How to treat uncommon EGFR mutations

Xabier Mielgo-Rubio, MD

Unidad de Oncología

Hospital Universitario Fundación Alcorcón, Madrid

Disclosures

- **Speaker or educational material:** Astra Zeneca, Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Roche, Pfizer
- **Consultant or Advisory Role:** Astra Zeneca, Boehringer, Pfizer
- **Research support:** Bristol Myers Squibb

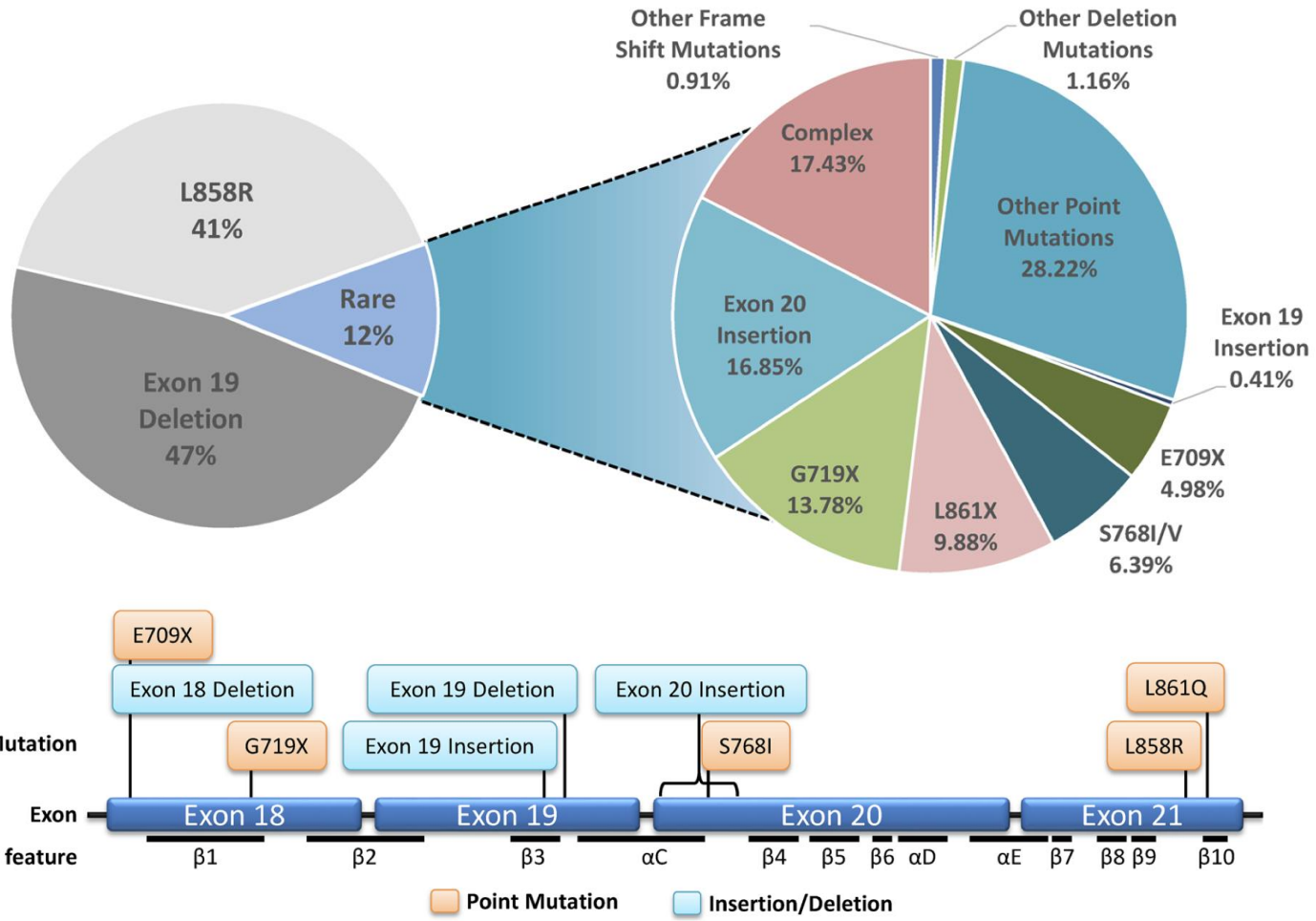
OUTLINE

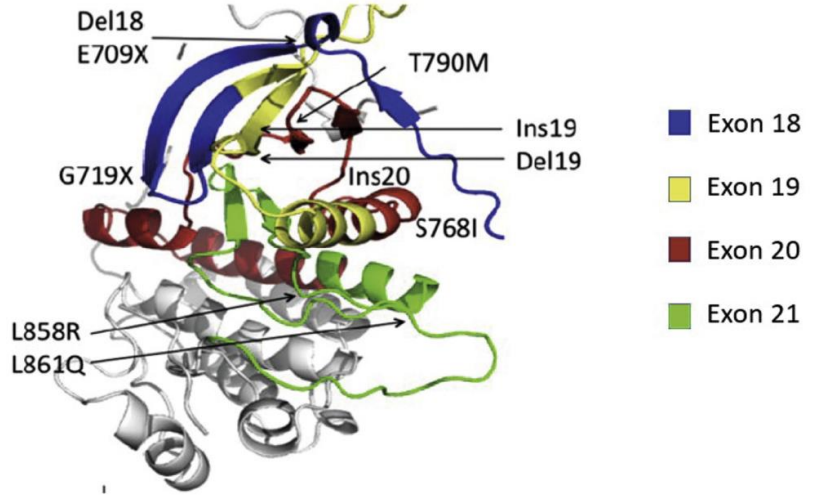
1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

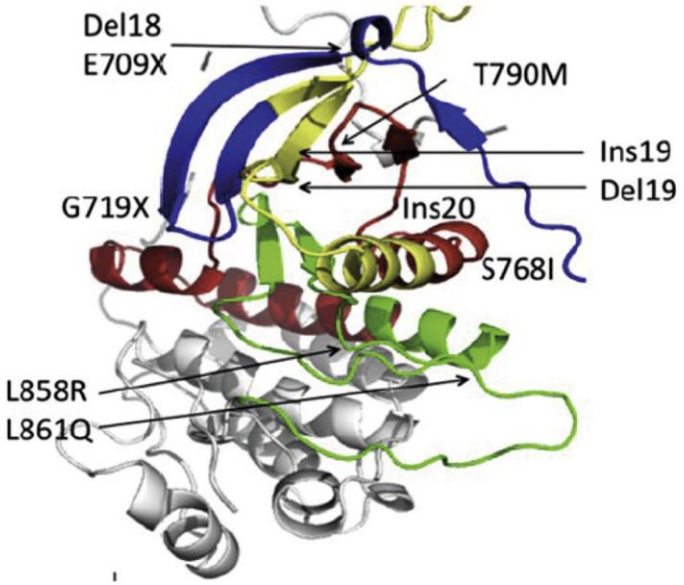
EGFR kinase domain mutations are hetereogeneous



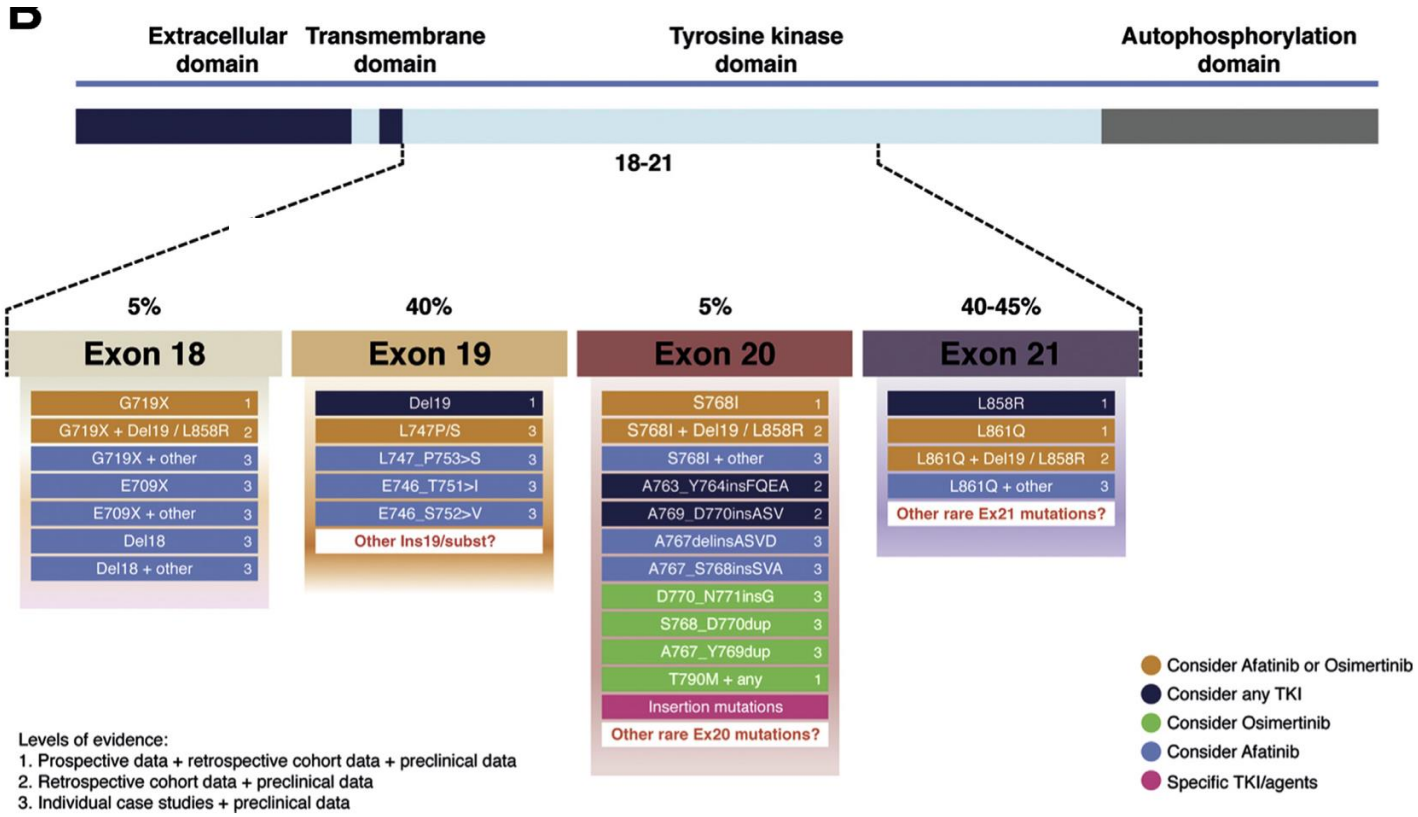


Harrison PT, Semin. Cancer Biol. 2020

EGFR kinase domain mutations classification by exon location



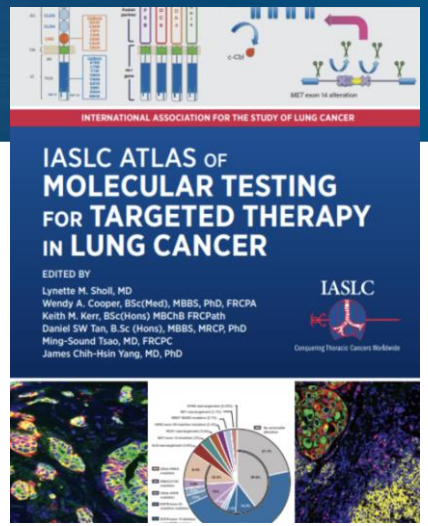
Exon 18
Exon 19
Exon 20
Exon 21



Passaro A, J Thor Oncol 2020

Types of uncommon EGFR mutations

*Uncommon EGFR mutations: **ANYTHING NOT COMMON OR T790M***



Exon 20 insertions

- The most common of the uncommon (≈ 12%)
- Very heterogenous
- NGS recommended

Compound EGFR mutations

- Any type of combination
- 4-26% of all EGFR mutations

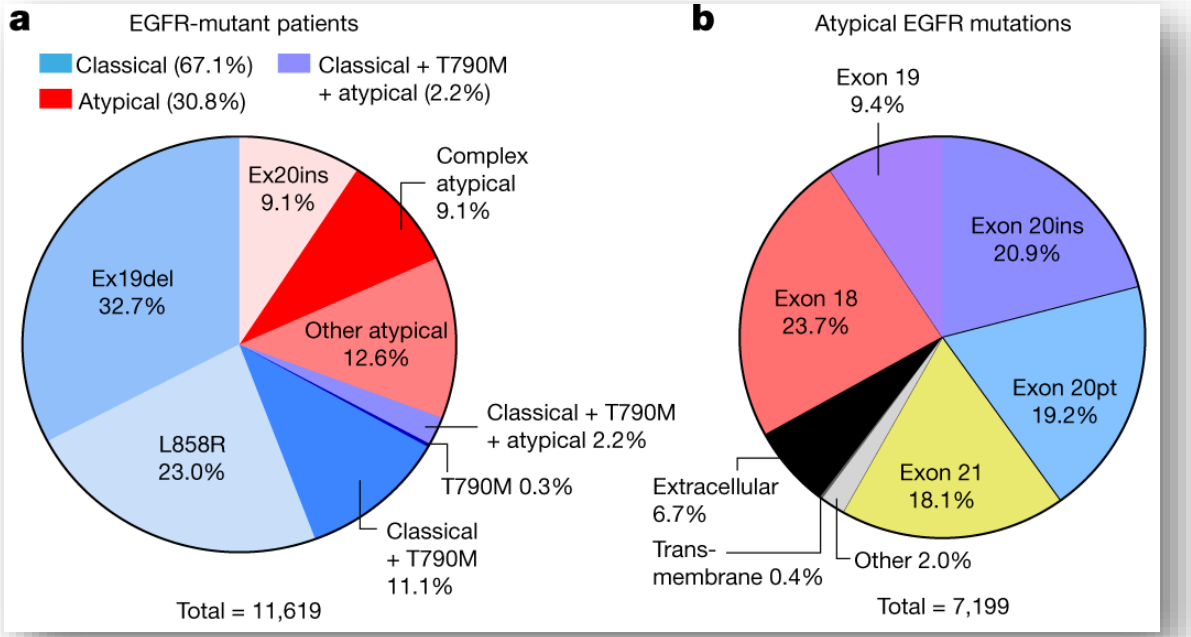
Other uncommon (or atypical) simple mutations

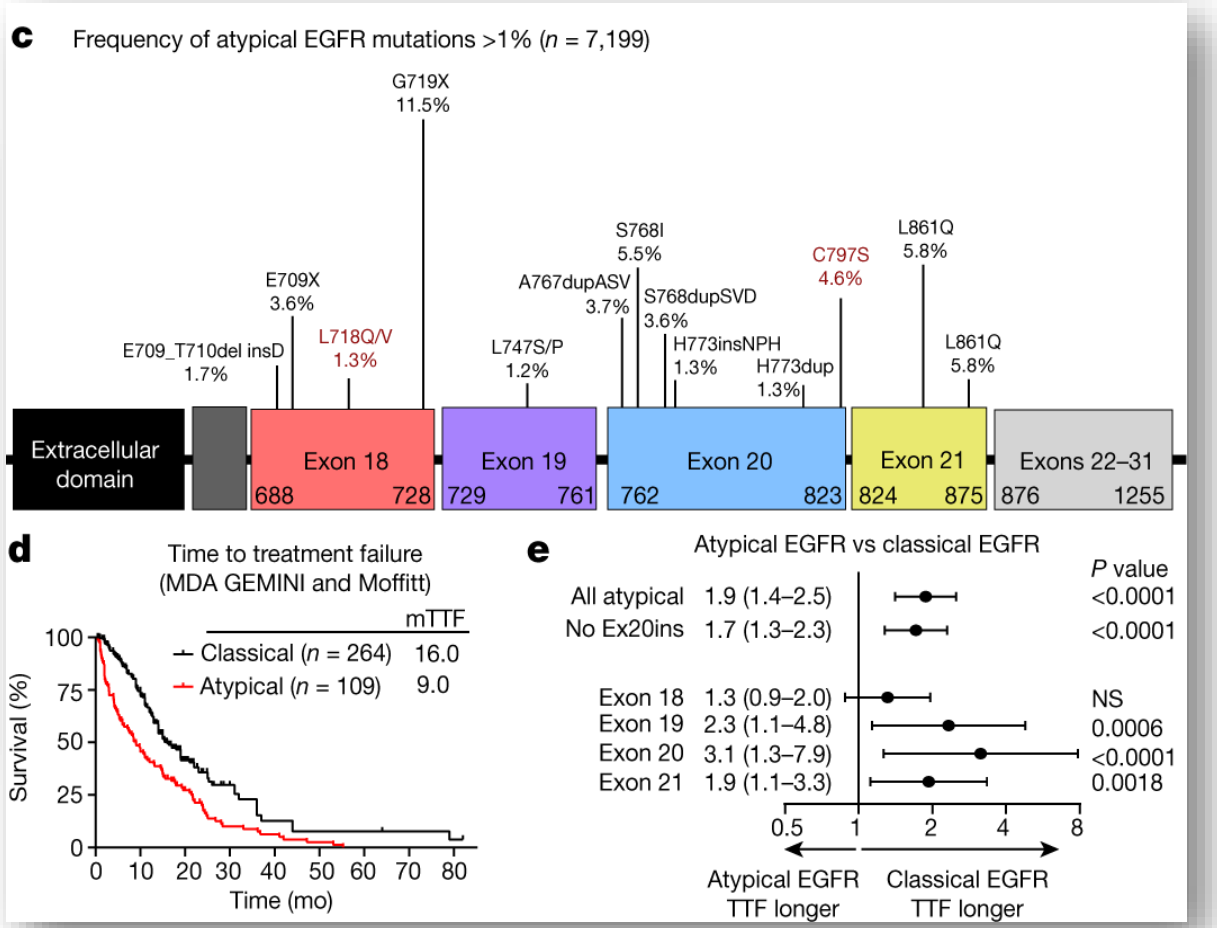
- All mutations except exon 19 deletions, L858R, and T790M mutations.
- G719X (ex18) > L861X (ex21) > S768I (ex20)
- Can be sensitive to EGFR TKIs

IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer. 2023

Types of uncommon EGFR mutations

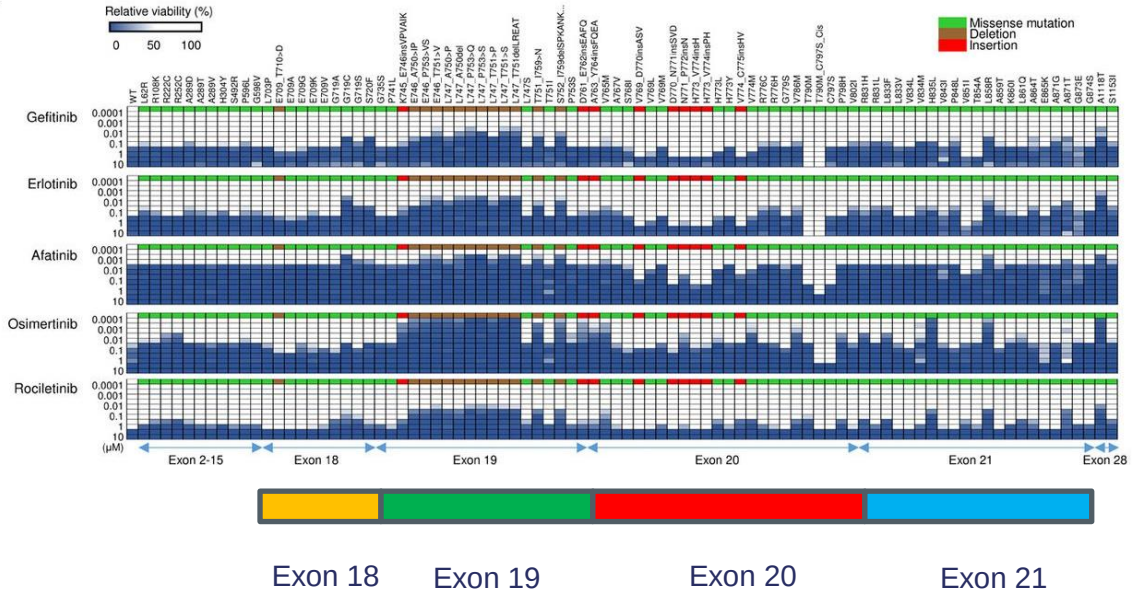
MD Anderson work: 5 patient databases with genomic profiling; 16715 EGFR-mutant patients



