KRAS-G12C: TAKING AIM AT THE UNDRUGGABLE

Melissa L. Johnson, MD

@MLJohnsonMD2

20 April 2024

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IASLC International Association for the Study of Lung Cancer — Conquering Thoracic Cancers Worldwide

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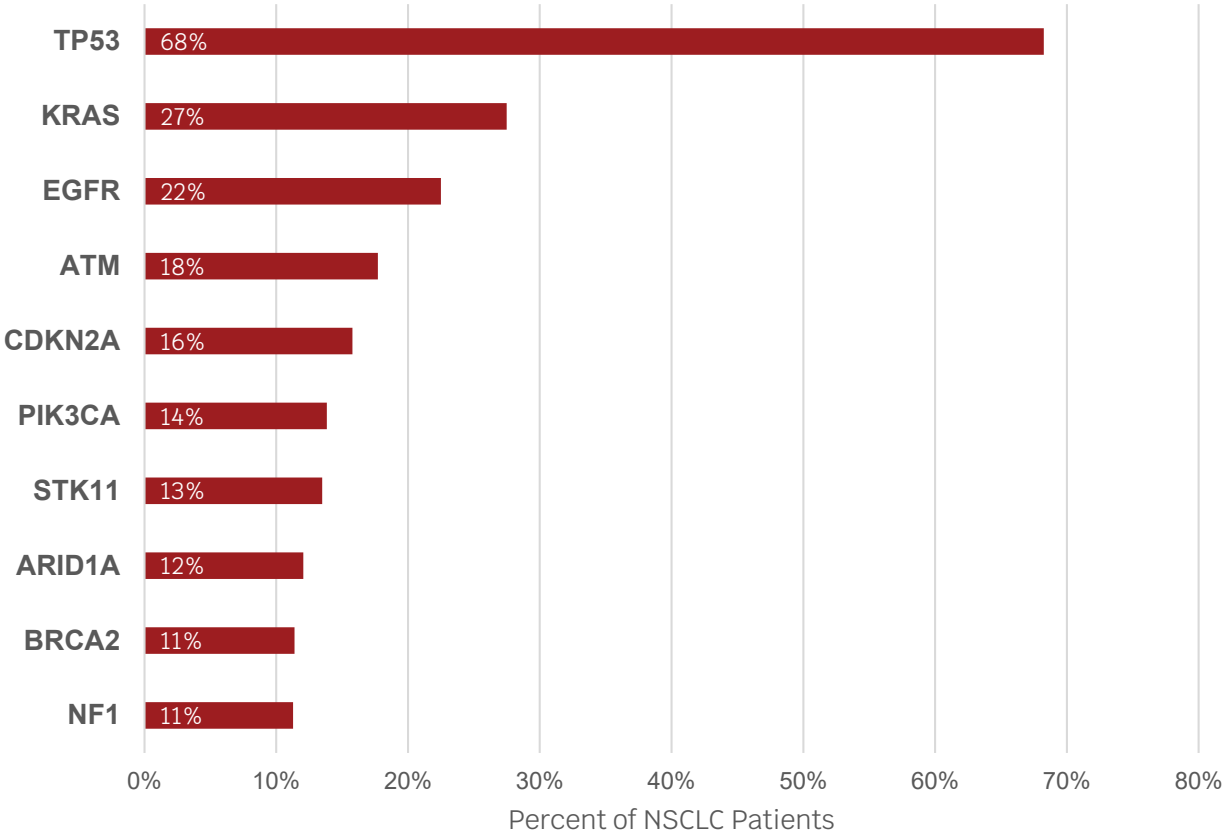
IDEOlogy Health — Creating Aha! Moments In Healthcare

(Ambitious) Agenda

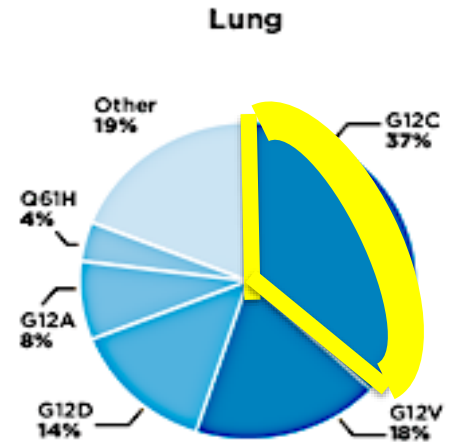
- Challenges in 2L drugging an “undruggable” pocket
- Building a better G12C inhibitor
- Leap to 1L ?!&%
- Acquired Resistance and Co-mutations

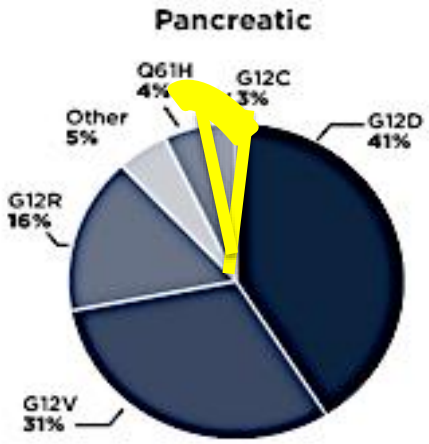
KRAS Mutations Across SCRI By Tumor Types

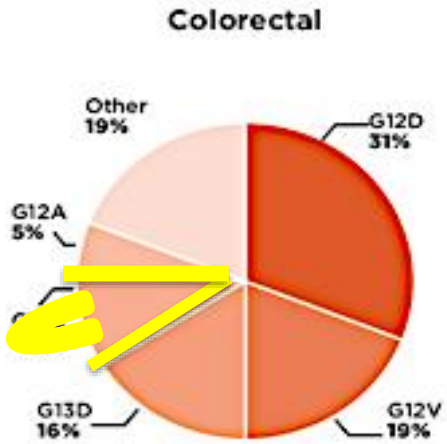
Frequency of activating KRAS mutations across tumor types within the Sarah Cannon network



Breakdown of frequently occurring KRAS mutations in lung, pancreatic, and colorectal cancers within the Sarah Cannon network.



