend to be younger, never-smokers, and with adenocarcinoma. Responses to crizotinib in patients whose cancers harbor ROS1 translocations, leading to FDA approval in this indication, have also been described.

### KRAS

KRAS is one of the most frequently mutated genes in lung cancer, occurring in ~25% of adenocarcinomas. KRAS mutations in lung cancer localize primarily to codons 12 and 13. KRAS mutations in lung cancer appear to be mutually exclusive with EGFR mutations and with ALK translocations and are more often associated with patients with a smoking history. KRAS mutations are associated with resistance to EGFR TKI therapy. Although no drugs are currently in development that directly target mutant KRAS, strategies using newer targeted therapies in combination with chemotherapy or other targeted therapies, for example, combined PI3K and MEK inhibition, are under clinical development.

### PIK3CA

Mutations in PIK3CA are clustered in two hotspot regions, exons 9 and 20, encoding the helical and kinase domains of the protein, respectively. These mutations result in heightened lipid kinase activity and constitutive PI3K-AKT signaling. There are multiple PI3K inhibitors in development, with specificity ranging from dual PI3K/MTOR inhibition to pan-PI3K to isoform-selective PI3K inhibitors. Preclinical data suggest that cancers harboring activating mutations in PIK3CA are among the most sensitive to single-agent PI3K pathway inhibitors, and clinical trials are underway in lung cancer examining this hypothesis.

### PTEN

The tumor suppressor gene PTEN encodes a lipid phosphatase that negatively regulates the PI3K-AKT pathway, and loss of PTEN leads to constitutive PI3K-AKT signaling. PTEN is inactivated in many cancers through various mechanisms. PTEN loss is more common in squamous cell cancers than adenocarcinomas. Clinical trials are assessing the efficacy of PI3K inhibitors in cancers with PTEN loss.

### FGFR1

FGFR1 is a potential target in squamous cell lung cancer. FGFR1 is a member of the FGFR family of RTKs. FGFR1 activation leads to downstream signaling via PI3K-AKT and RAS-MEK-MAPK. FGFR1 amplification is observed in ~20% of squamous cell cancer. In laboratory studies, inhibition of FGFR1 both in cancer cell lines and in mouse models harboring FGFR1 amplification leads to growth inhibition and apoptosis. Multiple FGFR inhibitors are in clinical development, many of which inhibit multiple tyrosine kinases in addition to FGFR1.

### PDGFRA

PDGFRA amplification is observed in lung squamous cell cancers. Inhibition of PDGFRA via shRNA knockdown or small molecule inhibition impairs cell survival and anchorage-independent growth, suggesting that PDGFRA may be a driver oncogene in a subset of cancers with PDGFRA amplification. Multiple PDGFR inhibitors are in clinical development. Similar to the FGFR1 inhibitors, many of these agents inhibit multiple kinases.

### DDR2

DDR2 is a RTK that binds collagen and promotes cell migration, proliferation, and survival. DDR2 mutations were identified in squamous cell lung cancers and cell lines. In cell lines with DDR2 mutations, suppression of DDR2 activity led to inhibition of proliferation. Ectopic expression of mutant DDR2 led to cellular transformation, although different mutations had varying levels of transformative capability. These results suggest that DDR2 mutations may be oncogenic and that cancers with these mutations may be sensitive to DDR2 kinase inhibitors.

### BRAF

BRAF mutations are found in 1%–3% of NSCLC. While V600E is the most common mutation, multiple other types of BRAF mutations have been reported in lung cancer, including G469A and D594G. While specific drugs such as vemurafenib are highly active in melanomas harboring BRAF V600E mutations, the activity of these drugs in BRAF mutant lung cancer remains to be assessed. Multiple trials assessing the activity of BRAF and MEK inhibitors are underway for cancers harboring BRAF mutations.

Targeted therapies are being developed in the metastatic, or stage IV, lung cancer setting. In metastatic lung cancer, surgery and radiation therapy are usually not indicated, and treatment centers on systemic therapy. Because these novel drugs show promise in the metastatic setting when used in cancers with specific genetic mutations, future directions may include implementing these treatment strategies in the adjuvant setting to improve cure rates.
References


