Update in Targeted Therapy for Non-Small Cell Lung Cancer

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Lung Cancer: Overview

- Second most common cancer in men and women – 235,760 new cases est.
- Leading cause of cancer deaths – 131,880 est.
  - Accounts for more deaths than breast, colon and prostate cancer combined
- Research is underfunded, but improving
- Unfavorable stage distribution at diagnosis – usually advanced
  - Screening may allow earlier diagnosis when potentially curable
- Types of lung cancer:
  - Non-small cell lung cancer (NSCLC): 87%
  - Small cell lung cancer (SCLC): 13%

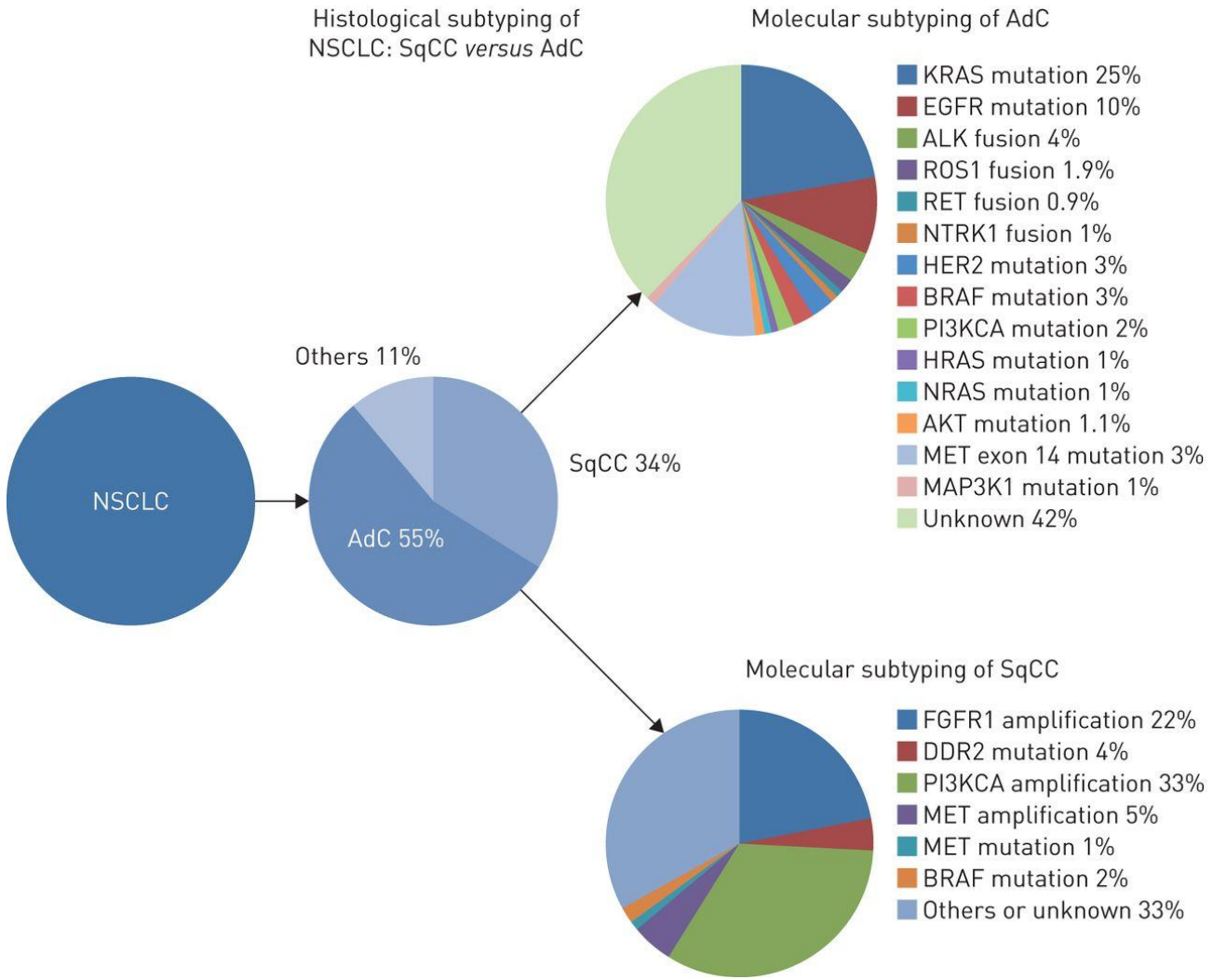
Lung Cancer: Facts

- Lung cancer is a largely preventable illness
  - Eliminating smoking could prevent ~150,000 cases yearly in the U.S.

- An increasing percentage of those diagnosed with lung cancer are never-smokers (15-20%)

- Lung cancer in non-smokers often has different biology and clinical behavior

Evolution of NSCLC Classification



Lukas Bubendorf et al. Eur Respir Rev 2017;26:170007

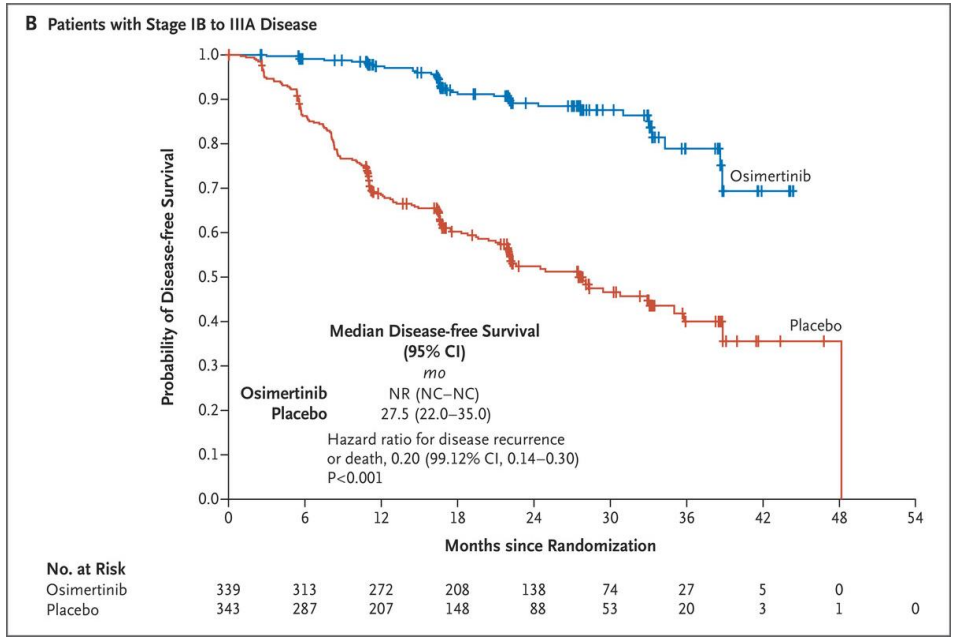
EGFR-Mutated NSCLC:

- Most common driver mutation in never/light-smokers with NSCLC
  - Common actionable mutations: Exon 19 del, L858R (exon 21)
  - Less common actionable mutations: G719X, S768I, L861Q
  - Exon 20 insertions: Previously resistant, now actionable

- Tyrosine kinase inhibitors commercially available:
  - First-generation: Gefitinib, erlotinib
  - Second-generation: Afatinib, dacomitinib
  - Third-generation: Osimertinib – first-line for advanced disease (FLAURA trial 2018)

Adjuvant Therapy for mEGFR+ NSCLC:

- ADAURA Trial – RP3 trial of osimertinib in <u>resected</u> stage IB – IIIA
  - Must have Ex19del or L858R
  - Osimertinib x 3 years after standard adjuvant treatment (chemo+/-XRT)



Y Wu et al. N Engl J Med 2020;383:1711-1723.

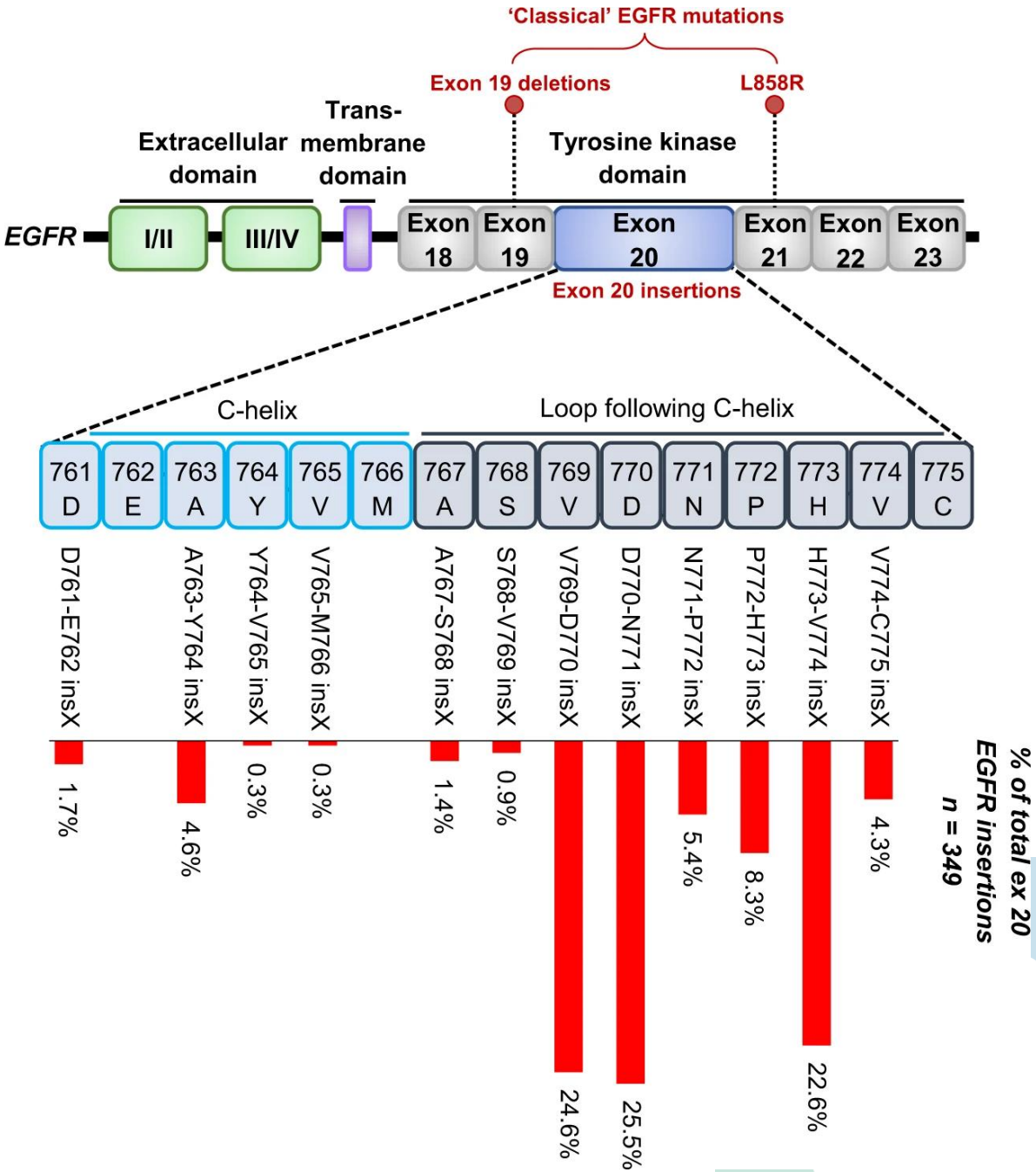
<u>Hazard Ratios for DFS:</u>

Stage IB	0.39
Stage II	0.17
Stage IIIA	0.12

Osimertinib is FDA-approved for adjuvant treatment of stage IB-IIIA NSCLC with EGFR ex19del or L858R after resection.