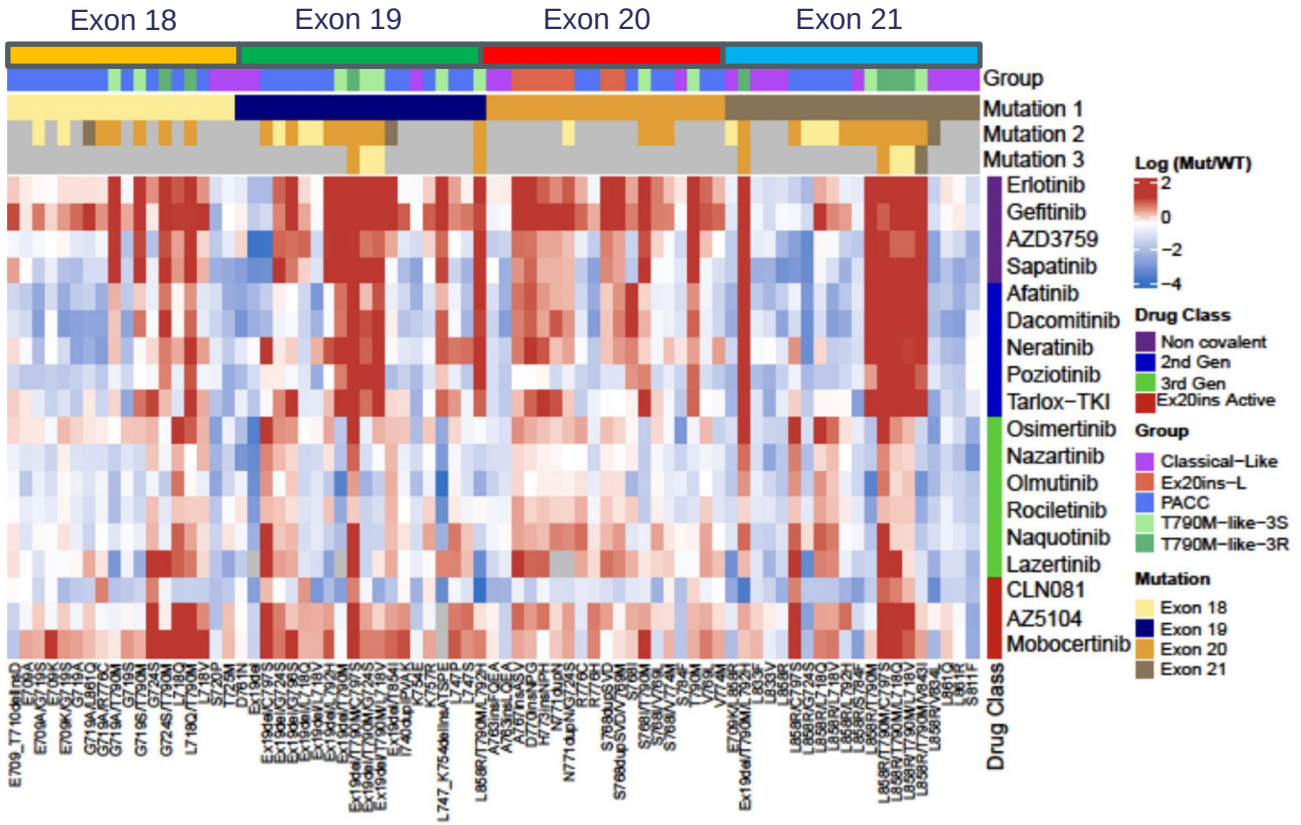


Robichaux, Nature 2021

Uncommon EGFR mutations have differential responses to TKIs

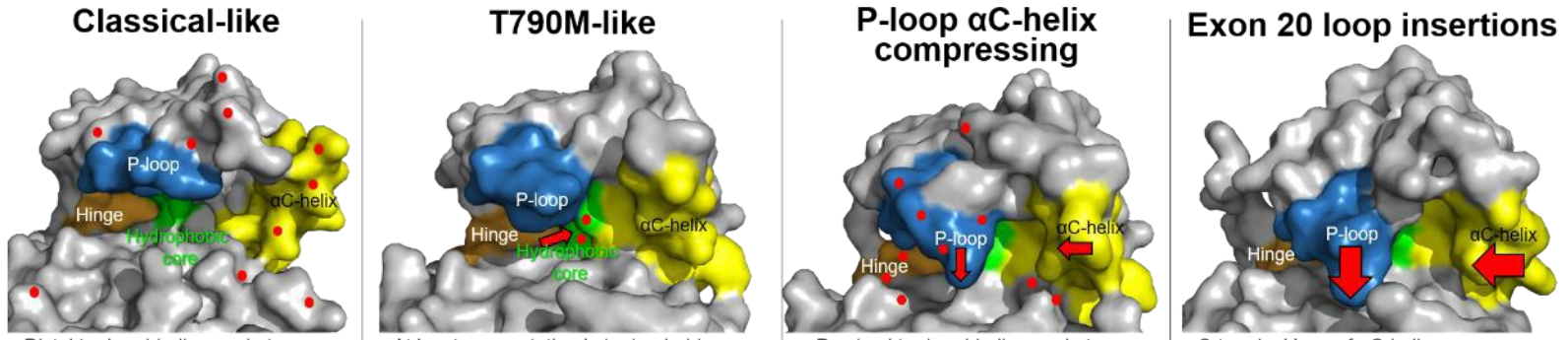


Kohsaka, Sci Transl Med 2017



Robichaux, Nature 2021

Structure/function classfication predicts drug response in EGFR mutant NSCLC



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

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

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

- 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

		T790M-3S	T790M-3R	Primary	Acquired	Ex20ins-NL	Ex20ins-FL
L858R	K754E	Classical/T790M	Ex19del/T790M/L792H	G719X	C797S	S768dupSVD	H773insNPH
Exon 19 deletions	T725M	G719X/T790M	L858R/T790M/L718X	S768I	L792H	A767dupASV	H773dupH
S720P	L833F/V	L747_K745delinsATSPE	Classical/T790M/C797S	L747P/S	G724S	D770insNPG	V774insAV
L861Q/R	A763insFQEA	S768I/T790M		E709_T710del insD	L718X	D770del insGY	V774insPR
S811F	A763insLQEA			V769L	T854I		

Drug Sensitivity/Selectivity

Sensitive & Selective

Resistant

	T790M-3S	T790M-3R		Ex20ins-NL	Ex20ins-FL
Third-generation Second-generation First-generation Exon20ins-specific	Third-generation PKCi ALKi Second-generation First-generation	PKCi ALKi Third-generation Second-generation First-generation	Second-generation First-generation Ex20ins-specific Third-generation	Ex20ins-specific Second-generation Third-generation First-generation	Ex20ins-specific Second-generation Third-generation First-generation

Mutation resulted structural change

⇕

Function

⇕

Drug sensitivity

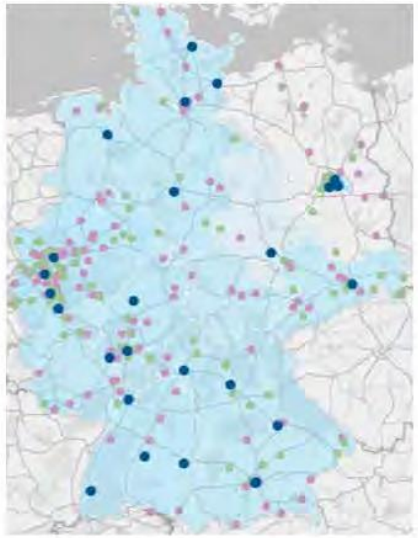
Robichaux, Nature 2021

ANALYSIS OF CLINICAL ACTIONABILITY OF ATYPICAL EGFR MUTATIONS

nNGM

National Network Genomic Medicine Lung Cancer

Funded by the German Cancer Aid since 2018
and the health insurance companies



24 University nNGM centers
at 26 sites

359 regional partners:
170 practices / MVZs
189 hospitals

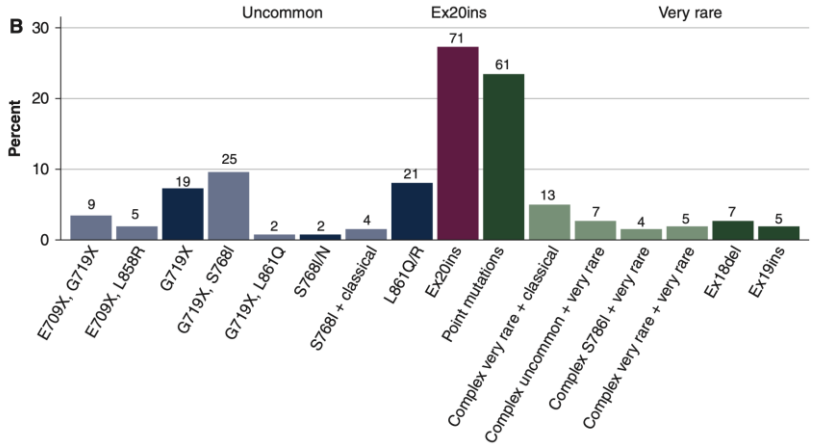
2022:
NGS of ca. 17.000 pts. with newly diagnosed advanced NSCLC
= ca. 50% of cases in Germany

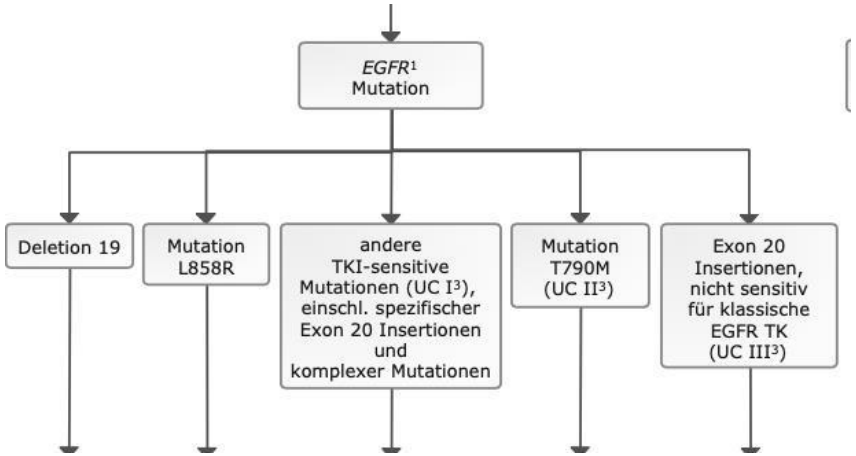
nNGM | National Network Genomic Medicine Lung Cancer

nNGM

1 nNGM UC1 TKI-sensitive *EGFR* mutations		
A	**G719X, S768X, L861X** mutations, alone or in complex with other uncommon mutations such as E709X or classical L858R or exon19 deletions (group 1 in nNGM clinical FUP cohort)	
B	**complex mutations containing** classical *EGFR* mutations **L858R or exon19 deletions** with very rare *EGFR* mutations	
C	**exon 19 insertions**	
D	**Specific exon 20 insertions**	
	Y763_V764insFQEV	EGFR-TKI naïve
	A767_V769dup	EGFR-TKI naïve
	N771_H773dup	2nd EGFR-TKI, switch from geftinib due to toxicities
	H773_V774insGHPH	EGFR-TKI naïve
	H773_V774insAH	EGFR-TKI naïve
E	**Specific very rare single point mutations**	
	E711Q	EGFR-TKI naïve
	P733Q	EGFR-TKI naïve
	L747P	EGFR-TKI naïve
		EGFR-TKI naïve
	P753L	5L (1L geftinib PFS 2.0 months, 2L erlotinib PFS 3.0 months, 4L & 5L chemo)
	E758G	EGFR-TKI naïve
	R776H	EGFR-TKI naïve
	Q791H	EGFR-TKI naïve
F	**Specific complex mutations: uncommon with very rare**	
	G719A, P753Q	EGFR-TKI naïve
G	**Specific complex mutations: very rare with very rare**	
	L833V, H835L	EGFR-TKI naïve

Novel classfication of clinical actionability





Uptake into national NSCLC guideline 2022

Janning, Ann Oncol 2022

NOVEL NNGM CLASSIFICATION OF RARE EGFR MUTATIONS

UC1: TKI-sensitive

UC2: de Novo T790M

UC3: Exon20 Insertions

UC4: Ultrarare Point/Compound Mutations

A	**G719X, S768X, L861X** mutations, alone or in complex with other uncommon mutations such as E709X or classical L858R or exon19 deletions (group 1 in nNGM clinical FUP cohort)	
B	**complex mutations containing** classical *EGFR* mutations **L858R or exon19 deletions** with very rare *EGFR* mutations	
C	**exon 19 insertions**	
D	**Specific exon 20 insertions**	
	Y763_V764insFQEV	EGFR-TKI naïve
	A767_V769dup	EGFR-TKI naïve
	N771_H773dup	2nd EGFR-TKI, switch from geftinib due to toxicities
	H773_V774insGHPH	EGFR-TKI naïve
	H773_V774insAH	EGFR-TKI naïve
E	**Specific very rare single point mutations**	
	E711Q	EGFR-TKI naïve
	P733Q	EGFR-TKI naïve
	L747P	EGFR-TKI naïve
		EGFR-TKI naïve
	P753L	5L (1L geftinib PFS 2.0 months, 2L erlotinib PFS 3.0 months, 4L & 5L chemo)
	E758G	EGFR-TKI naïve
	R776H	EGFR-TKI naïve
	Q791H	EGFR-TKI naïve
F	**Specific complex mutations: uncommon with very rare**	
	G719A, P753Q	EGFR-TKI naïve
G	**Specific complex mutations: very rare with very rare**	
	L833V, H835L	EGFR-TKI naïve

- Very rare single point mutations*
- Complex mutations: uncommon with very rare*
- Complex mutations: very rare with very rare*

*except those mentioned in nNGM UC1

EGFR TKI (Afa, Osi)

Osimertinib

Amivantamab

Preclinical testing/MTB

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

Finding the needle in the haystack

UNMET MEDICAL NEED

1-3% OF NSCLC patients with rare/atypical EGFR mutations

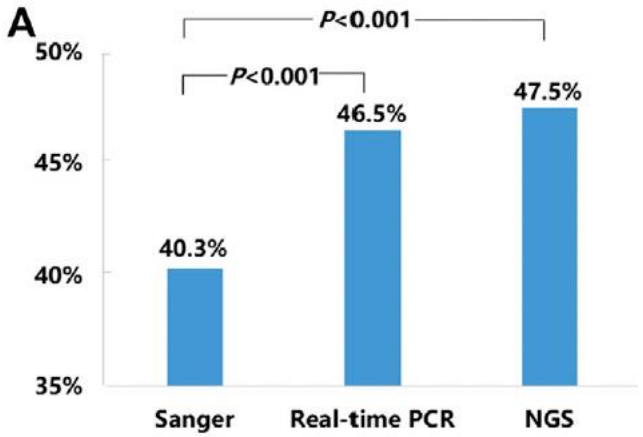
0,7-2% w/o Exon20 Insertions and T790M

Significant subgroup of patients with unmet medical need: > 2000 newly diagnosed patients in EU/Y

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Mutation detection rates of EGFR

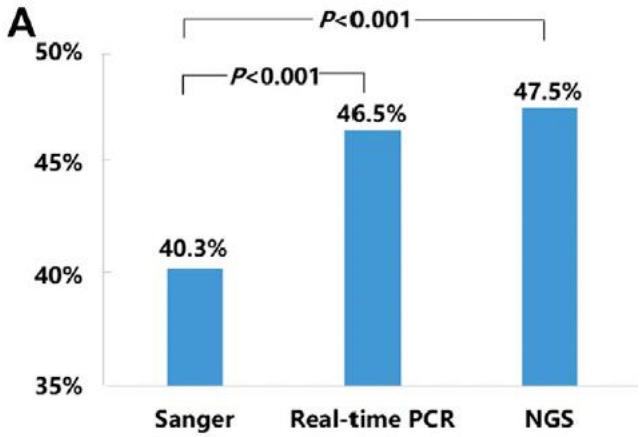


Mao, Pathol Oncol Res 2021

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Mutation detection rates of EGFR



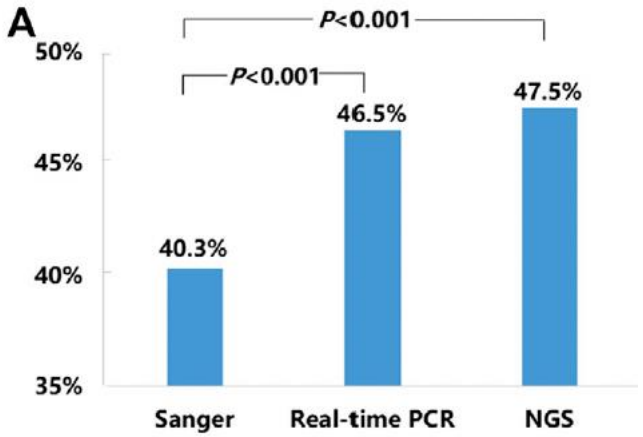
Specimens	Sanger sequencing	Real-time PCR	NGS
Number of samples	5,244	13,329	2,751
EGFR mutation rate	40.3%	46.5%	47.5%
EGFR mutation types	46%	36%	76%
Covered regions of *EGFR*	18–21 exons	18–21 exons hotspots[a]	All coding sequencing[b]
Covered non-*EGFR*	No	No	Yes[c]
Technical sensitivity	20%	1%	1%
Recommended TCC	≥40%	≥1%	≥1%
Mean TAT (days)	5	4	8

Mao, Pathol Oncol Res 2021

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Mutation detection rates of EGFR



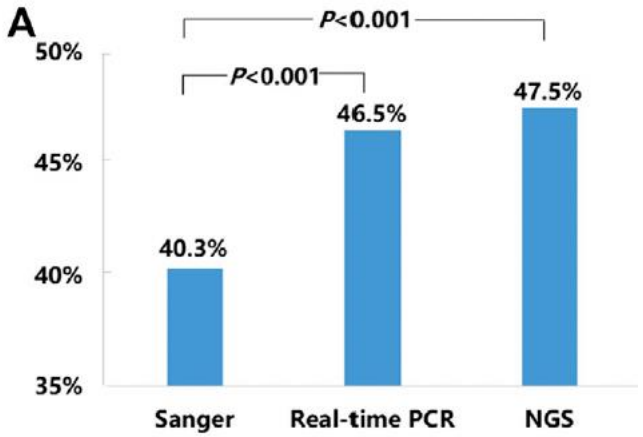
Specimens	Sanger sequencing	Real-time PCR	NGS
Number of samples	5,244	13,329	2,751
EGFR mutation rate	40.3%	46.5%	47.5%
EGFR mutation types	46%	36%	76%
Covered regions of *EGFR*	18–21 exons	18–21 exons hotspots[a]	All coding sequencing[b]
Covered non-*EGFR*	No	No	Yes[c]
Technical sensitivity	20%	1%	1%
Recommended TCC	≥40%	≥1%	≥1%
Mean TAT (days)	5	4	8

Mao, Pathol Oncol Res 2021

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Mutation detection rates of EGFR



