Updates in Targeted Therapies in Lung Cancer

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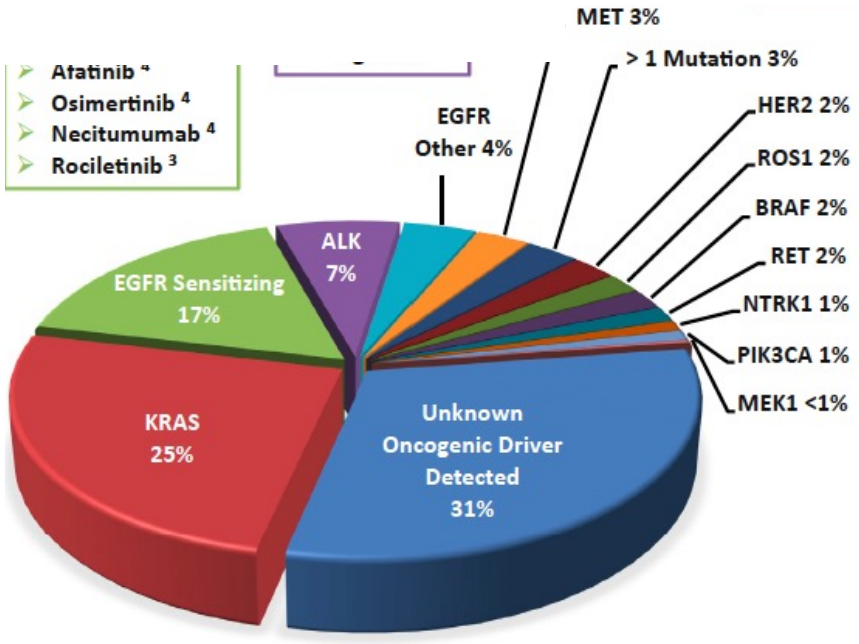
Progress in Targeted Therapy for NSCLC-Adenocarcinoma



FDA

KRAS G12C
adegrasib, sotorasib

EGFR exon 20 insertions
mobocertinib, poziotinib, amivantamab

FDA

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

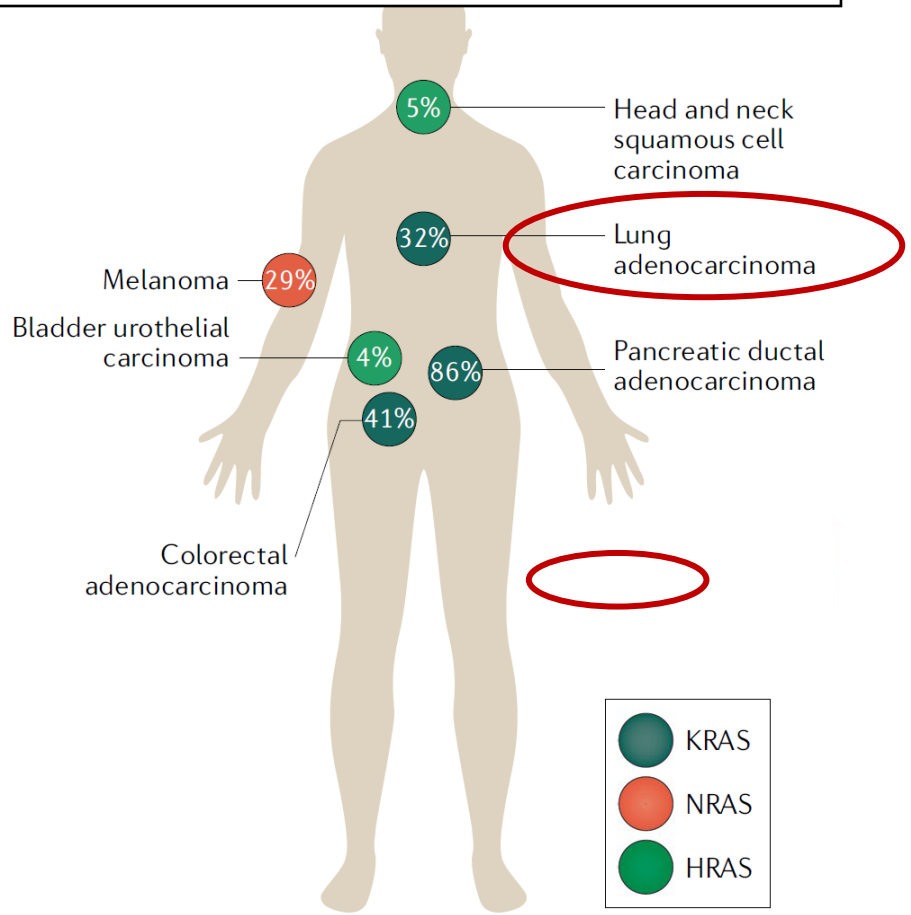
RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib,pralsetinib, RXDX-105

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

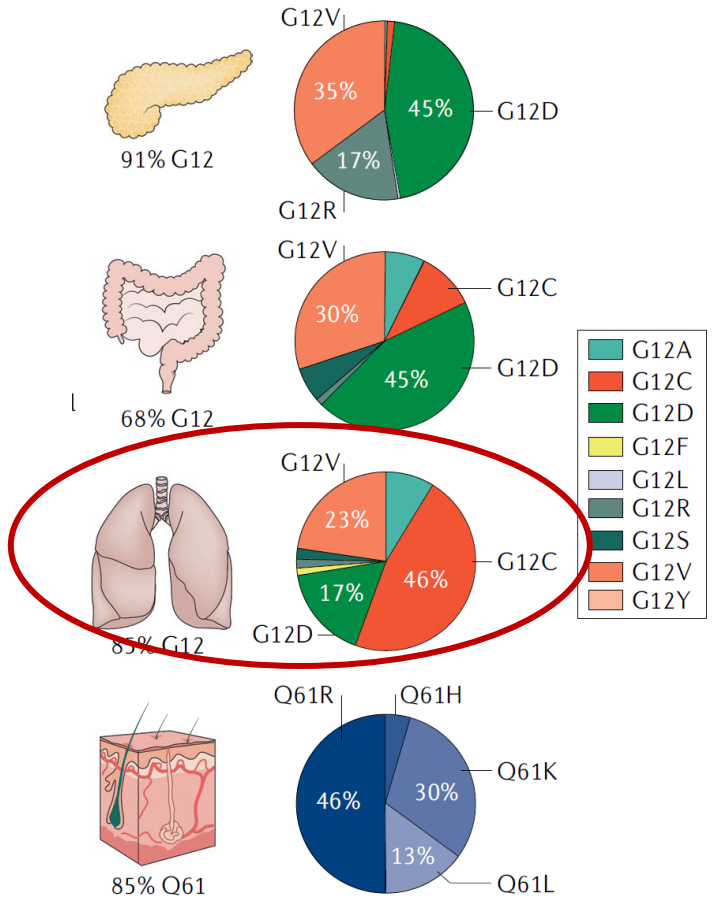
Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

KRAS mutations in cancer – Focus on NSCLC

Frequency of KRAS Mutations by Tumor Type

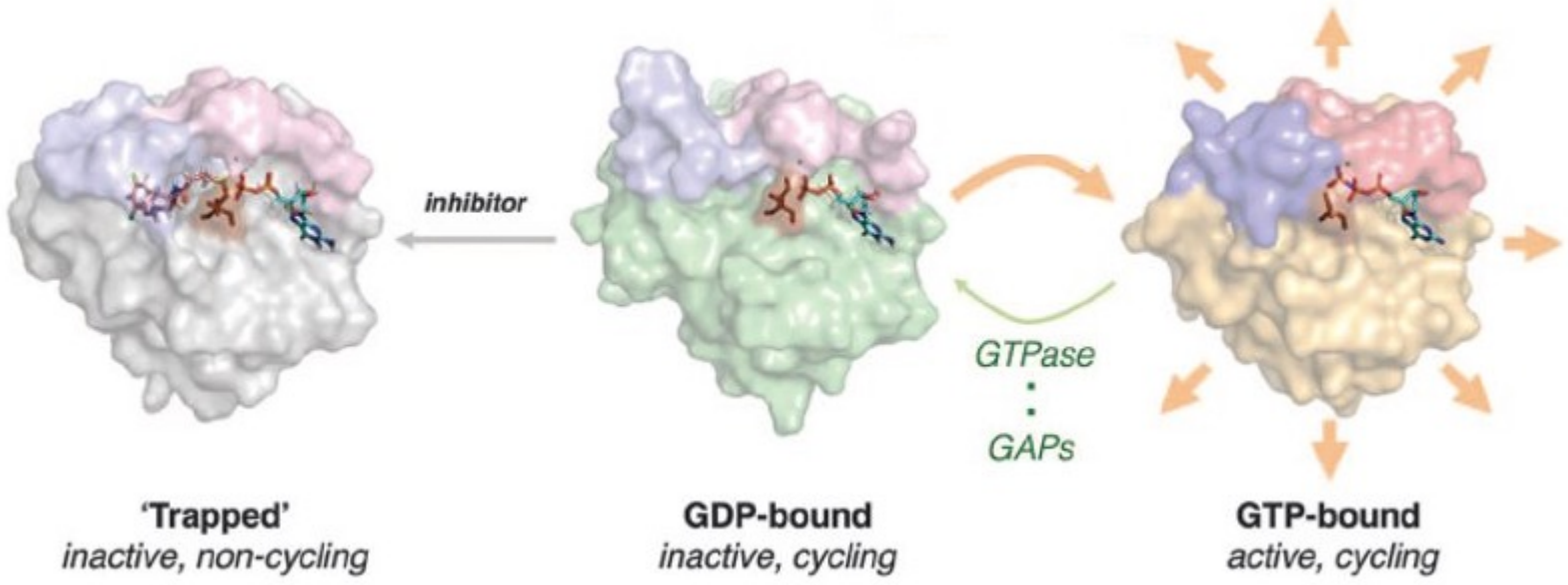


KRAS Mutation Subtypes By Tumor Tupe



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

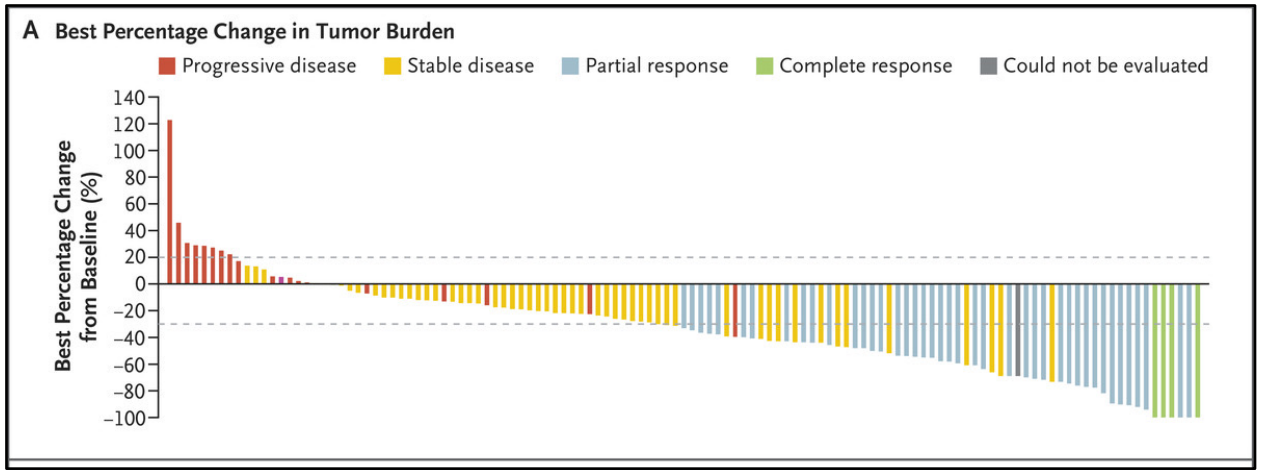
KRAS G12C Inhibitors Bind, Inactive GDP bound RAS and Trap It In Inactive State



