New Targets and Targeted Therapy

UCDAVIS COMPREHENSIVE CANCER CENTER

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NCI CCC
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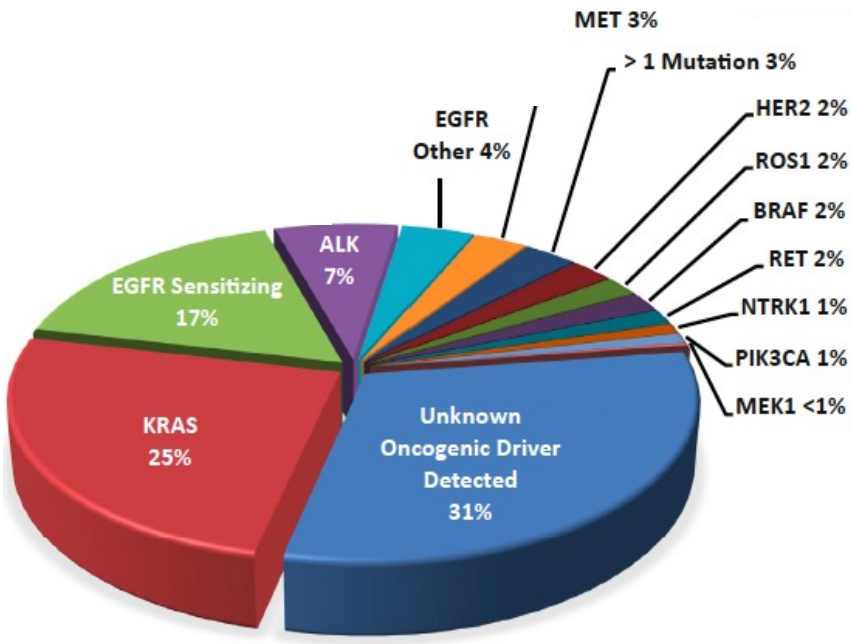
DISCLOSURES

Commercial Interest	Relationship(s)
Blueprint, Beigene, Daiichi Sankyo, EMD Serano, Janssen, Regeneron, Sanofi, Biodesix, Bayer, Turning Point, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Roche/Genentech, Boehringer Ingelheim, Merck, SeaGen	Consulting/Advisory Board
Merck, Novartis, AstraZeneca, Spectrum, Revolution Medicines, Arrivent, IO Biotech, Vitrac	Research Funding (To Institution)

New Targets and Targeted Therapies

- Overcoming EGFR-TKI Resistance
- Targeting Previously Undruggable Mutations (EGFR Exon 20 ins and KRAS)
- KRAS mutant NSCLC/Co-mutations that mediate resistance to systemic treatments (KEAP1/NFE2L2)

Progress in Targeted Therapy for NSCLC-Adenocarcinoma



KRAS G12C
adagrasib, sotorasib

EGFR exon 20 insertions
mobocertinib, poziotinib, amivantamab

EGFR:
gefitinib, afatinib, erlotinib, osimertinib, dacomitinib

ALK:
Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib, entrectinib

ROS1:
Crizotinib, cabozatinib, ceritinib, brigatinib, lorlatinib, entrectinib, ropotrectinib

BRAF:
Dabrafenib/trametinib, vemurafenib, dabrafenib

MET:
Crizotinib, cabozatinib, capmatinib, tepotinib, savolitinib, merestinib, glesatinib

HER2:
Trastuzumab emtansine, afatinib, dacomitinib, poziotinib, neratinib-temsirolimus, XMT-1522, TAK-788, Trastuzumab deruxtecan

RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib,pralsetinib, RXDX-105

NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

FLAURA: Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: Final overall survival data

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years old
- WHO performance status 0/1
- Exon 19 deletion/L858R (enrollment by local or central *EGFR* testing)
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable CNS metastases were allowed

Stratification by **mutation status** (exon 19 deletion/ L858R) and **race** (Asian/non-Asian)

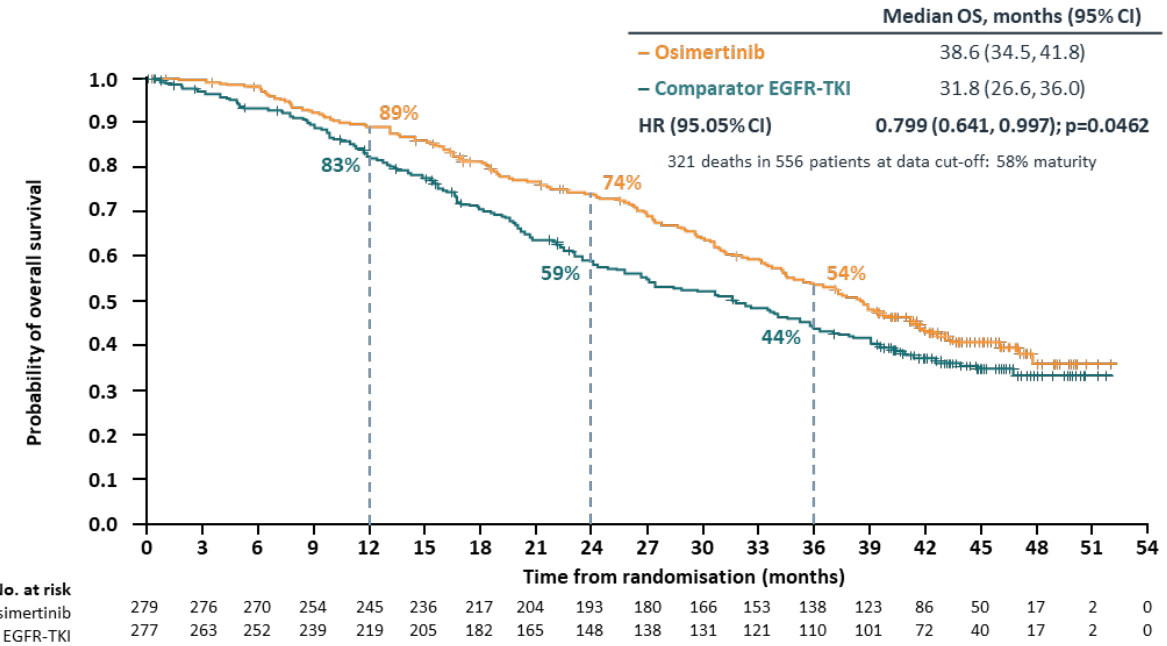
R 1:1

Osimertinib (80 mg po qd) (n=279)

Comparator EGFR-TKI; **Gefitinib** (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

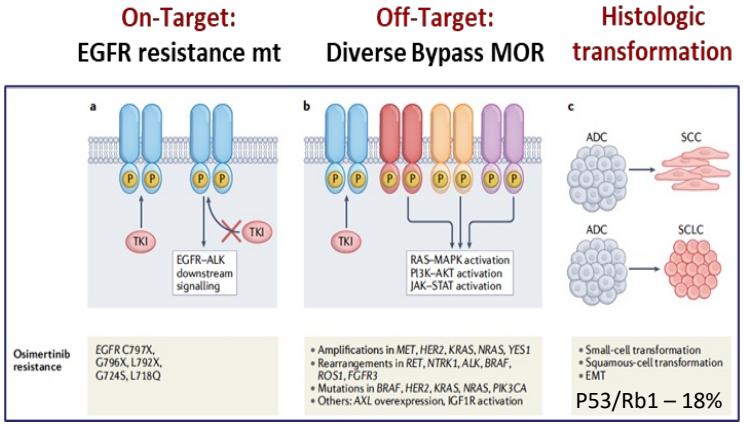
RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

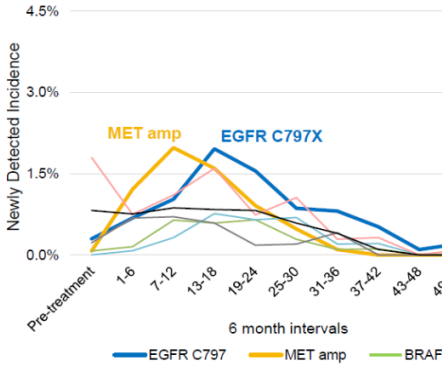


Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

Broad Mechanisms of Resistance to EGFR-TKI and Temporal Occurrence

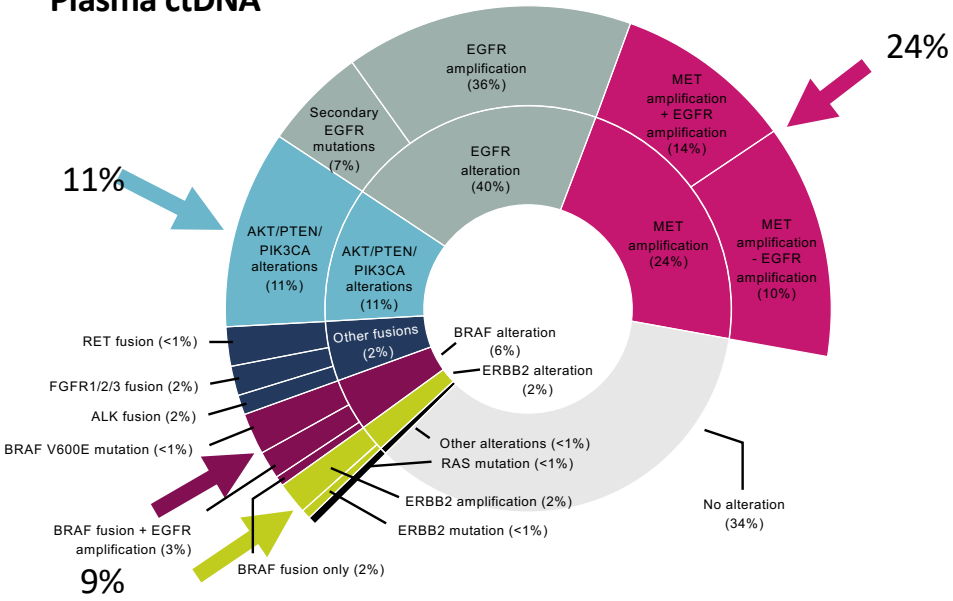


Cooper AS, et al. Nat Rev Clin Oncol 2022



Presented by S. Ramalingam WCLC 2022

Genomics from Orchard: N-174 tissue samples/concurrent Plasma ctDNA



- **Pre-Existing Comutations Mediating Resistance (Impact for locally advanced/early stage treatment)**
- **Resistance to Immunotherapy**

C797S-Active Compounds in Development: Preclinical Data

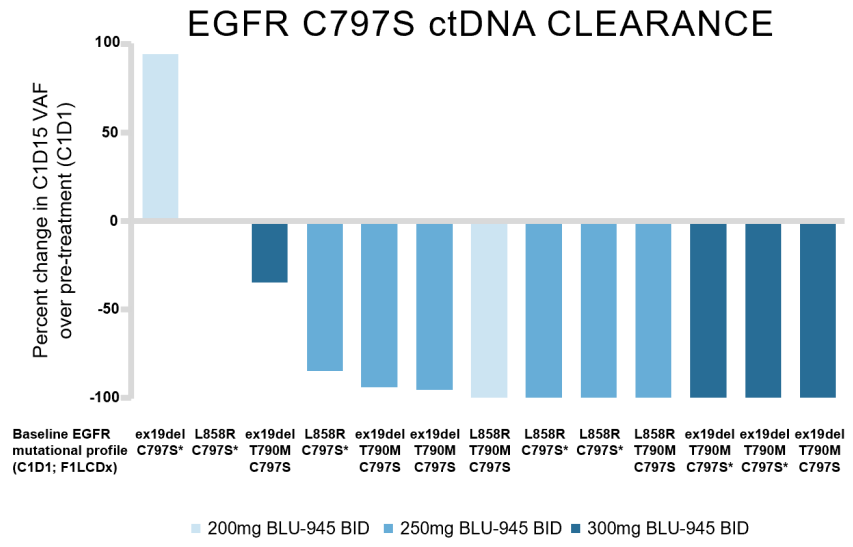
Compound	Del19	L858R	Del19/ T790 M	L858R/ T790M	Del19/ C797S	L858R/ C797S	Triple Mutant	Other	CNS?	Status
BLU-945	-	X	X	X	-	X	X		-	Phase 1/2 (NCT04862780)
BLU-701	X	X	-	-	X	X	X		X	Discontinued
BLU-525	X	X	-	-	X	X	X		X	Preclinical
BDTX-1535	X	X	-	-	X	X	X	Uncommon	X	Phase 1 (NCT05256290)
THE-349	X	X	X	X	X	X	X		X	Preclinical
H002	X	X	X	X	X	X	X		X	Phase 1/2 (NCT05552781)
BAY 2927088	X	X			X	X		Ex20ins		Phase 1 (NCT05099172)
JIN-A02	X	X	X	X	X		X		X	Phase 1/2 (NCT05394831)
BBT-176	X	X	X		X	X	X		X	Phase 1/2 (NCT04820023)

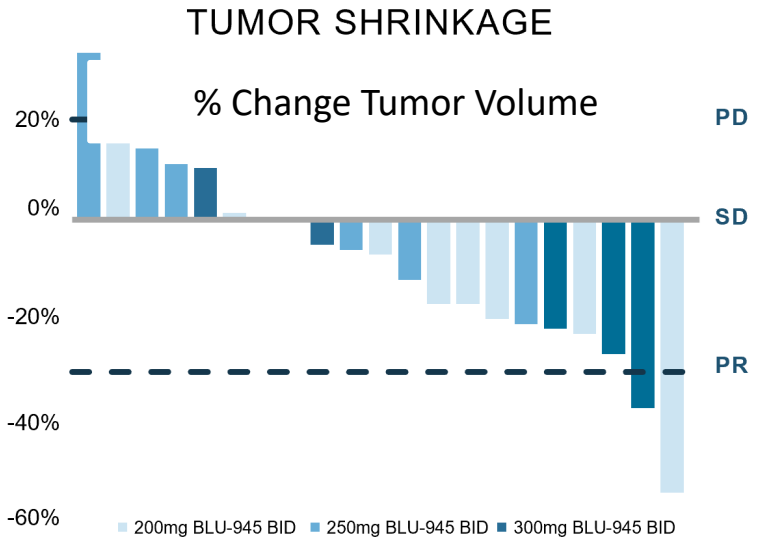
Predicted Not Active Predicted Active No available data

