SESSION VI: EGFR DISEASE

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

Treatment decisions in unfrequent mutations

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Disclosures

Employement

Sanidad de Castilla y León (SACYL)

Speaker's fees

Kyowa Kirin, Pierre-Fabre, Takeda, AstraZeneca, Bristol-Myers Squibb, Novartis, Roche, Pfizer, Aristo, Immunocore

Consulting

Roche, Astra-Zeneca, Boehringer Ingelheim, Novartis, Takeda

Research projects

Roche, Bristol-Myers Squibb, MSD, Boehringer Ingelheim, AstraZeneca

Congress travel and facilities

Takeda, Pfizer, Pierre-Fabre, Roche, MSD

Listed shares

None

Acknowledgements

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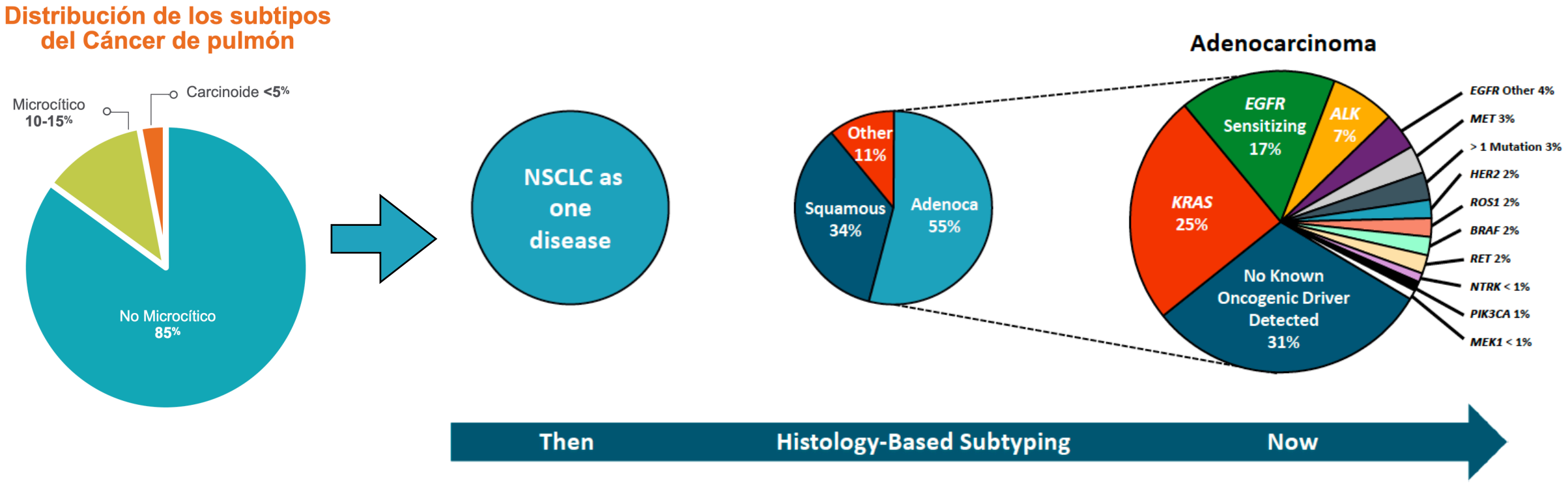
Schema

- ***Part 1: Intro. EGFR Mutations in NSCLC***
- ***Part 2: Uncommon EGFR mutations***
- ***Part 3: Treatment of EGFR uncommon mutations***
- ***Part 4: EGFR Ex20ins***
- ***Final Part: End***

1

EGFR mutations in NSCLC

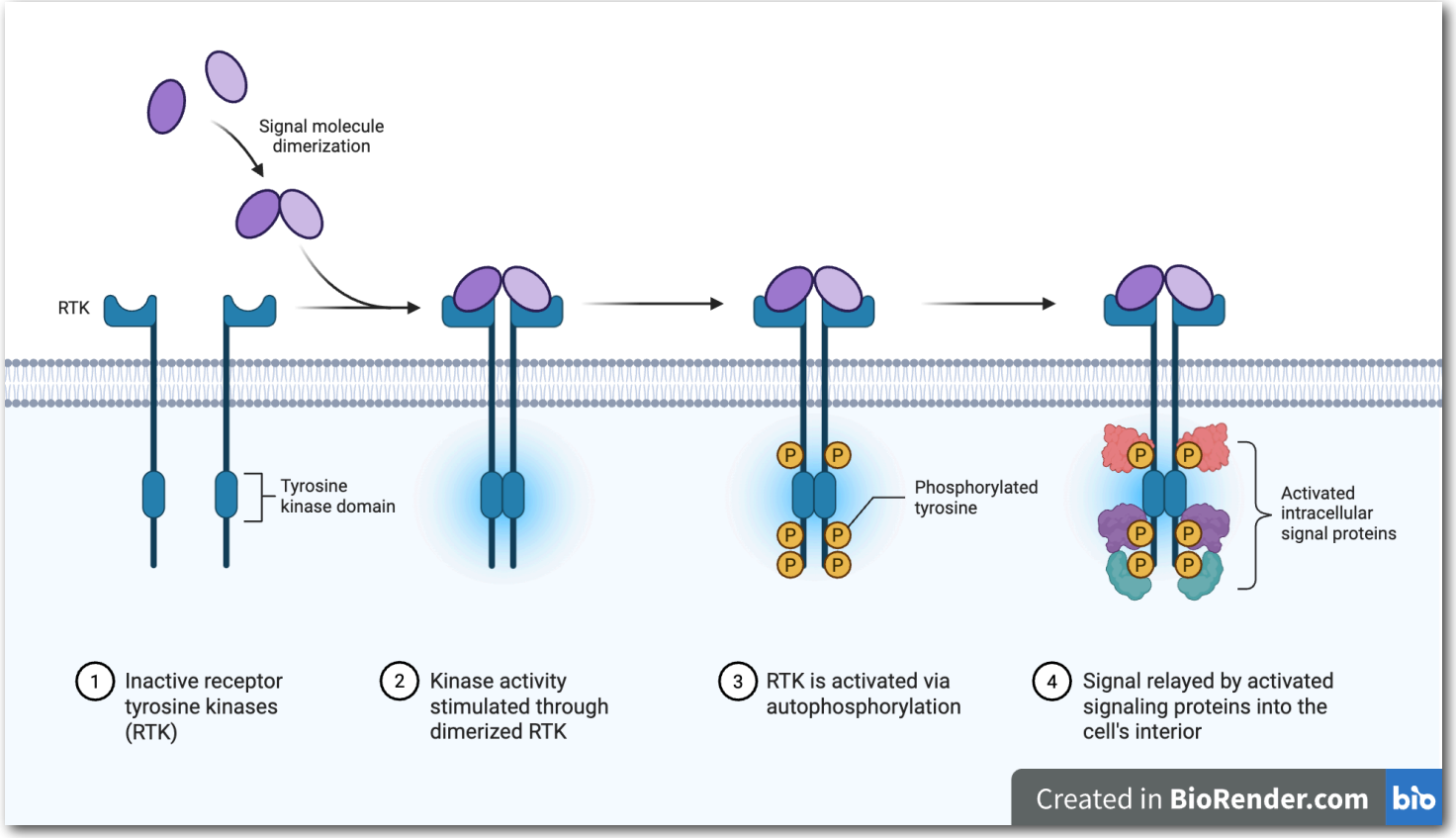
“The” Lung cancer



Taken from Pikor LA et al. Lung Cancer 2013; Li. JCO. 2013;31:1039; Tsao. J Thorac Oncol. 2016;11:613.

First EGFR description

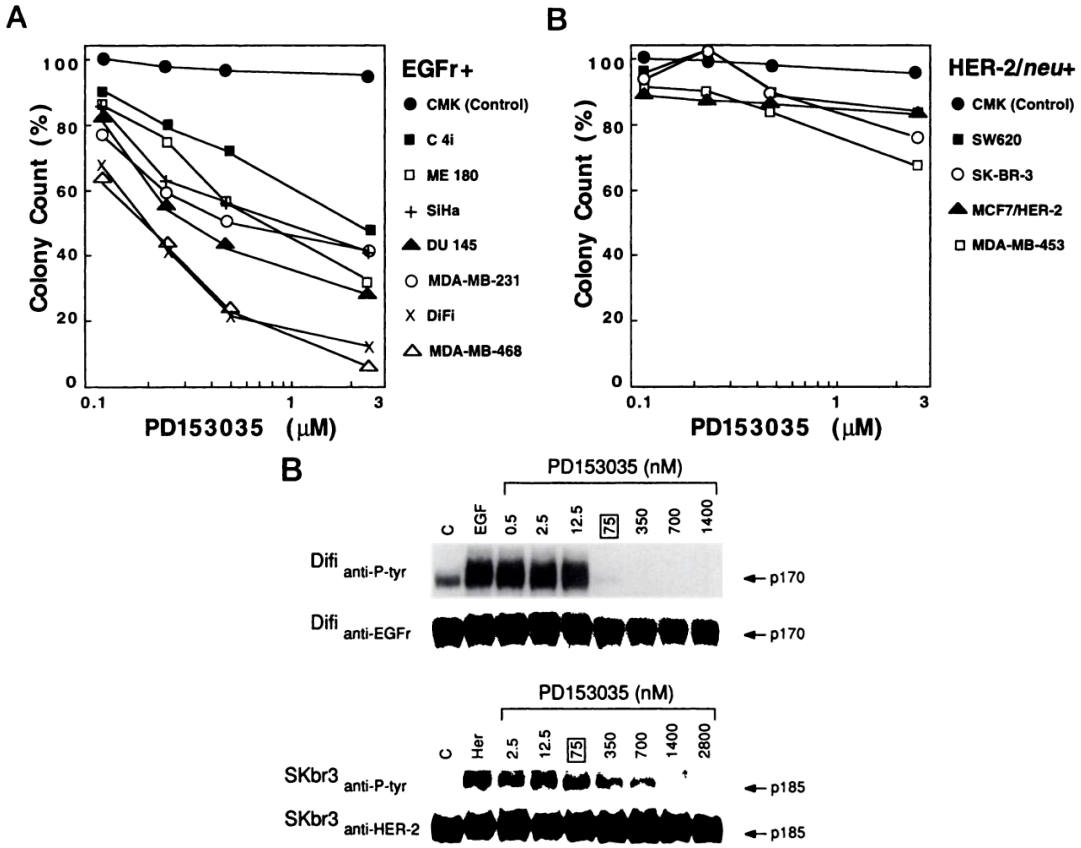
Specific binding site por EGF in human fibroblasts

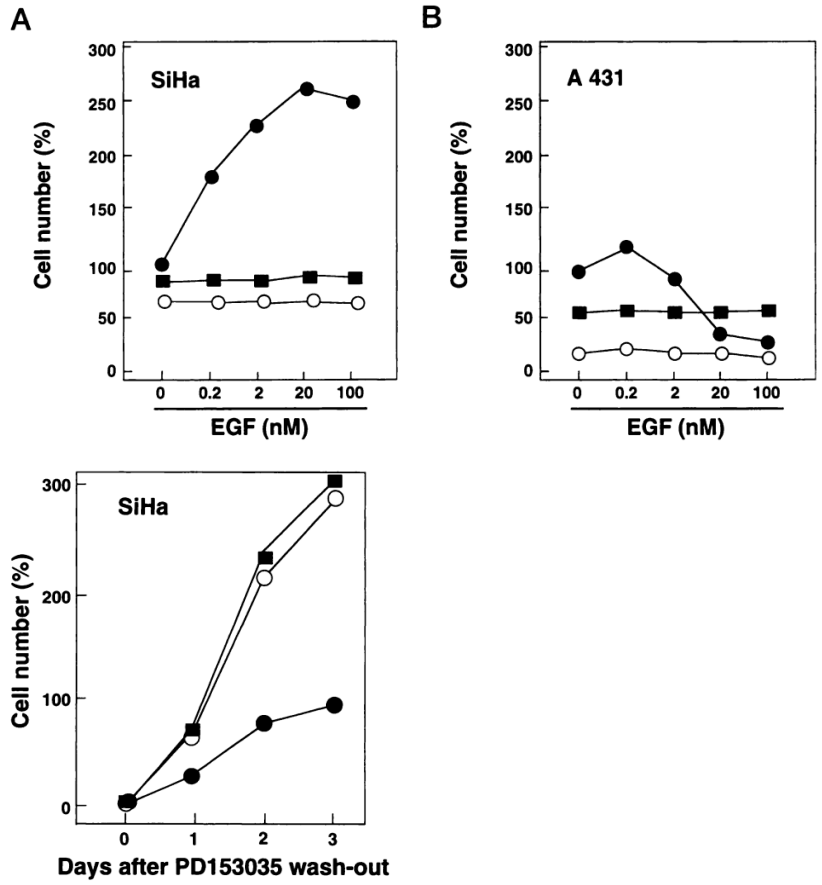


Carpenter G et al. J Biol Chem. 1975 Jun 10;250(11):4297-304.

EGFR-TKI inhibitors: Preclinical development

PD153035, precursor for Erlotinib & Gefitinib





Bos M et al. Clin Cancer Res (1997) 3 (11): 2099–2106.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

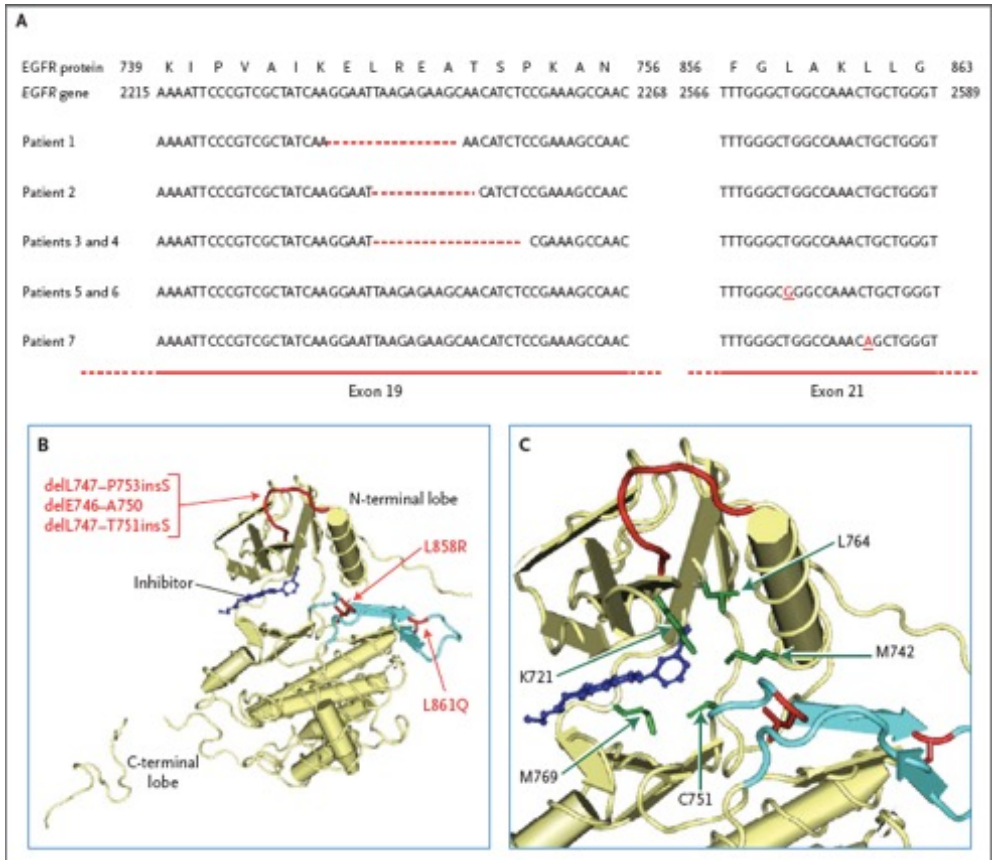
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Table 1. Characteristics of Nine Patients with Non–Small-Cell Lung Cancer and a Response to Gefitinib.

