EGFR TKI RESISTANCE & K-RAS MUTATIONS IN NSCLC

Edgardo S. Santos, M.D., FACP
Medical Oncology-Thoracic
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO
President, FLASCO Foundation

April 29, 2023

19th Annual

MIAMI CANCER MEETING

Conquering Cancer:
Improving Science, Promoting Precision Medicine & Developing Equity in Cancer Care

JW MARRIOTT MIAMI | MIAMI, FLORIDA

APRIL 28 - 30, 2023

Program Directors

Luis E. Raez, MD, FACP, FCCP
Chief Scientific Officer & Medical Director
Memorial Cancer Institute
Co-Director MCI/FAU Florida Cancer Center of Excellence
Research Professor Florida Atlantic University (FAU)
Past-President Florida Society of Clinical Oncology (FLASCO)
Miami, FL

Edgardo S. Santos Castillero, MD, FACP
Medical Oncologist - Thoracic
Clinical Associate Professor
Charles E. Schmidt College of Medicine
Florida Atlantic University
Treasurer, Florida Society of Clinical Oncology (FLASCO)
President, FLASCO Foundation
Boca Raton, FL

MEC THE MEDICAL EDUCATOR CONSORTIUM

OLA

CANCER EXPERT NOW

MECC GLOBAL MEETINGS
MEETINGS • EVENTS • CONFERENCE • COORDINATORS

EGFR TKI Resistance

A QUICK LOOK AT THE BACKGROUND

Dr. Roy Herbst

SOME INSIGHTS IN REFINIG EGFR CLASSIFICATION

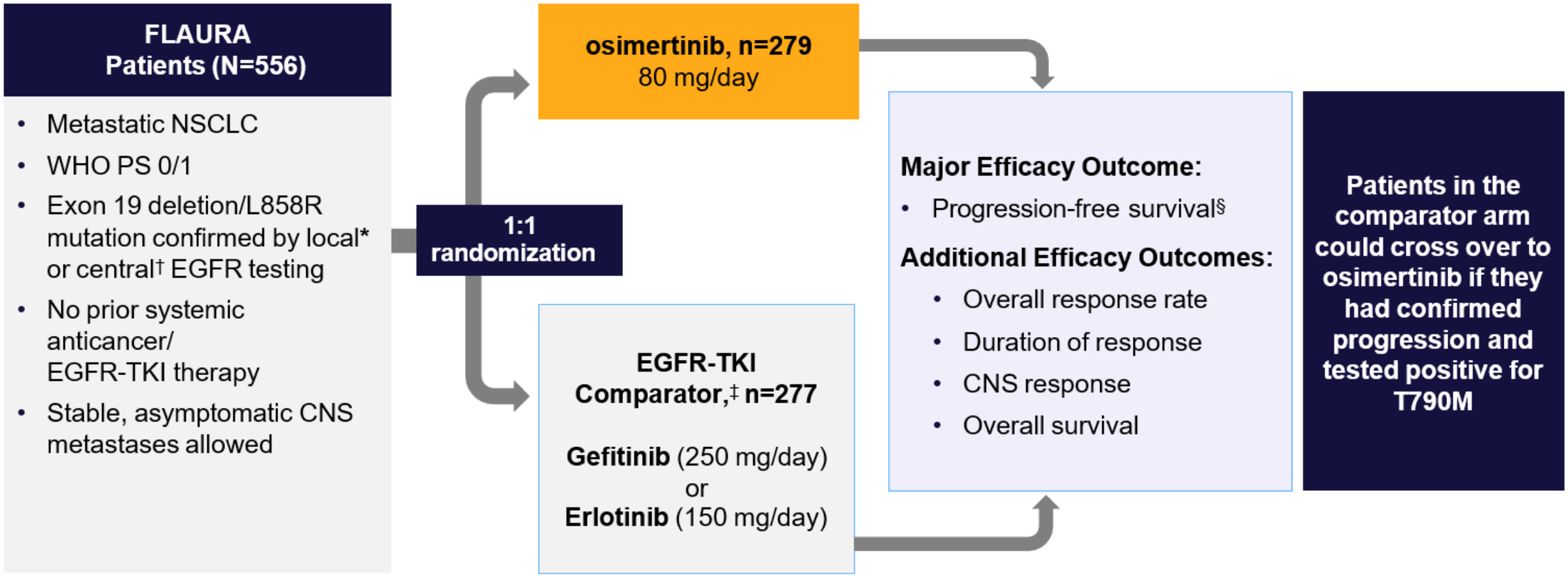
Dr. John Heymach

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

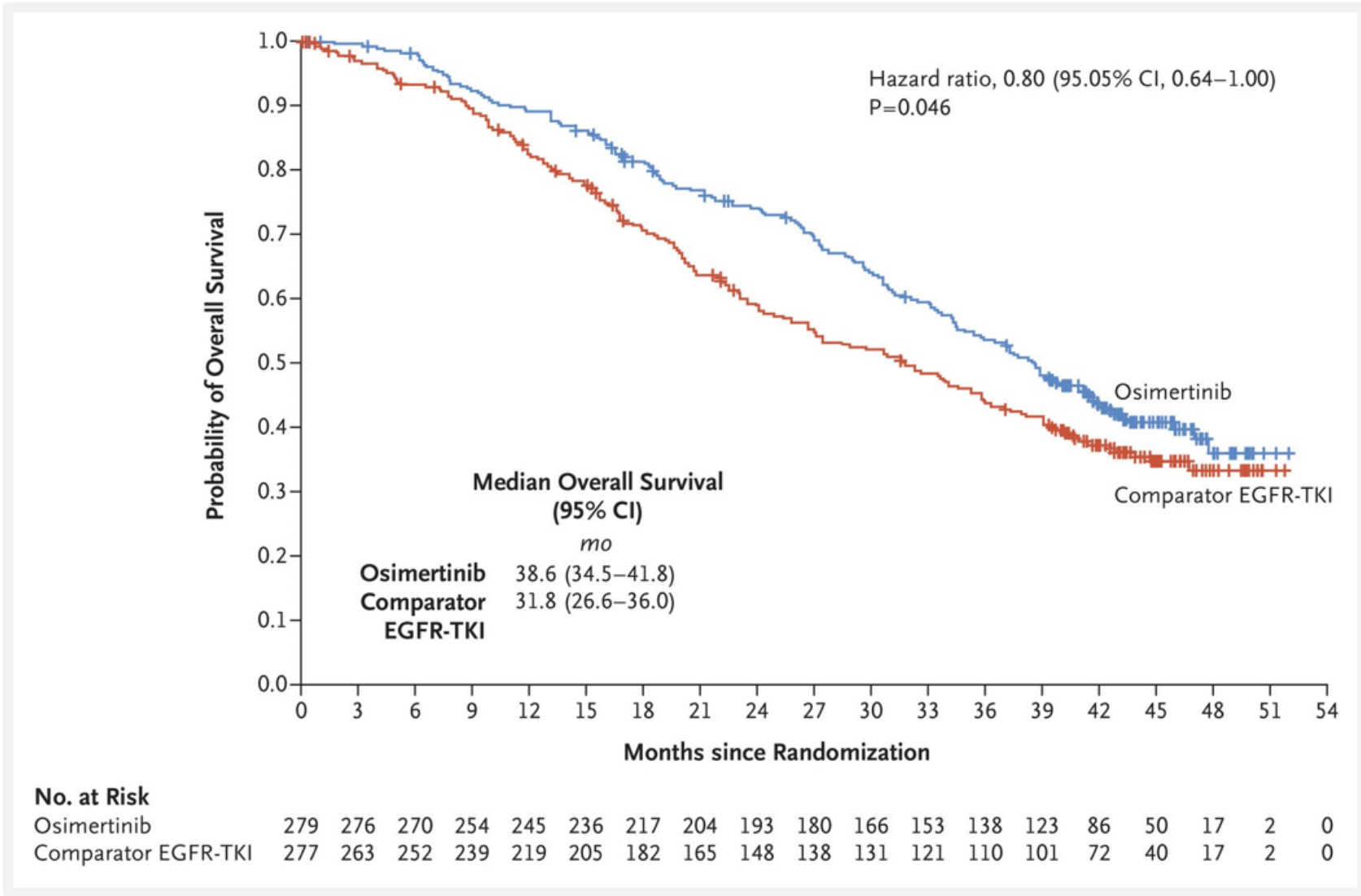
FLAURA is a Phase 3, Randomized, Double-Blind Trial in Patients With Previously Untreated EGFR Mutation-Positive Metastatic NSCLC



*No mandatory baseline CNS imaging

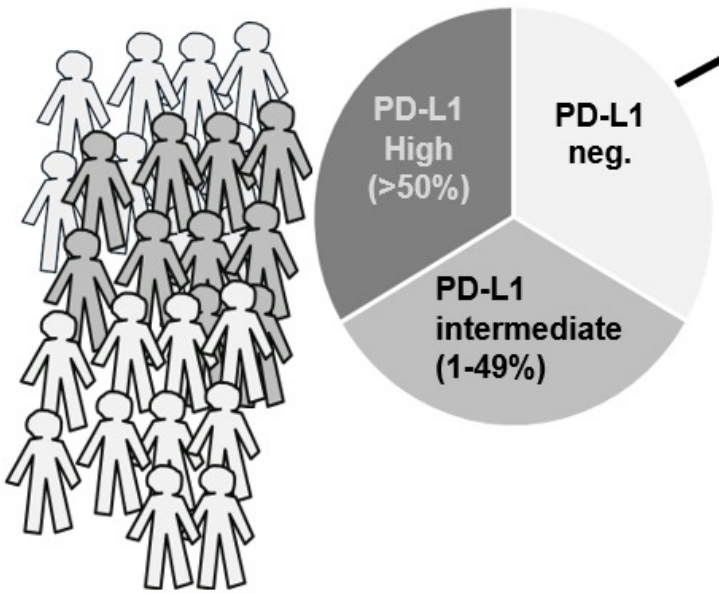
Soria JC et al. N Engl J Med. 2018; 378(2):113-125.

FLAURA: 1st gen EGFR TKI vs Osimertinib

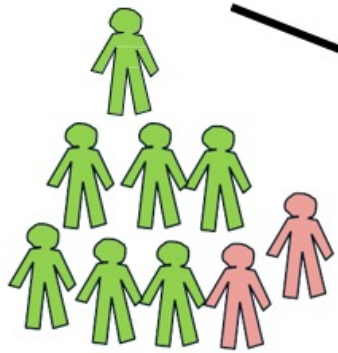


Immune and genomic landscape of NSCLC 2023

Driver negative: the immune pie (60%)

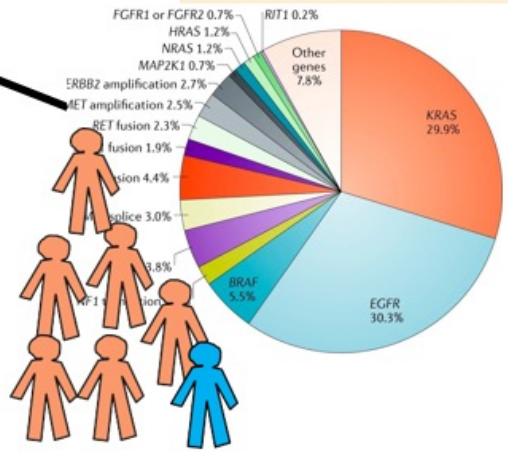


NSCLC

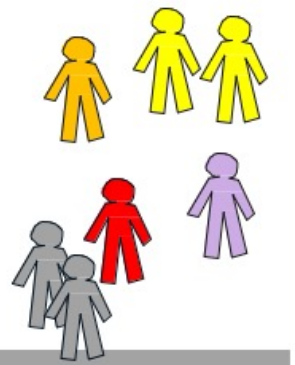


- Classical EGFR (10%)
- EGFR T790M
- EGFR atypicals (3%)
- EGFR Exon20 (2%)
- ALK fusion (4%)

Driver positive: the genomic pie (40%)



- KRAS G12C 12%
- HER2 mutant (3%)



- BRAF mutant (3%)
- ROS-1 mutant (1%)
- NTRK mutant (1%)
- MET ex14 (3%)
- RET fusion (1%)

Skoulidis and Heymach, Nat Rev Cancer 2019

The challenge: most studies focus on classical mutations (exon 19 deletion, L858R). But there are more than 100 mutations we see in the clinic, most without approved TKIs

Exon 18
A702T
E709A L858R
E709K L858R
E709 T710del insD
E709A
E709A G719A
E709A G719S
E709K
E709 G719S
L718Q T790M
G719A
G719A D761Y
G719A L861Q
G719A R776C
G719A T790M
G719A S768I
G719C S768I
G719S
G719S L861Q
G719S S768I
S720P
G724S
G724S Ex19del
G724S L858RI
G724S T790M
T725M
L718Q
L718Q Ex19del
L719Q L858R
L718V
L718V ex19del
L718V L858R

Exon 19
A750 I759del ins PN
Ex19del T790M
Ex19del T790M L718V
Ex19del T790M G724S
E738K
E746 A750del A647T
E746 A750del R675W
E746 T751del insV S768C
Ex19del C797S
Ex19del C796S
Ex19del L792H
Ex19del T854I
E749 A750del A647T
E749 A750del L41W
E749 A750del R451H
Ex19del E746 A750del
K754E
L747 E749del A750P
L747 T751del L861Q
Ex19del T790M C797S
Ex19del T790M L792H
I740dupIPVAK
D761N
T751 I759 delinsN
K757M L858R
K757R
L747 S752del A755D
L747P
L747S
L747S L858R
L747S V744M
E709 T710del insD S22R
S752 I759del V769M

Exon 20	
A767 V769dupASV	S768I
A767 S768insTLA	S768I L858R
S768 D770dupSVD	S768I L861Q
S768 D770dupSVD L858Q	S768I V769L
S768 D770dupSVD R958H	S768I V774M
S768 D770dupSVD V769M	H773R T790M
V769 D770insASV	I744 E749del insMKK
V769 D770insGSV	L747 K745 delinsATSPE
V769 D770insGVV	
V769 D770insMASVD	S784F
D770 N771insNPG	T790M
D770 N771insSVD	S811F
D770del insGY	
D770 N771 insG	
D770 N771 insY H773Y	
N771G	
N771dupN	
N771dupN G724S	
N771 P772insHH	
N771 P772insSVDNR	
N771 P773insDNP	
H773 V774 insNPH	
N773 V774insAH	
H773dupH	
H774 C775insHV	
V774 C775insPR	
A763insFQEA	
A763insLQEA	
G779F	
V769L	
V769M	
V774M	
R776C	
R776H	

Exon 21
L858R T790M C797S
L858R T790M L718Q
L858R T790M L718V
L833F
L833V
L858R
L858R A289V
L858R E709V
L858R L833F
L858R P100T
L858R P848L
L858R R108K
L858R R324H
L858R R324L
L858R S784F
L858R S784Y
L858R T725M
L858R V834L
L861Q
L861R
S768I T790M
L858R T790M V843I
L858R T790M L792H
L858R T790M
L858R L792H
L858R T854S
L858R C797S

Approved TKI

No Approved TKI

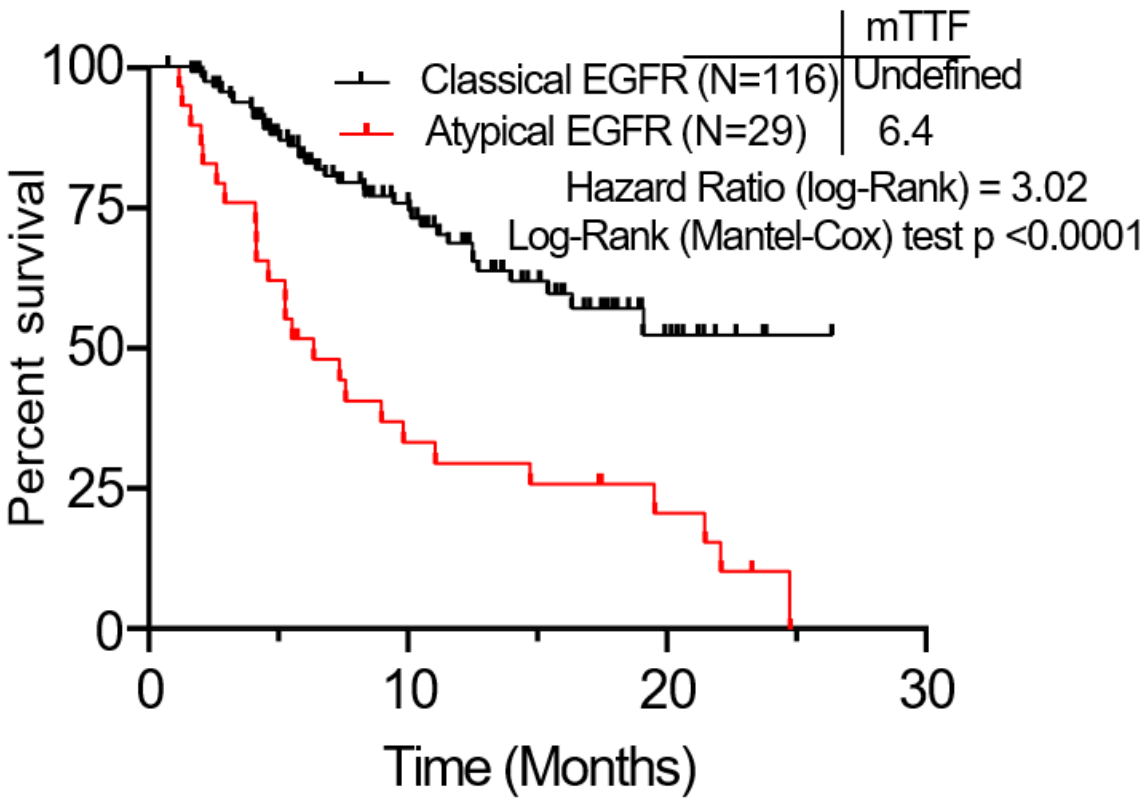
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Can't we just give everyone a third-generation TKI like osimertinib?

