Targeted Therapy in Lung Cancer: KRAS G12C, BRAF, RET

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Masters Lecture Series

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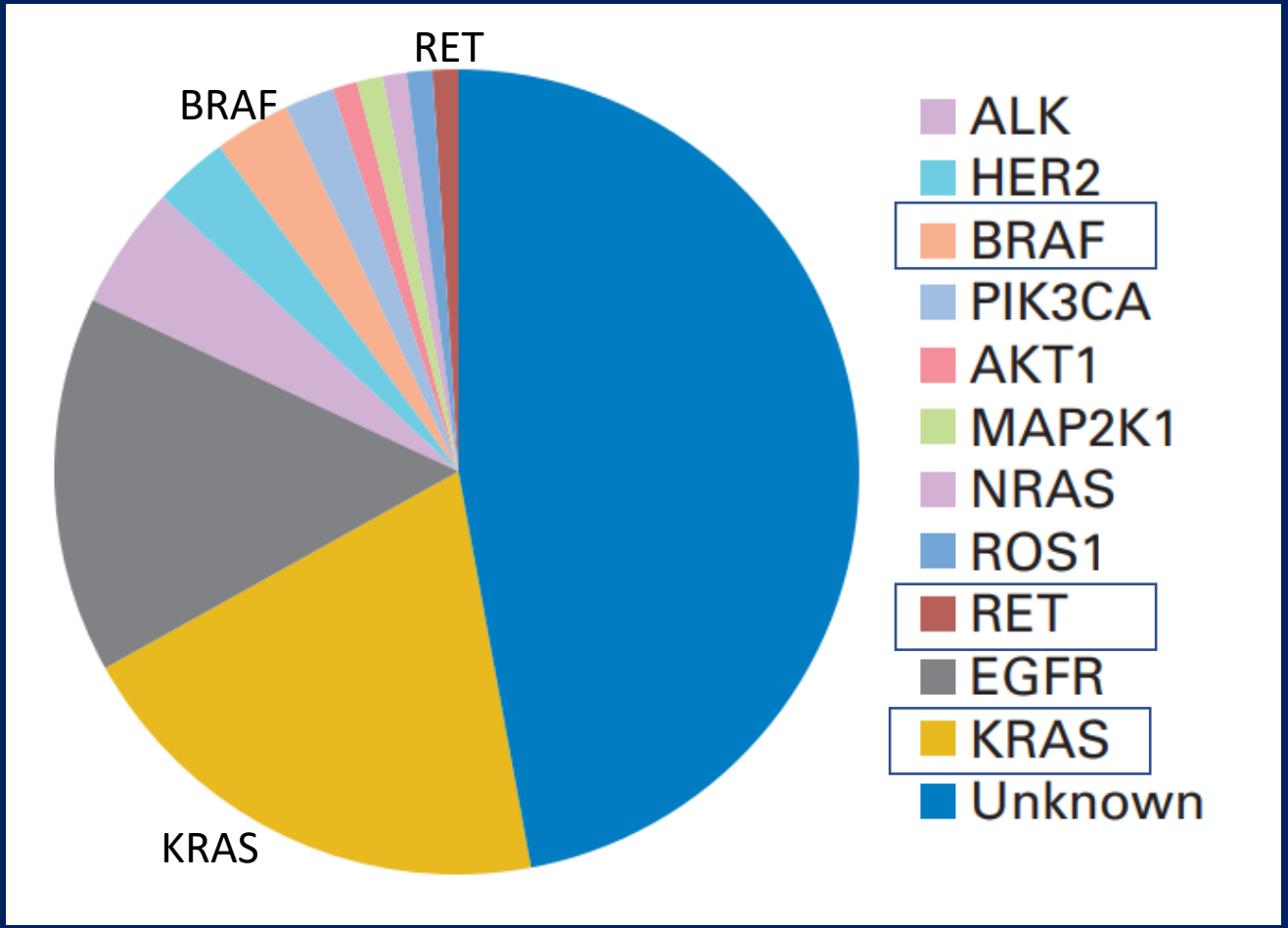
Agenda

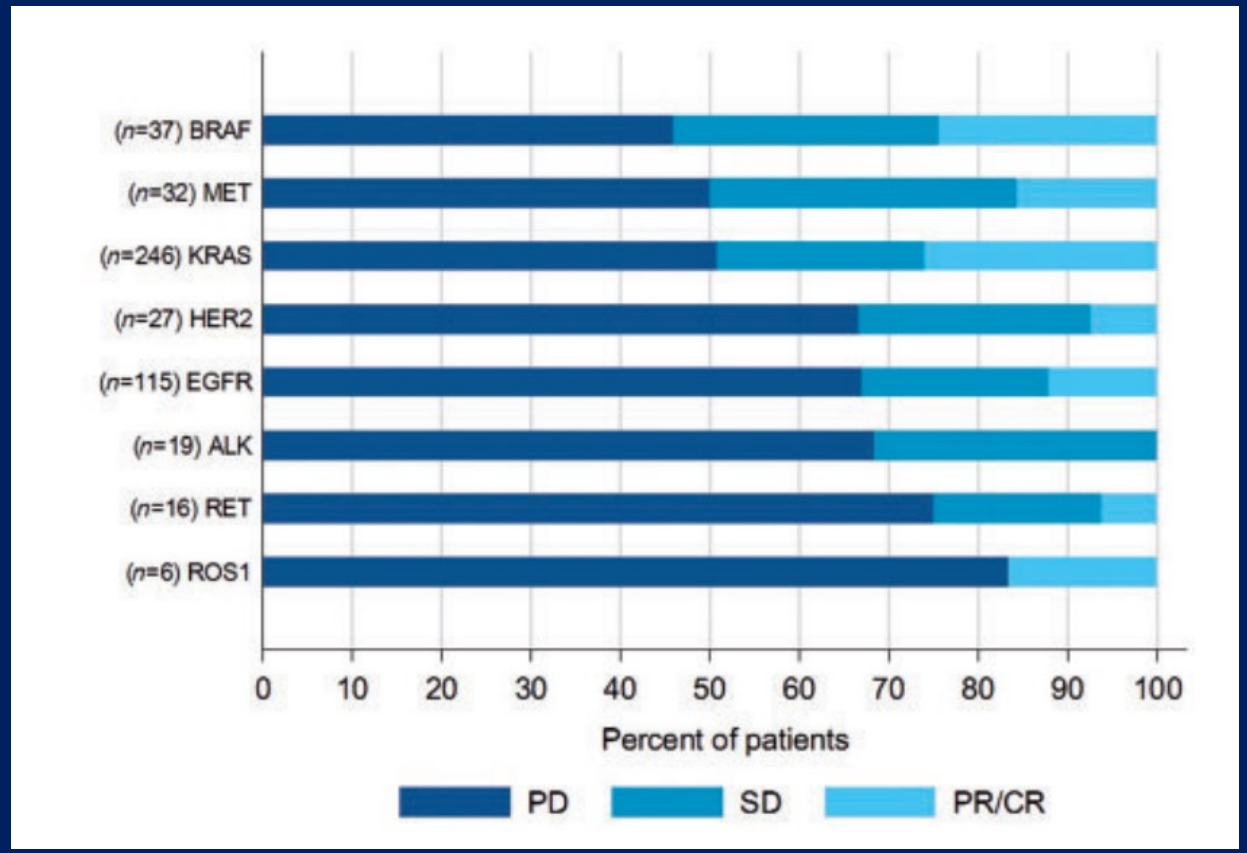
- Prevalence of genomic alterations in lung adenocarcinoma
- Targeted therapies for *KRAS* G12C
- Targeted therapies for *BRAF*
- Targeted therapies for *RET*