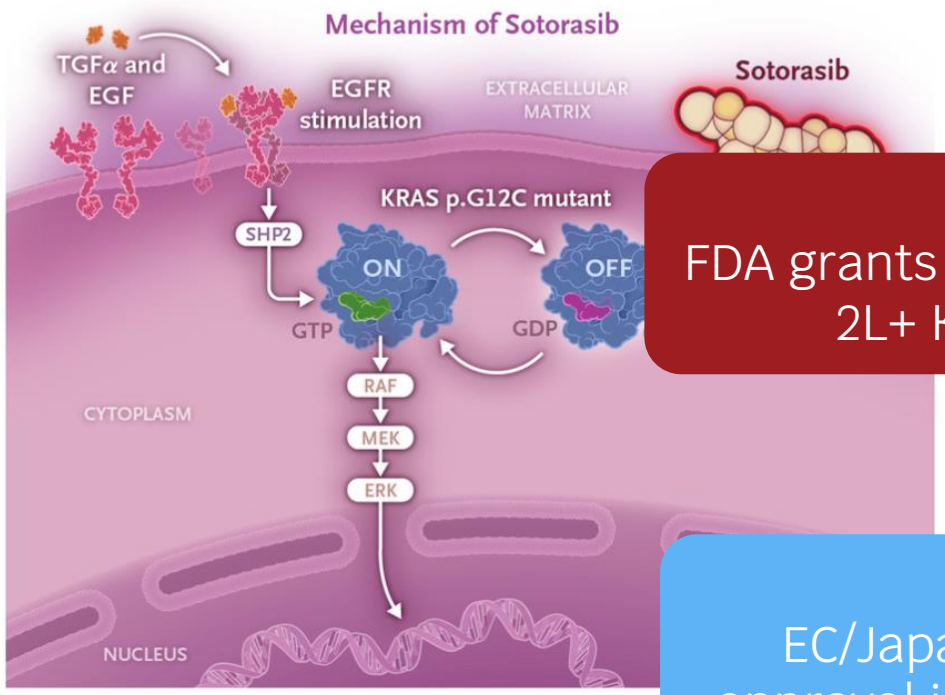




Provided by Sarah Cannon Personalized Medicine

Includes FMI, Guardant, and Caris NGS reports within Genospace across the Sarah Cannon network.

Sotorasib: CODEBREAK 100

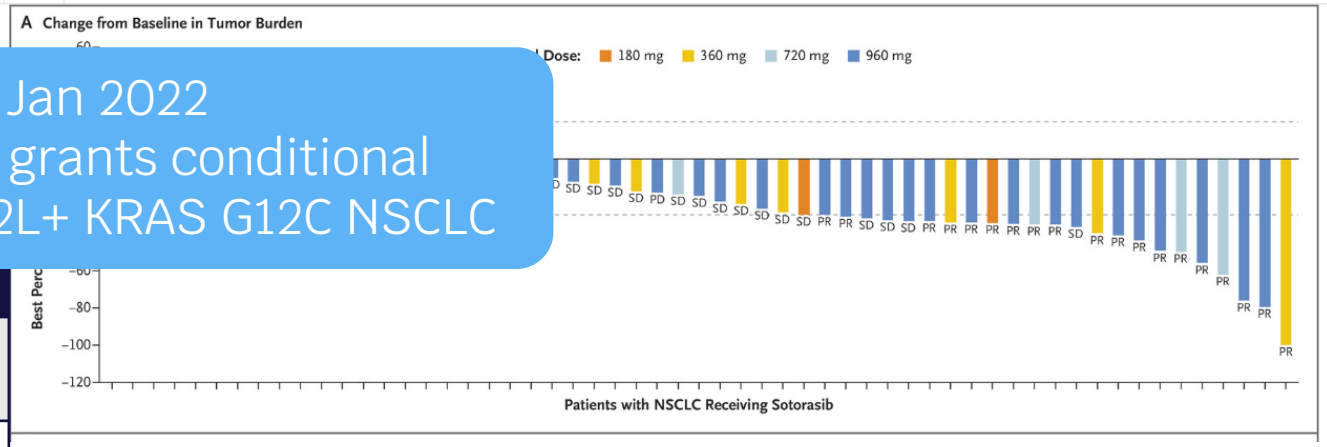


May 2021
FDA grants accelerated approval in 2L+ KRAS G12C NSCLC

Cancers with *KRAS* p.G12C Mutation

G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

Jan 2022
EC/Japan grants conditional approval in 2L+ KRAS G12C NSCLC

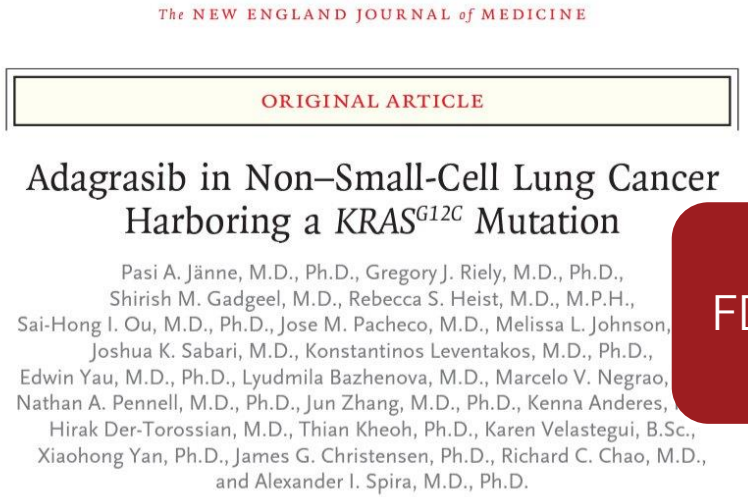


Phase 2 Data 2L KRAS G12C NSCLC

		ORR	DOR	PFS	OS
Sotorasib	960 mg QD	37%	11.1 m	6.8 m	12.5 m

Hong et al NEJM 2020; Skoulidis et al NEJM 2021

Adagrasib


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

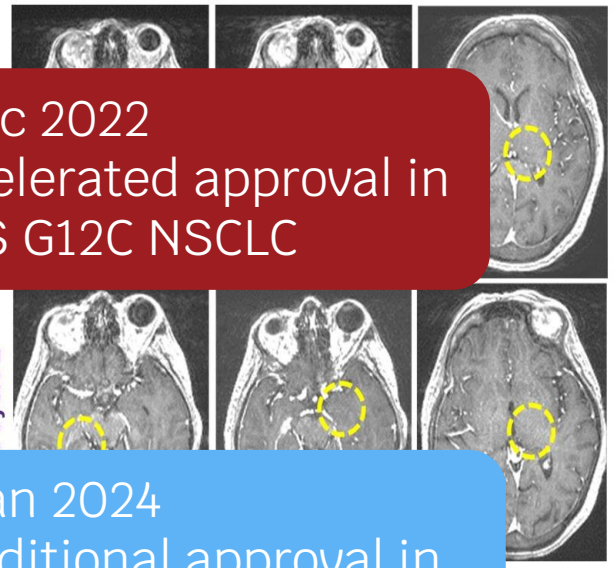
Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, Nathan A. Pennell, M.D., Ph.D., Jun Zhang, M.D., Ph.D., Kenna Anderes, Hirak Der-Torossian, M.D., Thian Kheoh, Ph.D., Karen Velastegui, B.Sc., Xiaohong Yan, Ph.D., James G. Christensen, Ph.D., Richard C. Chao, M.D., and Alexander I. Spira, M.D., Ph.D.