From P. Lito et al. Science 2016

KRAS G12C inhibitors have activity in *KRAS* G12C NSCLC

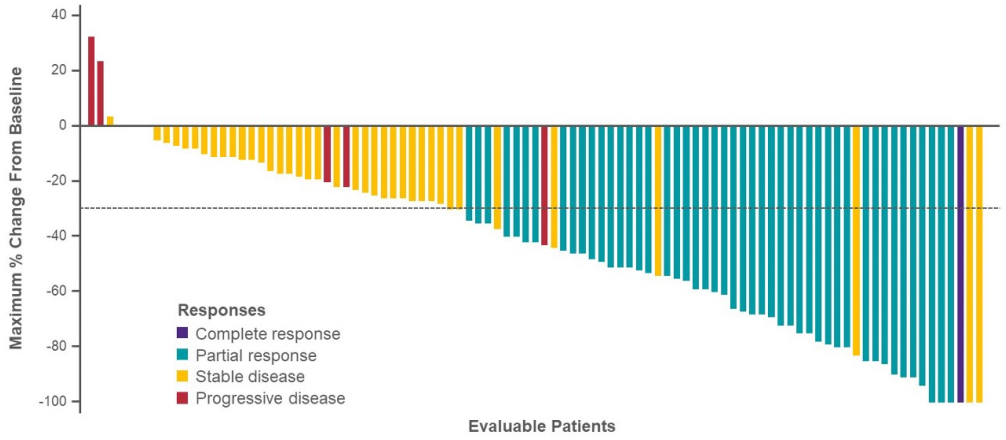
Sotorasib
CodeBreaK100 (Ph 2)



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

Toxicity of KRAS G12C Inhibitors

Treatment Related AEs	Sotorasib Phase II (n= 126)		Adagrasib Phase I/II (all cohorts pooled, n = 110)	
Treatment Related AEs Any Grade ≥ Grade 3 Leading to treatment D/C	69.8% 20.6% 7.1%		85% 32% 4.5%	
Most Common TRAEs				
	Any Grade	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Nausea	19%	0	54%	2%
Diarrhea	31.7%	4%	51%	0
Vomiting	7.9%	0	35%	2%
Fatigue	11.1%	0	32%	6%
ALT increase	15.1%	6.3%	20%	5%
AST increase	15.1%	5.6%	17%	5%

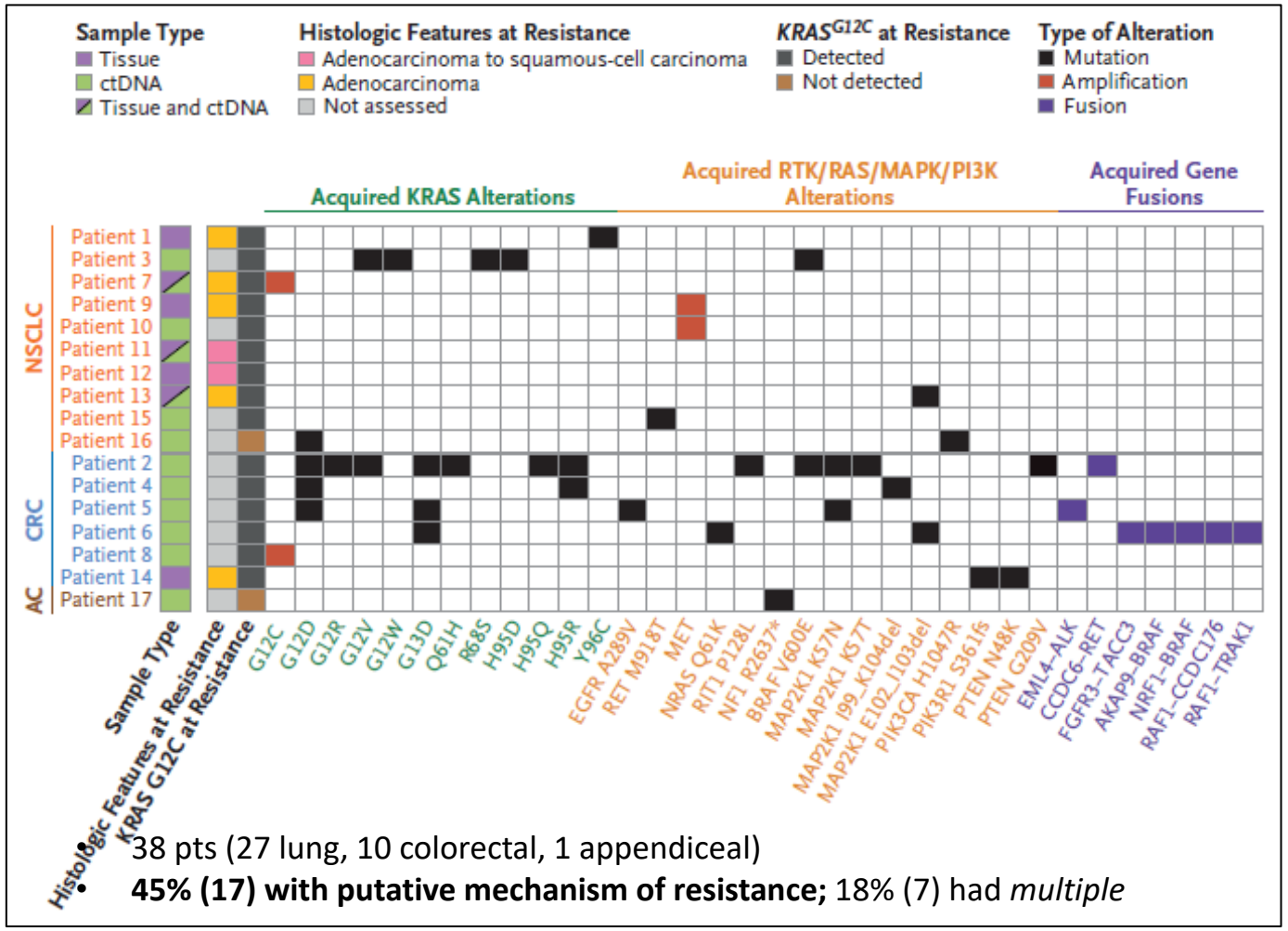
Table Courtesy of Dr. Rebecca Heist IASLC Targeted Therapies of Lung Cancer Meeting 2022

F Skoulidis et al. N Engl J Med 2021;384:2371-2381. Riely GR et al. European Lung Cancer Congress 2021

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

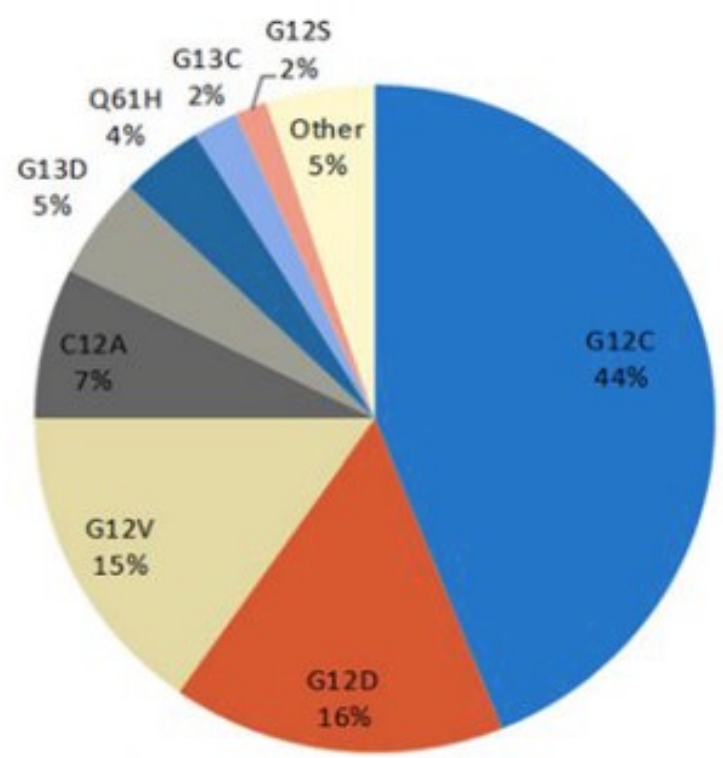


- 38 pts (27 lung, 10 colorectal, 1 appendiceal)
- **45% (17) with putative mechanism of resistance;** 18% (7) had *multiple*

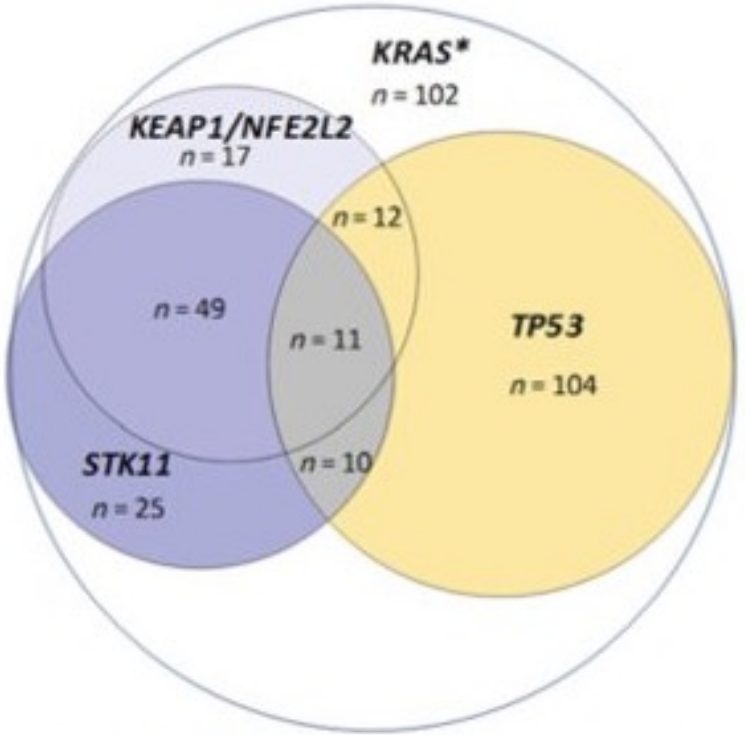
Awad M et al. N Engl J Med. 2021 Jun 24;384(25):2382-2393. Zhao et al Nature. 2021 Nov;599(7886):679-683.

