Stage IV KRAS Mutant Lung Cancer Case

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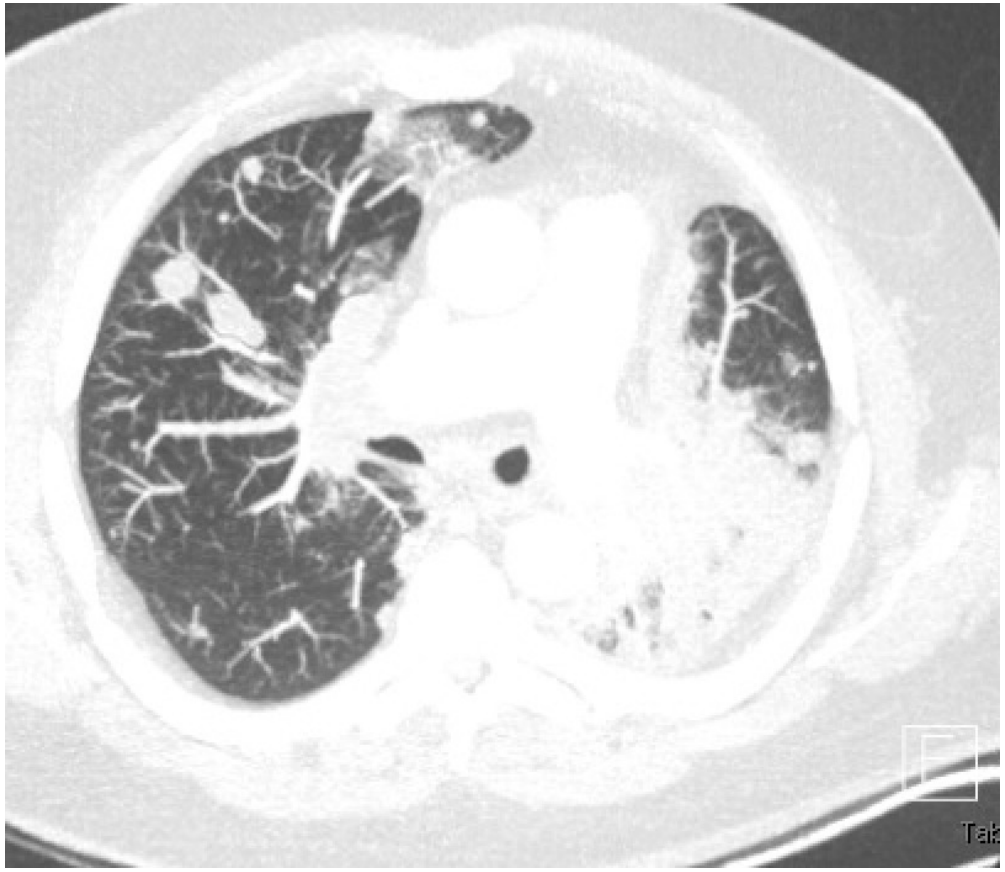
Case 1

A 63-year-old man, former 30 pk.yr smoker, presents with cough and SOB.

CT scan: Imaging with LUL primary, mediastinal & hilar adenopathy, plus bilateral lung & bone metastases.

Fine Needle Biopsy: NSCLC-adenocarcinoma (TTF1+)

Brain MRI without metastatic disease.



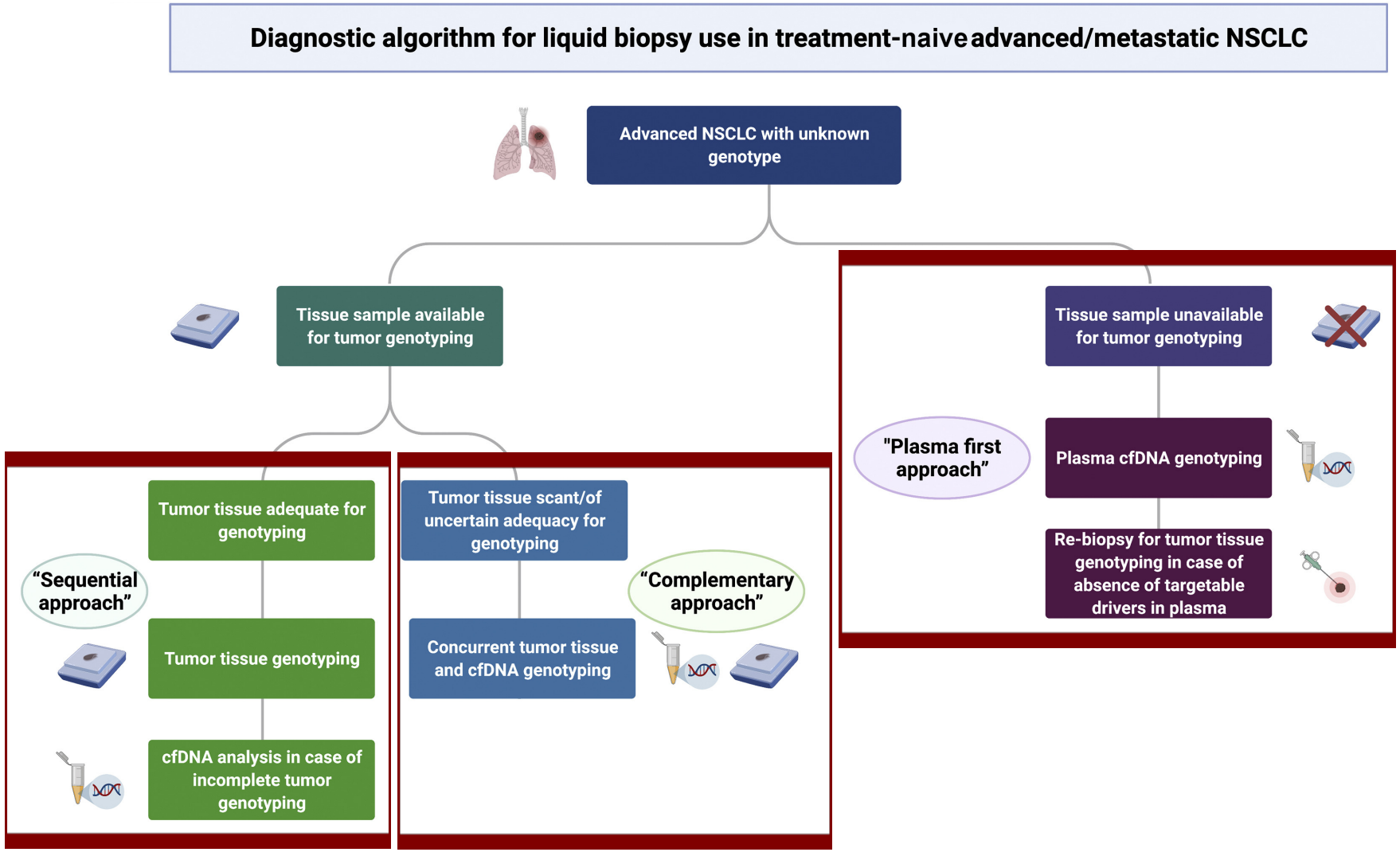
Case 1

63-year-old male with new diagnosis of stage IV lung adenocarcinoma with bilateral lung and bone metastases. PS=1.
You decide to perform broad comprehensive genomic profiling (CGP) for actionable molecular alterations. There is adequate tissue for next-generation sequencing (NGS).