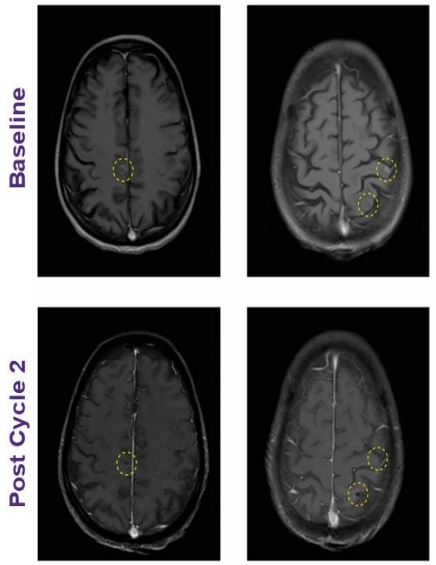
Dec 2022
FDA grants accelerated approval in 2L+ KRAS G12C NSCLC

Jan 2024
EC grants conditional approval in 2L+ KRAS G12C NSCLC

Phase 2 Data 2L KRAS G12C NSCLC					
		ORR	DOR	PFS	
Sotorasib	960 mg QD	37%	11.1 m	6.8	
Adagrasib	600 mg BID	43%	8.5 m	6.5 m	12.6 m

Adagrasib in Patients with Active, Untreated CNS Metastases





- **Cerebrospinal fluid**
  - 24.2 nM (14.6 ng/mL)
  - $K_{p,uu}$ = 0.51
- Two patients had CSF collected, with an average $K_{p,uu}$ of 0.47; this exceeds values for TKIs for which bo CNS penetration and antitumor activity in CNS metastases has been demonstrated[9]

Jannë et al., NEJM 2022; Spira et al., ASCO 2022; Sabari ASCO 2022

Codebreak 200

2L+ KRAS^{G12C} NSCLC

Sotorasib vs. Docetaxel

Key eligibility criteria

- Locally advanced/unresectable or metastatic *KRAS G12C*-mutated NSCLC
- **≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor***
- **No active brain metastases**
- ECOG performance status ≤ 1

Stratification factors

- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

Randomisation 1:1 (N = 345)

- **Sotorasib 960 mg oral daily N = 171**
- **Docetaxel 75 mg/m² IV Q3W N = 174**

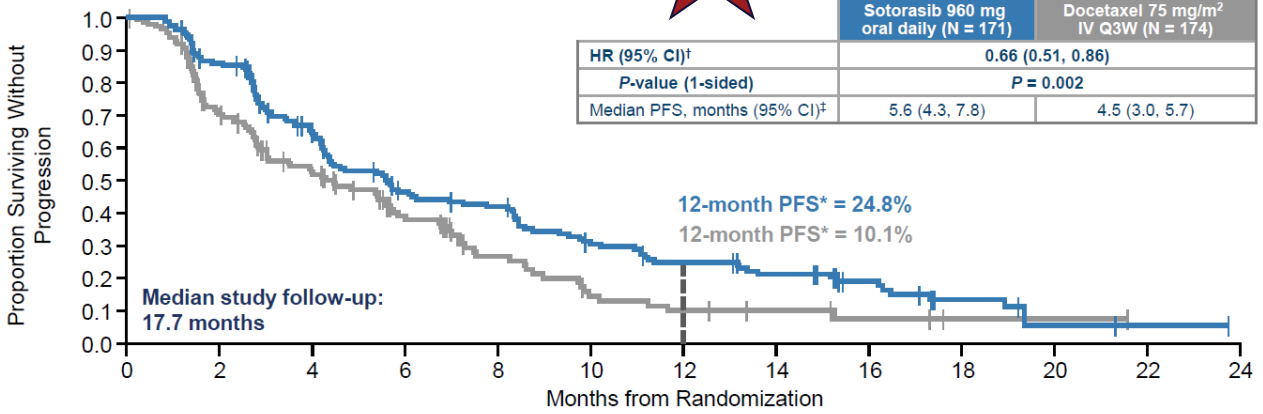
Sotorasib 960 mg oral daily Randomised: N = 171

Did not receive sotorasib n = 2

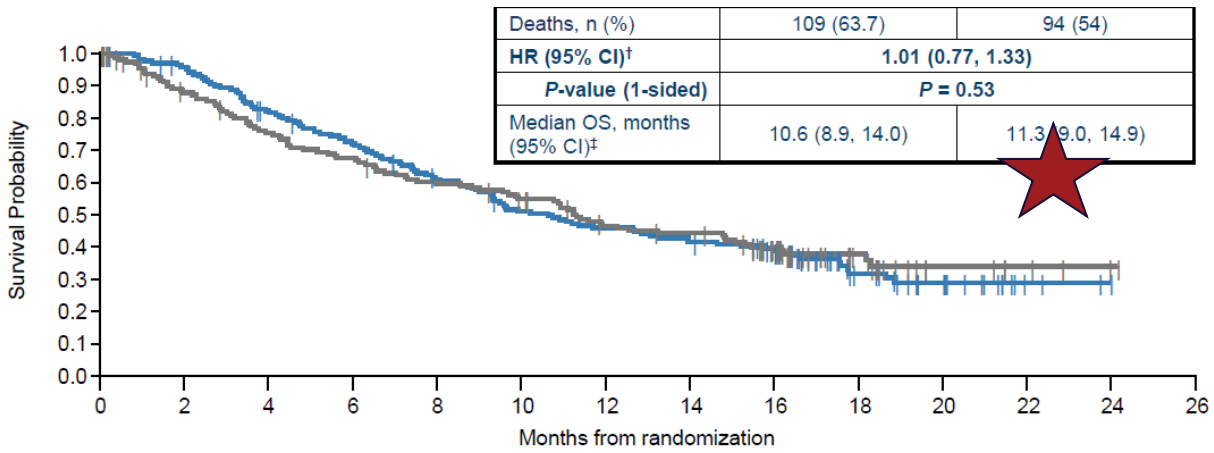
Docetaxel 75 mg/m² IV Q3W Randomised: N = 174

Did not receive docetaxel n = 23

Received treatment: N = 151



	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)



Deaths, n (%)	109 (63.7)	94 (54)
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)