Shum et al, AACR 2022; Tavera-Mendoza et al ENA 2022 #177; Lucas et al. ENA 2022. Abstract #64; Zhang et eal. ENA 2022 #236; Siegel et al. ENA 2022 #17; Lim et al ESMO 2021; Yun et al ESMO 2022 #999P

Slide courtesy of Julia Rotow, MD

BLU-945: Preliminary Efficacy Data
Monotherapy Cohorts, Top Dose Levels

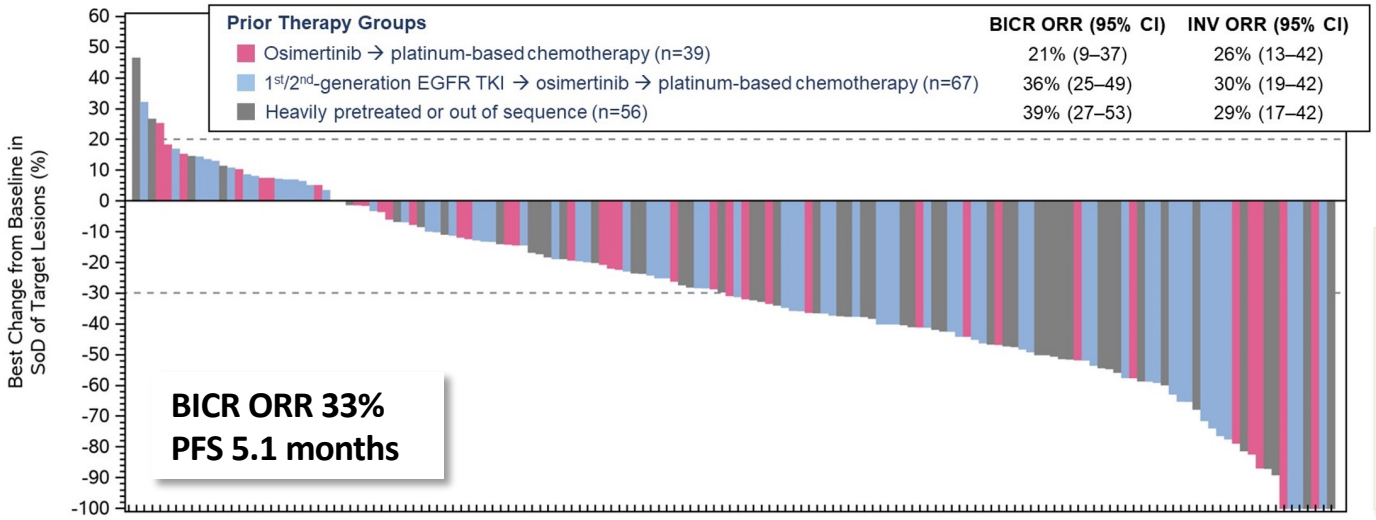




Adapted from: Mar, B. Presented to EGFR Exon 20 Research Consortium

Amivantamab + Lazertinib

EGFR/MET Bispecific +3rd Gen EGFR TKI
CHRYSALIS-2



In CHRYSALIS-1, MET/EGFR IHC score correlated with response (n=20)

ORR 90% if IHC+
ORR 10% if IHC-

Shu et al. ASCO 2022. #9006.; Bauml et al ASCO 2021 #9006

INSIGHT2: Tepotinib and Osimertinib

Key eligibility
- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by central/ local FISH testing (TBx) or central NGS testing (LBx)
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed

R 1:1

- **Tepotinib** 500 mg QD + **osimertinib** 80 mg QD
- **Tepotinib** monotherapy

Primary endpoint:
- ORR by IRC (patients with *MET*amp centrally confirmed by TBx FISH treated with tepotinib + osimertinib)

Secondary endpoints:
- ORR by IRC in patients with:
  - *MET*amp centrally confirmed by TBx FISH treated with tepolinib

Detection of *MET*amp

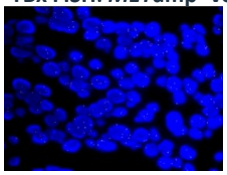
*MET*am definitions

TBx FISH: *MET* GCN ≥5 and/or *MET/CEP7* ≥2

and/or

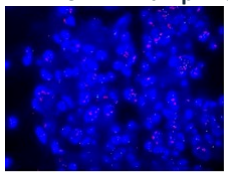
LBx NGS: *MET* GCN ≥2.3; Archer®

TBx FISH: *MET*amp -ve



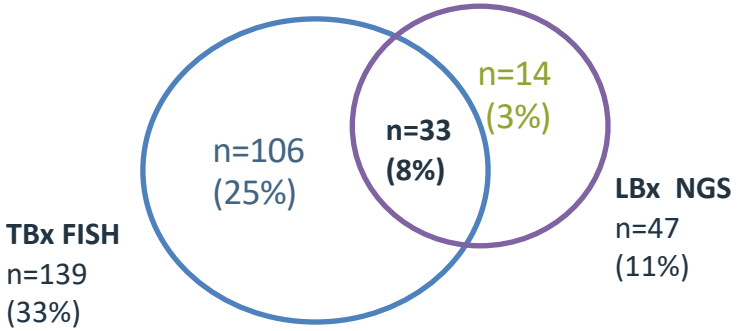
MET GCN, 2.33; *MET/CEP7*, 0.96

TBx FISH: *MET*amp +ve

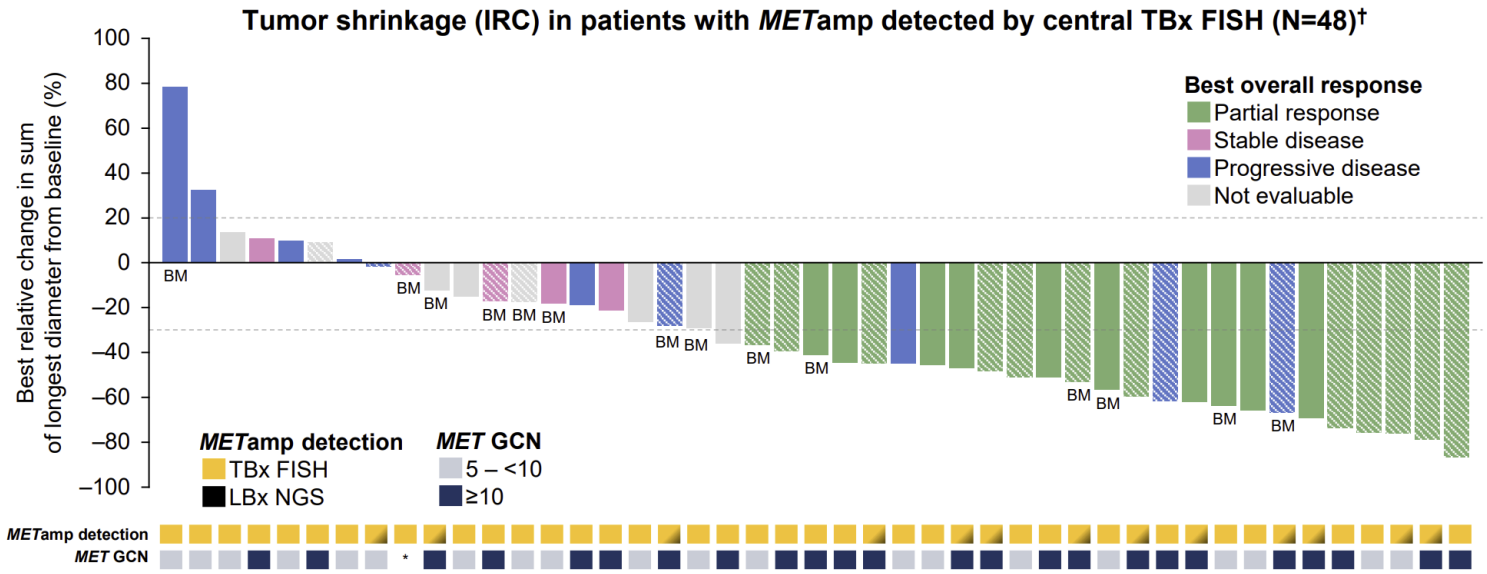


MET GCN, 17.4; *MET/CEP7*, 7.35

*MET*amp detected in 153/425 (36%) of pre-screened patients



INSIGHT 2: Osimertinib + Tepotinib for MET-amplified EGFRm NSCLC



ORR 45.8%-56.5% osimertinib + tepotinib

ORR 8.3% tepotinib monotherapy

EGFR + MET TKI Combinations

Osimertinib + Savolitinib for MET+ s/p Osimertinib

TATTON Phase Ib
FISH MET/CEP7 2+ or MET 5x+; IHC 3+ in 50%+; NGS 5X CNG)

ORR 30% post 3rd gen EGFRTKI

SAVANNAH Phase II
Definition MET+: IHC 50+ or FISH 5+ (62% screened)
Definition MET-high: IHC 90+/FISH 10+ (34% screened)

ORR 49%, PFS 7.1 mo MET-high

Osimertinib + Capmatinib for MET+ s/p Osimertinib

SAFFRON Phase III
NCT NCT05261399

GEOMETRY-E Phase III
Randomized osimertinib + capmatinib vs platinum doublet
NCT 04816214 → study

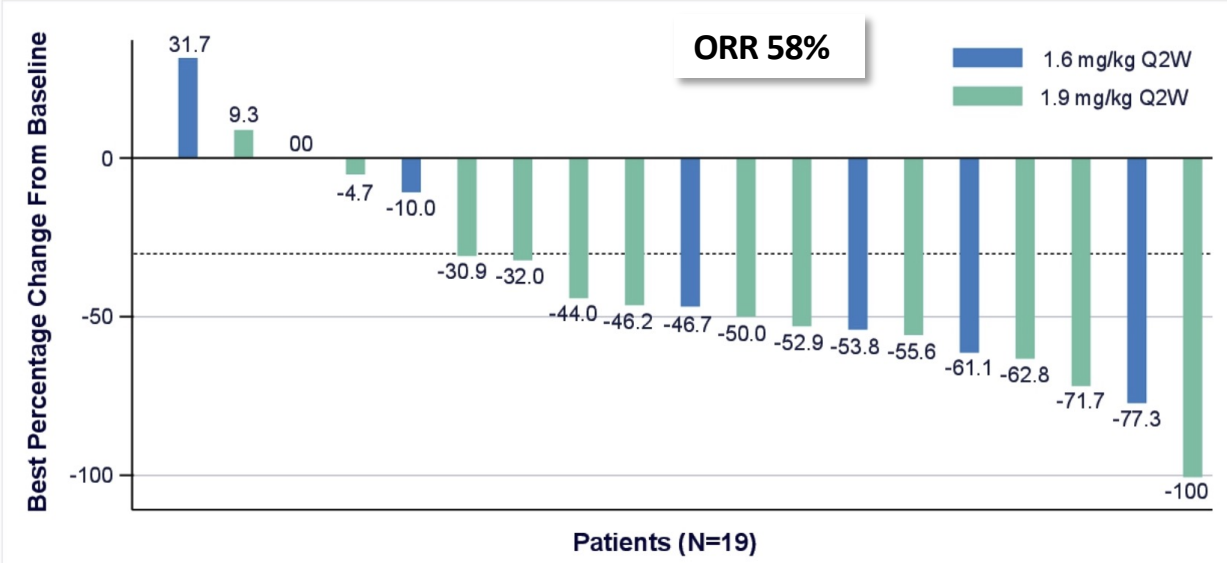
Key Takeaways

- Biomarker Definition of MET high
- What does that mean in the patient?
- Tumor Heterogeneity and response
- Single agent MET TKI likely unhelpful

Sequist et al, Lancet Oncology, 2020; Ahn et al, IASLC 2022 EP08.01-140; McCoach et al J Precision Oncol. 2021.

