SnapShot: Non-Small Cell Lung Cancer

Cancer Cell

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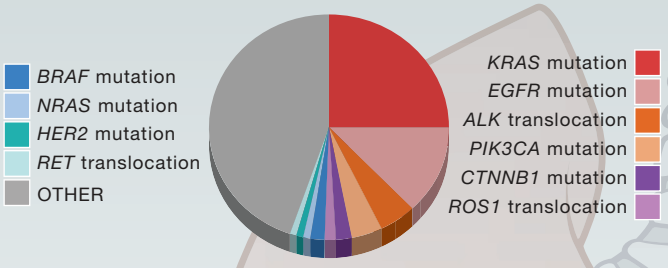
Stage	Est. %[a]	General treatment recommendations	5-year overall survival[b]	
			clinical stage	path. stage
IA	14%	Surgical resection	50%	73%
IB	10%	Surgical resection, can consider adjuvant chemotherapy in selected cases (e.g. tumor size > 4cm)	43%	58%
IIA	6%	Surgical resection followed by adjuvant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

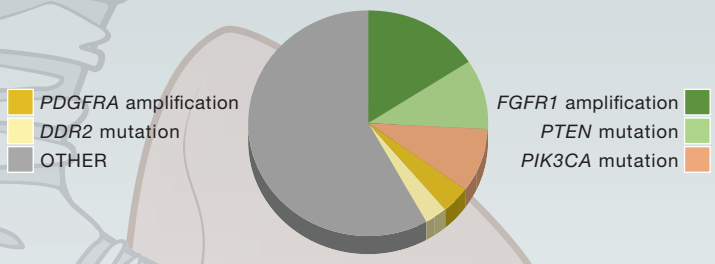
[a]Estimated from SEER validation set of proposed 7th edition IASLC staging.
[b]Overall survival is higher by pathologic stage because clinical stage, which is estimated by clinical characteristics based on CT scan, PET, etc., can underestimate the true stage.

Mutation spectrum in Adenocarcinoma

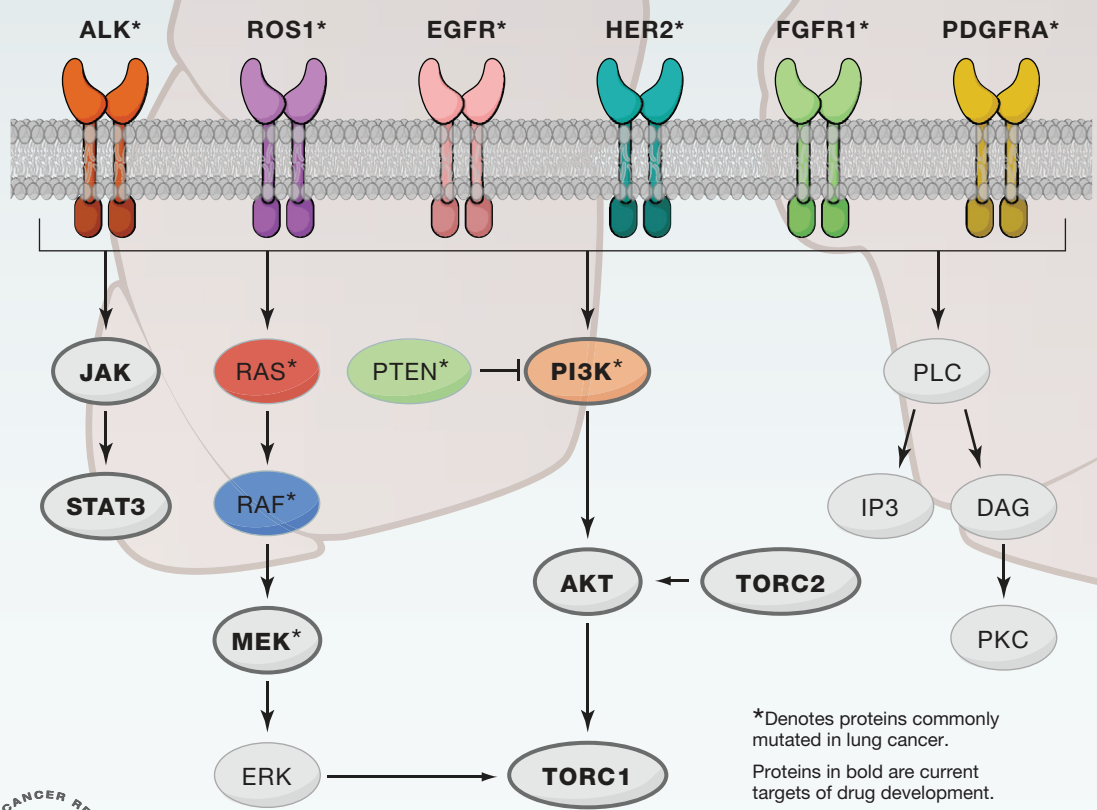


Mutations in *TP53* and *STK11/LKB1* are common occurrences, not included in pie chart due to high overlap with other mutations

Mutation spectrum in Squamous Cell Carcinoma



Mutations in *TP53* are a common occurrence, not included in pie chart due to high overlap with other mutations



*Denotes proteins commonly mutated in lung cancer.

Proteins in bold are current targets of drug development.

Target	Drug
EGFR	Erlotinib (approved)
	Gefitinib (approved)
	PF299804
	Afatinib (BIBW2992)
ALK	Crizotinib (approved)
	LDK378
	AP26113
	AF802
ROS1	Crizotinib
HER2	PF299804
	Afatinib (BIBW2992)
FGFR	BGJ398
	FP1039 (HGS1036)
	Ponatinib (AP24534)
FGFR/ PDGFRA/ VEGFR	BIBF1120
	Pazopanib
	Lenvatinib (E7080)
	Brivanib (BMS-582,664)
	Dovitinib (TKI258)
PDGFRA	MEDI575
	IMC-3G3
PI3K	BKM120
	PX-866
	GDC-0941
	SAR245408
PI3K/ MTOR	GDC-0980
	BEZ235
	SAR245409
MEK	MEK162
	GDC-0973
	GSK1120212
	MSC1936369B
STAT3	OPB51602
AKT	MK2206

See online version for legend and references.

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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 have been identified.

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.

PI3K

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.

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