Johnson ML et al., ESMO 2022

Codebreak 200

2L+ KRAS^{G12C} NSCLC

Sotorasib vs. Docetaxel

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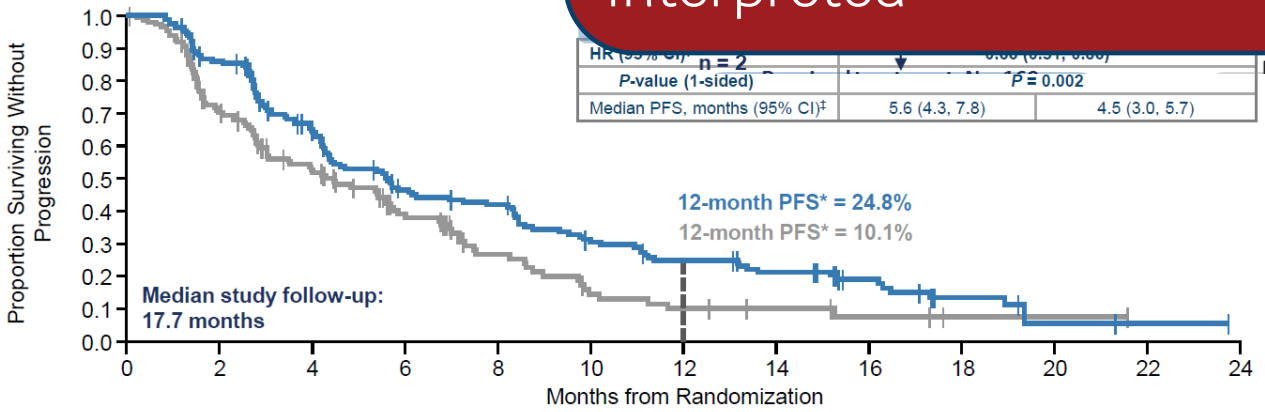
Randomisation 1:1 (N = 345)

Sotorasib 960 mg oral daily N = 171

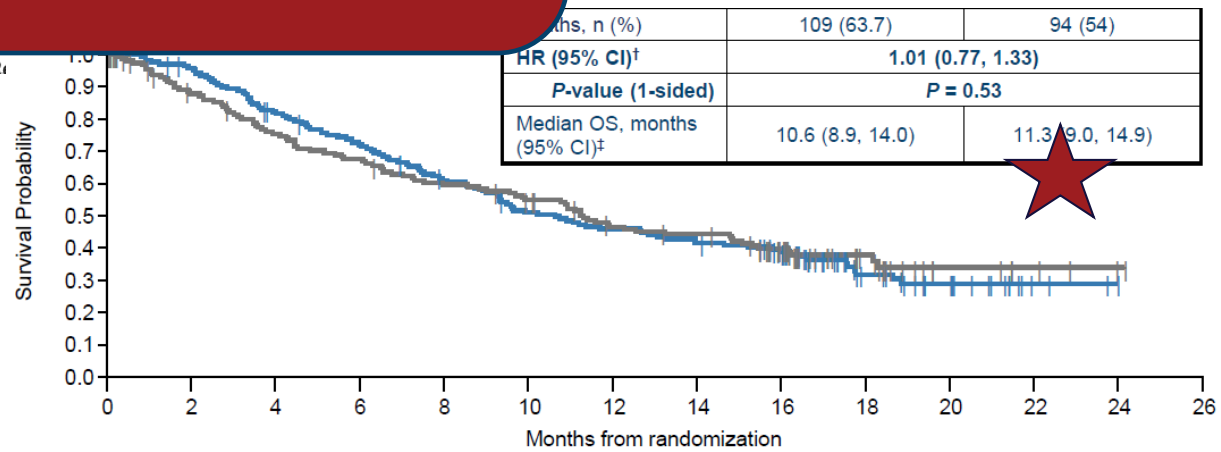
Docetaxel 75 mg/m² IV Q3W N = 174

October 2023

FDA ODAC voted 10-2 that primary end point PFS of CodeBreaK 200 cannot be reliably interpreted



HR (95% CI)‡	n = 2	
P-value (1-sided)	*P* = 0.002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)



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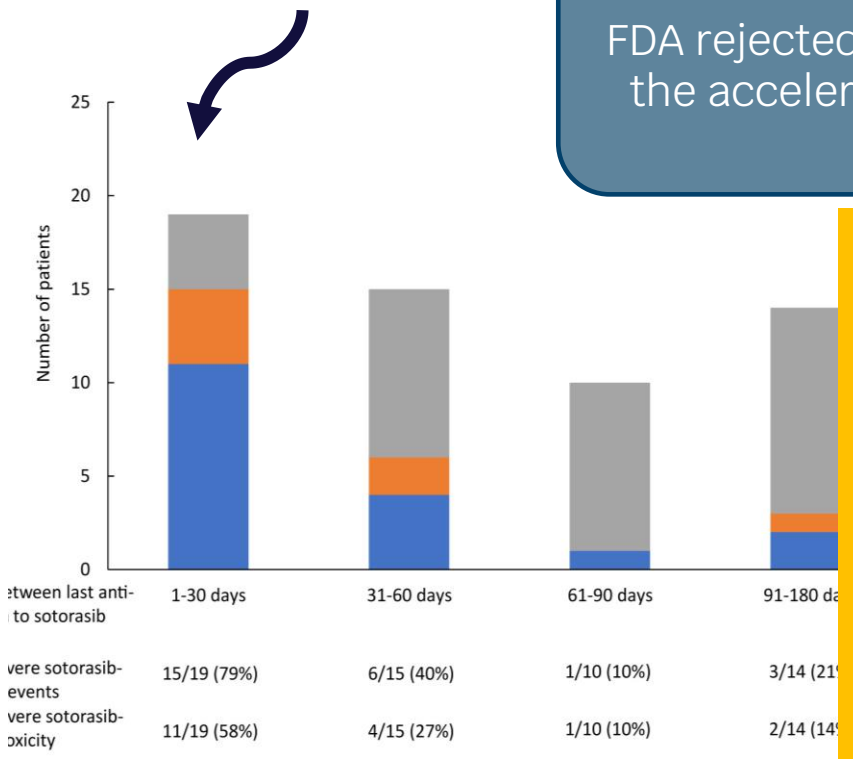
Johnson ML et al., ESMO 2022

Being first isn't always easy

IR-Hepatotox More Common at 0-30 days

Dec 2023

FDA rejected sNDA for full approval of sotorasib, but upheld the accelerated approval, original dose and issued a new postmarketing requirement



LUN 552 | 22118
"CodeBreaK 202"

Stage IV or advanced Stage IIIB or IIIC nonsquamous NSCLC with KRAS p. G12C mutation
PD-L1 (-) by local or central test