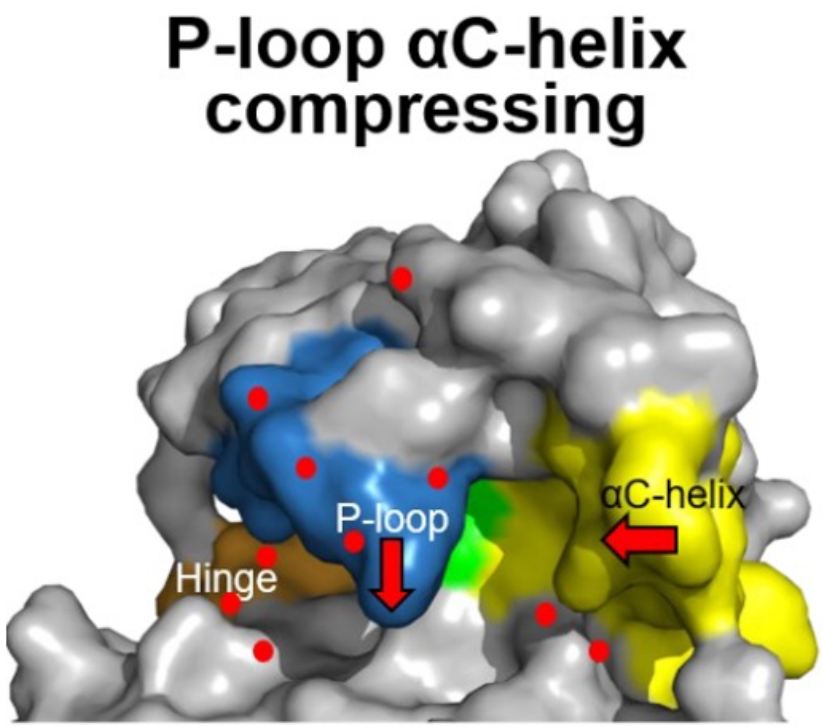
Time to treatment failure on osimertinib



- Significant heterogeneity in response to osimertinib
- One TKI unlikely to be optimal for all mutations
- Not practical to do trials for >100 individual mutations
- No trials cover the unmet need of large group of atypicals for which no drugs are approved
- Are there more useful way for classifying atypical EGFR mutations to improve TKI selection?

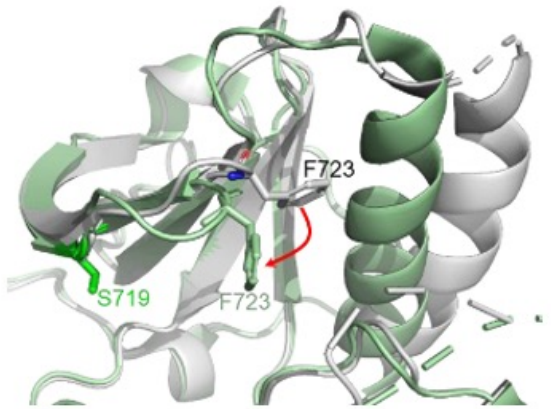
Robichaux et al 2021 Nature

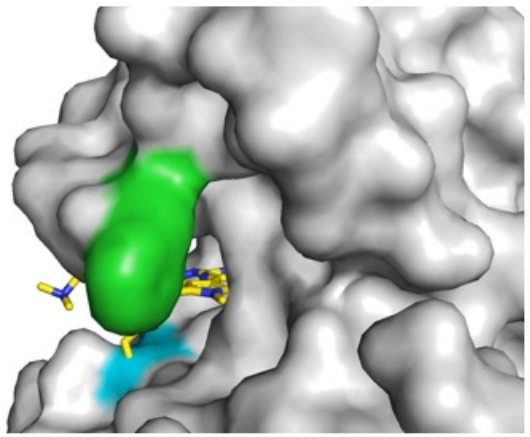
P-loop and a c-helix Compressing (PACC) mutations are predicted to the impact ATP-binding pocket and have enhanced sensitivity for 2nd gen TKIs

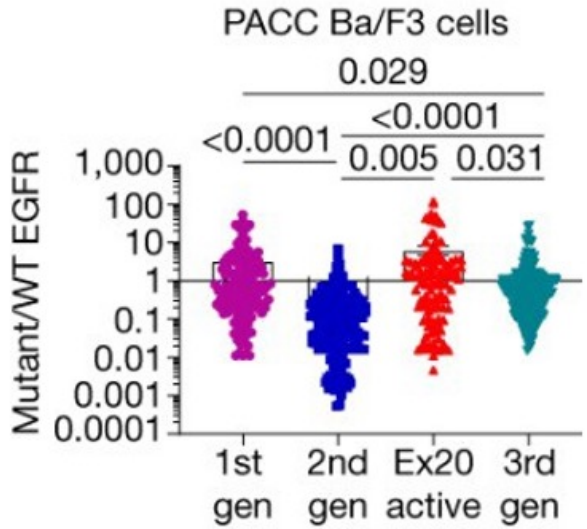


- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

EGFR G719S

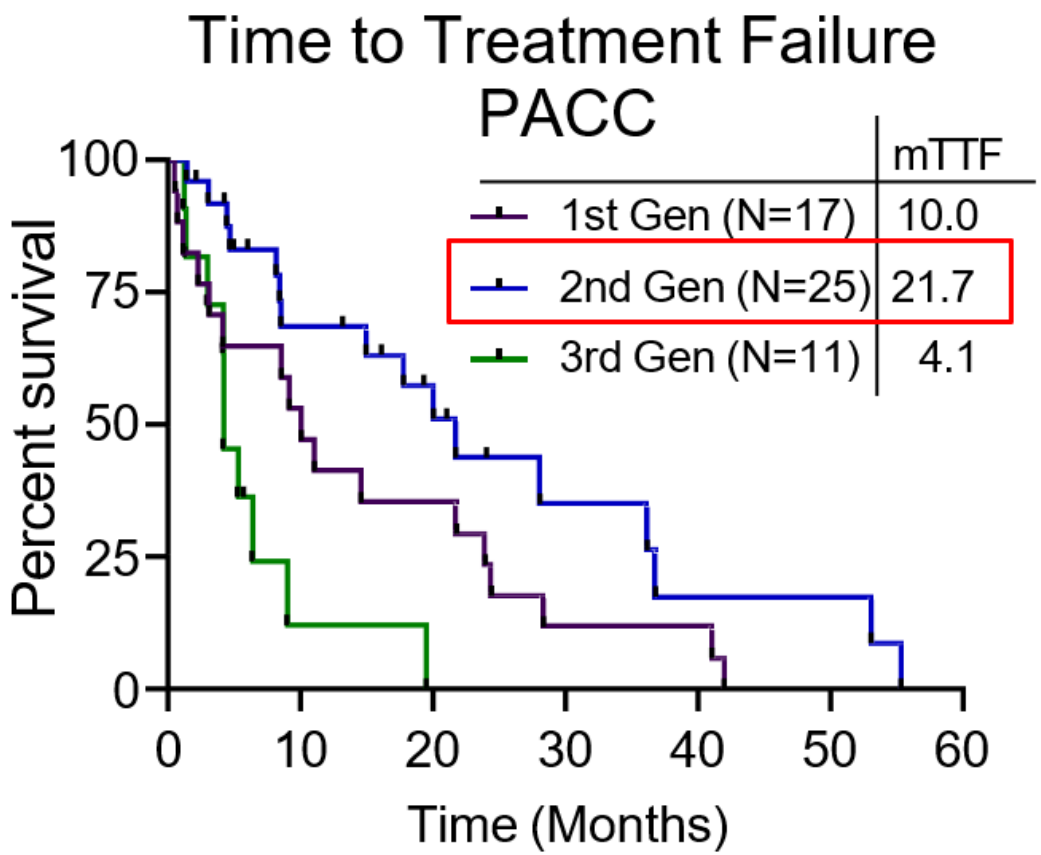


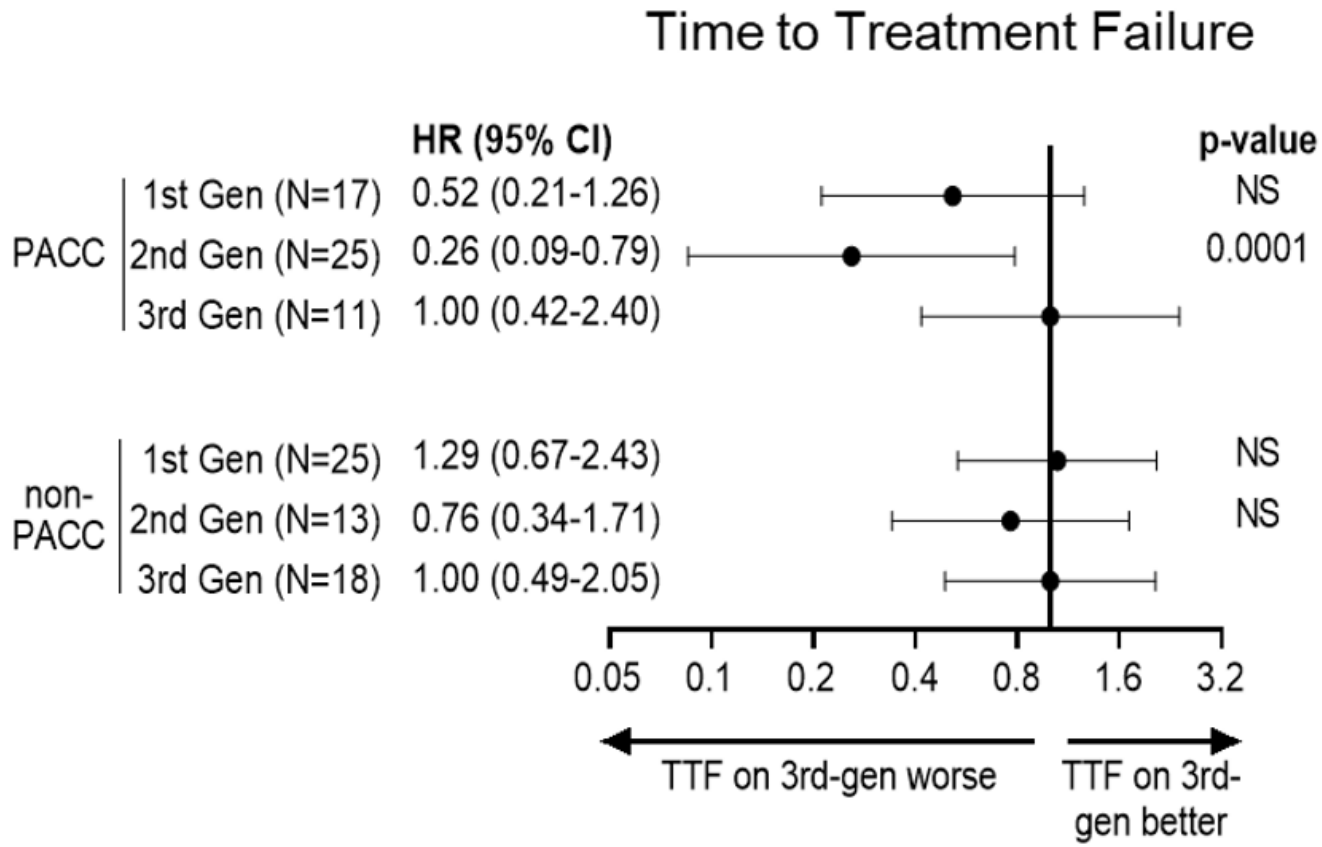




Robichaux et al 2021 Nature

Patients with PACC mutations have prolonged TTF with 2nd gen TKIs compared to 1st or 3rd gen TKIs→

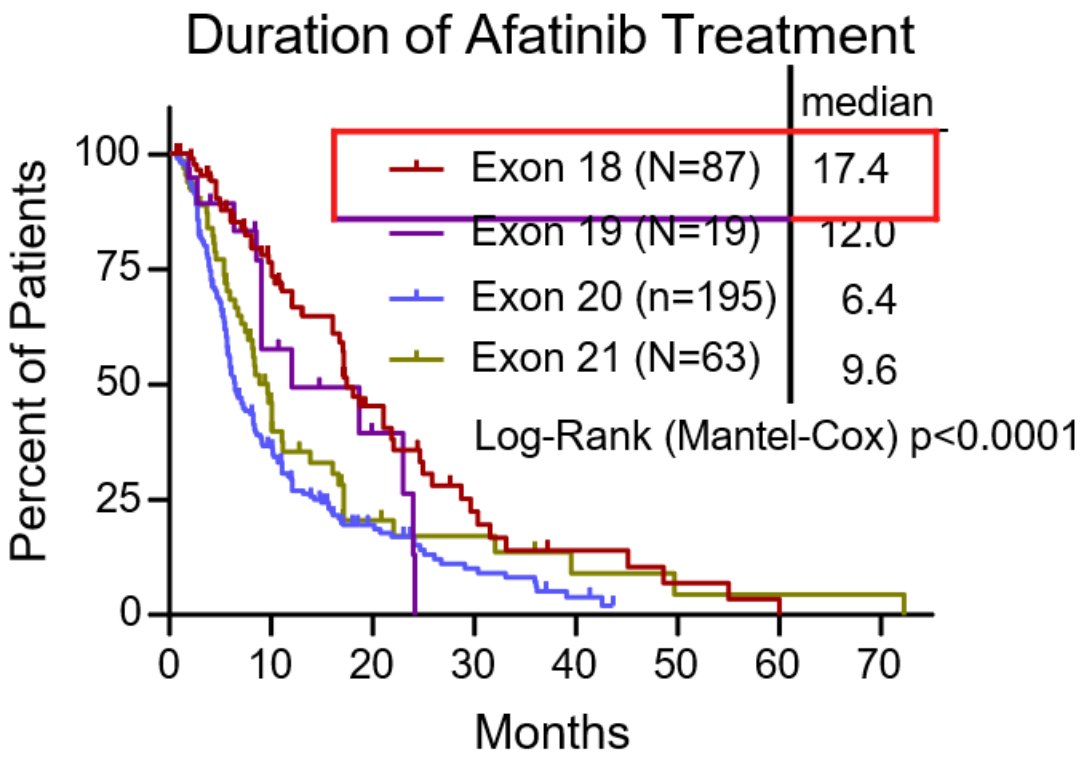




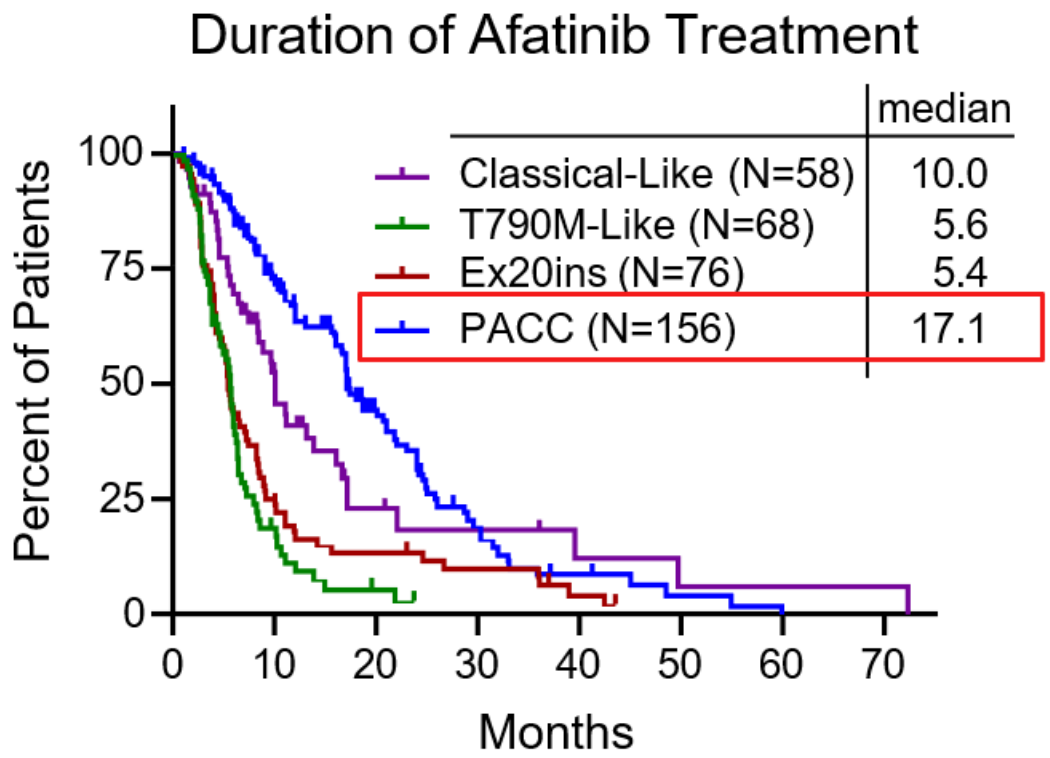
Robichaux et al 2021 Nature

Structure/function-based groups identifies larger subgroup of patients who benefit from afatinib treatment than exon-based groups