*in switch II pocket

Spectrum of KRAS mutations and Co-Mutations in NSCLC



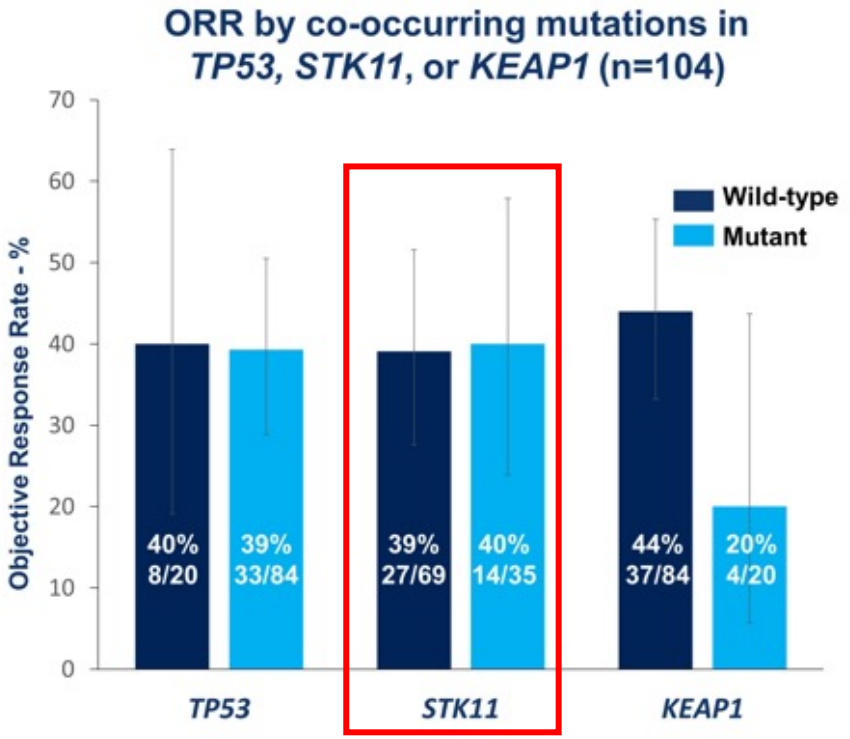
Arbour et al CCR 2018



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

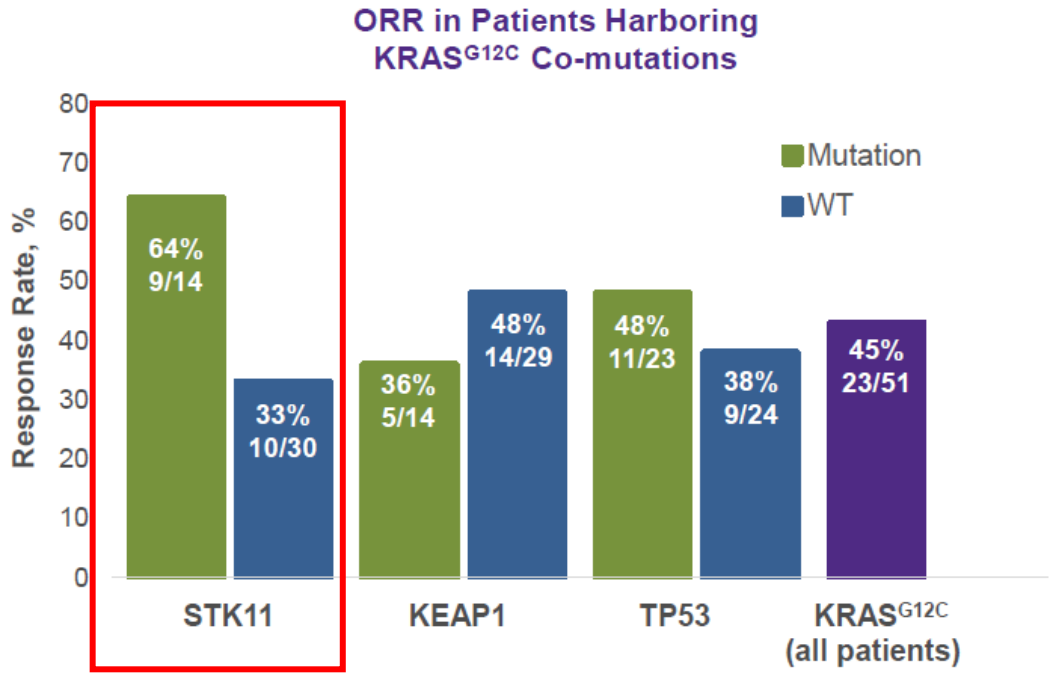
Does genomic context matter for KRAS G12C inhibitors?
Co-mutations

Sotorasib



F Skoulidis et al. ASCO 2021. N Engl J Med 2021;384:2371-2381.

Adagrasib



Riely GR et al. European Lung Cancer Congress 2021

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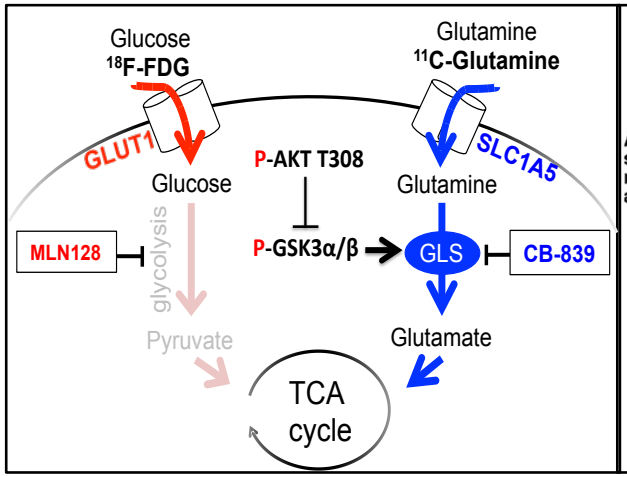
A Phase 1 Trial of Sapanisertib and CB-839 (Telaglenastat) in Patients With Advanced NSCLC (NCI 10327): Results from Dose Escalation

Jonathan W. Riess MD, MS
UC Davis Comprehensive Cancer
USA

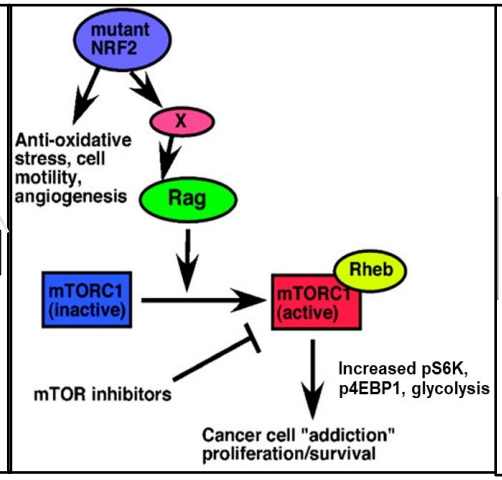
Upregulated Nrf2 is a Druggable Target in Squamous and KRAS mutant NSCLC

- 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)
- Keap1 loss promotes dependence on glutaminolysis in KRAS mut NSCLC (Romero et al Nat Med 2017)
- NRF2 upregulation activates mTOR pathways, driving glycolysis and proliferation/survival
- *NFE2L2* and *KEAP1* are mutated in 30% of SQCLCs (NFE2L2>KEAP1). ~20-25% of KRAS mutant NSCLC (KEAP1>NFE2L2)

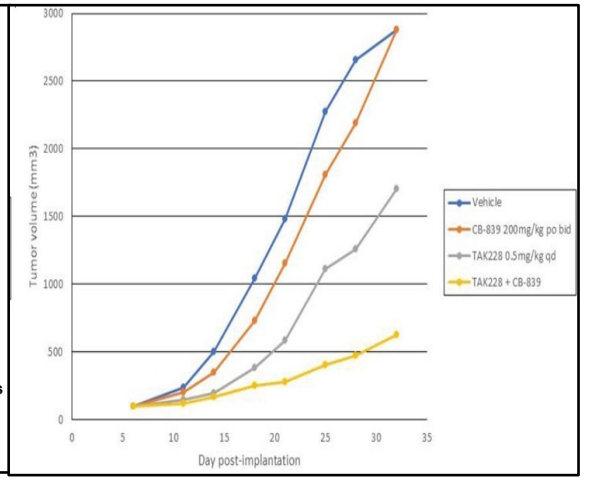


High uptake of glucose and glutamine to sustain SCC growth. Overcoming resistance to mTORi – GSK signaling axis with adaptive GLN metabolism.

Momcilovic et al Cancer Cell 2018



NRF2 upregulation is transforming and oncogenic. Activates TORC1 with increase in pS6K, p4EBP1, glycolysis, and proliferation/survival. (adapted from Shibata et al. CCR 2010)



Sapanisertib (TAK228/CB-228) and CB-839 exhibit synergistic anti-tumor activity in A549 *KRAS/KEAP1* co-mutant xenograft. Mice were treated with vehicle, CB-839, TAK228, or the combination of TAK228 + CB-389. **Courtesy of P. Paik et al.**

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Trial Schema and Patient Characteristics

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

Dose escalation to Recommended Expansion Dose

- **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

Dose Escalation Patient Characteristics	All (N=13)
Age, median (range) years	65 (40-78)
Gender, N (%)	
Male/Female	4 (31%)/9 (69%)
ECOG performance status, N (%)	
0	3 (23%)
1	10 (77%)
Histology, N (%)	
Adenocarcinoma	5 (38%)
Adenosquamous	1 (8%)
NSCLC-NOS	1 (8%)
Squamous	6 (46%)
Genomic Markers of Interest, N (%)	
KRAS+ (KEAP1/NFE2L2 wild-type)	3 (23%)
KRAS/KEAP1/NFE2L2 wild-type	4 (31%)
KRAS+/KEAP1+	1 (8%)
NFE2L2+	3 (23%)
KEAP1+	1 (8%)
KEAP1+/NFE2L2+	1 (8%)

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Dose Escalation: IQ 3+3 and Summary of Toxicity Observed

Dose Escalation Schedule (Q28D Cycle)		
Dose Level	Dose	
	Telaglenastat (CB-839) (PO BID)	Sapanisertib (CB-228) (PO nightly)
Level 2	800 mg	3 mg
Level 1*	800 mg	2 mg
Level -1	600 mg	2 mg QD
Level -2	600 mg	2 mg QD (M-F)
Level -3	400 mg	2 mg QD (M-F)

* starting dose

- **Main toxicities are GI (anorexia/nausea)**

N=3 (1 DLT)

N=10 (1 DLT)
[Minimum Recommended Expansion Dose (RED)]

- **Plan to re-escalate with intermediate doses of sapanisertib administered in the fed state**

Adverse events related to treatment with G3 or more than one grade 2 event (CTCAE v5)	Dose Level 1 Sapanisertib 2 mg QD + CB-839 800 MG BID (N=10)			Dose Level 2 Sapanisertib 3 mg QD + CB-839 800 MG BID (N=3)		
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
Lymphocyte count decreased	1(10%)	2(20%)	2(20%)	---	---	---
Anorexia	---	2(20%)	1(10%)	1(33%)	1(33%)	1(33%)
Pruritus	---	1(10%)	---	---	---	1(33%)
Rash	---	1(10%)	1(10%)	---	---	1(33%)
Nausea/Vomiting	5(50%)	---	1(10%)	---	3(100%)	---
Fatigue	5(50%)	1(10%)	---	1(33%)	2(67%)	---
Mucositis oral	3(30%)	---	---	1(33%)	1(33%)	---
Creatinine increased	1(10%)	---	---	---	1(33%)	---
Dehydration	---	---	---	---	1(33%)	---
Dysgeusia	1(10%)	---	---	---	1(33%)	---
Hypertriglyceridemia	4(40%)	1(10%)	---	---	---	---
Hyperglycemia	3(30%)	1(10%)	---	---	---	---
Dry mouth	1(10%)	1(10%)	---	1(33%)	---	---
Hyponatremia	1(10%)	1(10%)	---	---	---	---
Neutrophil count decreased	1(10%)	1(10%)	---	---	---	---
Pneumonitis	---	1(10%)	---	---	---	---
Weight loss	---	1(10%)	---	1(33%)	---	---

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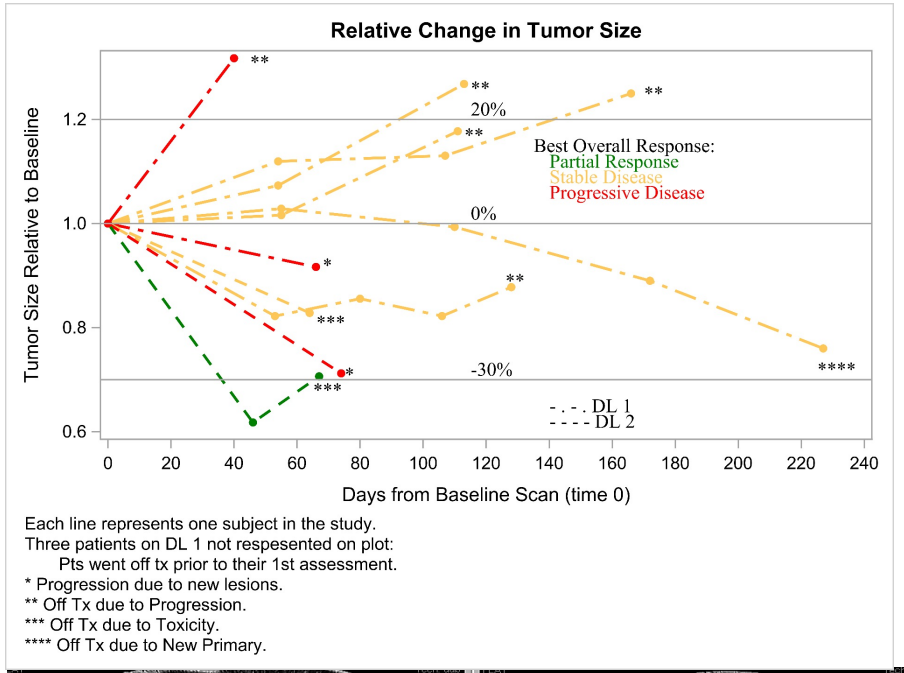
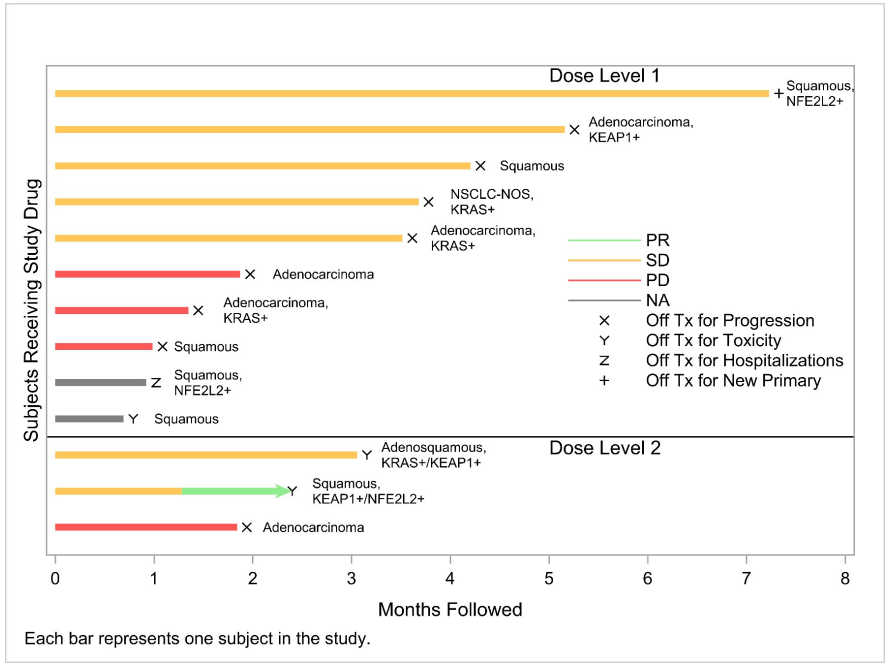
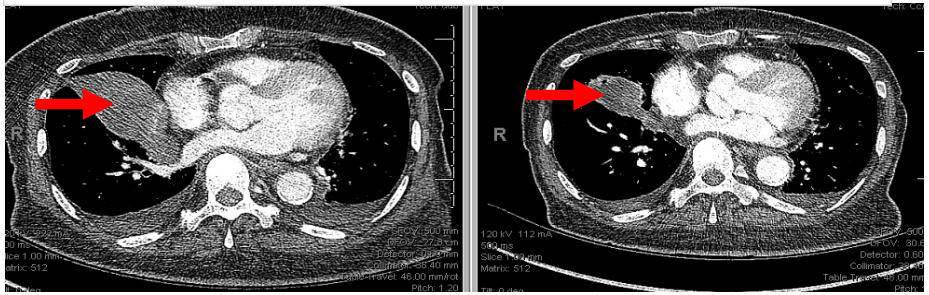