Patient No.	Sex	Age at Beginning of Gefitinib Therapy	Pathological Type*	No. of Prior Regimens	Smoking-Status†	Duration of Therapy	Overall Survival‡	*EGFR* Mutation§	Response¶
		yr				*mo*			
1	F	70	BAC	3	Never	15.6	18.8	Yes	Major; improved lung lesions
2	M	66	BAC	0	Never	>14.0	>14.0	Yes	Major; improved bilateral lung lesions
3	M	64	Adeno	2	Never	9.6	12.9	Yes	Partial; improved lung lesions and soft-tissue mass
4	F	81	Adeno	1	Former	>13.3	>21.4	Yes	Minor; improved pleural disease
5	F	45	Adeno	2	Never	>14.7	>14.7	Yes	Partial; improved liver lesions
6	M	32	BAC	3	Never	>7.8	>7.8	Yes	Major; improved lung lesions
7	F	62	Adeno	1	Former	>4.3	>4.3	Yes	Partial; improved liver and lung lesions
8	F	58	Adeno	1	Former	11.7	17.9	Yes	Partial; improved liver lesions
9	F	42	BAC	2	Never	>33.5	>33.5	No	Partial; improved lung nodules

- 9 patients (6 women)
- Non-smokers (or former)
- ADC or BAC
- 8/9 EGFR mutated
- All of them had response to gefitinib

Lynch T et al. N Engl J Med . 2004 May 20;350(21):2129-39



Those mutations…

…led these results

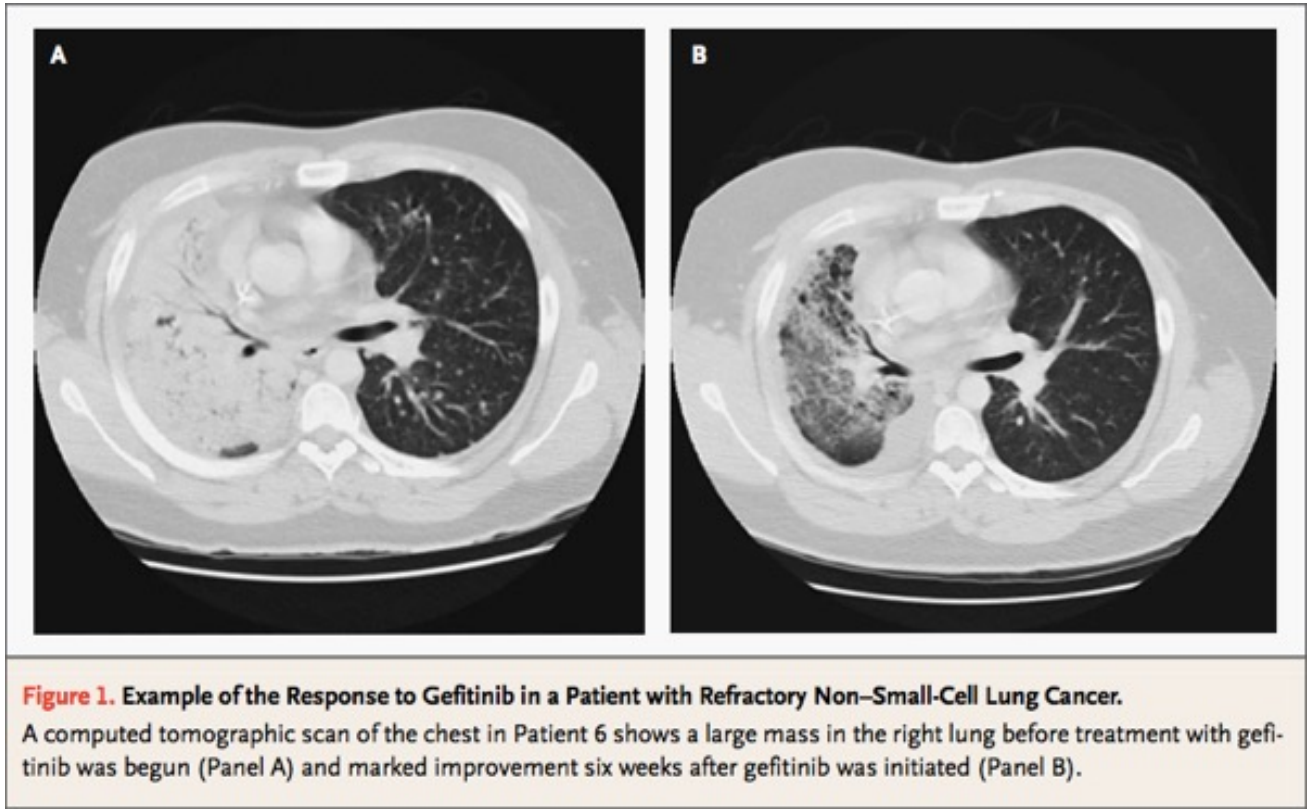


Figure 1. Example of the Response to Gefitinib in a Patient with Refractory Non–Small-Cell Lung Cancer.
A computed tomographic scan of the chest in Patient 6 shows a large mass in the right lung before treatment with gefitinib was begun (Panel A) and marked improvement six weeks after gefitinib was initiated (Panel B).

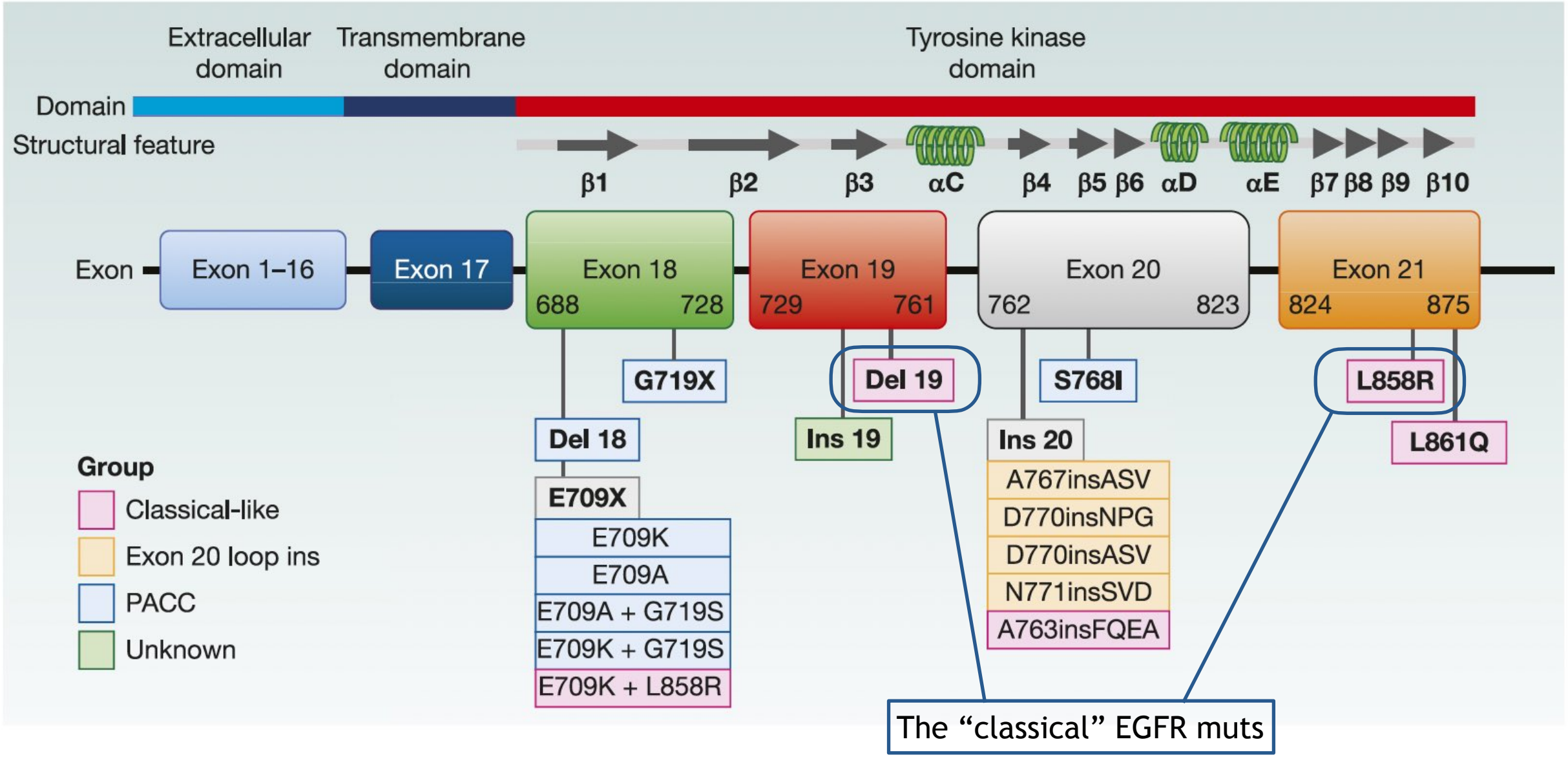
Lynch T et al. N Engl J Med . 2004 May 20;350(21):2129-39

1st line EGFR-TKIs randomized trials

Ensayo	EGFR TKI	Comparador	n	EGFR mutation	ORR (%)	SLP (m)	SG (m)
IPASS	Gefitinib	QT	1217	261*	71 vs 47 p<0.001	**9.5** vs 6.3 HR 0.48	**21.6** vs 21.9 HR 1.0
First-SIGNAL	Gefitinib	QT	309	42*	85 vs 38 p=0.002	**8.0** vs 6.3 HR 0.544 ns	**27.2** vs 25.6 HR 1.04
NEJGSG-002	Gefitinib	QT	224	224	74 vs 31 p<0.001	**10.8** vs 5.4 HR 0.30	**30.5** vs 23.6 HR 0.89 ns
WJTOG-3405	Gefitinib	QT	172	172	62 vs 32 p<0.0001	**9.6** vs 6.6 HR 0.52	**35.5** vs 38.8 HR 1.185
OPTIMAL	Erlotinib	QT	154	154	83 vs 36 p<0.0001	**13.7** vs 4.6 HR 0.16	**22.7** vs 28.9 HR 1.04
EURTAC	Erlotinib	QT	173	173	58 vs 15	**9.7** vs 5.2 HR 0.37	**19.3** vs 19.5 HR 1.04
LUX-Lung 3	Afatinib	QT	345	345	56 vs 23 p<0.001	**11.1** vs 6.9 HR 0.58	**28.2** vs 28.2 HR 0.88 ns
			308 common mutations	308	61 vs 22 p<0.0001	**13.6** vs 6.9 HR 0.47	-
ARCHER 1050	Dacomitinib	Gefitinib	227 vs 225	452	75 vs 72 HR 1.13	14.7 vs 9.2 HR 0.59	**34.1** vs 27.0 HR 0.75
FLAURA	Osimertinib	ITK 1L	279 vs 277	556	80 vs 76 HR 1.06	18.9 vs 10.2 HR 0.46	38.6 vs 31.8 HR 0.80

Mok T, et al. N Engl J Med 2009;361:947-57; Mitsumodi T, et 11. Lancet Oncol 2010;11:121-8; Mitsumodi T, et al. J Clin Oncol 2012;30(Suppl.):Abstract 7521; Maemondo M, et al. N Engl J Med 2010;362:2380-8; Zhou C, et al. Lancet Oncol 2011;12:735-42; Zhou C, et al. J Clin Oncol 2012;30(Suppl.):Abstract 7520; Rossell R, et al. Lancet Oncol 2012;13:239-46; Fukuoka M, et al. J Clin Oncol 2011;29:2866-74; Yang JC, et al. J Clin Oncol 2012;30(Suppl.):Abstract LBA7500; Mok TS et al. Lancet. 2017 Nov 18;390(10111): 2149-2158; Soria JC et al. N Engl J Med. 2018 Jan 11;378(2):113-125.

EGFR MUTATIONS SPECTRUM

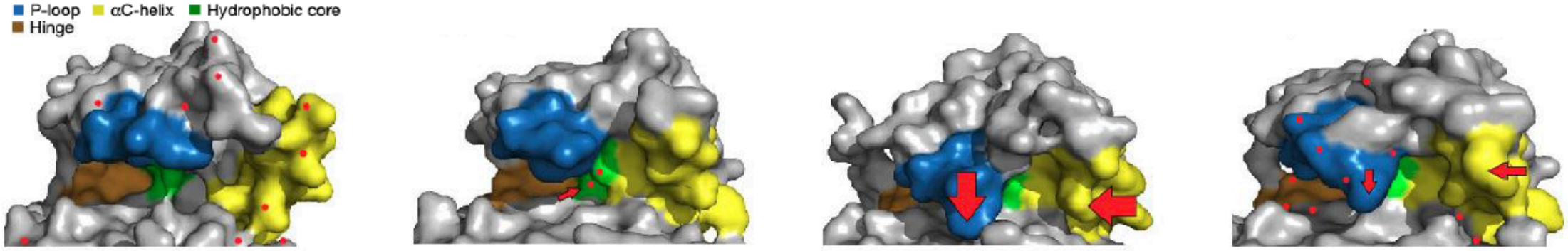


Maehara K . Published on X.com

Redefining *EGFR*: structure-function classification

Analyses of 16715 EGFR-mutated tumors. Defined 4 four structural subgroups based on conformational changes and drug sensitivity

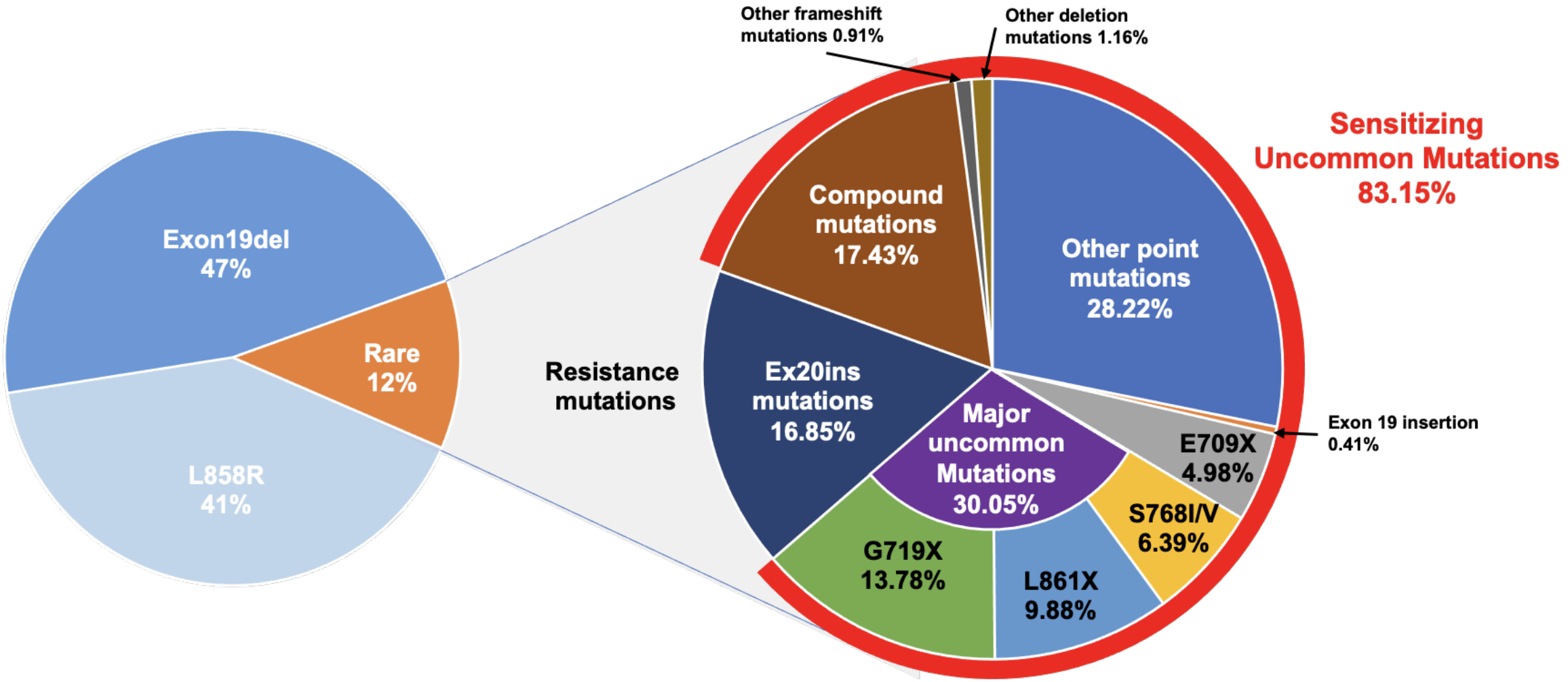
Red arrows: structural change compared to wildtype EGFR; Red dots: mutation location



	Classical-like	T790M-like	Exon 20 loop insertion	P-loop αC-helix compressing (PACC)
Description	**Distal to drug-binding pocket Modest to no impact on drug binding**	**At least 1 mutation in hydrophobic core Increased ATP affinity compared to classical-like Subgroups: T790M-like-3S, T790M-like-3R**	**C-terminal loop of αC-helix Indirect & substantial impact on drug binding Subgroups: near loop, far loop**	**Proximal to drug-binding pocket Direct/indirect impact on drug binding via displacement of P-loop ± αC-helix**
Representative mutations	L858R, Ex19dels, S720P, L861Q/R, S811F, K754E, T725M, L833F/V, A763insFQEA, A763insLQEA	T790M-3S: Classical/T790M, G719X/T790M, S768I/T790M; T790M-3R: Ex19del/T790M/L792H, L858R/T790M/L718X, Classical/T790M/ C797S	NL: S768dupSVD, A767dupASV, D770insNPG, D770del insGY; FL: H773insNPH, H773dupH, V774insAV, V774insPR	Primary: G719X, S768I, L747P/S, V769L, E709_T710 delinsD; Acquired: C797S, L792H, G724S, L718X, T854I
Drug selectivity	Selective: 3rd gen, 2nd gen, 1st gen, Ex20ins-active Intermediate Resistant	T790M-3S: 3rd gen; PKCi, ALKi; 2nd gen, 1st gen T790M-3R: PKCi, ALKi; 3rd gen, 2nd gen, 1st gen	Ex20ins-NL: Ex20ins-active, 2nd gen; 1st gen, 3rd gen Ex20ins-FL: Ex20ins-active; 2nd gen, 1st gen, 3rd gen	2nd gen 1st gen, Ex20ins-active 3rd gen