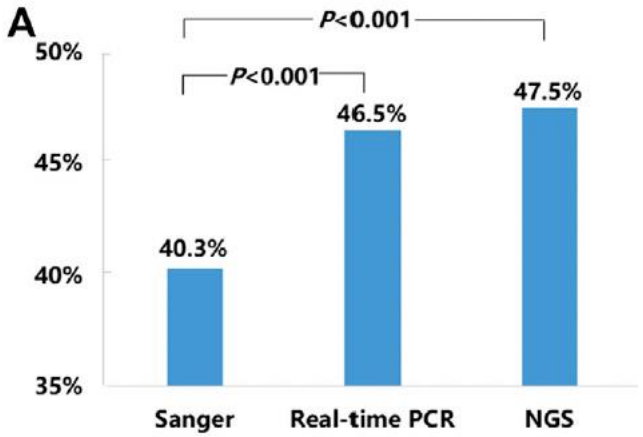
Specimens	Sanger sequencing	Real-time PCR	NGS
Number of samples	5,244	13,329	2,751
EGFR mutation rate	40.3%	46.5%	47.5%
EGFR mutation types	46%	36%	76%
Covered regions of *EGFR*	18–21 exons	18–21 exons hotspots[a]	All coding sequencing[b]
Covered non-*EGFR*	No	No	Yes[c]
Technical sensitivity	20%	1%	1%
Recommended TCC	≥40%	≥1%	≥1%
Mean TAT (days)	5	4	8

Mao, Pathol Oncol Res 2021

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Mutation detection rates of EGFR



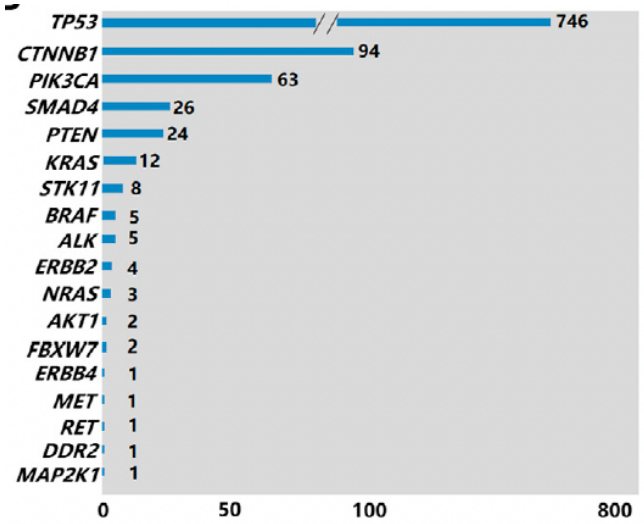
Specimens	Sanger sequencing	Real-time PCR	NGS
Number of samples	5,244	13,329	2,751
EGFR mutation rate	40.3%	46.5%	47.5%
EGFR mutation types	46%	36%	76%
Covered regions of *EGFR*	18–21 exons	18–21 exons hotspots[a]	All coding sequencing[b]
Covered non-*EGFR*	No	No	Yes[c]
Technical sensitivity	20%	1%	1%
Recommended TCC	≥40%	≥1%	≥1%
Mean TAT (days)	5	4	8

Mao, Pathol Oncol Res 2021

Uncommon EGFR mutations testing – What's best?

Mutation spectrum of EGFR from 21324 chinese NSCLC patients tested by multiple methods - CAP accredited lab

Non-EGFR co-mutations detected in EGFRm



Of the 1,308 cases with EGFR mutations found by NGS, **65.3%** of the cases (854/1,308) harbored **non-EGFR mutations** in 18 tumor-related genes, with TP53 being the most frequently mutated

Specimens	Sanger sequencing	Real-time PCR	NGS
Number of samples	5,244	13,329	2,751
EGFR mutation rate	40.3%	46.5%	47.5%
EGFR mutation types	46%	36%	76%
Covered regions of *EGFR*	18–21 exons	18–21 exons hotspots[a]	All coding sequencing[b]
Covered non-*EGFR*	No	No	Yes[c]
Technical sensitivity	20%	1%	1%
Recommended TCC	≥40%	≥1%	≥1%
Mean TAT (days)	5	4	8

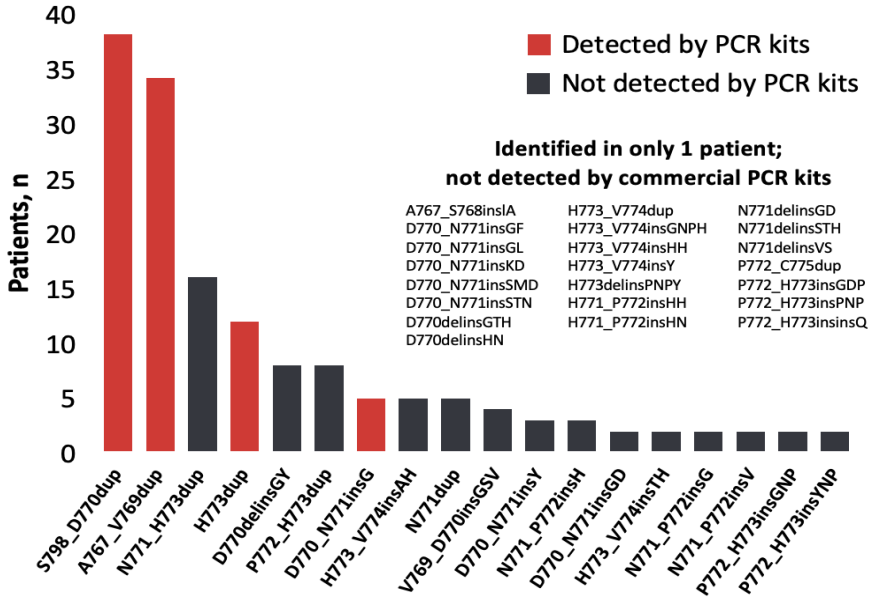
Mao, Pathol Oncol Res 2021

Uncommon EGFR testing- What's best?

NGS Is More Comprehensive Than PCR for Testing EGFR Exon 20 Insertions

- Due to the heterogeneity, **exon 20 insertions are not uniformly detected across commonly used PCR testing** methods for *EGFR* mutations
- For detection of *EGFR* exon 20 insertions, **NGS testing is more comprehensive than PCR**

GENIE: Expected PCR Detection Results[2]

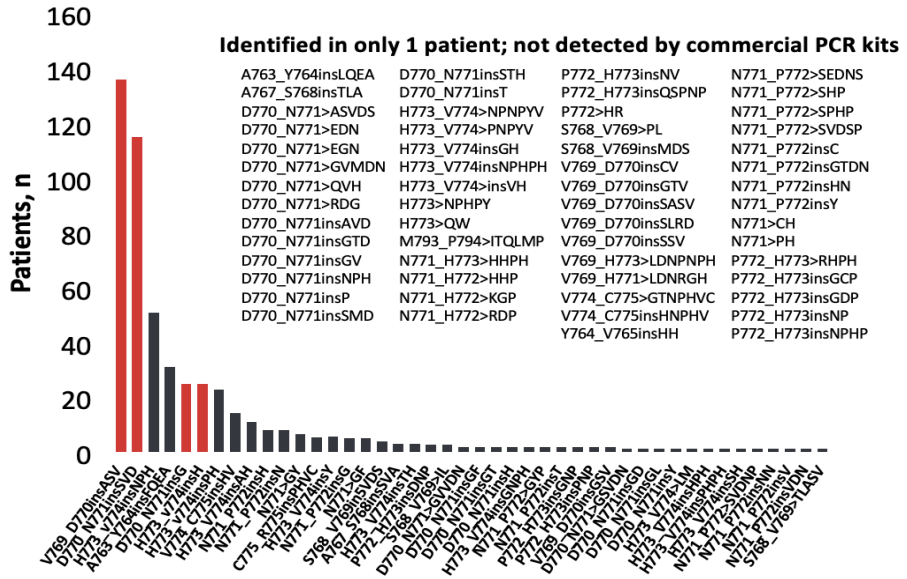


Identified in only 1 patient; not detected by commercial PCR kits

A767_S768insIA	H773_V774dup	N771delinsGD
D770_N771insGF	H773_V774insGNPH	N771delinsSTH
D770_N771insGL	H773_V774insHH	N771delinsVS
D770_N771insKD	H773_V774insY	P772_C775dup
D770_N771insSMD	H773delinsPNPY	P772_H773insGDP
D770_N771insSTN	H771_P772insHH	P772_H773insPNP
D770delinsGTH	H771_P772insHN	P772_H773insinsQ
D770delinsHN		

- PCR expected to **miss 49.1% of *EGFR* ex20ins** cases identified by NGS (PCR = 89; NGS = 175)

FoundationInsights®: Expected PCR Detection Results[2]



Identified in only 1 patient; not detected by commercial PCR kits

A763_Y764insLQEA	D770_N771insSTH	P772_H773insNV	N771_P772>SEDNS
A767_S768insTLA	D770_N771insT	P772_H773insQSPNP	N771_P772>SHP
D770_N771>ASVDS	H773_V774>NPNPYV	P772>HR	N771_P772>SPHP
D770_N771>EDN	H773_V774>PNPYV	S768_V769>PL	N771_P772>SVDSP
D770_N771>EGN	H773_V774insGH	S768_V769insMDS	N771_P772insC
D770_N771>GVMDN	H773_V774insNPHPH	V769_D770insCV	N771_P772insGTDN
D770_N771>QVH	H773_V774>insVH	V769_D770insGTV	N771_P772insHN
D770_N771>RDG	H773>NPHPY	V769_D770insSASV	N771_P772insY
D770_N771insAVD	H773>QW	V769_D770insSLRD	N771>CH
D770_N771insGTD	M793_P794>ITQLMP	V769_D770insSSV	N771>PH
D770_N771insGV	N771_H773>HHPH	V769_H773>LDNPNPH	P772_H773>RHPH
D770_N771insNPH	N771_H772>HHP	V769_H771>LDNRGH	P772_H773insGCP
D770_N771insP	N771_H772>KGP	V774_C775>GTNPHVC	P772_H773insGDP
D770_N771insSMD	N771_H772>RDP	V774_C775insHNPHV	P772_H773insNP
		Y764_V765insHH	P772_H773insNPHP

- PCR expected to **miss 51.4% of *EGFR* ex20ins** cases identified by NGS (PCR = 305; NGS = 627)

Bauml. WCLC 2020. Abstr FP07.12

Uncommon EGFR testing- What's best?

NGS Is More Comprehensive Than PCR for Testing EGFR Exon 20 Insertions

- Due to the heterogeneity, **exon 20 insertions are not uniformly detected across commonly used PCR testing** methods for *E*
- For detection of *EGFR* **han PCR**

- PCR expected to **miss 49.1% of *EGFR* ex20ins** cases identified by NGS (PCR = 89; NGS = 175)
- PCR expected to **miss 51.4% of *EGFR* ex20ins** cases identified by NGS (PCR = 305; NGS = 627)

Bauml. WCLC 2020. Abstr FP07.12

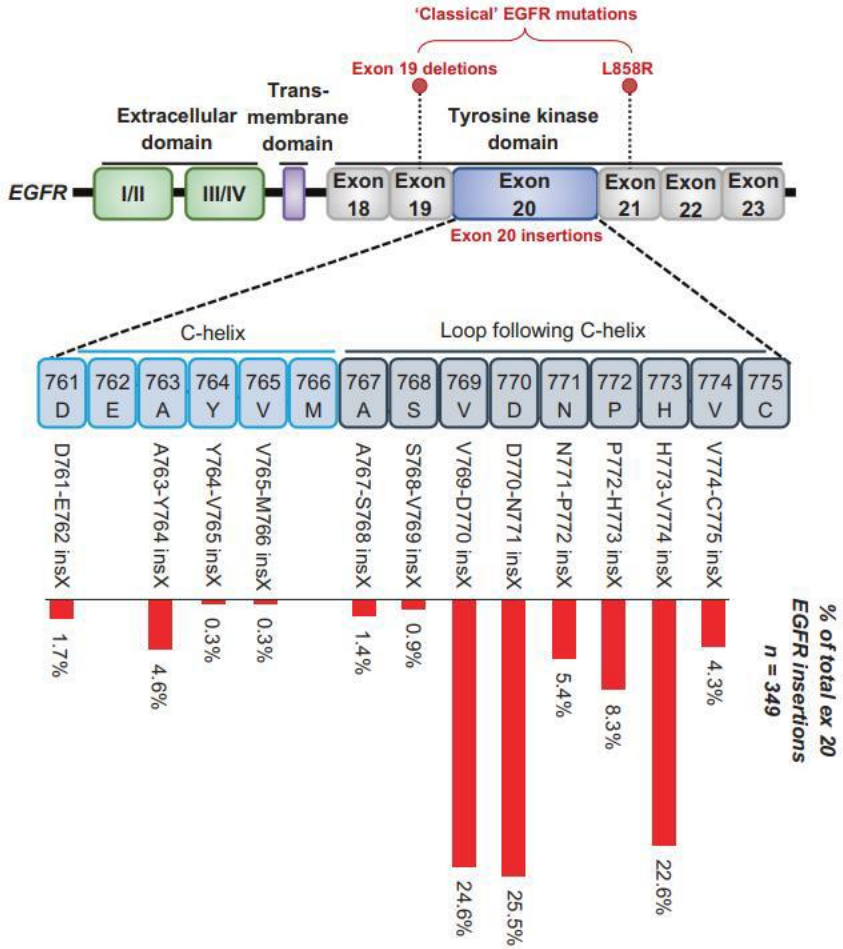
OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

EXON 20 INSERTIONS



Ins 20 variant (Parental Ba/F3 IC50 values)	Erlotinib	Gefitinib	Afatinib	Osimertinib	Mobocertinib	Poziotinib	Amivantamab	BAY2576568	BLU-451	Oric-114	Furmonertinib	Tarloxitinib
WT EGFR	71.0	55.5	3.8	350.5	34.5	6.49	0.9	273	921	2.3	109.9	N/A
A763_Y764insFQEA	21.0	90.0	0.4	51.1	3.1	1.90	N/A	N/A	61	0.9	N/A	15.2
V769_D770insASV	80.0	287.4	10.3	61.1	2.1	2.13	0.6	15.3	78	N/A	14	675.9
D770_N771insNPG	469.0	941.0	9.0	27.2	1.3	0.73	N/A	N/A	7	2.7	11	N/A
D770_N771insSVD	528.0	918.4	41.3	226.7	6.5	1.5	1.4	11.1	53	N/A	N/A	990.1
H773_V774insNPH	191.2	1132.8	18.9	153.6	2.6	31.93	N/A	67.9	75	N/A	20	714.0

IC50 >100 | IC50 < 10 to ≤ 100 | IC50 ≤ 10

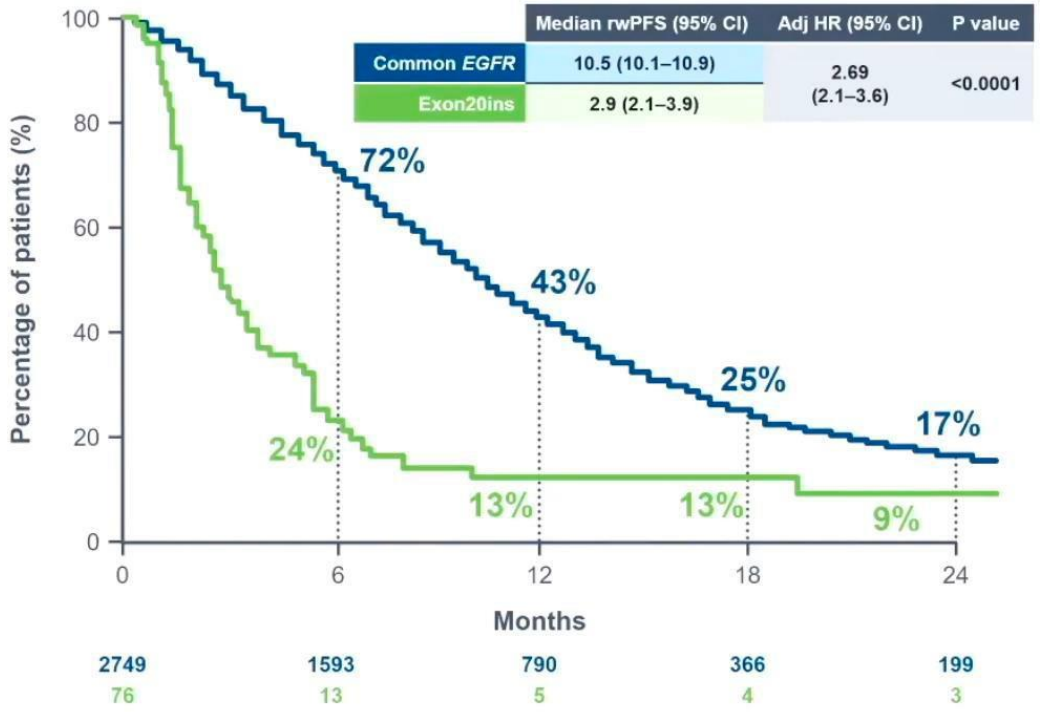
Vise, Signal Trans Targ Ther 2019; Low, Ther Adv Med Oncol 2022

RWD: EXON21Ins - worse prognosis

Real-world overall survival

75% increased risk of death with *EGFR* exon20ins compared with c*EGFR*; (Adj HR, 1.75 [95% CI, 1.45–2.13]; p<0.0001)

Real-world PFS



170% increased risk of progression or death on TKI treatment with *EGFR* exon20ins compared with c*EGFR*; (Adj HR, 2.7 [95% CI,2.06–3.55]; p<0.0001)

Girard, WCLC 2020

RWD response and outcomes in Exon20Ins

- Platin-based chemo alone or in combination with other therapy was the most common 1L therapy
- **IO therapy** was associated with poor confirmed rwORR and survival, consistently in the 1L and ≥2L
- **EGFR TKIs** had limited clinical benefit with a poor confirmed rwORR in 1L and ≥2L

Table 3. Confirmed rwORR and survival outcomes by therapy

Cohort	N	Confirmed rwORR (95% CI)	Median OS (95% CI), months	Median rwPFS (95% CI), months
1L: Platinum	41	19.5% (8.8%, 34.9%)	17.0 (10.5, 33.2)	5.7 (3.0, 10.9)
1L: IO + Platinum	16	18.8% (4.0%, 45.6%)	11.3 (5.6, NR)	4.5 (1.2, 10.3)
1L: IO monotherapy	11	9.1% (0.2%, 41.3%)	11.0 (1.2, NR)	3.1 (1.1, 5.2)
1L: EGFR TKI	37	2.7% (0.1%, 14.2%)	10.7 (3.4, 22.3)	3.3 (2.2, 6.6)
≥2L post-platinum: IO monotherapy	20	5.0% (0.1%, 24.9%)	7.1 (2.5, 10.1)	2.2 (1.7, 3.0)
≥2L post-platinum: EGFR TKI	10	10.0% (0.3%, 44.5%)	12.2 (1.3, 17.8)	3.4 (0.0, 5.9)

1L, first line; CI, confidence interval; IO, immuno-oncology; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; rwORR, real-world overall response rate.