Each line represents one subject in the study.
Three patients on DL 1 not respesented on plot:
Pts went off tx prior to their 1st assessment.
* Progression due to new lesions.
** Off Tx due to Progression.
*** Off Tx due to Toxicity.
**** Off Tx due to New Primary.

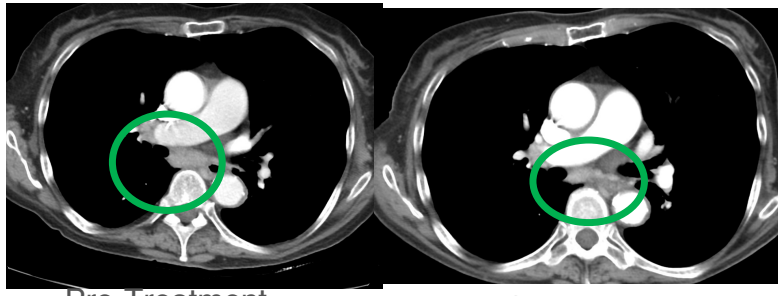


Each bar represents one subject in the study.



Pre-treatment On Treatment

KRAS G13C/KEAP1 Adenosquamous NSCLC



Pre-Treatment On Treatment

NFE2L2 mutant Squamous NSCLC

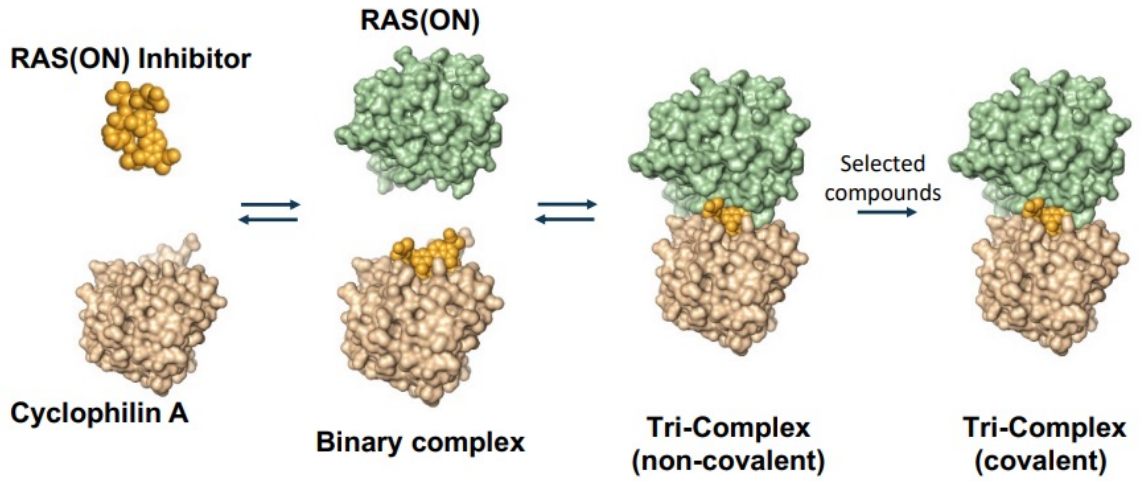
Take Home Points

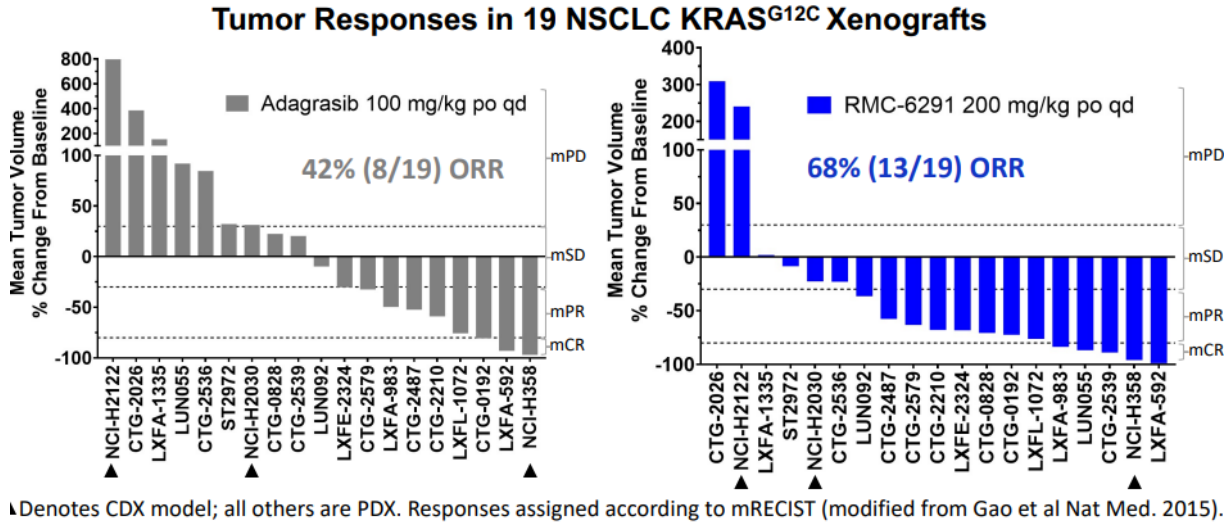
- Sapanisertib (CB228) and Telaglenastat (CB839) are safe and tolerable in combination at the minimum recommended expansion dose (RED)
- Preliminary efficacy observed in both squamous and KRAS mutant lung cancers with NRF2 activation including a PR in a squamous NSCLC harboring an NFE2L2 mutation.
- Next steps to re-escalate in the fed state for the final recommended expansion dose.

RAS(ON) Inhibitors

- Less susceptible to adaptive resistance compared to GDP bound RAS

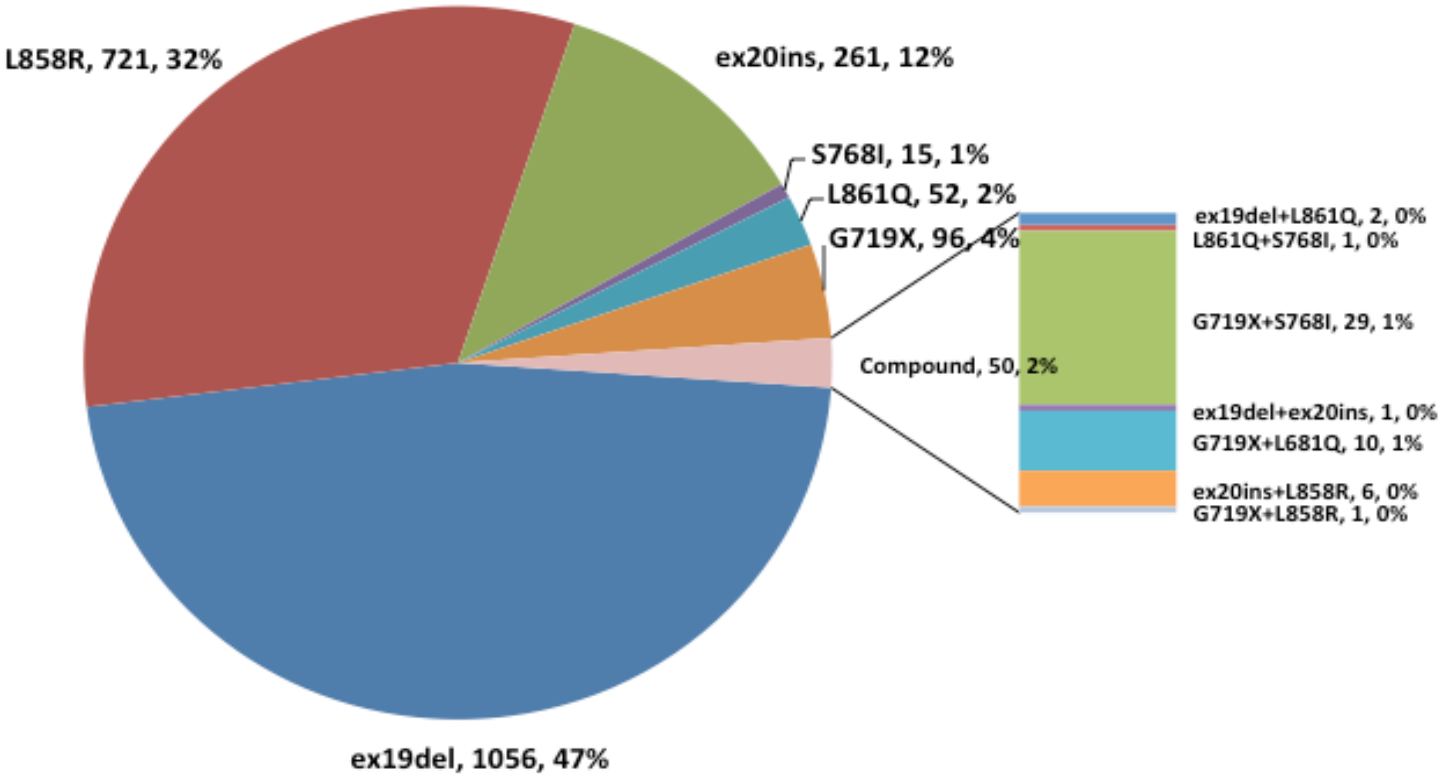
- RMC-6291 KRAS G12C (ON) inhibitor
- RMC-9805 KRAS G12D (ON) inhibitor
- RMC-6236-Pan RAS(ON)





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

Frequency and Distribution of 2,251 *EGFR* mutations in NSCLC Detected by Broad Genomic Profiling.



JW Riess et al. Journal of Thoracic Oncology 2018.