Robichaux, Le and Heymach et al. Nature 2021

EGFR uncommon mutations: Frequency



Harrison PT et al. Semin Cancer Biol. 2020;61:167

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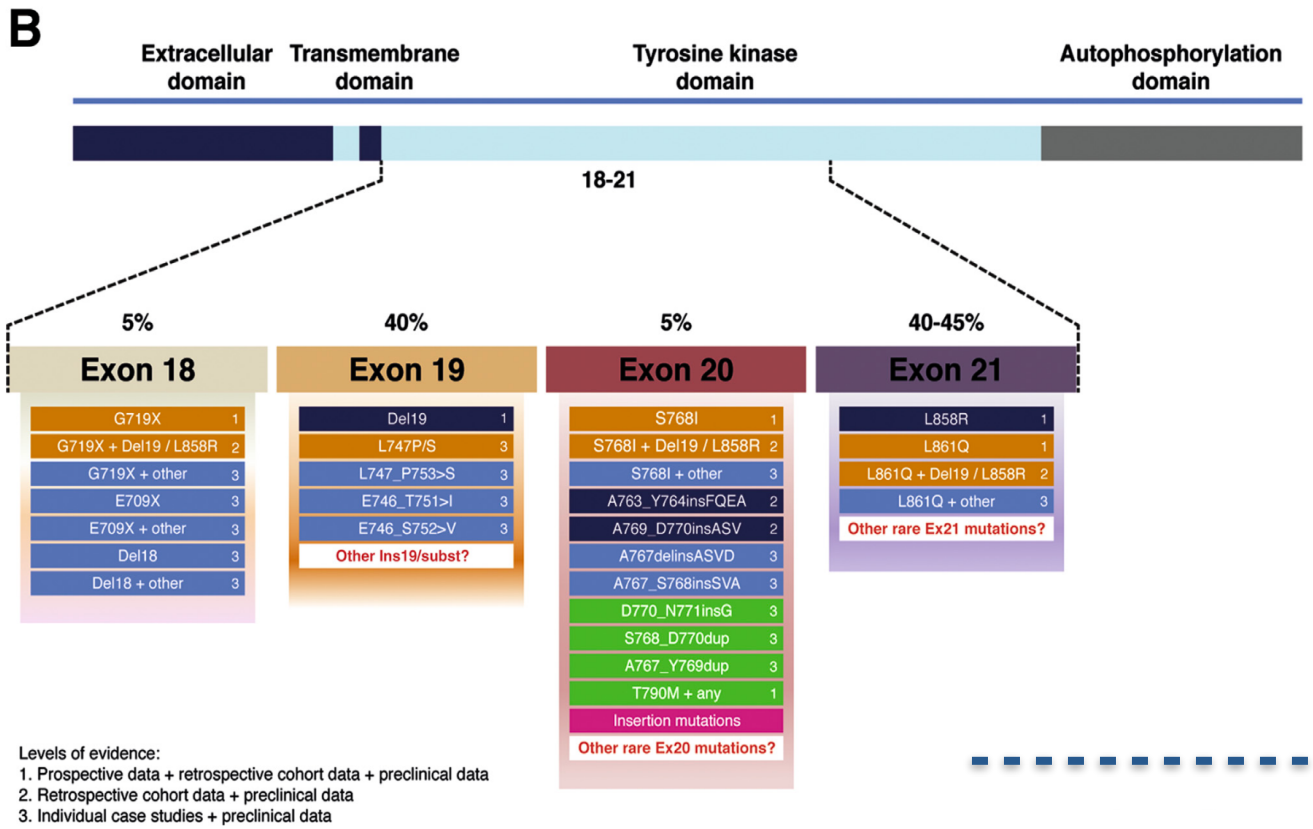
Uncommon EGFR mutations

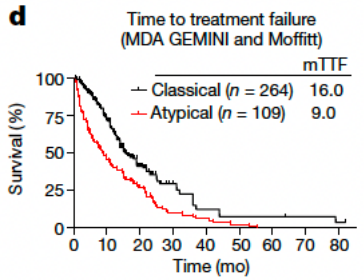
What we are talking about today: EGFR Uncommon mutations

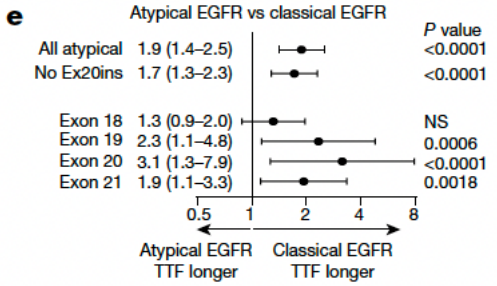


-10-20% of patients with NSCLC harbor uncommon *EGFR* mutation that **have variable sensitivity to different *EGFR* TKIs**

-**More than 600 *EGFR*** variants are described, many of which are “uncharted territory” in terms of oncogenic pathways impact and sensitivity

-Major uncommon mutations: Ex18 G719X, Ex20 S768I, Ex 21 L861Q





- **Clinical features:**
  - **54%** of patients will develop **CNS metastases**
  - **Ex18 G719X** may be associated with current or former **smokers** with no gender predilection
  - -Uncommon *EGFR* mutations are associated with **worse patient outcomes**

Passaro et al. J thor Oncol, 2020; Attili et al. Current Oncology, 2022

Uncommon: Known from the beginning

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

A

activation loop

L858R	KTPQHVKITDFGRAKLLGAEEKEYH	870
EGFR	KTPQHVKITDFGLAKLLGAEEKEYH	870
BRAF	HEDLTVKIGDFGLATVKSRWSGSHQ	608

B

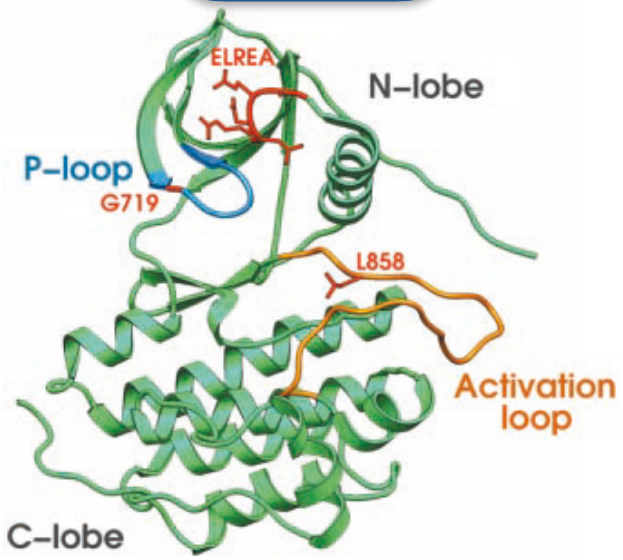
P-loop

G719S	ETEFKKIKVLSSGAFGTVYKGLWIP	733
EGFR	ETEFKKIKVLGSGAFGTVYKGLWIP	733
BRAF	DGQITVGQRIGSGSFGTVYKGKWHG	477

C

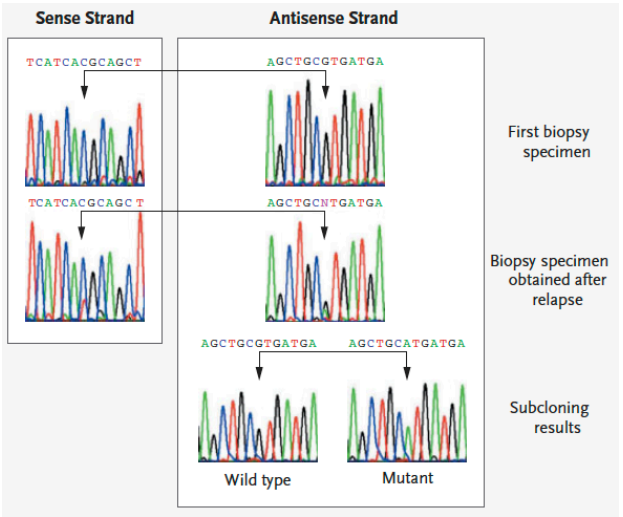
Del-1	VAIK-----T-SPKANKEILDEAYV	765
Del-2	VAIKELREAT-------LDEAYV	765
Del-3	VAIKE---PT-SPKANKEILDEAYV	765
Del-4	VAIKE------SKANKEILDEAYV	765
Del-5	VAIKV------PKANKEILDEAYV	765
EGFR	VAIKELREAT-SPKANKEILDEAYV	765
BRAF	VAVKMLNVTAPTPQQLQAFKNEVGV	503

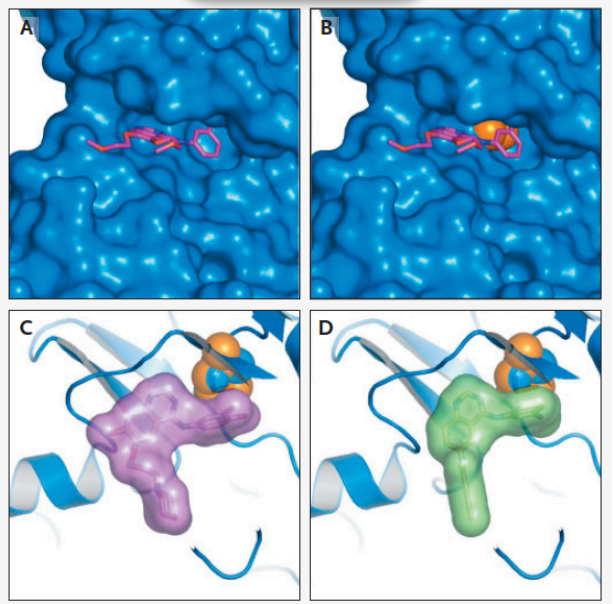
G719S



EGFR Mutation and Resistance of Non-Small-Cell Lung Cancer to Gefitinib

T790M

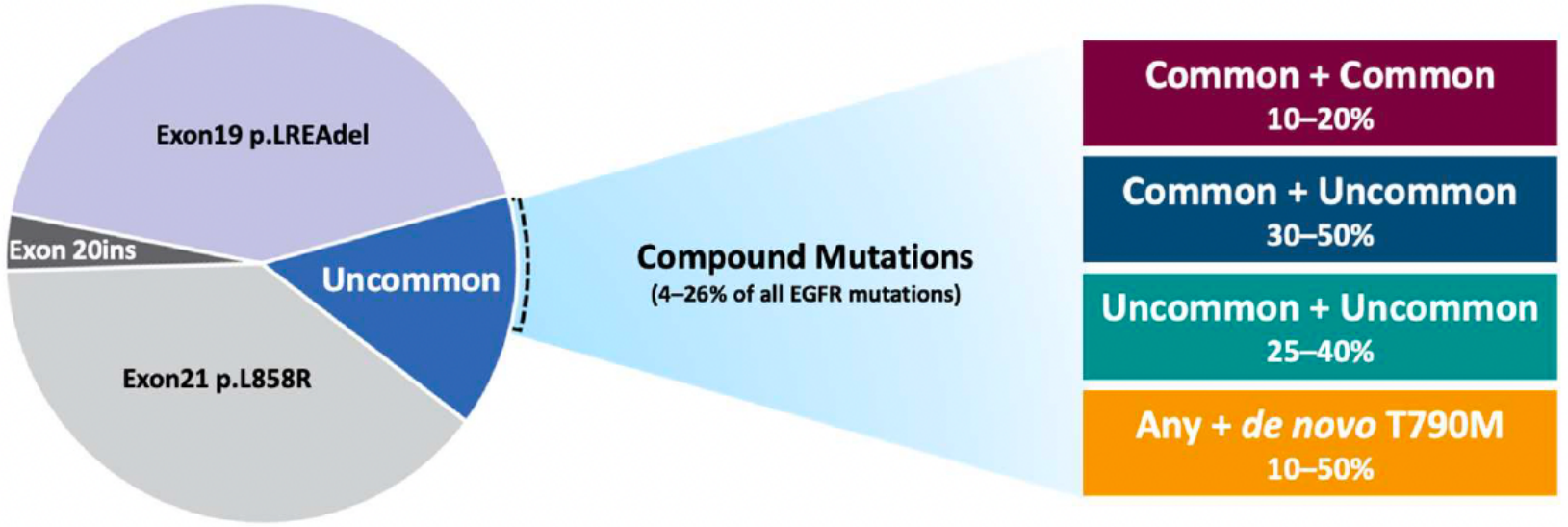




Paez J et al. Science. 2004;304(5676):1497–1500; Kobayashi S et al. N Engl J Med. 2005;352(8):786–792

UNCOMMON *EGFR* MUTATIONS: COMPOUND MUTATIONS

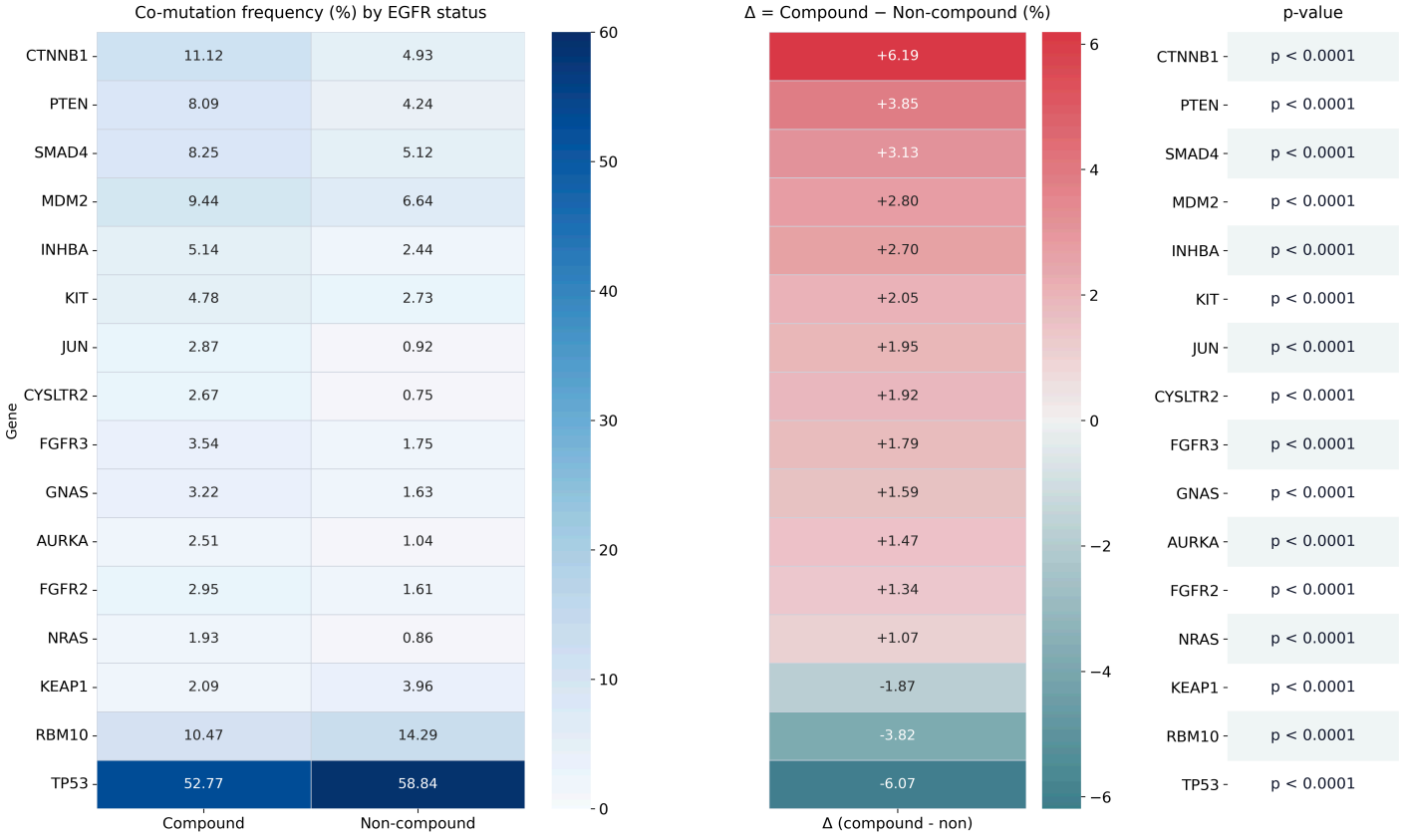
”Subclonal” *EGFR* mutations with a low variant allele frequency