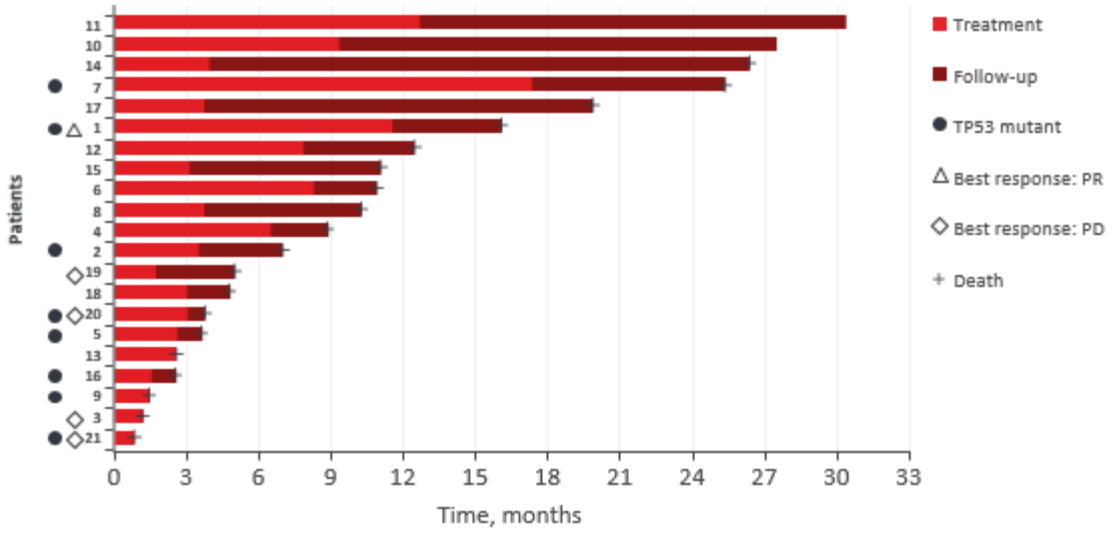
Ou, J Clin Oncol. 2021;39(suppl 15). Abstract 9098

3rd G EGFR TKIs: Efficacy Results in Patients With *EGFR* Exon 20 Insertions

A Retrospective Study in *EGFR* Exon 20 Insertion+ NSCLC: Response to Osimertinib[1,a]

Mutation	ORR, %	PFS, Median, months	OS, Median, months
Exon 20 mutations (n=21)	5% (1 PR)	3.6 (95% CI, 2.6-4.5)	8.7 (95% CI, 1.1-16.4)

Swimmer Plot of PFS and OS After Osimertinib[1,a]



A Phase 2 Study in EGFR Exon 20 Insertion+ NSCLC: Response to Osimertinib[2,b]: POSITION 20

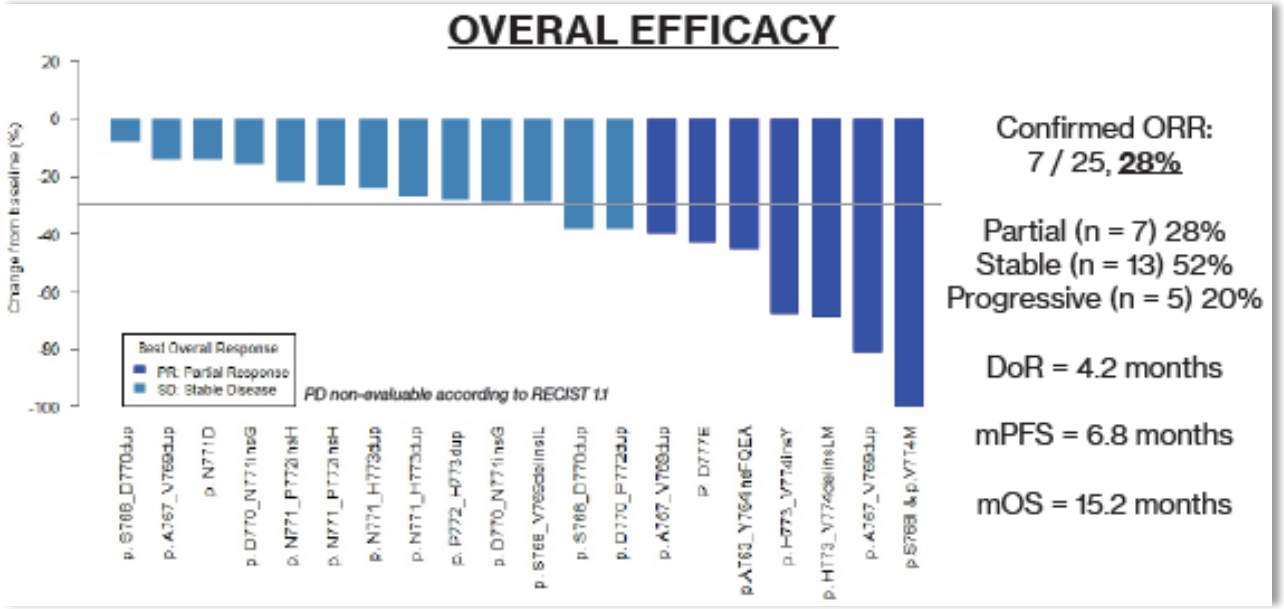
Osimertinib in Treating Patients With Stage IIIB-IV or Recurrent Non-small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03191149

Recruitment Status : Suspended (Other - response analysis)
First Posted : June 19, 2017
Last Update Posted : February 2, 2022

OVERAL EFFICACY



Confirmed ORR: 7 / 25, **28%**

Partial (n = 7) 28%
Stable (n = 13) 52%
Progressive (n = 5) 20%

DoR = 4.2 months

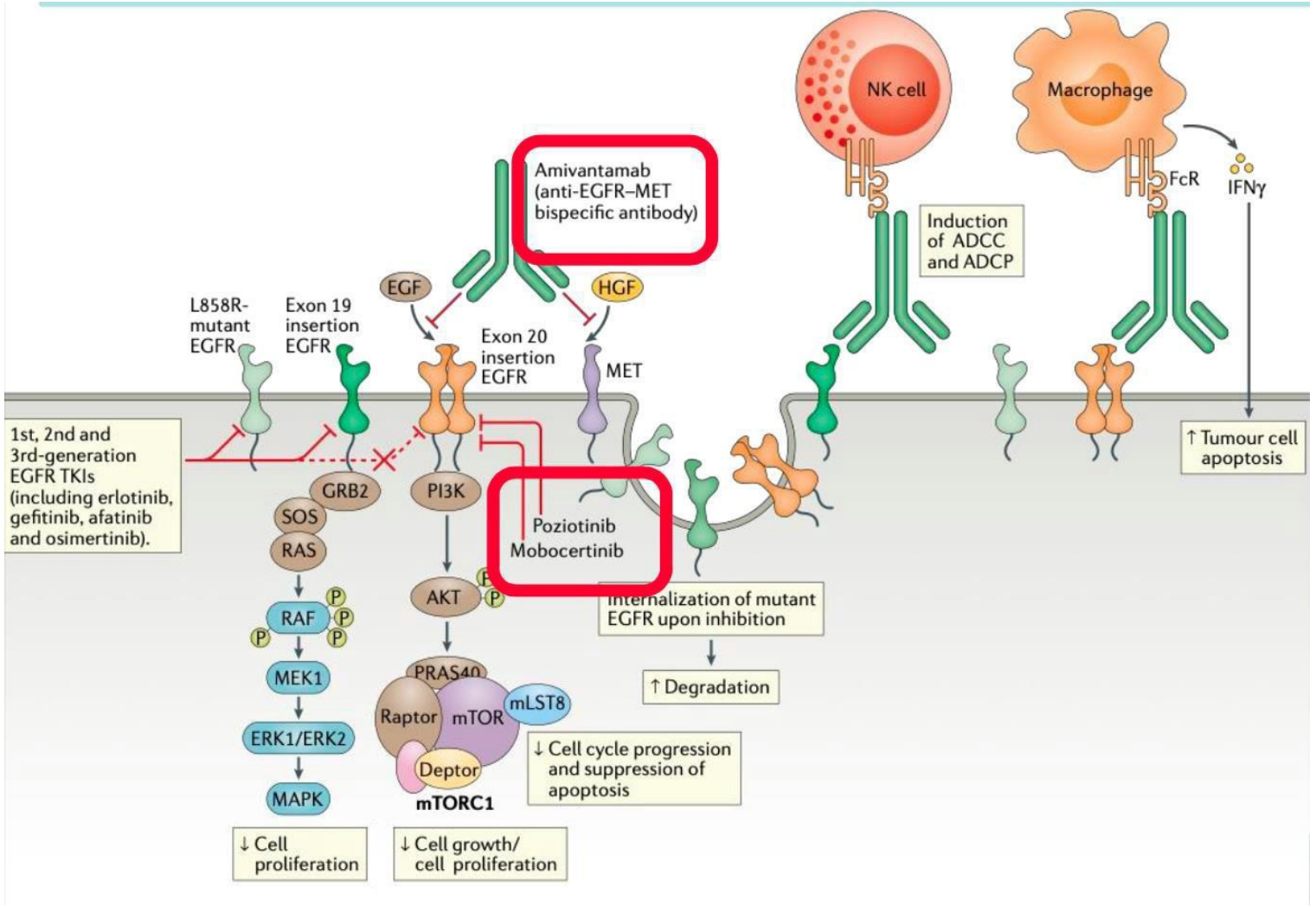
mPFS = 6.8 months

mOS = 15.2 months

. Van Veggel. Lung Cancer. 2020; Zwierenga, ESMO 2021 Abstract 1214P

Exon20Ins: new therapeutic options

- Amivantamab (bispecific c-MET-EGFR antibody)
- Exon20Ins specific TKI
  - Mobocertinib
  - Poziotinib
  - Others

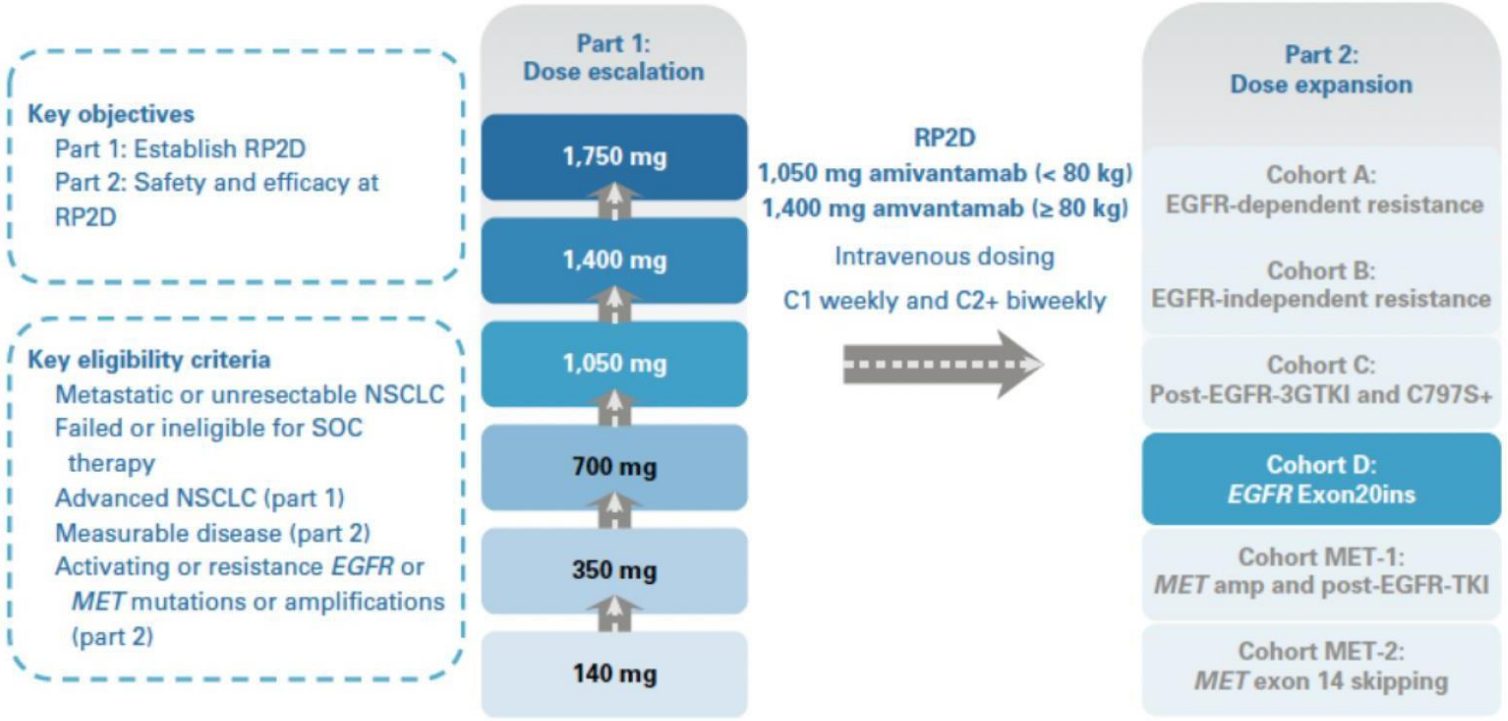


Friedlander, Nat Rev Clin Oncol 2021

Exon20Ins - AMIVANTAMAB

CHRYSALIS 1: Amivantamab (tras varias líneas de tratamiento)

Phase I/II



Friedlander, Nat Rev Clin Oncol 2021

Exon20Ins- AMIVANTAMAB in PRETREATED- Chrysalis

Phase I/II

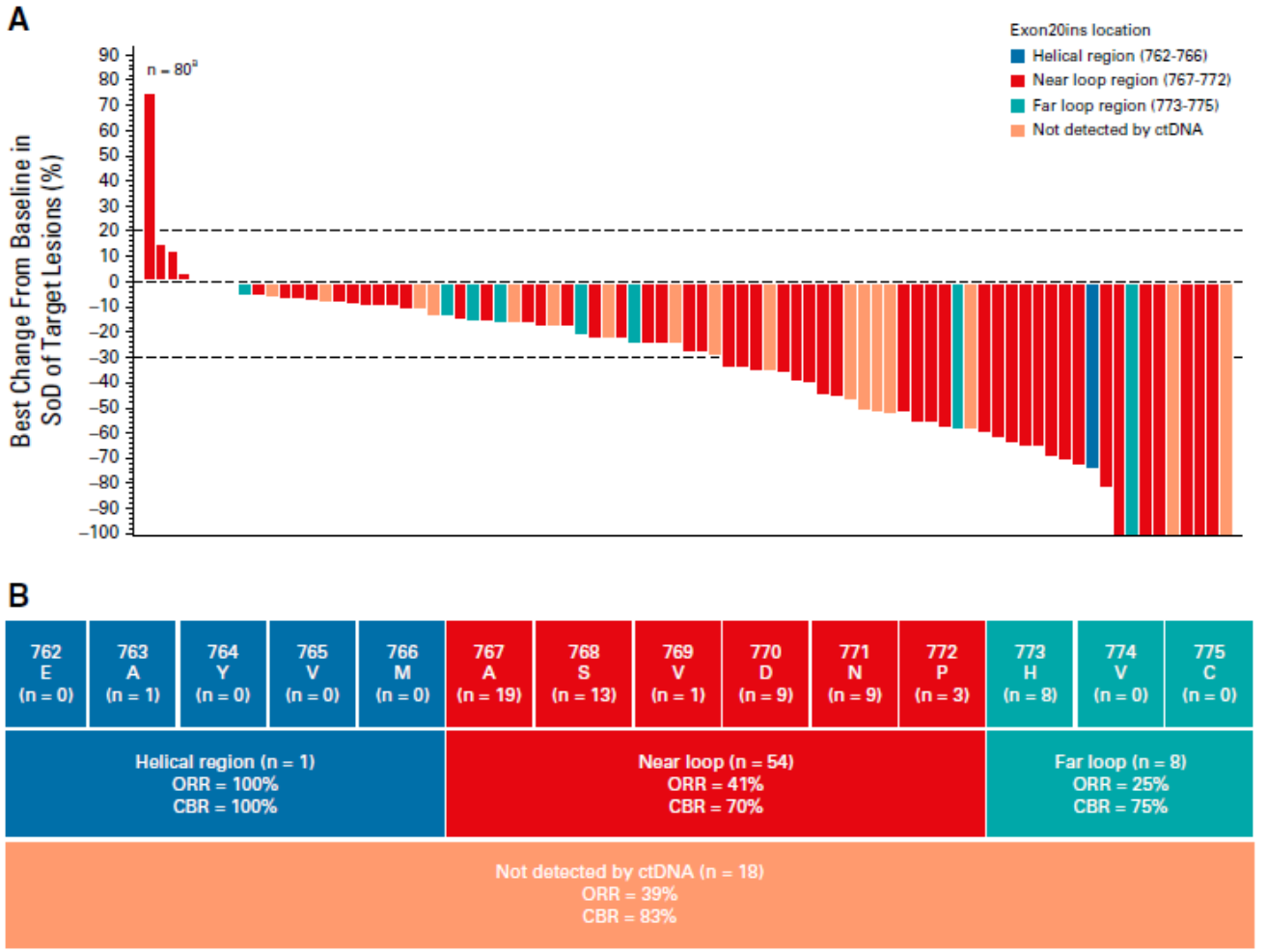
Median PFS was 8.3 months (95% CI, 6.5 to 10.9) by BICR and investigator (95% CI, 5.5 to 10.6)

Median OS was 22.8 months (95% CI, 14.6 to not reached)

TABLE 3. Response as Assessed by Blinded Independent Central Review

Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

Median Follow Up: 9,7m (range, 1,1-29.3 m)



Park, J Clin Oncol 2021

Exon20Ins- AMIVANTAMAB in PRETREATED- Chrysalis

Phase I/II

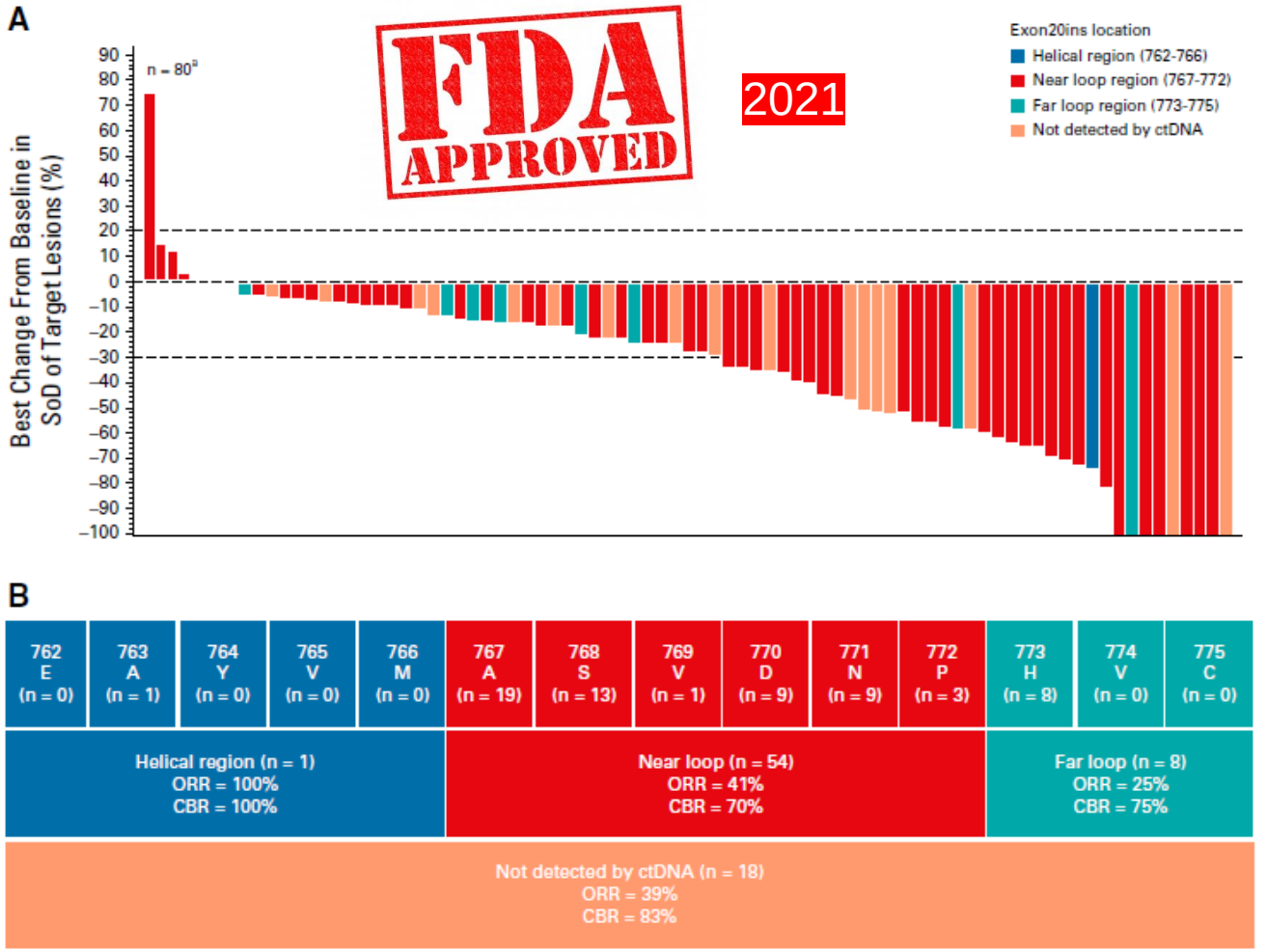
Median PFS was 8.3 months (95% CI, 6.5 to 10.9) by BICR and investigator (95% CI, 5.5 to 10.6)

Median OS was 22.8 months (95% CI, 14.6 to not reached)

TABLE 3. Response as Assessed by Blinded Independent Central Review

Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

Median Follow Up: 9,7m (range, 1,1-29.3 m)



Park, J Clin Oncol 2021

Exon20Ins- AMIVANTAMAB in PRETREATED- Chrysalis

Safety profile (dose-escalation)

Treatment-related dose reductions occurred in 15 patients (13%):

- Rash (11 [10%]) being most frequently reported.