Molecular alterations in lung adenocarcinoma

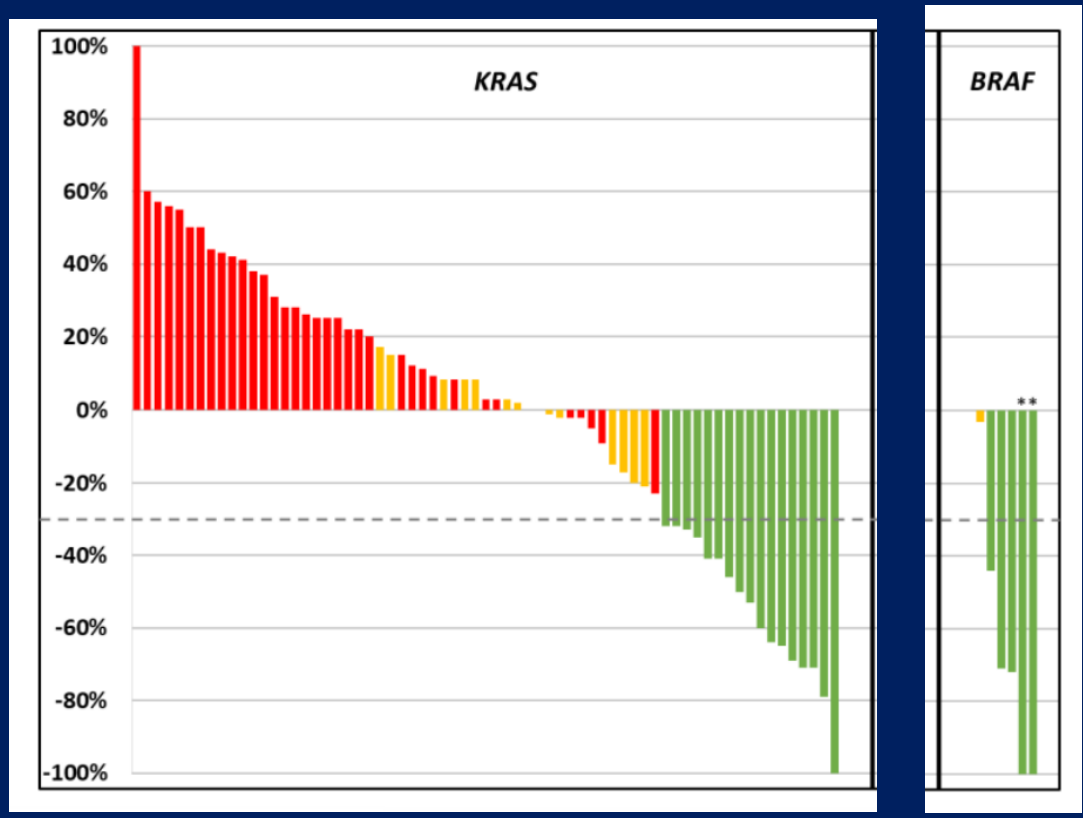


Li. JCO 2013

Differential responses to checkpoint inhibitor monotherapy by oncogenic driver



Mazieres et al. Ann Oncol 2019

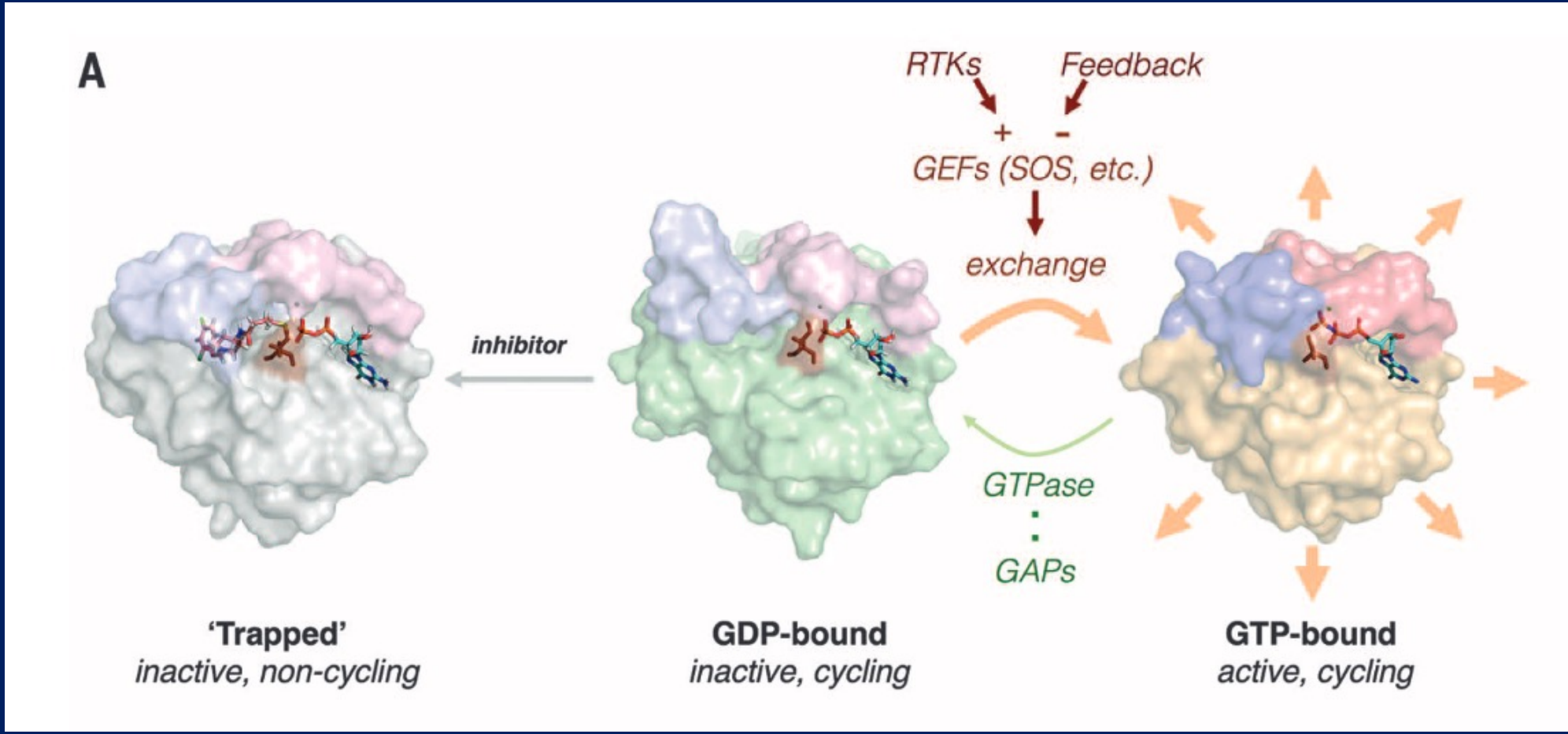


Negrao et al. JITC 2021

Agenda

- Prevalence of genomic alterations in lung adenocarcinoma
- Targeted therapies for *KRAS* G12C
- Targeted therapies for *BRAF*
- Targeted therapies for *RET*

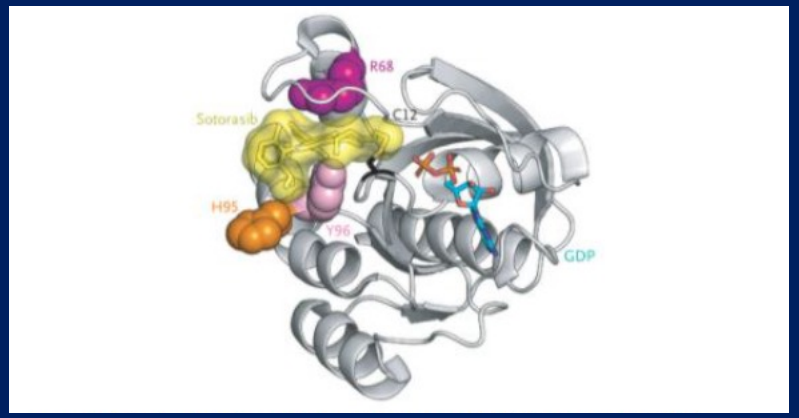
The Biology of *KRAS* G12C Inhibition



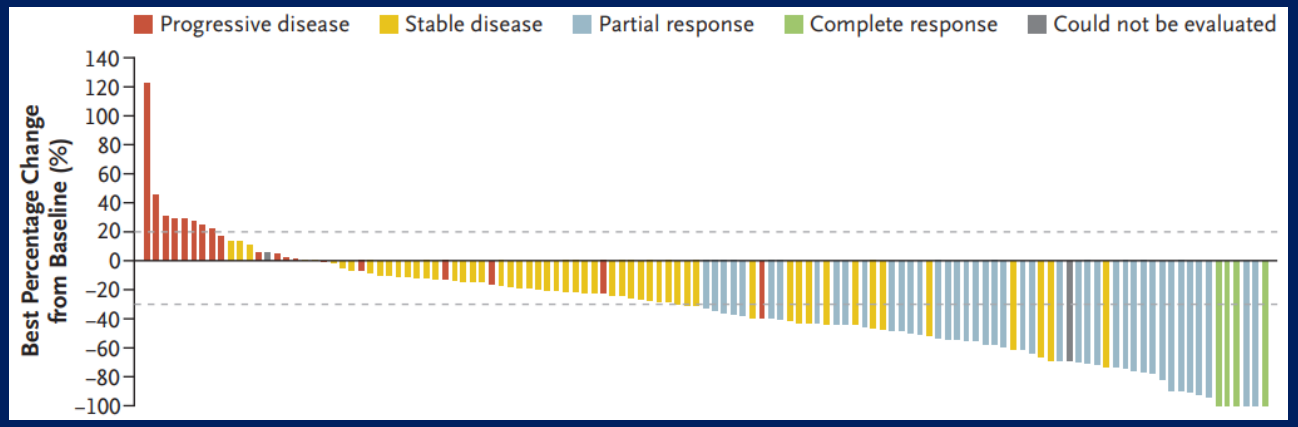
Lito et al. Science 2016, Ostrem et al. Nature 2013

Sotorasib and Adagrasib are novel inhibitors of *KRAS* G12C

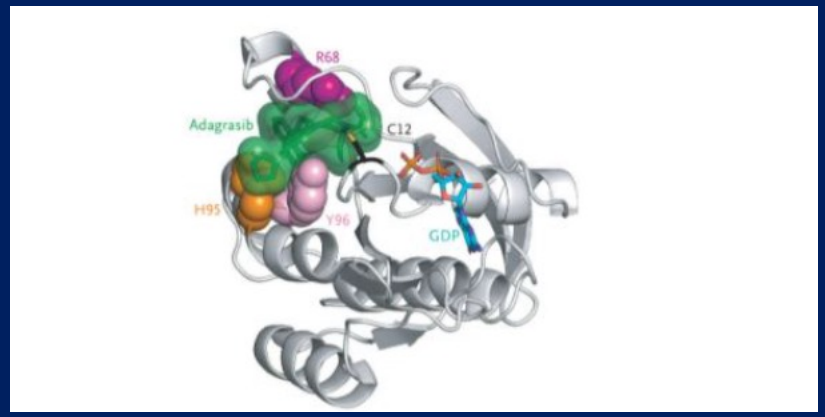
Sotorasib (AMG 510)



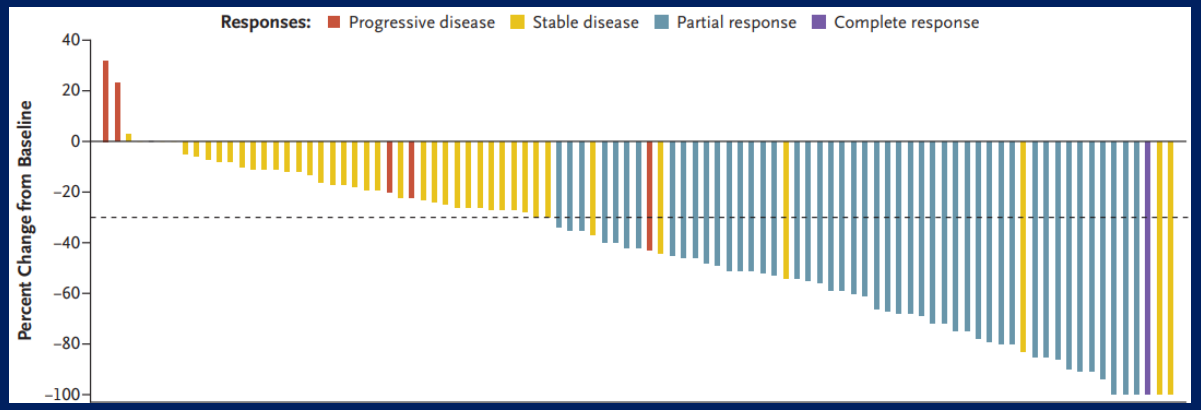
ORR 37.1%, mDoR 11.1m, mPFS 6.8m, mOS 12.5m



Adagrasib (MRTX 849)