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

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)

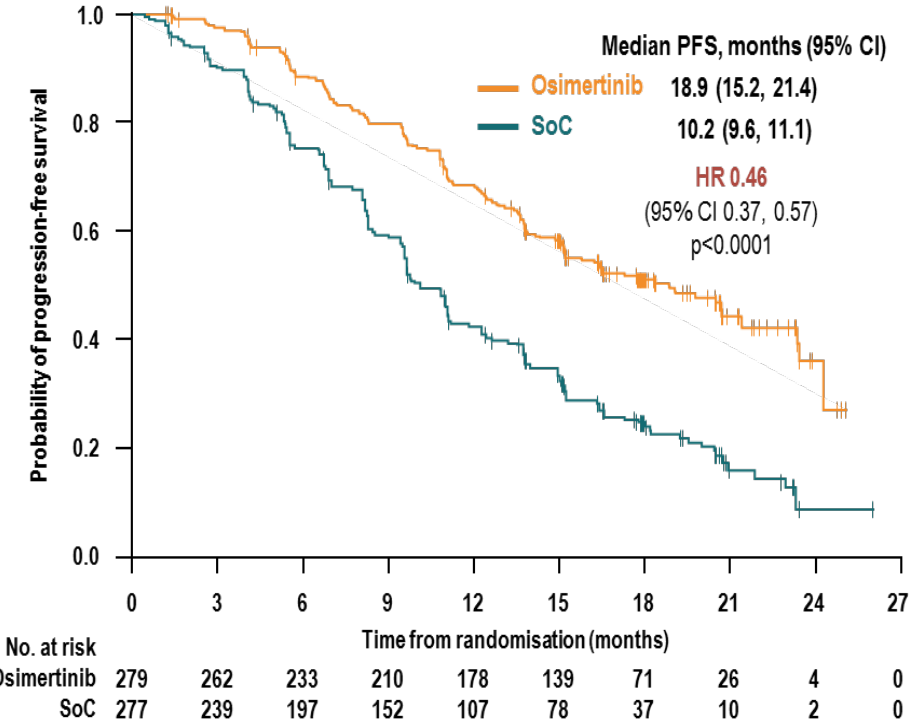
R 1:1

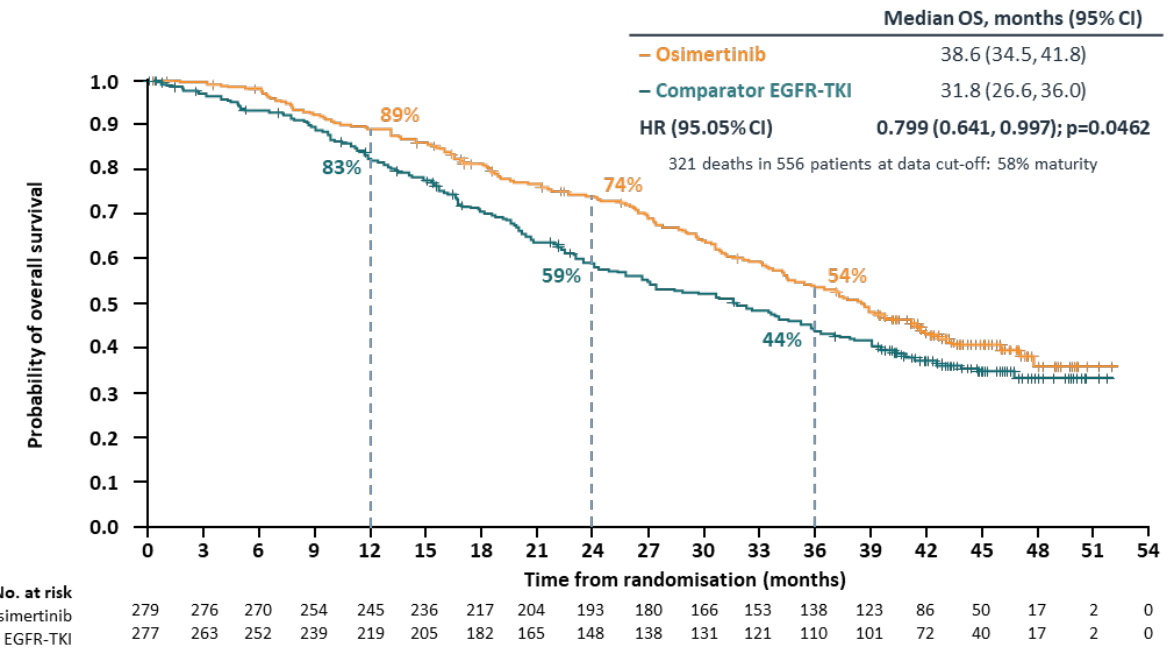
Osimertinib (80 mg po qd) (n=279)

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

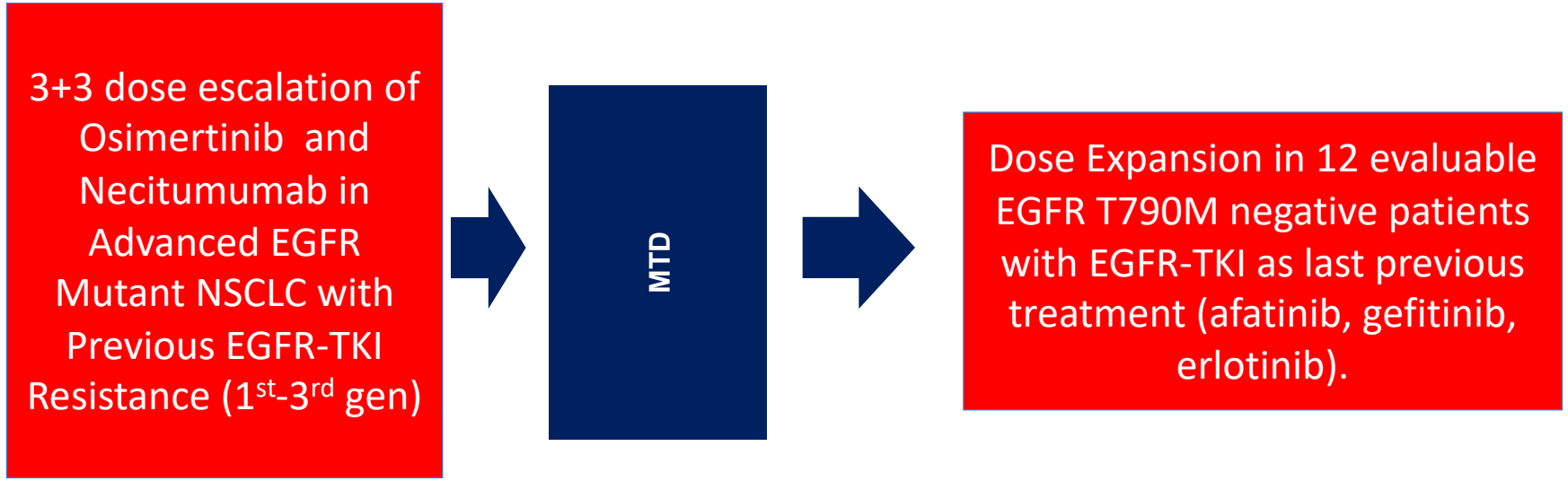
Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity





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

A Phase I Trial of Osimertinib and Necitumumab in EGFR Mutant NSCLC with Previous EGFR-TKI Resistance



Primary Endpoint: Safety and Tolerability
Main Secondary Endpoint:
ORR is T790M negative population

Molecular Studies
Biopsy – Pre-treatment and post progression for EGFR T790M, EGFR FISH and NGS
Plasma cfDNA for EGFR-TKI resistance mechanisms
Creation of EGFR-TKI resistant PDX
Single Cell NGS for Intratumoral Heterogeneity

Clinical and Radiographic Responses in Unmet EGFR-mutant Patient Populations: EGFR T790M negative after erlotinib and in C797S positive lung cancer after osimertinib