Five patients (4%) had treatment-related discontinuation:

- Rash and IRR in two (1.8%) each
- Paronychia in one (1%).

There were no treatment-related grade 5 events.

Median Follow Up: 5,1 m (range, 0,2-29,3 m)

	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
Most Common AE (≥ 10%)	Total, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade ≥ 3, No. (%)	Total, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade ≥ 3, No. (%)
Rash[b]	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)
Pruritus	19 (17)	11 (10)	8 (7)	0	49 (19)	40 (16)	9 (4)	0
Fatigue	21 (18)	15 (13)	4 (4)	2 (2)	47 (18)	29 (11)	16 (6)	2 (1)
Cough	16 (14)	11 (10)	5 (4)	0	40 (16)	25 (10)	15 (6)	0
Decreased appetite	16 (14)	7 (6)	9 (8)	0	39 (15)	23 (9)	16 (6)	0
Dry skin	18 (16)	18 (16)	0	0	33 (13)	32 (12)	1 (0.4)	0
Increased alanine aminotransferase	17 (15)	15 (13)	1 (1)	1 (1)	30 (12)	22 (9)	5 (2)	3 (1)
Vomiting	12 (11)	10 (9)	2 (2)	0	29 (11)	22 (9)	6 (2)	1 (0.4)
Myalgia	14 (12)	12 (11)	2 (2)	0	28 (11)	23 (9)	5 (2)	0
Dizziness	9 (8)	8 (7)	0	1 (1)	28 (11)	24 (9)	3 (1)	1 (0.4)
Headache	8 (7)	4 (4)	3 (3)	1 (1)	28 (11)	17 (7)	8 (3)	3 (1)

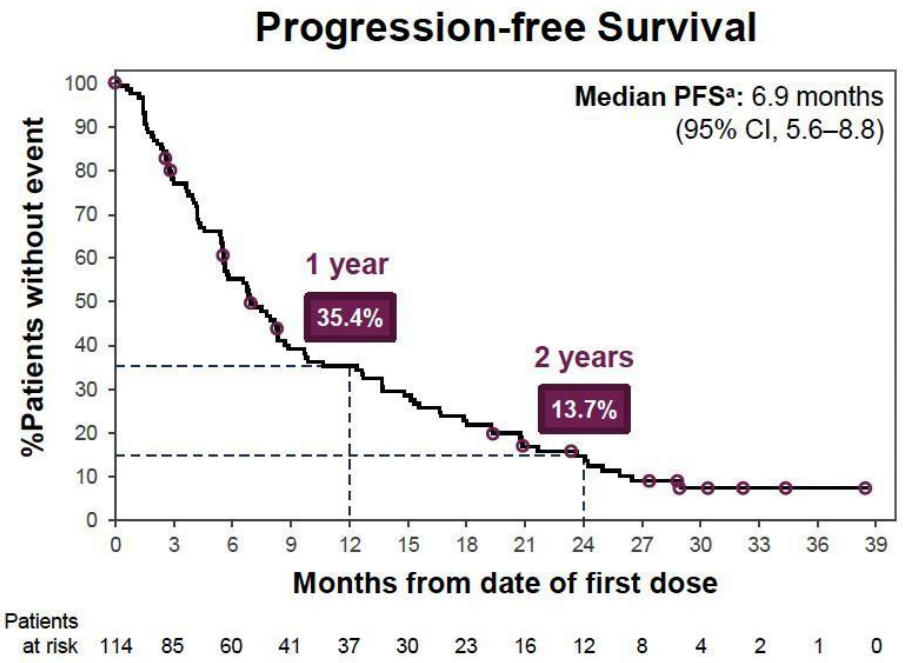
TABLE 2. Summary of AEs

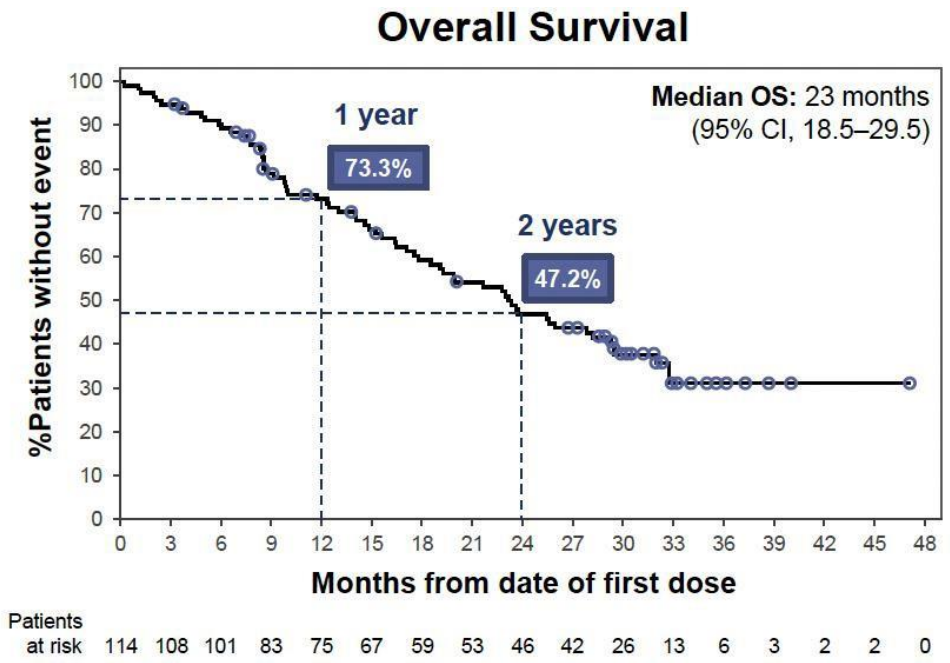
Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption[a]	40 (35)	88 (34)

Park, J Clin Oncol 2021

Exon20Ins- AMIVANTAMAB in PRETREATED- Chrysalis

Long-term outcomes





- Better if no alterations in RAS/RAF/MEK
- Better if Partial Response

- As of 12 Sept 2022, the median follow-up was 19.2 months and median duration of treatment was 7.5 months, with 48 of 114 (42%) patients alive

Garrido, ELCC 2023

15th CONGRESS on Lung CANCER 23&24 november 2023

PAPILLON

MADRID 2023 ESMO congress

Amivantamab Plus Chemotherapy vs Chemotherapy as First-line Treatment in *EGFR* Exon 20 Insertion–mutated Advanced Non-small Cell Lung Cancer (NSCLC)

Primary Results From PAPILLON, a Randomized Phase 3 Global Study

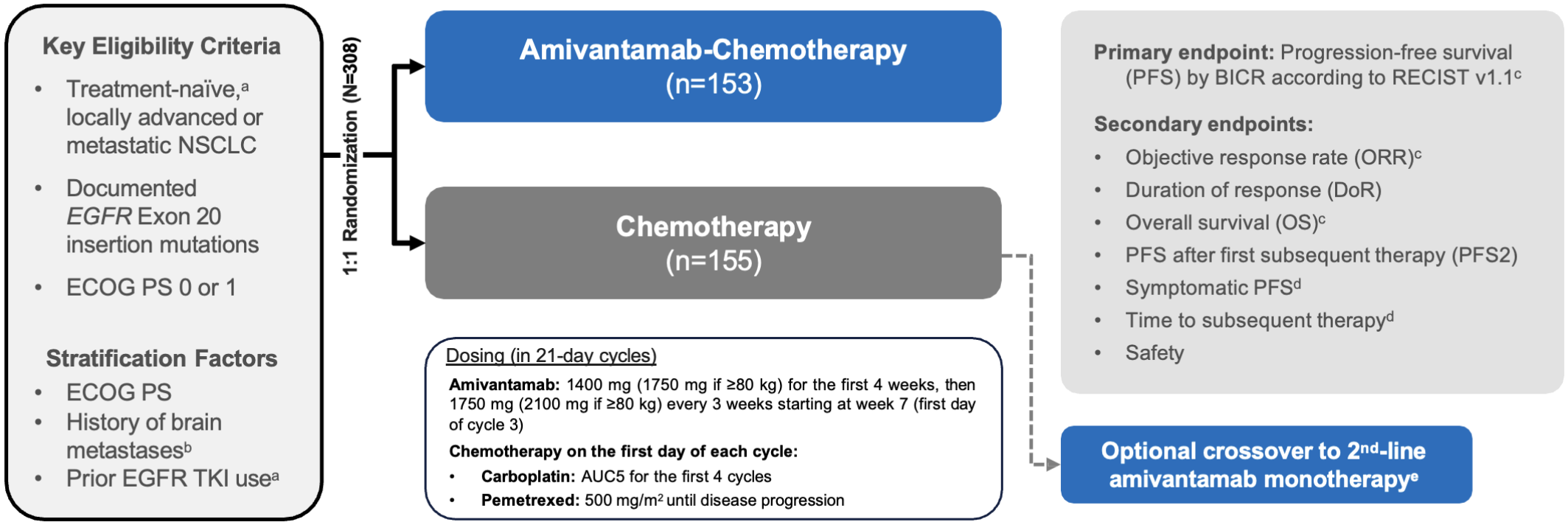
Nicolas Girard,[1] Keunchil Park,[2,*] Ke-Jing Tang,[3] Byoung Chul Cho,[4] Luis Paz-Ares,[5] Susanna Cheng,[6] Satoru Kitazono,[7] Muthukkumaran Thiagarajan,[8] Jonathan W. Goldman,[9] Joshua K. Sabari,[10] Rachel E. Sanborn,[11] Aaron S. Mansfield,[12] Jen-Yu Hung,[13] Sanjay Popat,[14] Josiane Mourão,[15] Archan Bhattacharya,[16] Trishala Agrawal,[17] S. Martin Shreeve,[18] Roland E. Knoblauch,[17] Caicun Zhou[19]

[1]Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France and Paris Saclay University, UVSQ, Versailles, France; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [4]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Hospital Universitario 12 de Octubre, Madrid, Spain; [6]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [7]Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [8]General Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [9]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA; [10]NYU Langone Health, New York, NY, USA; [11]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [14]Royal Marsden Hospital NHS Foundation Trust, London, UK and The Institute of Cancer Research, London, UK; [15]Barretos Cancer Hospital, Barretos, Brazil; [16]Janssen R&D, High Wycombe, UK; [17]Janssen R&D, Spring House, PA, USA; [18]Janssen R&D, San Diego, CA USA; [19]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.

*Current Affiliation: MD Anderson Cancer Center, Houston, TX, USA.

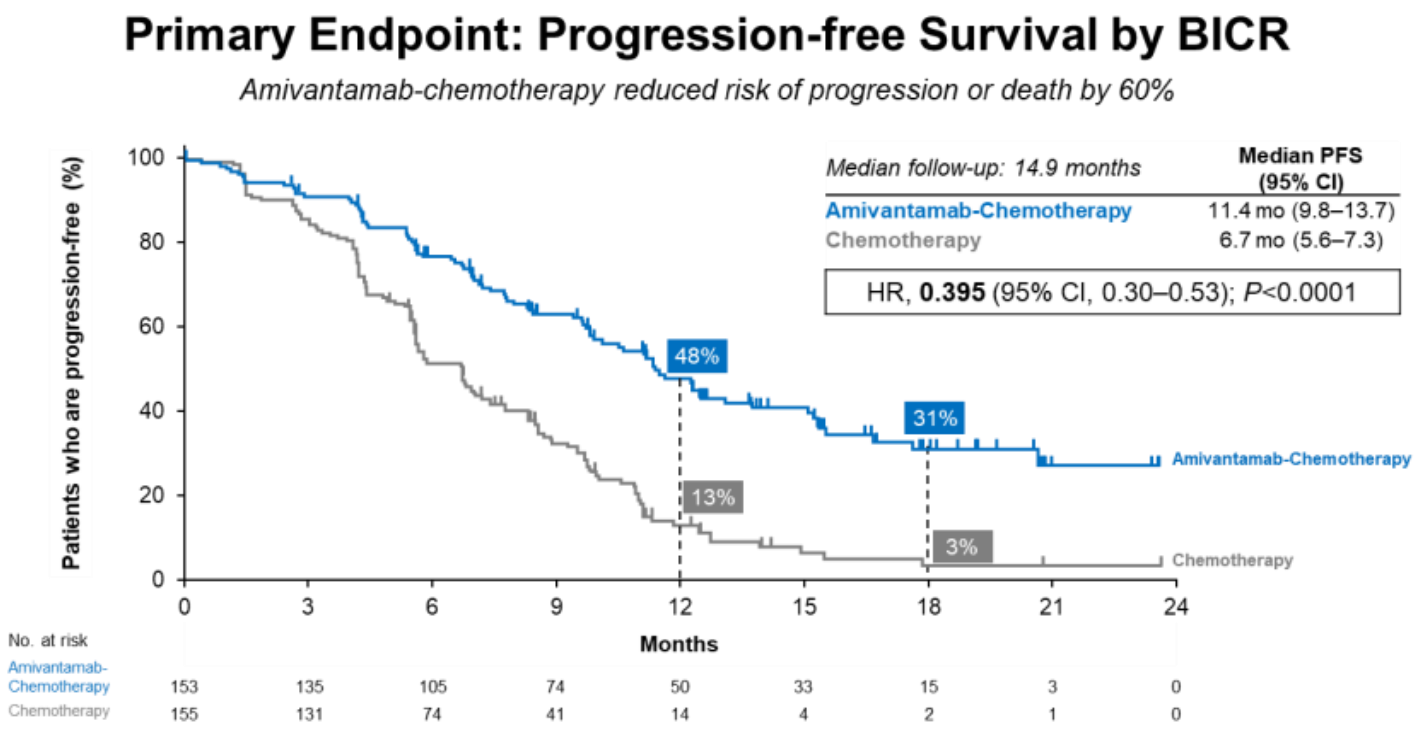
Exon20Ins – AMIVANTAMAB 1L - PAPILLON

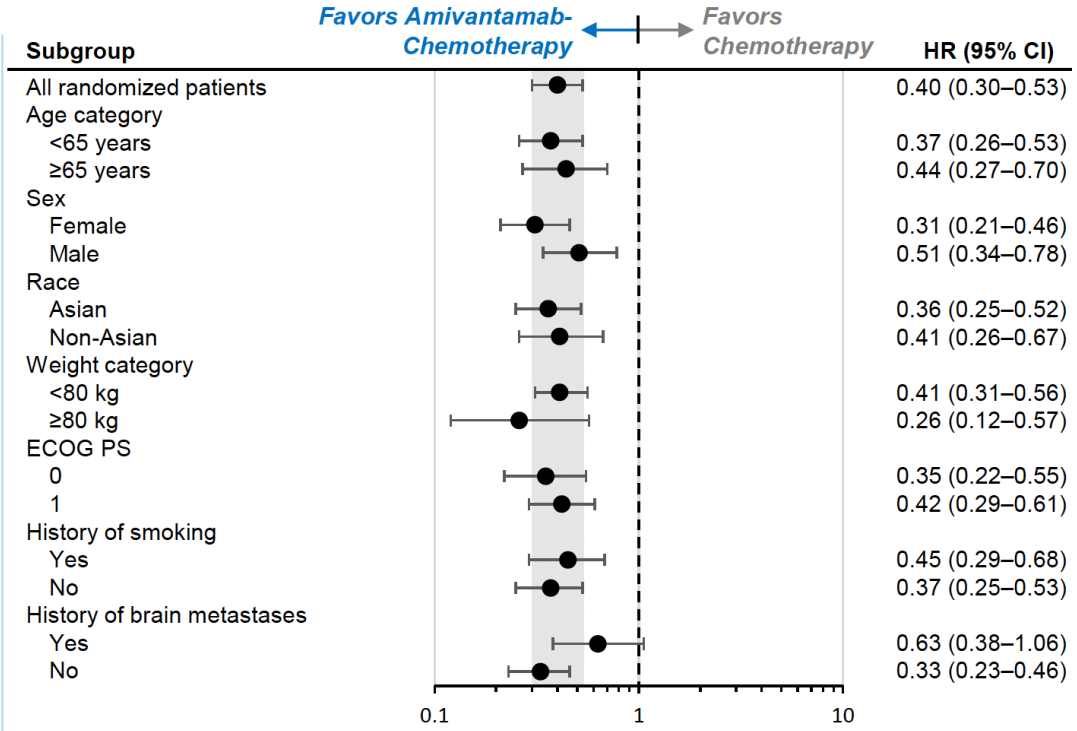
Study design



Exon20Ins – AMIVANTAMAB 1L - PAPILLON

Primary objective of the study: PFS by BICR





Consistent PFS benefit by investigator: 12.9 vs 6.9 mo(HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001a)

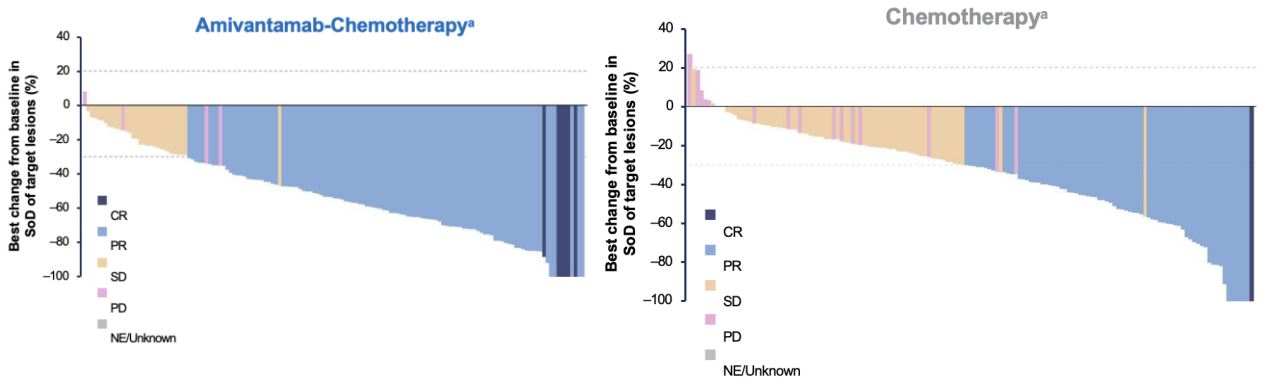
Girard, ESMO 2023

Exon20Ins – AMIVANTAMAB 1L - PAPILLON

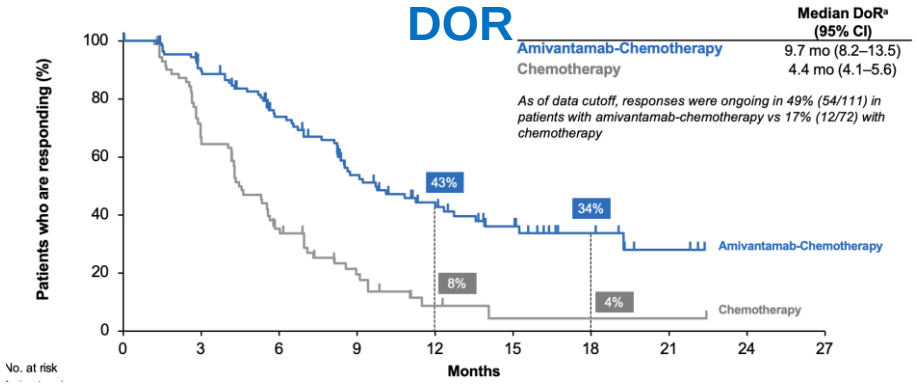
Efficacy data

BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)
Median time to response	6.7 wk (range, 5.1–72.5)	11.4 wk (range, 5.1–60.2)