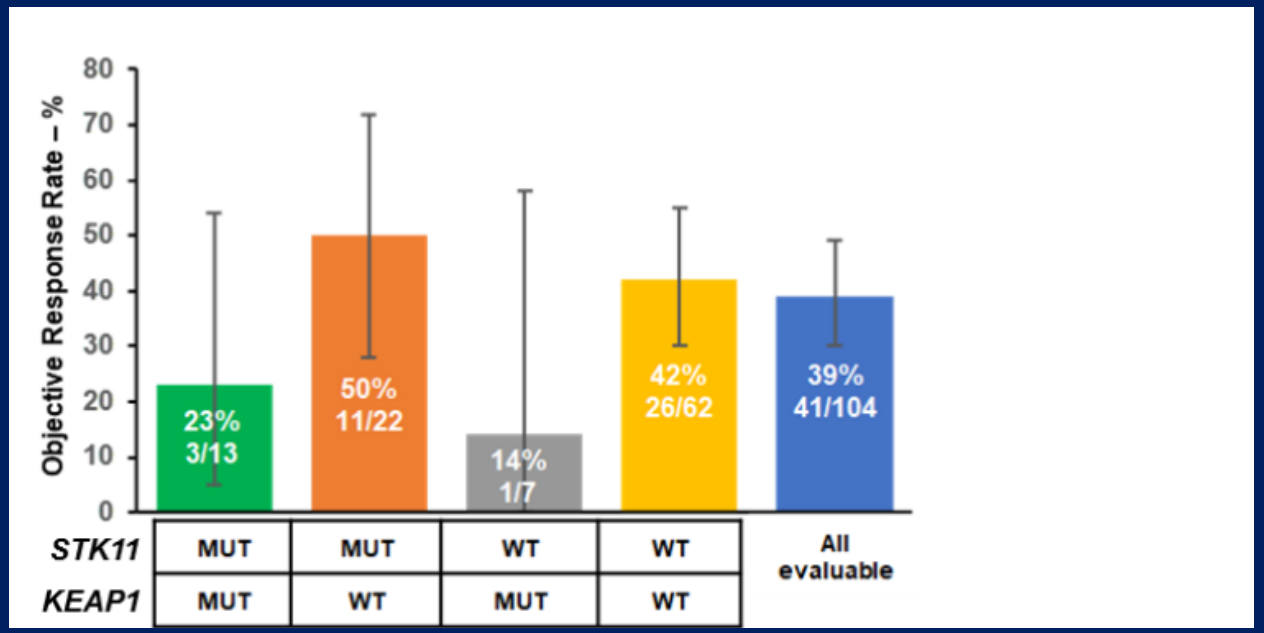
ORR 42.0%, mDOR 8.5 mo, mPFS 6.5m, mOS 12.6m



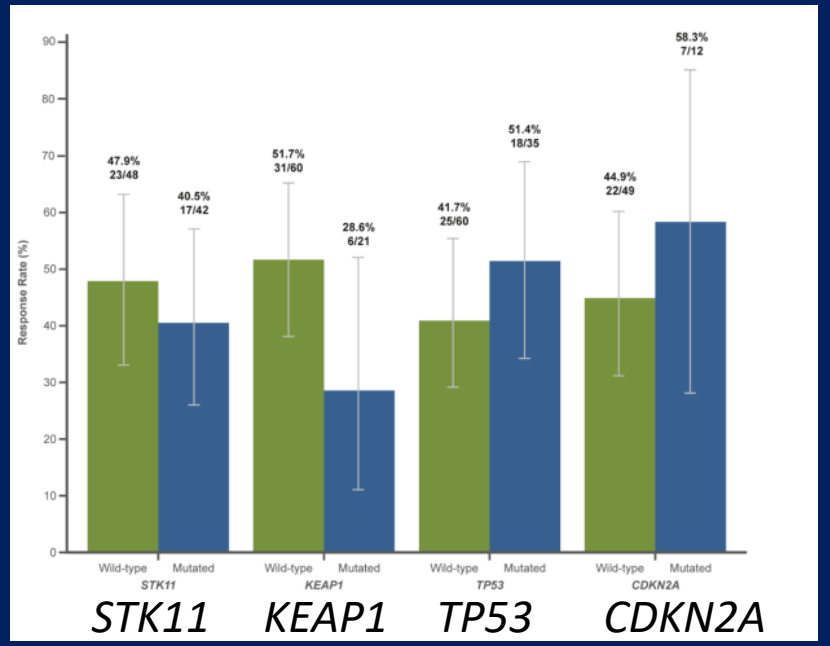
Skoulidis F et al. NEJM 2021; Janne et al. NEJM 2022; Awad et al. NEJM 2021

Impact of *KRAS* co-mutations on clinical efficacy

Sotorasib (AMG 510)



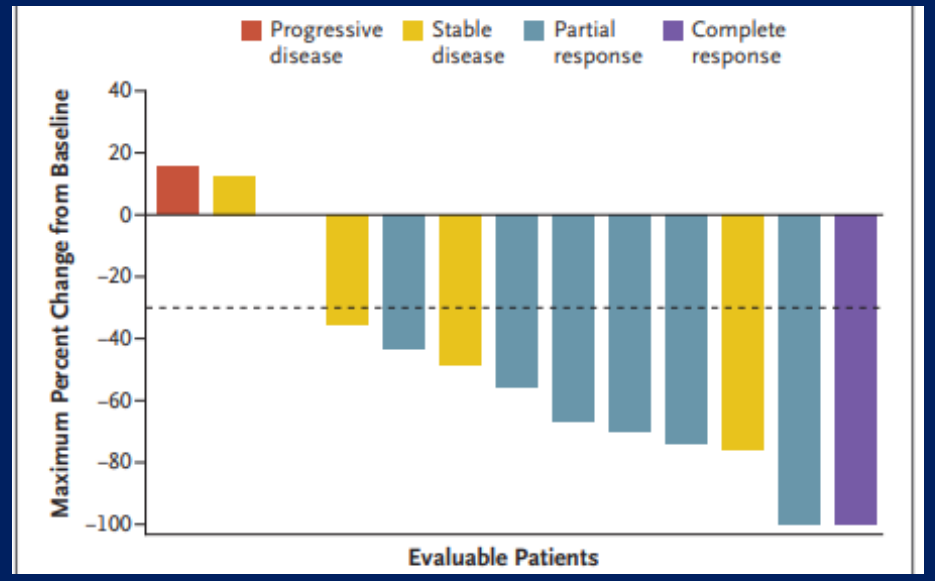
Adagrasib (MRTX 849)



Skoulidis F et al. ASCO Meeting 2021; Janne et al. NEJM 2022

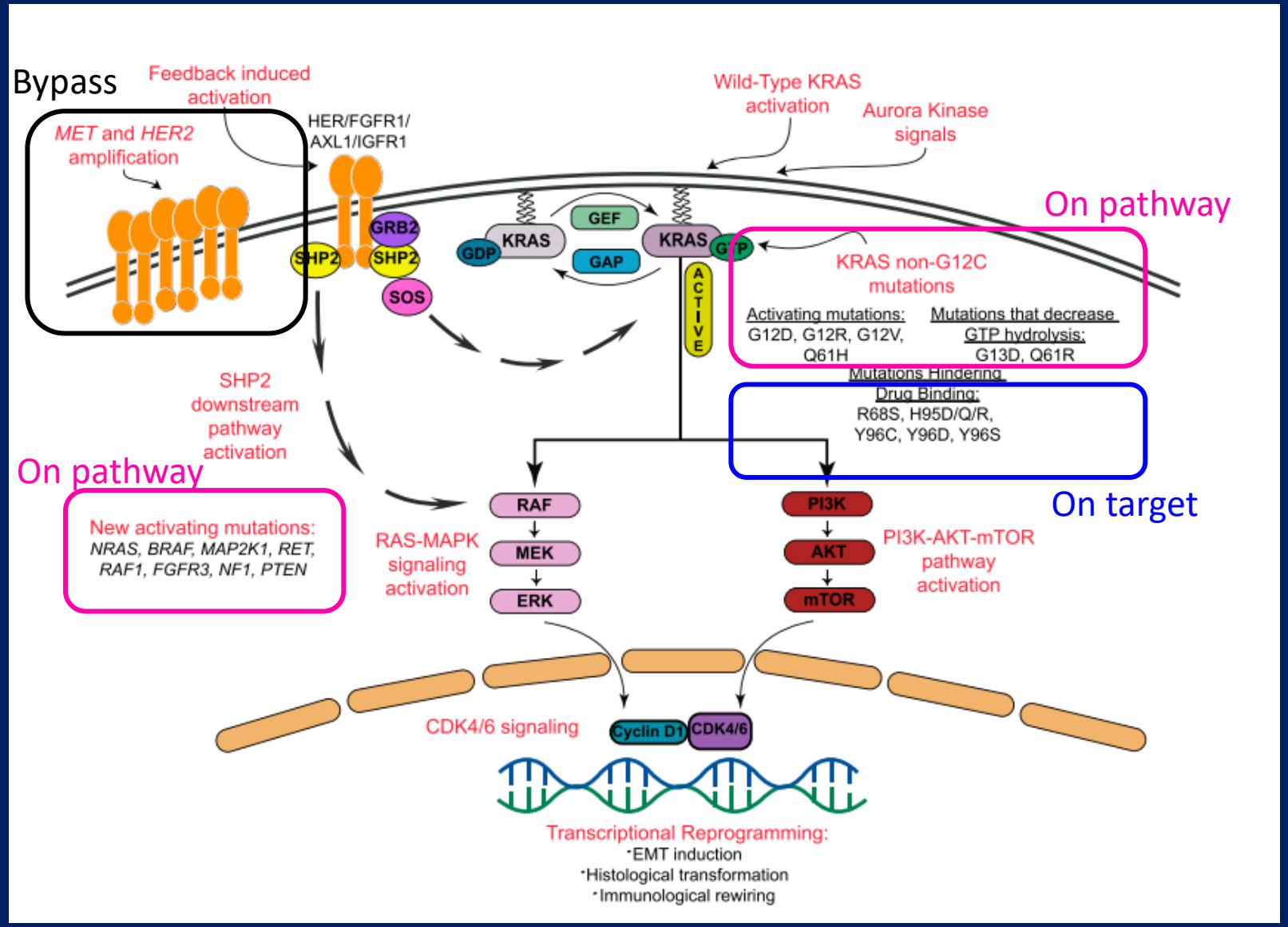
Potential Intracranial Activity of *KRAS* G12C inhibitors

Sotorasib	Adagrasib
13% (2 / 16)	33% (11 / 33)