Question 1: How would you proceed with testing, given anticipated turn-around-times (TRT)?

1. **Send plasma only for GCP by ctDNA NGS (~7-day TRT)**
2. **Send tumor tissue only for CGP by NGS (~14-day TRT)**
3. **Send both plasma ctDNA + repeat tissue biopsy for CGP by NGS (~14-day total TRT)**

Updated IASLC Consensus Statement on Liquid Biopsy in NSCLC: 2021



Rolfo, Gandara et al. JTO 2021

Case 1

- **Molecular testing by plasma NGS comprehensive genomic profiling reveals: KRAS G12C mutation + STK11 mutations. These findings are duplicated in subsequent tissue NGS analysis.**
- **PD-L1 (22C3) TPS = 1%.**

Case 1

For this 63 y/o patient with stage IV lung adenocarcinoma, former smoker.
PS=1. Testing: KRAS G12C + STK11 mutation & PD-L1 TPS = 1%

Question 2: What do you recommend for first-line systemic therapy?

1. Platinum chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA

2. Pemetrexed/carboplatin/pembrolizumab (KN 189)

3. Nivolumab + ipilimumab (CM 227)

4. Paclitaxel/carboplatin/bevacizumab/atezolizumab (IMpower 150)

5. Sotorasib or Adagrasib

Immunotherapy therapeutic landscape in advanced NSCLC: Phase III Trials in 1st Line Therapy

Study	Drug (vs CT)	PD-L1 selection	Control	Primary endpoint	HR primary endpoint	Result	Publication
KN-024	Pembro	≥50%	Platinum CT	PFS	0.50	Positive	Reck et al. *NEJM* 2016
CM026	Nivo	≥5%	Platinum CT	PFS	1.15	Negative	Carbone et al. *NEJM* 2017
KN-042	Pembro	≥1%	Platinum CT	OS	0.81 0.69 (50%)	Positive	Mok et al. *Lancet* 2019
IMpower110	Atezo	≥1%	Platinum CT	OS in TC3/IC3	0.59	Positive	Herbst et al. *NEJM* 2020
EMPOWER-Lung 1	Cemi	≥50%	Platinum CT	PFS, OS	0.54 (PFS) 0.57 (OS)	Positive	Sezer et al. *Lancet* 2021
MYSTIC	Durva or Durva/Tremi	≥25%	Platinum CT	PFS, OS	0.87 (PFS) durva 0.76 (OS) durva	Negative	Rizvi et al. *JAMA Oncol* 2020
CM227	Nivo or Nivo-Ipi	<1%/≥1% & TMB ≥10	Platinum CT	PFS, OS	0.58 (PFS) in TMB-H 0.62 (OS) in <1% 0.79 (OS) in ≥1%	Positive	Hellmann et al. *NEJM* 2018 Hellman et al. *NEJM* 2019
CM9LA	Nivo-Ipi-CT	≥1%	Platinum CT	OS	0.66	Positive	Paz Ares et al. *Lancet Oncol* 2021
KN-189 (NSQ)	Pembro-CT	≥1%	Platinum CT	PFS	0.52	Positive	Ghandi et al. *NEJM* 2018
KN-407 (SQ)	Pembro-CT	None	Platinum-Nab Pac	PFS, OS	0.56 (PFS) 0.64 (OS)	Positive	Paz Ares et al. *NEJM* 2018
IMpower150 (NSQ)	Atezo + Bev/Pac/Carbo	None	Bev/Pac/Carbo	PFS, OS	ACBP 0.71 (PFS) ACBP 0.78 (OS)	Positive	Socinski et al. *NEJM.* 2018
IMpower131 (SQ)	Atezo + nab Pac/Carbo	None	Pac/Carbo	PFS, OS	0.71 (PFS) 0.88 (OS)	Positive (PFS)	Jotte et al. *J Thorac Oncol* 2020
EMPOWER-Lung 3	Cemi-CT	None	Platinum CT	PFS, OS	0.56 (PFS) 0.71 (OS)	Positive	Gogishvili et al. Nat Med 2022
POSEIDON	Durva+Tremi-CT	None	Platinum CT	PFS, OS	0.77 (OS)	Positive	Johnson et al. JCO 2022