Telisotuzumab vedotin + Osimertinib
MET-ADC + EGFR TKI

MET-overexpression: IHC 3+ in at 25% of tumor cells



Goldman et al. ASCO 2022. #9013

Other Bypass Tracts That Are Potentially Actionable

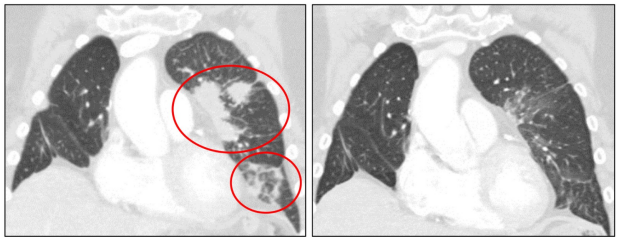
ALK Fusions	**Osimertinib + Alectinib** 6 months DoR	Case Reports
BRAF Fusions	**Osimertinib + Trametinib** Response, D/c at 5 mo (Tox)	Case Report
BRAF V600E	**Dabrafenib/Trametinib** 7-8 months DoR **Osimertinib+Vemurafenib** 7+ months DoR	Case

Z. Piotrowska et al. Cancer Discovery 2022

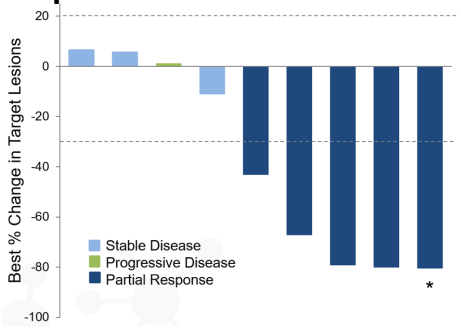
Osimertinib + RET TKI in Acquired Resistance Mediated by RET Fusion

Pralsetinib

B



Selpercatinib

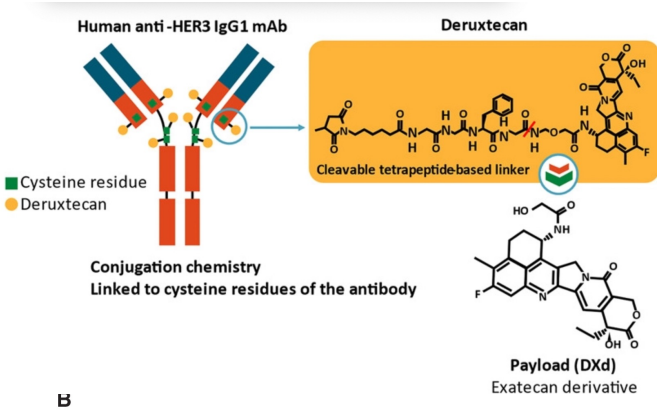


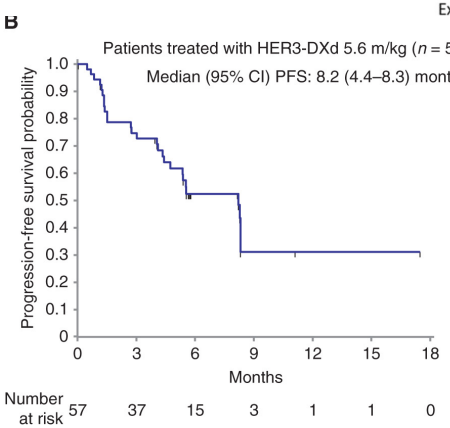
Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

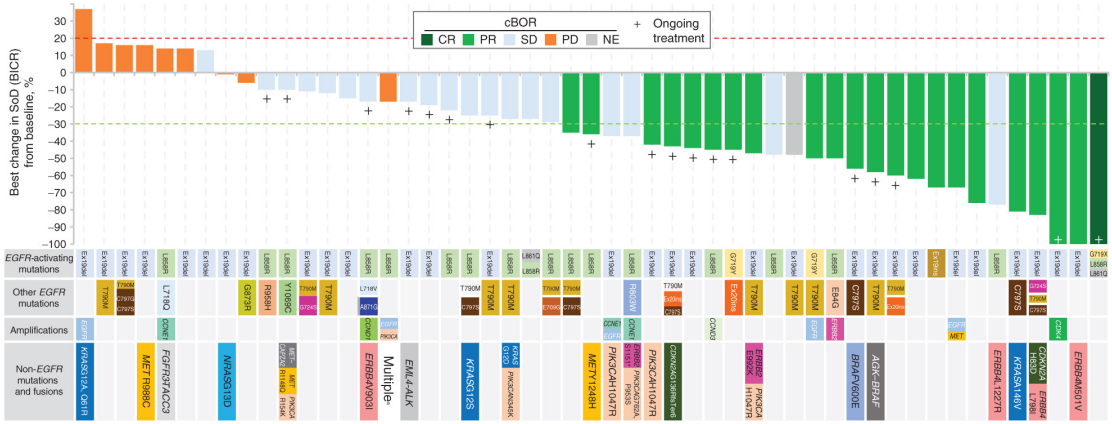
*One partial response unconfirmed

One patient with clinical progression without radiographic evaluation not shown

Patritumab deruxtecan in EGFR-mutated NSCLC with PD on Prior EGFR-TKI

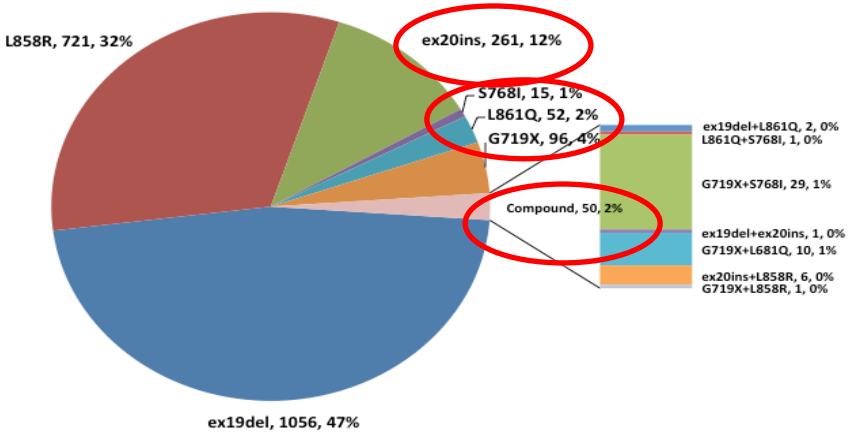


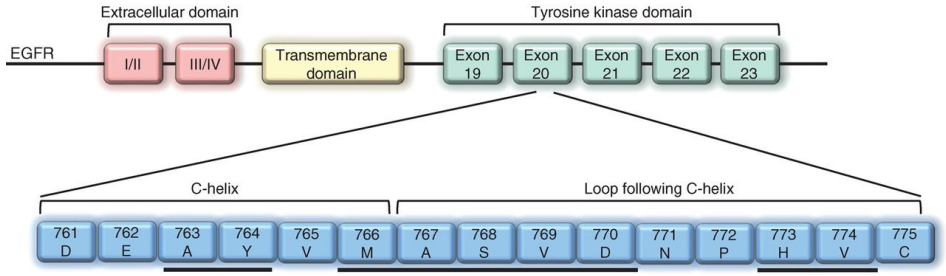


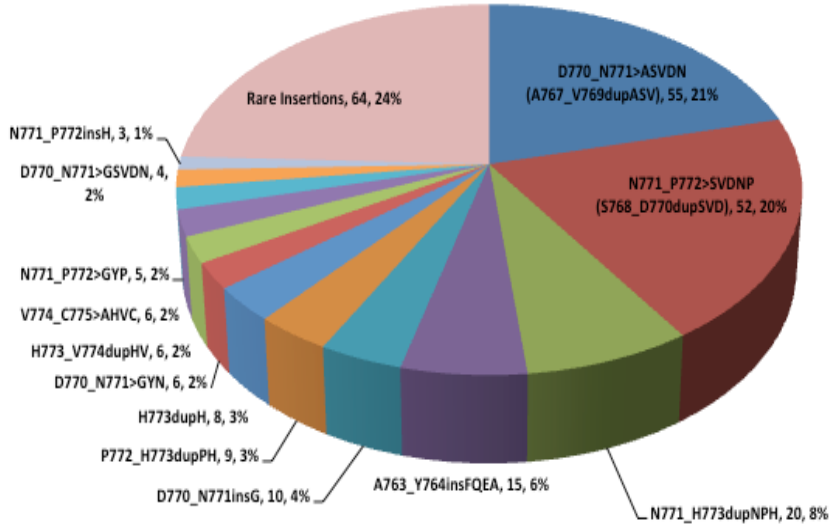


P. Janne et al. Cancer Discovery 2022.

EGFR mutations are heterogeneous





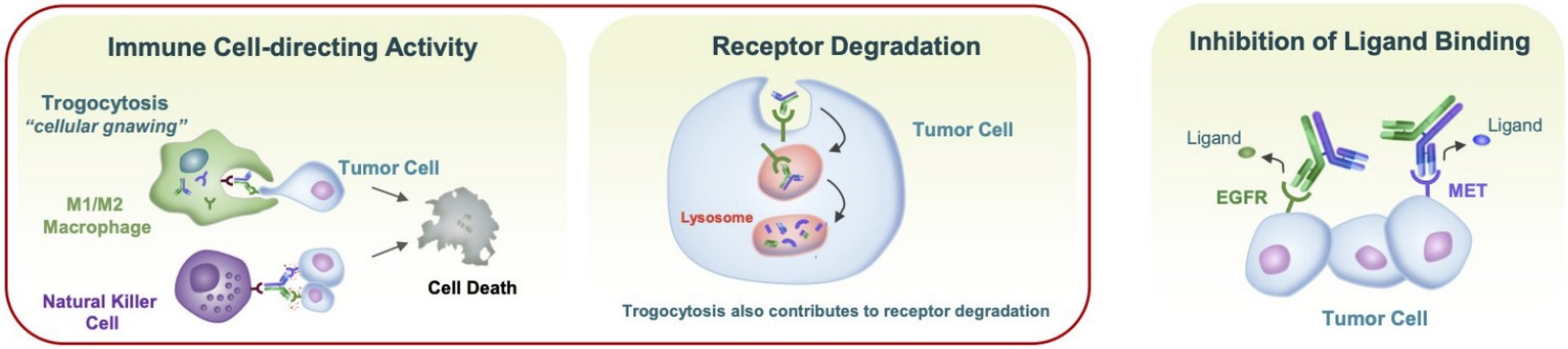


Meador, L. Sequist, Z. Piotrowska. Cancer Discov. 2021, 2021 Sep;11(9):2145-2157. Y. Elamin et al Cancer Cell 2022 40: 754-67. JW Riess et al JTO 2018. 13:10. P1560-1568,

Amivantamab: EGFR-MET Bispecific Antibody

- Fully human EGFR-MET bispecific antibody with immune cell-directing activity[1-2]
- Targets activating and resistance EGFR mutations and MET mutations and amplifications[3-4]
- Demonstrated monotherapy activity in patients with diverse EGFRm disease including EGFR Exon19del, L858R, T790M, C797S, Exon20ins, and MET amplification[3-4]

MOA Relevant to EGFR Exon20ins-mutated NSCLC



[1]Vijayaraghavan *Mol Cancer Ther* 19(10):2044. [2]Yun *Cancer Discov* 10(8):1194. [3]Haura *JCO* 37(15_suppl):9009. [4]Park *JCO* 38(15_suppl):9512
EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer

Sabari, et al; WCLC20

Amivantamab Efficacy in EGFR Exon ins20

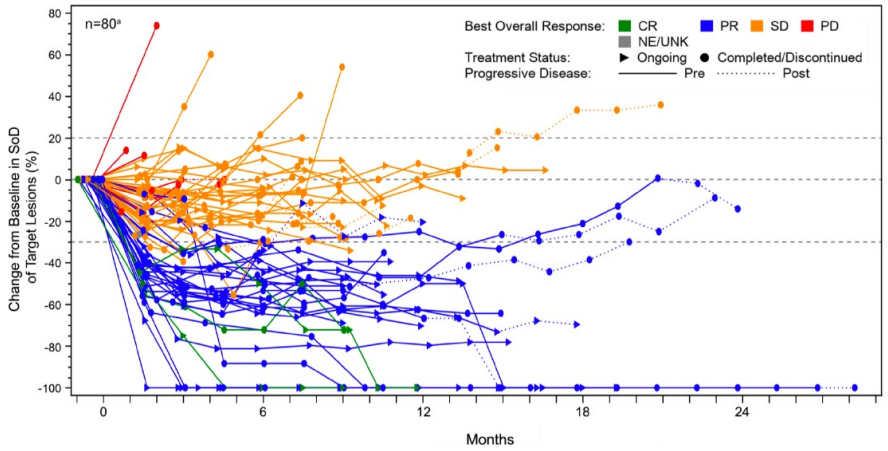
Amivantamab: Efficacy by BICR

BICR-assessed Response	Efficacy Population (n=81)
Overall response rate	**40%** (95% CI, 29–51)
Median duration of response	**11.1 months** (95% CI, 6.9–NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	1 (1)
Clinical benefit rate[a]	74% (95% CI, 63–83)

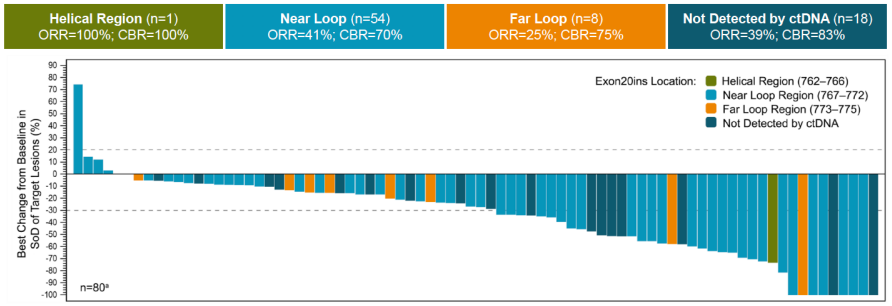
Median follow-up: 9.7 months (range, 1.1–29.3)

mPFS: 8.3 mo (95% CI, 6.5-10.9)
mOS: 22.8 mo (95% CI, 14.6-NR)