Skoulidis F et al. NEJM 2021; Janne et al. NEJM 2022

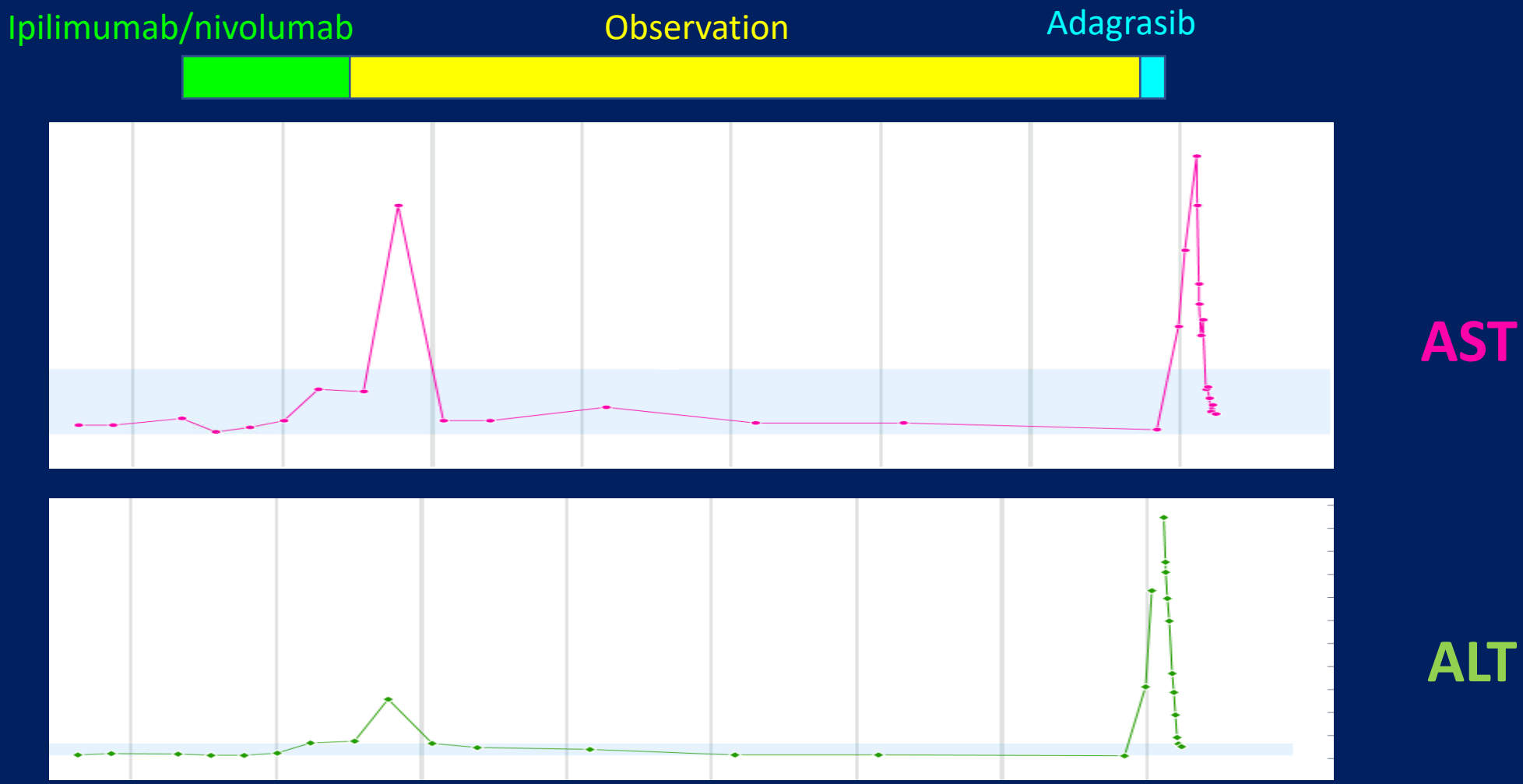
Mechanisms of Resistance to *KRAS* G12C Inhibitors



Luo et al. ASCO Educational Book 2022

A 71 year old woman with non-small cell lung cancer with *KRAS* G12C mutation, PD-L1 5 – 10%, developed grade 2 hepatotoxicity after ipilimumab/nivolumab, which improved on steroids. At time of disease progression, she was started on adagrasib.

A 71 year old woman with non-small cell lung cancer with *KRAS* G12C mutation, PD-L1 5 – 10%, developed grade 2 hepatotoxicity after ipilimumab/nivolumab, which improved on steroids. At time of disease progression, she was started on adagrasib, resulting in grade 3 hepatotoxicity



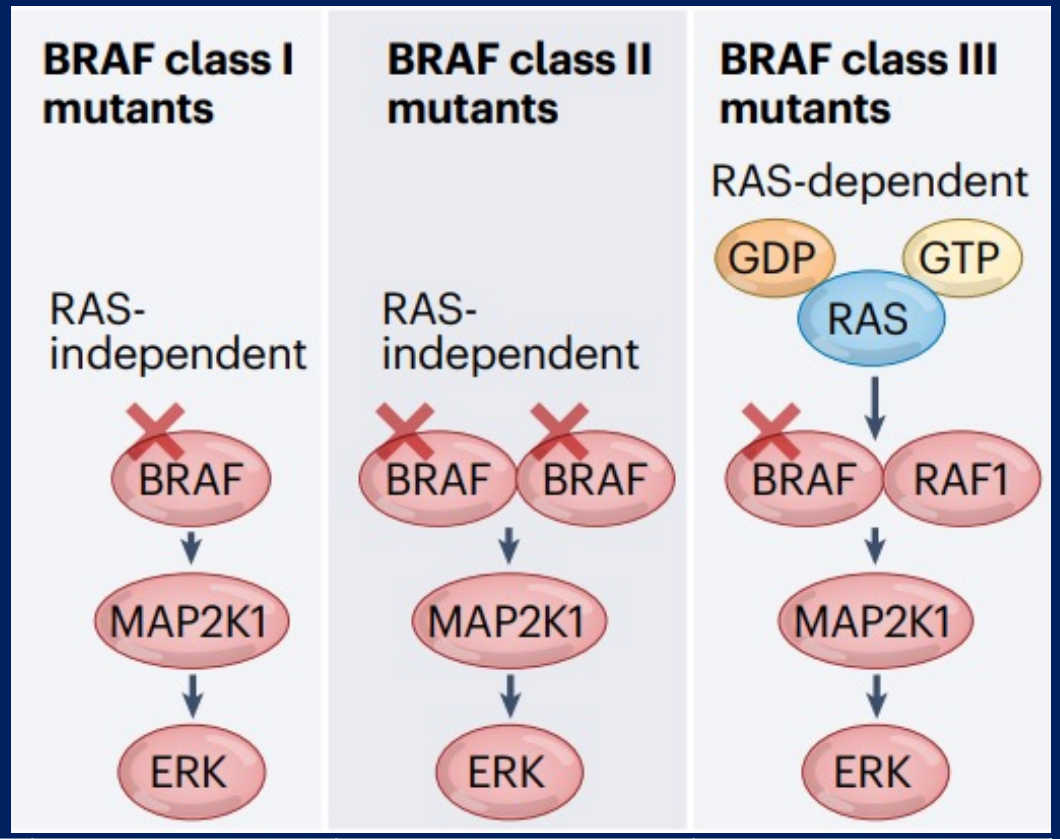
Learning points:

- **Hepatotoxicity occurs in 15 – 30% of patients on Kras G12C inhibitors**
- **Caution when using Kras G12C inhibitors in patients with a history of liver disease**

Agenda

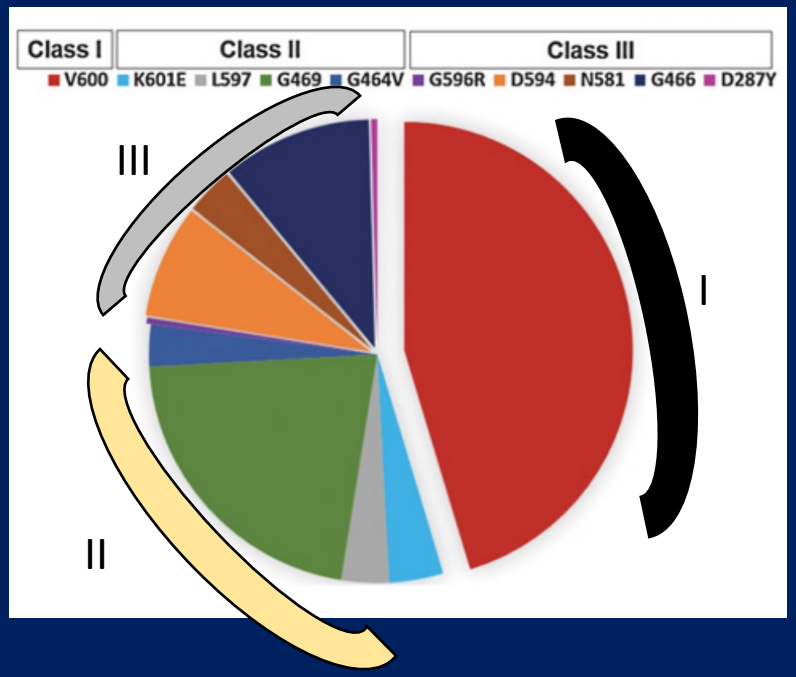
- Prevalence of genomic alterations in lung adenocarcinoma
- Targeted therapies for *KRAS* G12C
- Targeted therapies for *BRAF* mutants
- Targeted therapies for *RET* alterations

BRAF mutant non-small cell lung cancer



	I	II	III
BRAF kinase activity	High	High/Intermed	Impaired
Dimer dependent	No	Yes	Yes
RAS dependent	No	No	Yes

- *BRAF* alterations in 4 – 5% NSCLC
- V600E is the most common *BRAF* mutation ~40% (class I)
- Class II/III are more likely to have brain metastases, worse clinical outcomes, and shorter PFS with platinum based chemotherapy