Sotorasib + Carboplatin + Pemetrexed

Pembrolizumab + Carboplatin + Pemetrexed

0 PART B

parison to CODEBREAK 200

	Sotorasib 240 mg (N=105)	Difference 960mg-240mg[a] (90% CI)	Sotorasib 960 mg CB-200 (N=171)[1]
	32.7 (23.8, 42.6)	24.8 (16.9, 34.1)	6.9 (-3.4, 17.1)	28.1%
	2 (1.9)	3 (2.9)		
	32 (30.8)	23 (21.9)		
	86.5 (78.5, 92.4)	81.9 (73.2, 88.7)	4.9 (-3.7, 13.5)	82.5
	13.8 (5.6, NE)	12.5 (7.0, NE)		8.64

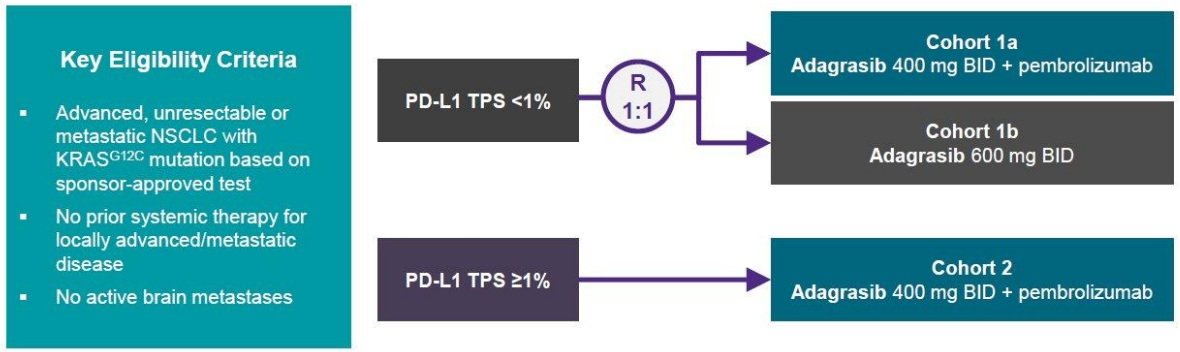
nd DCR were numerically higher in the g arm compared with the 240 mg arm

TUAL PLENARY
ERT COMMENTARY

X: @DrSanjayPopat

Chour A et al Journal of Thoracic Oncology 2023 1814(

KRYSTAL-7: phase 2 experience additive ?



Outcome Measures
Primary: ORR (RECIST 1.1)
Secondary: PFS, DOR, 1-year survival rate, OS, safety, PK

ESMO 2023: Cohorts 1a and 2c combo cohorts

PDL1 50% (n=54) median FU 10.1 mo

Two grade 5 TRAEs (pneumonitis, pneumonia)

TRAEs resulted in IP dc (both drugs) in 6/148 (4%)

24 (16%) had gr3/4 ALT/AST inc; 3 were recurrent s/p steroids

ORRs in KRAS G12C and PDL1 >50%:

- ORR 63% (32/51)
- Med PFS NR (8.2-NE); 60% PFS @12 mo

Median time to response: 1.4 months

KN42 (PDL1 ≥50)[2]
ORR: 40%
Med PFS 7.1 mo
Med OS 20 mo

KN 42 (KRAS G12C)[3]
ORR: 67%
Med PFS 15 mo
Med OS NR (23-NR)

1 Garassino ESMO 2023; 2 Mok Lancet Onc 2019; 3 Herbst ESMO-IO 2019

What do KRYSTAL-7 and KRYSTAL-17 need to show?[1]

KRYSTAL-7
LUN 482 | 20270

Phase 2

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation based on sponsor-approved test
- No prior systemic therapy for locally advanced/metastatic disease
- No active brain metastases

PD-L1 TPS <1% → R 1:1
- **Cohort 1a** Adagrasib 400 mg BID + pembrolizumab
- **Cohort 1b** Adagrasib 600 mg BID

PD-L1 TPS ≥1%
- **Cohort 2** Adagrasib 400 mg BID + pembrolizumab

Outcome Measures
Primary: ORR (RECIST 1.1)
Secondary: PFS, DOR, 1-year survival rate, OS, safety, PK

Phase 3

PD-L1 ≥ 50%

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation
- No prior systemic therapy for locally advanced/metastatic disease

R 1:1
- Adagrasib 400 mg BID + Pembrolizumab
- Pembrolizumab + Pemetrexed + Platinum-based Chemotherapy

KRYSTAL-17
23051

Key Eligibility Criteria (N=90, estimated)

- Unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation
- No prior systemic therapy for locally advanced/metastatic NSCLC, including:
  - Chemotherapy (Cohort E only)
  - CPI (Cohort E only)
  - Any therapy targeting $KRAS^{G12C}$ mutation (all Cohorts)
  - Maintenance therapy following completion of 4–6 cycles of a first-line platinum-based regimen (Cohort C only)
- No active brain metastases
- No radiation (≥30 Gy) to lung within 6 months before first dose of study treatment

Cohort C TPS <50%
- **Platinum** and **Pemetrexed** + **Pembrolizumab** Q3W (4 cycles)*
- Enroll
- **Adagrasib** 400 mg BID + **Pembrolizumab** + **Pemetrexed** Q3W (SLI†)
- **Adagrasib** 400 mg BID + **Pembrolizumab** (up to 31 cycles) + **Pemetrexed** Q3W

Cohort E‡ TPS <50%
- **Adagrasib** 400 mg BID + **Pembrolizumab** + **Platinum** and **Pemetrexed** Q3W (SLI†)
- **Adagrasib** 400 mg BID + **Pembrolizumab** + **Platinum** and **Pemetrexed** Q3W (4 cycles)
- **Adagrasib** 400 mg BID + **Pembrolizumab** (up to 31 cycles) + **Pemetrexed** Q3W

KN 189 (PDL1 <50%)[2]
ORR: 33-50%
Med PFS: 9 mo
Med OS: 21.8 mo

KN 189 (KRAS all PDL1 levels)[3]
ORR 50%
Med PFS 11.3 mo;
Med OS G12C 18.1

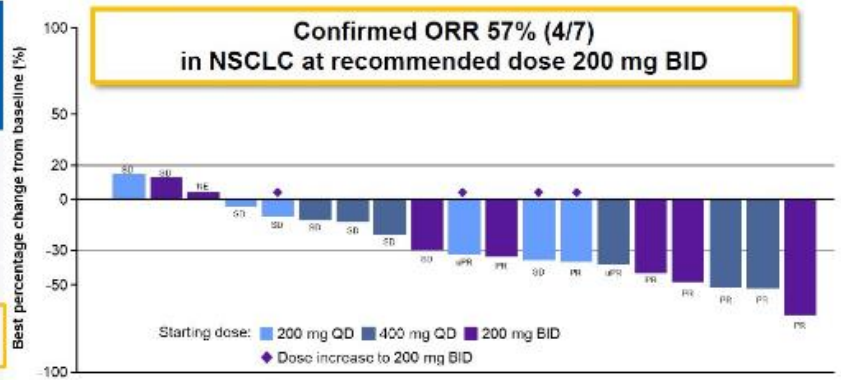
[1]Spira ASCO Daily News, 2023; [2] Gandhi NEJM 2018; [3] Gadgeel Annals of Oncology 2019

“Second-gen” KRAS Inhibitors: More Combinable and Better Tolerated ?