Parameters

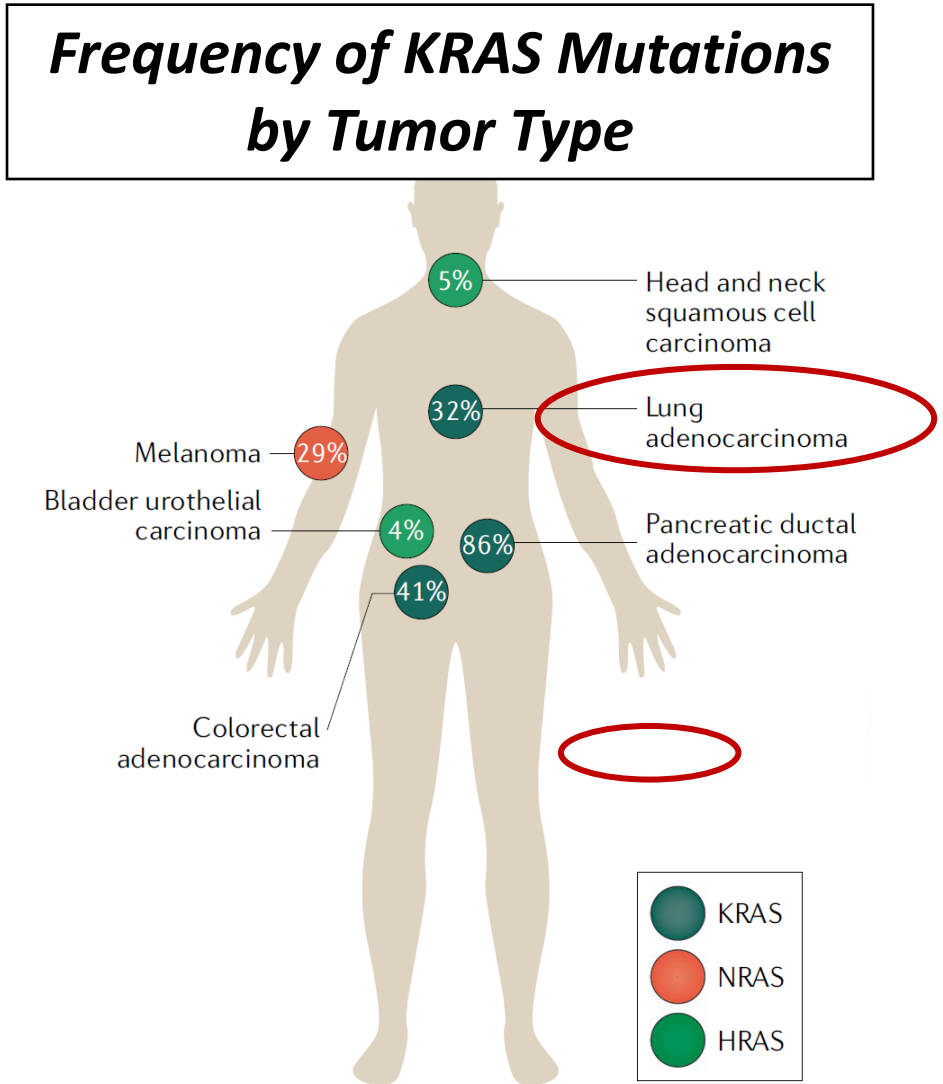
Test Regimen
ICI Monotherapy
ICI+CT
ICI+CT+Bev
ICI + CTLA-4

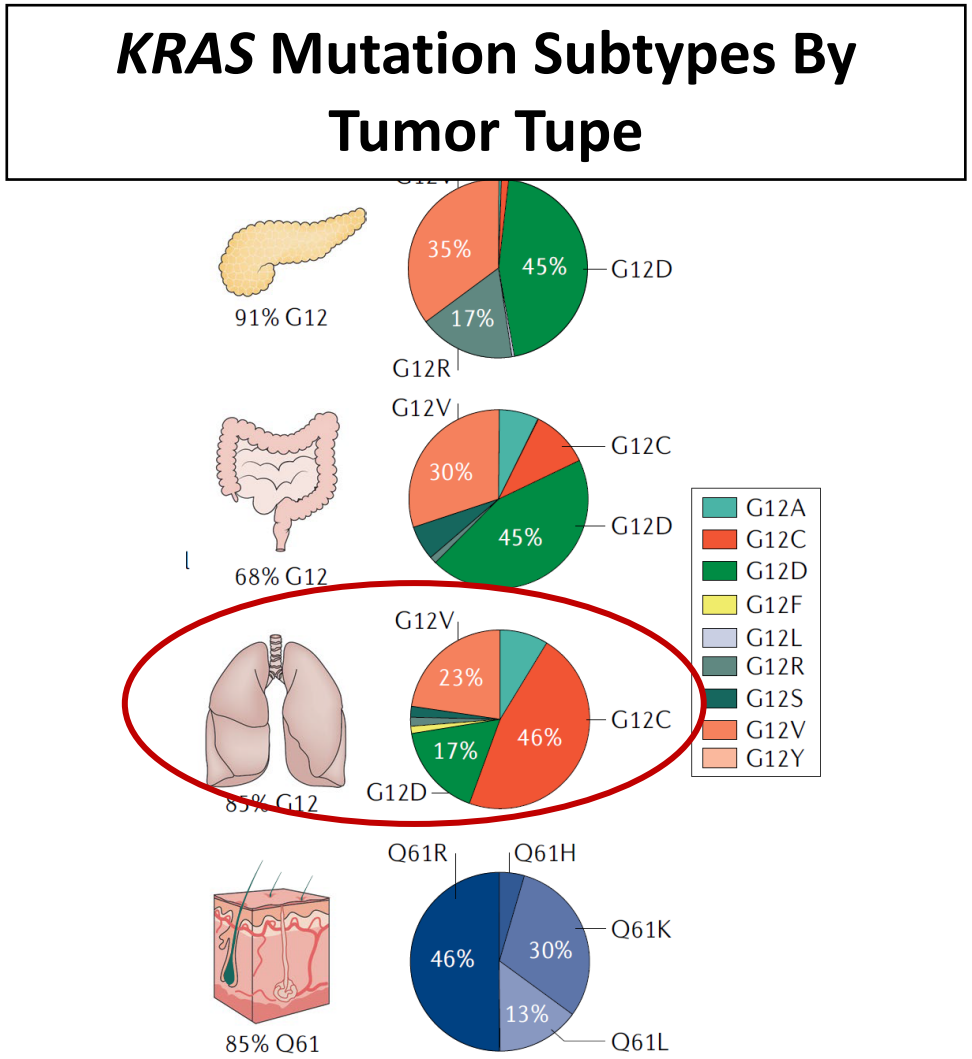
Biomarker
None
PD-L1
TMB

Histology
All
SQ
NSQ

Primary Endpoint
PFS
OS
Both

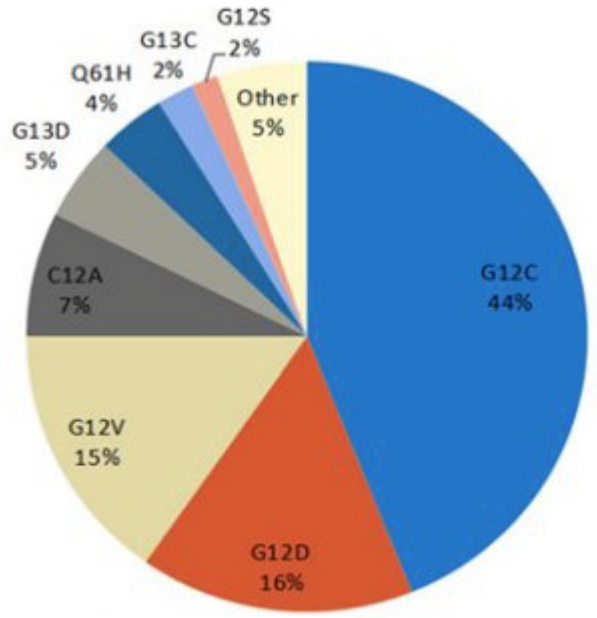
KRAS mutations in cancer – Focus on NSCLC