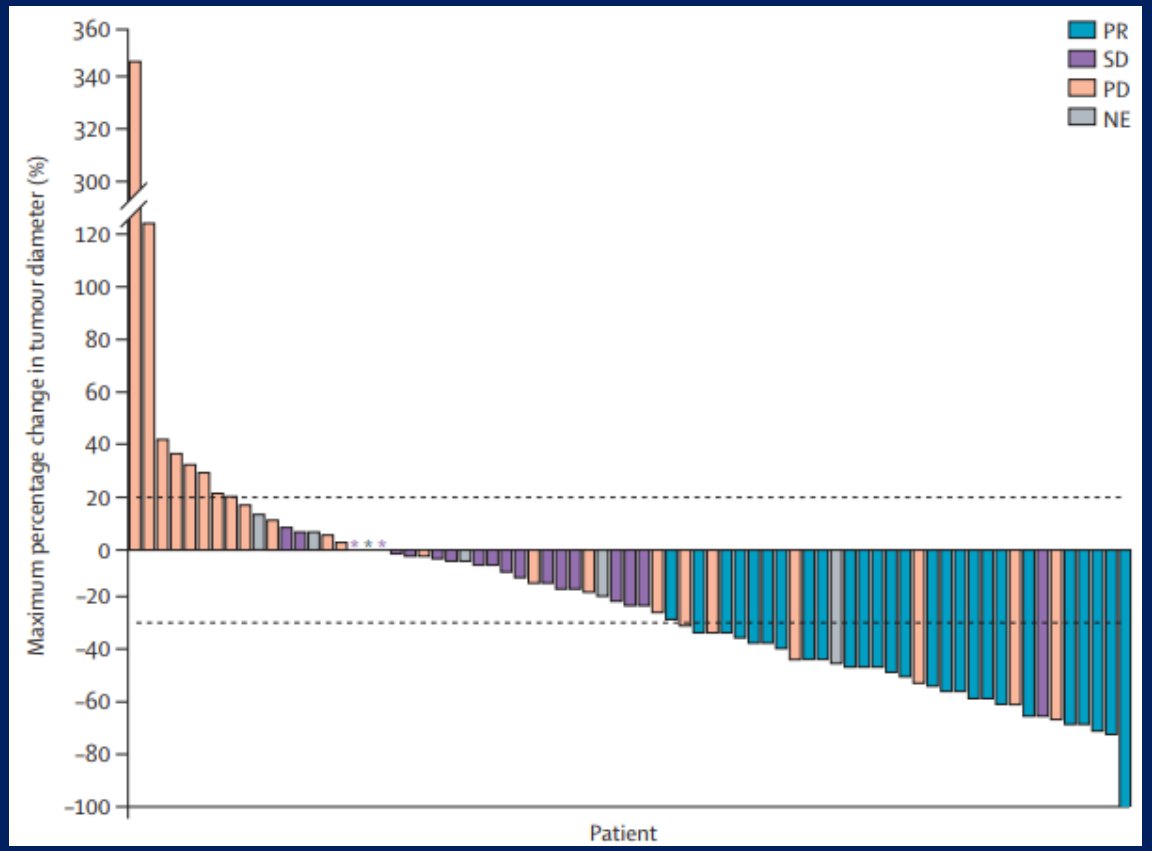


Harada et al. Nat Rev Clin Oncol 2023; Dagogo-Jack CCR 2019

Outcomes with BRAF inhibitor therapy in NSCLC with V600E mutations

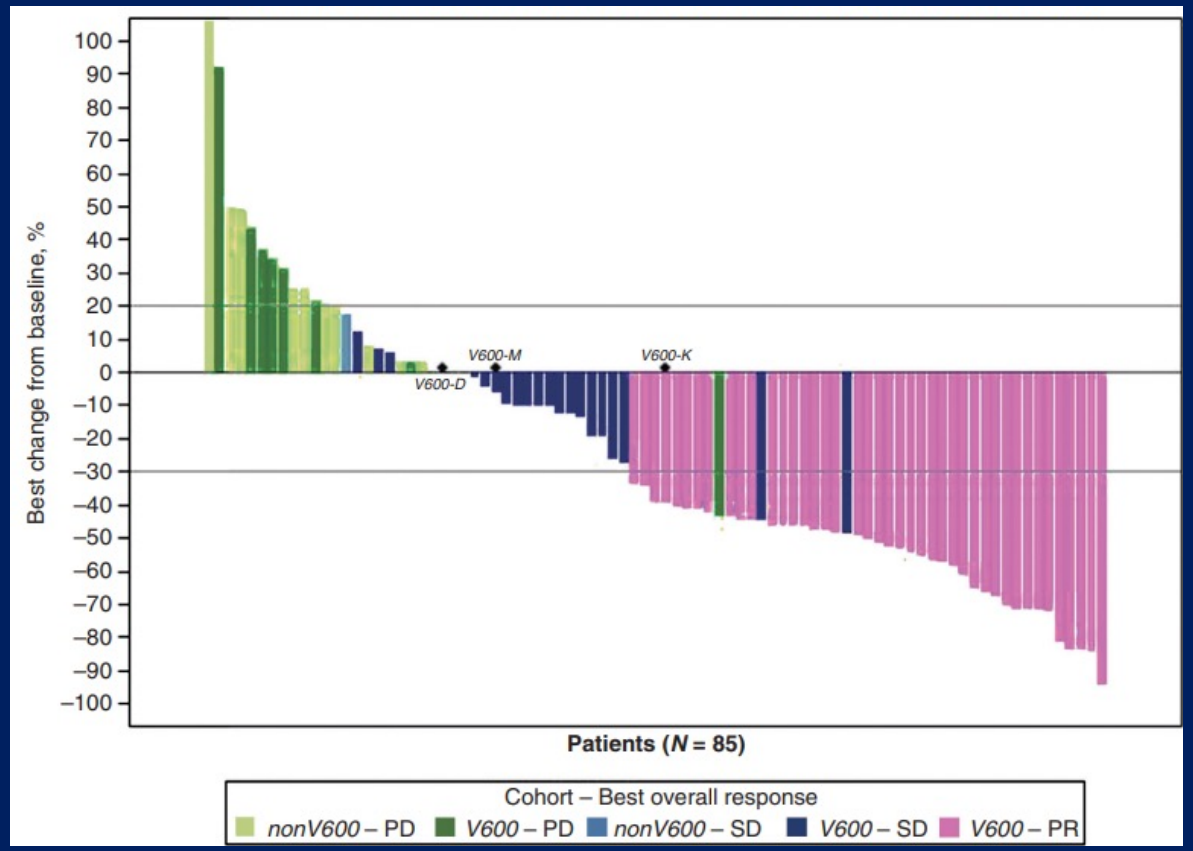
Dabrafenib

ORR 33%, mDoR 9.6 mo, mPFS 5.5 mo, mOS 12.7 mo



Vemurafenib

ORR 44% (V600E) and 0% (nonV600E),mDoR 6.4 mo, mPFS 5.2 mo, mOS 10 mo

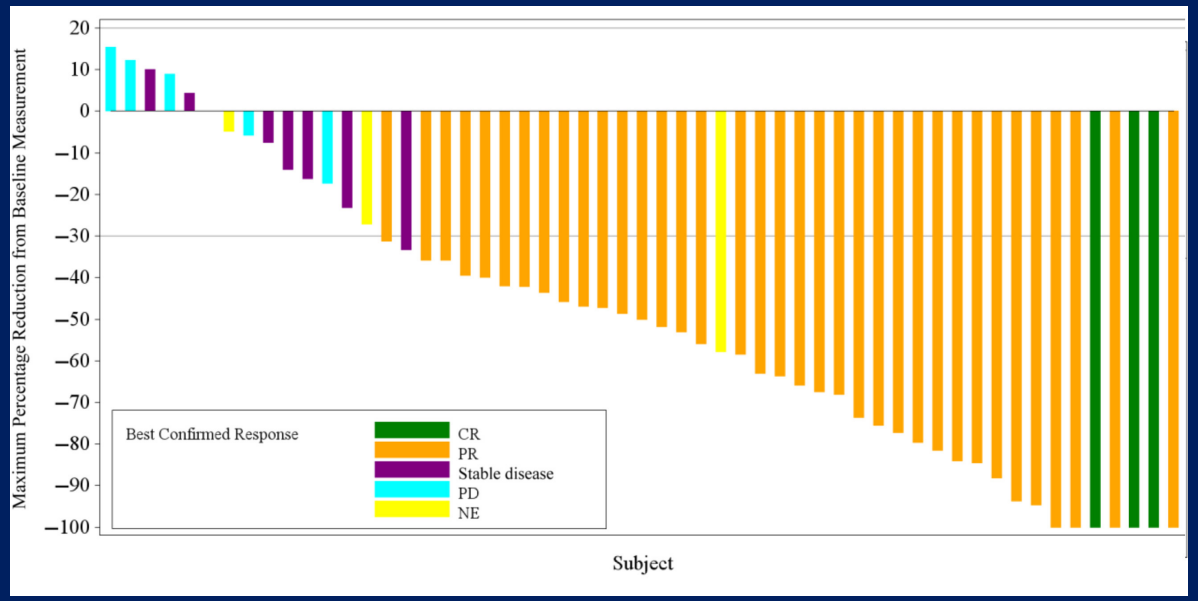


Panchard et al. Lancet Oncol 2016; Mazieres et al. Ann Oncol 2020

Outcomes with BRAF + MEK inhibitor therapy in NSCLC with V600E mutations

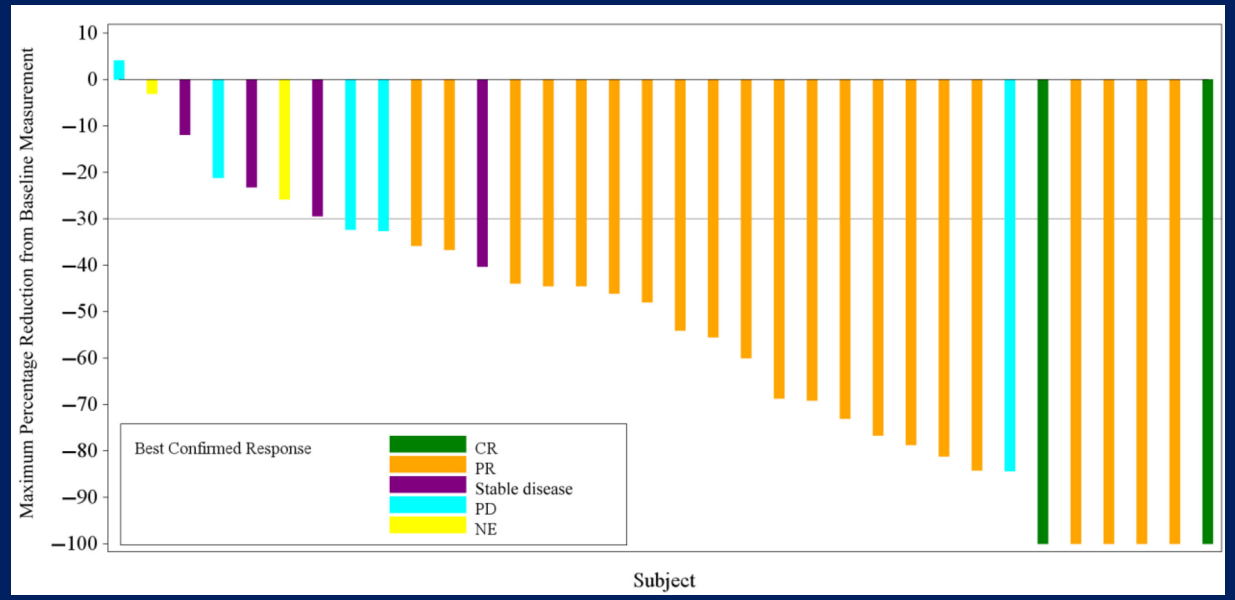
Pre-treated

ORR 68.4%, mDoR 16.6 mo, mPFS 10.2 mo, mOS 18.2 mo



Treatment-naive

ORR 63.9 %, mDoR 16.3 mo, mPFS 10.8 mo, mOS 17.3 mo

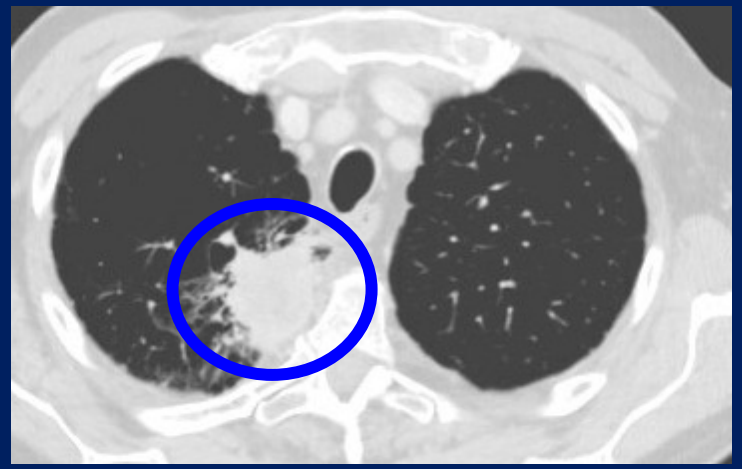


Take home message: Similar clinical efficacy in pre-treated and first line setting