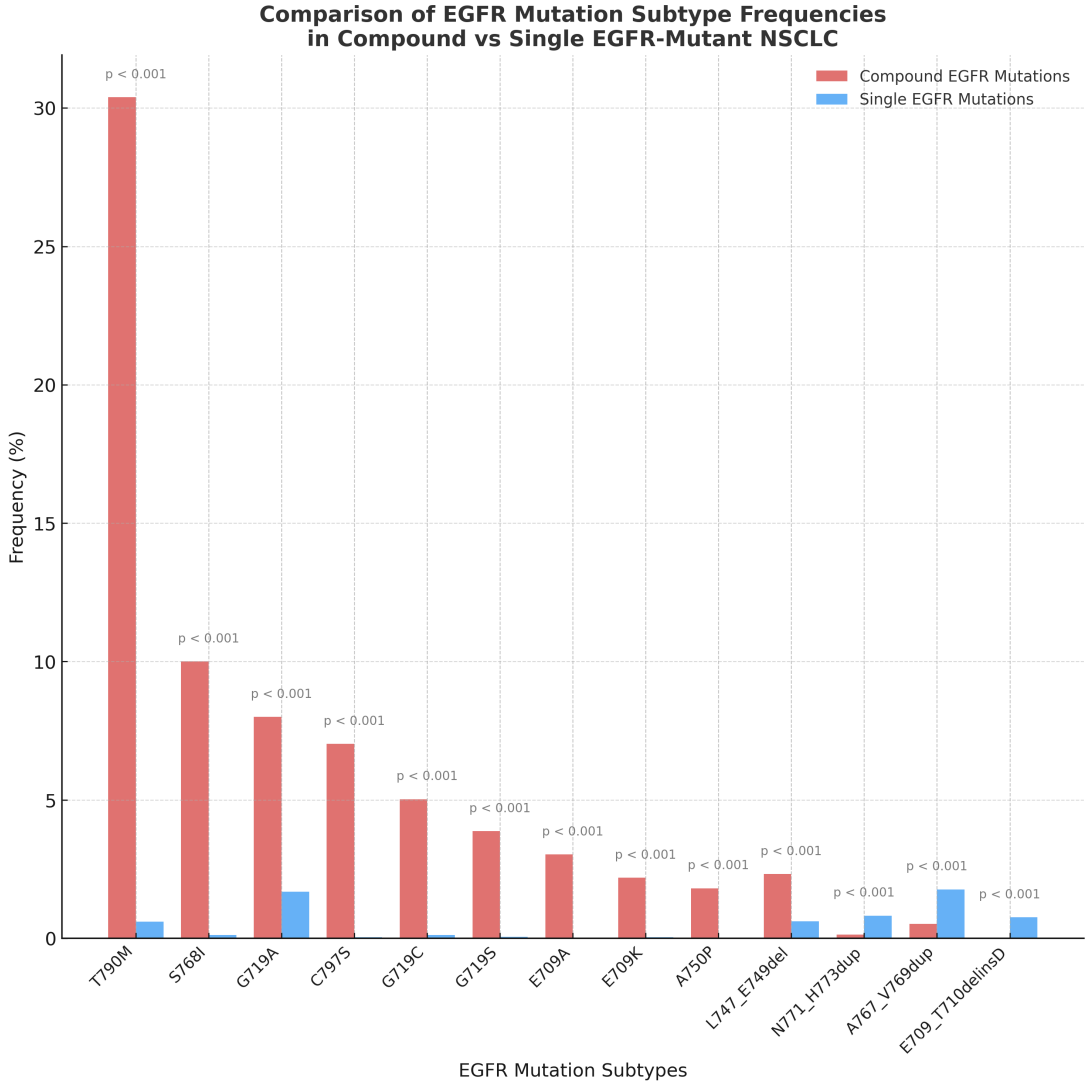
- They may occur in isolation or coexist with a common/uncommon mutations (termed as “complex” or “compound” mutation). ***EGFR* ex18 G719X partner of >90% of compound mutations**
- The **wide heterogeneity of uncommon mutations**, and the existence of compound mutations in up to **25% of the cases complicate treatment decisions**
- The sensitivity or resistance of compound mutations to *EGFR* TKIs seems to be largely influenced by the accompanying mutation

Passaro et al. J Thor Oncol, 2020; Attili et al. Curr Oncol, 2022

Genomic landscape and co-mutation profiles in compound EGFR-mutants



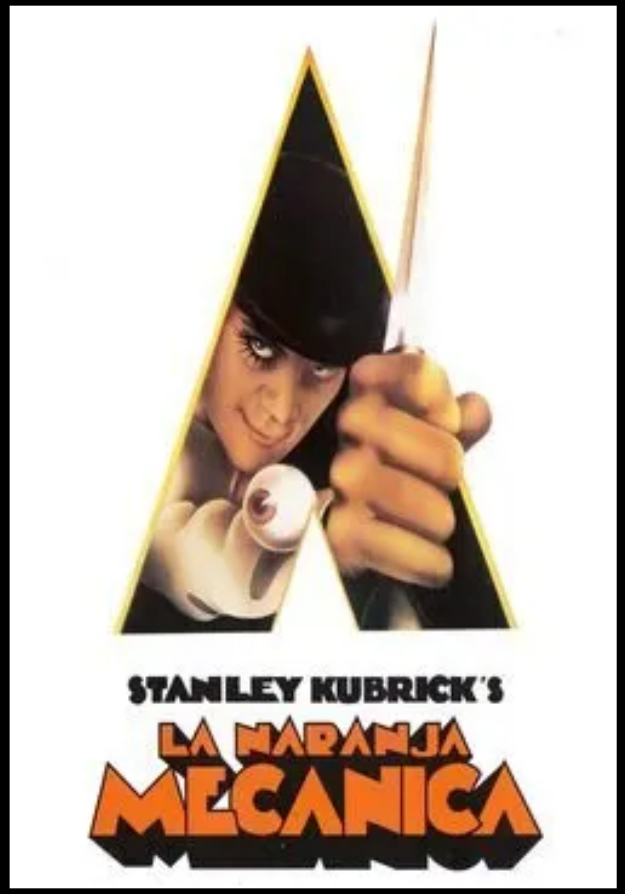
All pairwise group comparisons reported as p < 0.0001 (user-provided).



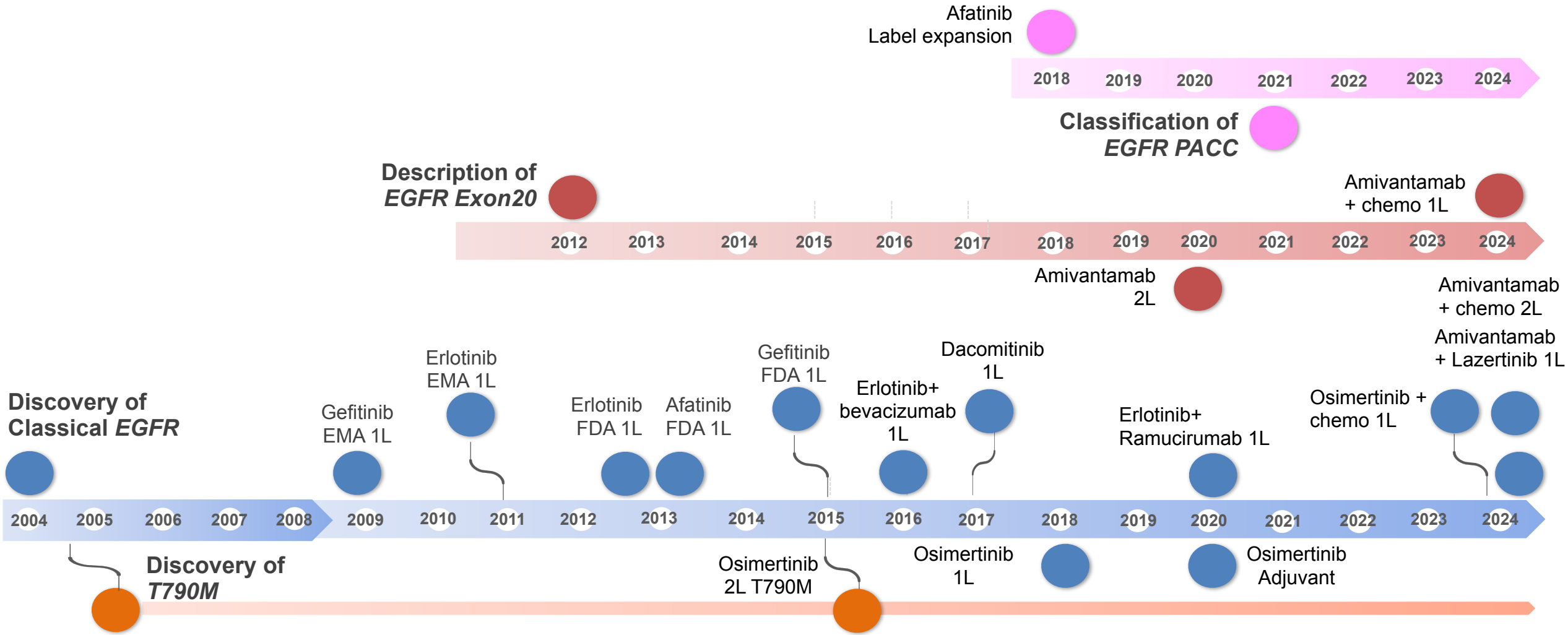
Al-rabi K, et al. ESMO Annual Congress 2025

3

Treatment of EGFR uncommon mutations



EGFR MUTATIONS IN NSCLC: TREATMENT



www.drugs.com; www.fda.gov

EGFR MUTATIONS IN NSCLC: SENSITIVIY PROFILE

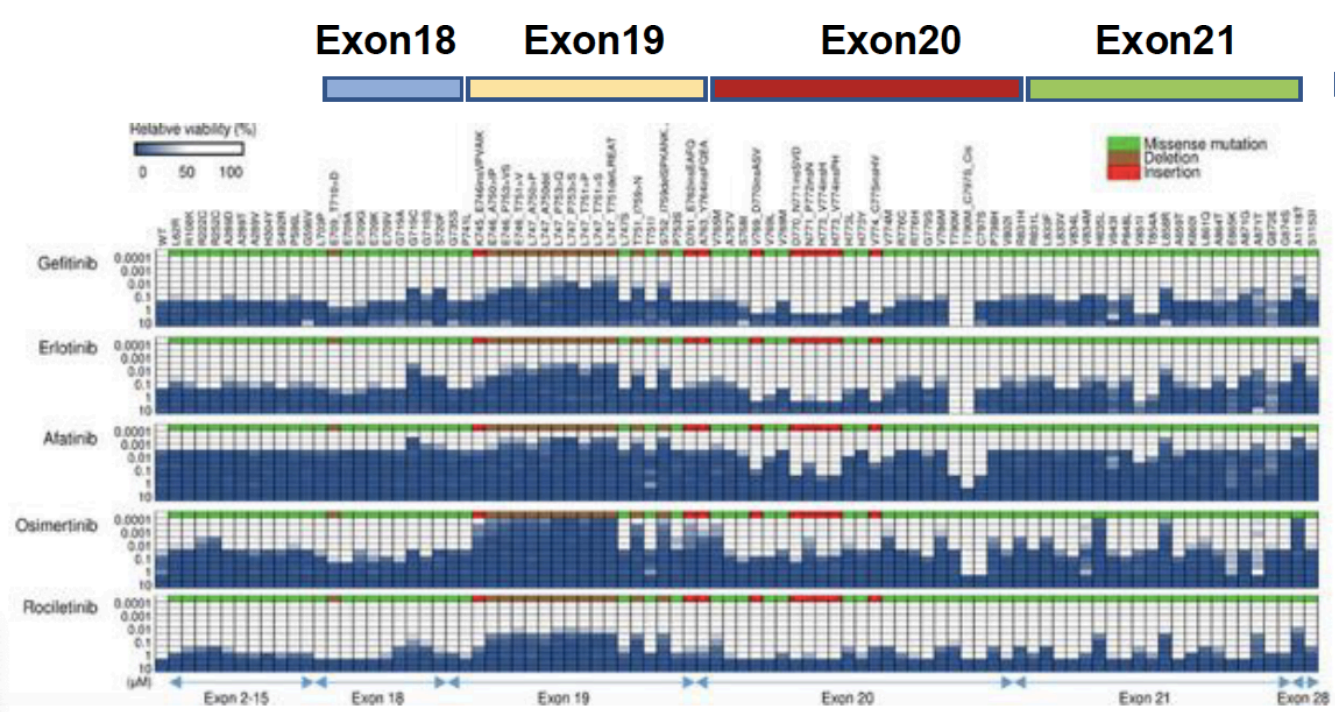
Table 2. Summary of the *in vitro* sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKI

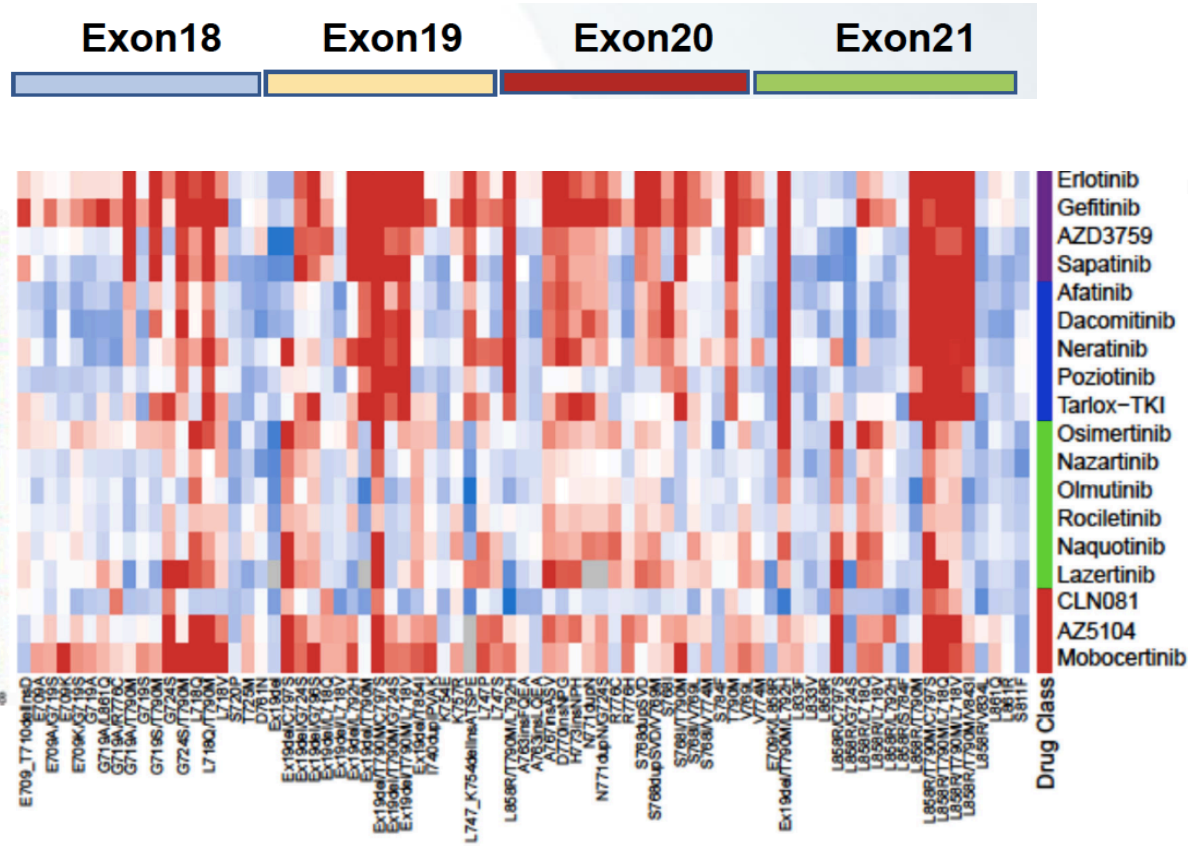
Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delL747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753insS	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		3403	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10 000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10 000	64	140		3	28
	T790M	T790M+L858R	>10 000	>10 000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10 000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448–2717)	(2717–4040)	(69–130)	(166–238)	(N/A–132)	(400–600)	N/A–N/A