Opnurasib (JDQ443)

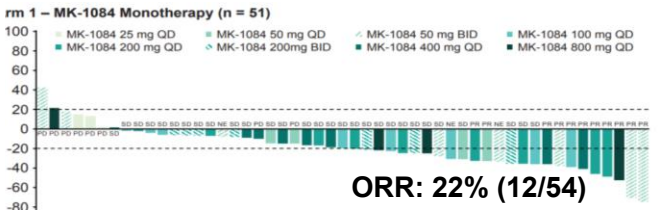
Cassier et al., ASCO 2023

Best overall response, investigator assessed per RECIST v1.1	All patients with NSCLC, n=20, n (%)
PR (confirmed)	7 (35.0)
SD	11 (55.0)
PD	0
NE	2 (10.0)
ORR (confirmed and unconfirmed)	**9 (45.0)**
ORR (confirmed)	7 (35.0)

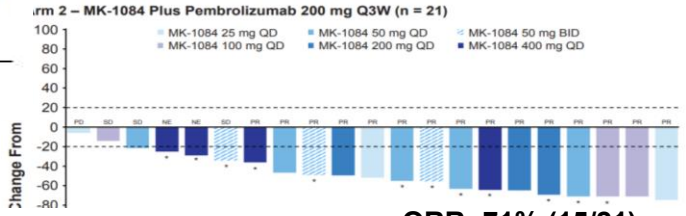


MK-1084 +/- Pembro

Rojas et al., ESMO 2023



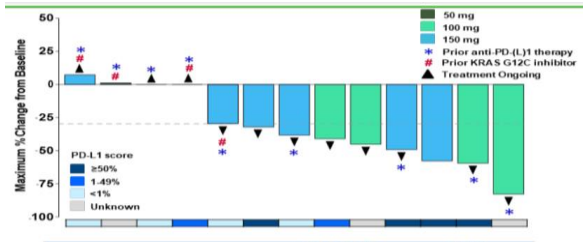
ORR: 22% (12/54)



ORR: 71% (15/21)

Olomorasib (LY3537982)

Murciano-Goroff et al., AACR 2023

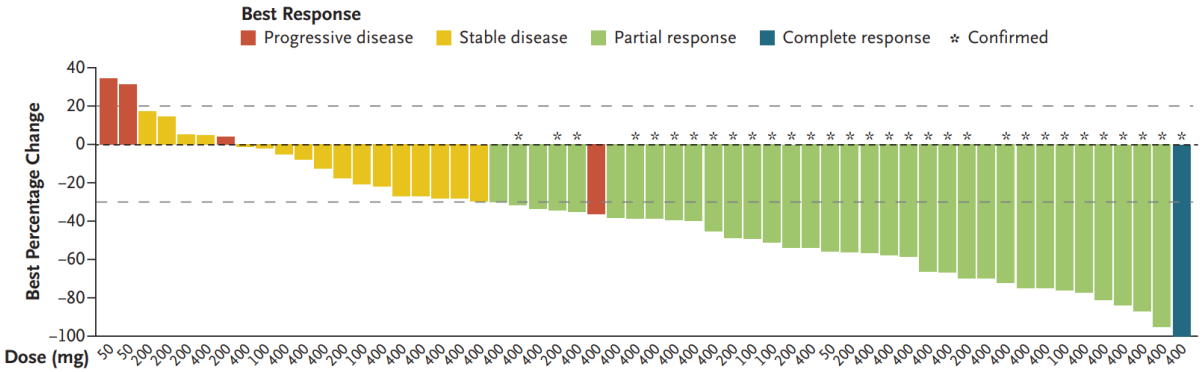


Efficacy Evaluable Patients[a]	KRAS G12Ci naive n = 9	Prior KRAS G12Ci n = 4
Overall Response Rate[b], % (n/N)	78% (7/9)	25% (1/4)
Best overall response		
CR, n (%)	-	-
PR, n (%)	7 (78)	1 (25)
SD, n (%)	2 (22)	2 (50)
PD, n (%)	-	1 (25)
DCR, n (%)	9 (100)	3 (75)

ORR: 78% (7/9) G12 naive)
ORR: 25% (G12C exp)

Divarasib (GDC-6036)

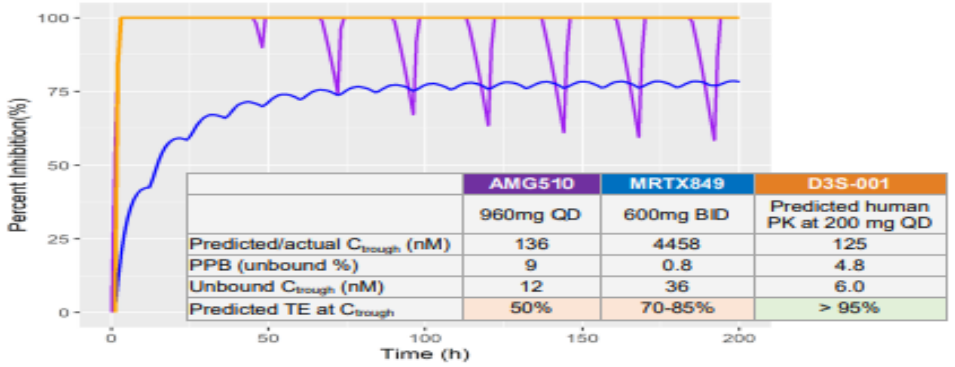
Sacher et al., NEJM 2023



Confirmed ORR: 53.4% (30/56)

D3S-001

Zhang et al. EORTC-NCI-AACR, 2022



	AMG510	MRTX849	D3S-001
	960mg QD	600mg BID	Predicted human PK at 200 mg QD
Predicted/actual C_{trough} (nM)	136	4458	125
PPB (unbound %)	9	0.8	4.8
Unbound C_{trough} (nM)	12	36	6.0
Predicted TE at C_{trough}	50%	70-85%	> 95%

1L KRAS-G12C Trials

LUN 540 | 23049
"Krascendo-170 Lung"

- ≥18 years of age
- Unresectable/metastatic *KRAS* G12C+ NSCLC
- Non-squamous histology
- Measurable disease per RECIST v1.1
- No prior systemic treatment
- Available tissue sample
- ECOG performance status 0 or 1