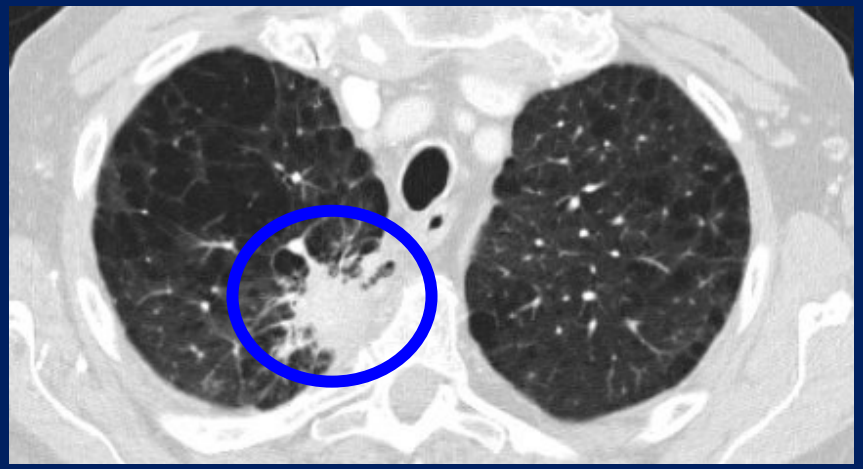
Planchard et al. JTO 2022

78 year old gentleman with metastatic lung adenocarcinoma with metastases to the brain and right pelvis who received radiation to pelvic mass and brain metastases prior to establishing care. Genomics studies showed BRAF K601N mutation and PD-L1 70%. He was subsequently started carboplatin/pemetrexed/pembrolizumab.

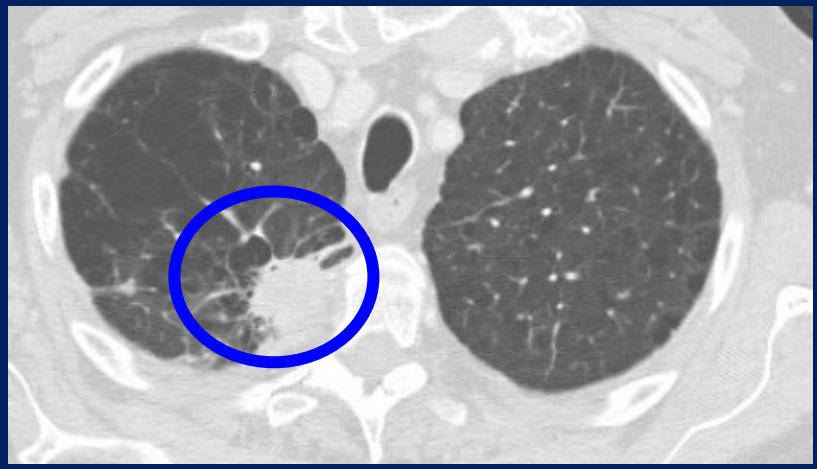
Pre-treatment



After 2 cycles



After 4 cycles



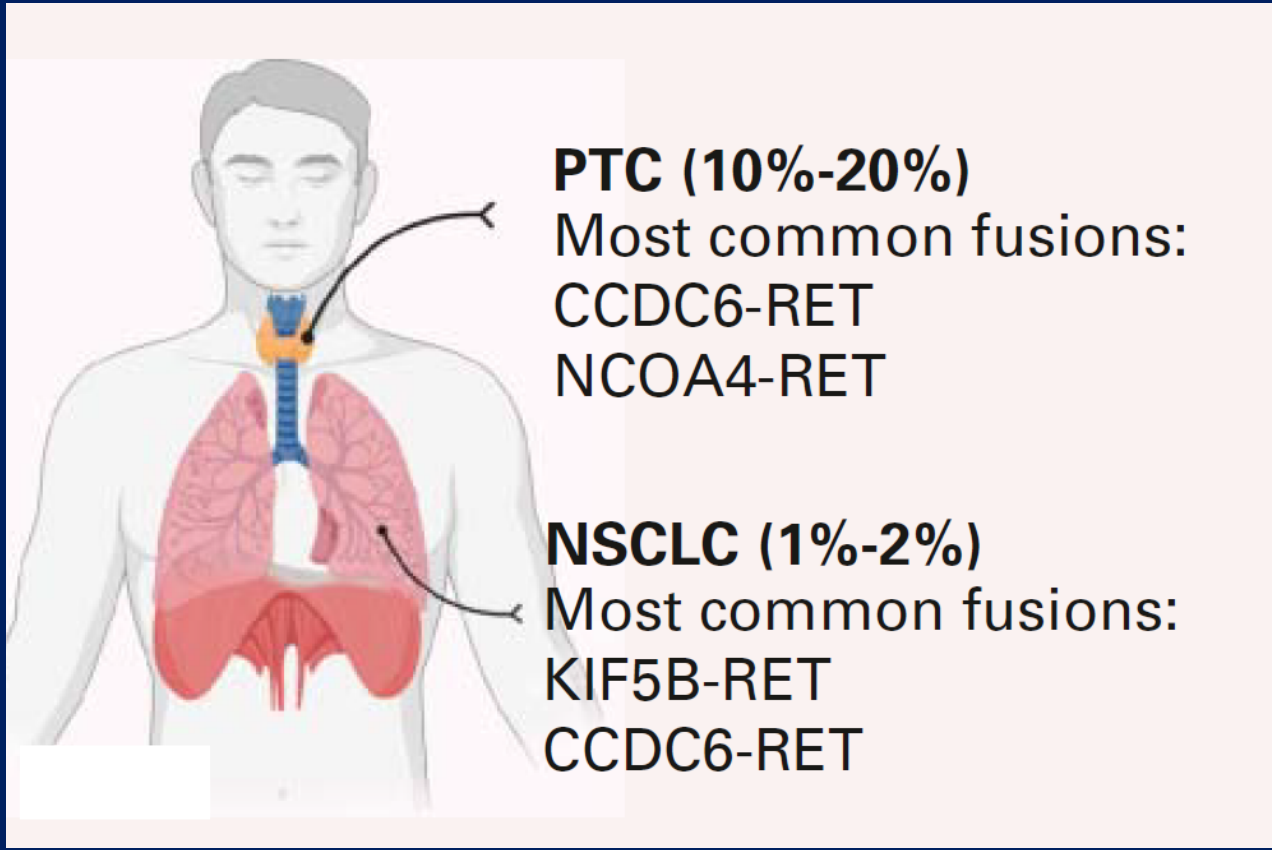
Learning point:

- **There is an unmet need for novel therapies for NSCLC with BRAF class II mutations**

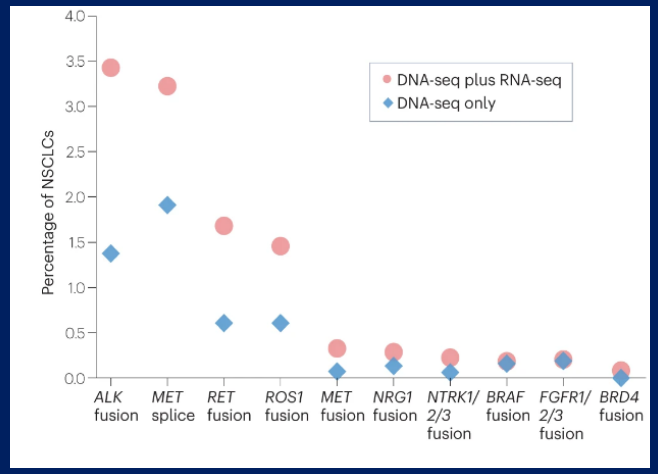
Agenda

- Prevalence of genomic alterations in lung adenocarcinoma
- Targeted therapies for *KRAS* G12C
- Targeted therapies for *BRAF* mutants
- Targeted therapies for *RET* alterations

RET Fusions in Lung Cancer



- Identified in 1 – 2% of NSCLC
- Genomic panels including DNA and RNA-seq can maximize detection of RET fusions



Adapted from Lin and Gainor. JCO 2023; Harada et al. Nat Rev Clin Oncol 2023

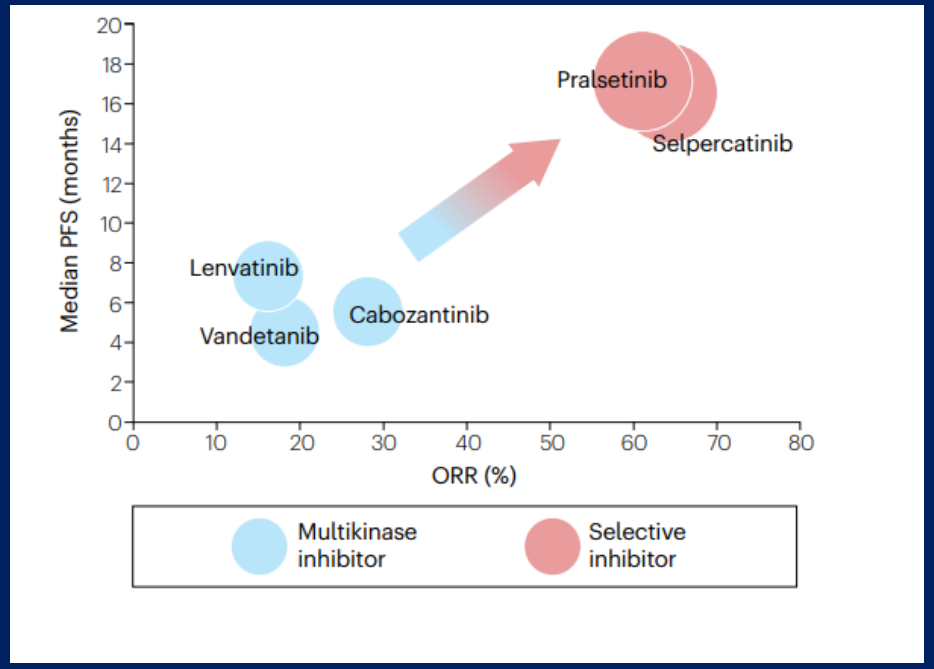
Development of selective RET inhibitors has improved outcomes for patients