Exon-based groups

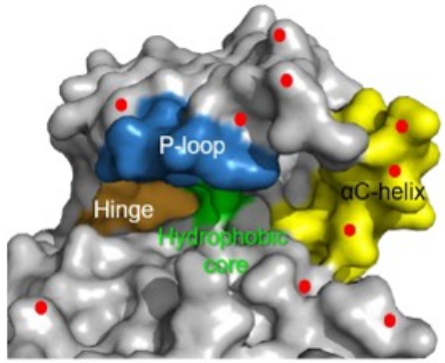


Structure/function-based groups



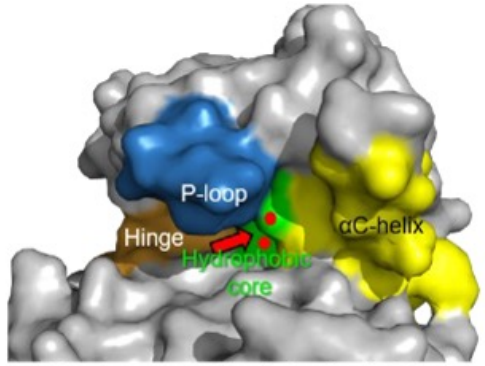
Robichaux et al 2021 Nature

Classical-like



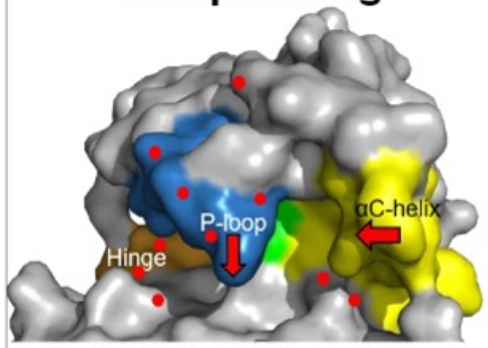
- Distal to drug binding pocket
- Modest to no impact on drug binding

T790M-like



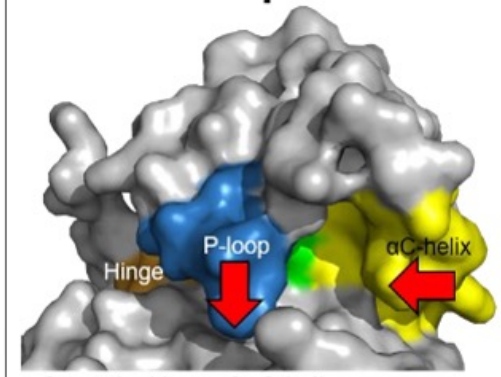
- At least one mutation in hydrophobic core
- Increased affinity for ATP compared to classical-like mutations
- Two subgroups:
  - T790M-like-3S
  - T790M-like-3R

P-loop αC-helix compressing



- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

Exon 20 loop insertions



- C-terminal loop of αC-helix
- Indirect and substantial impact on drug binding (both P-loop and αC-helix)
- Two subgroups:
  - Ex20ins-near loop (light red)
  - Ex20ins- far loop (dark red)

Representative Mutations

L858R	K754E
Exon 19 deletions	T725M
S720P	L833F/V
L861Q/R	A763insFQEA
S811F	A763insLQEA

T790M-3S	T790M-3R
Classical/T790M	Ex19del/T790M/L792H
G719X/T790M	L858R/T790M/L718X
L747_K745delinsATSPE	Classical/T790M/C797S
S768I/T790M	

Primary	Acquired
G719X	C797S
S768I	L792H
L747P/S	G724S
E709_T710del insD	L718X
V769L	T854I

Ex20ins-NL	Ex20ins-FL
S768dupSVD	H773insNPH
A767dupASV	H773dupH
D770insNPG	V774insAV
D770del insGY	V774insPR

Drug Sensitivity/Selectivity

Sensitive & Selective

Resistant

Third-generation
Second-generation
First-generation
Exon20ins-specific

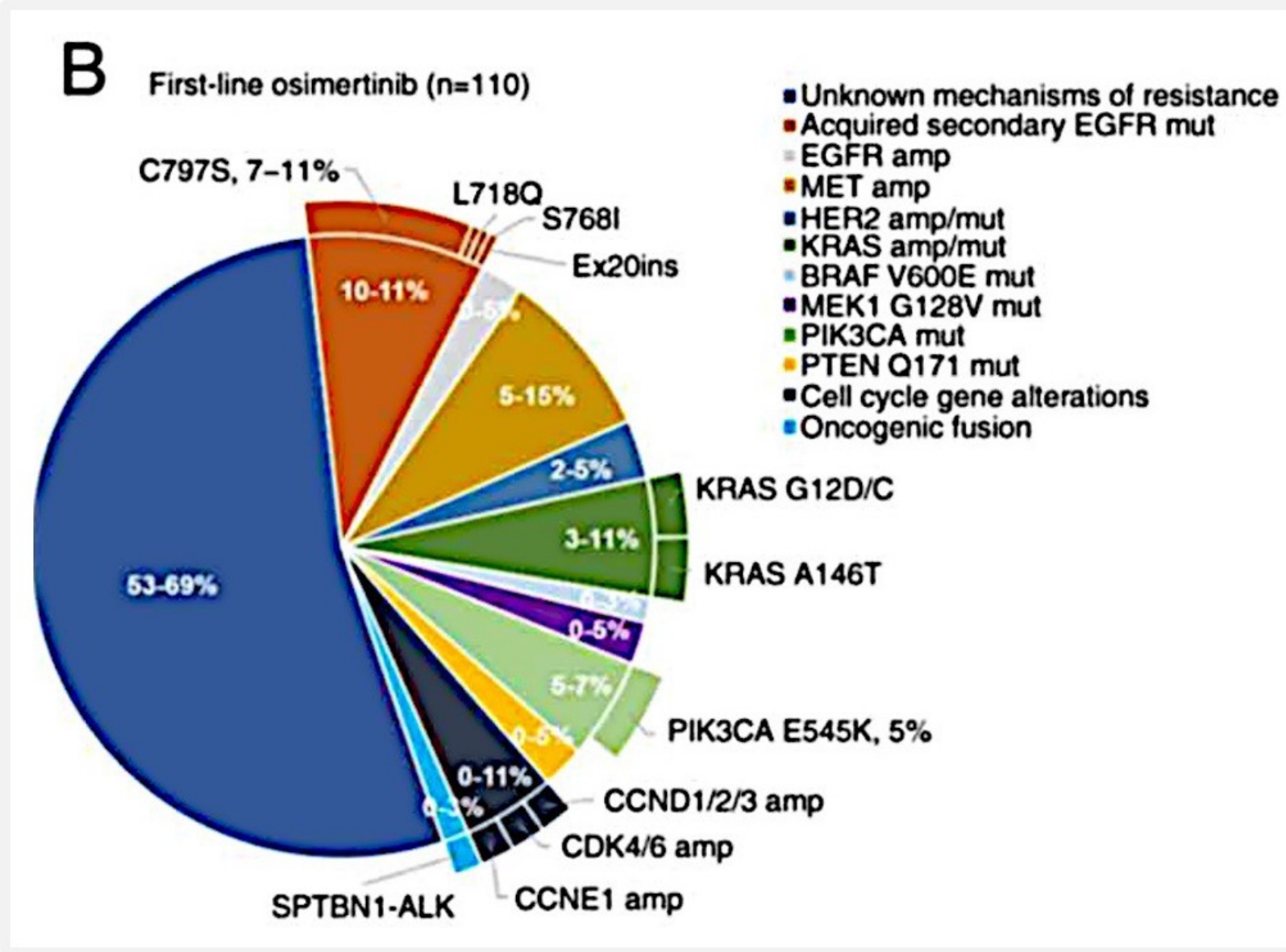
T790M-3S	T790M-3R
Third-generation	PKCi
PKCi	ALKi
ALKi	Third-generation
Second-generation	Second-generation
First-generation	First-generation

Second-generation
First-generation
Ex20ins-specific
Third-generation

Ex20ins-NL	Ex20ins-FL
Ex20ins-specific	
Second-generation	Ex20ins-specific
Third-generation	Second-generation
First-generation	Third-generation
	First-generation

Robichaux et al 2021 Nature

Resistance to 1L Osimertinib (FLAURA)

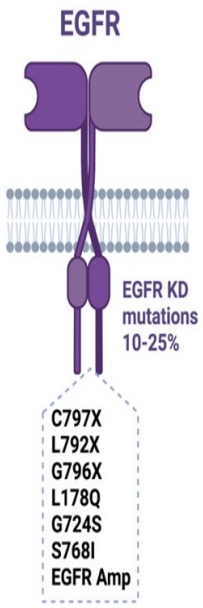


He et al. IJO 2021

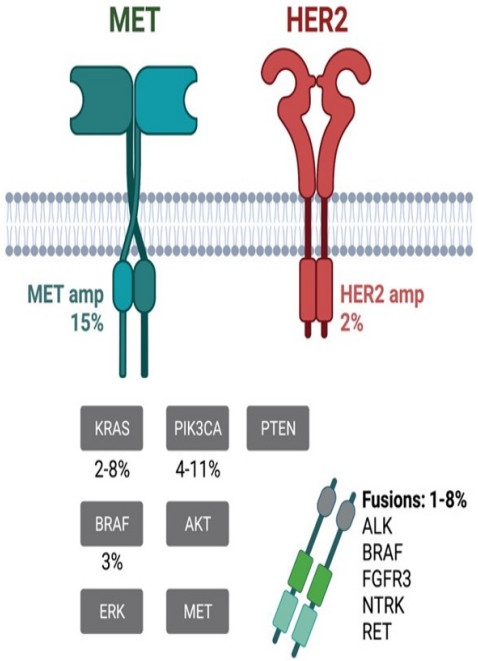
19th Annual
MIAMI CANCER MEETING
Conquering Cancer:
Improving Science, Promoting Precision
Medicine & Developing Equity in Cancer Care
JW MARRIOTT MIAMI | MIAMI, FLORIDA
APRIL 28 - 30, 2023

Novel Approaches in EGFR-Mutant Lung Cancer

On-Target resistance

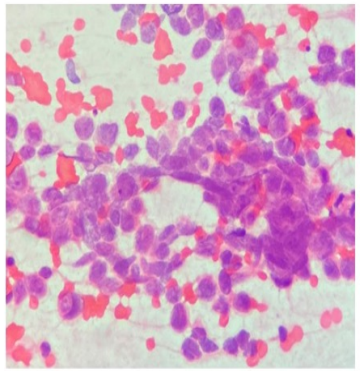


Bypass resistance



Histologic transformation

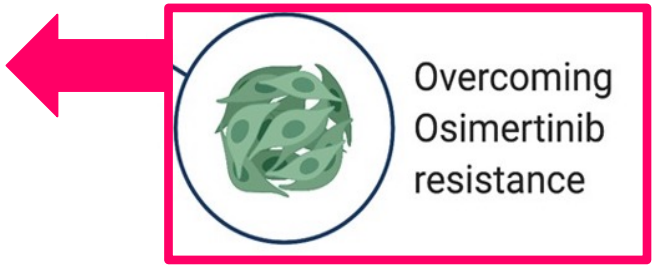
Small cell lung cancer: 5-15%



TP53 mutations
RB1 mutations

Apoptotic defects: BIM Deletion
Epigenetic modifications

A. Passaro et al. Nature Cancer 2021
A. Leonetti et al. British Journal of Cancer 2019



C797S-Active Compounds in Development: Preclinical Data

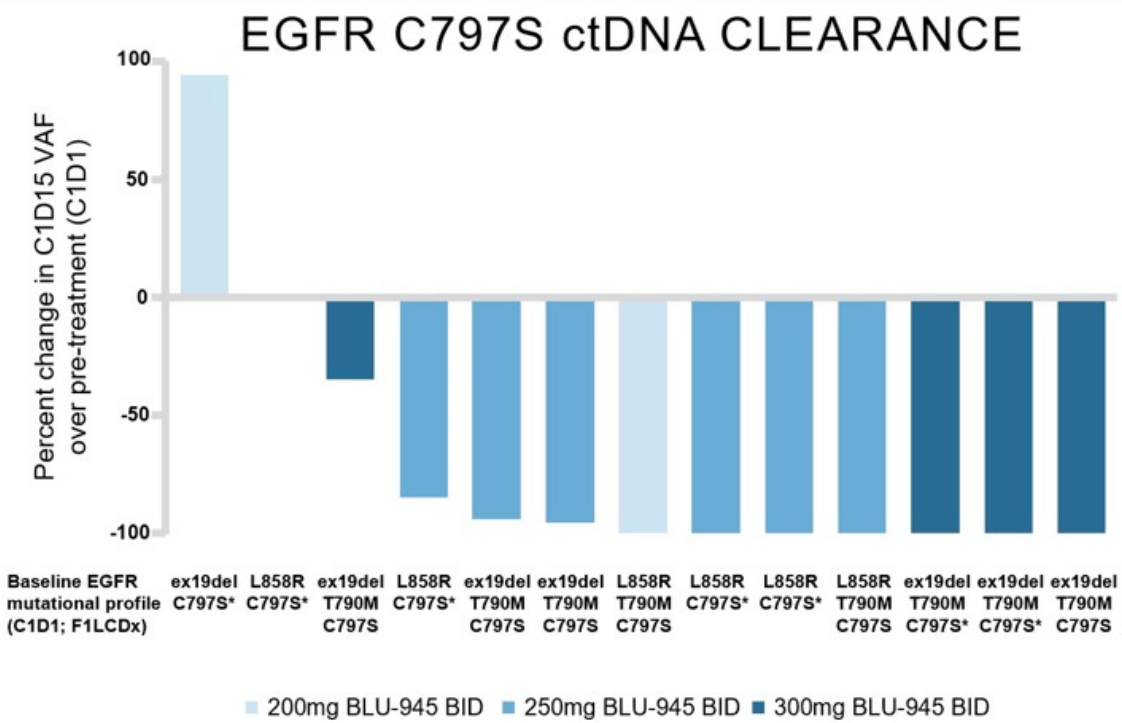
Compound	Del19	L858R	Del19/ T790M	L858R/ T790M	Del19/ C797S	L858R/ C797S	Triple Mutant	Other	CNS?	Status
BLU-945	-	X	X	X	-	X	X		-	Phase 1/2 (NCT04862780)
BLU-701	X	X	-	-	X	X	X		X	Discontinued
BLU-525	X	X	-	-	X	X	X		X	Preclinical
BDTX-1535	X	X	-	-	X	X	X	Uncommon	X	Phase 1 (NCT05256290)
THE-349	X	X	X	X	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)

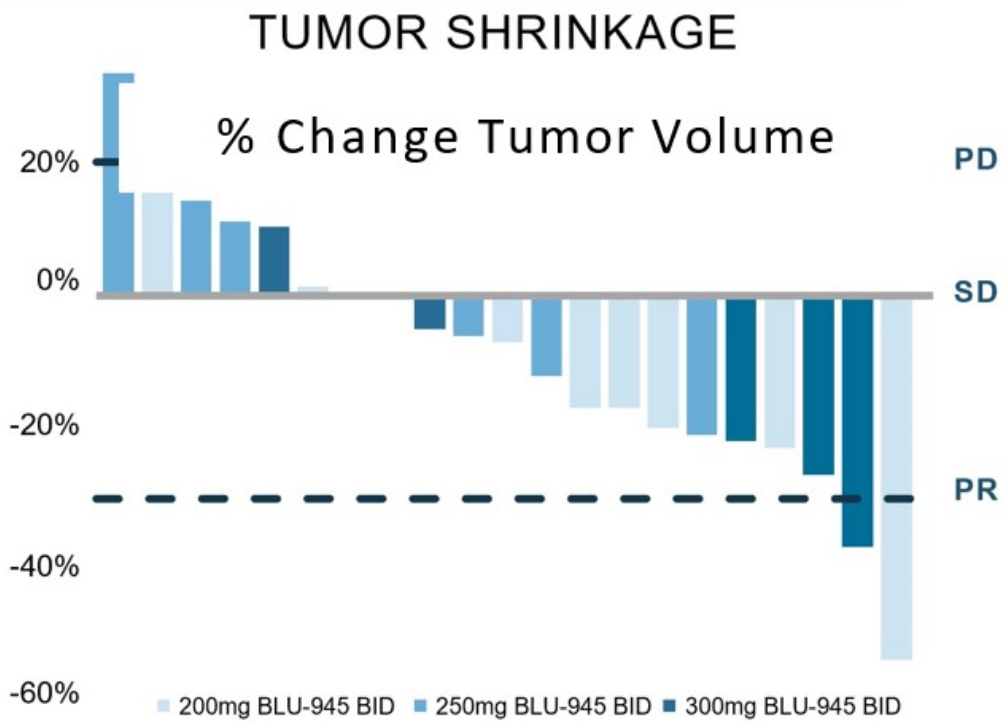
Predicted Not Active Predicted Active No available data