Kobayashi et al. Cancer Sci, 2016

Kobayashi et al. Cancer Sci, 2016

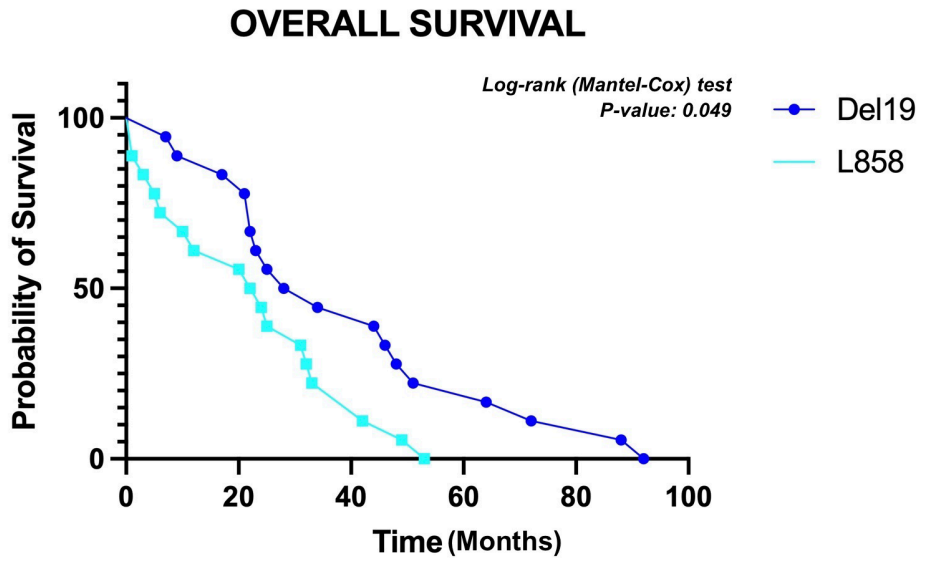
PRECLINICAL RESPONSE TO TKIs

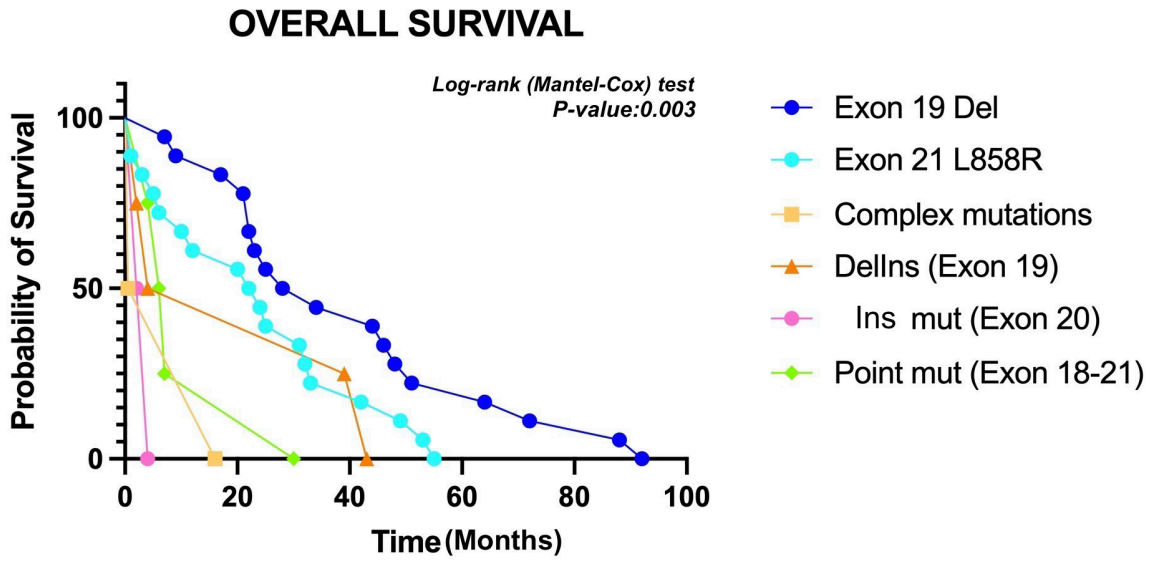


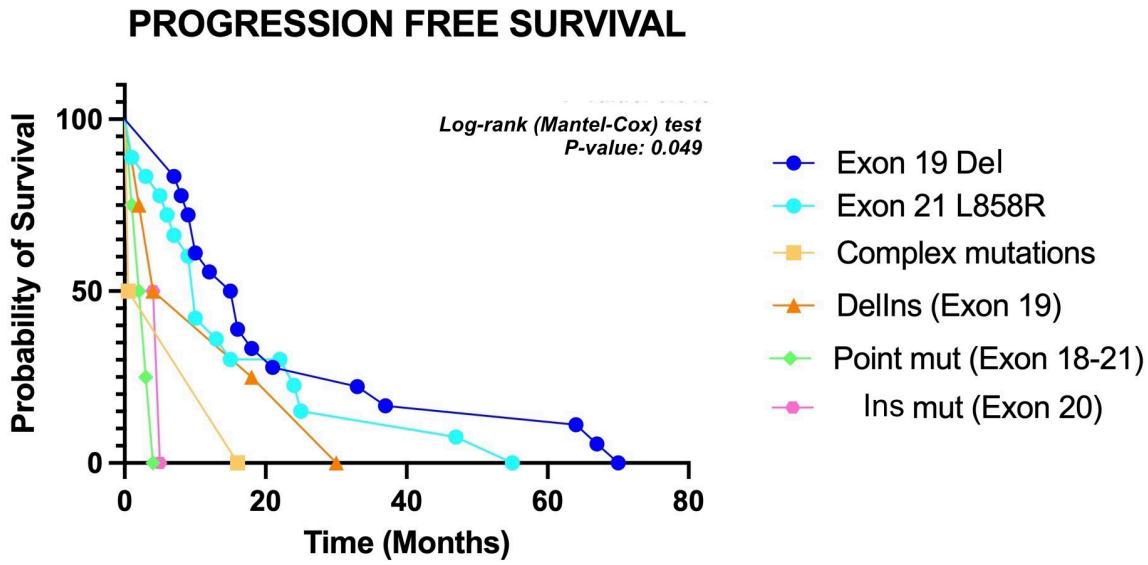


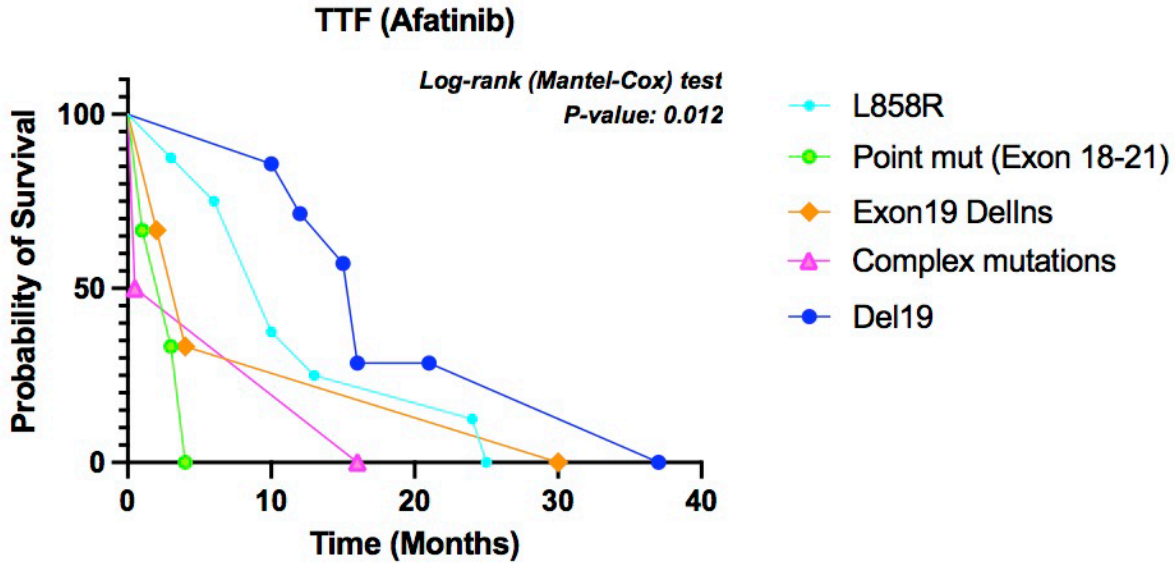
Koshaka et al. Sci Transl Med, 2017, Robichaux et al Nature 2021

Common and uncommon mutations in NSCLC: differences in response to treatment with tyrosine kinase inhibitors







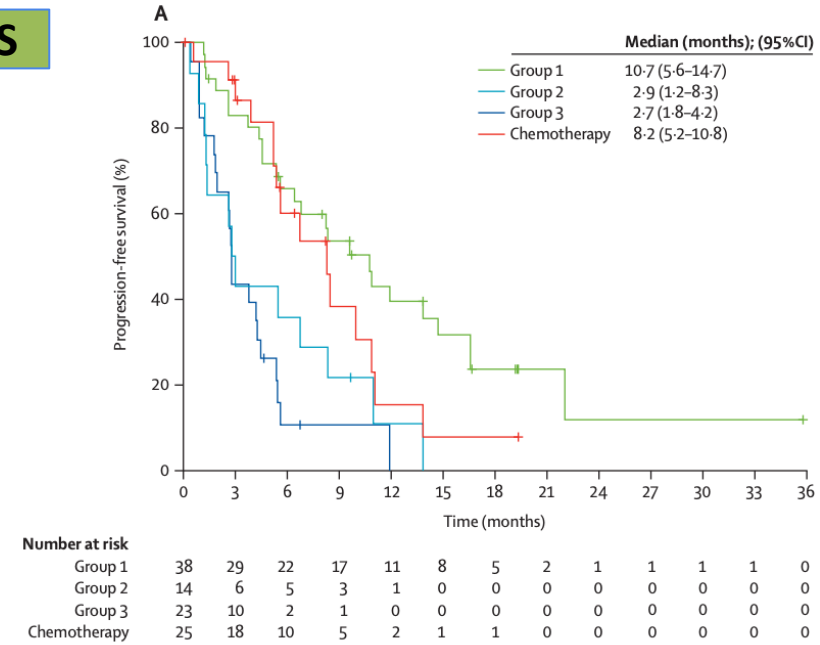


Sciortino C et al. ESMO Congress 2022

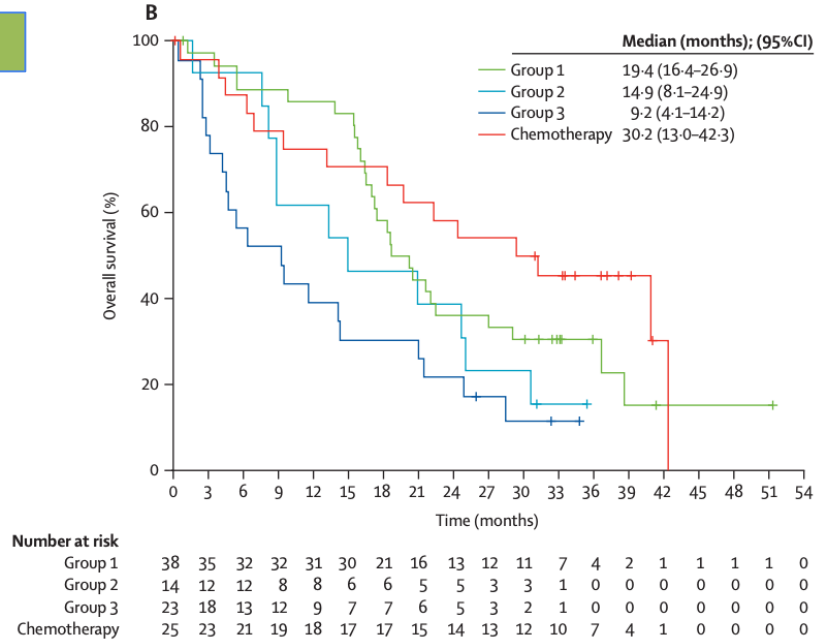
THE AFATINIB EVIDENCE

Retrospective: Combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

PFS



OS



	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

ORR:

- G719X: 78%
- L861Q: 56%
- S768I: 100%

Similar PFS w/wo brain mets:

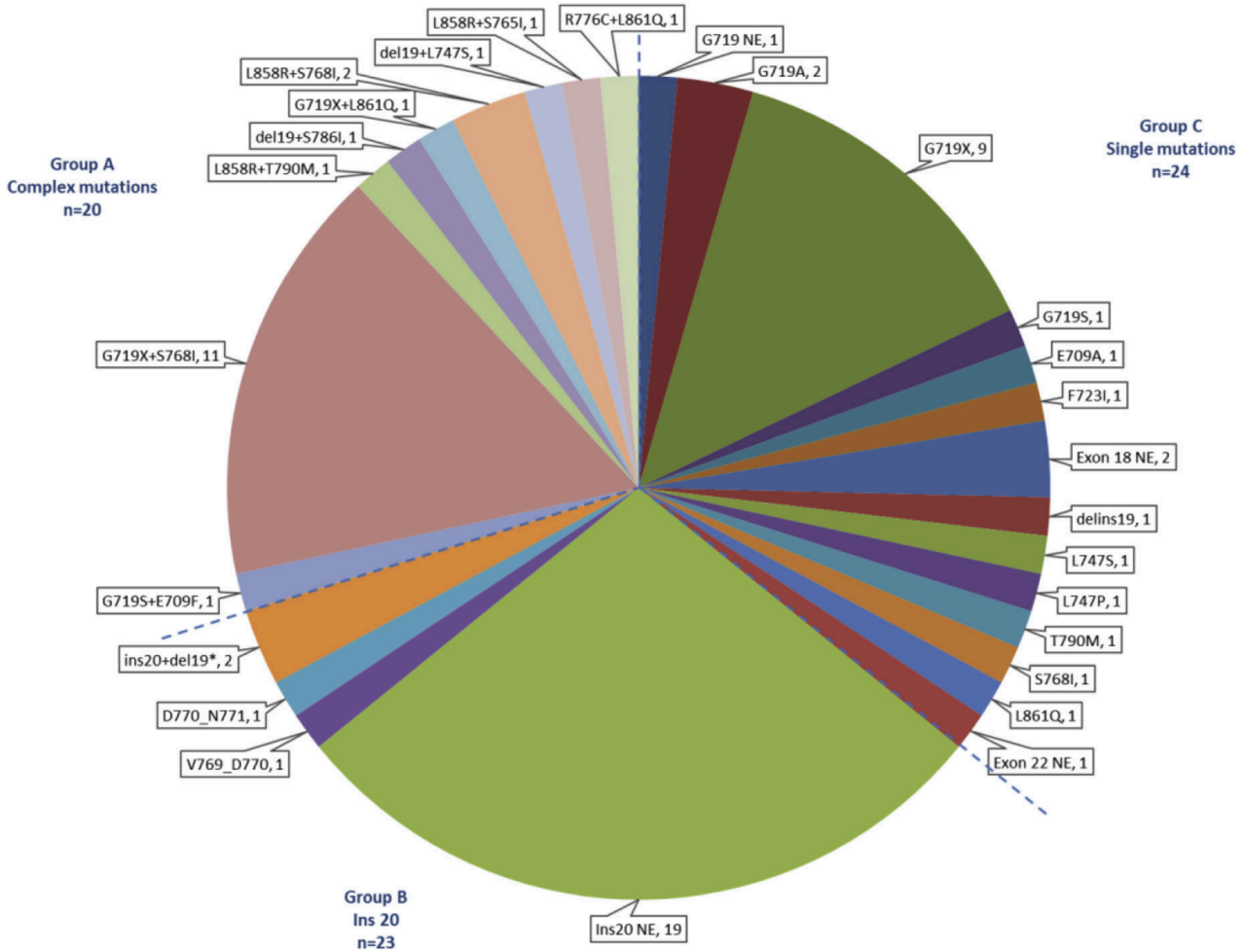
Afatinib vs. CT = 8.2 vs 5.4 m

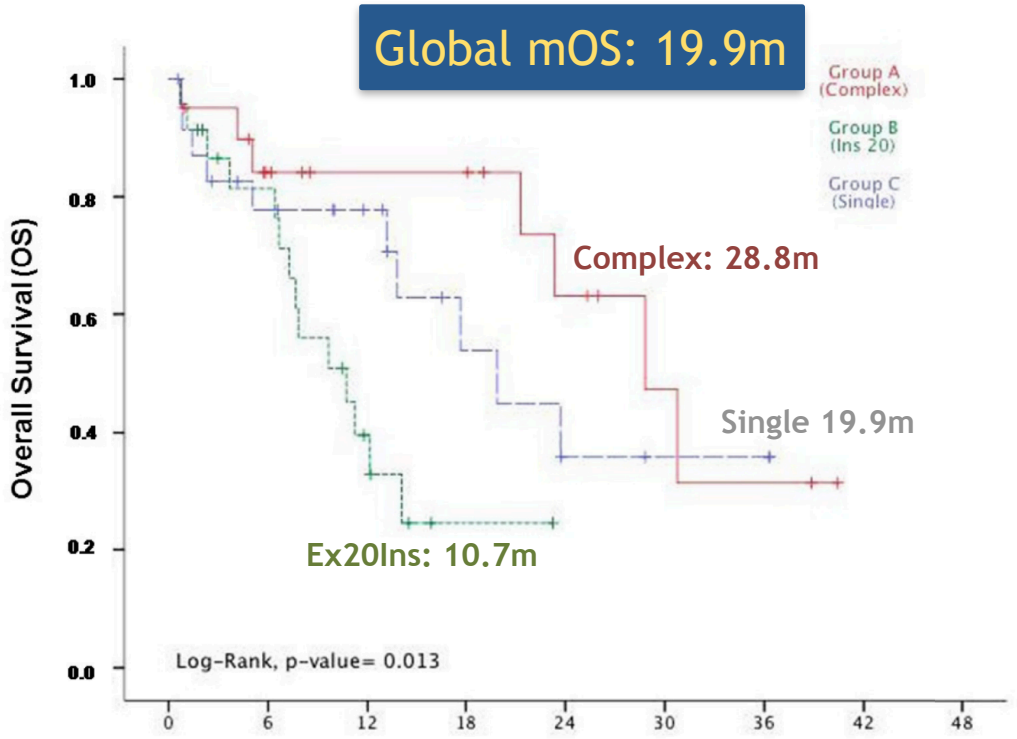
(HR: 0.50; *p* = 0.0297)