EGFR exon 20 insertion:

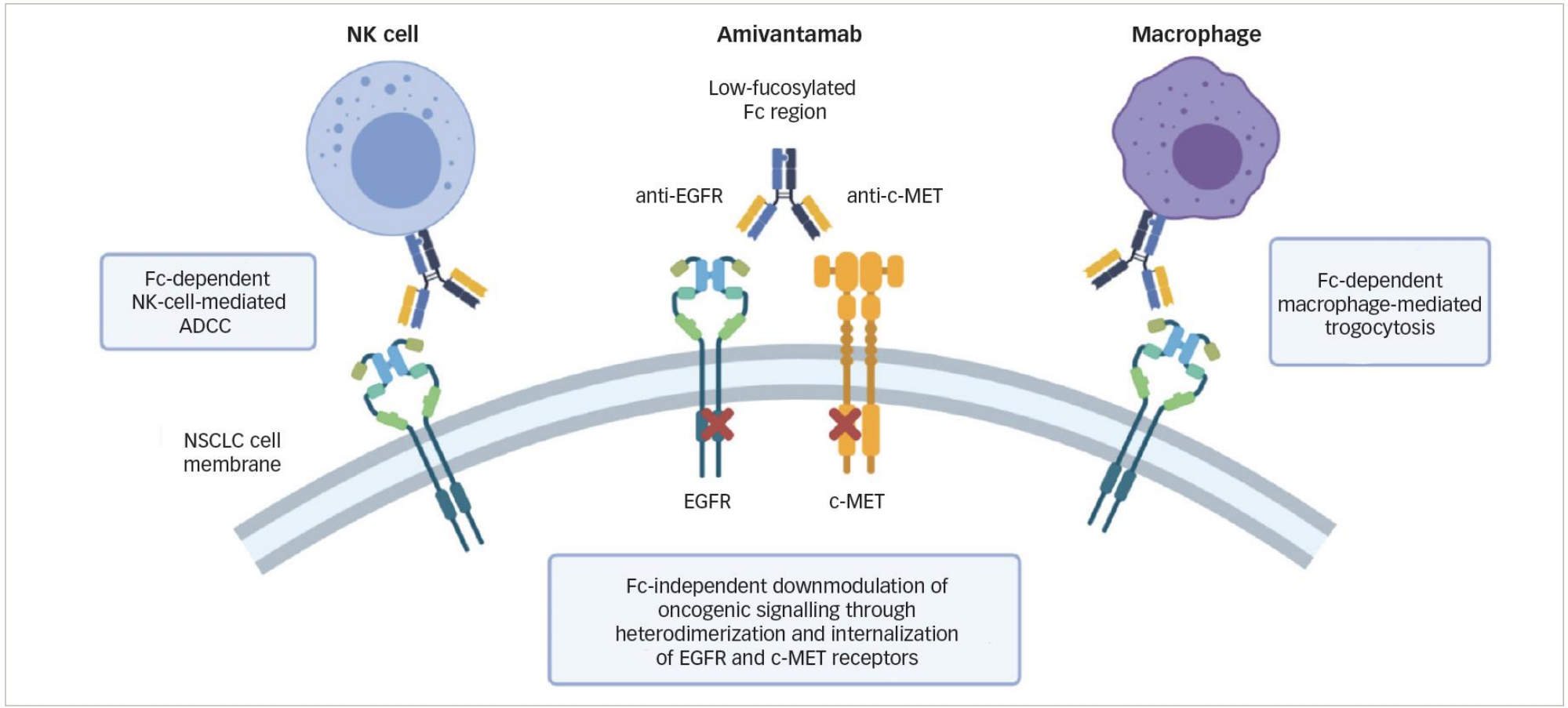
- Activating mutations that are usually resistant to TKIs
- Represent 4-10% of EGFR muts
- Conformation of kinase domain variably resistant to EGFR TKIs
- Development of new compounds to target EGFR ex20ins mutations
  - Amivantimab
  - Mobocertinib



Vyse et al. Sig Transduct Target Ther. 2019; 4, 5.

EGFR exon 20 insertion:

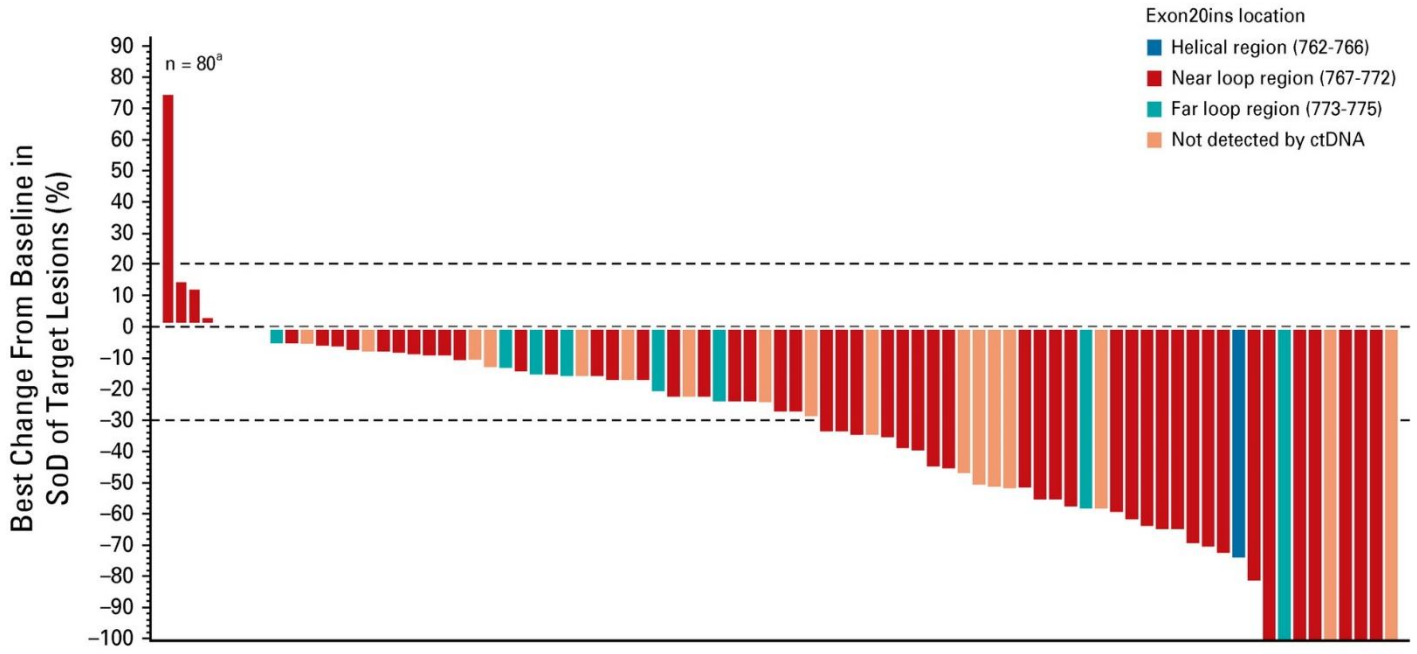
- Amivantamab:
- EGFR/c-MET bispecific antibody



https://doi.org/10.17925/OHR.2021.17.1.42

EGFR exon 20 insertion:

- CHRYSALIS Trial of Amivantamab:
- Phase I dose-escalation/dose-expansion study
- Previously-treated NSCLC (post-platinum)



Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

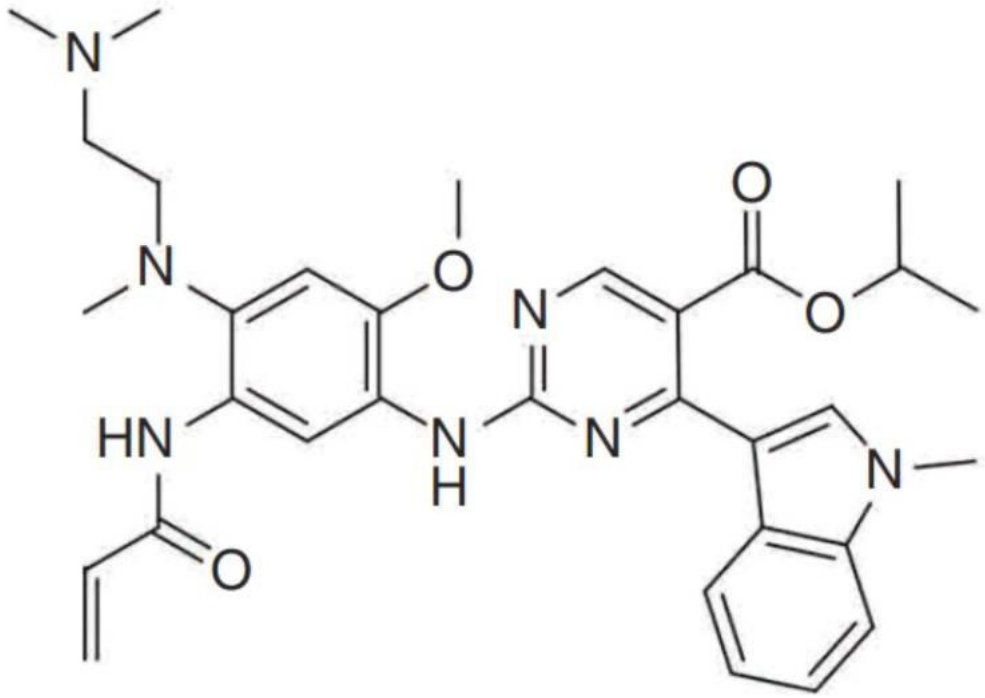
mDOR: 11.1 months
mPFS: 8.3 months
mOS: 22.8 months

Amivantamab granted accelerated approval in May 2021 for previously-treated EGFR ex20ins+ NSCLC after platinum-based chemotherapy.

Park et al. *J Clin Oncol*. 2021;39(30):3391-3402

EGFR exon 20 insertion:

- Mobocertinib (TAK-788):
- Covalent, irreversible inhibitor designed to selectively target the ex20ins mutant forms of both EGFR and HER2 kinases over wild-type EGFR
- Broadly active across different EGFR ex20ins mutations

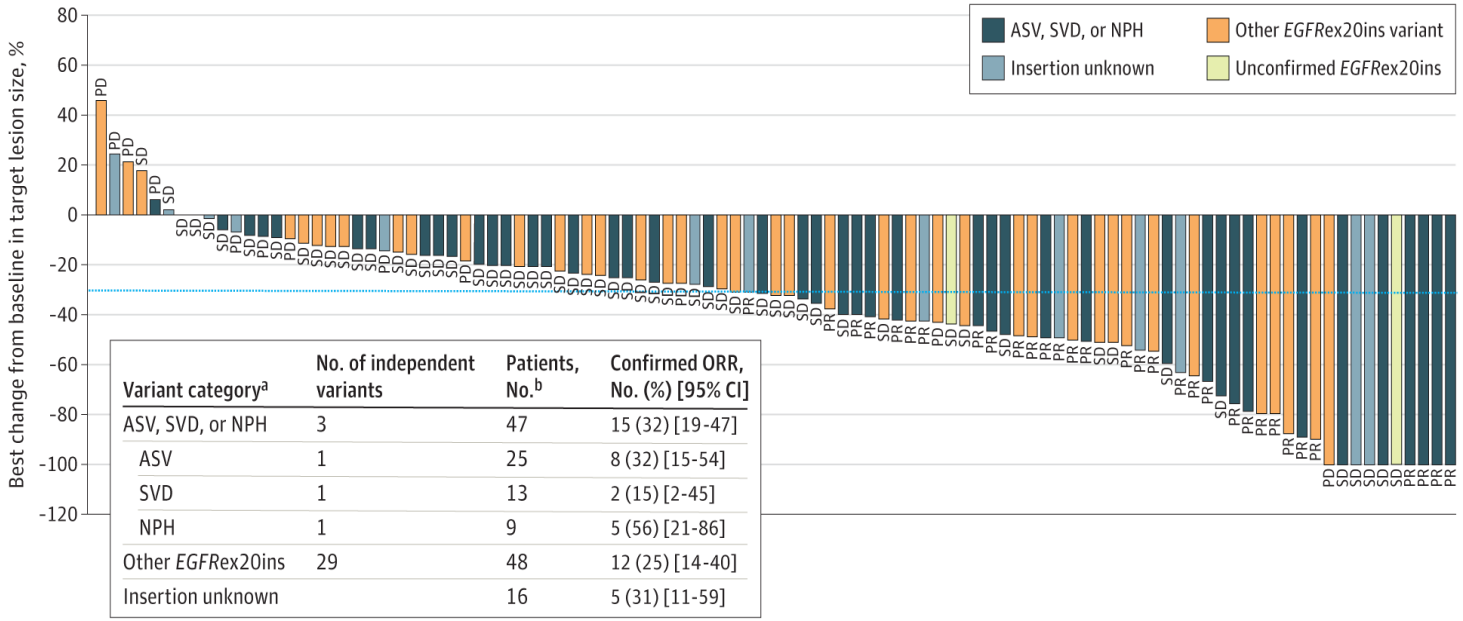


Zhang et al. *Lung Cancer (Auckl)*. 2021;12:61-65.