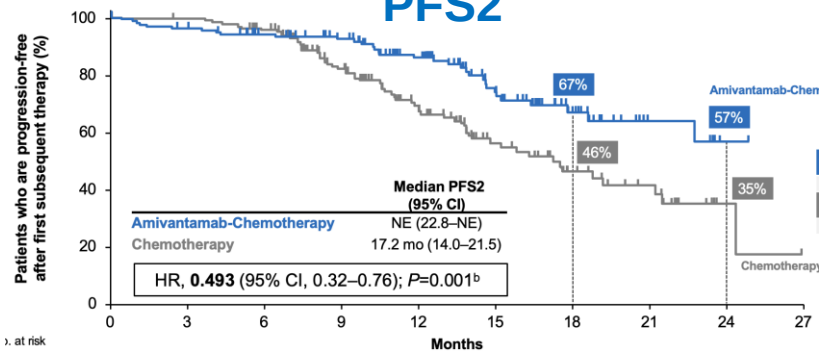
ORR



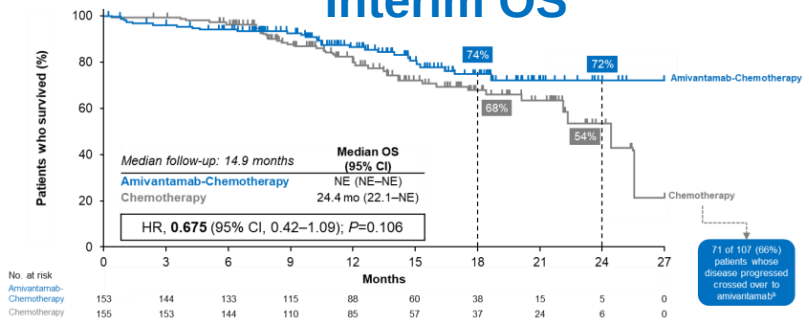
DOR



PFS2



Interim OS



Girard, ESMO 2023

Exon20Ins – AMIVANTAMAB 1L - PAPILLON

Safety data

	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Median treatment duration, months (range)	9.7 (0.1–26.9)	6.7 (0–25.3)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1–4)	4 (1–5)
Pemetrexed	13 (1–34)	10 (1–37)

Treatment-emergent AEs, n (%)	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Any AEs	151 (100)	152 (98)
Grade ≥3 AEs	114 (75)	83 (54)
Serious AEs	56 (37)	48 (31)
AEs leading to death	7 (5)	4 (3)
Any AE leading to treatment:		
Interruptions of any agent	104 (69)	56 (36)
Related interruptions of amivantamab	63 (42)	–
Reductions of any agent	73 (48)	35 (23)
Related reductions of amivantamab	54 (36)	–
Discontinuations of any agent	36 (24)	16 (10)
Related discontinuations of amivantamab	10 (7)	–
Discontinuations of all study agents due to AEs	12 (8)	12 (8)

- Similar rate of serious AEs, AEs leading to death and discontinuation due to AEs.
- Treatment-related discontinuations of amivantamab wer low (7%)

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

- EGFR- and MET-related AEs were increased, primarily grade 1-2
- CT-associated hematologic and GI toxicities were comparable except neutropenia
- Neutropenia was transient; majority of events were not serious, low discontinuations
- Pneumonitis was reported in 4 (3%) Amivantamab + CT

Girard, ESMO 2023

Exon20Ins – AMIVANTAMAB 1L - PAPILLON

Safety data

	Amivantamab-Chemotherapy (n=151)	Chemotherapy (n=155)
Median treatment duration, months (range)	9.7 (0.1–26.9)	6.7 (0–25.3)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1–4)	4 (1–5)
Pemetrexed	13 (1–34)	10 (1–37)
Interruptions of any agent	104 (69)	56 (36)
Related interruptions of amivantamab	63 (42)	–
Reductions of any agent	73 (48)	35 (23)
Related reductions of amivantamab	54 (36)	–
Discontinuations of any agent	36 (24)	16 (10)
Related discontinuations of amivantamab	10 (7)	–
Discontinuations of all study agents due to AEs	12 (8)	12 (8)

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

Amivantamab-chemotherapy represents the new standard of care for first-line *EGFR* Ex20ins advanced NSCLC

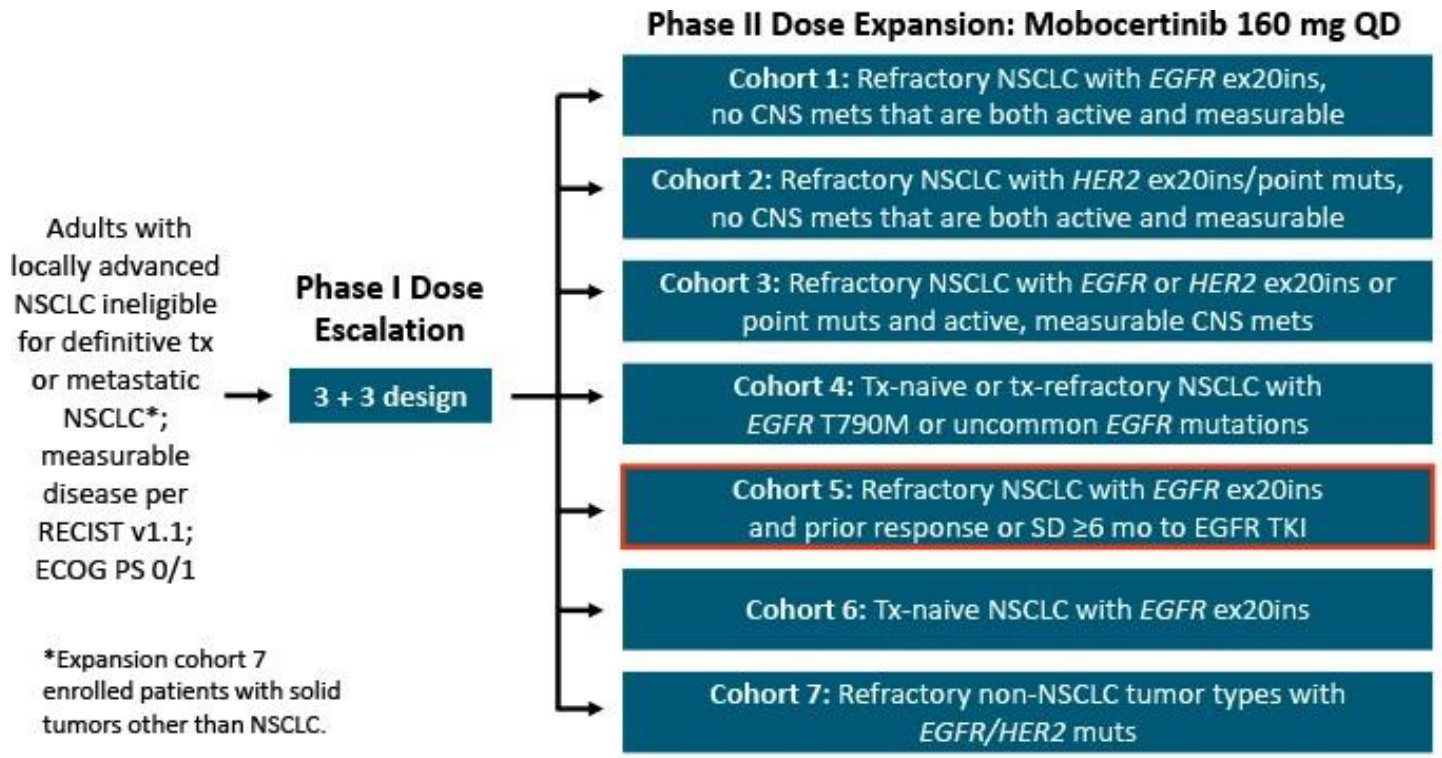
- Similar rate of serious AEs, AEs leading to death and discontinuation due to AEs.
- Treatment-related discontinuations of amivantamab wer low (7%)

- EGFR- and MET-related AEs were increased, primarily grade 1-2
- CT-associated hematologic and GI toxicities were comparable except neutropenia
- Neutropenia was transient; majority of events were not serious, low discontinuations
- Pneumonitis was reported in 4 (3%) Amivantamab + CT

Girard, ESMO 2023

Exon20Ins – MOBOCERTINIB in PRETREATED – EXCLAIM Trial

Exclaim Trial



EXCLAIM Extension Cohort: previously treated advanced NSCLC with *EGFR* ex20ins

Current analysis:

- Patients with refractory *EGFR* ex20ins+ metastatic NSCLC with disease progression after response or SD for ≥6 mo on prior EGFR TKI therapy (n = 20)
  - Data cutoff: November 1, 2020
  - Median f/u: 14.2 mo (range: 5.2-21.2)

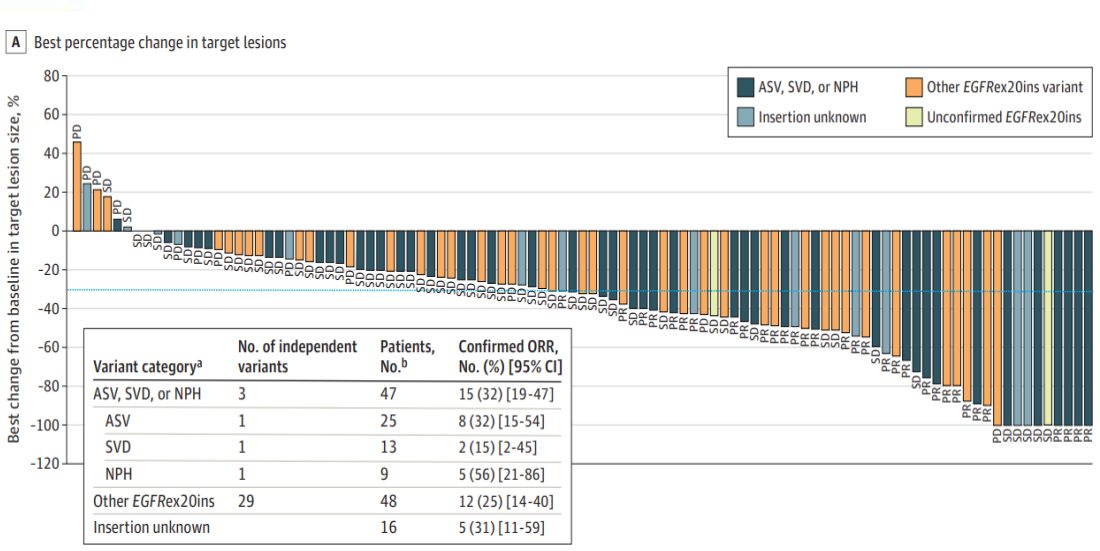
- **Primary endpoint (phase II):** ORR by RECIST v1.1
- **Select secondary endpoints (phase II):** ORR by IRC, BOR, DCR, DoR, TTR, PFS, OS, safety/tolerability

Spia, WCLC 2021; Zhou, JAMA Oncol 2021

Exon20Ins – MOBOCERTINIB in PRETREATED – EXCLAIM Trial

Mobocertinib efficacy

Parameter	PPP Cohort (N=114)	EXCLAIM Cohort (N=96)
Median time on treatment, mo (range)	7.0 (0–31)	6.5 (0–14)
Confirmed ORR per IRC, n (%) [95% CI]	30 (26) [19–35]	22 (23) [15–33]
Confirmed ORR per investigator, n (%) [95% CI]	40 (35) [26–45]	31 (32) [23–43]
Median DOR per IRC, mo [95% CI][a]	17.5 (8.3–NE)	NE (8.3–NE)
Median DOR per investigator, mo [95% CI][a]	13.9 (5.6–NE)	NE (5.5–NE)
DCR per IRC, n (%) [95% CI][b]	89 (78) [69–85]	73 (76) [66–84]
DCR per investigator, n (%) [95% CI][b]	89 (78) [69–85]	72 (75) [65–83]
Median PFS per IRC, mo [95% CI]	7.3 (5.5–10.2)	7.3 (5.5–10.2)
Median PFS per investigator, mo [95% CI]	7.3 (5.5–8.1)	7.1 (5.6–7.8)



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]

- 78% and 84% of patients had DOR >6 months in PPP and EXCLAIM cohorts, respectively (per IRC)
- At the time of data cutoff, over 50% of responses were ongoing in both cohorts

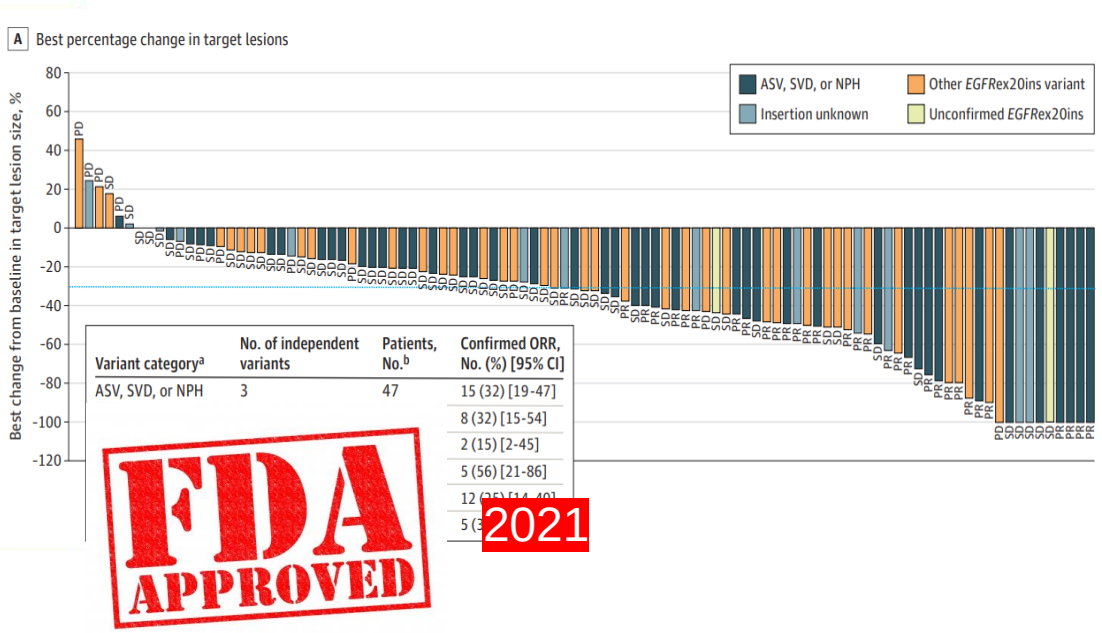
Spia, WCLC 2021; Zhou, JAMA Oncol 2021

Exon20Ins – MOBOCERTINIB in PRETREATED – EXCLAIM Trial

Mobocertinib efficacy

Parameter	PPP Cohort (N=114)	EXCLAIM Cohort (N=96)
Median time on treatment, mo (range)	7.0 (0–31)	6.5 (0–14)
Confirmed ORR per IRC, n (%) [95% CI]	30 (26) [19–35]	22 (23) [15–33]
Confirmed ORR per investigator, n (%) [95% CI]	40 (35) [26–45]	31 (32) [23–43]
Median DOR per IRC, mo [95% CI][a]	17.5 (8.3–NE)	NE (8.3–NE)
Median DOR per investigator, mo [95% CI][a]	13.9 (5.6–NE)	NE (5.5–NE)
DCR per IRC, n (%) [95% CI][b]	89 (78) [69–85]	73 (76) [66–84]
DCR per investigator, n (%) [95% CI][b]	89 (78) [69–85]	72 (75) [65–83]
Median PFS per IRC, mo [95% CI]	7.3 (5.5–10.2)	7.3 (5.5–10.2)
Median PFS per investigator, mo [95% CI]	7.3 (5.5–8.1)	7.1 (5.6–7.8)

- 78% and 84% of patients had DOR >6 months in PPP and EXCLAIM cohorts, respectively (per IRC)
- At the time of data cutoff, over 50% of responses were ongoing in both cohorts

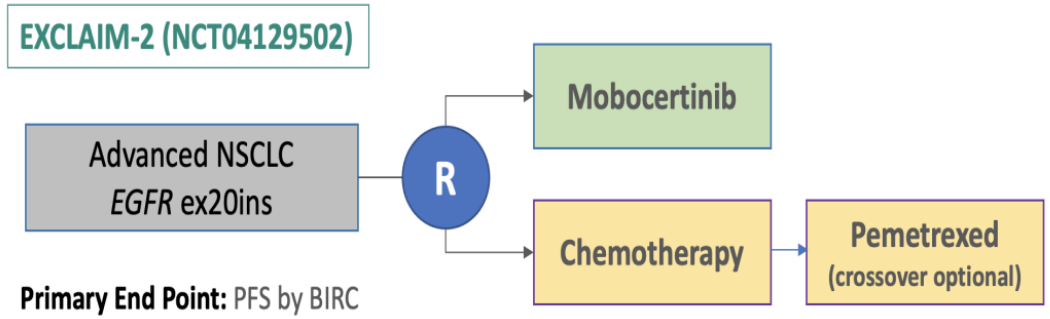


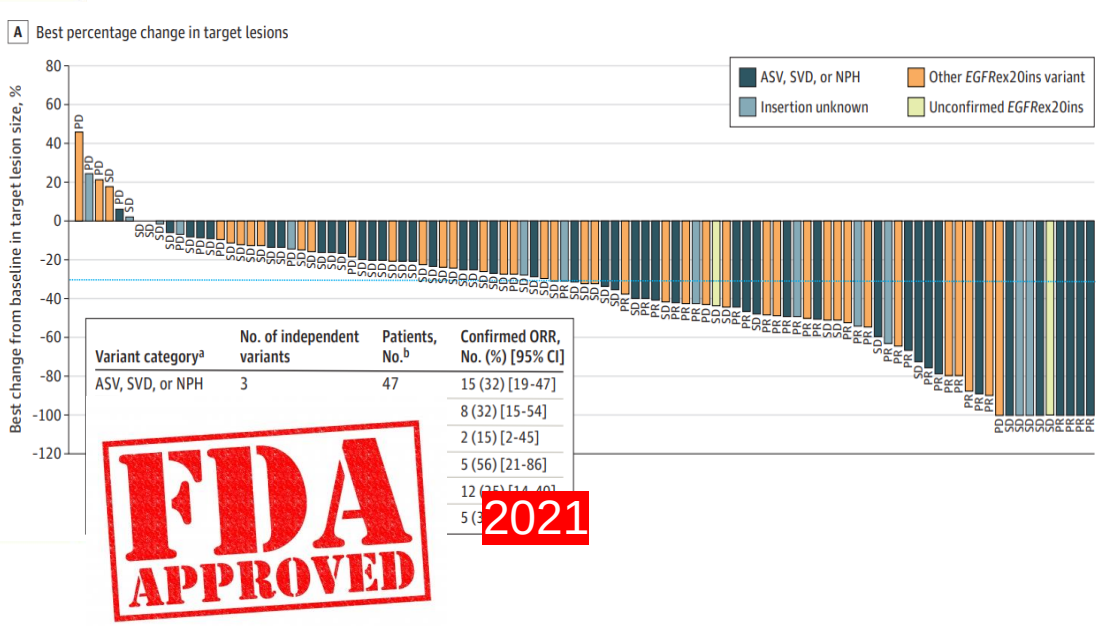
Exon20Ins – MOBOCERTINIB in PRETREATED – EXCLAIM Trial