Amivantamab: Responses Over Time



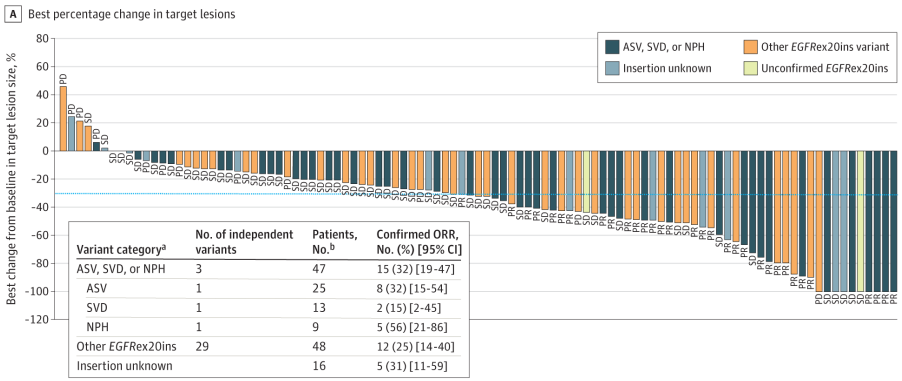
Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



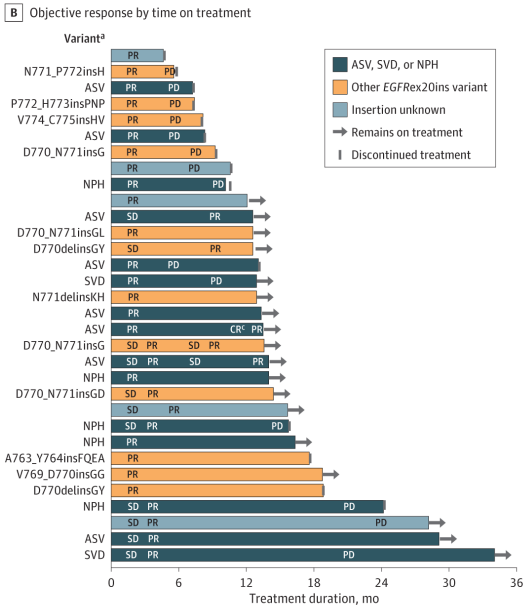
25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

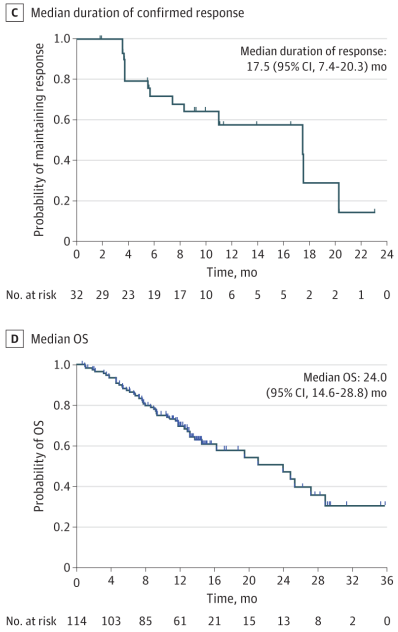
K. Park et al JCO 2021

Mobocertinib in EGFR Exon20in NSCLC



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]



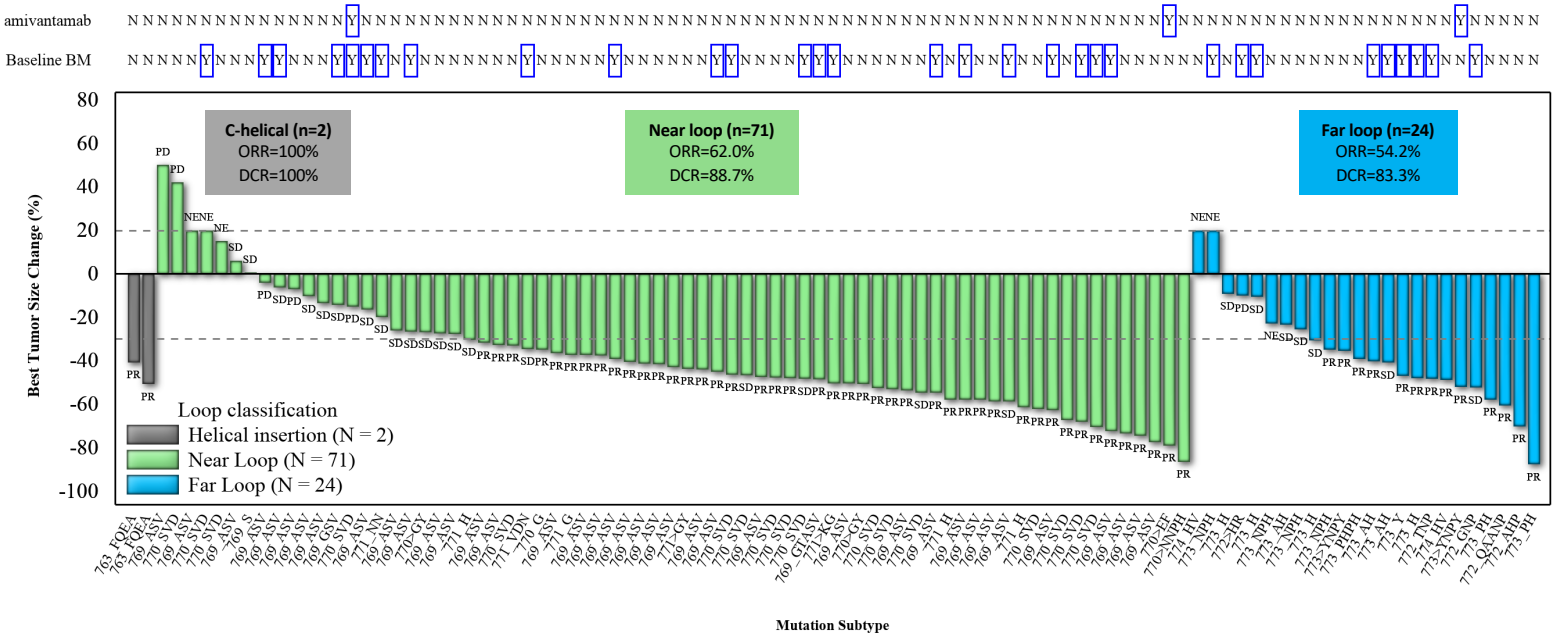


ORR=28%
mPFS: 7.3 mo (95% CI, 5.5-9.2)
mDoR: 17.5 months (95% CI, 7.4-20.3)
mOS: 24.0 mo (95% CI, 14.6-28.8)

C. Zhou et al. Jama Onc 2021.

Abstract #9002

Sunvozertinib Activity by Location of EGFR Exon 20 Ins Subtypes



	Mobocertinib [1,a] (N=114)	Amivantamab[2] (N=81)	CLN-081 (TAS6417) [6] (N=42)[c]	Sunvozertinib (DZD9008) (N=97) WUKONG6
Investigator assessed				
ORR, %	35%	36%	38%	46.4%
Disease control rate, %	78%	73%	96%	
Duration of response, mos	11.2 mo	-	-	
IRC assessed (95% CI)				
ORR, %	28% (20-37%)	40% (29-51%)	-	60.8% (50.4-70.6%)
Disease control rate, %	78%	74%	-	87.6%
Duration of response, months	17.5 mo	11.1 mo	10 mo	64.4% responding at median fup of 5.6 mo.
PFS, months	7.3 mo	8.3 mo	10 mo	-
Brain Mets, ORR (N=)	-	-	33% (N=3)	44% (N=25) From pooled WUKONG studies

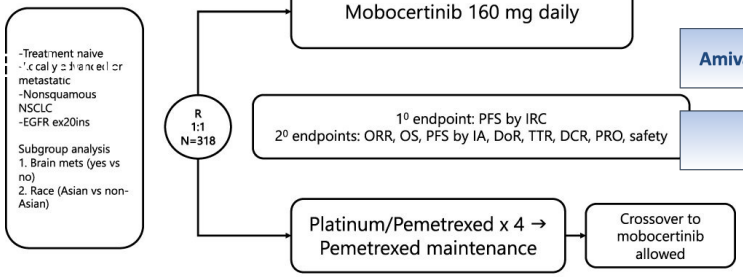
EGFR Exon 20 ins TKI with Putative CNS Penetration

Blu-451
Oric-114
Furmonertinib

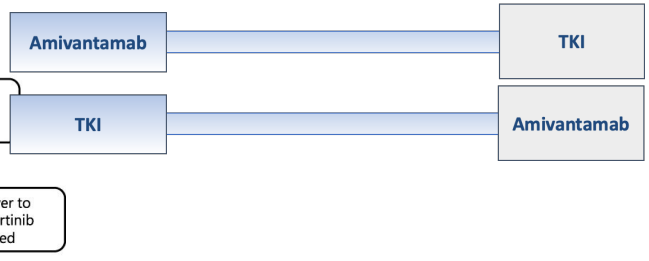
Zhou C. et al. *JAMA Oncol.* 2021 Oct 14;e214761. [Epub ahead of print]. Park K, et al. *J Clin Oncol.* 2021;39:3391-3404. 3. Nagasaka M, et al. Presented at: WCLC;2021. Abstract P50.04. 4. Piotrowska Z, et al. Presented at: ASCO;2020. Abstract 9513. 5. Zwierenga F, et al. Presented at: ESMO;2021. Abstract 1214P. 6. Piotrowska Z, et al. Presented at: ASCO; 2021. Abstract 9077. 7. Janne P, et al. Presented at: WCLC;2021. Abstract OA15.02.

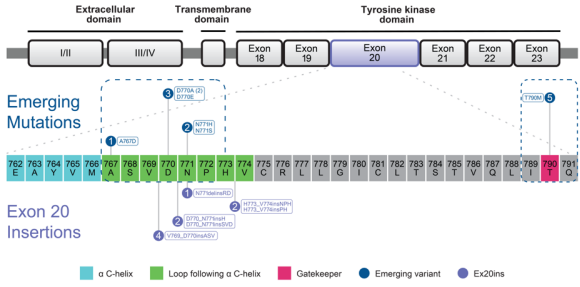
EGFR Exon 20 Ins NSCLC: Future Strategies

First-Line

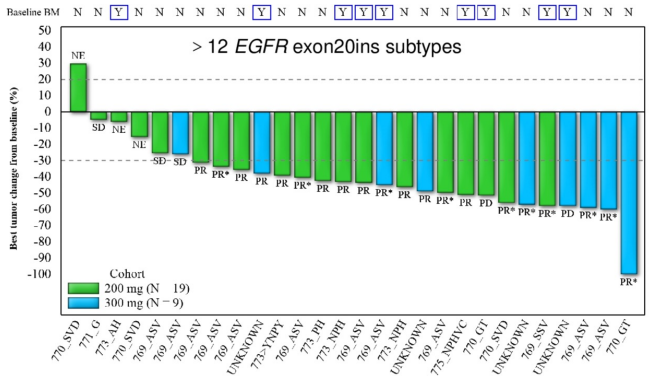


Sequencing

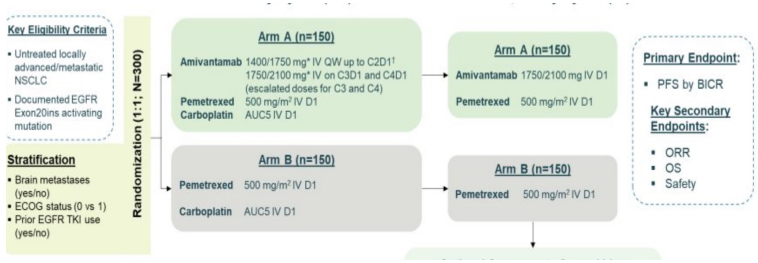




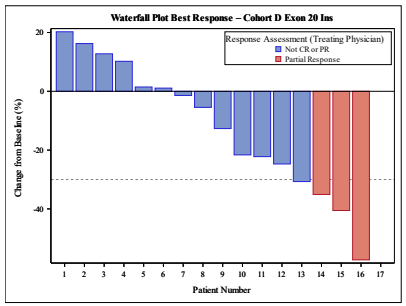
Sunvozertinib in Tx Naïve ORR=73.1% (19/26)



PAPILLON

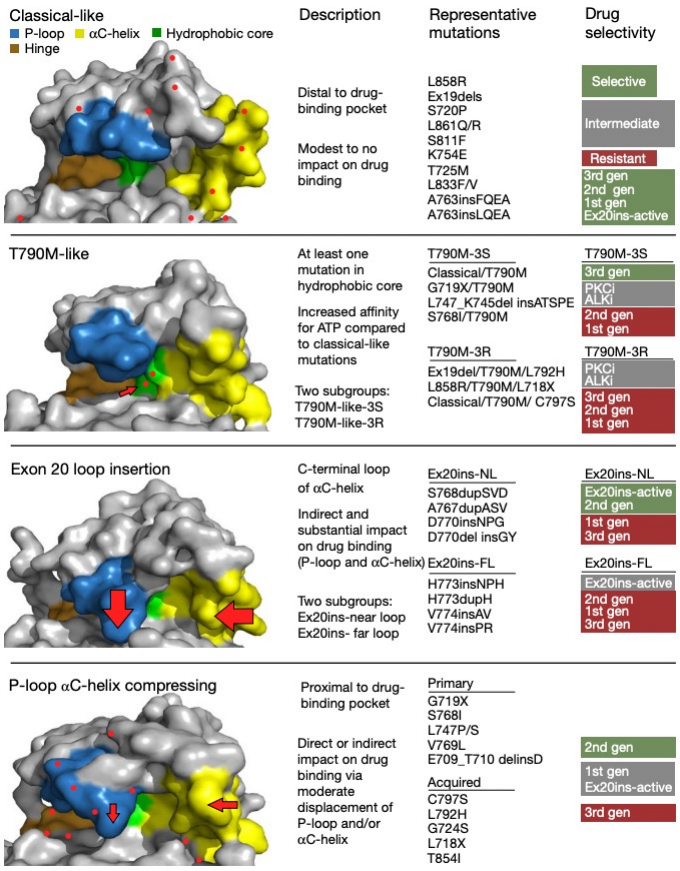


EGFR Exon 20 TKI + EGFR moAB



1. Vincent, S et al. ASCO 2022. 5. Xu, Y. et al. ASCO 2023.
2. Zhang SS, Zhu VW. Lung Cancer (Auckl). 2021
3. Agrawal T, WCLC 2020
4. Riess JW et al, ASCO 2022