Yang et al. Lancet Oncol 2015; Schuler et al. J Thor Oncol, 2016

THE AFATINIB EVIDENCE

Retrospective: Spanish multicenter Registry

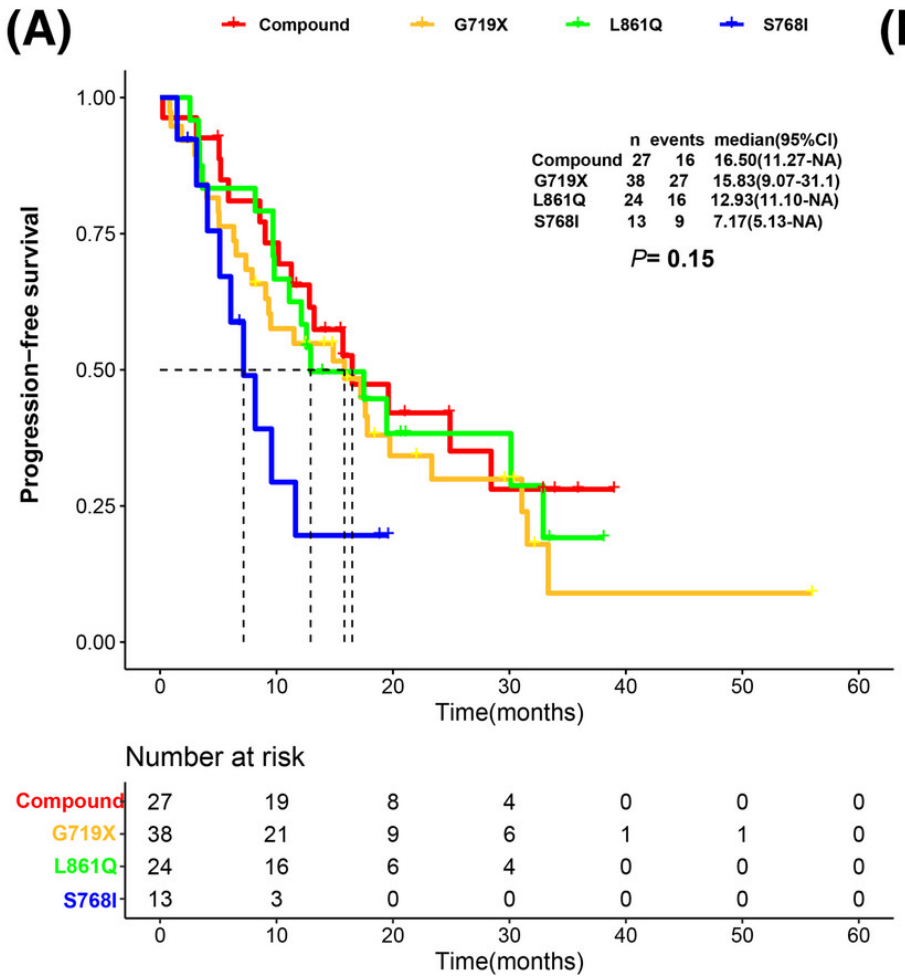


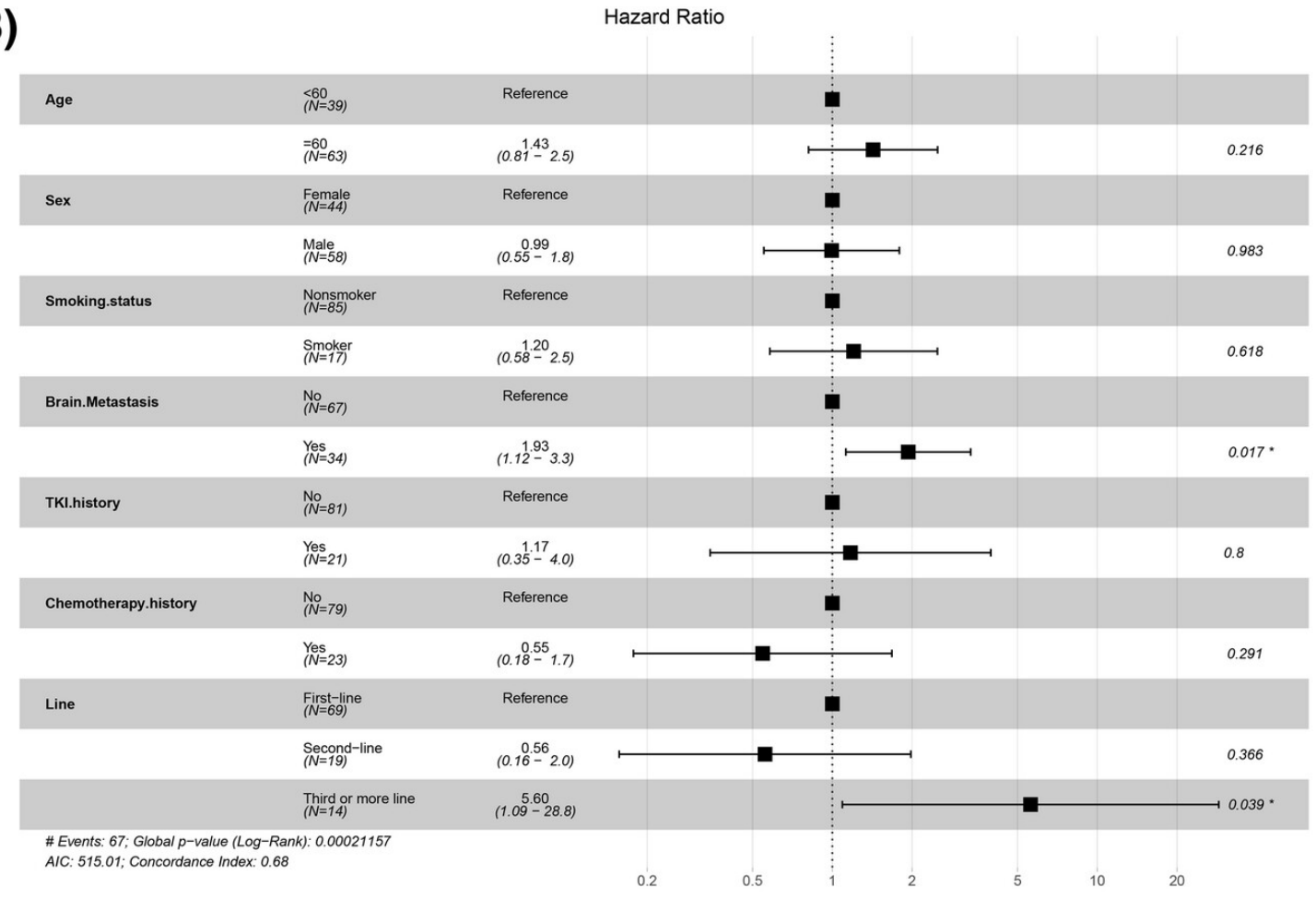


Moran T et al. Clin Lung Cancer. 2020 Sep;21(5):428-436.e2.

Afatinib efficacy with EGFR G719X/L861Q/S768I

Retrospective: Chinese Analysis





Pang L, et al. Cancer, 2022

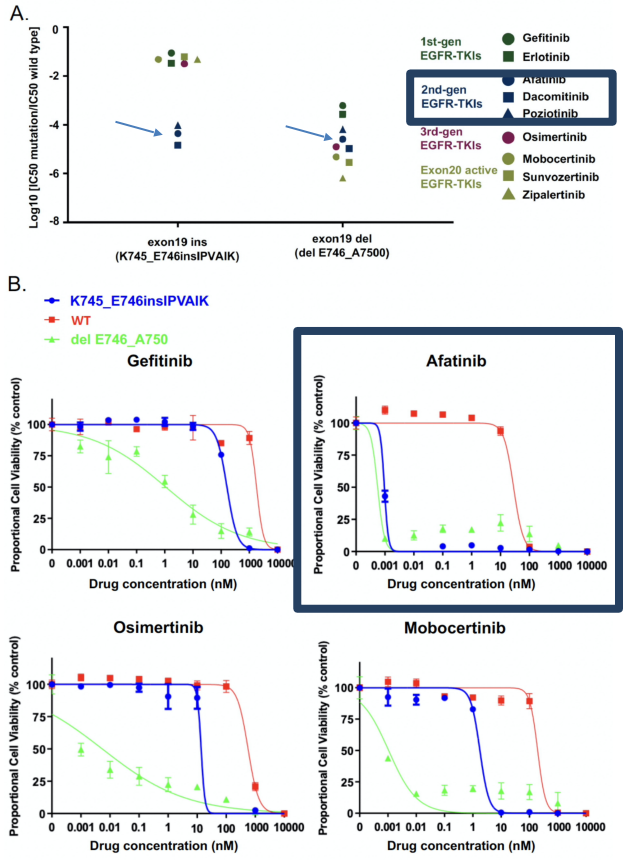
UNCOMMON *among uncommon: EGFR Ins19*

Registry LC-SCRUM-Asia

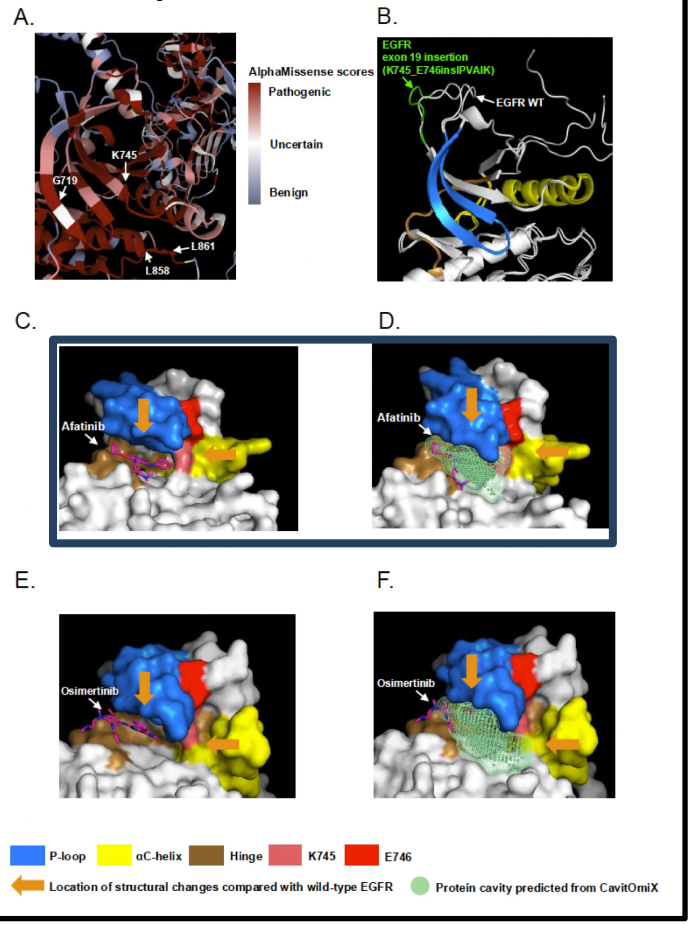
16204 pts screened: 13 Ins19 (0.1%)

EGFR inhibitors in EGFR Ins19

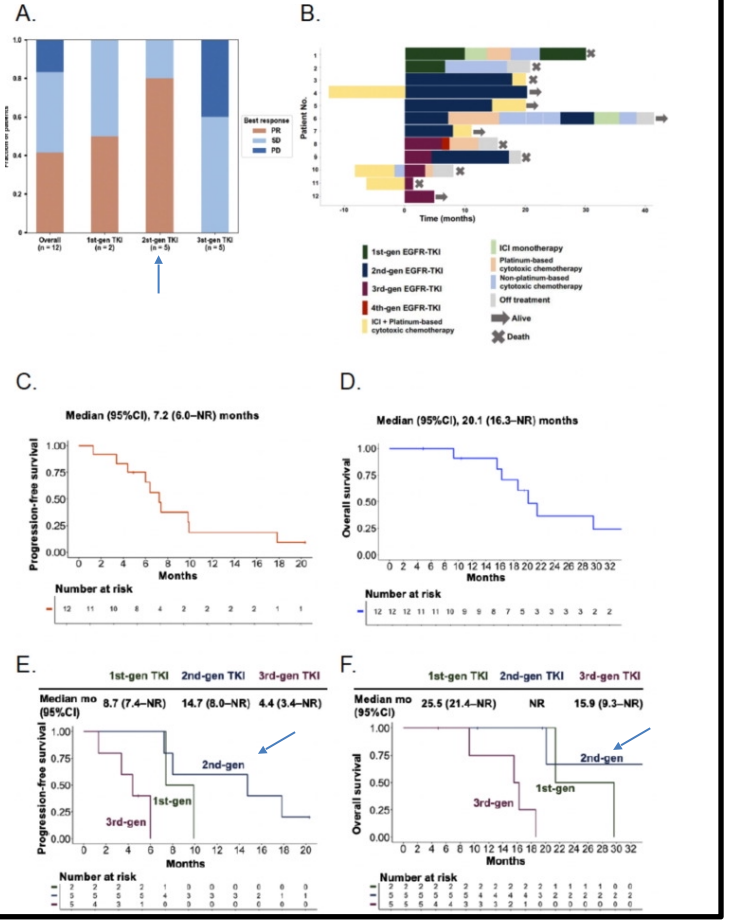
Ba/F3 models of EGFR 19ins and del to probe EGFR-TKis



Stuctural modeling of EGFR ex19ins in complex with EGFR-TKis



Survival outcome of EGFR-TKIs for pts with EGFR ex19ins



Uehara Y et al. Lung Cancer. 2025 Apr:202:108479.