Mobocertinib efficacy

Parameter	PPP Cohort (N=114)	EXCLAIM Cohort (N=96)
Median time on treatment, mo (range)	7.0 (0–31)	6.5 (0–14)
Confirmed ORR per IRC, n (%) [95% CI]	30 (26) [19–35]	22 (23) [15–33]
Confirmed ORR per investigator, n (%) [95% CI]	40 (35) [26–45]	31 (32) [23–43]
Median DOR per IRC, mo [95% CI][a]	17.5 (8.3–NE)	NE (8.3–NE)
Median DOR per investigator, mo [95% CI][a]	13.9 (5.6–NE)	NE (5.5–NE)
DCR per IRC, n (%) [95% CI][b]	89 (78) [69–85]	73 (76) [66–84]
DCR per investigator, n (%) [95% CI][b]	89 (78) [69–85]	72 (75) [65–83]
Median PFS per IRC, mo [95% CI]	7.3 (5.5–10.2)	7.3 (5.5–10.2)
Median PFS per investigator, mo [95% CI]	7.3 (5.5–8.1)	7.1 (5.6–7.8)

- 78% and 84% of patients had DOR >6 months in PPP and EXCLAIM cohorts, respectively (per IRC)
- At the time of data cutoff, over 50% of responses were ongoing in both cohorts





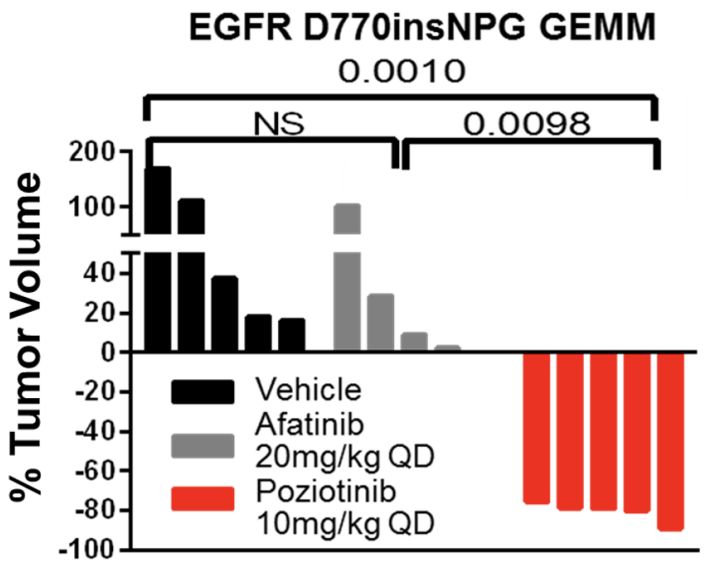
Press release on Oct. 02, 2023

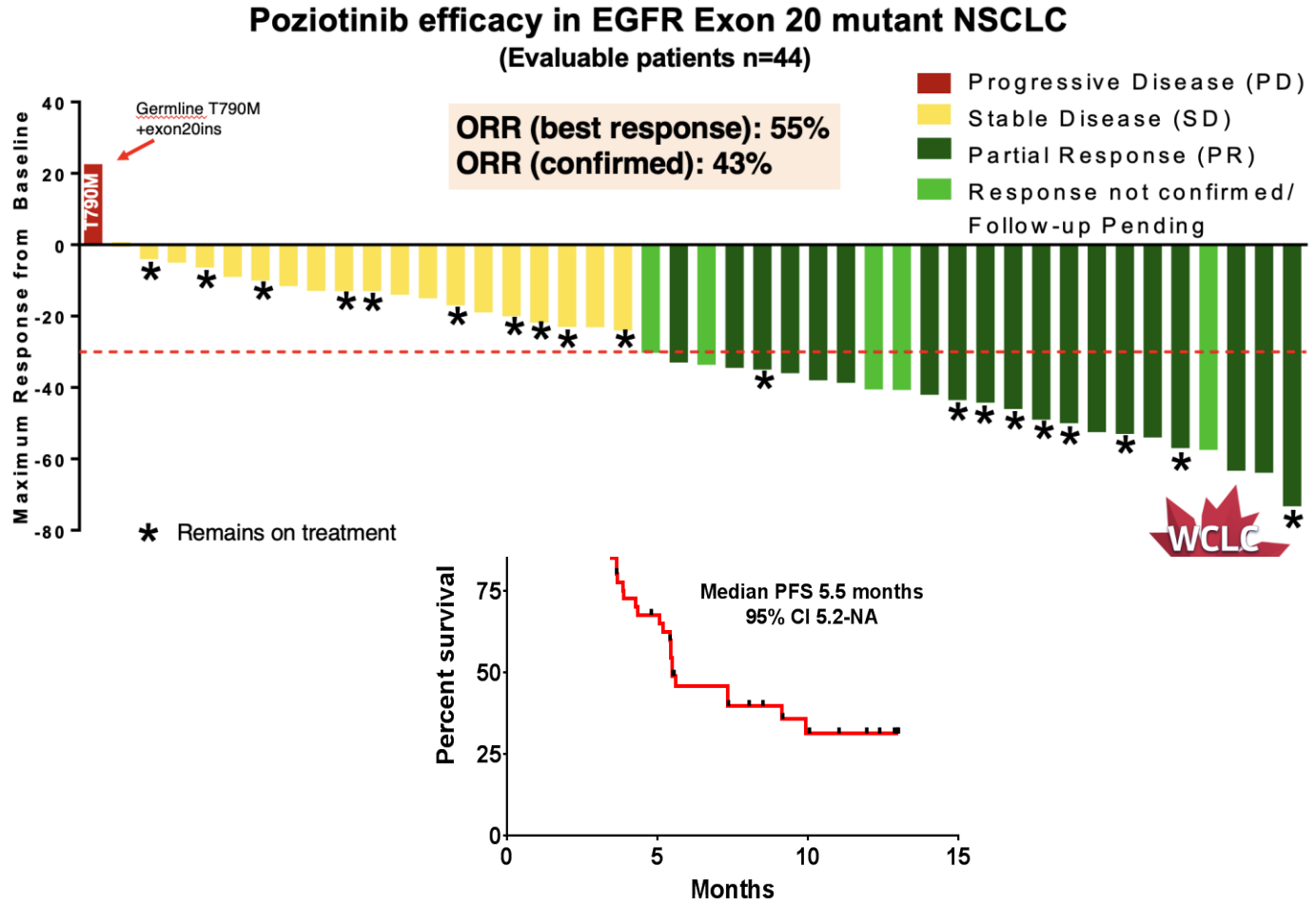
Voluntary withdrawal of mobocertinibin the U.S. based on the outcome of the Phase 3 EXCLAIM-2 which **did not meet its primary endpoint**.

Spia, WCLC 2021; Zhou, JAMA Oncol 2021

Exon20Ins – POZIOTINIB in PRETREATED – ZENITH20 (multicohort phase II)

ZENITH20 Poziotinib efficacy in cohort 1 EGFR Exon20ins





Heymach, WCLC 2018

Exon20Ins-directed therapies in pretreated pts: efficacy and toxicity summary

			Efficacy		Toxicity		
Drug	Study	N	ORR	mPFS	Rash all/G3	Diarrhoea	Other
Mobocertinib	II	114	28%	7,3 mo	45%/0%	91%/21%	
Poziotinib	II	42	31%	5,5 mo	90%/34%	92%/22%	
Sunvozertinib	II	104	61%	NR	80%/1%	20%/3%	
Zipalertinib	I/IIa	73	38,4%	10 mo	80%/1%	30%/3%	
Furmonertinib	II	26	46%	NR	21%/0%	86%/0%	

Zhou, JAMA Oncol 2022, Elamin, Cancer Cell 2022, Wang, ASCO 2023; Piatrowska, J Clin Oncol 2023; Han, WCLC 2023

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OTHER UNCOMMON MUTATIONS

1st Generation TKIs

- Not included in pivotal trials
- Retrospective and case reports

2nd Generation TKIs

- Lux-lung 2/3/6 included 11% patients with uncommon mutations (100 uncommon, 75 receiving afatinib
- AFANDA ambispective cohort study with dacomitinib or afatinib

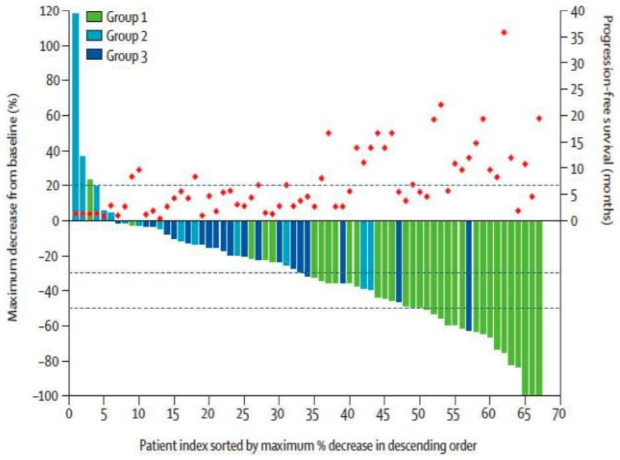
3rd Generation TKIs

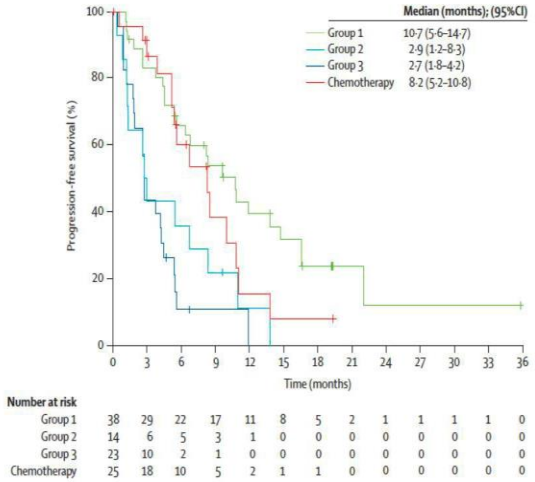
- Retrospective multicenter UNICORN study: 60 pts treated with osimertinib
  - -Group A: uncommon.
  - -Group B: common + uncommon
- Phase II UNICORN study with osimertinib: 40 pts
- Phase II *KCSG-LU15-09* study with osimertinib: 35 pts

OTHER UNCOMMON MUTATIONS: AFATINIB 1L

2nd Generation TKIs: AFATINIB Lux-Lung 2/3/6 pool

838 pts randomly assigned LL2/3/6 → 100 uncommon EGFRm → 75 receiving afatinib





	Objective response	Duration of response (months)	Disease control	Progression-free survival (months)	Overall survival (months)
Group 1 (n=38)*	27 (71·1%, 54·1–84·6)	11·1 (4·1–15·2)	32 (84·2%, 68·7–94·0)	10·7 (5·6–14·7)	19·4 (16·4–26·9)
Group 2 (n=14)†	2 (14·3%, 1·8–42·8)	8·2 (4·1–12·4)	9 (64·3%, 35·1–87·2)	2·9 (1·2–8·3)	14·9 (8·1–24·9)
Group 3 (n=23)‡	2 (8·7%, 1·1–28·0)	7·1 (4·2–10·1)	15 (65·2%, 42·7–83·6)	2·7 (1·8–4·2)	9·2 (4·1–14·2)

Data are n (%, 95% CI) or median (95% CI). *Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others). †Consists of patients with de-novo Thr790Met mutations. ‡Consists of patients with exon 20 insertions.

European Lung

Genotypes		ORR, n (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)
G719X (n=18)	G719X (n=8) G719X + T790M (n=1) G719X + S768I (n=5) G719X + L861Q (n=3) G719X + T790M + L858R (n=1)	14 (78)	13.8 (6.8-NE)	26.9 (16.4-NE)
L861Q (n=16)	L861Q (n=12) L861Q + G719X (n=3) L861Q + Del19 (n=1)	9 (56)	8.2 (4.5-16.6)	16.9 (15.3-22.0)
S768I (n=8)	S768I (n=1) S768I + G719X (n=5) S768I + L858R (n=2)	8 (100)	14.7 (2.6-NE)	NE (3.4-NE)

Note: A patient may be presented in more than 1 category.

Yang, Lancet Oncol 2015

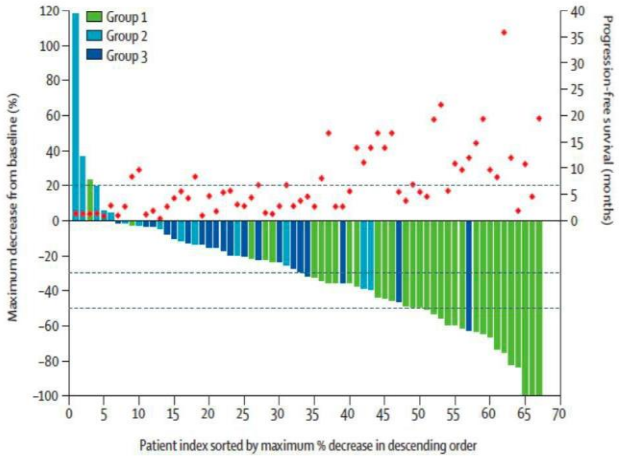
OTHER UNCOMMON MUTATIONS: AFATINIB 1L

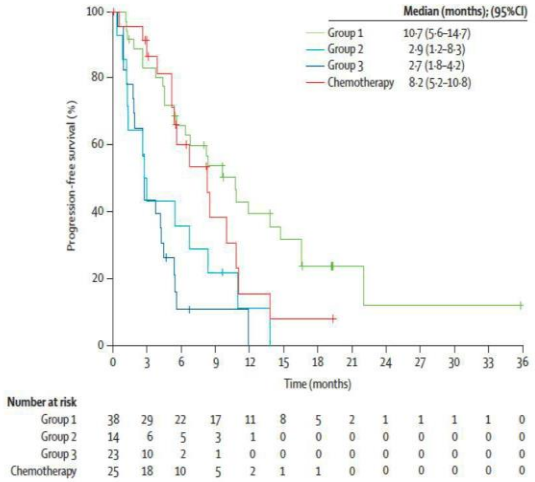
FDA APPROVED 2018

L861Q, G719X and S768I.

2nd Generation TKIs: AFATINIB Lux-Lung 2/3/6 pool

838 pts randomly assigned LL2/3/6 → 100 uncommon EGFRm → 75 receiving afatinib





	Objective response	Duration of response (months)	Disease control	Progression-free survival (months)	Overall survival (months)
Group 1 (n=38)*	27 (71·1%, 54·1–84·6)	11·1 (4·1–15·2)	32 (84·2%, 68·7–94·0)	10·7 (5·6–14·7)	19·4 (16·4–26·9)
Group 2 (n=14)†	2 (14·3%, 1·8–42·8)	8·2 (4·1–12·4)	9 (64·3%, 35·1–87·2)	2·9 (1·2–8·3)	14·9 (8·1–24·9)
Group 3 (n=23)‡	2 (8·7%, 1·1–28·0)	7·1 (4·2–10·1)	15 (65·2%, 42·7–83·6)	2·7 (1·8–4·2)	9·2 (4·1–14·2)

Data are n (%, 95% CI) or median (95% CI). *Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others). †Consists of patients with de-novo Thr790Met mutations. ‡Consists of patients with exon 20 insertions.

European Lung

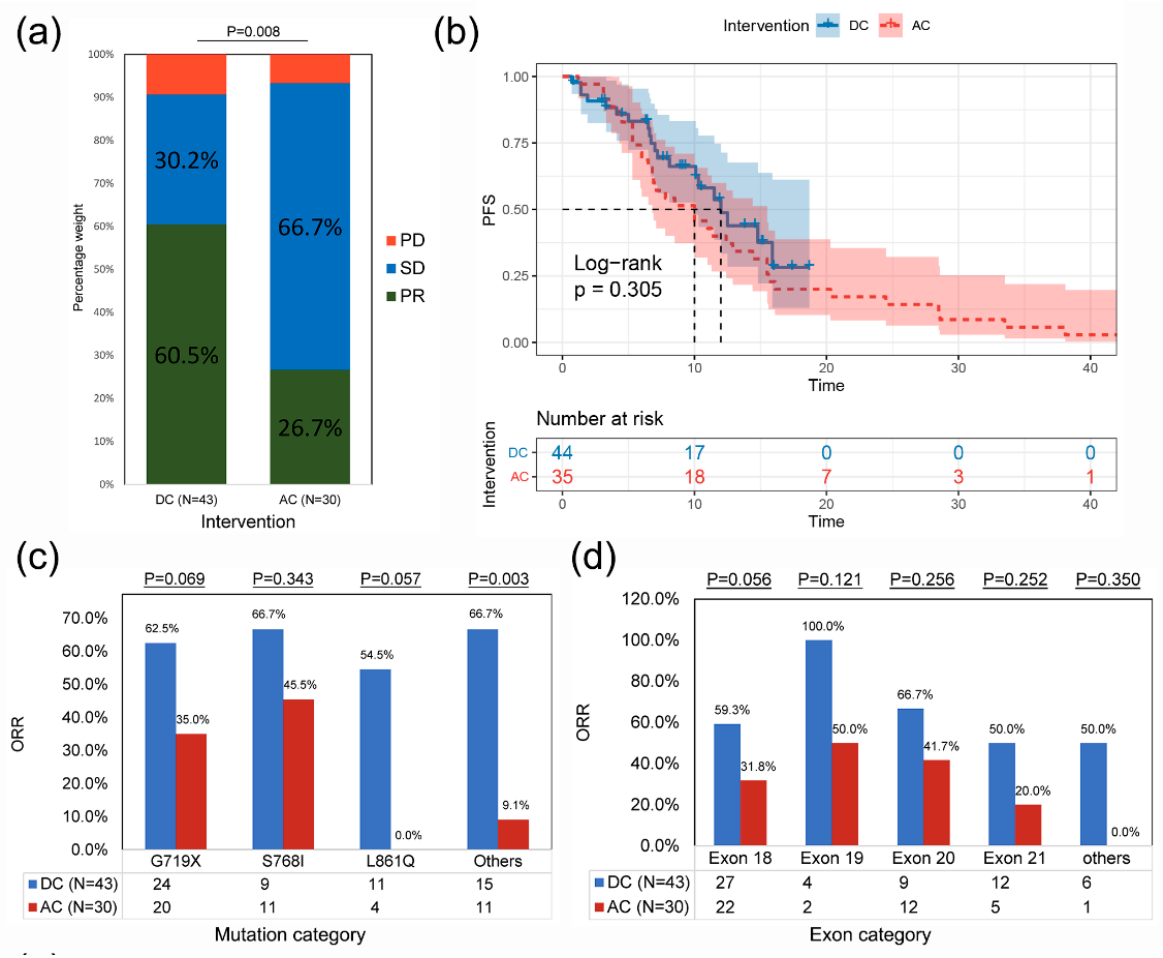
Genotypes		ORR, n (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)
G719X (n=18)	G719X (n=8) G719X + T790M (n=1) G719X + S768I (n=5) G719X + L861Q (n=3) G719X + T790M + L858R (n=1)	14 (78)	13.8 (6.8-NE)	26.9 (16.4-NE)
L861Q (n=16)	L861Q (n=12) L861Q + G719X (n=3) L861Q + Del19 (n=1)	9 (56)	8.2 (4.5-16.6)	16.9 (15.3-22.0)
S768I (n=8)	S768I (n=1) S768I + G719X (n=5) S768I + L858R (n=2)	8 (100)	14.7 (2.6-NE)	NE (3.4-NE)

Note: A patient may be presented in more than 1 category.