Osimertinib Efficacy in Atypical EGFR Mutations

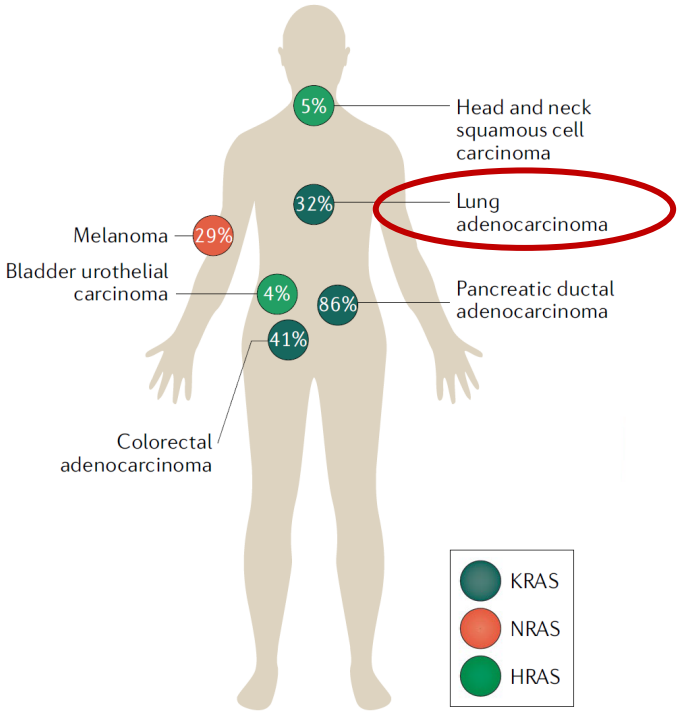


Robichaux et al. Nature 2021.

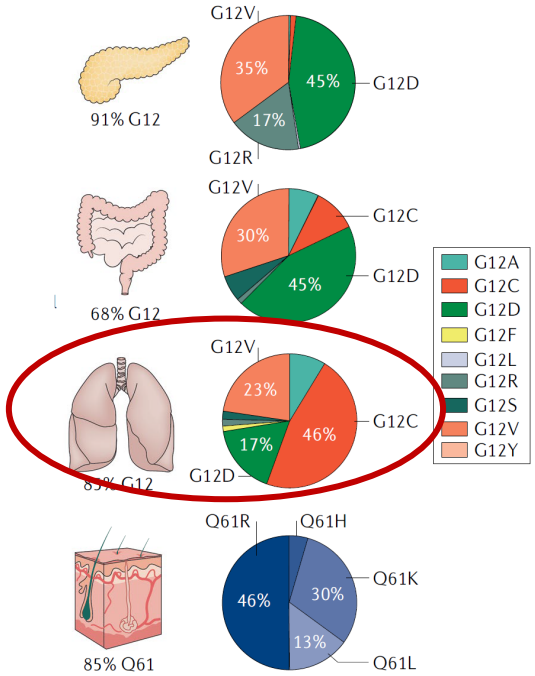
- Structure-Function relationship and classification predicts TKI activity in EGFR mutant NSCLC.
- Role of EGFR moAb and bispecifics by mutation needs to be more fully explored.

KRAS mutations in cancer – Focus on NSCLC

Frequency of KRAS Mutations by Tumor Type

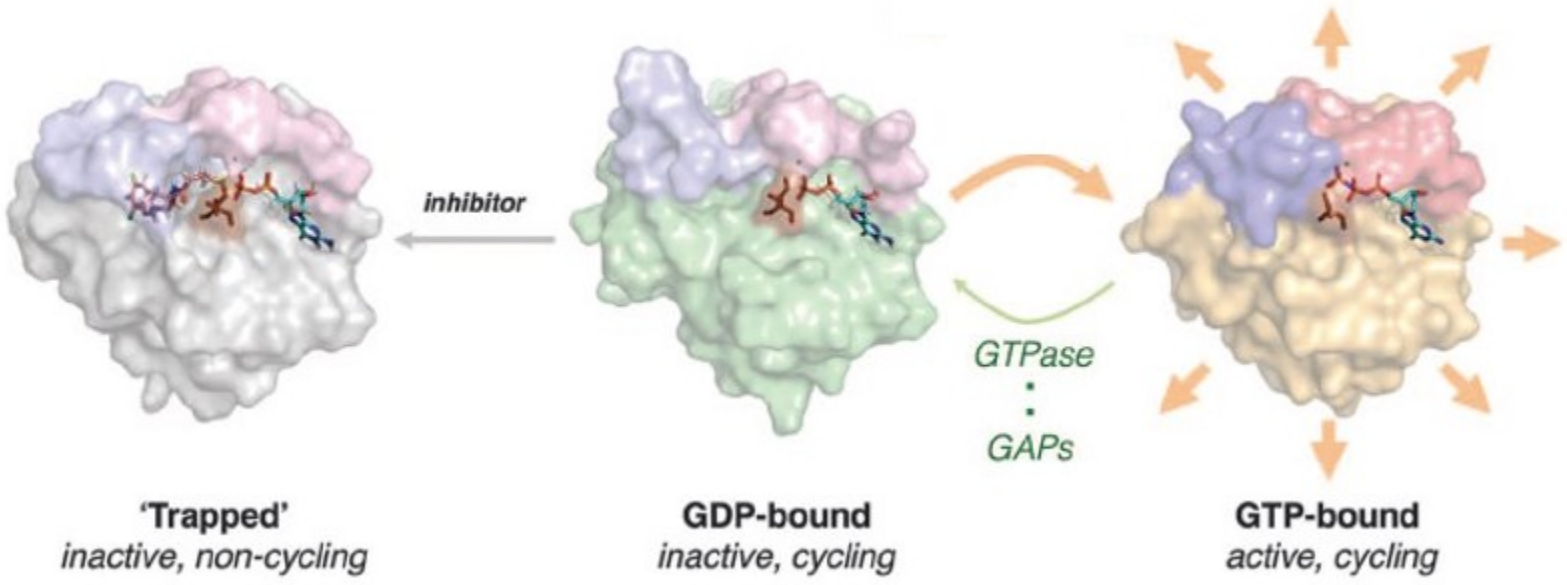


KRAS Mutation Subtypes By Tumor Tupe



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

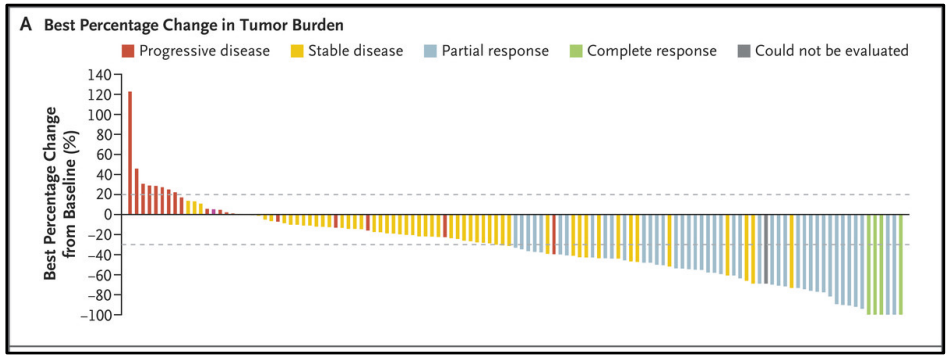
KRAS G12C Inhibitors Bind, Inactive GDP bound RAS and Trap It In Inactive State



From P. Lito et al. Science 2016

KRAS G12C inhibitors have activity in *KRAS* G12C NSCLC

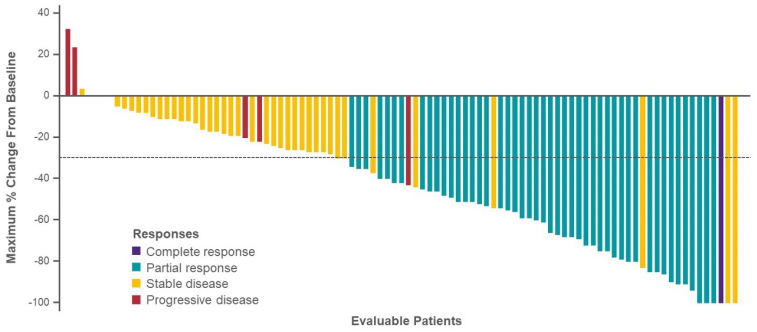
Sotorasib
CodeBreaK100 (Ph 2)



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.

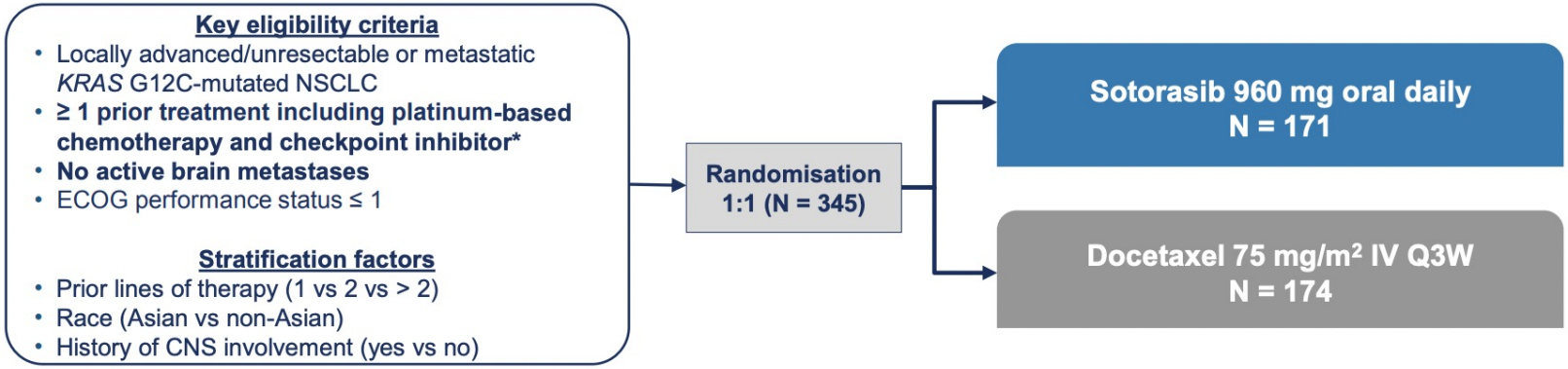
Adagrasib
KRYSTAL-1 study (Ph 1/1b & 2)



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 Phase 3 Study Design



Primary Endpoint: PFS by BICR

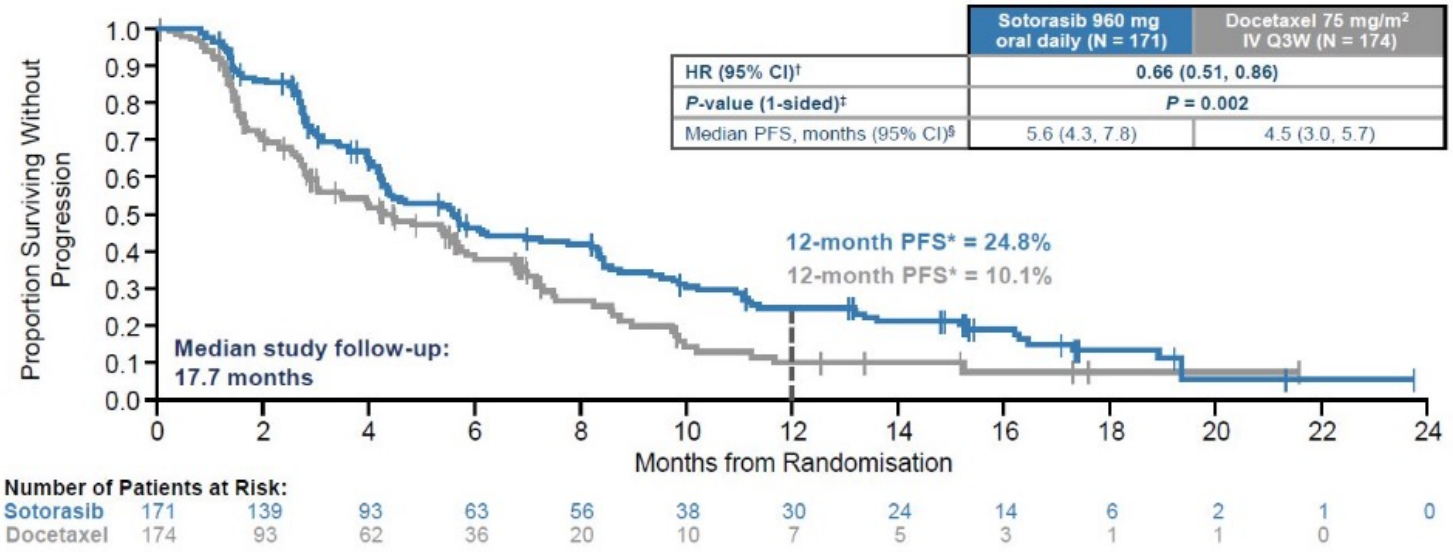
Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR)**, safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

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)