EGFR exon 20 insertion:

- EXCLAIM Trial of Mobocertinib:
- Phase I/II open-label, non-randomized
- Previously-treated NSCLC (post-platinum)

Outcome	No. (%) EXCLAIM cohort (n = 96)
IRC-assessed confirmed objective response[b]	
Patients, No. (%) [95% CI]	24 (25) [17-35]
Complete response	0
Partial response	24 (25)
Stable disease[c]	49 (51)
Not evaluable	10 (10)
Confirmed disease control rate, No. (%) [95% CI][d]	73 (76) [66-84]



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

mDOR: 17.5 months
mPFS: 7.3 months
mOS: 24.0 months

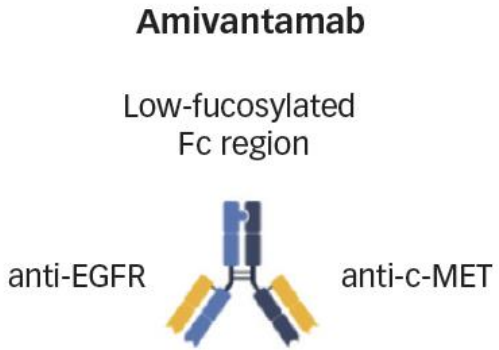
Mobocertinib granted accelerated approval in September 2021 for previously-treated EGFR ex20ins+ NSCLC after platinum-based chemotherapy.

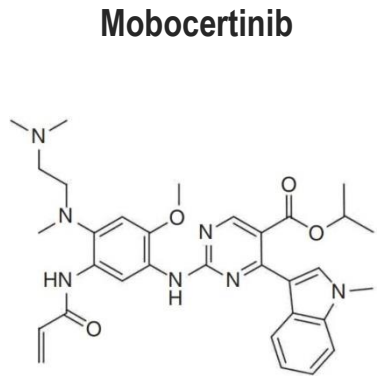
Zhou et al. *JAMA Oncol*. Oct 2021;e214761.

EGFR exon 20 insertion:

Amivantamab vs. Mobocertinib:

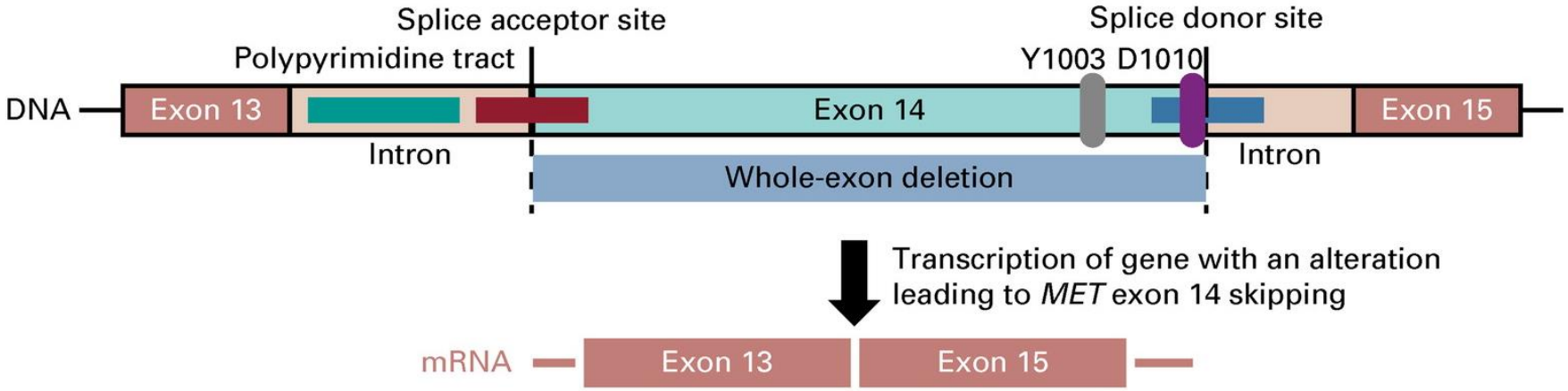
- No head-to-head data
- Similar PFS and OS
- Higher ORR with amivantamab
- Longer DOR with mobocertinib
- Fewer grade 3-4 toxicities with amivantamab
- Neither has significant CNS activity
- Oral administration of mobocertinib
- Ongoing studies in first-line therapy for ex20ins+ NSCLC:
  - Chemotherapy +/- amivantamab (PAPILLON)
  - Chemotherapy vs. mobocertinib (EXCLAIM-2)





MET exon 14 skipping mutation:

- Represents 3-4% of NSCLC
- More common in adenosquamous and pulmonary sarcomatoid carcinoma
- More likely in older, female, and never-smokers
- MET exon 14 contains a key regulatory region for receptor signaling
- Loss of exon 14 in MET gene leads to overactive protein and cell proliferation



METex14 targeted therapy:

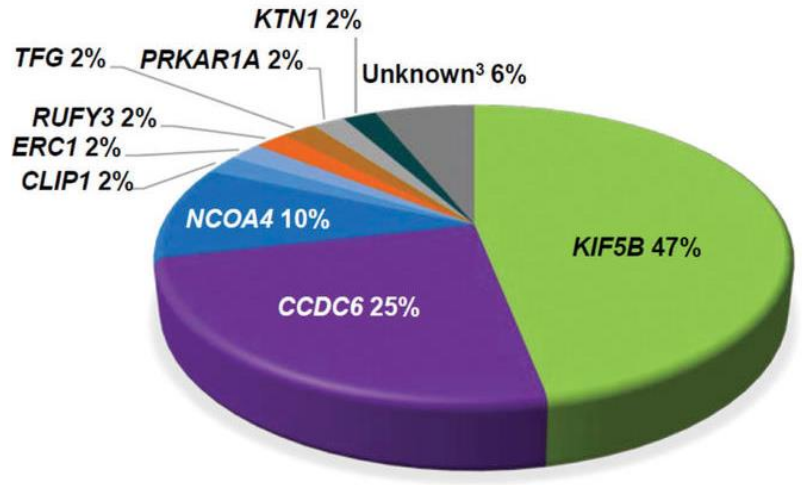
Drug		ORR (%)	mDOR (mos.)	mPFS (mos.)	Grade 3-4 Toxicities (%)	Ref.
Capmatinib	Treatment-Naive	68	12.6	12.4	67	Wolf et al.
	Previously-Treated	41	9.7	5.4		
Tepotinib	Treatment-Naive	44	10.8	8.5	27	Paik et al.
	Previously-Treated	48	11.1			