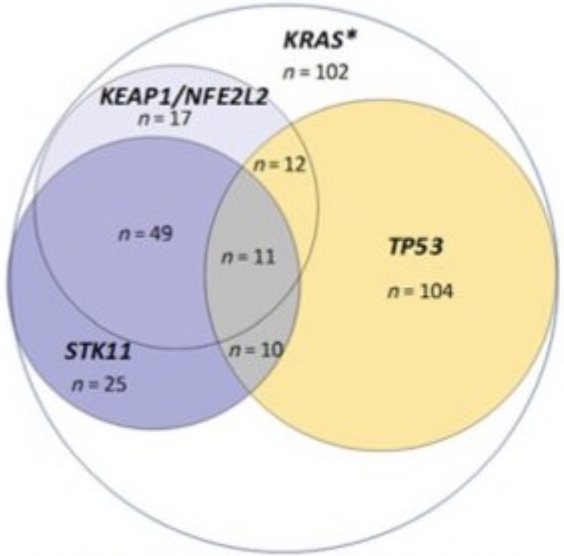




Figures from Moore AR et al. Nat Rev Drug Discov 19, 533–552 (2020).

Spectrum of KRAS mutations and Co-Mutations in NSCLC



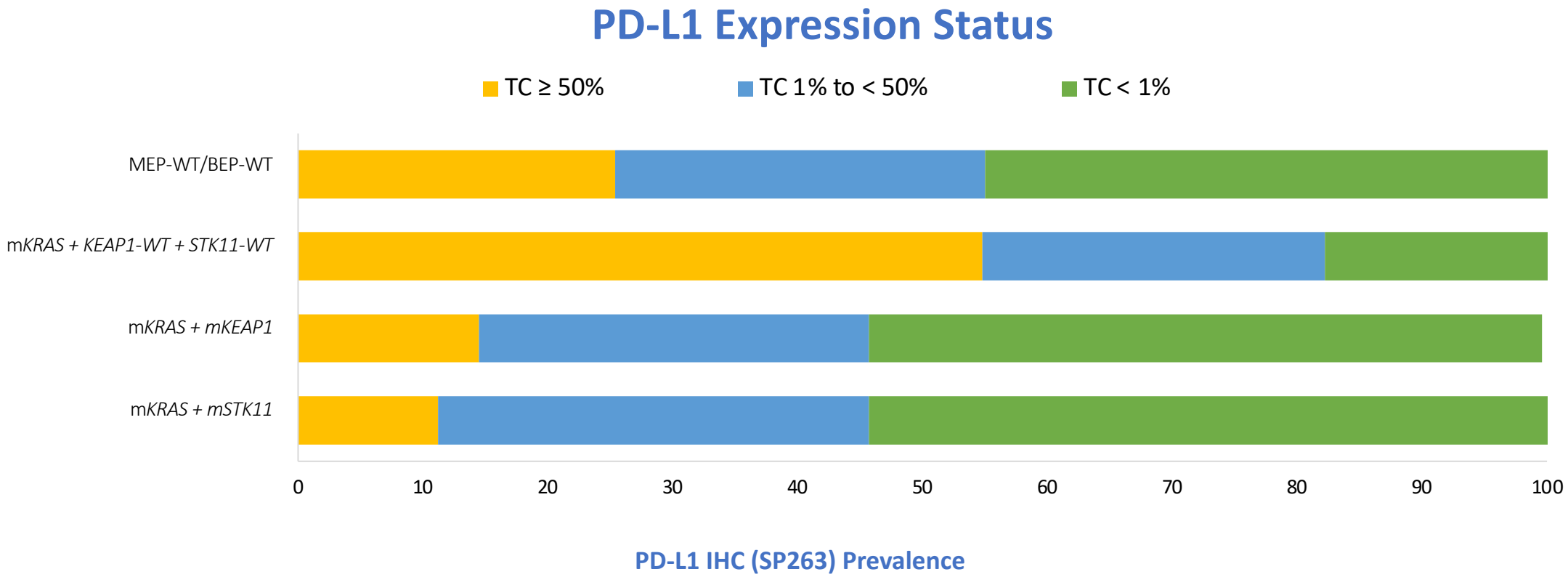


*KRAS (*n* = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al CCR 2018

Effect of *STK11/KEAP1* Co-Mutations on Clinical Benefit in Patients With m*KRAS* Tumors *(cont'd)*

Figure 4. OS (A), PFS (B) and PD-L1 Expression Status (C) in Patients With *KRAS* Mutations and *STK11/KEAP1* Co-Mutations *(cont'd)*



PFS, progression-free survival; OS, overall survival.
West et al. Presented at ESMO Virtual Meeting. 2020.

Case 1

The patient is treated with carboplatin/pemetrexed/pembrolizumab and achieves a partial response for 6 months.

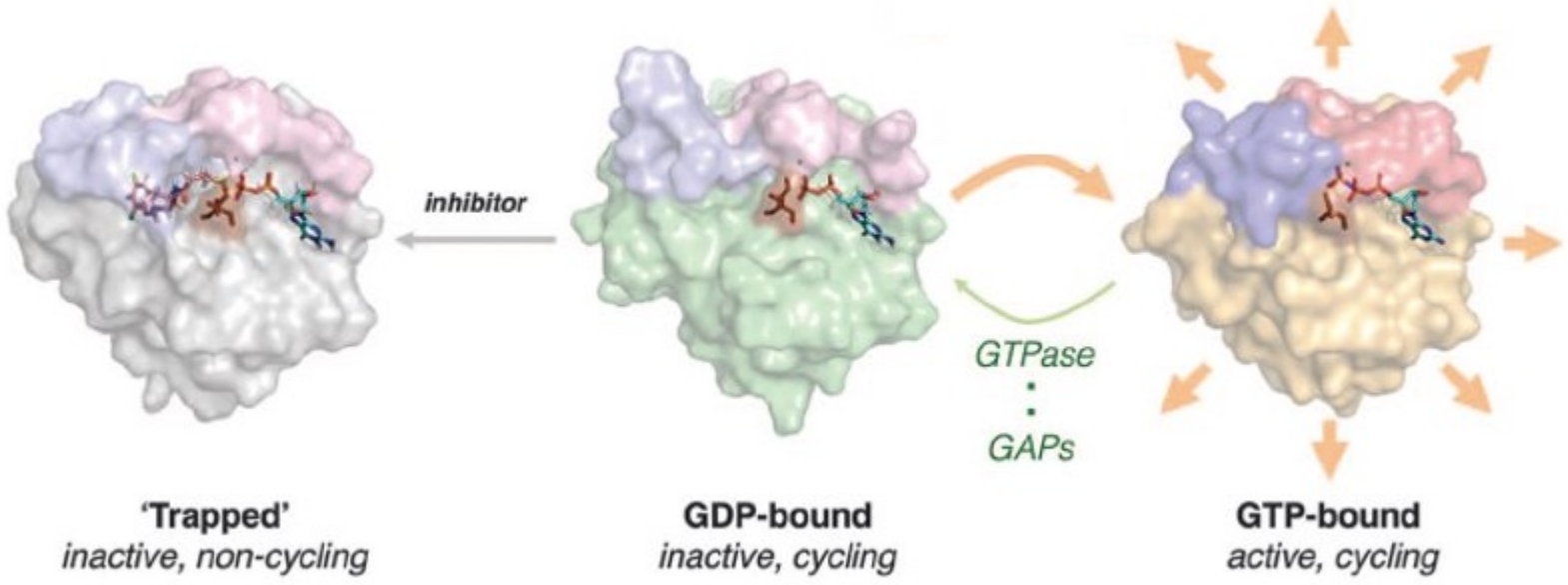
However, at 6 months there is progressive disease in 3 sites (2 new bone lesions & growth of a pulmonary nodule from 2 to 5 cm.