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

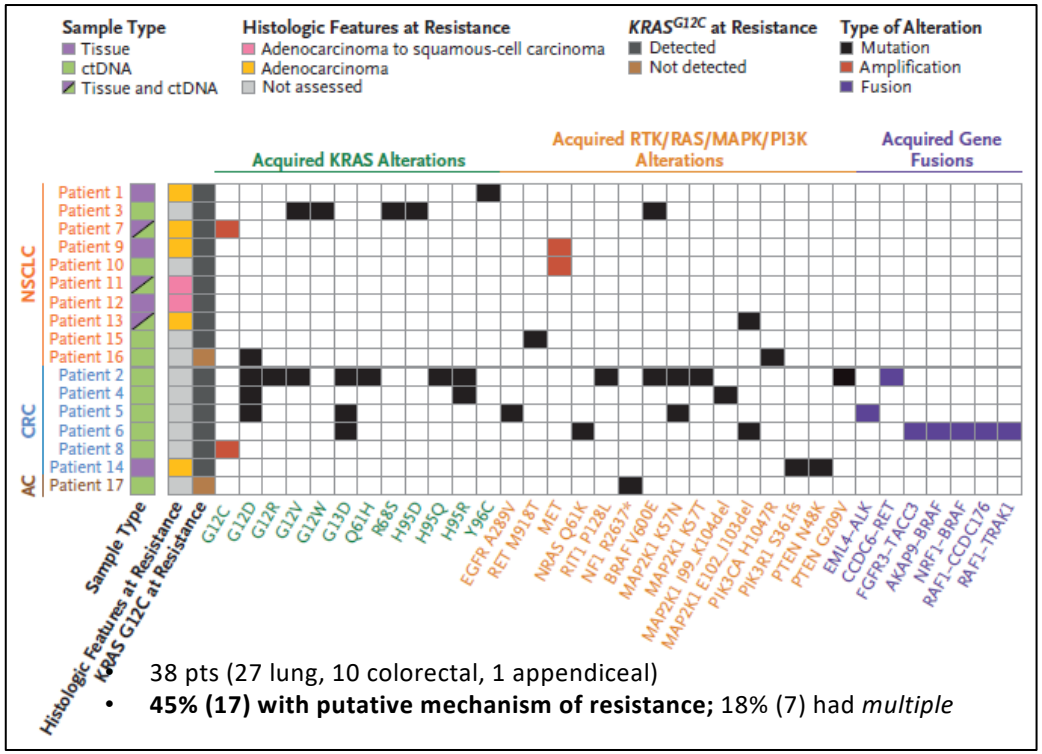
ORR 28.1% vs. 13.2%
mOS 10.6 (soto) vs. 11.3 months (doce). No difference in OS.
34% crossover in docetaxel arm

M. Johnson et al ESMO 2022

Acquired resistance to KRAS G12C inhibitors

- **On-target resistance (*in green*)**
  - *KRAS* G12D/R/V/W, G13D, Q61H, **R68S, H95D/Q/R, Y96C***
  - High level *KRAS* G12C amplification
- **Bypass resistance (*in orange*)**
  - *MET* amplification
  - Activating mutations in *NRAS, BRAF, MAP2K1, RET*
  - Oncogenic fusions *ALK*, *RET, BRAF, RAF1, FGFR3*
  - LOF *NF1, PTEN*
- **Histologic transformation**
  - 2/9 NSCLC adenoca→ squamous

ADAGRASIB

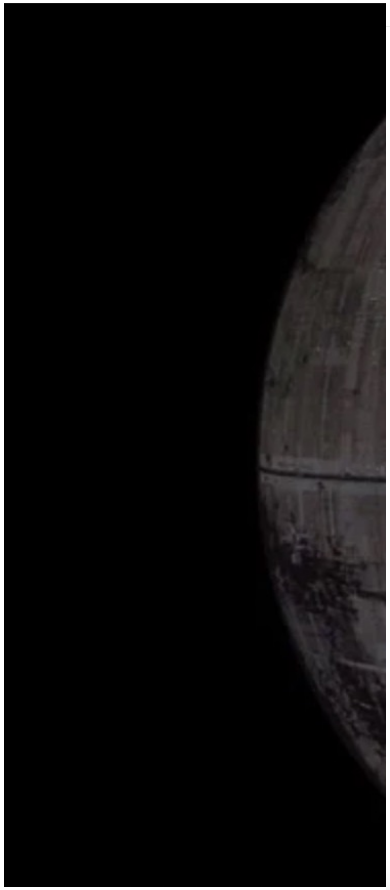


38 pts (27 lung, 10 colorectal, 1 appendiceal)

- **45% (17) with putative mechanism of resistance;** 18% (7) had *multiple*

*in switch II pocket

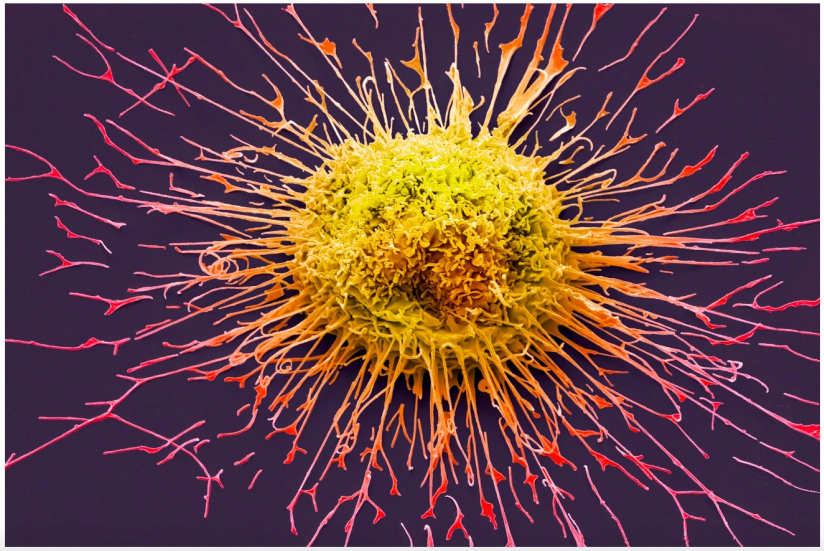
Awad M et al. N Engl J Med. 2021 Jun 24;384(25):2382-2393. Zhao et al Nature. 2021 Nov;599(7886):679-683.



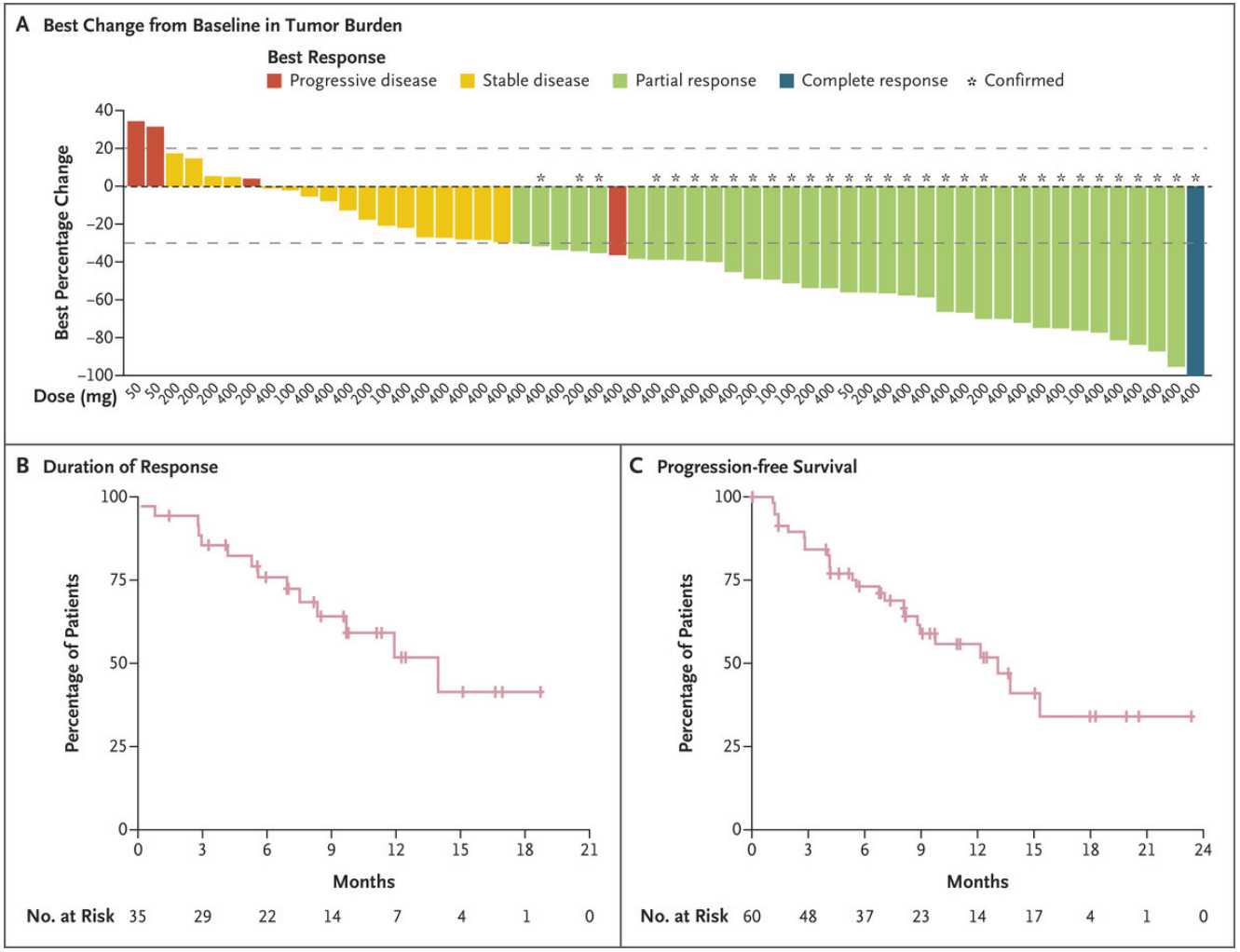
The New York Times

How Scientists Shot Down Cancer's 'Death Star'

No drug could touch a quivering protein implicated in a variety of tumors. Then one chemist saw an opening.

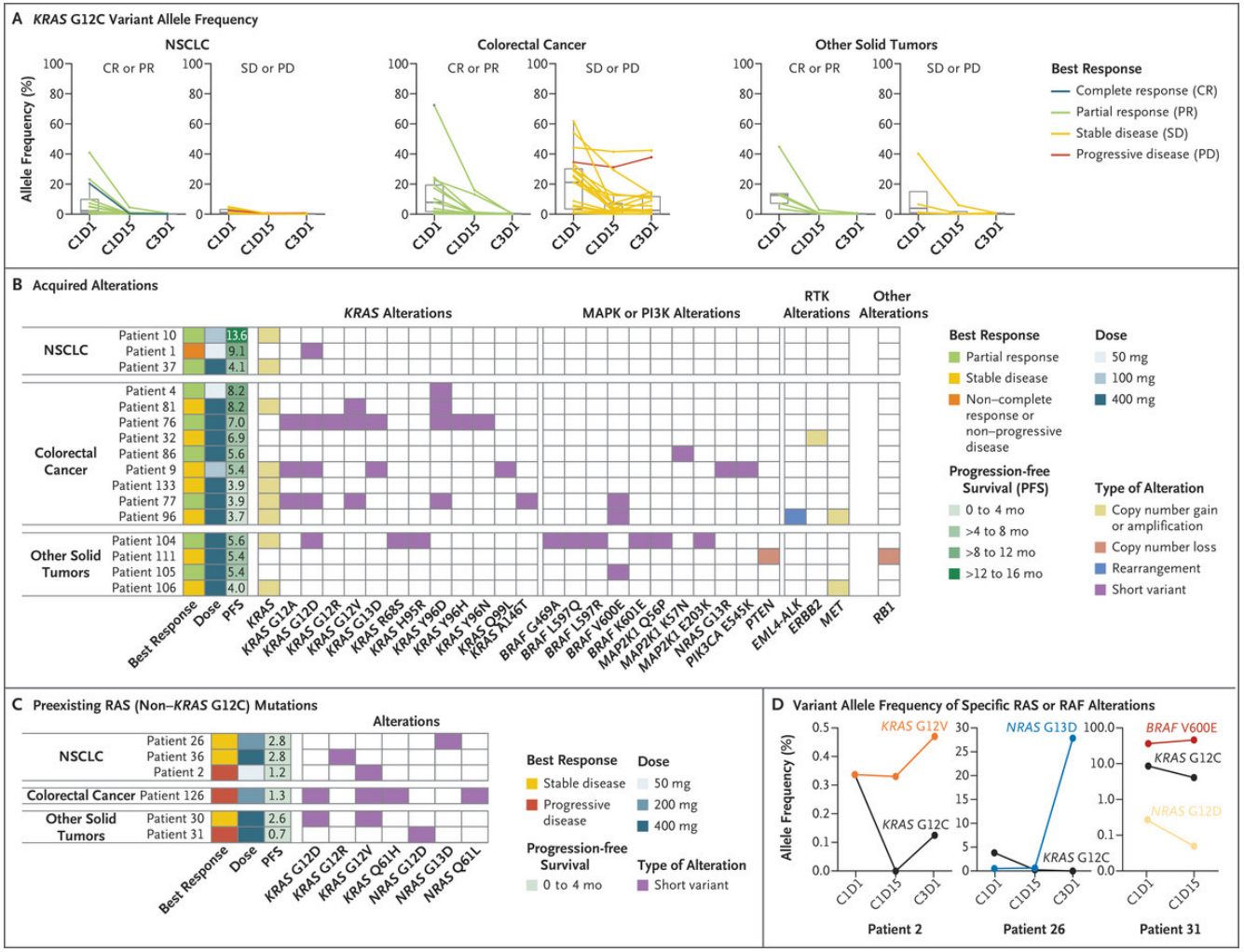


Antitumor Activity of Divarasib in Patients with KRAS G12C Non–Small-Cell Lung Cancer (NSCLC).