E19del/EGFR^{T790M} negative

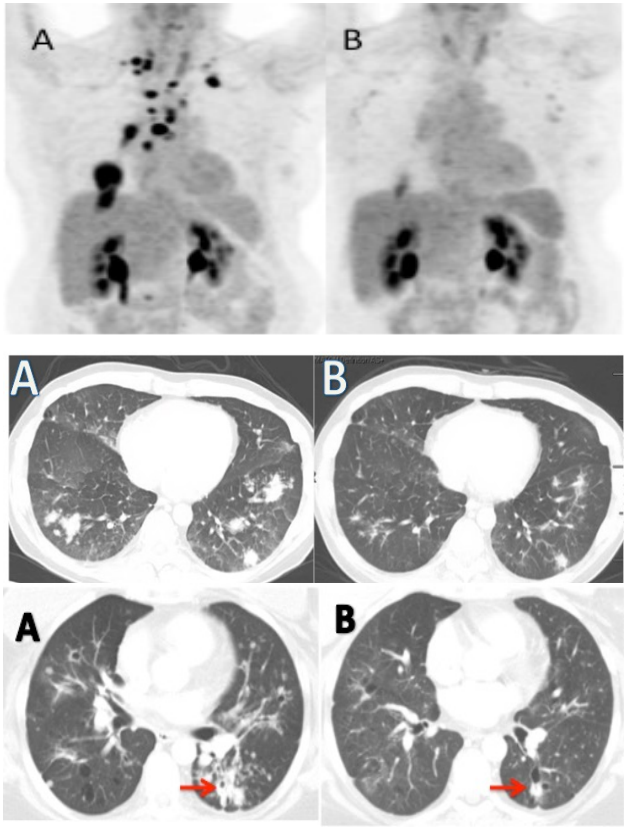
PD on erlotinib

E19del/T790M^{pos}/C797S^{pos}

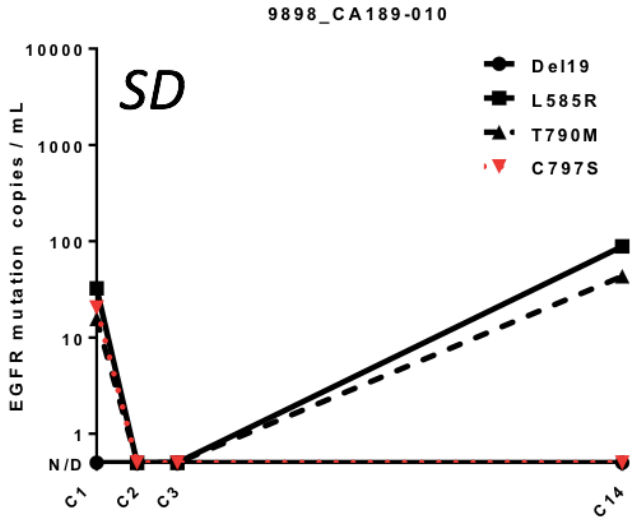
PD on osimertinib

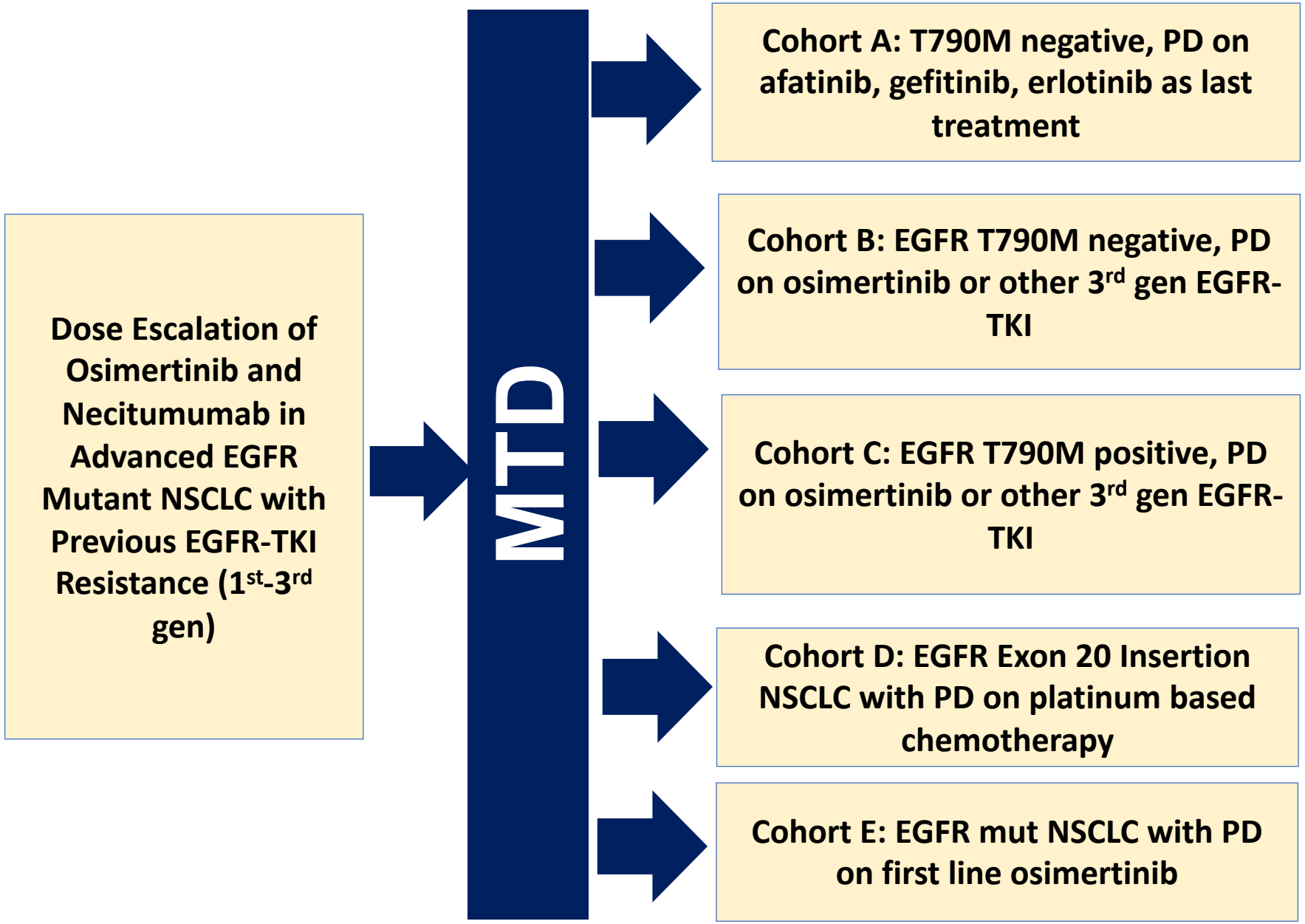
E19del/T790M^{pos}/C797S^{pos}

PD on osimertinib



Baseline On Treatment




Dose Escalation of Osimertinib and Necitumumab in Advanced EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (1st-3rd gen)
MTD
Cohort A: T790M negative, PD on afatinib, gefitinib, erlotinib as last treatment
Cohort B: EGFR T790M negative, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort C: EGFR T790M positive, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort D: EGFR Exon 20 Insertion NSCLC with PD on platinum based chemotherapy
Cohort E: EGFR mut NSCLC with PD on first line osimertinib

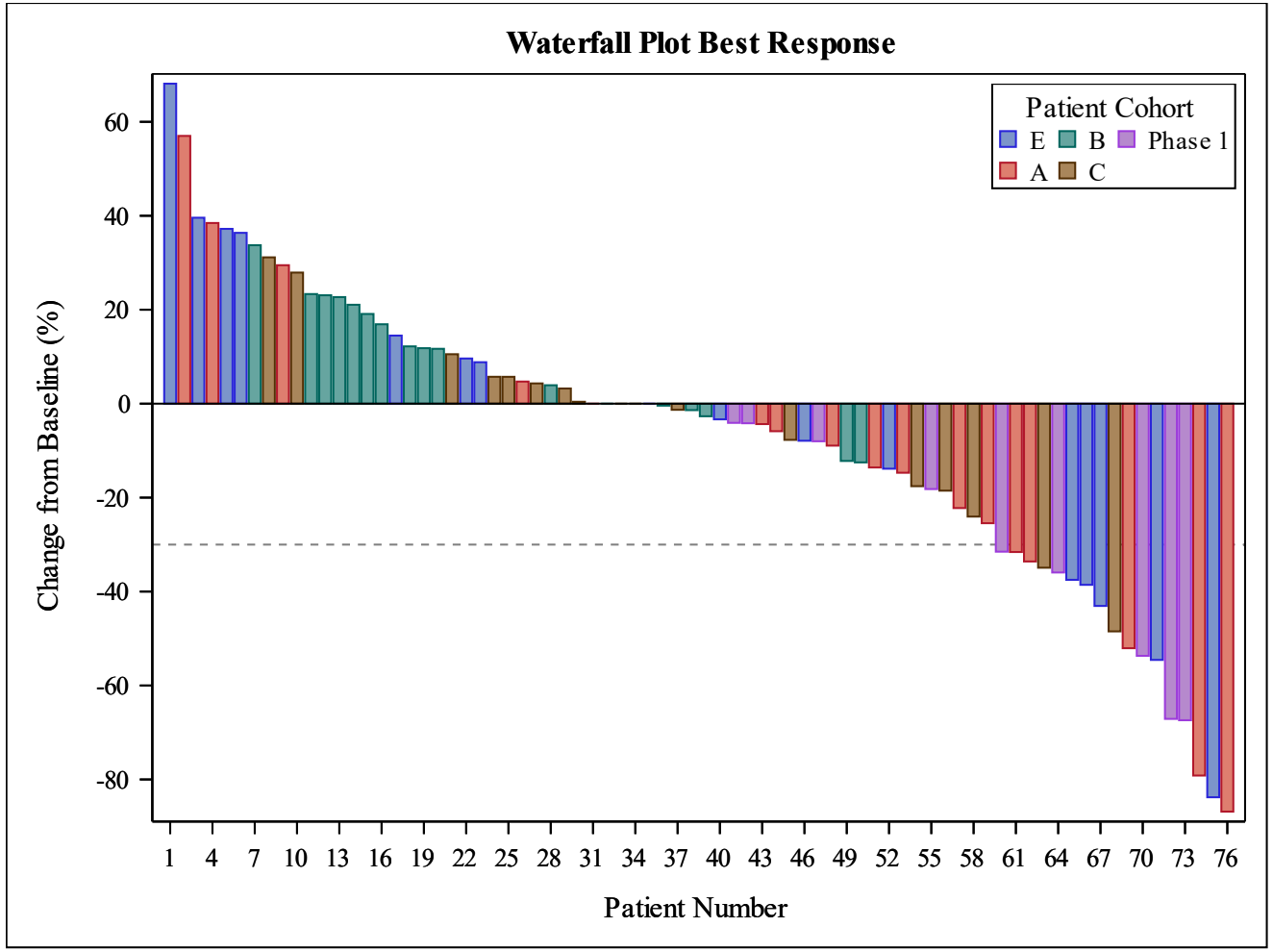
Summary of Results

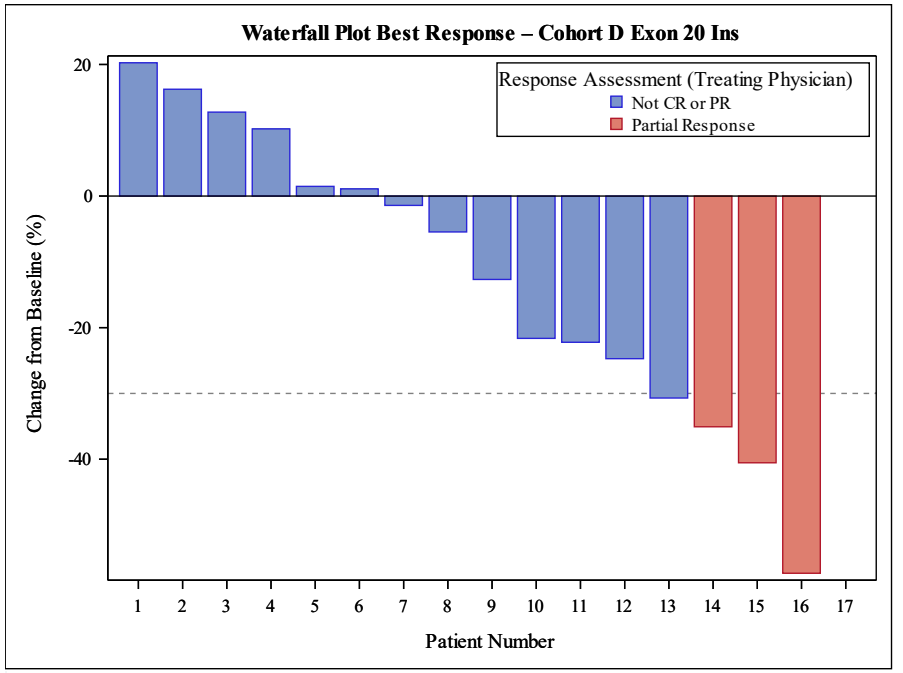
	Number of Patients with this Grade (N=97)	
Toxicity	Grade 1-2	≥Grade 3
Rash maculo-papular/acneiform/pustular	64	20
Diarrhea	32	1
Mucositis oral	23	2
Lymphocyte count decreased	12	4
Dyspnea	1	2
Hypophosphatemia	9	1
Hypokalemia	8	1
Infusion related reaction	7	1
Lipase Increased	0	1
AST/ALT Elevation	11	1
Sinus bradycardia	2	1
Thromboembolic event	3	1
Pneumonitis	1	2
Dehydration	0	1
Bone pain	0	1
Dry skin	50	1
Facial Abrasion	35	1
Fatigue	41	2
Electrocardiogram QT corrected interval prolonged	19	2
White blood cell decreased	13	1
Anemia	14	1
Weight loss	13	1

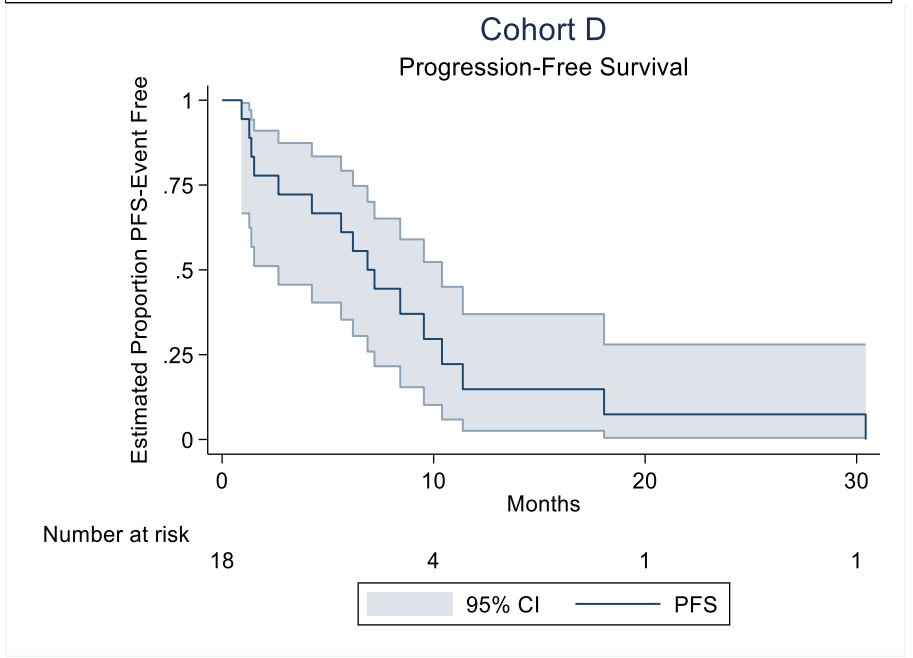
Summary of Response and Progression-Free Survival			
Cohort	**# Patients**	**Response**	**Median PFS in Months (90% confidence interval)***
Dose Escalation	**10**	**5 PR (3 cPR)**	**9.7 (5.3, 13.7)**
(A) T790M^{neg} PD on 1st/2nd gen TKI as last therapy	**18**	**4 PR (3 cPR)****	**3.9 (1.3, 5.7)**
(B) T790M^{neg} PD on 3rd gen TKI	**18**	**0**	**1.5 (1.2, 2.6)**
(C) T790M^{pos} PD on 3rd gen TKI	**18**	**2 PR (both cPR)**	**3.9 (2.4, 5.6)**
(D) EGFR ex20ins PD on chemotherapy	**18**	**4 PR (3 cPR)****	**6.9 (4.1, 11.4)**
(E) PD on 1L osimertinib	**18**	**3 PR (all cPR)****	**2.3 (1.4, n/a)**
***n/a means that the upper limit of the confidence interval was not reached at the time of the analysis; ** cohort met pre-specified efficacy endpoint cPR=confirmed partial response**			

- In the dose escalation portion of the study the recommended expansion dose was determined to be osi 80 mg qd and neci 800 mg D1, D8 IV on q21d cycle.
- 101 patients accrued (97 evaluable). Drug related ≥Gr 3 AEs were seen in 38% of pts, mainly rash (21%).
- ORR among all pts was 19% (95% CI 11-27%) that varied across cohorts.