At 6 months there is progressive disease in bone liver and LN. PS remains 1.

Question 3: In this case with KRAS G12C and STK11 mutation TPS = 1%, what do you recommend for at this point?

1. **Switch to sotorasib or adagrasib.**
2. **Switch to docetaxel/ramucirumab (REVEL).**
3. **SBRT to all sites of PD & continue pemetrexed & pembrolizumab maintenance therapy**
4. **Switch to nivolumab/ipilumumab**

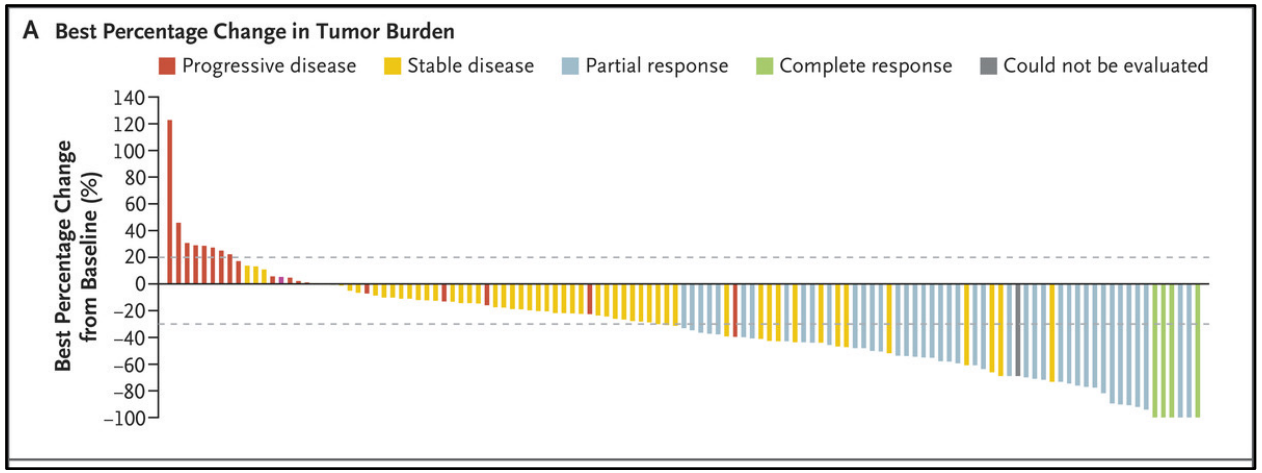
KRAS G12C Inhibitors Bind, Inactive GDP bound RAS and Trap It In Inactive State



From P. Lito et al. Science 2016

KRAS G12C inhibitors have activity in *KRAS* G12C NSCLC

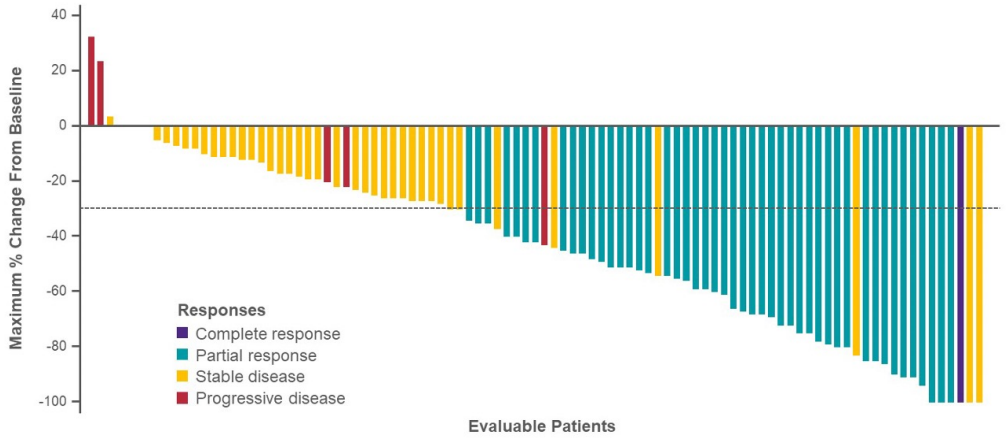
Sotorasib
CodeBreaK100 (Ph 2)



N=124 pts at 960 mg po qd
Median 2 prior lines of therapy
81% received both platinum and anti-PD-(L)1
ORR 37.1% (95% CI 28.6-46.2) // **DCR 80.6%** (95% CI 72.6-87.2)
mDOR 11.1 mo (95% CI 6.9-NE); **mPFS 6.8 mo** (95% CI 5.1-8.2)
mOS 12.5 mo (95% CI 10.0-NE)*

*median f/u 15.3 months F Skoulidis et al. N Engl J Med 2021;384:2371-2381.