A Sacher et al. N Engl J Med 2023;389:710-721.

Biomarkers of Response and Resistance to Divarasib



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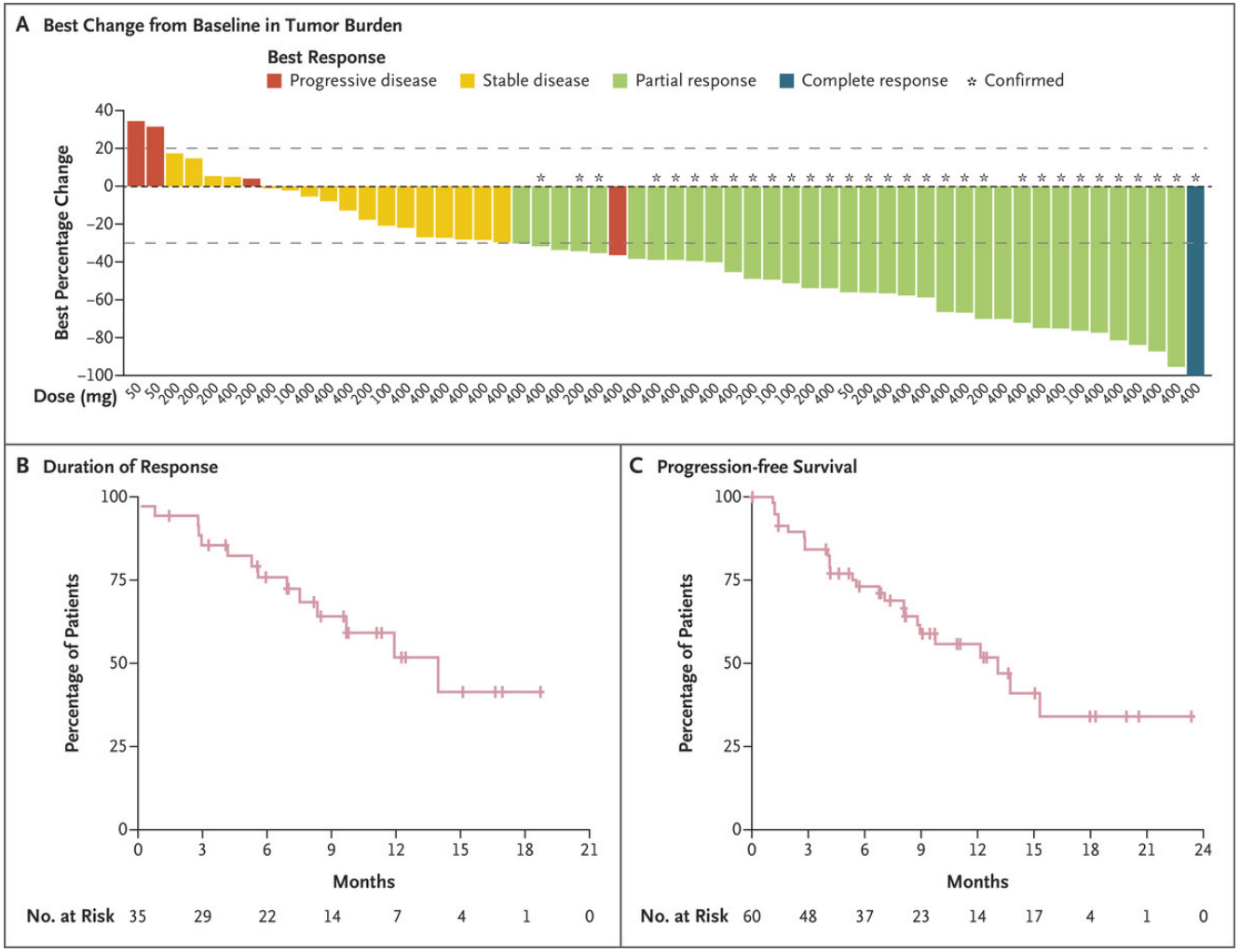

A Sacher et al. N Engl J Med 2023;389:710-721.

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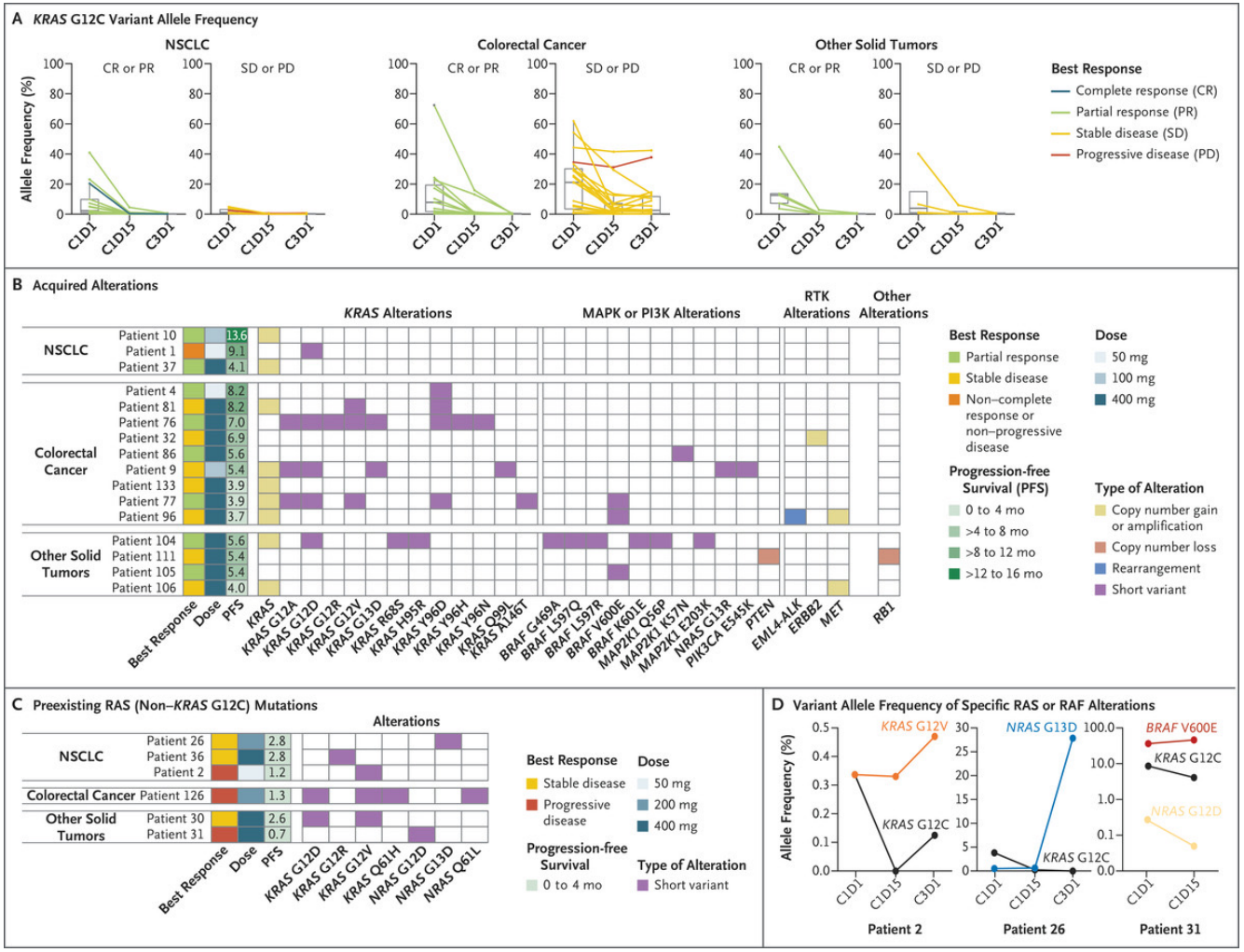
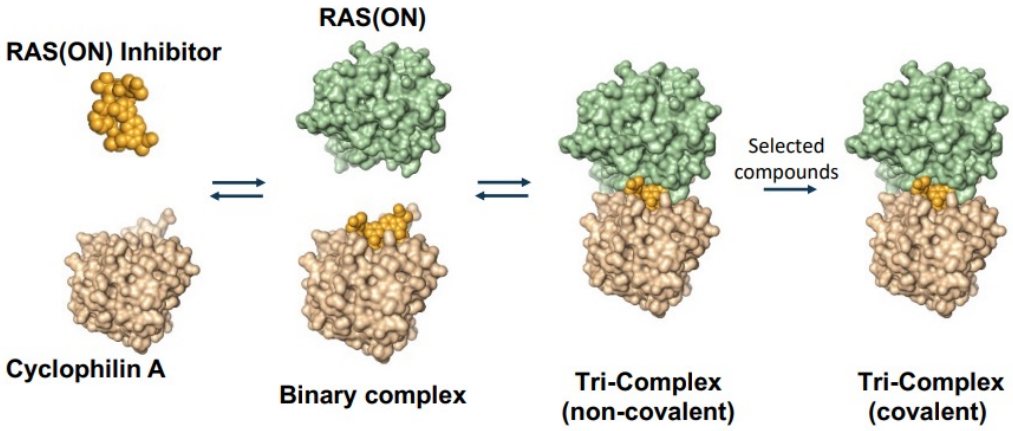


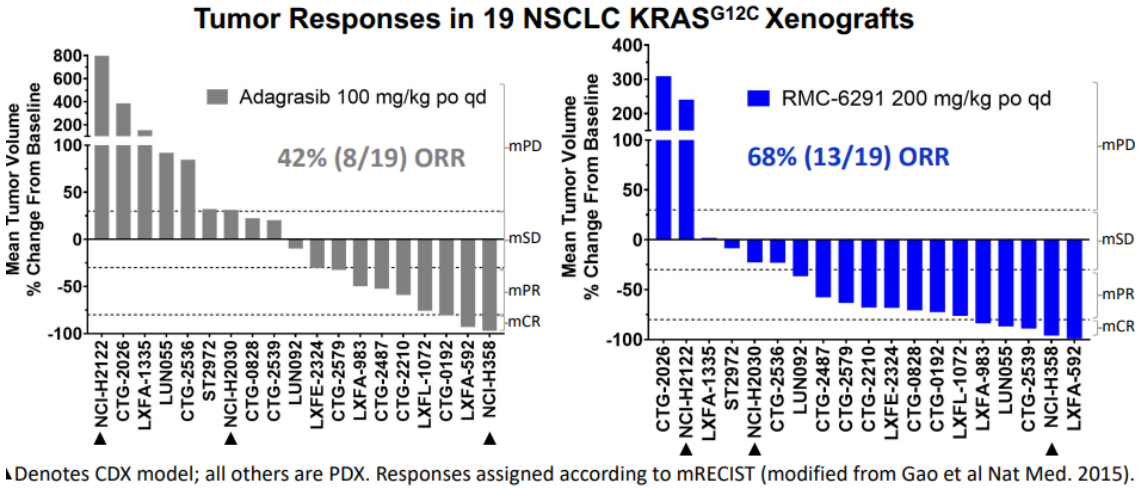
A Sacher et al. N Engl J Med 2023;389:710-721.

RAS(ON) Inhibitors

- Less susceptible to adaptive resistance compared to GDP bound RAS

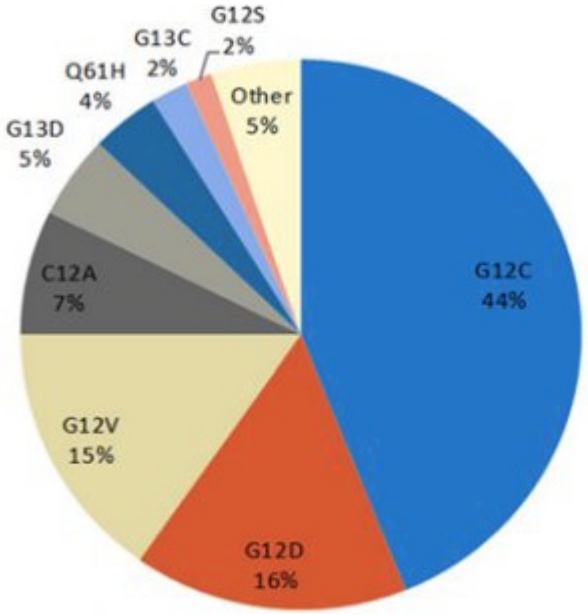


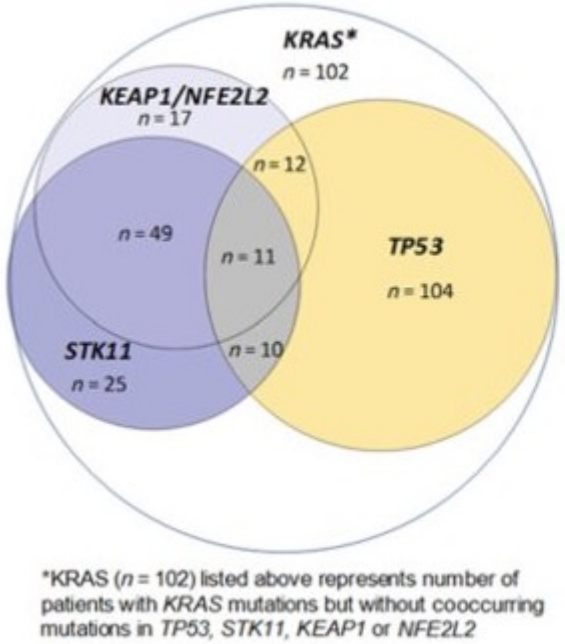
- RMC-6291 KRAS G12C (ON) inhibitor
- RMC-9805 KRAS G12D (ON) inhibitor
- RMC-6236-Pan RAS(ON)