Yang, Lancet Oncol 2015

OTHER UNCOMMON MUTATIONS: DACOMITINIB 1L

2nd Generation TKIs: DACOMITINIB – AFANDA ambispective cohort study in China



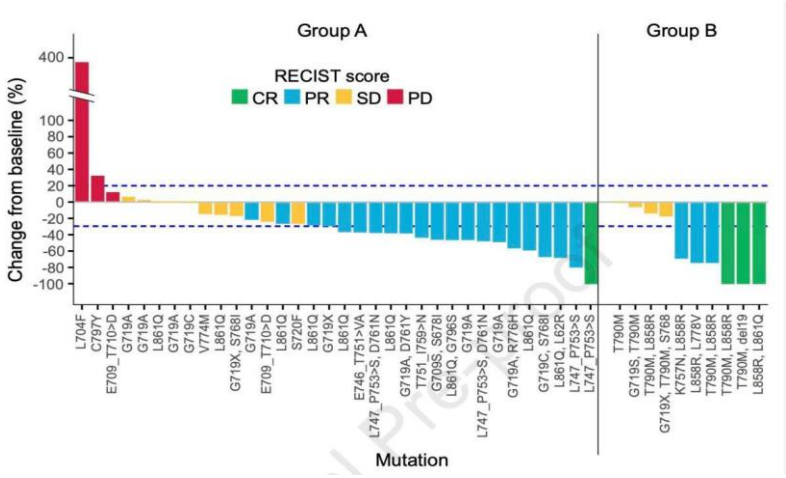
Li, Cancers 2022

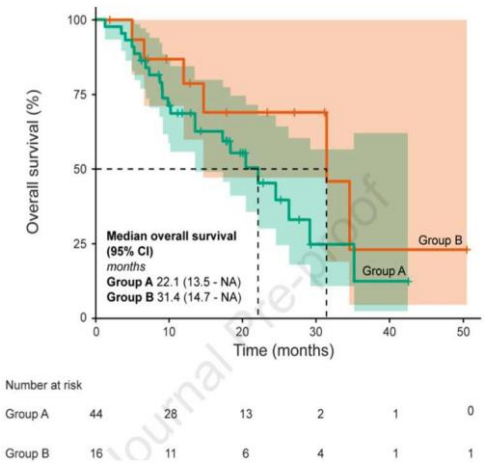
OTHER UNCOMMON MUTATIONS – OSIMERTINIB 1L

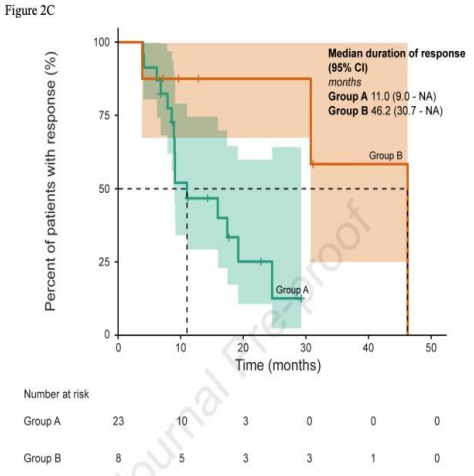
3rd Generation TKIs: UNICORN retrospective

Table 2. Efficacy of Osimertinib in Various Subgroups

Patient Subgroups	n (% of 60)	RR[a] (95% CI)	PFS, mo (95% CI)	OS, mo (95% CI)	DOR, mo (95% CI)
All patients	60 (100)	61 (47-73)	9.5 (8.5-17.4)	24.5 (17.4-35.1)	17.4 (9.1-NA)
Group A: only uncommon	44 (73)	60 (45-74)	8.6 (7.3-13.5)	22.1 (13.5-NA)	11.0 (9.0-NA)
Group B: uncommon with L858R/del19[b]/T790M	16 (27)	61 (35-82)	30.0 (12.7-NA)	31.4 (14.7-NA)	46.2 (30.7-NA)
G719X	18 (30)	47 (26-69)	8.8 (7.9-NA)	NA (17.4-NA)	9.1 (8.6-NA)
G719X, group A	16 (27)	53 (30-75)	8.6 (6.9-NA)	18.4 (10.2-NA)	9.1 (8.6-NA)
L861Q	12 (20)	80 (49-94)	16 (11-NA)	26.3 (22.1-NA)	16 (11-NA)
L861Q, group A	11 (18)	78 (45-94)	15.7 (8.9-18.8)	25.9 (21.8-NA)	16.0 (9.0-NA)
T790M	9 (15)	44 (19-73)	12.7 (9.5-NA)	NA (12-NA)	46.2 (3.8-NA)
TP53 mutant	21 (35)	60 (36-80)	8.5 (6.8-22.1)	26.3 (13.5-NA)	9.0 (7.9-NA)







Bar, J Thor Oncol 2022

OTHER UNCOMMON MUTATIONS – OSIMERTINIB 1L

3rd Generation TKIs: UNICORN phase II (Tokyo Cooperative Oncology Group)

Solitary mutations (n = 22)	
Overall response rate, % (90% CI)	45.5 (26.9-65.3)
Disease control rate, % (95% CI)	81.8 (61.5-92.7)
Progression-free survival, median (95% CI), mo	5.4 (3.6-22.7)
Overall survival, median (95% CI), mo	23.0 (12.3-NR)
Duration of response, median (95% CI), mo	22.7 (3.6-22.7)

Compound mutations (n = 18)	
Overall response rate, % (90% CI)	66.7 (43.7-83.7)
Disease control rate, % (95% CI)	100.0 (82.4-100)
Progression-free survival, median (95% CI), mo	9.8 (5.1-NR)
Overall survival, median (95% CI), mo	NR
Duration of response, median (95% CI), mo	NR (5.7-NR)

Okuma, JAMA Oncol 2023

OTHER UNCOMMON MUTATIONS – OSIMERTINIB 1L

3rd Generation TKIs: UNICORN phase II (Tokyo Cooperative Oncology Group)

Solitary mutations (n = 22)	
Overall response rate, % (90% CI)	45.5 (26.9-65.3)
Disease control rate, % (95% CI)	81.8 (61.5-92.7)
Progression-free survival, median (95% CI), mo	5.4 (3.6-22.7)
Overall survival, median (95% CI), mo	23.0 (12.3-NR)
Duration of response, median (95% CI), mo	22.7 (3.6-22.7)

Compound mutations (n = 18)	
Overall response rate, % (90% CI)	66.7 (43.7-83.7)
Disease control rate, % (95% CI)	100.0 (82.4-100)
Progression-free survival, median (95% CI), mo	9.8 (5.1-NR)
Overall survival, median (95% CI), mo	NR
Duration of response, median (95% CI), mo	NR (5.7-NR)

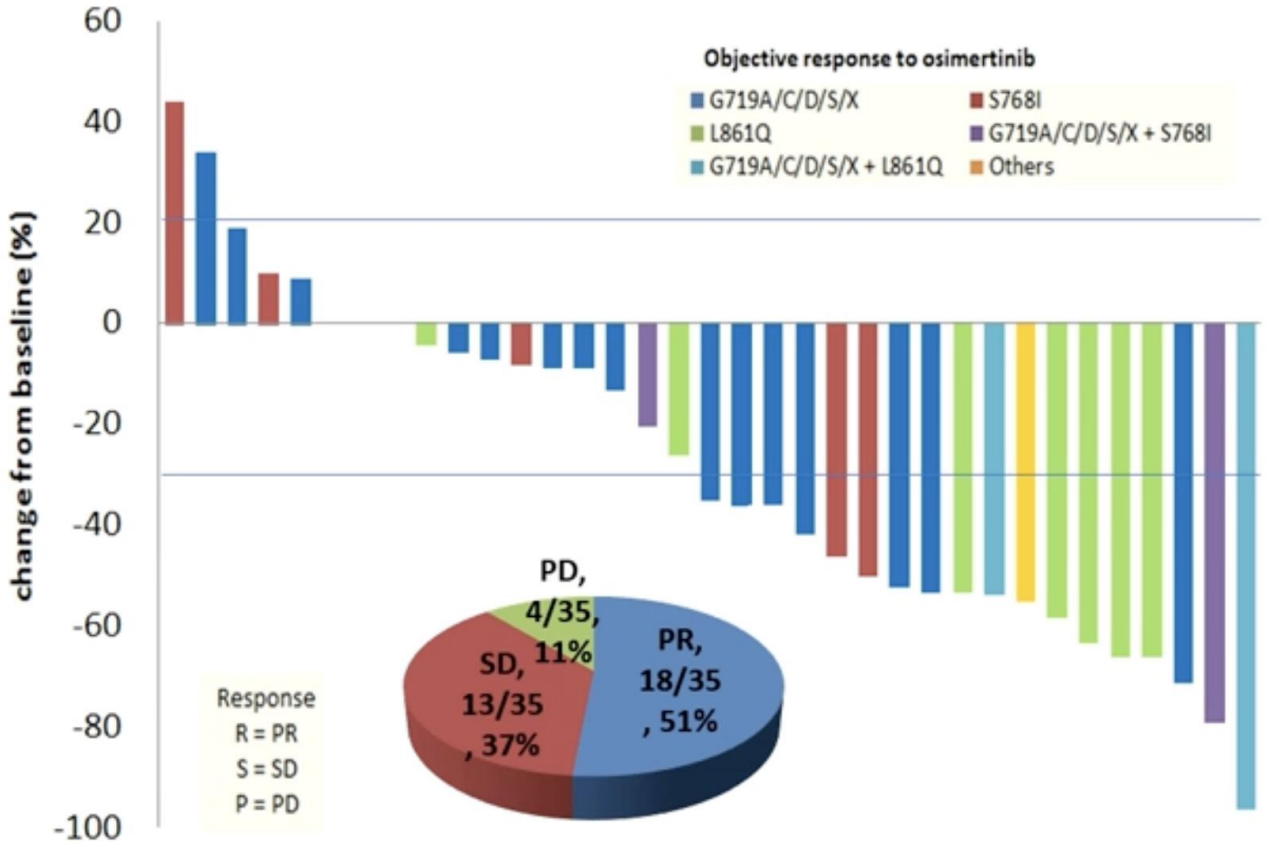
Uncommon and uncommon mutations (n = 11)	
Overall response rate, % (90% CI)	54.5 (28.0-78.7)
Disease control rate, % (95% CI)	100.0 (74.1-100.0)
Progression-free survival, median (95% CI), mo	9.7 (3.7-NR)
Overall survival, median (95% CI), mo	NR (9.8-NR)
Duration of response, median (95% CI), mo	NR (5.6-22.7)

Common and uncommon mutations (n = 7)	
Overall response rate, % (90% CI)	85.7 (54.8-96.0)
Disease control rate, % (95% CI)	100.0 (64.6-100.0)
Progression-free survival, median (95% CI), mo	15.2 (2.9-NR)
Overall survival, median (95% CI), mo	NR (9.7-NR)
Duration of response, median (95% CI), mo	NR (5.8-NR)

Okuma, JAMA Oncol 2023

OTHER UNCOMMON MUTATIONS – OSIMERTINIB 1L

3rd Generation TKIs: KCSG-LU15-09 phase II



L861Q: RR 78%

Clinical response	Osimertinib (n=35)
Objective response rate (95% CI)	51% (34, 68)
Disease control rate (95% CI)	89% (78, 99)
Median progression-free survival, months (95% CI)	8.0 (5.7, 10.3)
Median overall survival, months (95% CI)	27.0 (19.3, 34.7)
Median duration of response, months (95% CI)	13.0 (9.1, 16.9)
Median progression-free survival 2, months (95% CI)	16.0 (8.5, 23.5)

- **Median follow-up duration**: 61.0 months

Cho, J Clin Oncol 2019; Cho, WCLC 2023

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

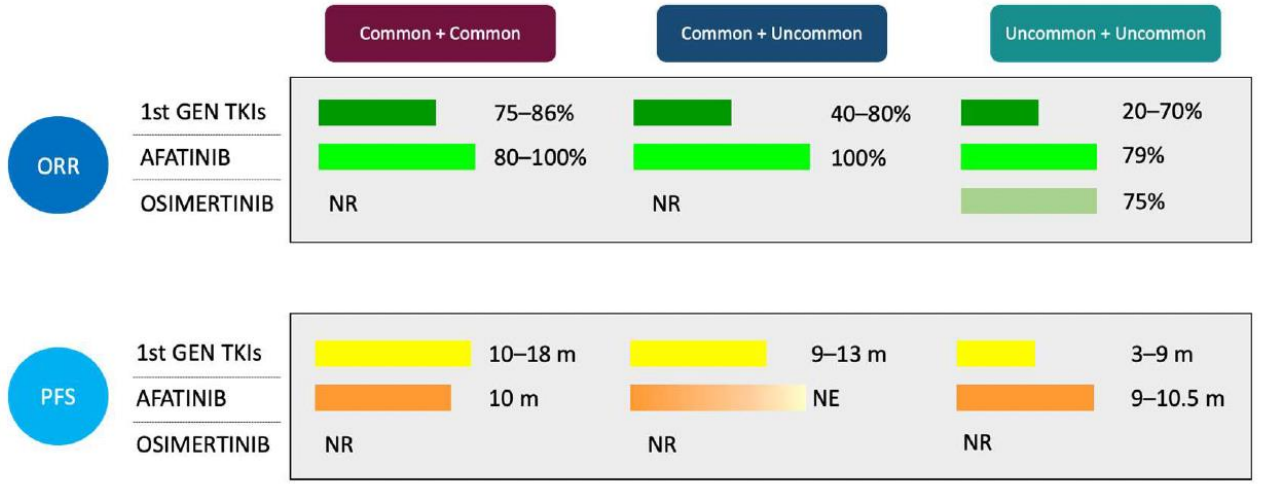
OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

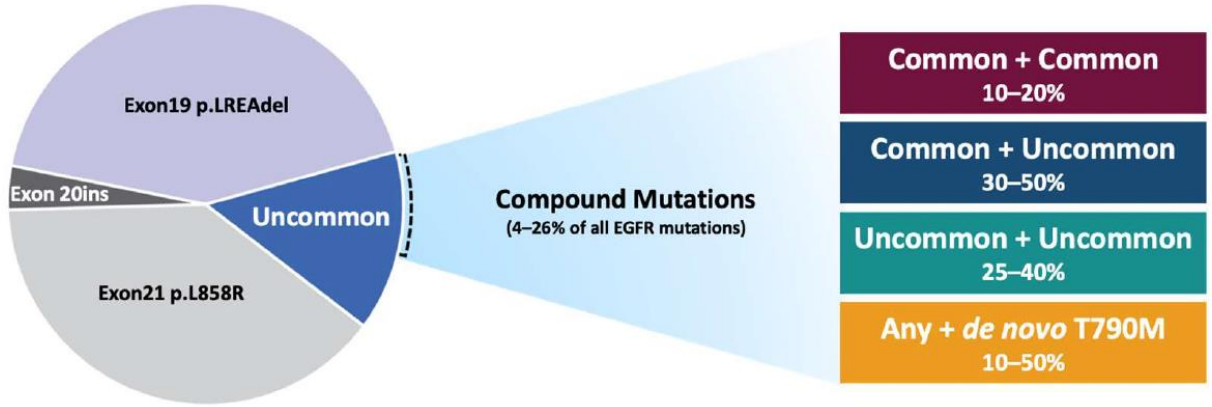
COMPOUND EGFR MUTATIONS

Frequency and subtypes according to a 2022 Systematic Review

Study	Region	Patients Screened (N)	Testing Method	*EGFR* Mut Rate (N, %)	*EGFR* Compound Mut Rate (N, % of *EGFR* Mut)
Syahruddin et al., 2018 [7]	Indonesian	1779	PCR HRM RFLP	791 (44.4)	154 (19.5)
Zaini et al., 2019 [8]	Indonesian	116	PCR HRM RFLP	69 (63.2)	18 (26)
Jing et al., 2018 [9]	China	112	NGS	58 (51.8)	11 (18.9)
Mao et al., 2021 [11]	China	21,324	NGS + qPCR + Sanger	9,621 (47.5)	642 (6.7)
Wen et al., 2019 [14]	China	1200	NGS	571(47.6)	87 (15.3)
Zhou et al., 2021 [12]	SW China (Q vs. non-Q)	2146	ARMS-PCR	346 (46) Q 710 (51) non-Q	151 (43.6) Q 74 (10.4) non-Q
Namba et al., 2019 [10]	Japan	531	MBS	64 (n.e.) [1]	8 (12.5)
Shi et al., 2013 [13]	Malaysia	484	ARMS + HRM	221 (45.7)	9 (4)
Evans et al., 2019 [15]	EU	17,782	qPCR	1,737 (10.7)	79 (4.9)
Sousa et al., 2020 [17]	EU	1228	Sanger	252 (20.5)	19 (7.5)
Martin et al., 2019 [16]	EU	2906	Sanger	408 (14)	22 (5.4)



*Sensitivity of the co-mutation drivers the overall response to different TKIs



Potential activity

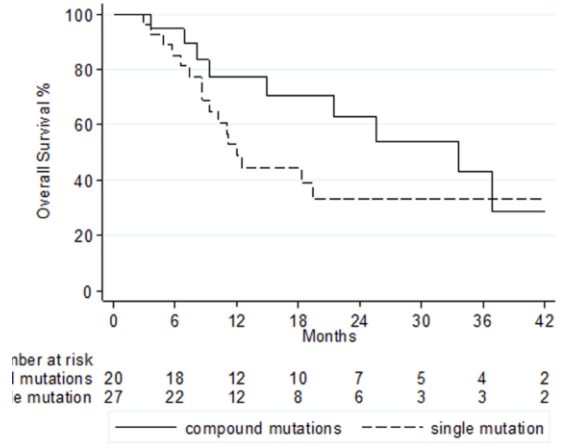
3rd G* > 2nd G > 1st G

2nd G > 3rd G* > 1st G

2nd G > 3rd G

3rd G

*lacking data



Attili, Current Oncol 2022; Rossi, Curr Probl Cancer 2022

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

So…how to treat uncommon EGFR mutations?

EGFR Exon20Ins → Amivantamab + chemotherapy (Papillon)

S768I, L861Q, G719X → Afatinib or Osimertinib

Compound mutations

- Common + common → Osimertinib or Afatinib
- Common + uncommon → Afatinib
- Uncommon + uncommon → Afatinib
- Any + T790M → Osimertinib

Highly recommended to discuss in MTB

Other rare mutations → Discuss in MTB, search evidence in a database as OncoKB, consider 2nd/3erd G depending on available evidence

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

OUTLINE

1. Uncommon EGFR mutation subtypes and classification
2. Molecular testing options
3. Exon 20 Insertions
4. Other uncommon EGFR point mutations
5. Compound mutations
6. How to treat uncommon mutations algorithm
7. Conclussions

TAKE HOME MESSAGES

- Sensitive methods sequencing the entire EGFR gene is recommended to identify and characterize uncommon mutations, NGS preferred.

- Exon20Ins is a distinct entity with low activity of classical TKIs
  - Amivantamab + chemotherapy significantly improved PFS vs chemo in 1st line (new SoC)
  - Several promising specific TKIs in development

- EGFR TKIs should be considered in frontline treatment of G719X, L861X and S768I
  - Available evidence suggest better outcomes with 2nd G TKIs (afatinib) in G719X and S768I and 3rd G in L861Q

- Few clinical data in compound mutations
  - Sensitivity of the co-mutation drivers the overall response to different TKIs

- Further research is needed


15th
MADRID
CONGRESS
on Lung CANCER
23&24
November 2023
#15CongressGECP
Fundación
GECP
lung cancer
research
Muchas Gracias