Adagrasib
KRYSTAL-1 study (Ph 1/1b & 2)

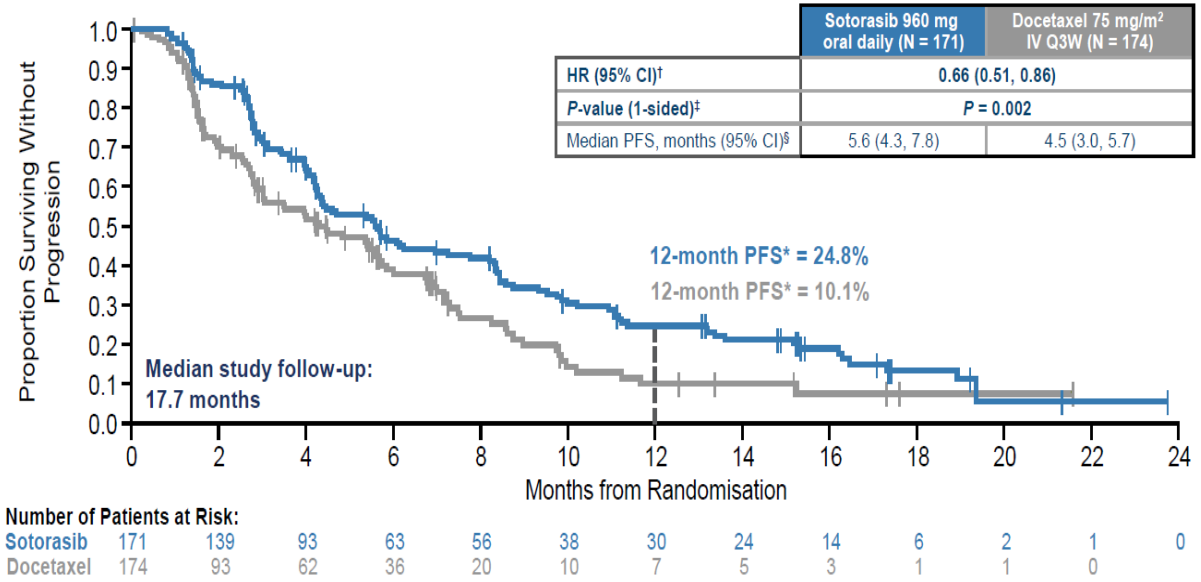


N=112 pts at 600 mg po bid
98% received both chemo and anti-PD-(L)1
ORR 43% // **DCR 80% // mPFS 6.5 months** (95% CI 4.7-8.4)
mOS 12.6 months (95% CI 9.2-19.2)

Spira A. ASCO 2022

CodeBreaK 200: Sotorasib vs Docetaxel

Primary Endpoint: PFS by BICR

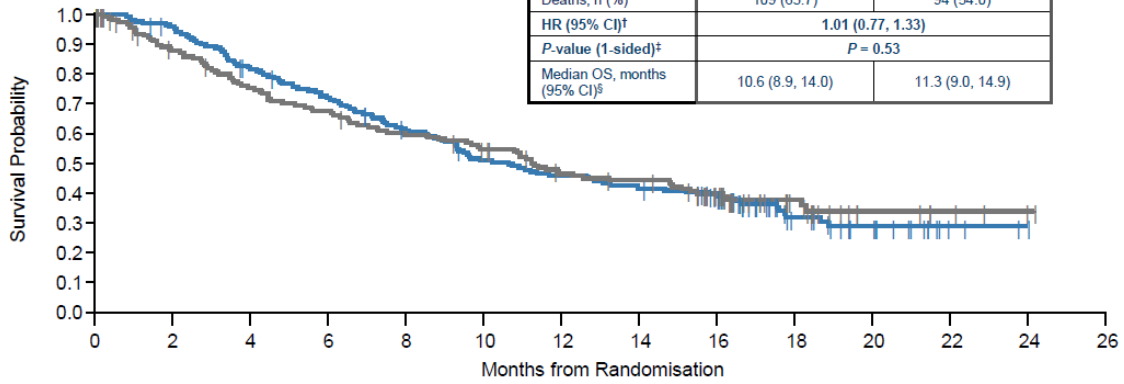


	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

OS: Sotorasib vs Docetaxel



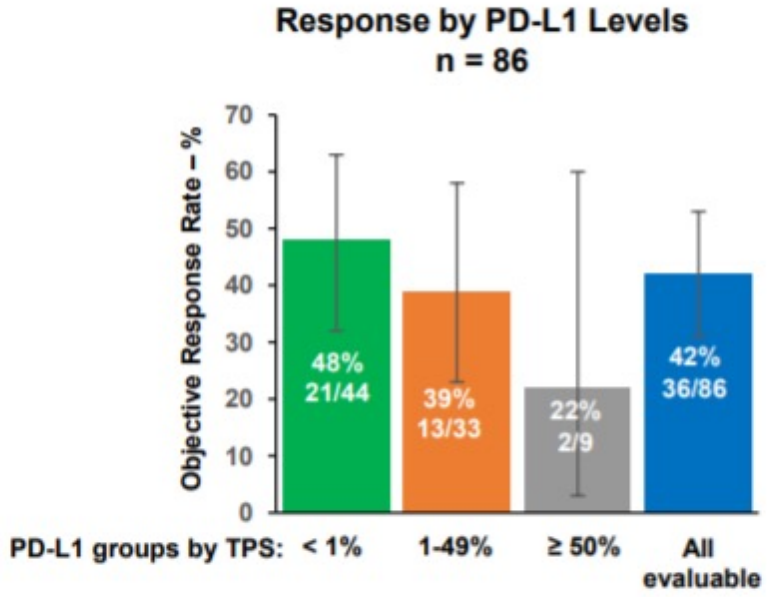
	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

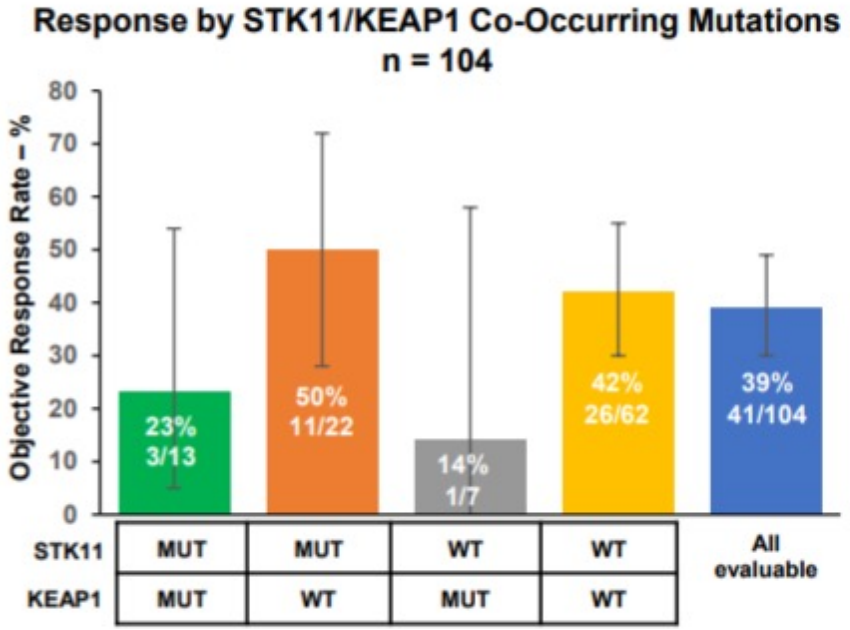
Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