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

Spectrum of KRAS mutations and Co-Mutations in NSCLC

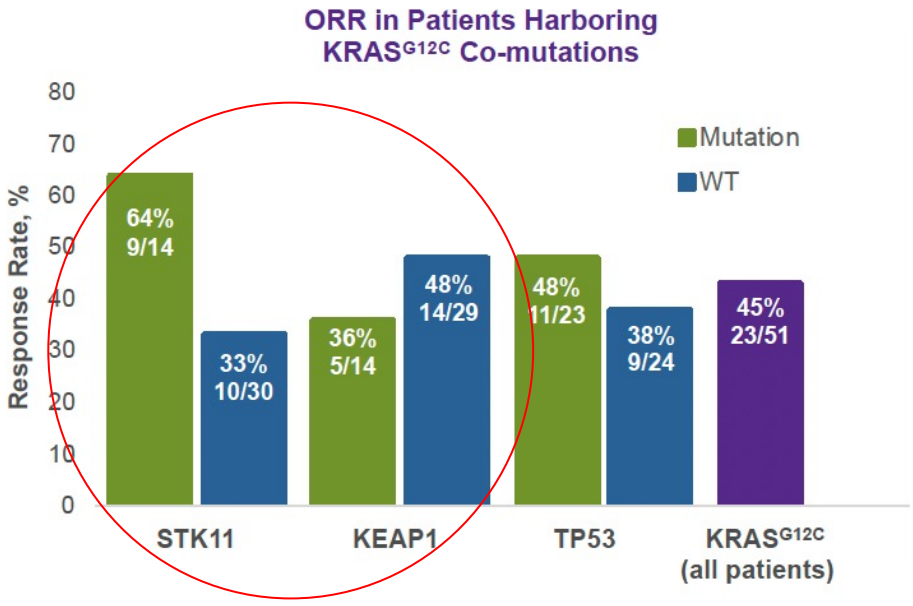




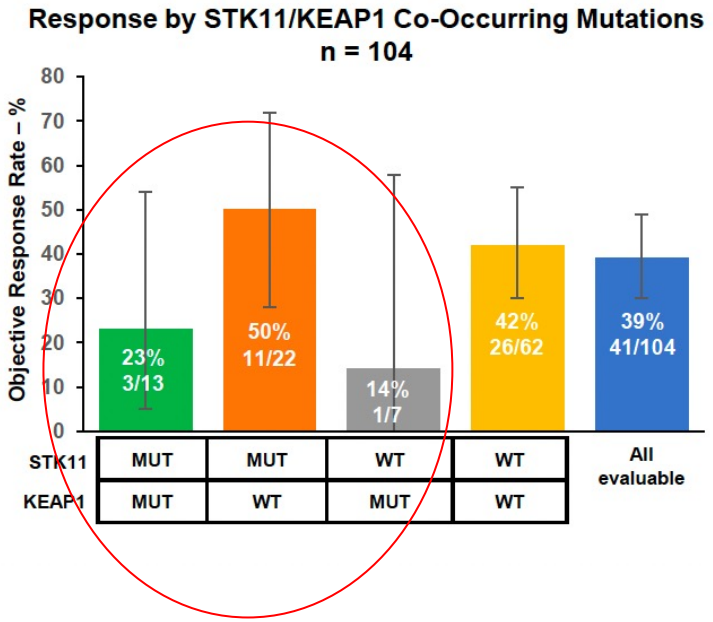
Arbour et al CCR 2018

Differential Efficacy in Co-Occuring Mutations in KRAS G12C NSCLC

Adagrasib (MRTX849)



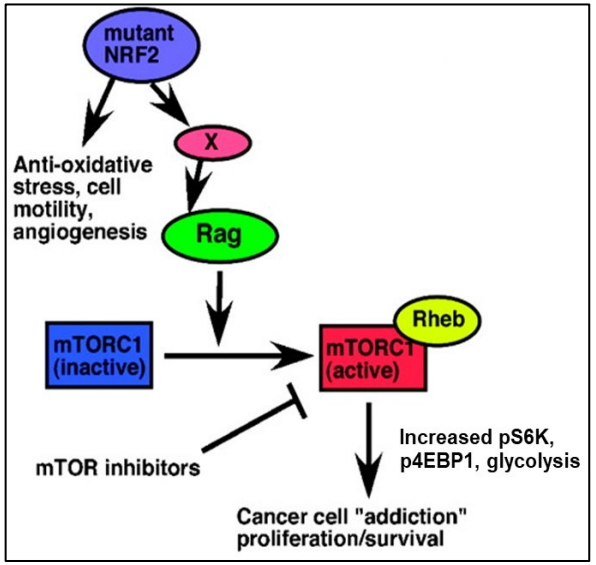
Sotorasib (AMG510)



Li et al WCLC 2020

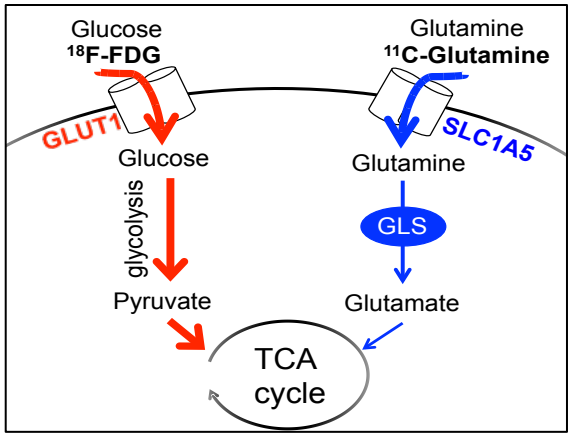
Upregulated Nrf2 is a Druggable Target in Squamous NSCLC and KRAS mutant NSCLC

- Nrf2 (encoded by NFE2L2) is a transcription factor that binds to antioxidant response elements (AREs)
- Keap1, the product of *KEAP1*, sequesters Nrf2 to the cytoplasm (negative regulator)
- Worse outcomes to systemic treatments in retrospective studies (Frank et al CCR 2018).
- *NFE2L2* and *KEAP1* are mutated in 30% of SQCLCs (NFE2L2>KEAP1). ~20-25% of KRAS mutant NSCLC (KEAP1>NFE2L2)
  - Transforming, oncogenic
  - NFE2L2 mutations disrupt KEAP1 binding and upregulate mTOR through RagD



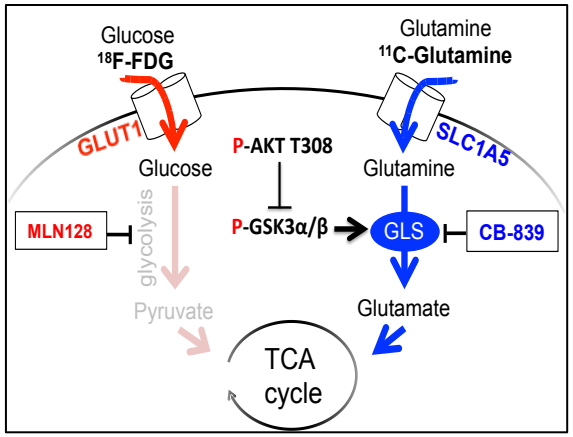
Adaptive Glutamine Metabolism by GSK3 Signaling Axis Circumvents MLN0128 Inhibition of Glycolysis in Squamous NSCLC

Glucose and Glutamine Dependent Metabolism

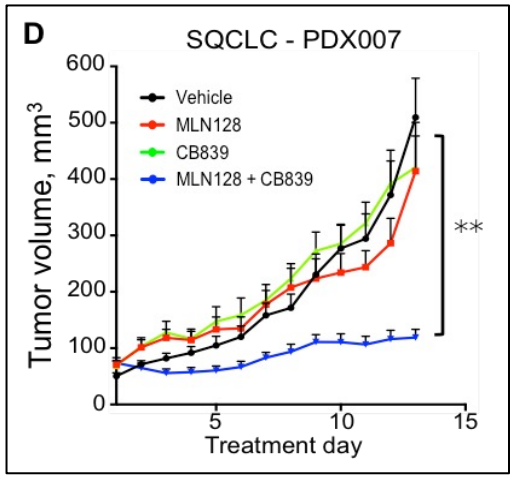


Basal metabolism – high uptake of glucose and glutamine to sustain SCC growth

Adaptive Glutamine Metabolism



Overcoming resistance – GSK signaling axis with adaptive GLN metabolism



Actionable in vivo with dual mTOR and GLS inhibition

From the Shackelford lab. Momcilovic et al. Cancer Cell 2018.

A Phase 1 Trial of MLN0128 (Sapanisertib) and CB-839 in Advanced NSCLC (NCI 10327)

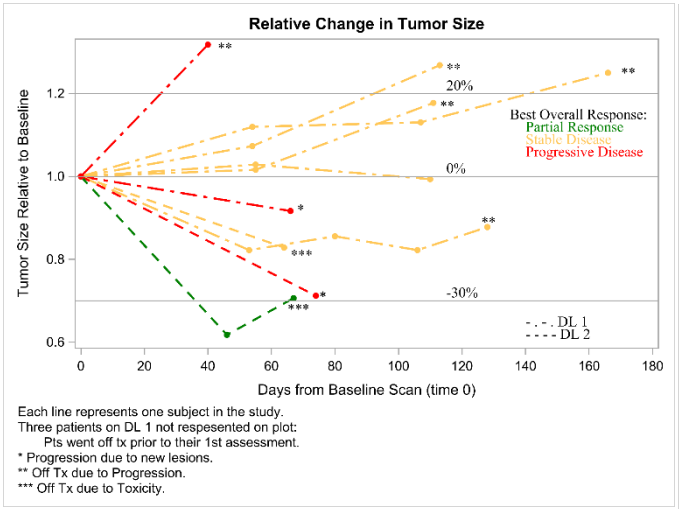
Stage IV NSCLC
PD on or after platinum and/or PD-(L)1
PS 0-2

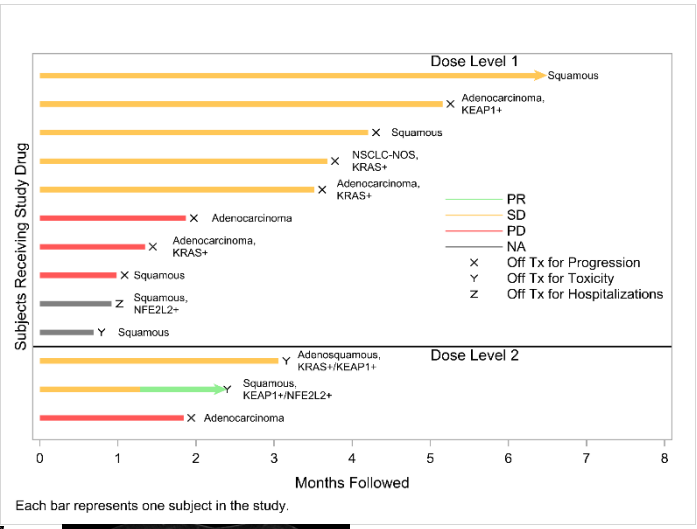
Dose escalation to Recommended Expansion Dose

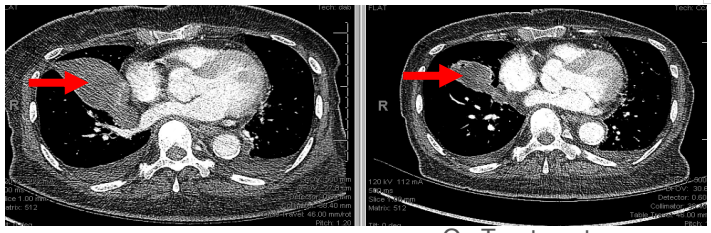
- **Genomic Profiling: Tissue and plasma NGS**
- **Plasma metabolite and PK profiling** (Joel Reid/Ian Lanza Mayo)
- **Intratumoral metabolic signaling profiling** (IHC Panel) (David Shackelford UCLA)
- **Paired ^{18}F-Glutamine-PET (^{18}F-Gln) and ^{18}FDG-PET analyses** (MSKCCC and UCD)

- Cohort A: LUSC harboring *NFE2L2* mutations (N=14)
- Cohort B: LUSC harboring *KEAP1* mutations (N=14)
- Cohort C: LUAD harboring KRAS mut with *KEAP1 or NFE2L2* mutations (N=14)
- Cohort D: LUSC negative for NFE2L2/KEAP1 mutations (N=14)

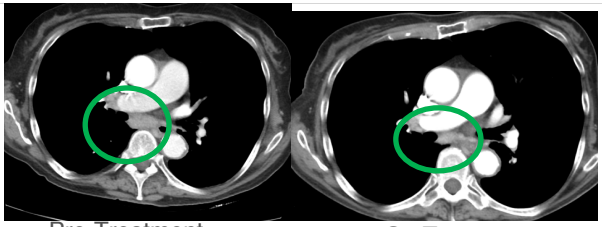
co-PIs: JW Riess, Paul Paik







Pre-treatment On Treatment
KRAS G13C/KEAP1 Adenosquamous NSCLC



Pre-Treatment On Treatment
NFE2L2 mutant Squamous NSCLC

Conclusions

- Effective targeted therapeutics against 8+ mutations comprising over a third of lung adenocarcinoma.
- Next generation agents in development as well as targeted therapy of bypass tracts and ADCs
- Still targets with unmet need – KRAS G12D, PIK3CA and others.