Efficacy Across Cohorts





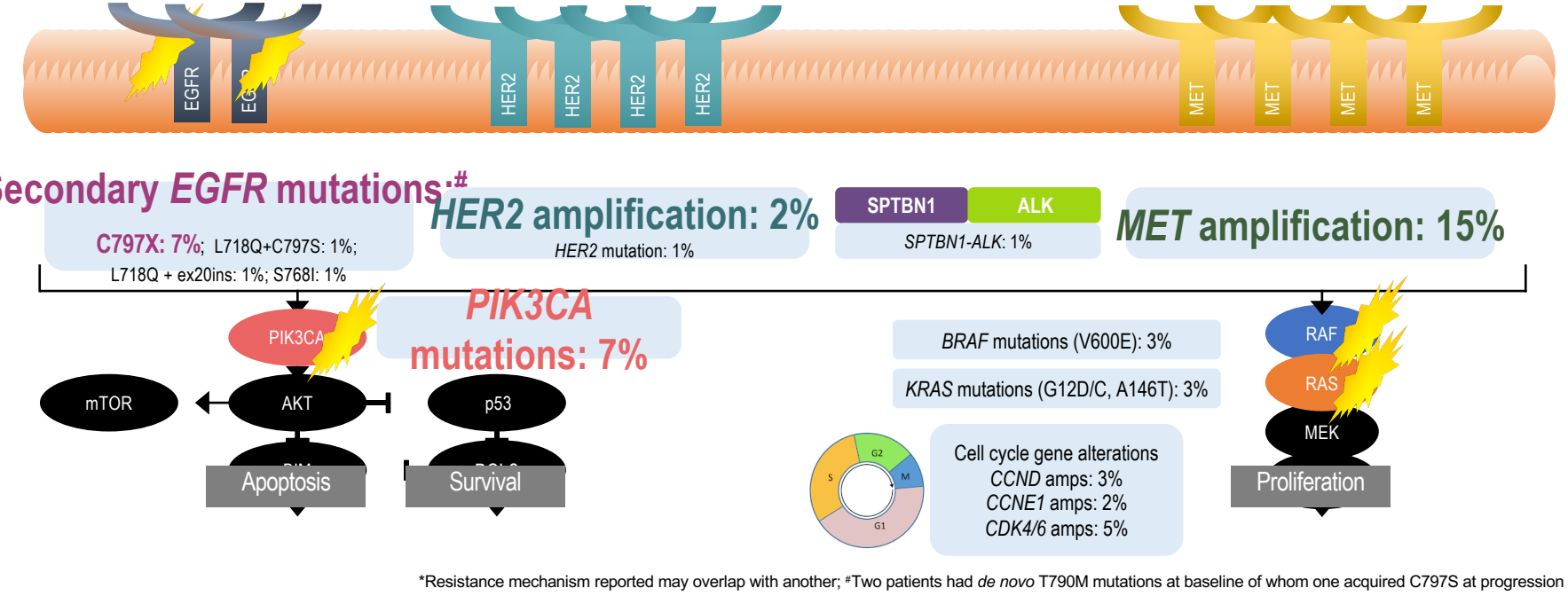


Summary

- The RP2D (Osi 80 mg qd and Neci 800 mg D1, D8 IV on q21d cycle) is feasible and tolerable with rash as main G3+ adverse event.
- Osi/Neci was active in select settings of EGFR-TKI resistance, meeting its prespecified efficacy endpoint in T790M^{neg} PD on 1st/2nd gen TKI as last therapy (ExC A), EGFR ex20ins post-chemo (ExC D) and PD on 1L osimertinib (ExC E).
- mPFS with Osi+Neci in the EGFR Exon 20 insertion cohort was within the range of current EGFR Exon 20 ins agents in development. Dual blockade with EGFR TKIs with exon 20 insertion activity in combination with an EGFR monoclonal antibody warrants further development in patients with this uncommon EGFR-mutation.
- Provides a paradigm to build upon with osi+monoclonal antibody (Lazertinib+Amivantamab moAB ORR 37%, Shu et al ASCO 2022)

RESULTS of CURRENT STUDY: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- **No evidence of acquired EGFR T790M**
- **The most common resistance mechanisms were *MET* amplification and *EGFR* C797S mutation**
  - **Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations**



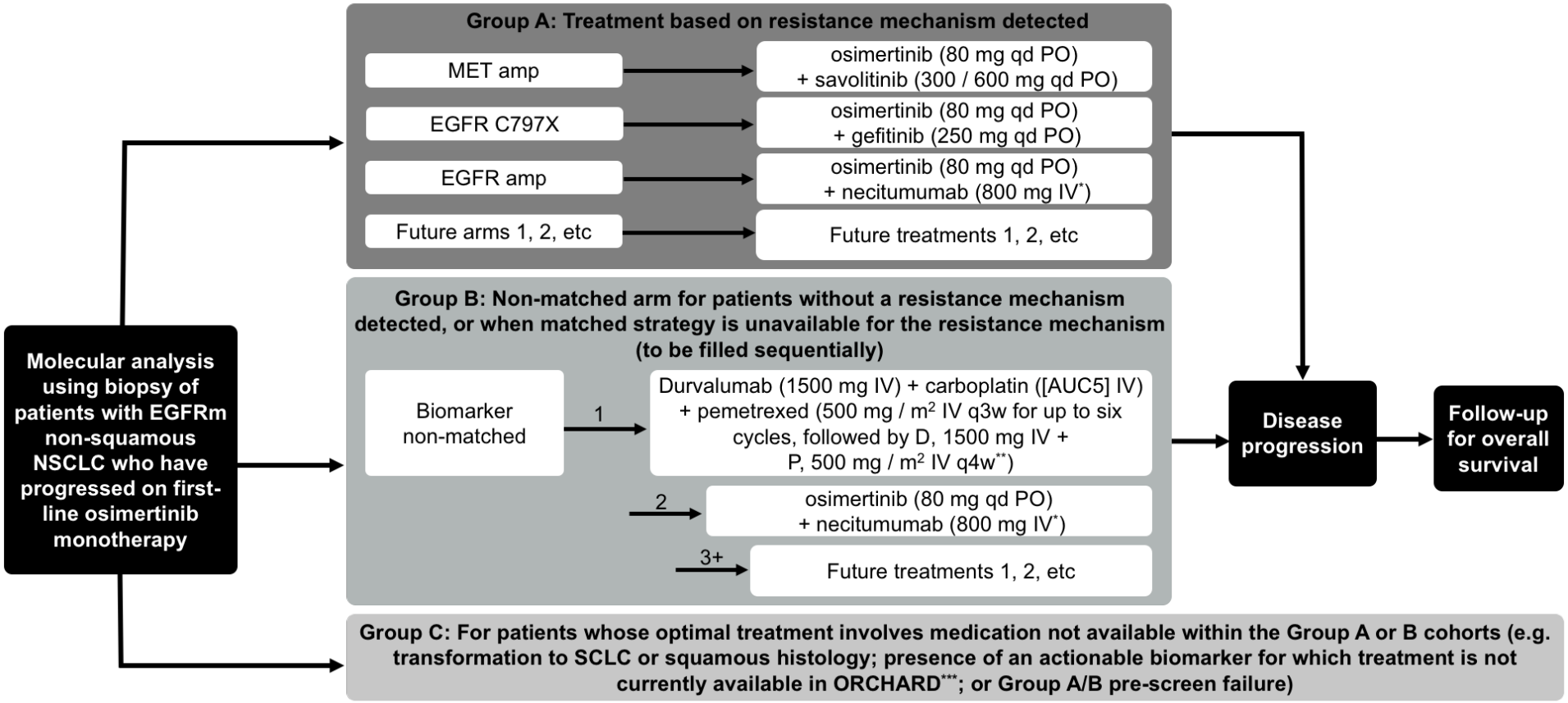
*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

SCLC (Histologic Transformation)

ORCHARD: a Phase II platform study in patients with advanced NSCLC who have progressed on first-line osimertinib therapy

Helena Yu[1], Sarah B. Goldberg[2], Xiuning Le[3], Zofia Piotrowska[4], Paul Smith[5], Ilhem Mensi[5], Bistra Kirova[5], Juliann Chmielecki[6], Xiaocheng Li-Sucholeicki[6], Philip Szekeres[5], Gail Doughton[5], Gargi Patel[5,7], Phil Jewsbury[5], Jonathan W. Riess[8]

Figure 1. ORCHARD study design



4th Generation EGFR Inhibitors can target both T790M and C797S

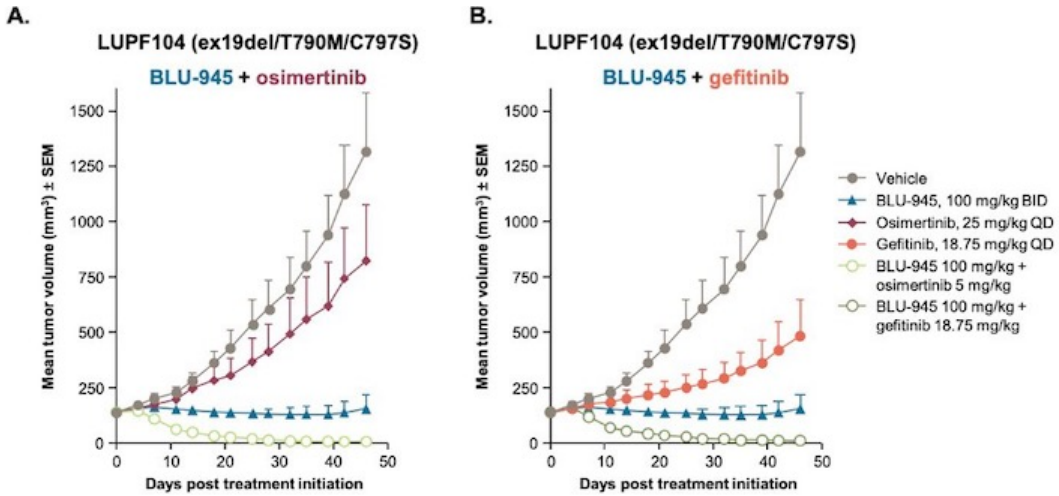
BLU-945 is a highly potent and selective EGFR+ T790M/C797S inhibitor

- Highly potent inhibitor of EGFR+/T790M/C797S and EGFR+/T790M resistant mutants
- Excellent EGFR WT and overall kinome selectivity
- BLU-945 only inhibits 1% of the kinome >90% at a concentration of 3 μM
- Selectivity profile enables combinations to cover wide spectrum of resistant mechanisms

Table 1: BLU-945 is a subnanomolar EGFR+/T790M/C797S and EGFR+/T790M inhibitor with >900-fold selectivity over EGFR WT

Compound	Enzyme activities IC_{50} (nM) at 1 mM ATP with enzyme-inhibitor pre-incubation						
	L8585R	L858R/ T790M	L858R/ T790M/C797S	ex19del (746–750)	ex19del/ T790M	ex19del/ T790M/C797S	EGFR WT
BLU-945	7.1	0.4	0.5	71.4	0.8	0.8	736.3
Erlotinib	0.3	3132.7	5654.7	0.2	1394.7	1906.6	9.8
Gefitinib	0.1	1667.2	3921.8	0.1	632.7	1219.7	3.5
Osimertinib	0.9	0.6	5461.6	0.8	0.6	649.9	1.6

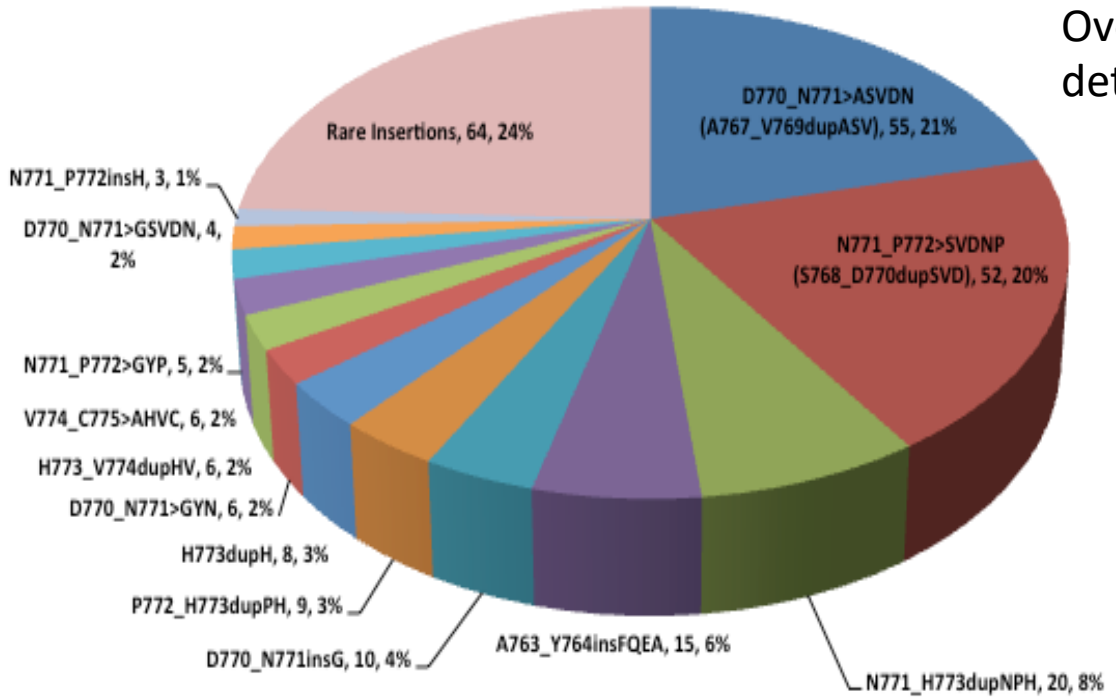
ATP, adenosine triphosphate; IC_{50}, half maximal inhibitory concentration.