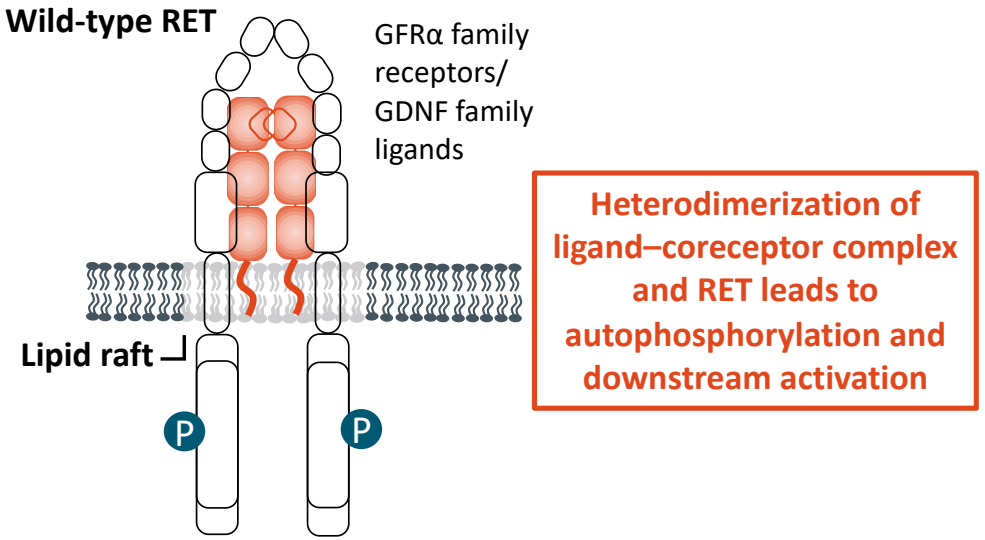
- Capmatinib and tepotinib are both FDA-approved for NSCLC with METex14
- NCCN recommends first-line therapy with either agent
- Similar response rates and progression-free survival
- Both agents have evidence of CNS activity
- Toxicity profile may favor tepotinib, but discontinuation rates were similar (~10%)

Wolf J, et al. N Engl J Med. 2020;383(10):944-957.
Paik PK, et al. N Engl J Med. 2020;383(10):931-943.

RET fusion mutations:

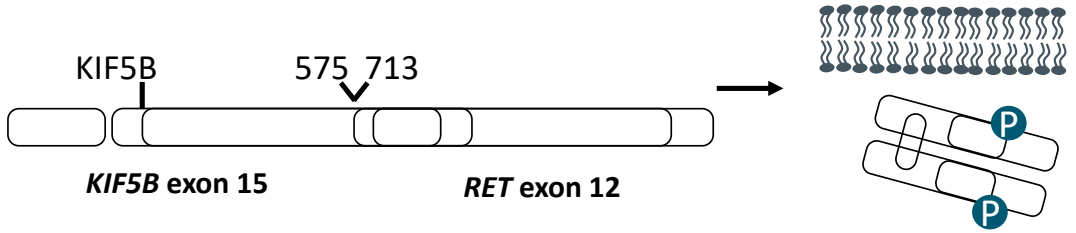
- *RET* gene fusions give rise to chimeric, cytosolic proteins with constitutively active RET kinase domain
- Found in 1-2% of NSCLC (non-squamous)
- More common in young, never-smokers





Heterodimerization of ligand–coreceptor complex and RET leads to autophosphorylation and downstream activation

Most Common *RET* Translocation in Lung Adenocarcinoma: KIF5B-RET



Activation of downstream pathways:

- MAPK, PI3K, JAK-STAT, PKA, PKC
- Cell proliferation signals

Drilon AE, et al. J Clin Oncol. 2018;36:(suppl; abs 102).
Gubens et al, http:/clinicaloptions.com

RET fusion targeted therapy:

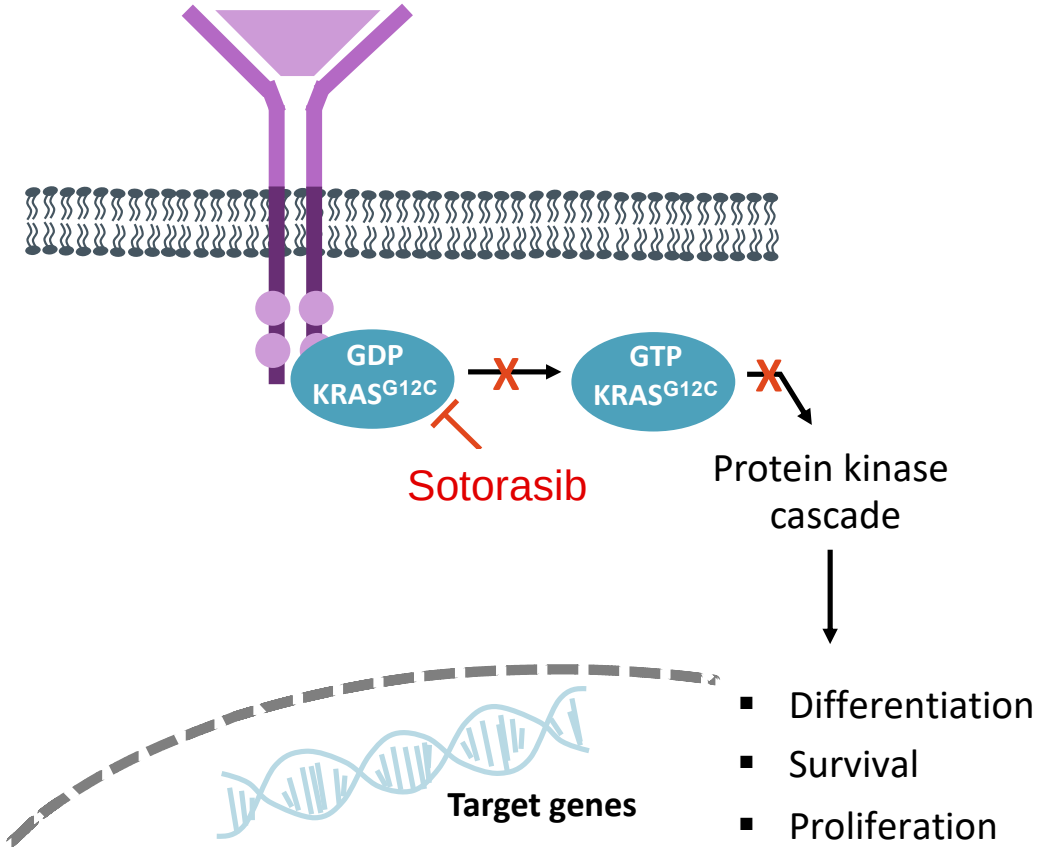
Drug		ORR (%)	mDOR (mos.)	mPFS (mos.)	Grade 3-4 Toxicities (%)	Ref.
Selpercatinib	Treatment-Naive	85	NR	NR	28	Drilon et al.
	Previously-Treated	64	17.5	16.5		
Pralsetinib	Treatment-Naive	70	9.0	9.1	48	Gainor et al.
	Previously-Treated	61	NR	17.1		