Multikinase inhibitors

- **Cabozantinib**
- **Vandetanib**
- **Lenvatinib**

Selective RET inhibitors

- **Selpercatinib**
- **Pralsetinib**



Harada et al. Nat Rev Clin Oncol 2023

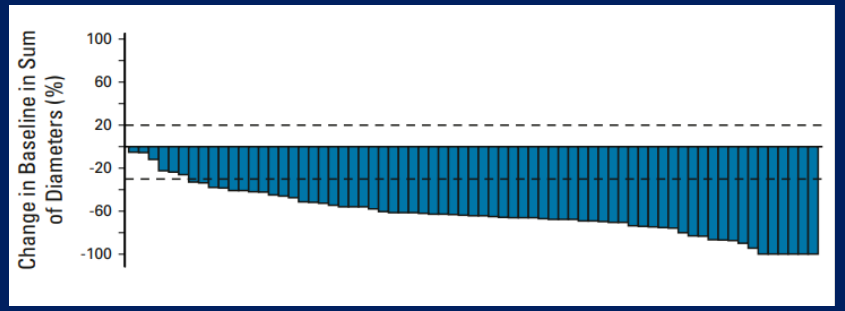
Robust Clinical Efficacy of Selective RET Inhibitors

Selpercatinib (LIBRETTO-001)

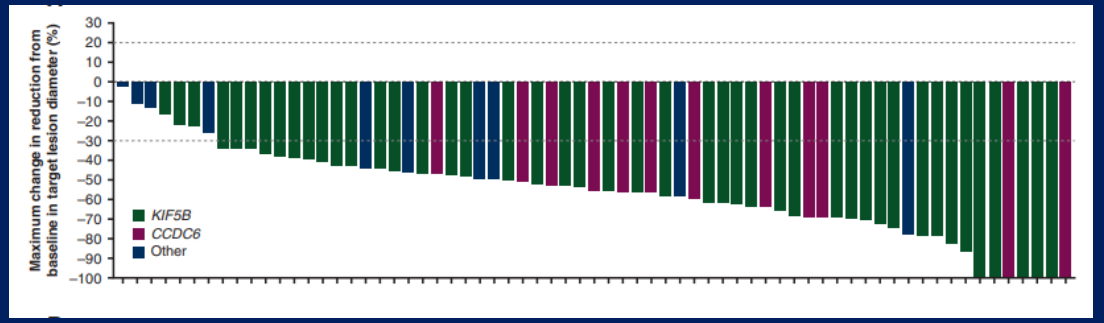
Pralsetinib (ARROW)

Treatment naive

ORR = 84%, mDoR = 20.2 mo

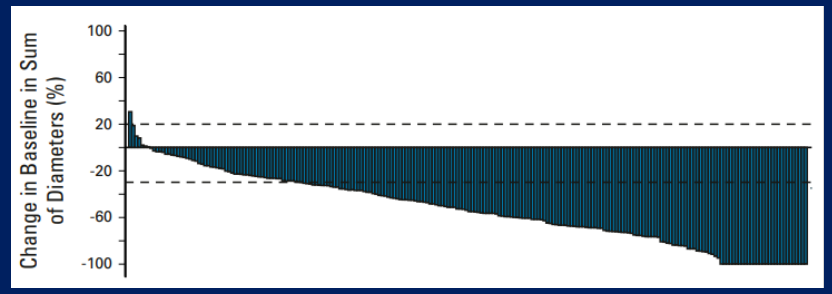


ORR = 72%; mDoR = not reached

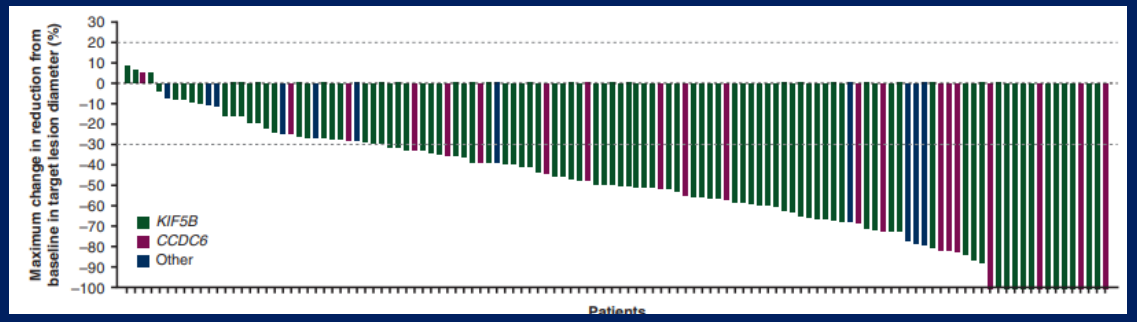


Previously treated

ORR = 61%; mDoR = 28.6 mo



ORR = 59%, mDoR = 22.3 mo

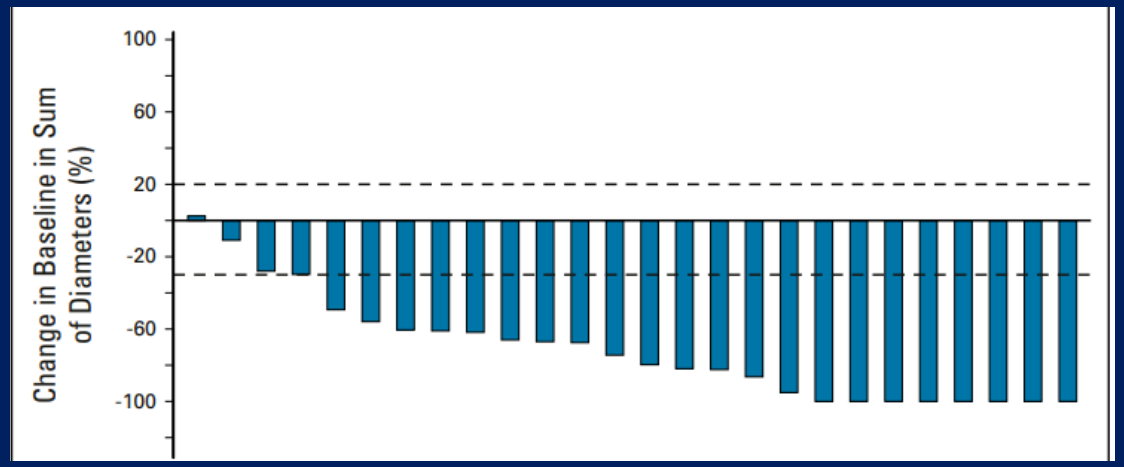


Drilon et al. J Clin Oncol 2022; Griesinger et al. Annals Oncol 2022; Drilon et al. NEJM 2020; Gainor et al. Lancet 2021

Selective RET Inhibitors Have CNS Activity

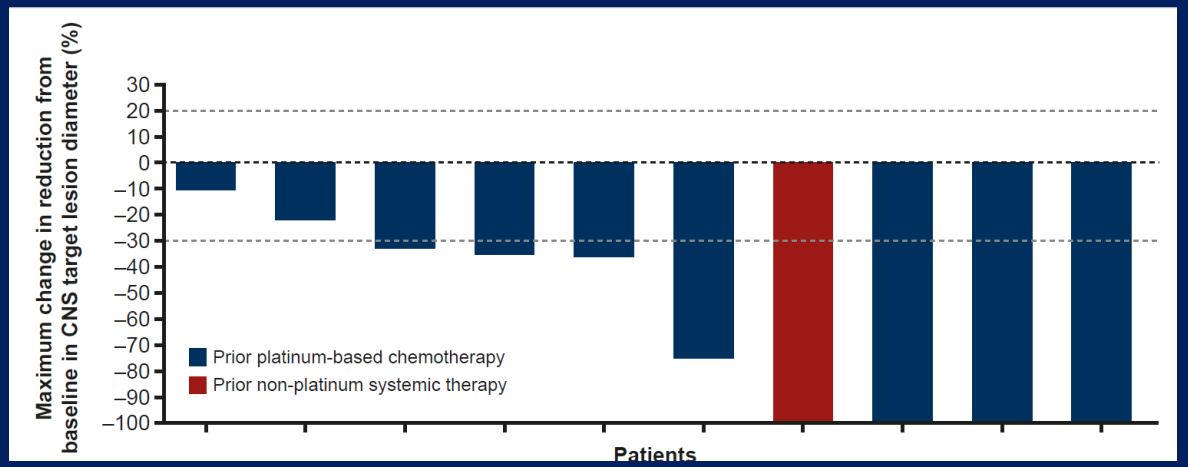
Selpercatinib (LIBRETTO-001)

iORR = 85%; iDoR = 9.4 mo



Pralsetinib (ARROW)

iORR = 70%; iDoR = 10.5 mo



Drilon et al. J Clin Oncol 2022; Griesinger et al. Annals Oncol 2022; Drilon et al. NEJM 2020; Gainor et al. Lancet 2021