UNCOMMON *EGFR* MUTATIONS IN NSCLC: AFATINIB EVIDENCE

Prospective: ACHILLES/TORG1834 (phase III) *Afatinib vs. Chemo in EGFR uncommon mut patients*

Key inclusion criteria
- Locally advanced/metastatic Non-Sq NSCLC
- ≥20 years
- ECOG performance status 0 / 1
- Sensitizing uncommon mutation*
- No prior systemic anticancer /EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification factors
- Mutation status (Single vs Compound)
- Stage (III/IV vs Recurrence)
- CNS metastasis (Yes vs No)
- Afatinib dose (30 mg vs 40 mg)

R 109

1 → **Platinum + Pemetrexed ** Until PD (n=36)**

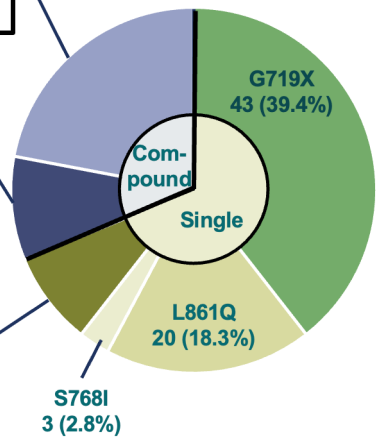
2 → **Afatinib 40mg or 30mg *** Until PD (n=73)**

Clinical trial information: jRCTs031180175

Uncommon/Uncommon 24(22.0%)
G719X+S768I 10
G719X+E709X 7
G719X+L861Q 4
G719X+Others 3

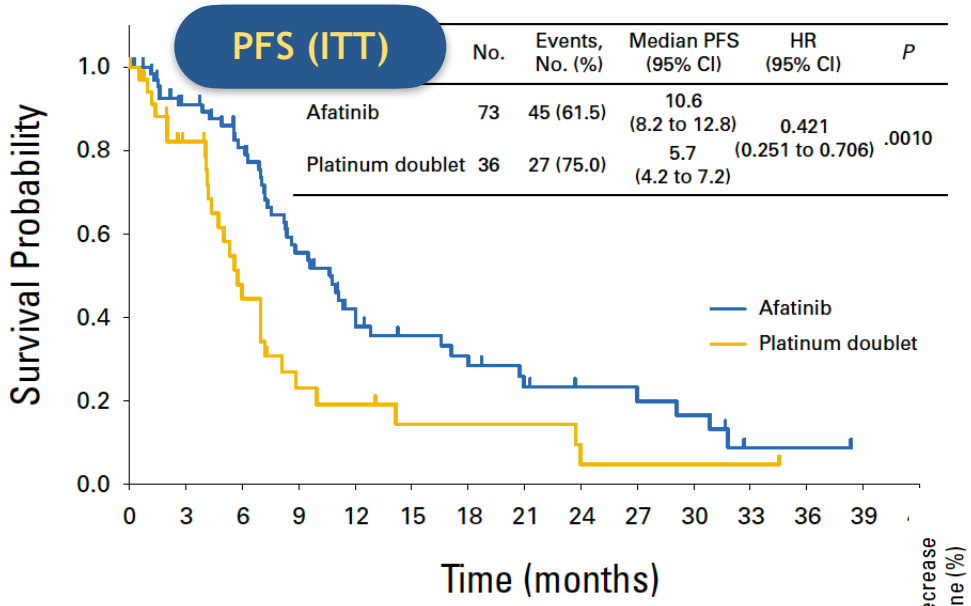
Common/Uncommon 10(9.2%)
L858R+Others 6
Ex19del+Others 4

Other Uncommon 9(8.3%)
Ex18del 4
Ex19del 2
E709X 2
L747P 1



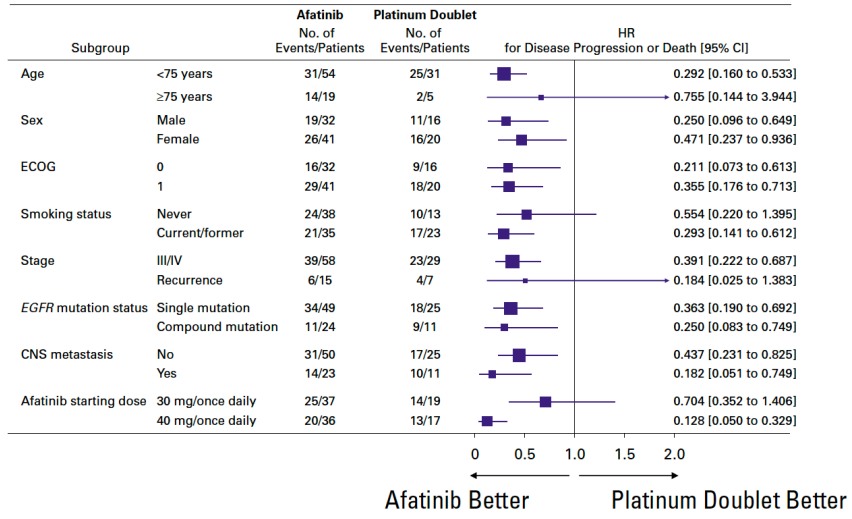
PFS (ITT)

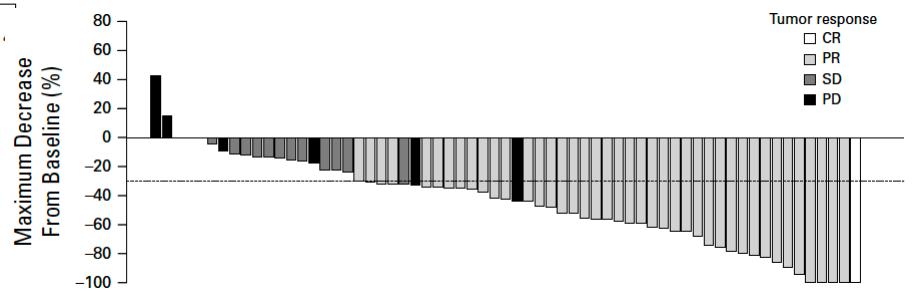
	No.	Events, No. (%)	Median PFS (95% CI)	HR (95% CI)	P
Afatinib	73	45 (61.5)	10.6 (8.2 to 12.8)	0.421 (0.251 to 0.706)	.0010
Platinum doublet	36	27 (75.0)	5.7 (4.2 to 7.2)		



No. at risk (No. censored):

Afatinib	73 (0)	57 (10)	46 (15)	30 (17)	20 (20)	15 (22)	13 (22)	9 (23)	7 (25)	6 (25)	5 (25)	1 (27)	1 (27)	0 (28)
Platinum doublet	36 (0)	25 (5)	13 (6)	6 (7)	5 (7)	3 (8)	3 (8)	3 (8)	1 (8)	1 (8)	1 (8)	1 (8)	0 (9)	0 (9)

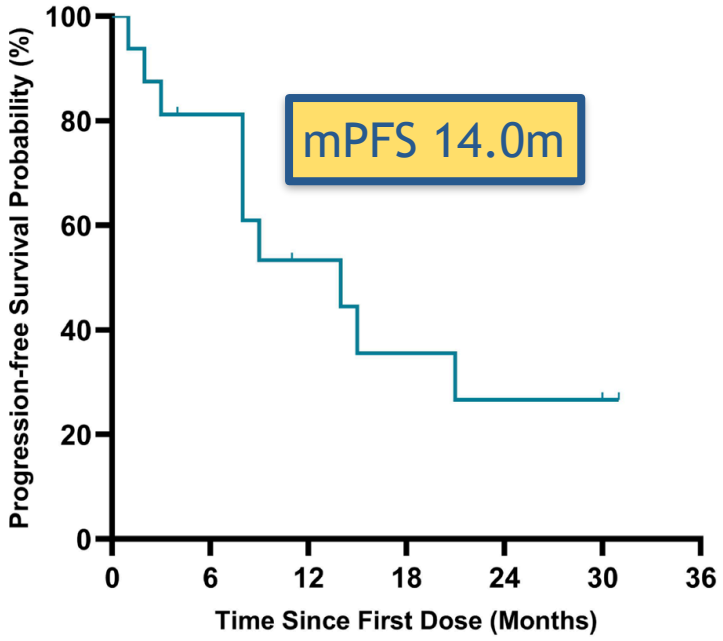


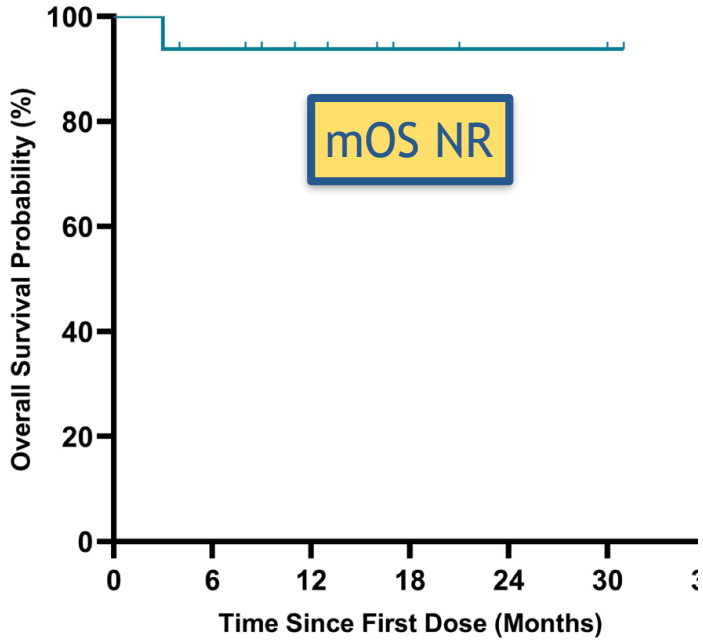


Miura S et al. ESMO 2023; Miura S et al J Clin Oncol 43, 2049-2058(2025)

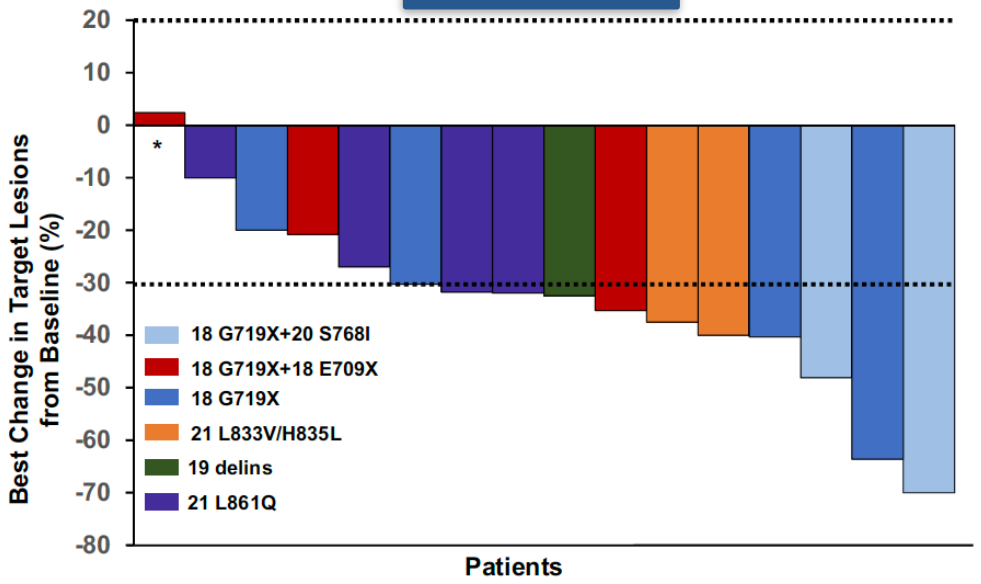
Dacomitinib efficacy: ambispective study

2019-2021
n = 16





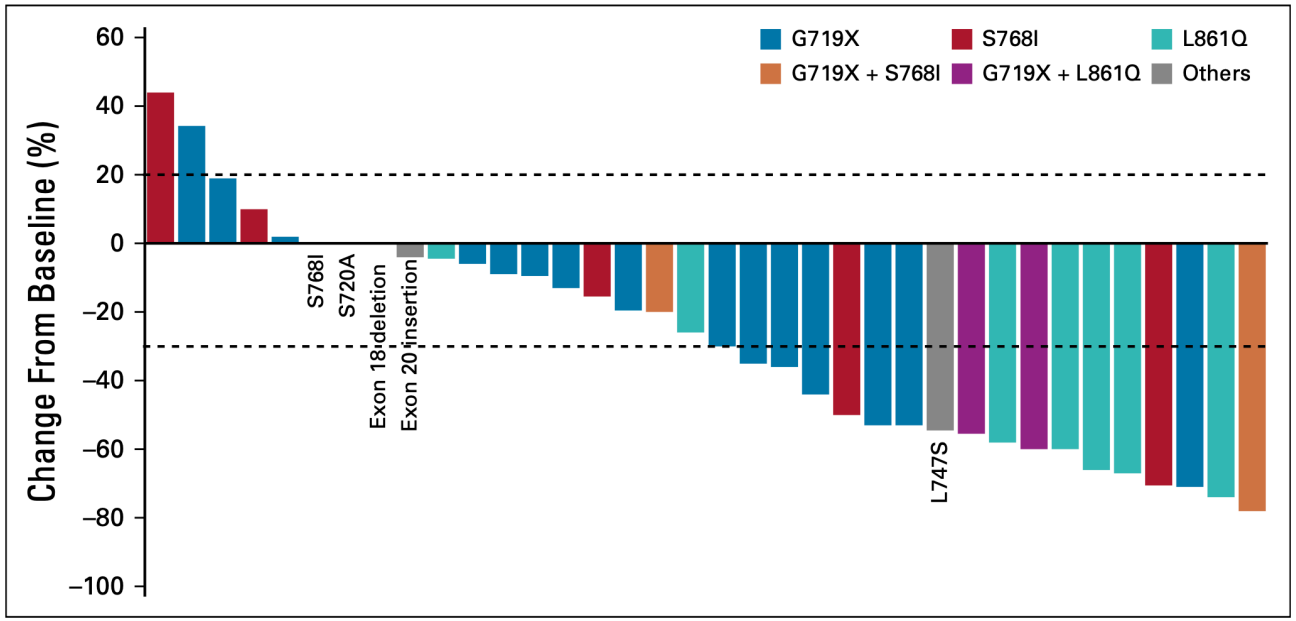
ORR 68.8%
DCR 93.8%
icORR 100%



Pu X et al. BBMC Cancer. 2023 Oct 16;23(1):982

ROLE OF OSIMERTINIB IN *EGFR* UNCOMMON MUTATIONS

KCSG-L U15-0 (phase II)



Mutation	Objective Response		Median Progression-Free Survival, Months (95% CI)
	No. (%)	95% CI	
G719X (n = 19)	10 (53)	28 to 77	8.2 (6.2 to 10.2)
G719X (n = 15)			
G719X + S768I (n = 2)			
G719X + L861Q (n = 2)			
L861Q (n = 9)	7 (78)	44 to 100	15.2 (1.3 to 29.1)
L861Q (n = 7)			
L861Q + G719X (n = 2)			
S768I (n = 8)	3 (38)	0 to 81	12.3 (0 to 28.8)
S768I (n = 6)			
S768I + G719X (n = 2)			

-KCSG-L U15-0 indicated that patients with tumors harboring major uncommon mutations were generally sensitive to osimertinib

- The response rates in patients with G719X (n=19), L861Q (n=9), and S768I (n=8) were 53%, 78%, and 38%, respectively

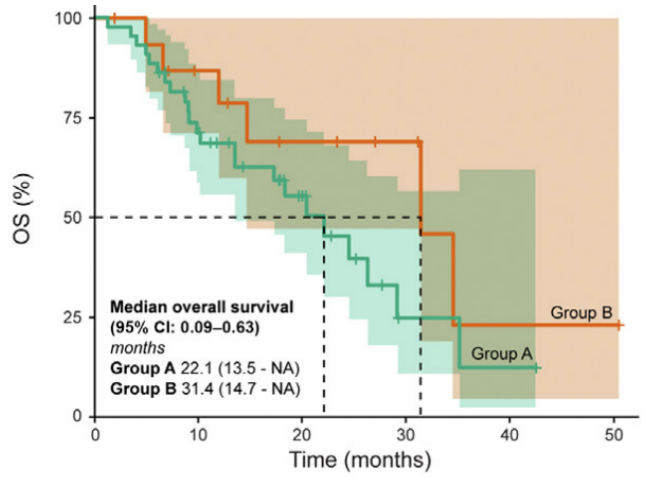
In contrast to afatinib and osimertinib, a subanalysis of **the phase 3 NEJ-002 trial** (gefitinib versus chemotherapy) indicated that the G719X, S768I, and L861Q mutations were less sensitive to gefitinib, with a response rate of 20%.