- Selpercatinib and pralsetinib are both FDA-approved for NSCLC with RET fusion
- NCCN recommends first-line therapy with either agent
- Similar response rates and toxicity profile
- Both agents cross blood-brain barrier and have evidence of CNS activity

Drilon A, et al. *N Engl J Med*. 2020;383(9):813-824.
Gainor, et al. *Lancet Oncol*. 2021;22(7):959-969.

KRAS G12C:

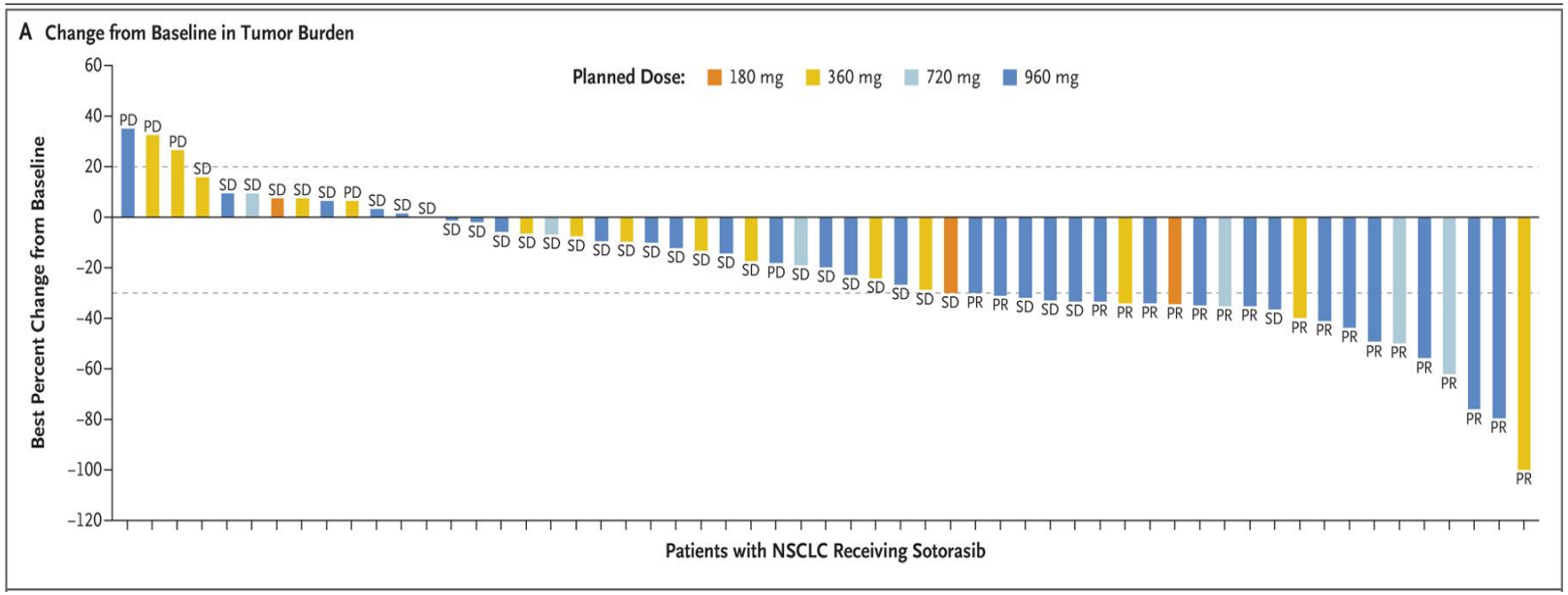
- KRAS mutations are the most common mutations in NSCLC
  - Found in ~25% non-squamous NSCLC
  - Rare in squamous cell carcinoma
  - KRAS G12C ~13%
- Initial attempts at targeting KRAS directly were disappointing
  - Long thought to be “undruggable”
  - High affinity for GTP
  - Inaccessible binding sites
- Sotorasib is an irreversible KRAS inhibitor
  - Binds to inactive conformation of KRAS G12C
  - Prevents cycling to active form
  - Blocks downstream signaling



Gubens et al, http:/clinicaloptions.com

KRAS G12C targeted therapy with sotorasib:

- CodeBreaK100 Trial – Phase 1/2 dose-escalation and expansion study
  - Advanced solid tumors with KRAS G12C
  - Most common adverse events: diarrhea and nausea
  - Recommended phase 2 dose: 960 mg daily