Johnson ML, et al. ESMO 2022. Abstract LBA10

Tumor Response by PD-L1 Levels & STK11/KEAP1 Co-Occurring Mutations



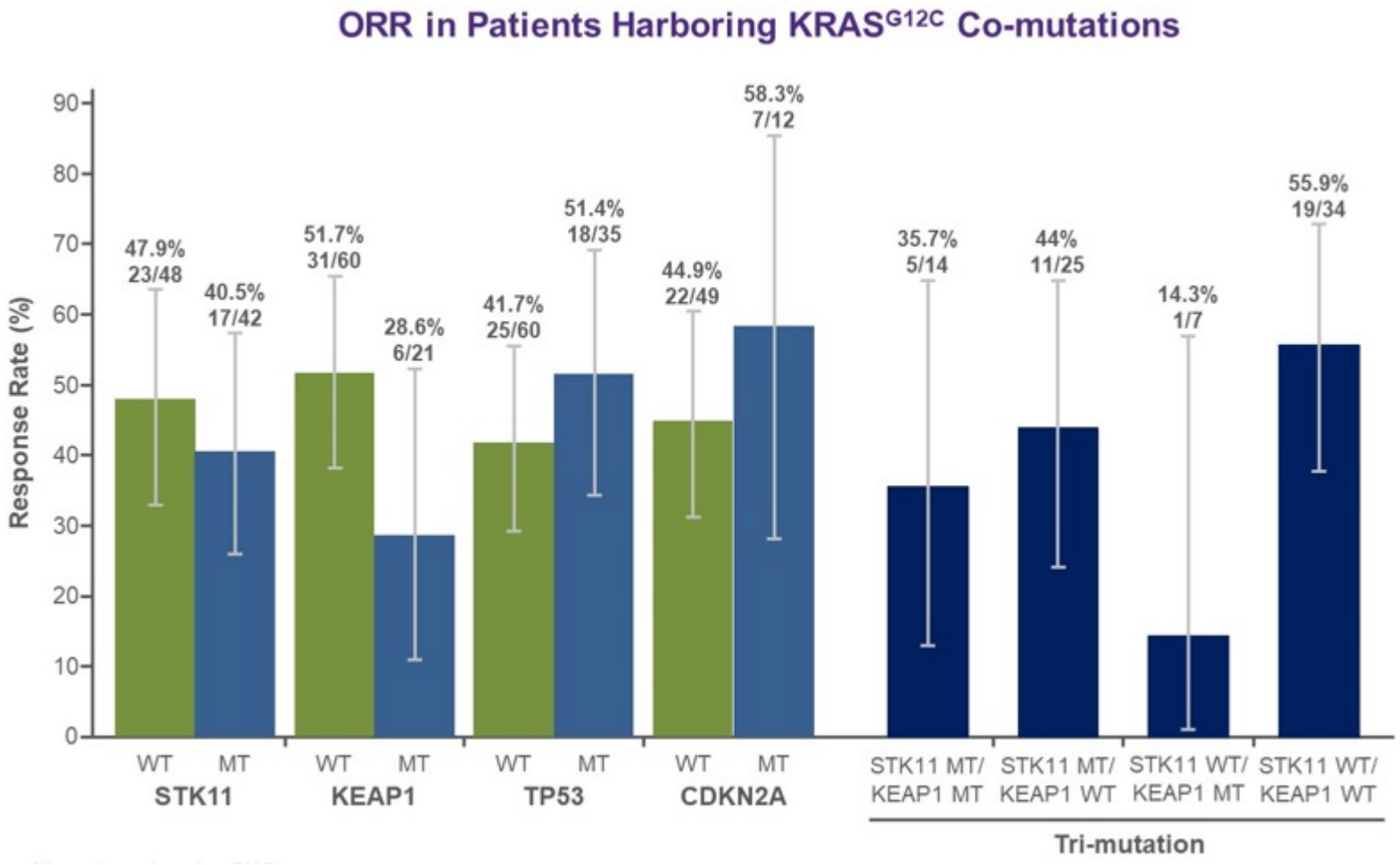


Li et al. *WCLC* 2020

IASLC 2021 Targeted Therapies of Lung Cancer Meeting
FEBRUARY 17 - 21, 2021 | WORLDWIDE VIRTUAL EVENT

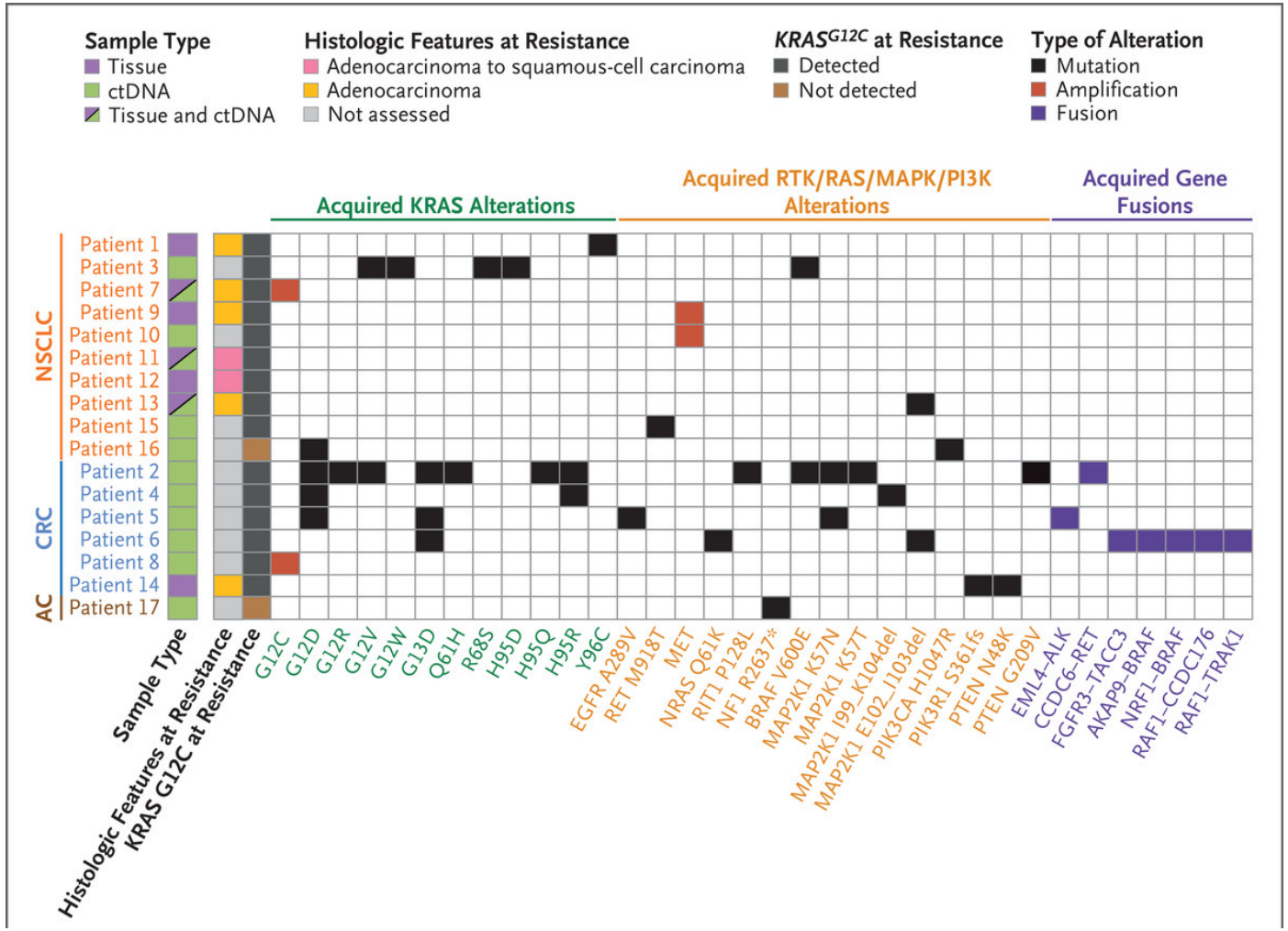
- Patient sample size too small to draw firm conclusions, but
- **PD-L1 status:** ORR lowest in cases with PD-L1 50%
- **Co-Mutations:** ORR lowest in cases with KEAP1 mutation