Cohort A
PD-L1 tumour cell expression ≥1%

Cohort B
Any PD-L1 tumour cell expression

Divarasib + pembrolizumab

Divarasib + pembrolizumab + platinum-based CT‡ and pemetrexed

FCS-N
FCS-S
FCS-E
FCS-P
HOC
BRCC
VOA

Phase 3 Portion

- Stage IIIB-IIIC or Stage IV NSCLC
- Evidence of *KRAS G12C* mutation
- Must have known PD-L1expression
  - Part A: ≥50%
  - Part B: 0% to 100%
- Measurable disease per RECIST v1.1
- ECOG performance status of 0 or 1

Part A

Tumor PD-L1 expression ≥50%

Olomorasib† + pembrolizumab‡
or
Placebo¶ + pembrolizumab‡

Part B

Tumor PD-L1 expression 0-100%

Olomorasib† + pembrolizumab‡ + pemetrexed§ + platinum‖
or
Placebo¶ + pembrolizumab‡ + pemetrexed§ + platinum‖

ACS
MOH
NWCS
WVCI
OHC
Prisma
RMCC

TxO-Gulf Coast
TxO- Central/South
VCS

SCRI TBD | 23341
LUN 544 | 22322
"SUNRAY-01"

Proposed Global Randomized Phase 3 Trial in Patients with Previously-Treated RAS Mutant NSCLC

Trial Design[1]

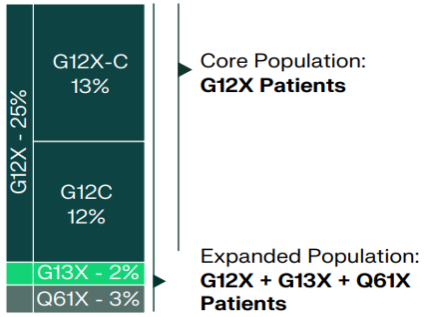
R → RMC-6236
R → Docetaxel

Endpoints
PFS
OS
Patient Reported Outcomes

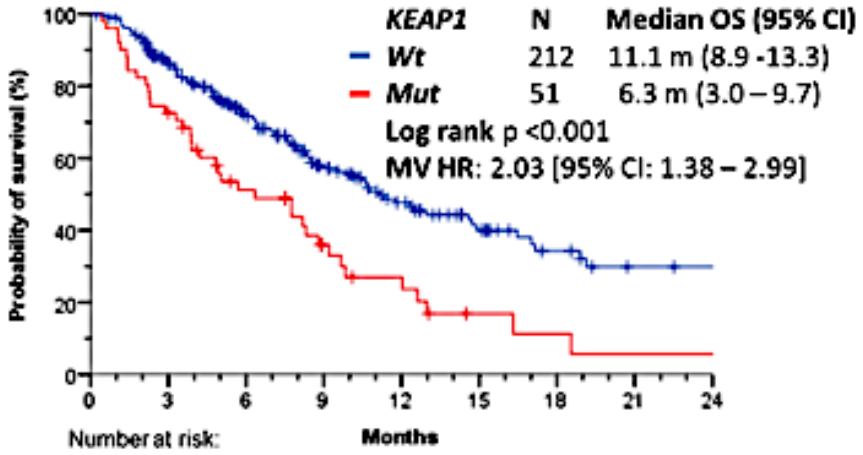
- **N** > 400 patients
- **Prior therapies**: Anti-PD-(L)1 and platinum-containing regimen in metastatic setting; RAS inhibitor naïve (including G12C inhibitor)
- **Biomarker**: RAS G12X, G13X, or Q61X mutation
- **Study Initiation**: Aiming for 2024

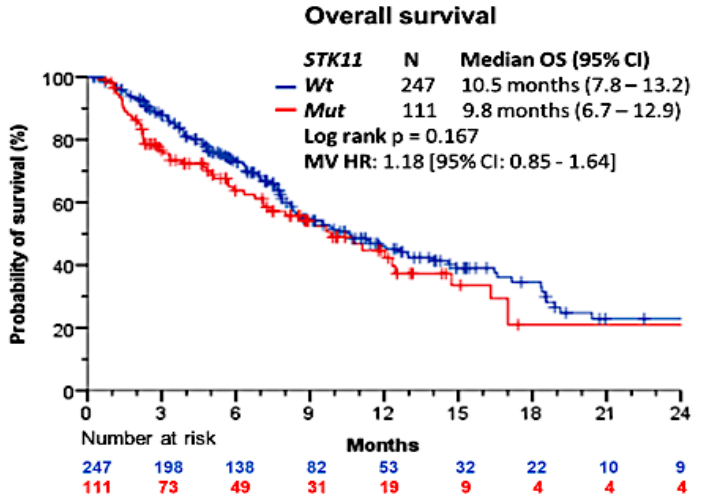
- Potential for nested trial design to enable evaluation of core

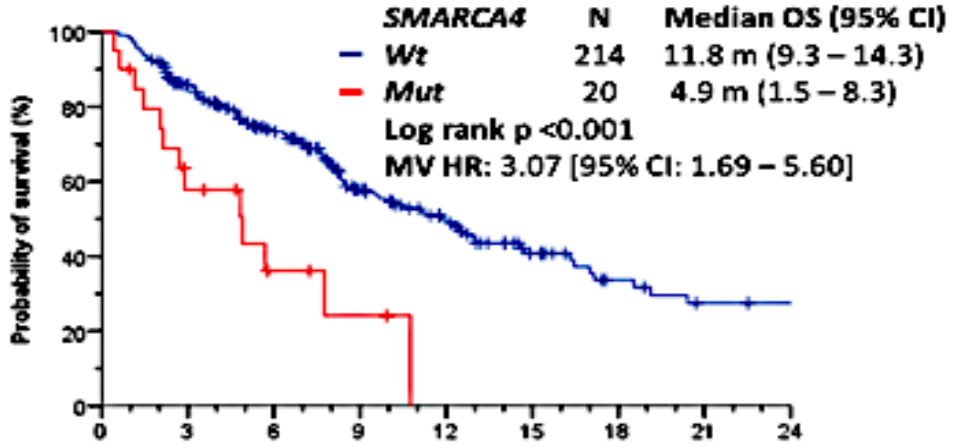
Potential Patient Populations[1,2]

