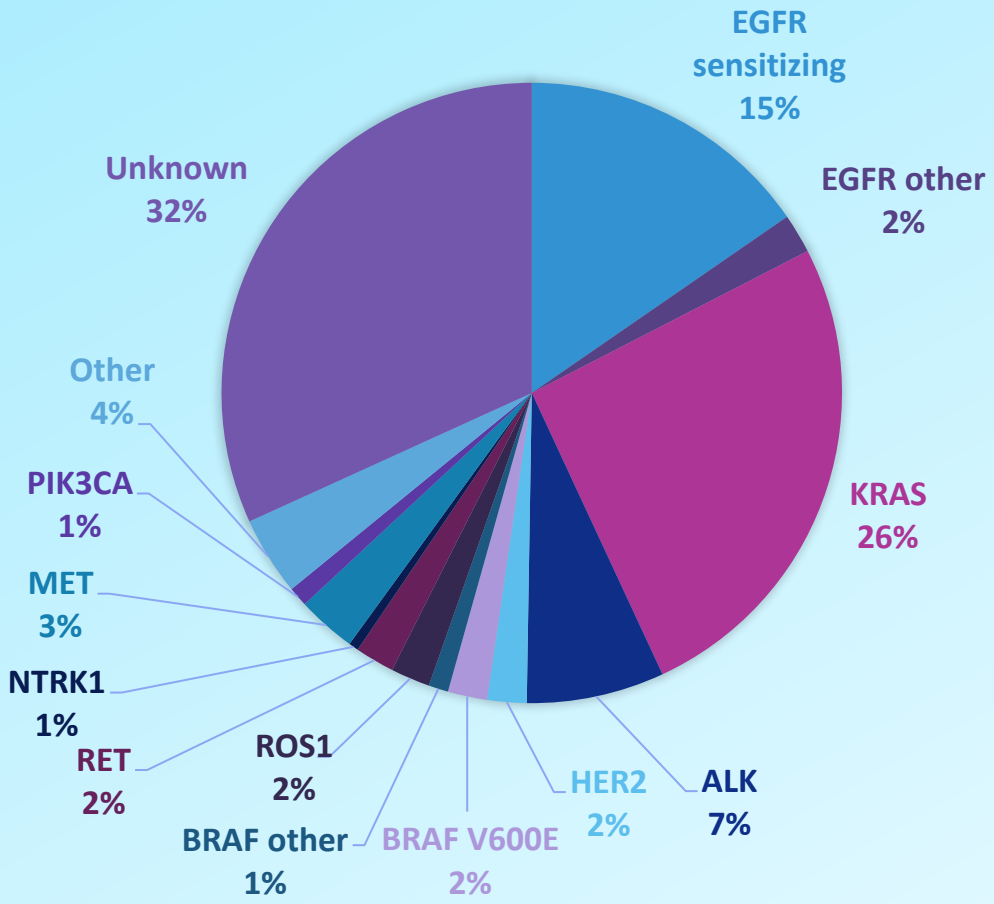
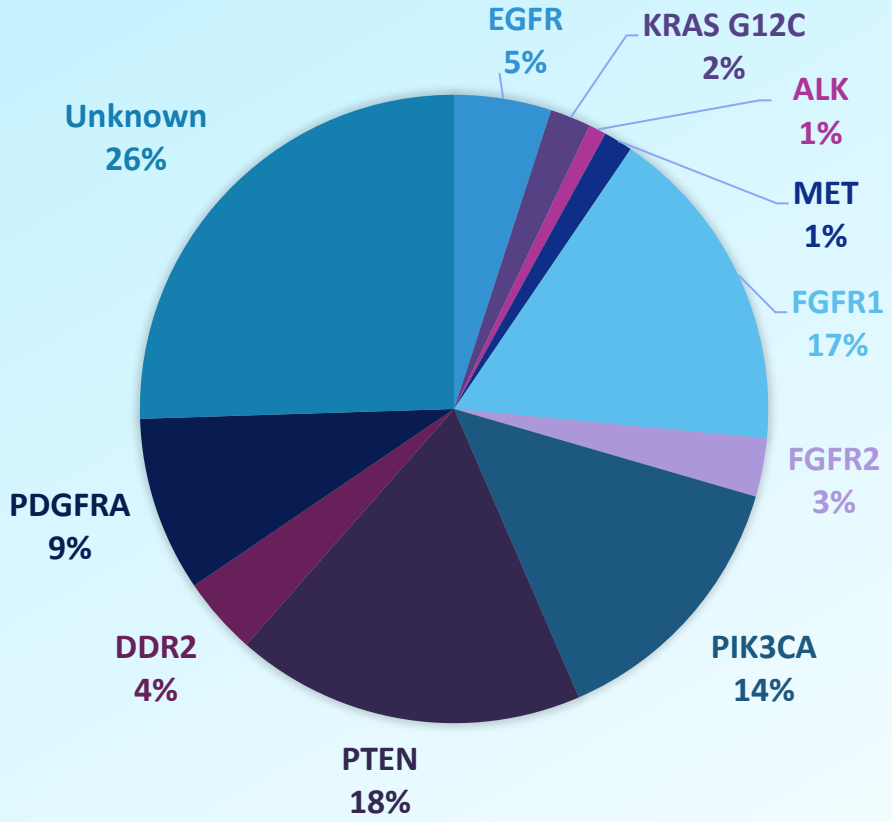
Oncogenic Driver Mutations in Advanced NSCLC