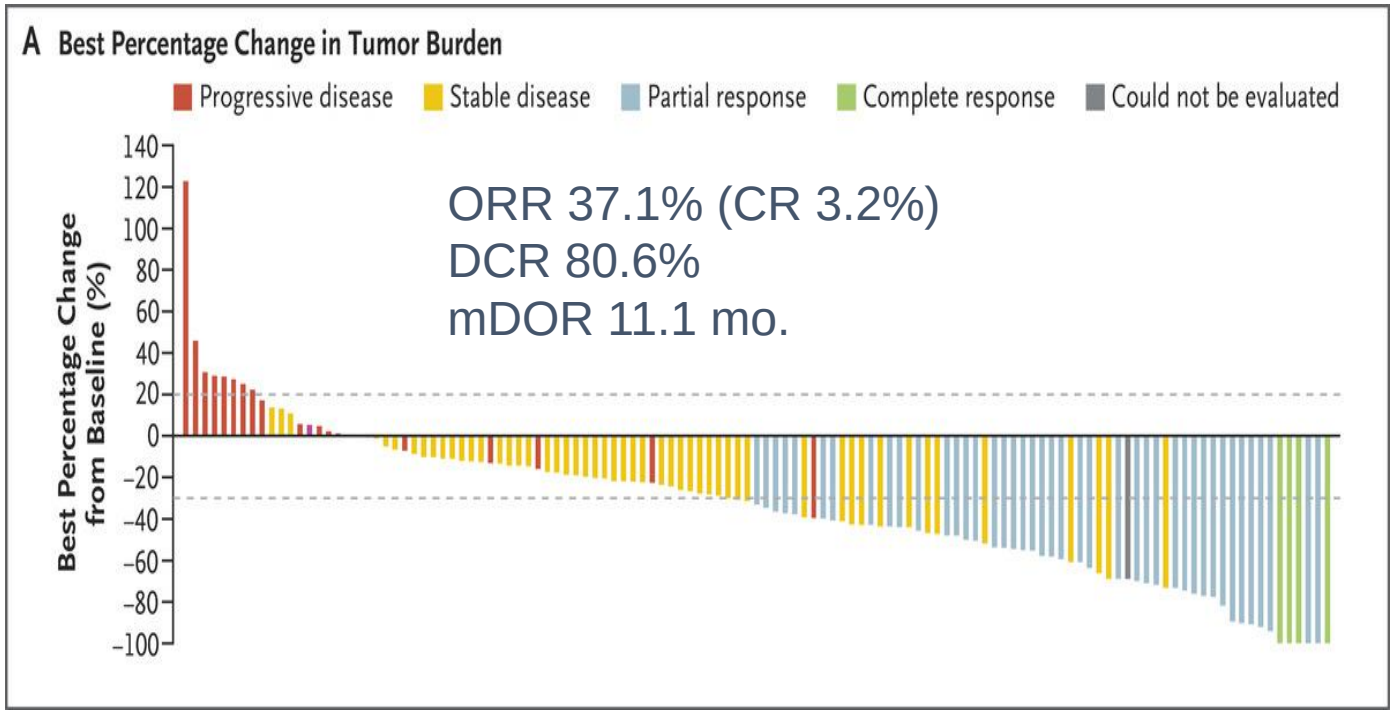
Phase I results for NSCLC:

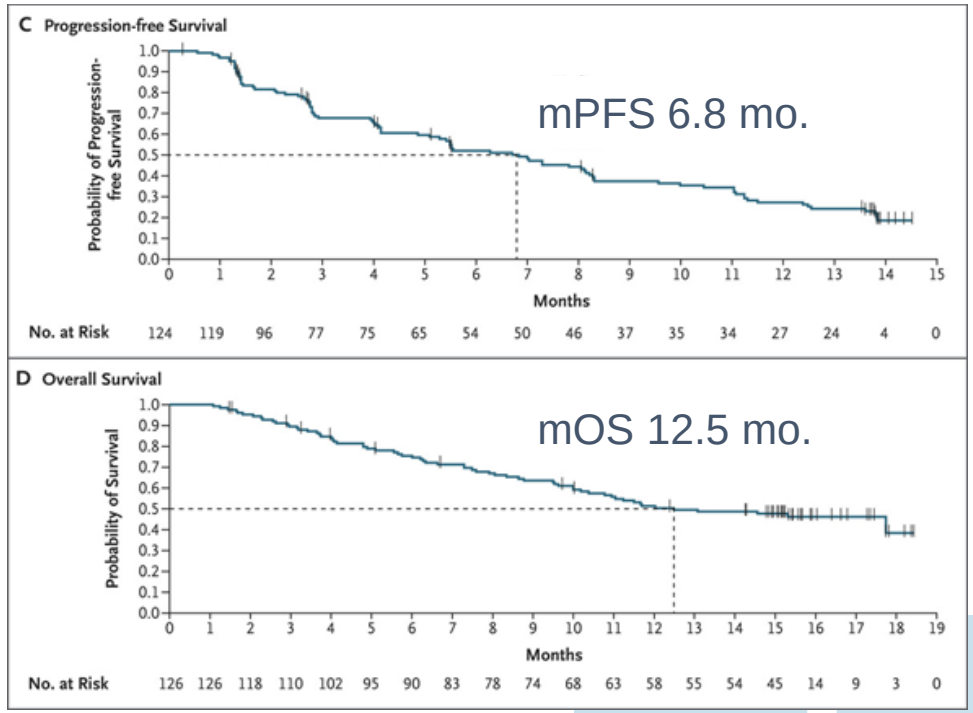
- ORR 32.2%
- DCR 88.1%
- mPFS 6.3 months
- Evidence of CNS activity

Hong DS, et al. *N Engl J Med*. 2020;383(13):1207-1217.

Sotorasib in Advanced KRAS G12C+ NSCLC:

CodeBreaK100 Trial – Phase 2 NSCLC cohort (previously-treated):





- Treatment-related grade 3-4 toxicity was 20.6%
  - Diarrhea, nausea, LFT abnormalities most common AE, rare ILD/pneumonitis
- FDA-approved for previously-treated NSCLC with KRAS G12C mutation.

Skoulidis F, et al. *N Engl J Med*. 2021;384(25):2371-2381.

Conclusions:

- NSCLC is not one disease, but many diseases defined by molecular subtypes
- Targeted therapy improves outcomes and is often the first-line of therapy for patients with actionable mutation
- Molecular profiling is key to identifying actionable mutations in patients with advanced disease and in adjuvant setting
- Molecular profiling should be performed at the time of diagnosis to help guide therapy
  - Tissue testing should be performed whenever feasible
  - Plasma-based testing may complement tissue testing and should also be considered at the time of diagnosis of advanced disease