Preliminary Exploratory Correlative Analysis of Co-Mutations with KRASG12C and Response Rate in Patients with NSCLC treated with Adagrasib



Spira AI, et al. ASCO 2022. Abstract 9002

Putative Mechanisms of Acquired Resistance to Adagrasib Treatment

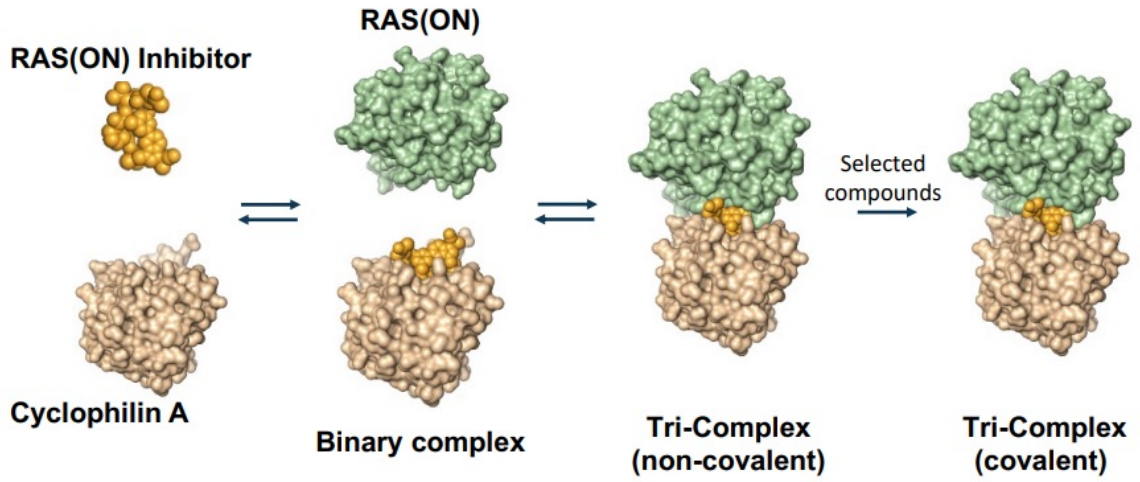


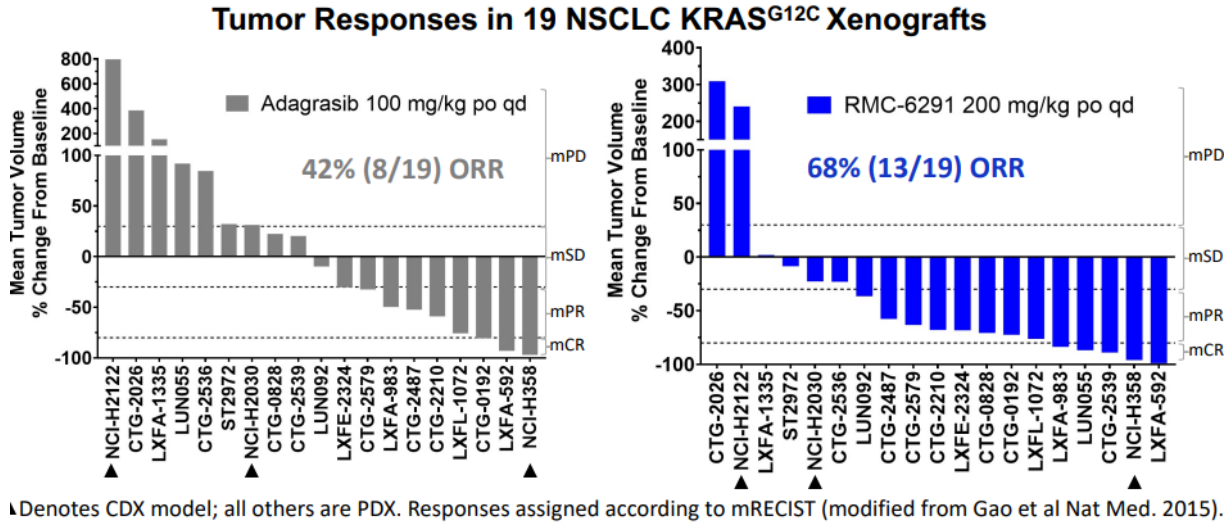
Awad MM et al. N Engl J Med 2021;384:2382-2393.

RAS(ON) Inhibitors

- Less susceptible to adaptive resistance compared to GDP bound RAS

- RMC-6291 KRAS G12C (ON) inhibitor
- RMC-9805 KRAS G12D (ON) inhibitor
- RMC-6236-Pan RAS(ON)





Kelsey S. AACR-NCI-EORTC 2021. Hofmann MH, et al. Cancer Discov. 2022 Apr 1;12(4):924-937.