- Single agent BLU-945 was sufficient for tumor stasis in this model
- Co-dosing BLU-945 with either osimertinib or gefitinib led to significant tumor regression
- Single agent and combination doses were well tolerated in the animal model
- Data suggest that BLU-945 can be combined with other EGFR TKIs to address allelic EGFR heterogeneity

Schalm et al., ESMO 2020

Frequency of Unique EGFR Exon 20 Insertions Detected by Comprehensive Genomic Profiling.



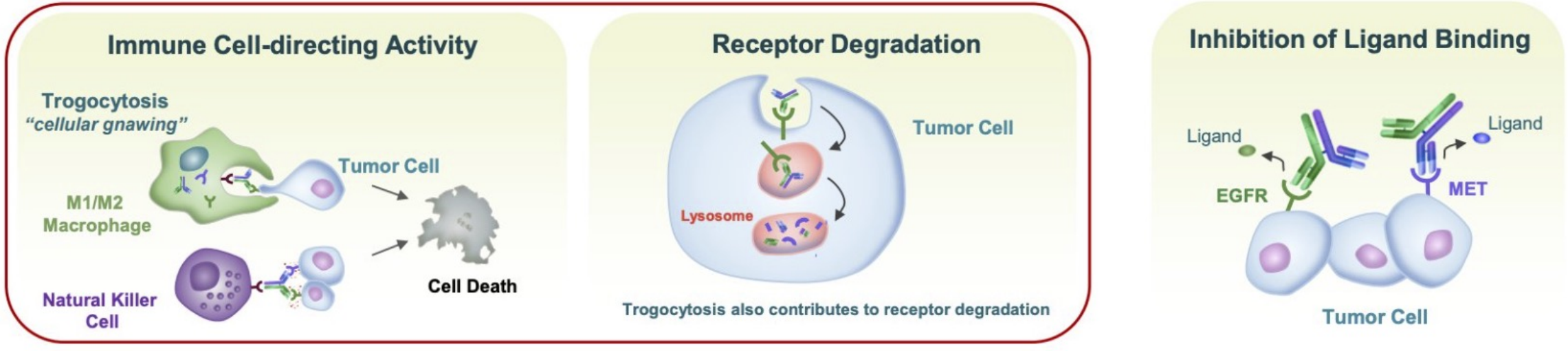
Over 60 unique insertions detected

JW Riess et al. Journal of Thoracic Oncology 2018.

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

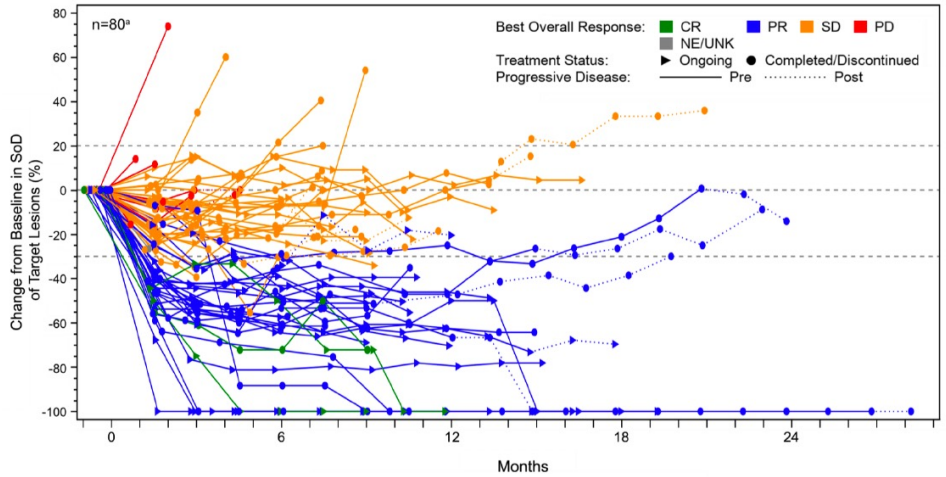
Amivantamab: Efficacy by BICR

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)

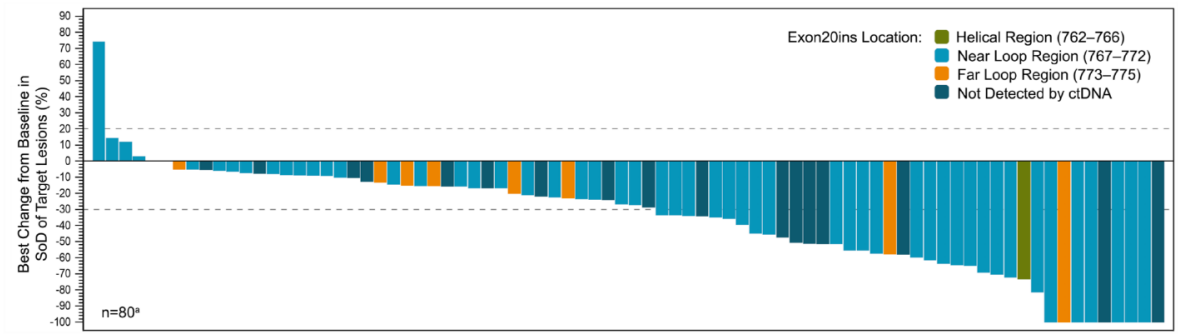
mPFS: 8.3 mo (95% CI, 6.5-10.9)
mOS: 22.8 mo (95% CI, 14.6-NR)

Amivantamab: Responses Over Time



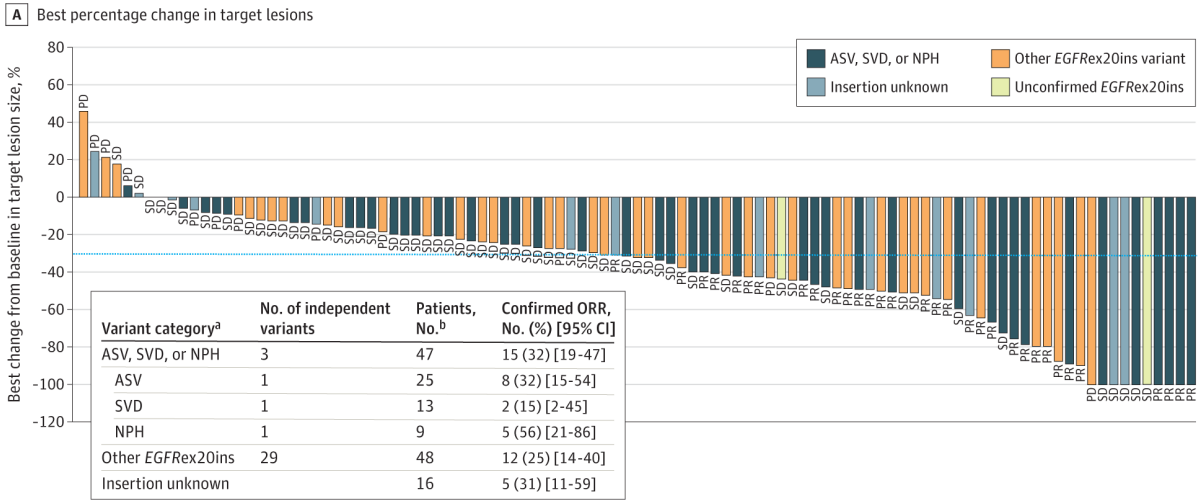
st ORR by Insertion Region of Exon 20 (detected by ctDNA)

Helical Region (n=1)	Near Loop (n=54)	Far Loop (n=8)	Not Detected by ctDNA (n=18)
ORR=100%; CBR=100%	ORR=41%; CBR=70%	ORR=25%; CBR=75%	ORR=39%; CBR=83%

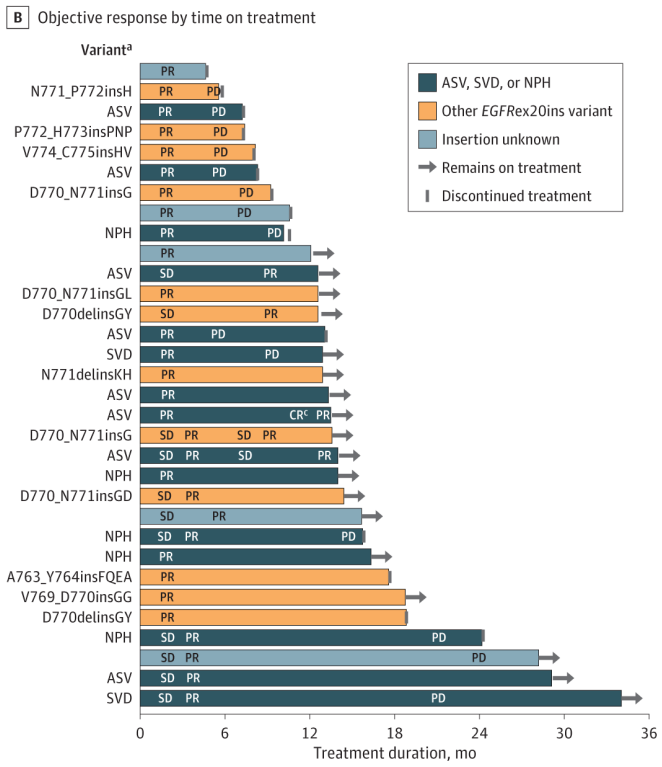


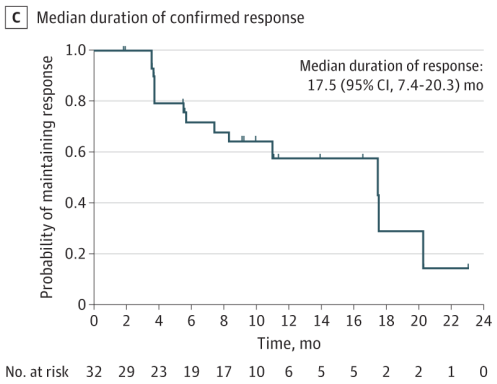
25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

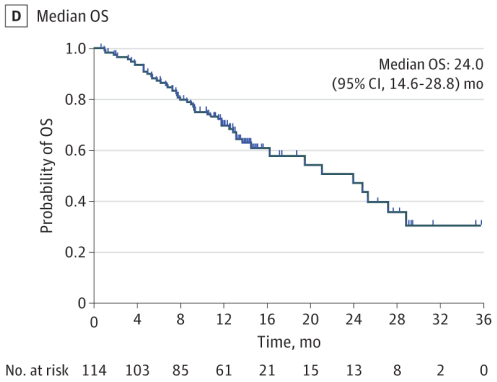
Mobocertinib in EGFR Exon20in NSCLC



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]







C. Zhou et al. Jama Onc 2021.

Summary

- New direct KRAS G12Ci have good clinical activity
- Need to address comutations, new potentially actionable targets
- Next gen KRAS (on) and pan-ras inhibitors are next steps to target KRAS
- Need to target mechanism of EGFR TKI resistance
- New EGFR Exon 20 ins drugs now in clinic – personalize choice based upon pt characteristics.
- Paradigm of TKI + moAb holds promise