Toxicities of Selective RET Inhibitors

Edema

Diarrhea

Xerostomia

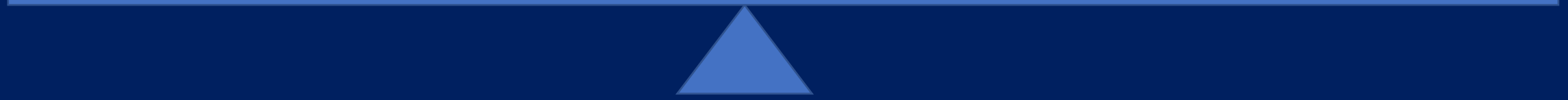
Hypersensitivity

Neutropenia
Anemia
Leukopenia

Hypertension

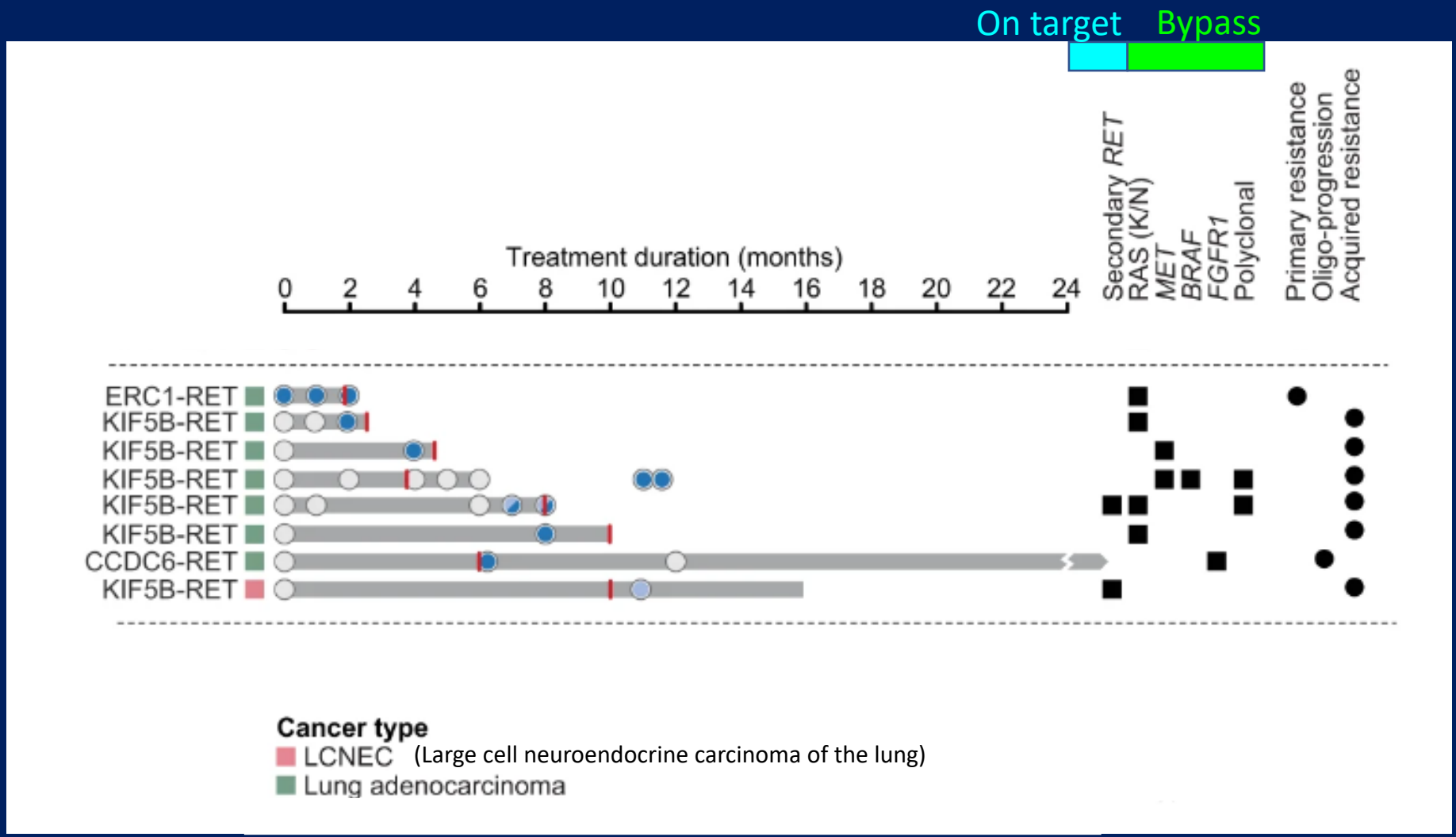
Transaminitis

False renal insufficiency



Drilon et al. J Clin Oncol 2022; Griesinger et al. Annals Oncol 2022; Drilon et al. NEJM 2020; Gainor et al. Lancet 2021

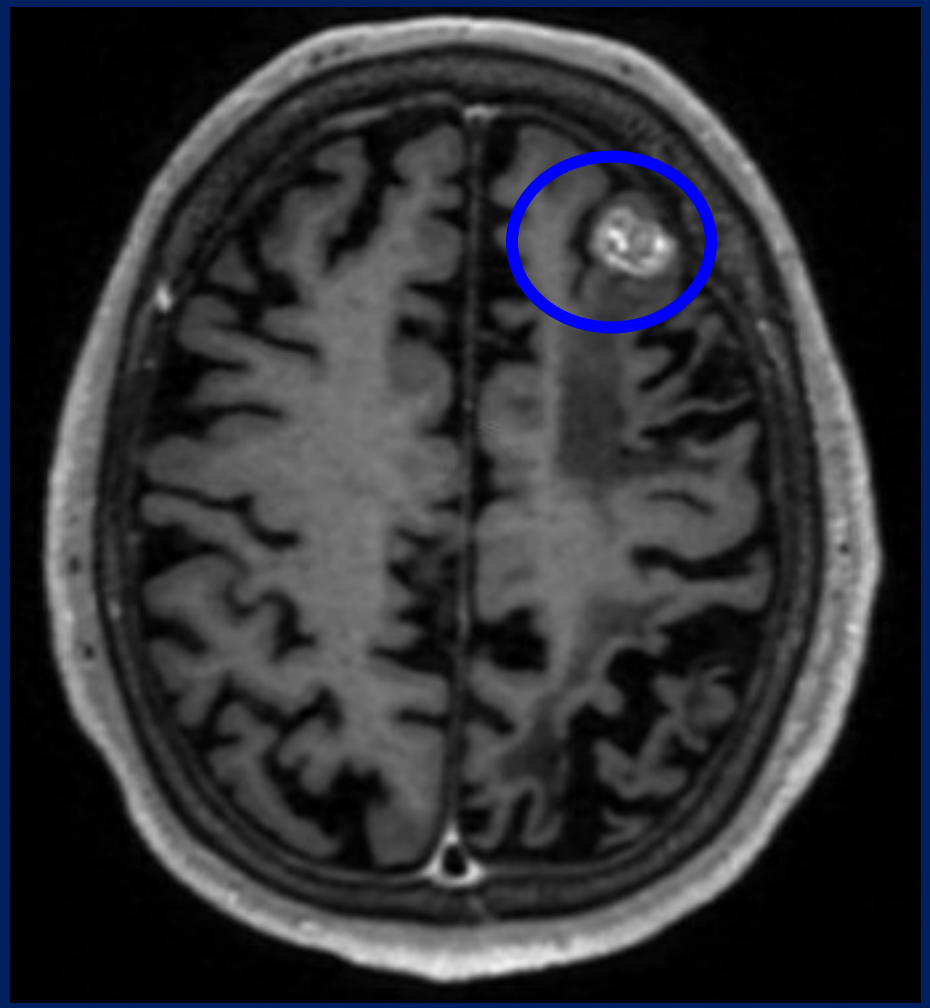
Mechanisms of Resistance to Selective RET Inhibitors



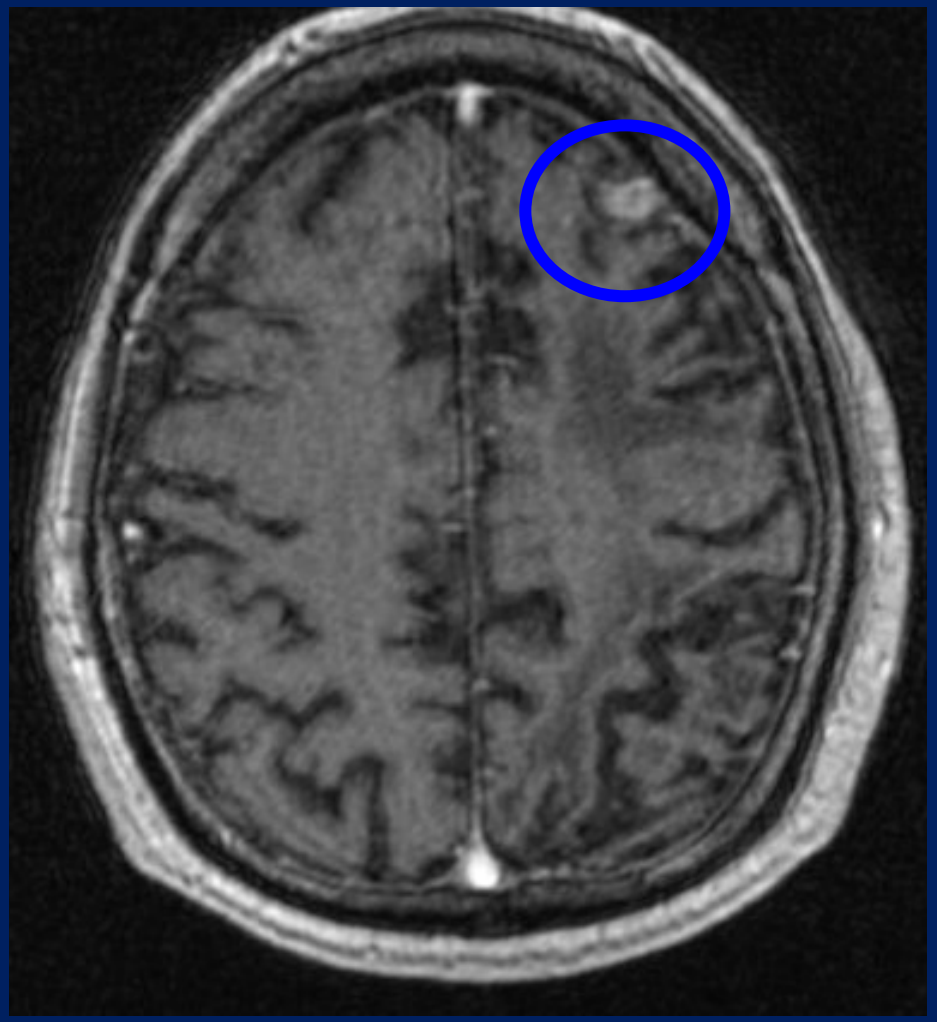
Rosen et al. Nat Commun 2022

73 year old male with history of metastatic RET+ NSCLC adenocarcinoma presented with brain metastases. He did not tolerate selpercatinib due to anasarca. He experienced intracranial response on pralsetinib

Pre-treatment



Post-treatment



<u>Learning points</u>:

- **RET inhibitors appear to have some intracranial activity**
- **Peripheral edema is a side effect experienced by some patients (24% S, 10% P)**

Take-home points

- Lung cancer with alterations in *KRAS* and *BRAF* and more responsive to immunotherapy than cancers with alterations in *RET*
- Adagrasib and sotorasib are 2 FDA approved inhibitors of advanced NSCC with *KRAS* G12C mutation after one prior line of therapy
- Dabrafenib + trametinib have comparable efficacy in treatment-naïve and in pre-treated NSCLC patients with *BRAF* V600E mutations
- Selpercatinib and pralsetinib are 2 FDA approved inhibitors of metastatic NSCLC with *RET* fusion

Future directions

- Future strategies for targeting *KRAS* mutant lung cancers will need to be informed by their molecular diversity and co-mutation status
- Novel strategies are required for targeting *BRAF* dimers to overcome class II and III mutations
- An understanding of mechanisms of resistance to *RET* inhibitors needs to translate to next-generation therapies