Adenocarcinoma



Squamous cell carcinoma



NSCLC, non-small cell lung cancer.

Adib E et al. *Genome Med*. 2022;14:39; Hirsch FR et al. *Lancet*. 2016;388:1012-1024.

NCCN Guideline Recommendations for Molecular Testing in Advanced and Metastatic NSCLC

Gene(s)	Potential Alterations	Recommendation	
		Adenocarcinoma	Squamous cell carcinoma
EGFR	Exon 19 deletion, exon 21 L8585R, exon 21 L861Q, exon 18 G719X, exon 20 S768I, exon 20 insertion	Category 1	Consider
KRAS	G12C mutation	Category 1	Consider
ALK	Rearrangements	Recommended	Consider
ROS1	Rearrangements	Recommended	Consider
BRAF	V600E	Recommended	Consider
NTRK1/2/3	Fusions	Recommended	Consider
MET	Exon 14 skipping mutation	Recommended	Consider
RET	Rearrangements	Recommended	Consider
ERBB2 **(HER2)**	Mutations	Recommended	Consider

All patients with advanced or metastatic NSCLC should also receive PD-L1 testing (category 1)

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023. Updated April 13, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450.

NCCN Guideline Recommendations for Molecular Testing in Advanced and Metastatic NSCLC

- Comprehensive NGS-based molecular testing strongly recommended in metastatic disease (plus PD-L1 testing in all patients)
  - Goal is to test for all recommended biomarkers, with the possibility of detecting rarer alterations that have FDA approved therapies and/or identifying candidates for clinical trials
  - Plasma-based testing can be used when biopsy tissue is limited
- Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable (eg, rapid PCR-based testing followed by NGS)
- Important to understand the spectrum of alterations included in each specific test
- Additional testing methodologies that may be used include FISH, IHC, or Sanger sequencing; important to understand strengths and weaknesses of each methodology
- Smoking history should not be a factor in making decisions about molecular testing

Broad NGS-based Testing Caveats

- Long turnaround times
- May be more challenging to interpret because more likely to find novel mutations and/or variants of unknown significance
- May detect but does not provide definitive information on inherited cancer syndromes

Single or Small Gene Set Testing Caveats

- May miss potentially clinically relevant mutations outside the sequence(s) covered
- Sequential testing may exhaust tissue before all biomarkers are tested for, particularly given need to test for PD-L1 as well

NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

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