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



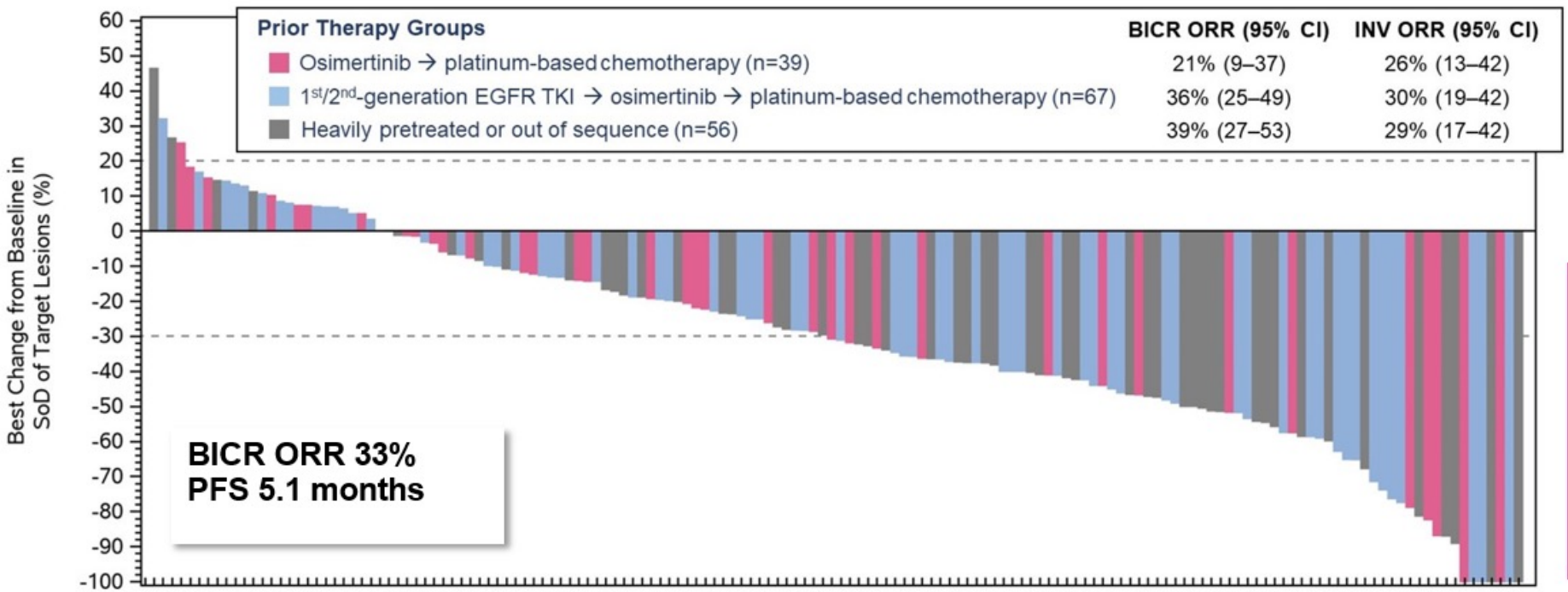


Adapted from: Mar, B. Presented to EGFR Exon 20 Research Consortium

Amivantamab + Lazertinib

EGFR/MET Bispecific +3rd Gen EGFR TKI

CHRYSALIS-2



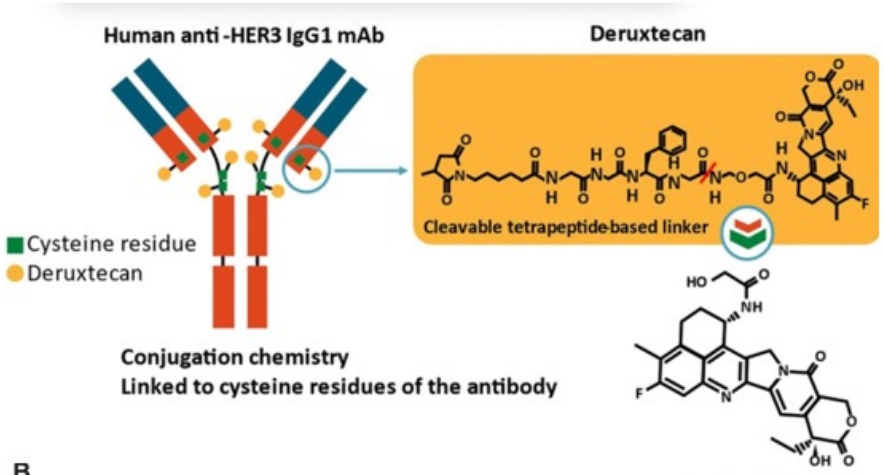
In CHRYSALIS-1, MET/EGFR IHC score correlated with response (n=20)

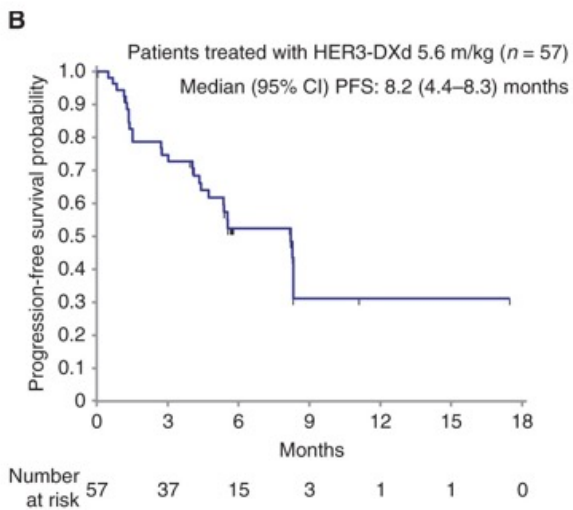
ORR 90% if IHC+

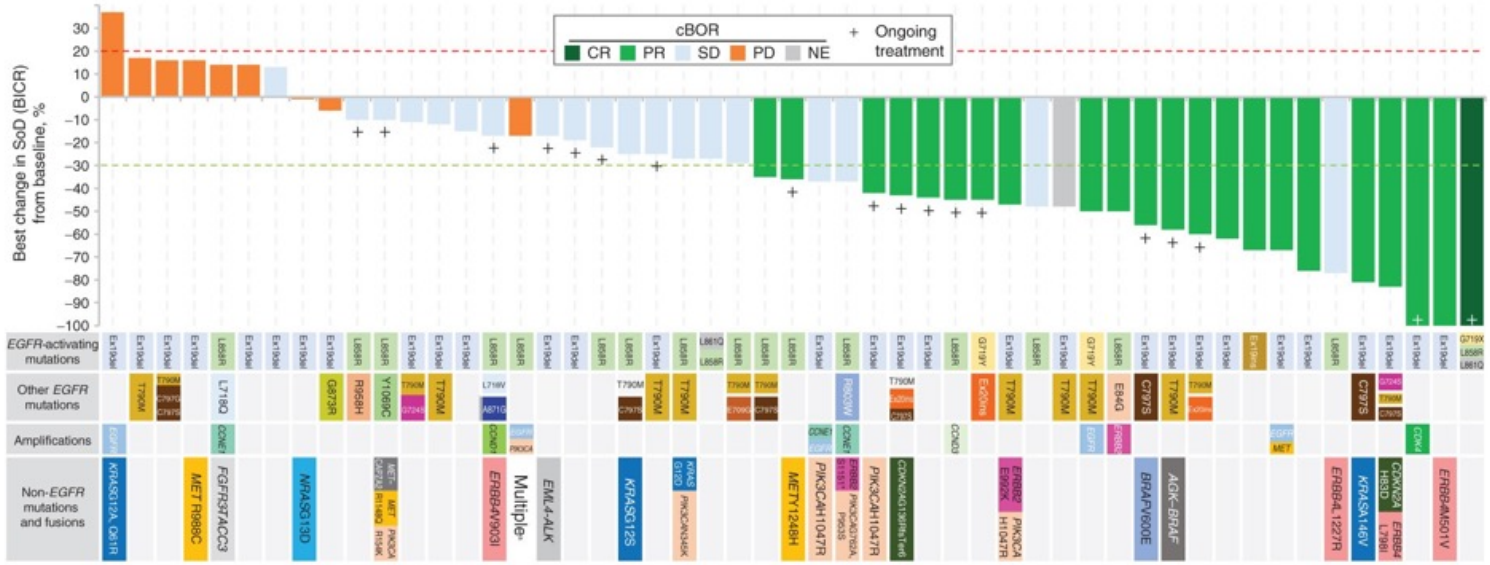
ORR 10% if IHC-

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

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







P. Janne et al. Cancer Discovery 2022.

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

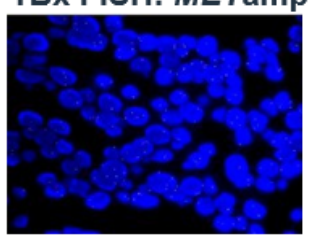
*MET*am definitions

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

and/or

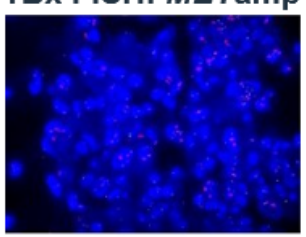
LBx NGS: *MET* GCN ≥2.3; Archer®

TBx FISH: *MET*amp -ve



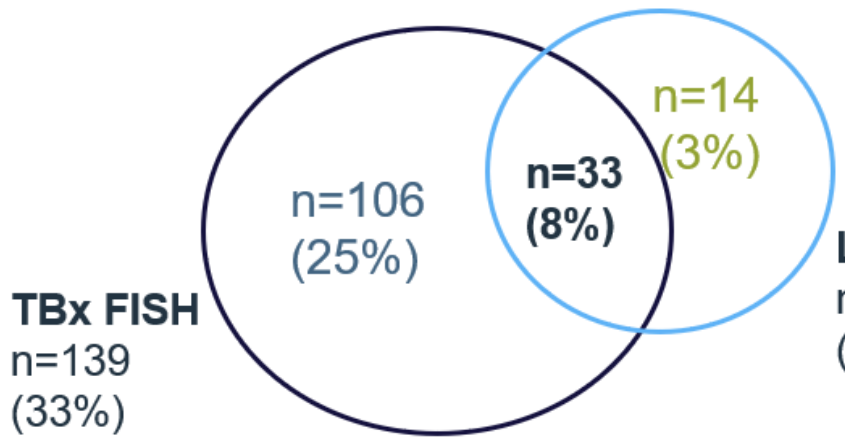
MET GCN, 2.33; *MET/CEP7*, 0.96

TBx FISH: *MET*amp +ve



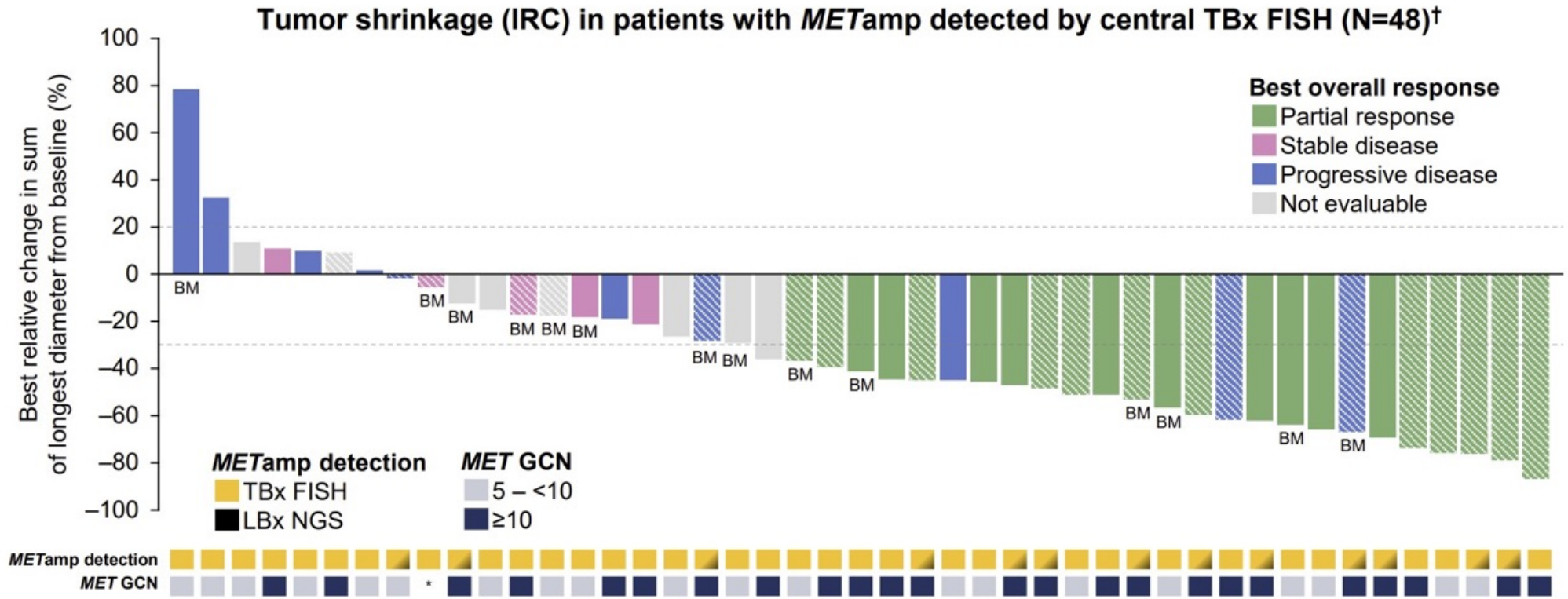
MET GCN, 17.4; *MET/CEP7*, 7.35

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



Riess J. Texas Lung Conference, Austin, TX, March 2023.

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 EGFR TKI

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
ORR 9% if not 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 enrollment terminated

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 I Oncol. 2021.

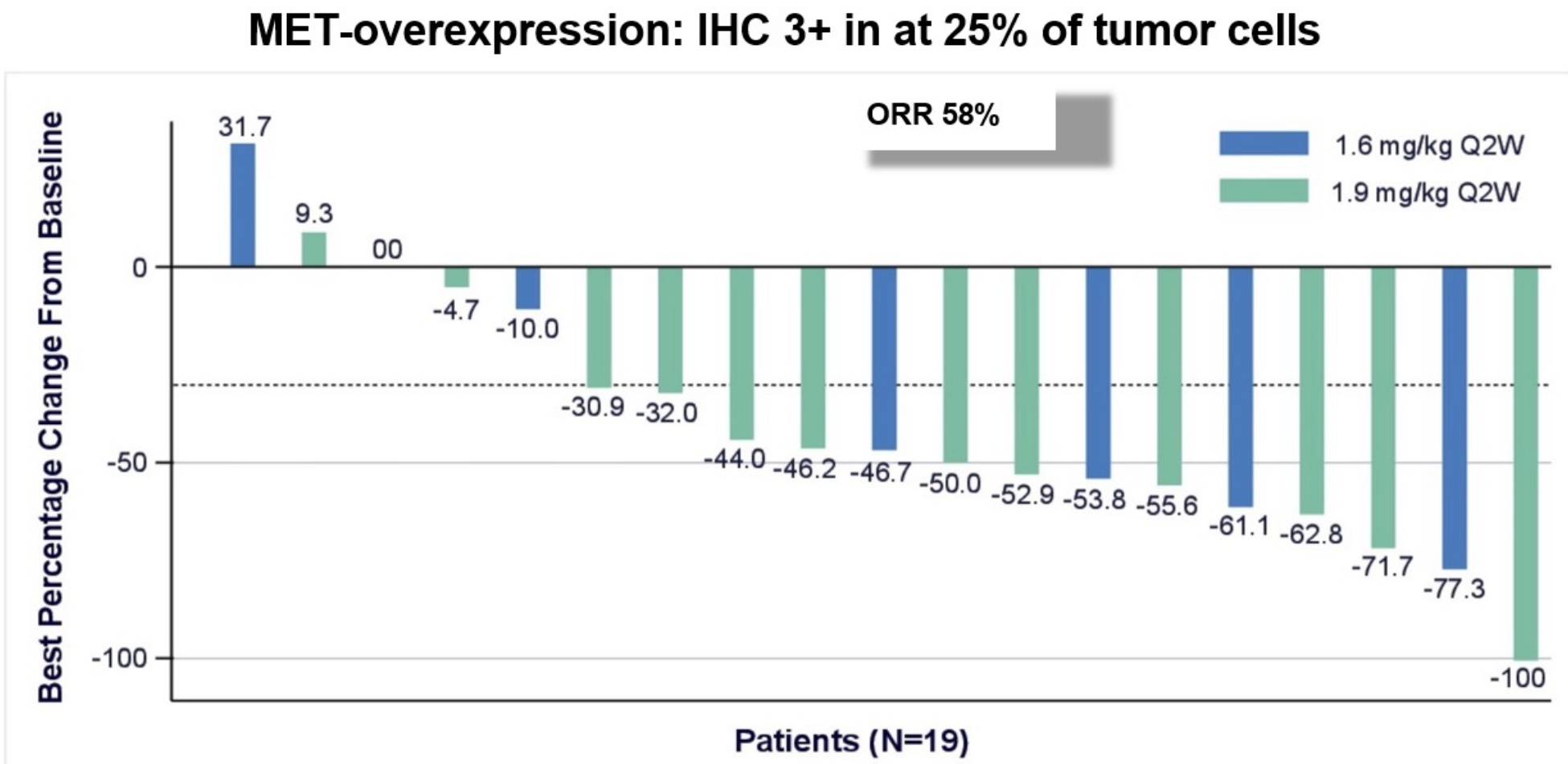
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Telisotuzumab vedotin + Osimertinib

MET-ADC + EGFR TKI



Goldman et al. ASCO 2022. #9013

Novel Therapies Post-Osimertinib w MET as Target

Outcomes	Amivantanab + Lazertinib N = 45	Amivantanab + Lazertinb PD Chemo N = 162	Osimertinib + Savolitinib N = 69	Teliso-V + Osimertinib N = 25
Trial	CHRYSALIS	CHRYSALIS-2	TATTON (B1)	
Target	EGFR/MET	EGFR/MET	EGFR/MET	MET Expression
ORR	36%	33%	30%	58%
mDOR (months)	9.6 (95% CI: 5.3-NR)	9.6 (95% CI: 7.0-NR)	7.9 (95% CI: 6.9-11.2)	Not reported
mPFS (months)	4.9 (95% CI: 3.7-9.5)	5.1 (95% CI: 4.2-6.9)	5.4 (95% CI: 4.1-8.0)	Not reported
Grade ≥ 3 TRAE	16%	38%	57%	32%

BC Cho et al. Presented at ASCO 2021
CA Shu et al. Presented at ASCO 2022
L Sequist et al. Lancet Oncology 2020
JW Goldman et al. Presented at ASCO 2022

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Other Bypass Tracts That Are Potentially Actionable

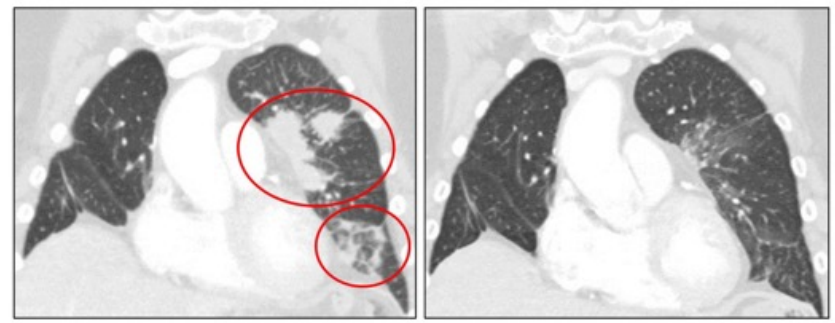
ALK Fusions	**Osimertinib + Alectinib** 6 months DoR Case Reports
BRAF Fusions	**Osimertinib + Trametinib** Response, D/C at 5 mo (Tox) Case Report
BRAF V600E	**Osimertinib + Dabrafenib/Trametinib** 7-8 months DoR **Osimertinib+Vemurafenib** 7+ months Do Case Reports

Jebbink et al. MA02.07. WCLC 2021; Schrock JTO 2018; Offin et al JCP Precis Oncol. 2018; Ribero et al, npj precision oncology 2021; Huang et al JTO 2019; Sun et al Thorac Cancer 2022; Dagogo-Jack et al. JTO. 2019
J. Rotow et al. WCLC 2021
Z. Piotrowska et al. Cancer Discovery 2018.