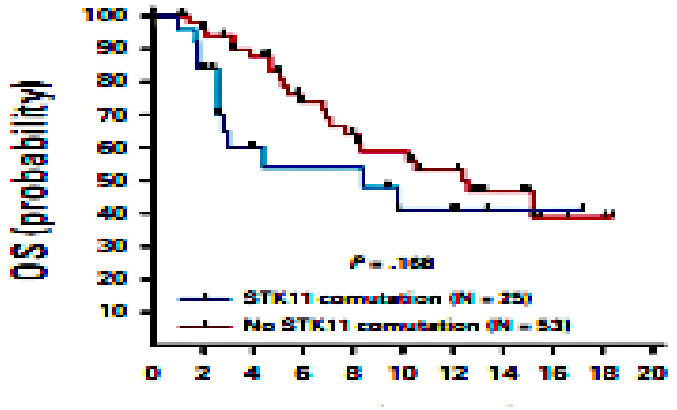


Impact of Co-mutations KEAP1, SMARC4 and STK11 on Overall Survival when treated with KRAS G12C inhibitors



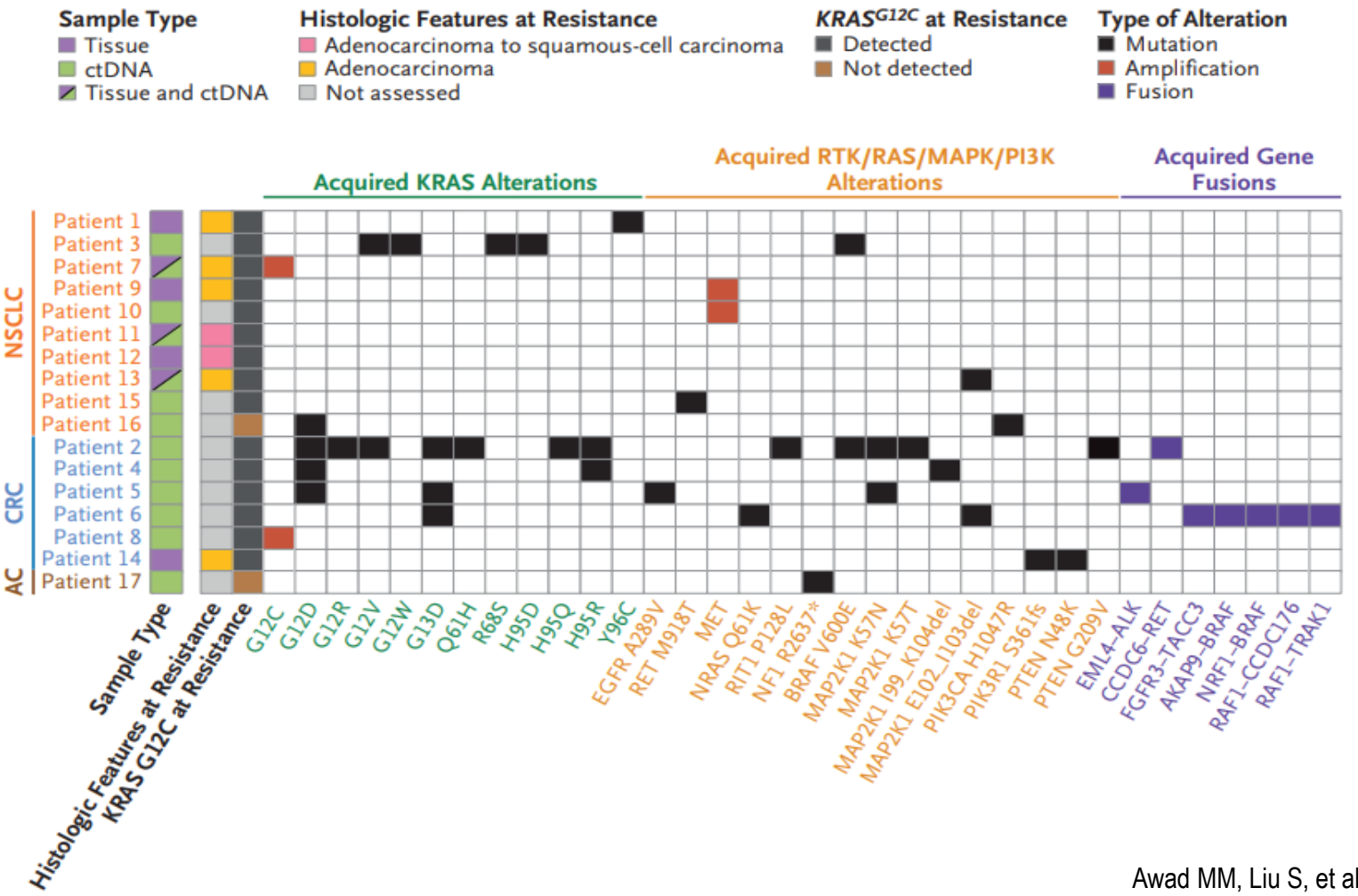


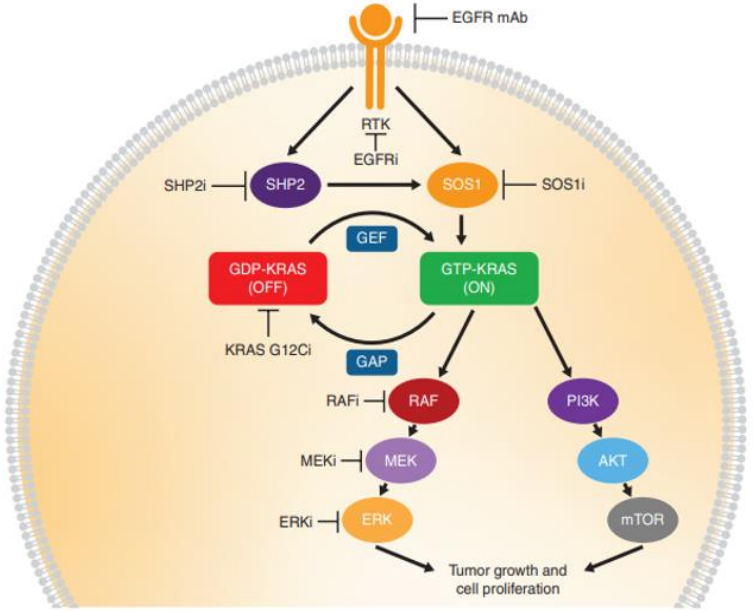




Negrao MV, et al, *Cancer Discovery*, 2023 Apr 17;CD-22-1420
Thummalapalli…Arbour et al. JCO Practice 2022.

Acquired Resistance to KRAS^{G12C} Inhibitors





Awad MM, Liu S, et al, *N Engl J Med* 2021; 384:2382-2393; Hofmann, et al. *Cancer Discov.* 2022

Conclusions: KRAS-G12C inhibitors

It's not easy to take aim against the undruggable

Moving to 1L …is it really better for all? Can it really work for longer than chemoIO?

Addressing acquired resistance early only worth it if combination toxicity manageable