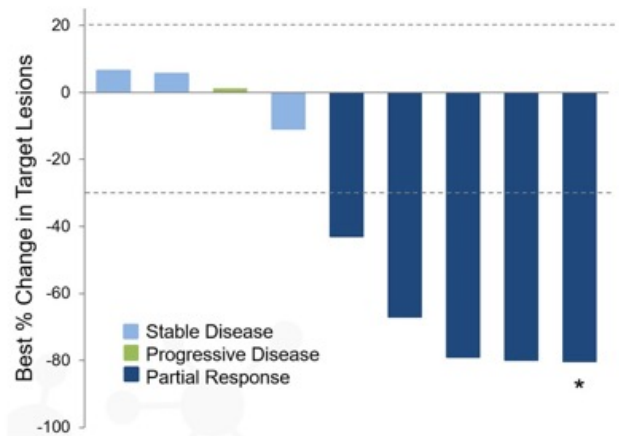
Osimertinib + RET TKI in Acquired Resistance Mediated by RET Fusion

Pralsetinib

B



Selpercatinib

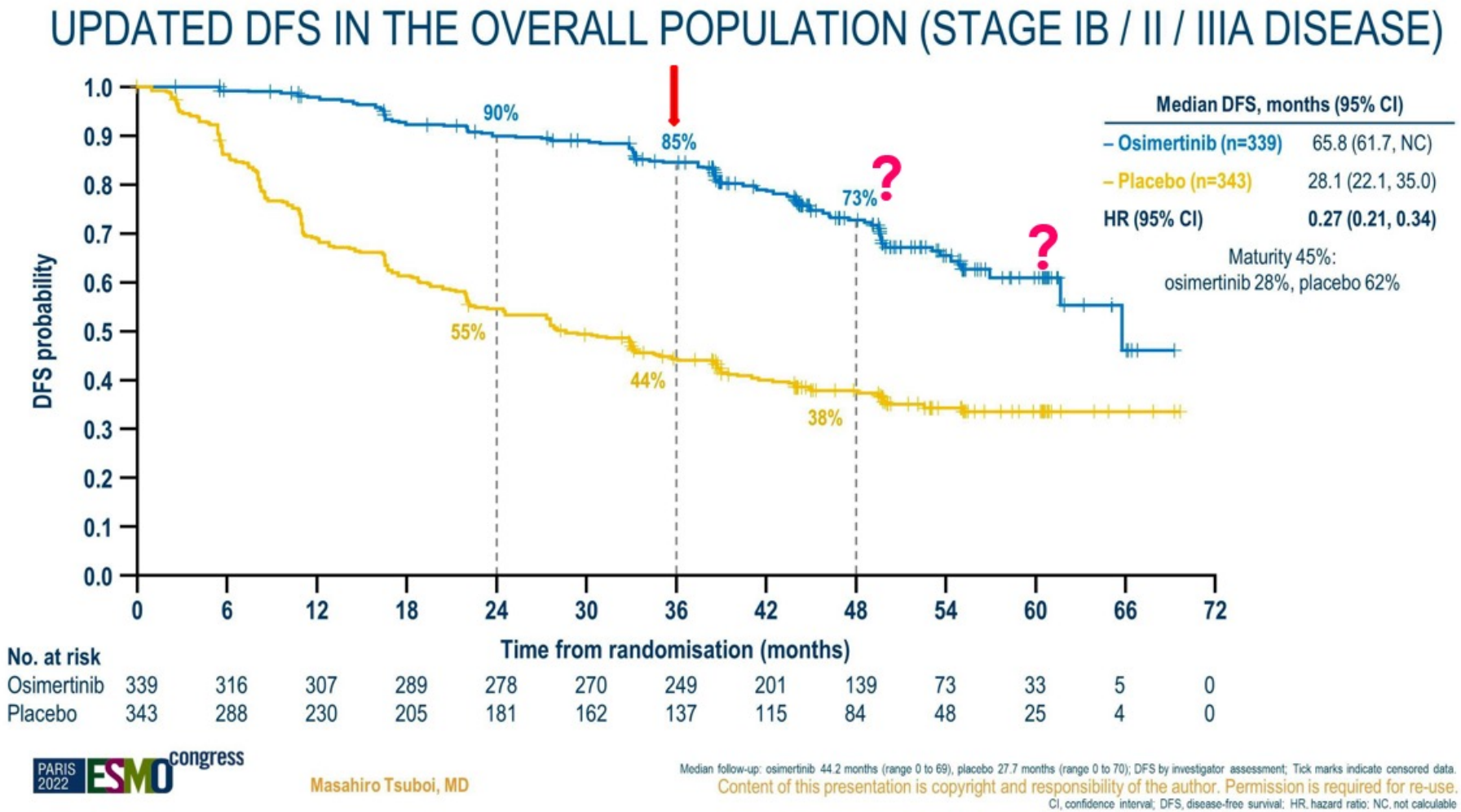


Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

*One partial response unconfirmed

One patient with clinical progression without radiographic evaluation not shown

Overcoming Resistance in Earlier Stage Disease



PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable

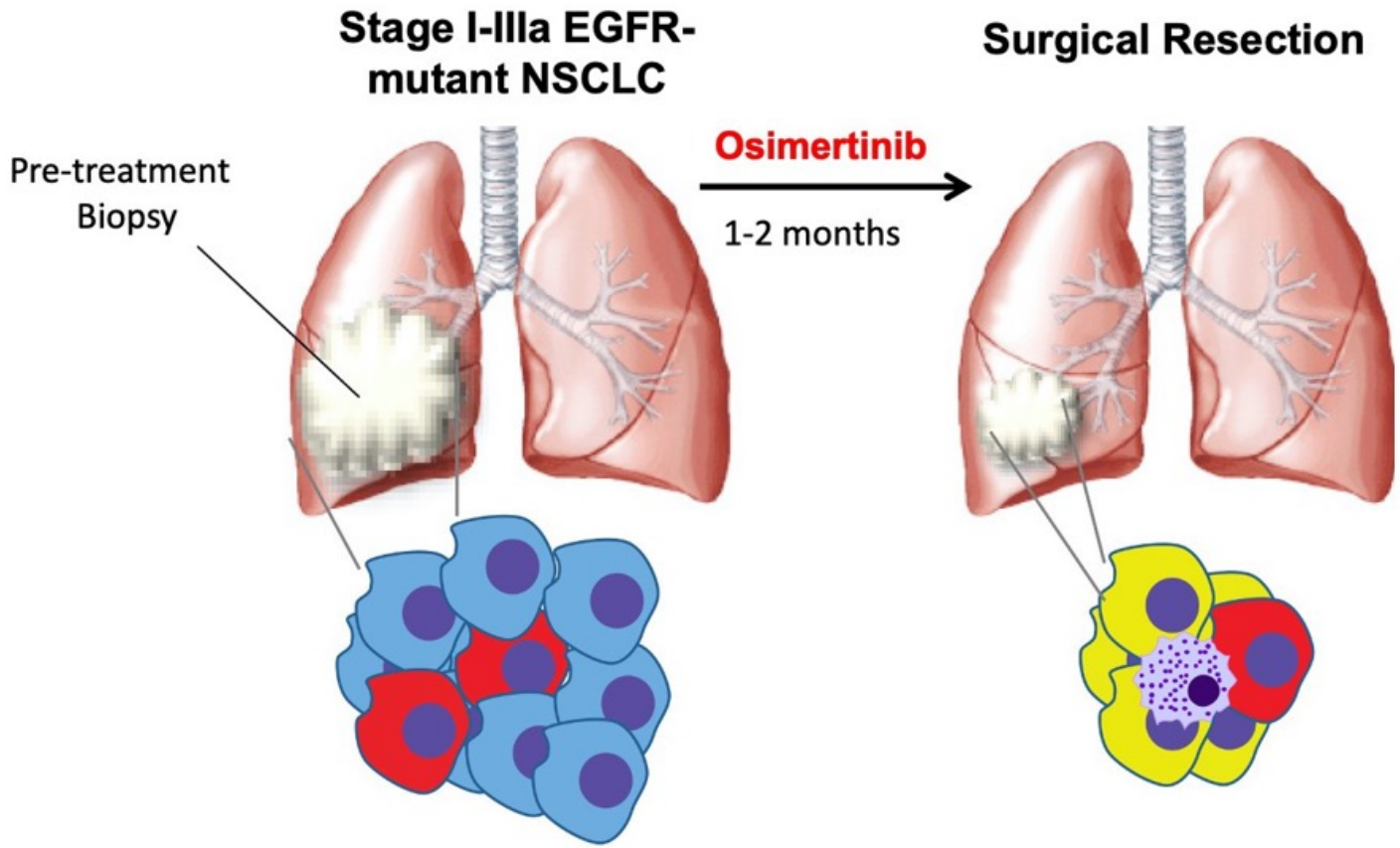
Tsuboi. ESMO Paris 2022

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Neoadjuvant Osimertinib in Stage I-IIIA NSCLC: Interim analysis of first 13 patients



Primary Endpoint:

MPR: ~15%

Safety:

Secondary Efficacy:

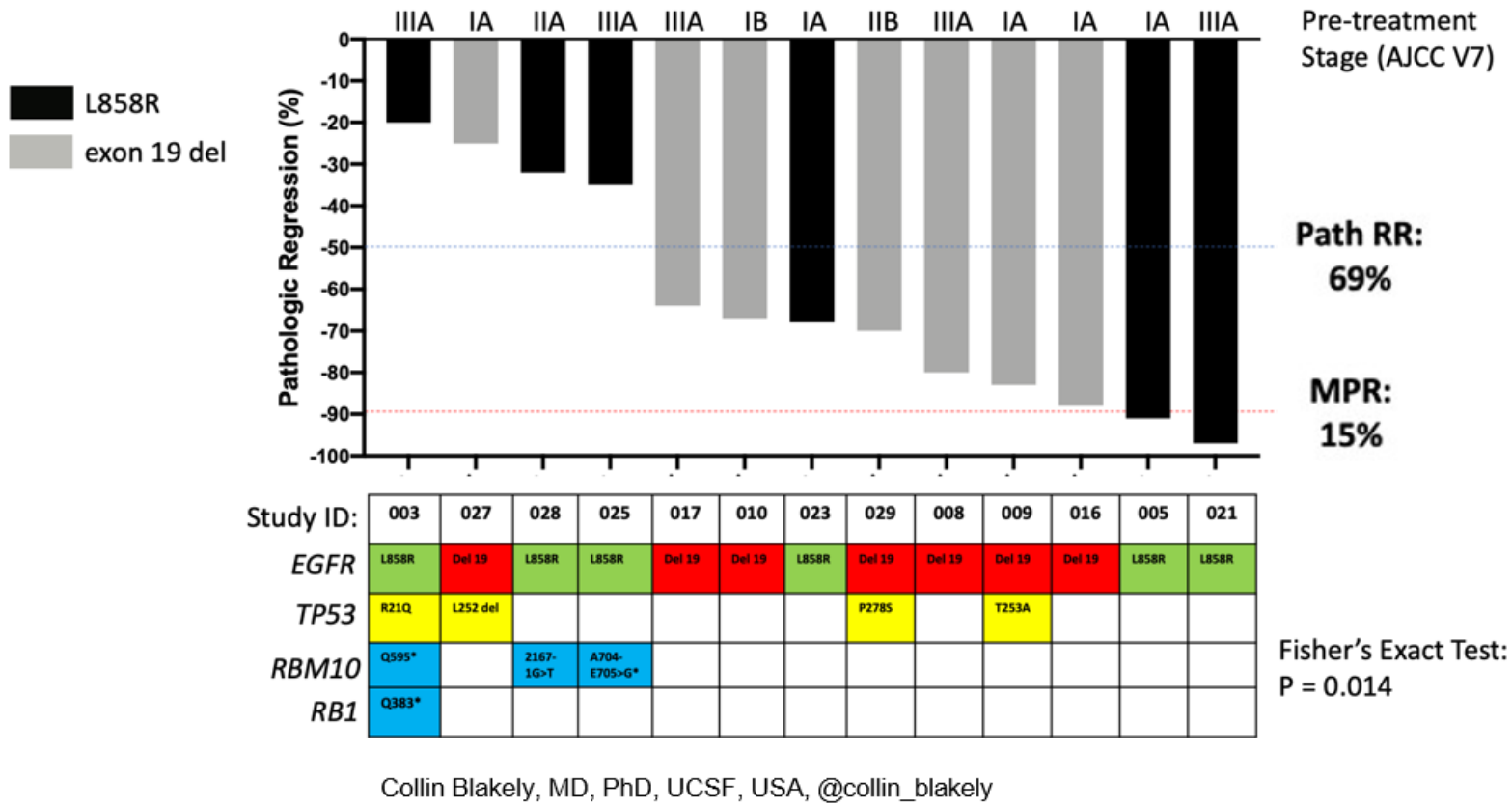
80% LN downstaging (4/5)
46% ORR
0% PCR
DFS/OS: TBD

Exploratory:

RBM10 commutations
AT2 – diff
WNT/b-catenin activation
T-Cell infiltration

Blakely, IASLC WCLC, 2021

Co-occurring RBM10 mutations correlate with lack of pathological response



Collin Blakely, MD, PhD, UCSF, USA, @collin_blakely

Blakely, IASLC WCLC, 2021

19th Annual

MIAMI CANCER MEETING

Conquering Cancer:
Improving Science, Promoting Precision
Medicine & Developing Equity in Cancer Care

JW MARRIOTT MIAMI | MIAMI, FLORIDA

APRIL 28 - 30, 2023

Program Directors

Luis E. Raez, MD, FACP, FCCP
Chief Scientific Officer & Medical Director
Memorial Cancer Institute
Co-Director MCI/FAU Florida Cancer Center of Excellence
Research Professor Florida Atlantic University (FAU)
Past-President Florida Society of Clinical Oncology (FLASCO)
Miami, FL

Edgardo S. Santos Castillero, MD, FACP
Medical Oncologist - Thoracic
Clinical Associate Professor
Charles E. Schmidt College of Medicine
Florida Atlantic University
Treasurer, Florida Society of Clinical Oncology (FLASCO)
President, FLASCO Foundation
Boca Raton, FL

MEC THE MEDICAL EDUCATOR CONSORTIUM

OLA

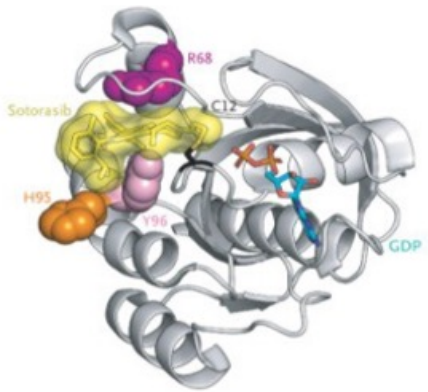
CANCER EXPERT NOW

MECC GLOBAL MEETINGS
MEETINGS • EVENTS • CONFERENCE • COORDINATORS

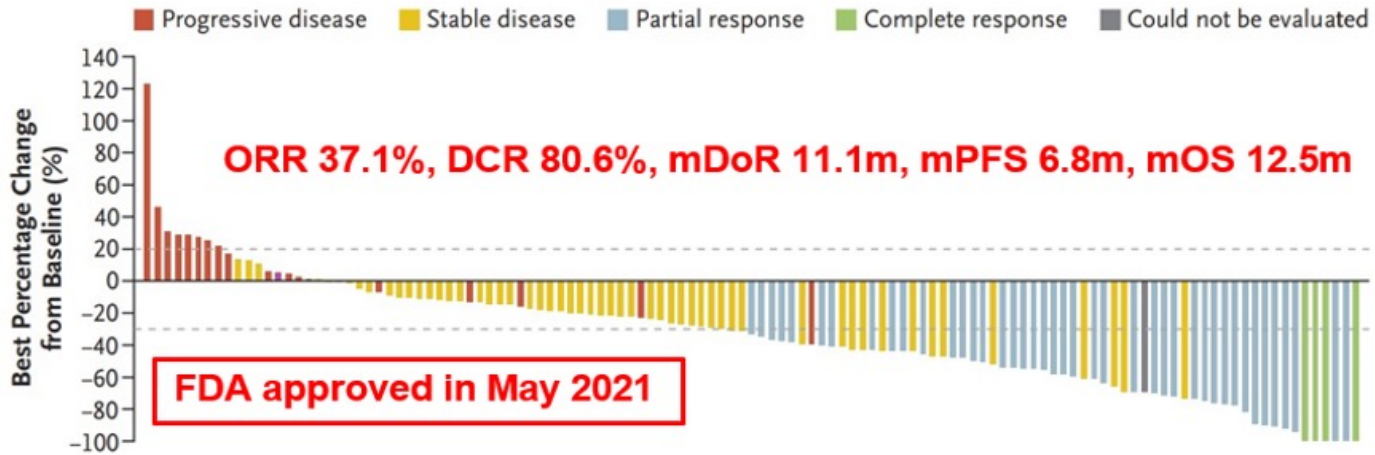
K-Ras Mutation

Covalent *KRAS*^{G12C} Inhibitors: A Breakthrough in Targeted Cancer Therapy:

A. Sotorasib (AMG 510)

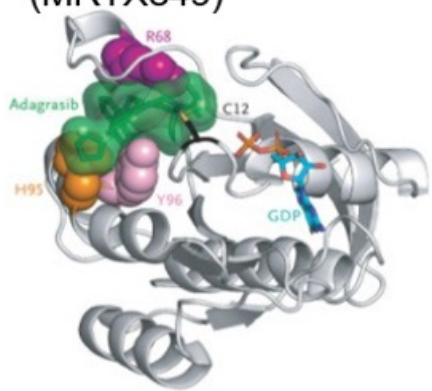


Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393

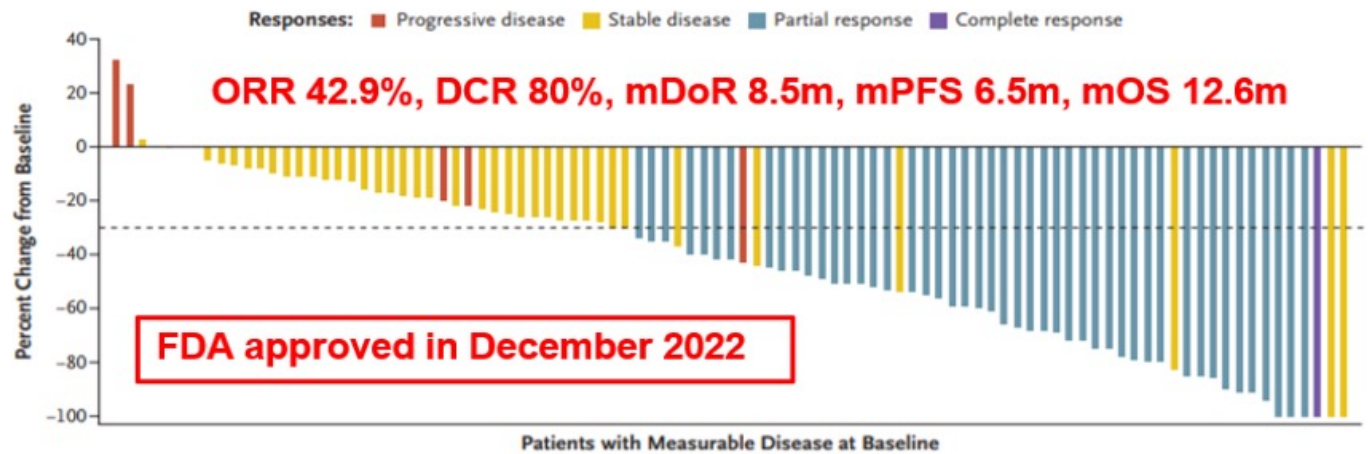


Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B. Adagrasib (MRTX849)



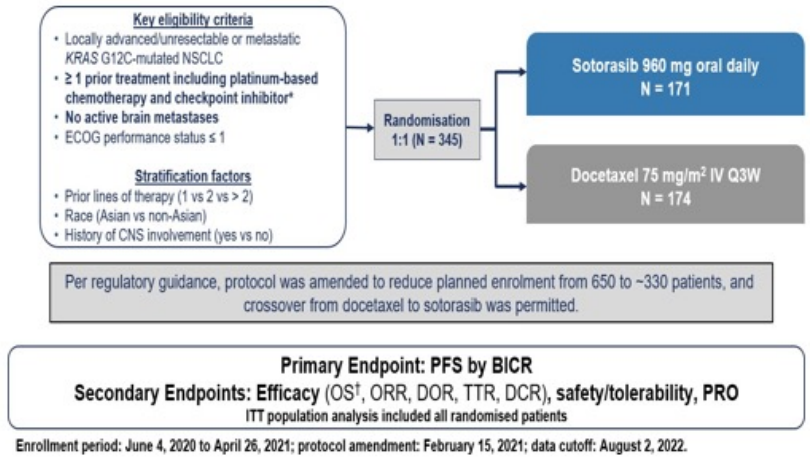
Awad MM et al. *N Engl J Med* 2021 Jun24;384(25):2382-2393



Jänne PA al. *N Engl J Med* 2022 Jul 14;387(2):120-131 (Epub 2022 June 3)

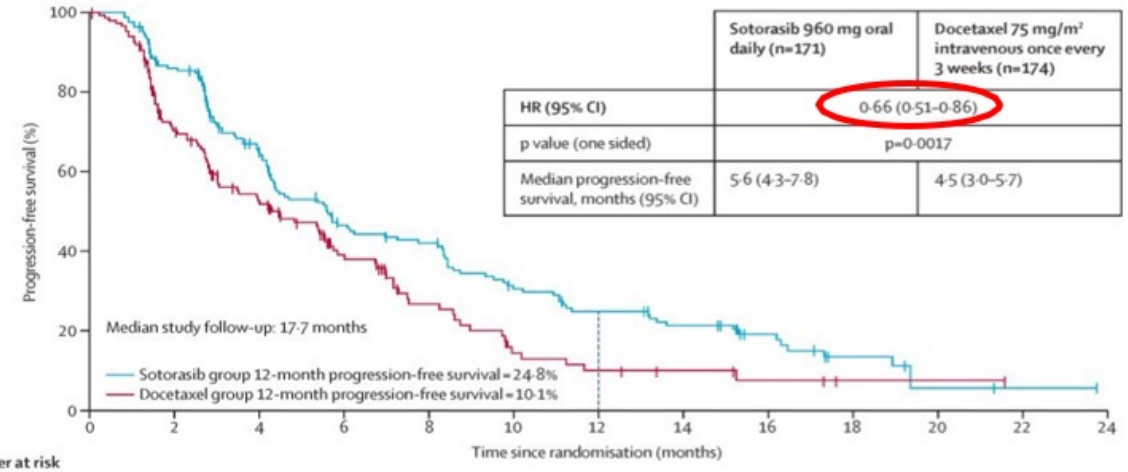
CodeBreaK200 : Phase III RCT of Sotorasib vs Docetaxel in previously treated advanced *KRAS*^{G12C}-mutant NSCLC

A.



Johnson ML et al., ESMO Congress, 2022

B.



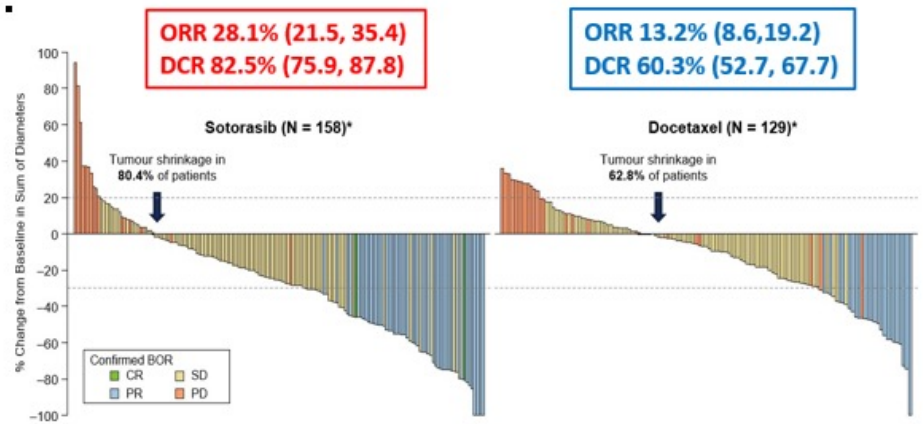
	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

Number at risk (number censored)

Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

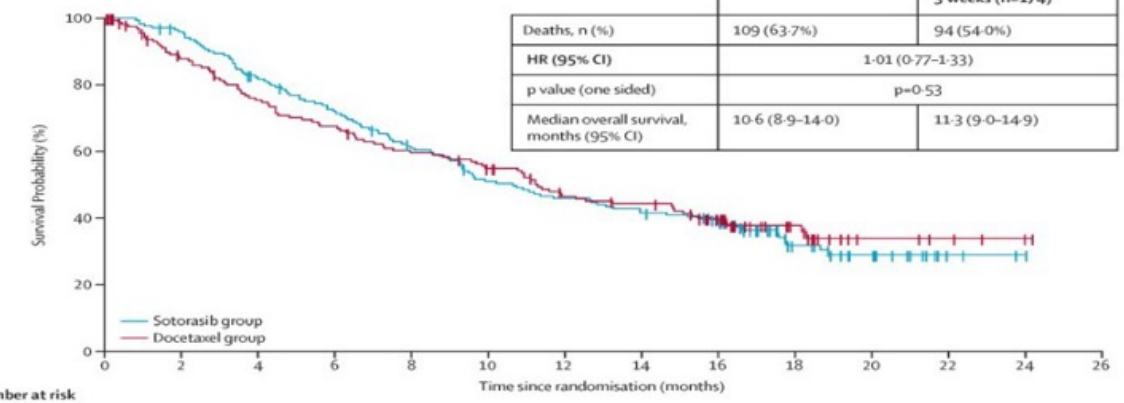
de Langen AJ et al., *Lancet.* 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

C.



Johnson ML et al., ESMO Congress, 2022

D.



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
Deaths, n (%)	109 (63·7%)	94 (54·0%)
HR (95% CI)	1·01 (0·77–1·33)	
p value (one sided)	p=0·53	
Median overall survival, months (95% CI)	10·6 (8·9–14·0)	11·3 (9·0–14·9)

Number at risk (number censored)

Sotorasib group	171 (0)	162 (2)	137 (2)	119 (1)	98 (3)	81 (1)	73 (0)	66 (0)	56 (6)	25 (24)	15 (8)	3 (12)	0 (3)
Docetaxel group	174 (0)	135 (20)	115 (1)	103 (0)	90 (1)	81 (2)	65 (4)	61 (1)	44 (11)	20 (22)	7 (11)	4 (3)	1 (3)

de Langen AJ et al., *Lancet.* 2023 Mar 4;29(3):593-604. Epub 2023 Mar 16

Treatment-related Adverse Events

Sotorasib (CodeBreaK100)

Treatment-Related Adverse Events (TRAEs) Occurring in > 5%	Any Grade N = 126 n (%)	Grade 3 N = 126 n (%)
Any TRAEs	88 (69.8)	25 (19.8)
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
ALT increase	19 (15.1)	8 (6.3)
AST increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)
Maculopapular rash	7 (5.6)	0

- 0.8% G4 TRAEs (pneumonitis and dyspnea). No G5 TRAEs
- Dose modification due to TRAEs in 22.2%
- Treatment discontinuation due to TRAEs in 7.1%

Skoulidis F et al., ASCO 2021

Warnings and Precautions

- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis

Adagrasib (KRYSTAL-1)

	Adagrasib Monotherapy (N=116) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grades 3–4**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs[a], n (%)		
Diarrhea	73 (63%)	1 (<1%)
Nausea	72 (62%)	5 (4%)
Vomiting	55 (47%)	1 (<1%)
Fatigue	47 (41%)	5 (4%)
ALT increase	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
AST increase	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)

- 2 G5 TRAEs (cardiac failure, pulmonary hemorrhage)
- Dose reduction due to TRAEs in 52% and interruption in 61%
- Treatment discontinuation due to TRAEs in 7%

Spira A et al., ASCO 2022

Warnings and Precautions

- GI adverse reactions
- QTc Interval Prolongation
- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis

Intracranial activity of sotorasib in *KRAS*^{G12C}-mutant NSCLC with stable brain metastases (CodeBreaK100)

- Per central RANO BM review, 16/174 (9.2%) patients had baseline and ≥1 on-treatment evaluable scans*:
  - Nine patients had 1 lesion; 2 had 4 lesions; 5 had ≥ 5 lesions

Best Response by RANO, n (%)	Patients with Target and Non-target CNS Lesions Sotorasib 960 mg (n = 3)	Patients with only Non-target CNS Lesions Sotorasib 960 mg (n = 13)	All Patients with Evaluable BM Sotorasib 960 mg (N = 16)†
Complete response	0	2 (15)	2 (13)
Stable disease	1 (33)	11 (85)	12 (75)
Progressive disease	2 (67)	0	2 (13)

- Overall, intracranial disease control was achieved in 14/16 patients (88%) with evaluable BM

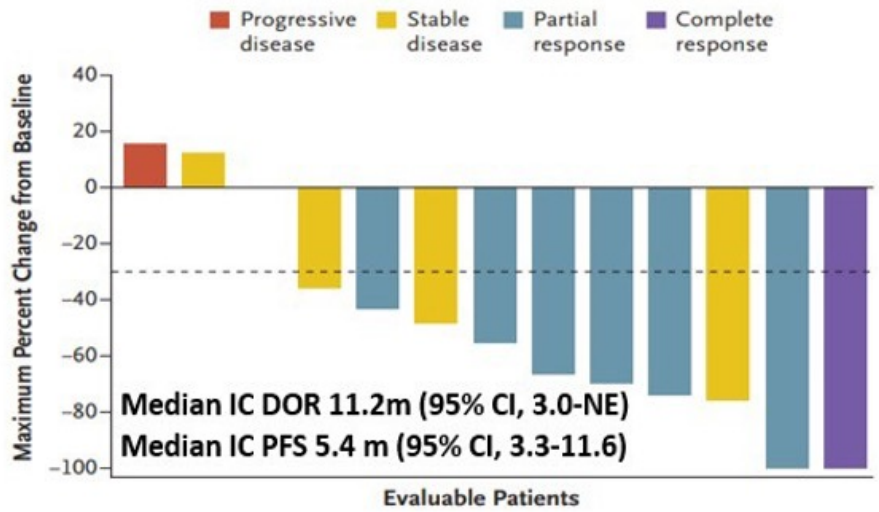
*Forty patients were identified by investigator as having BM; 16 patients with evaluable BM were identified per central review.
†Nine patients had 1 lesion; 2 had 4 lesions; 5 had ≥ 5 lesions.
BM, brain metastases; CNS, central nervous system; RANO, Response Assessment in Neuro-Oncology.

Intracranial activity of adagrasib in *KRAS*^{G12C}-mutant NSCLC

Previously treated and stable brain mets

Best Overall Response	Overall (n=33)[b]	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)[c]
IC ORR, n (%)	11 (33%)	4 (21%)	7 (54%)
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	28 (85%)	17 (89%)	11 (85%)

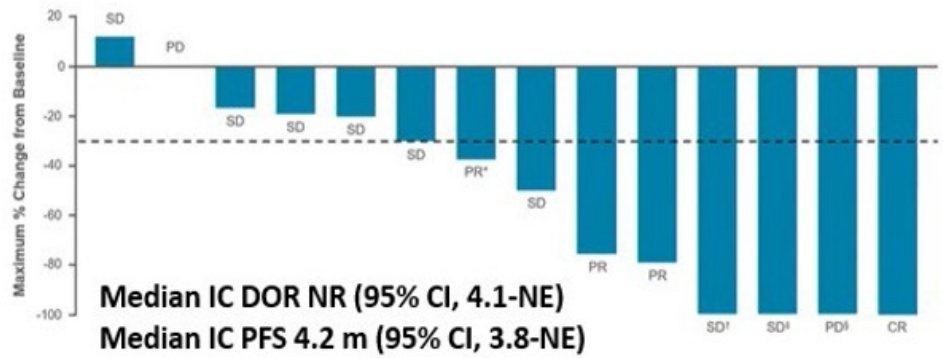
Spira A et al., ASCO 2022



Jänne PA al. *N Engl J Med* 2022

Active, untreated brain mets

Efficacy Outcome	Patients with Non-target Lesions Only (n=4)	Patients with Target Lesions (n=15)[a]	Overall (n=19)[b]
Objective response rate, n (%)	2 (50%)	4 (27%)	6 (32%)
Best overall response, n (%)			
Complete response (CR)	2 (50%)	1 (7%)	3 (16%)
Partial response (PR)	0	3 (20%)[c]	3 (16%)[c]
Stable disease (SD)	2 (50%)	8 (53%)	10 (53%)
Progressive disease (PD)	0	2 (13%)	2 (11%)
Not evaluable	0	1 (7%)[d]	1 (5%)[d]
Disease control rate, n (%)	4 (100%)	12 (80%)	16 (84%)



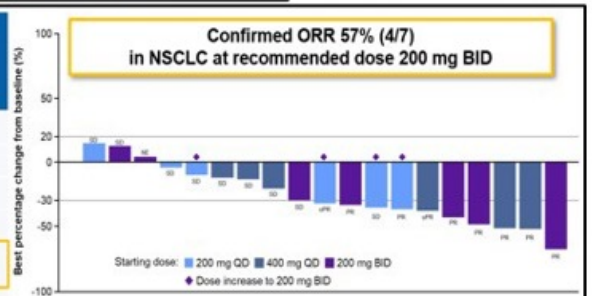
- Objective IC responses were observed in 32% (95% CI, 12.6–56.6)[a]
- IC DCR was 84% (95% CI, 60.4–96.6)

Sabari J et al., ASCO 2022

Other off state-selective KRAS^{G12C} inhibitors in clinical development:

KontRASt-01: JDQ443

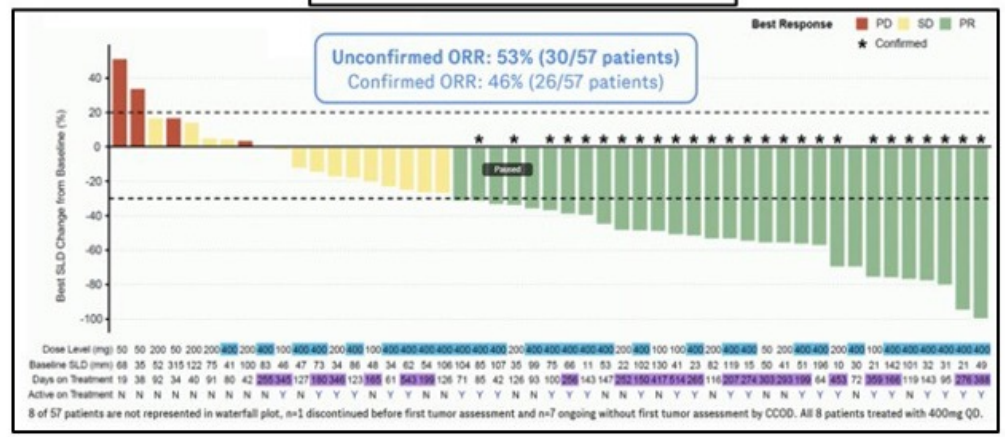
Best overall response, investigator assessed per RECIST v1.1	All patients with NSCLC, n=20, n (%)
PR (confirmed)	7 (35.0)
SD	11 (55.0)
PD	0
NE	2 (10.0)
ORR (confirmed and unconfirmed)	**9 (45.0)**
ORR (confirmed)	7 (35.0)



Data presented with a cut-off date of January 5, 2022. Waterfall plot: 19 (95.0%) NSCLC patients with available change from baseline tumor assessments; data are plotted out of N=20 NSCLC patients in JDQ443 single-agent cohorts. Responses are investigator assessed per RECIST v1.1. Two (10.0%) patients had a uPR, which contributed toward the ORR (confirmed and unconfirmed).
uPR = unconfirmed PR pending confirmation; treatment ongoing with no PD. One of two patients with a uPR had confirmed PR after the data cut-off.
BID, twice daily; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily.
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Tan DSW et al., AACR 2022

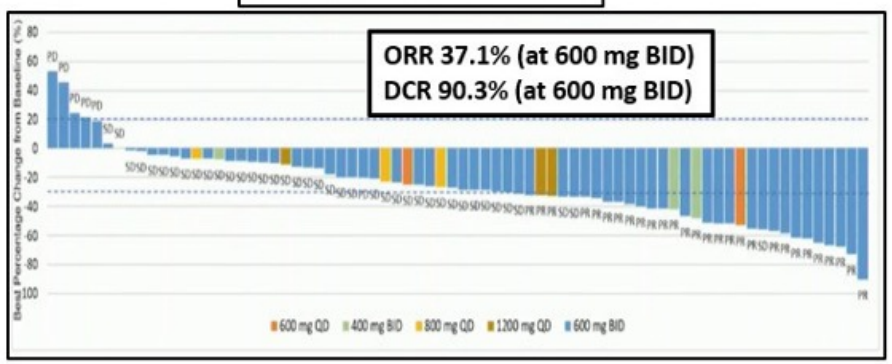
NCT04449874: GDC-6036



8 of 57 patients are not represented in waterfall plot, n=1 discontinued before first tumor assessment and n=7 ongoing without first tumor assessment by CCOD. All 8 patients treated with 400mg QD.

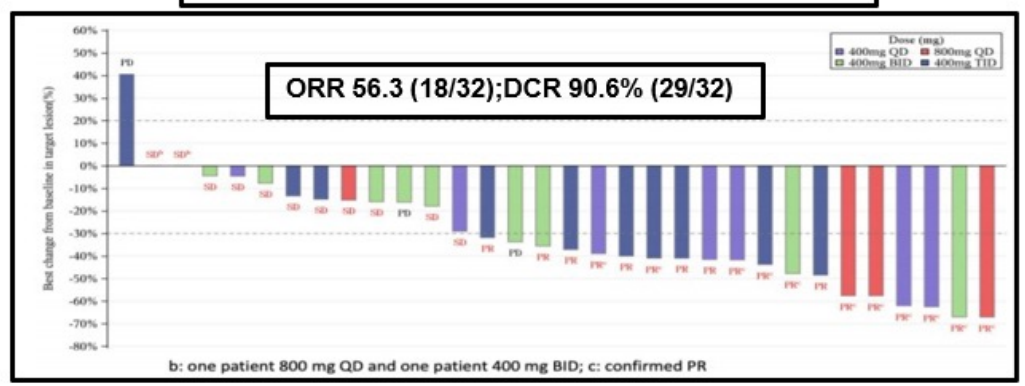
Sacher A et al., ESMO 2022

NCT03600883: D-1553



Lu S et al., WCLC 2022

NCT05009329: JAB-21822 (Glecirasib)



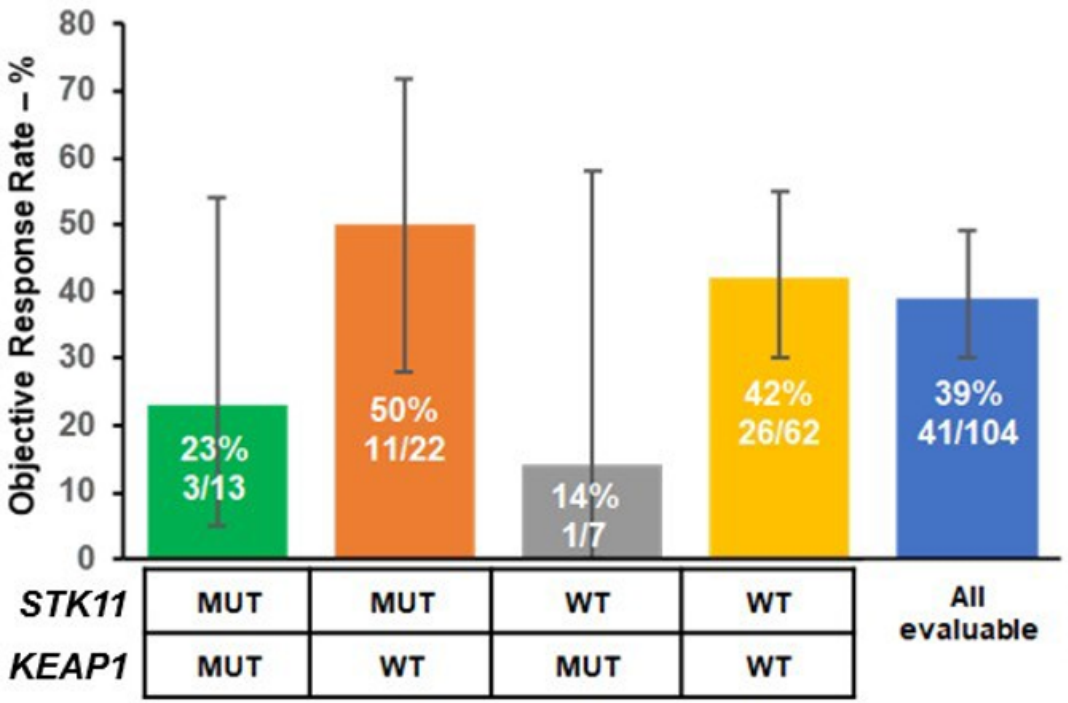
b: one patient 800 mg QD and one patient 400 mg BID; c: confirmed PR

Li J et al., ASCO 2022

Impact of Key Co-mutations of Sotorasib and Adagrasib Clinical Efficacy:

A.

Sotorasib (CodeBreaK100)

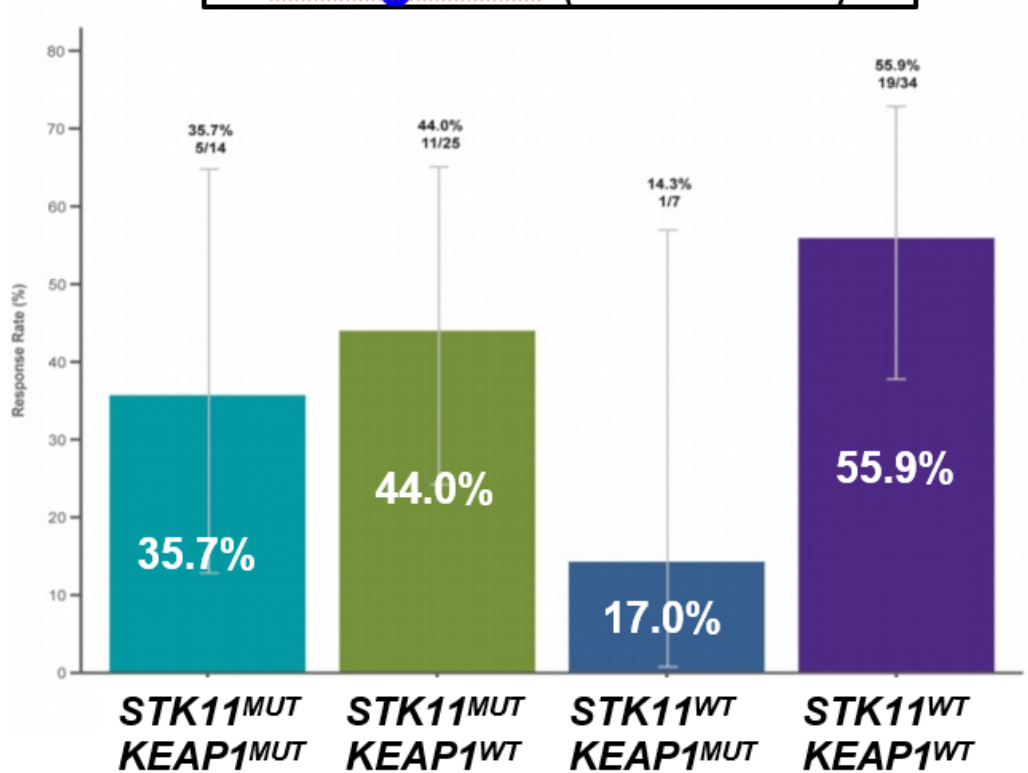


Skoulidis F et al., ASCO 2021

Skoulidis F et al. *N Engl J Med* 2021 Jun 24;384(25):2371-2381

B.

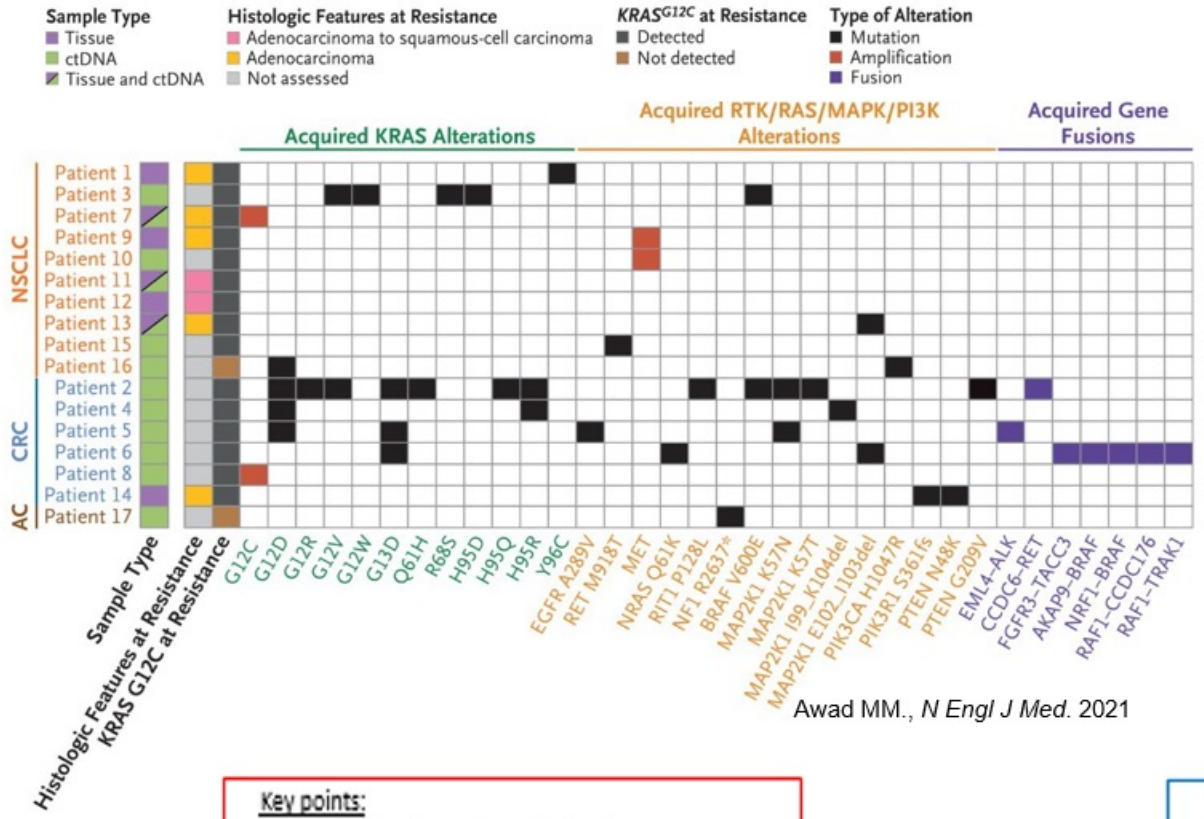
Adagrasib (KRYSTAL-1)



Adapted from Jänne PA al. *N Engl J Med* 2022 Jul 14;387(2):120-131 (Epub 2022 June 3)

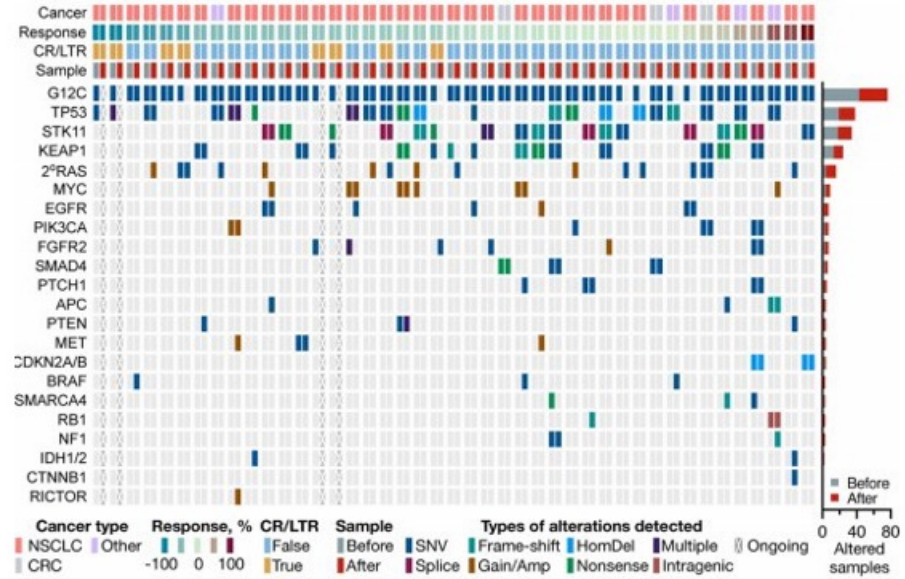
Emerging mechanisms of acquired resistance to KRAS p.G12C inhibitors

A.



Awad MM., *N Engl J Med*. 2021

B.



Zhao Y et al., *Nature*. 2021

Key points:

- Diverse mechanisms of acquired resistance
- Multiple mechanisms may coexist in the same patient (polyclonal res – convergent evolution)
- Some mechanisms may be unique to certain inhibitors (such as mutations involving H95)
- In many cases no mechanisms has been identified

Outstanding questions:

- Full spectrum of primary and acquired resistance mechanisms
- Is acquired resistance stochastic or predetermined?
- Why do some patient develop a single and others multiple mechanisms?
- Impact of DoR on patters of acquired resistance mechanisms?
- Impact of comutations on patterns of acquired resistance.
- Are secondary alterations at low MAF real drivers of resistance?
- Strategies to forestall or overcome clinical resistance

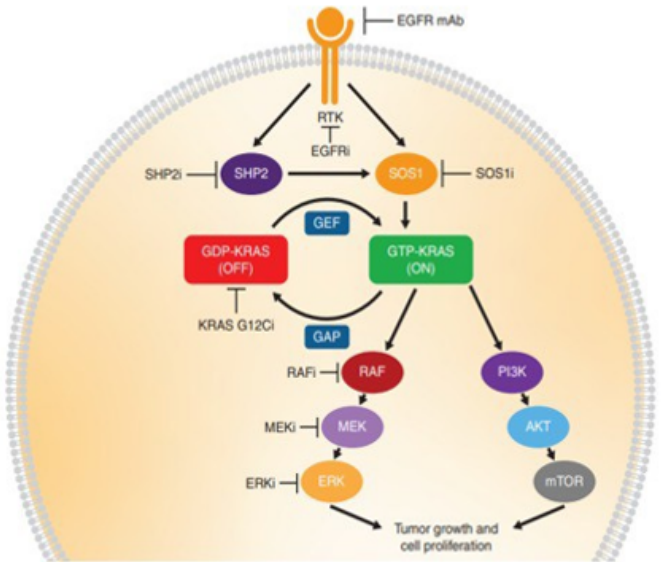
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

KRAS^{G12C} inhibitor phase IB/II combination protocols:

A.



Hofmann MH et al., *Cancer Discov*, 2022

B.

Sotorasib combinations

NSCLC	Mono	2L mono dose comparison	2
		2L mono v. docetaxel confirmatory	3
		1L mono STK11/PD-L1 neg biomarker	2
	Mono	Mono brain mets	1b
	PD1 Combo	PD-1 combo	1b
		PD-L1 combo	1b
	Chemo Combo	Chemo combo	1b
		1L Chemo combo in PD-L1 neg	3
	Novel Combo	Panitumumab combo	1b
		Palbociclib combo	1b
		SHP2i RevMed combo	1b
		SHP2i Novartis combo	1b
		SOS1 combo	1b

Adagrasib combinations

Adagrasib *KRAS G12C Inhibitor*	2L NSCLC	Monotherapy
		POC Combo: SHP2, SOS1, CDK4/6, Pan-EGFR, EGFR
	1L NSCLC	Monotherapy: STK11 co-mutations and TPS <1%
		Combo: Pembrolizumab (PD-1)
	2L CRC	Combo: Cetuximab (EGFR)
	3L+ CRC and Pancreatic	Monotherapy Combo: Cetuximab (EGFR)

Sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS*^{G12C}-mutant NSCLC: CodeBreaK100/101

A.

CodeBreaK 100/101 Study Design

- Phase 1b multicenter, open-label studies

Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior KRAS^{G12C} inhibitor
- No active brain mets

Screening/Enrollment

Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg / 720 mg / 360 mg / 240 mg / 120 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
	OR	OR
	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)

Primary endpoints: safety
Key secondary endpoints: ORR, DOR, DCR, PK

*Not all doses were tested for each cohort.
DCR, disease control rate; PK, pharmacokinetics; Q3W, every 3 weeks.

Snapshot: April 15, 2022

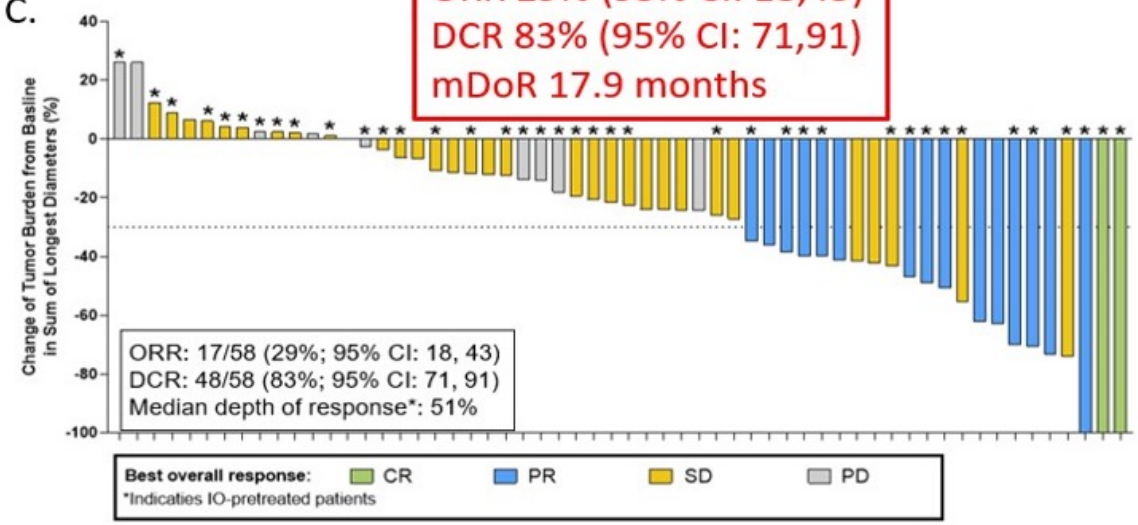
B.

Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

C.

ORR 29% (95% CI: 18,43)
DCR 83% (95% CI: 71,91)
mDoR 17.9 months

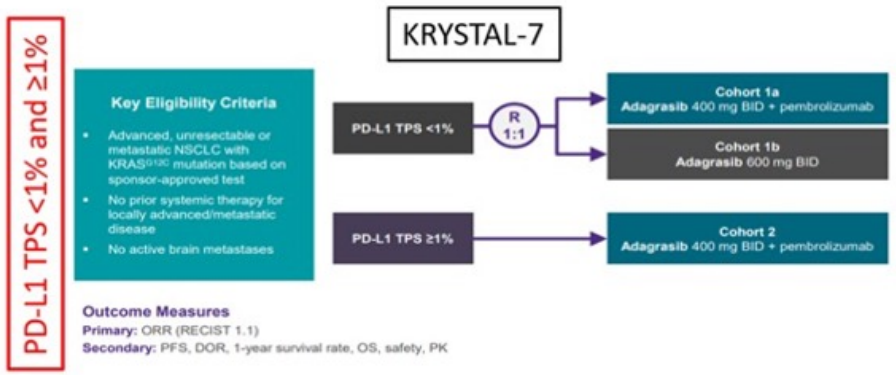


Hepatotoxicity with some KRAS^{G12C}i underscores need to optimize schedule, dose and patient selection

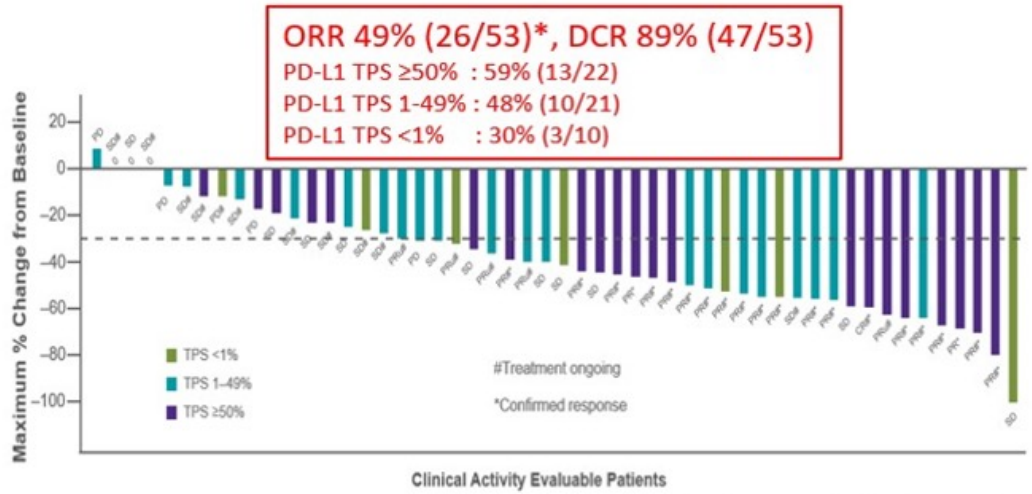
Li B et al., WCLC 2022

Adagrasib in combination with pembrolizumab in treatment-naïve *KRAS^{G12C}*-mutated NSCLC: KRYSTAL-7 phase 2 trial

A.



B.

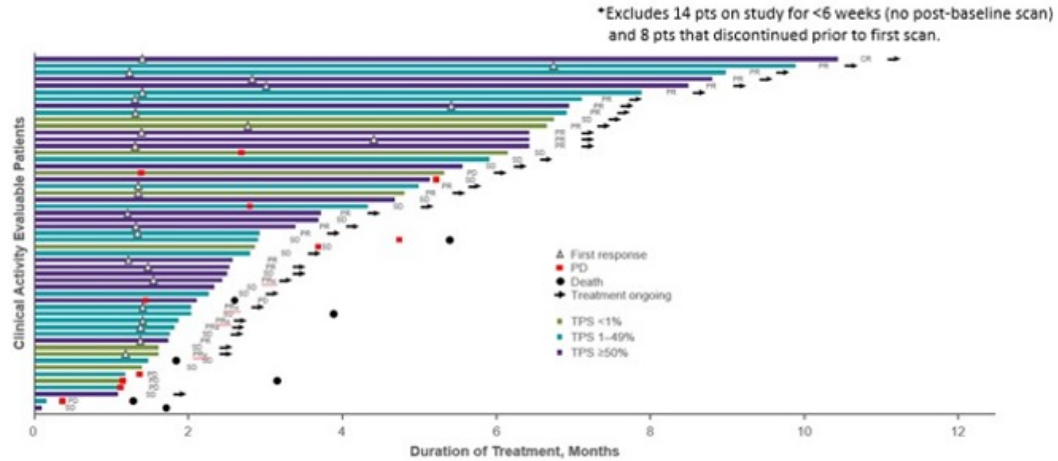


C.

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

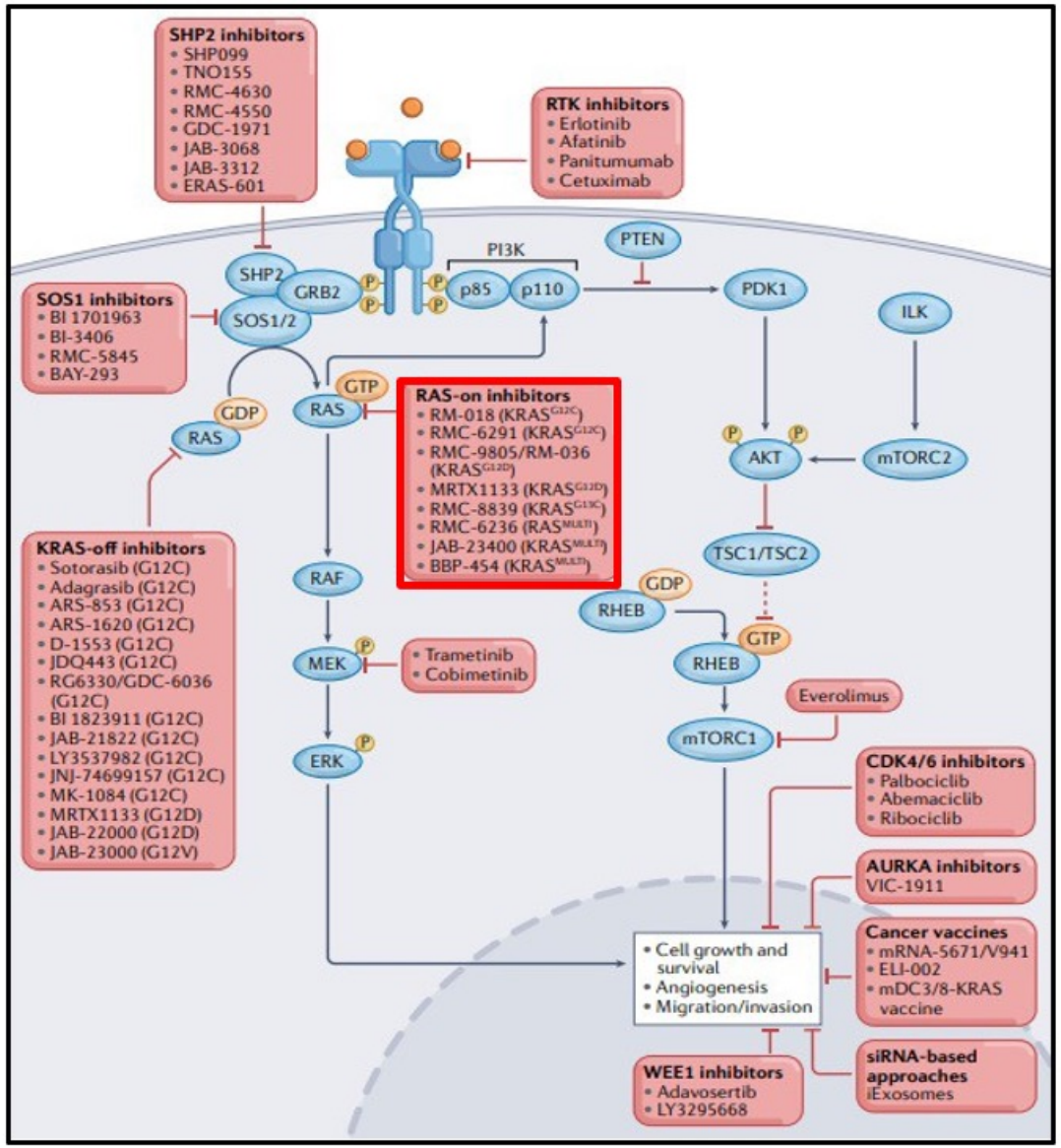
- There were no Grade 5 TRAEs
- Median time to onset for ALT increase and AST increase was 26 and 37 days, respectively; only 1 patient experienced new onset treatment-related ALT/AST increase after 3 months
- TRAEs led to adagrasib dose reduction in 23/75 (31%) patients and to dose interruption in 31/75 (41%) patients
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[c] patients

D.



Jänne PA et al., ESMO Immuno-Oncology, 2022

Emerging novel approaches to target *KRAS*-mutant tumors

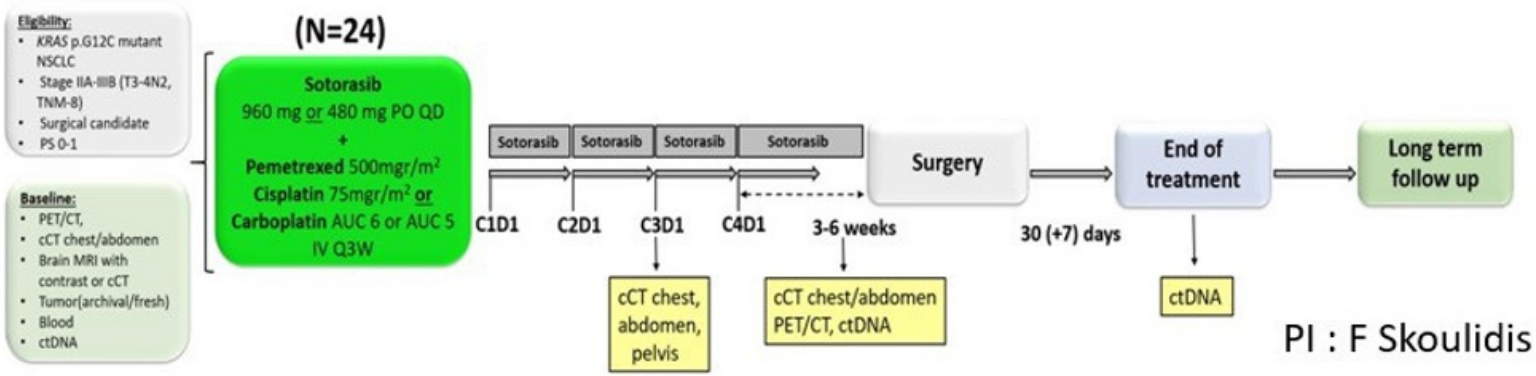


RAS degraders		
$KRAS^{G12C}$	LC-2 (PROTAC)	Preclinical studies
$KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ and $KRAS^{Q61H}$	K27-SPOP	Preclinical studies
RAS toxins		
Pan-RAS	$RRSP\text{-}DT_B$	Preclinical studies
Adoptive cell therapy		
$KRAS^{G12V}$	Specific TCRs	Clinical trials (NCT04146298)
$KRAS^{G12D}$	Specific TCRs	Preclinical studies
Cancer vaccines		
$KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ and $KRAS^{G13D}$	mRNA-5671/V941	Clinical trials (NCT03948763)
$KRAS^{G12C}$, $KRAS^{G12V}$, $KRAS^{G12D}$, $KRAS^{G12A}$, $KRAS^{G13D}$ or $KRAS^{G12R}$	Mutant KRAS-targeted long-peptide vaccine	Clinical trials (NCT04117087)
$KRAS^{G12C}$, $KRAS^{G12V}$, $KRAS^{G12D}$ or $KRAS^{G12R}$	mDC3/8-KRAS vaccine	Clinical trials (NCT03592888)
$KRAS^{G12D}$ or $KRAS^{G12R}$	ELI-002 2P	Clinical trials (NCT04853017)
KRAS siRNAs		
Various mutant KRAS mRNAs	Various nanoparticle-based technologies	Preclinical studies
$KRAS^{G12D}$ mRNA	iExosomes	Clinical trials (NCT03608631)

Punekar SR et al., Nat Rev Clin Oncol 2022

Moving KRAS^{G12C} inhibitors to early-stage, surgically resectable NSCLC

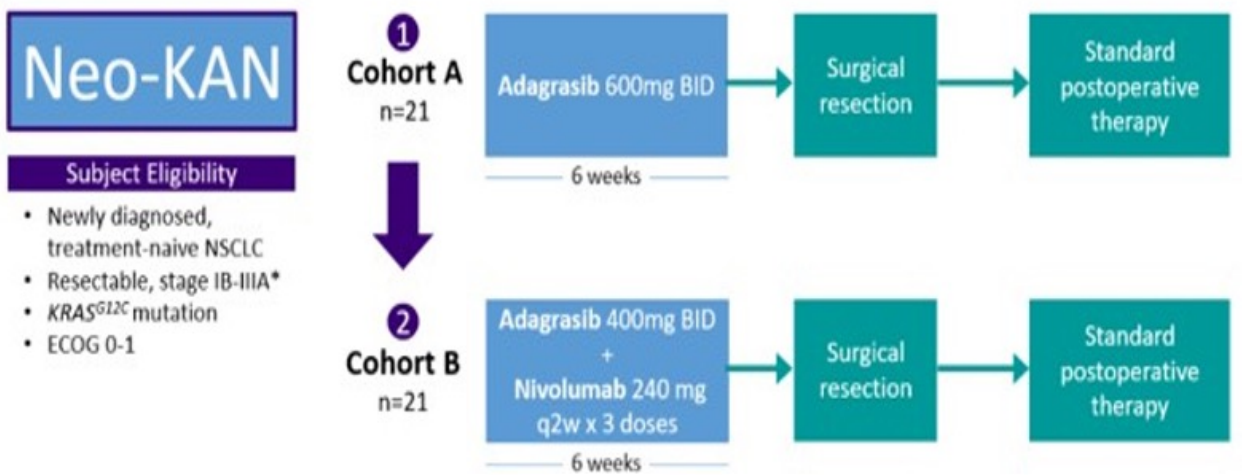
A Phase II Study of Neoadjuvant Sotorasib in Combination with Cisplatin or Carboplatin and Pemetrexed For Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a *KRAS p.G12C* Mutation (NCT05118854)



Recruiting

PI : F Skoulidis

Phase 2 Trial of Neoadjuvant KRAS G12C Directed Therapy With Adagrasib (MRTX849) With or Without Nivolumab in Resectable Non-Small Cell Lung Cancer (Neo-KAN) (NCT05472623)



Not yet recruiting

PI : K Marrone

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Conclusions

@EdgardoSantosMD
1-305-742-8214

- For atypical EGFR mutations, a structure/function approach predicts drug response bette than standard exon-based strategies
- The refined classification presented today may translate into an era of new studies and new treatment options for atypical EGFR mutations
- Targeted therapy approaches can overcome Osimertinib resistance (in some instances)
- Tumor heterogeneity may limit activity
- More work needs to be done regarding EGFR-TKI resistance in the neoadjuvant and adjuvant setting
- Understanding mechanisms of *de novo* and acquired resistance to $KRAS^{G12C}$ inhibitors.
- Optimal and tailored therapeutic combinations to enhance the efficacy of $KRAS^{G12C}$ inhibitors.

Conclusions

@EdgardoSantosMD
1-305-742-8214

- First-line metastatic studies of KRASi in combination with chemotherapy and/or immunotherapy.
- Identification of biomarkers of response to monotherapy and distinct combinations with KRASi.
- Clinical development of novel mutant-selective inhibitors (both G12C and non-G12C) including RAS(ON) inhibitors.
- Clinical development of mutant-selective RAS(ON) and pan-RAS inhibitors.
- Moving KRASi in the neoadjuvant setting.
- More questions than answers; important clinical trials ongoing for both EGFR & KRAS fields.