Cho et al. JCO 2019

ROLE OF OSIMERTINIB IN *EGFR* UNCOMMON MUTATIONS

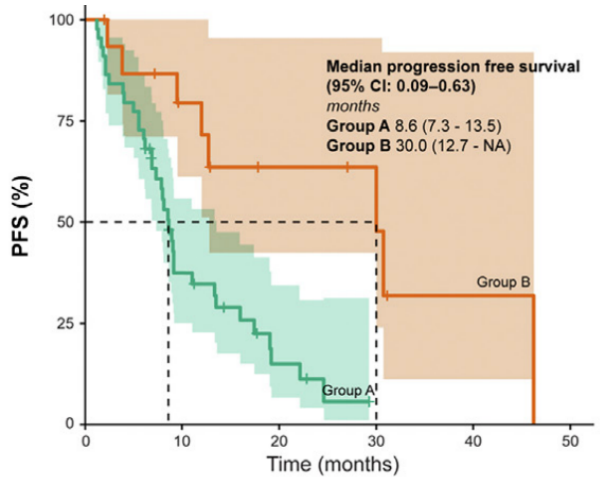
UNICORN (RWD)

International Case Series on efficacy of Osimertinib in Real-Life Practice upfront



Number at risk

Group A	44	28	13	2	1	0
Group B	16	11	6	4	1	1



Number at risk

Group A	44	14	4	0	0	0
Group B	16	10	5	4	1	0

**Uncommon mut (Group A) vs. Uncommon compound + Common (Group B):

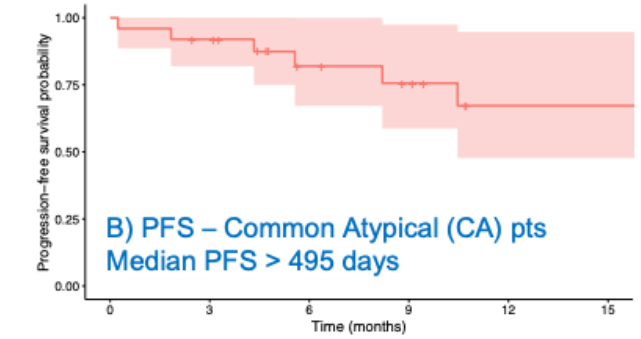
-OS: HR 0.55 (95% CI: 0.22–1.36, p= 0.19)

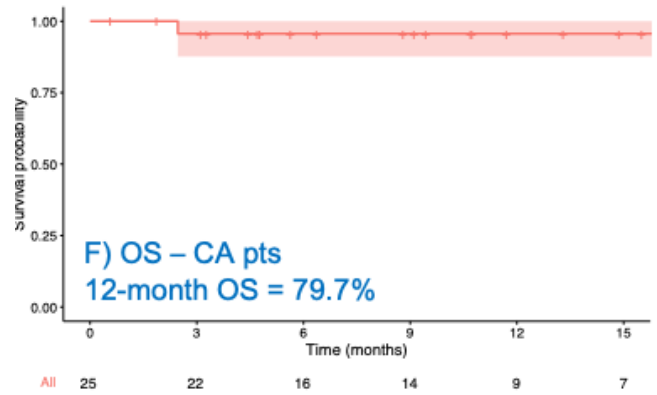
-PFS: HR 0.24 (95% CI: 0.09–0.63, p= 0.0017)

**Uncommon *EGFR* mutations: ORR was 60%, mPFS 8.6 months, and mOS 22.1 months

OCELOT (phase II)

Osimertinib upfront in NSCLC + major uncommon EGFR mut

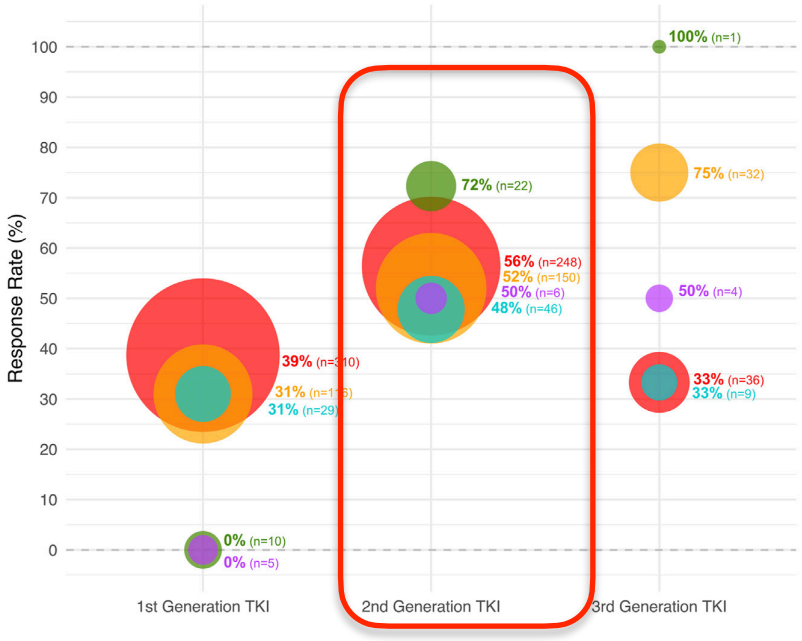




ORR 50%
DCR 85%

Bar et al. J Thor Oncol, 2023; Breadner et al. ESMO 2023

Systematic review: Uncommon EGFR & responses with different TKI generations. Single and compound muts.

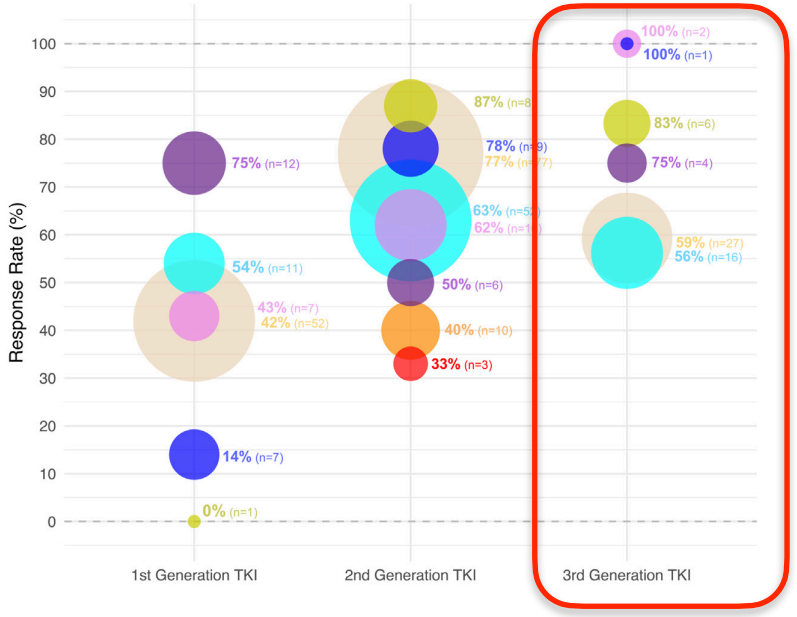


Legend:
- each bubble represents the response rate for a mutation (color-code) with response rate and number of patients (n)
- the size of each bubble is proportional to the number of patients.

Single

Uncommon EGFR mutations:

- G719X
- L861Q
- S768I
- L747X
- E709X



Legend:
- each bubble represents the response rate for a mutation (color-code) with response rate and number of patients (n)
- the size of each bubble is proportional to the number of patients.

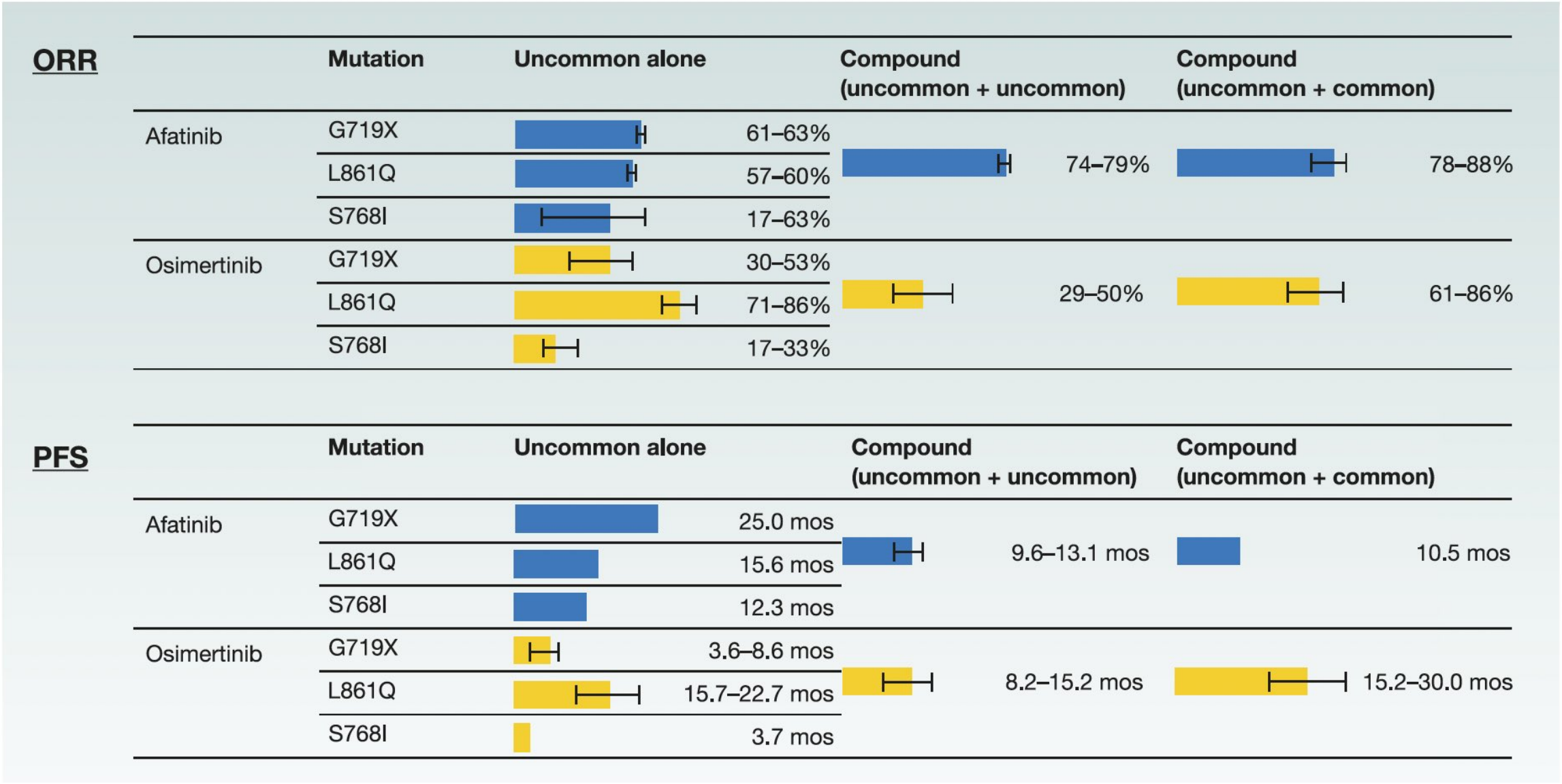
Compound

Uncommon Compound EGFR mutations:

- G719X - CM with common
- G719X - CM with uncommon
- L861Q - CM with common
- L861Q - CM with uncommon
- S768I - CM with common
- S768I - CM with uncommon
- E709X - CM with common
- E709X - CM with uncommon

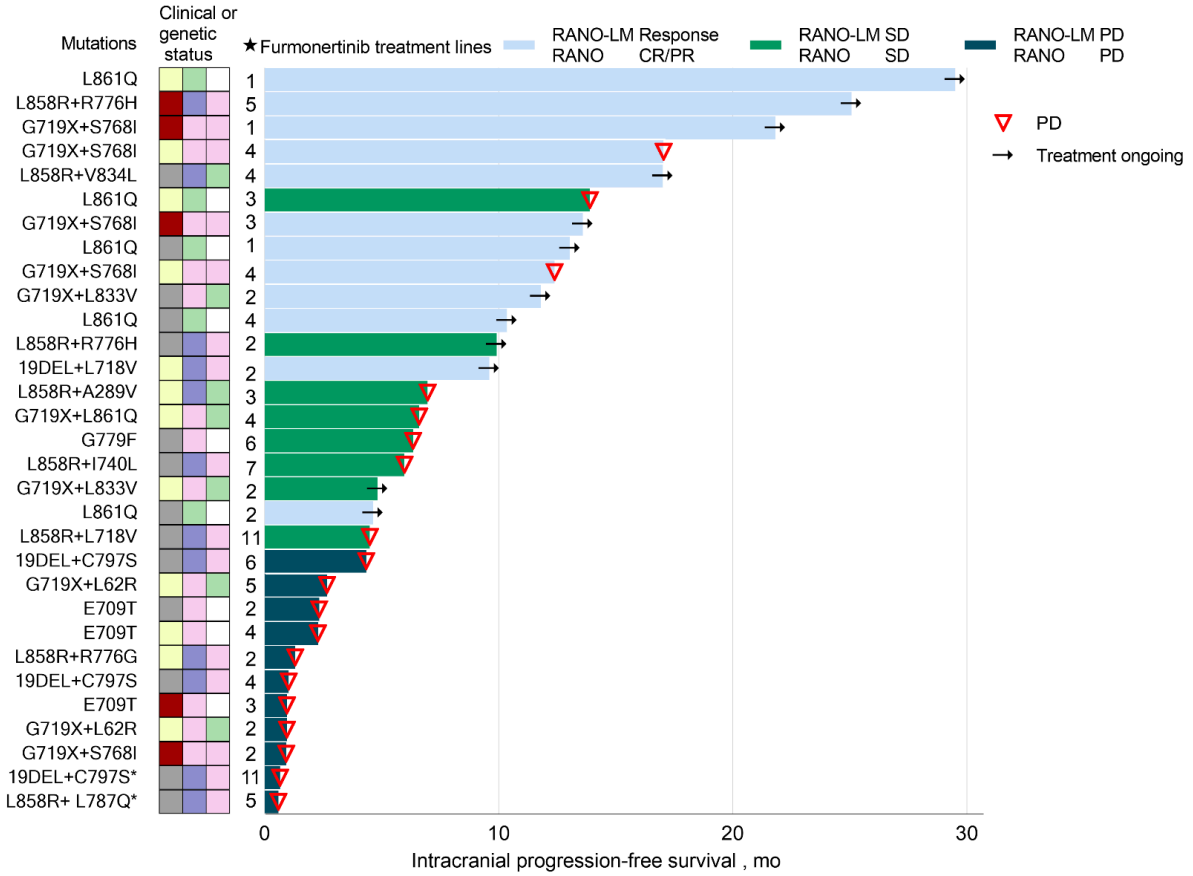
Borgeaud M et al. Journal of Thoracic Oncology, Volume 19, Issue 7, 973 - 983

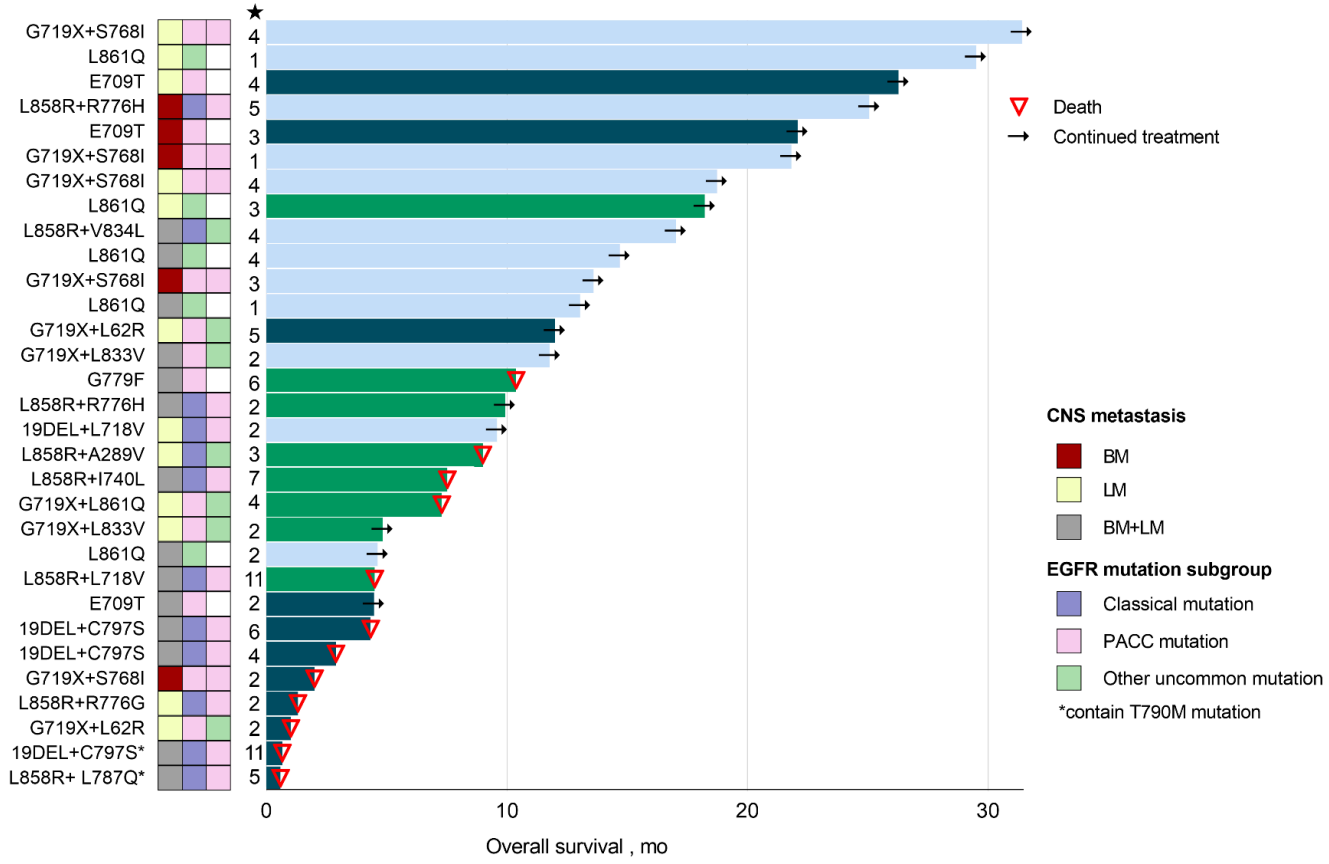
AFATINIB vs OSIMERTINIB IN EGFR UNCOMMON MUTATIONS



Maehara K . Published on X.com

Furmonertinib: Uncommon EGFR + Brain mets



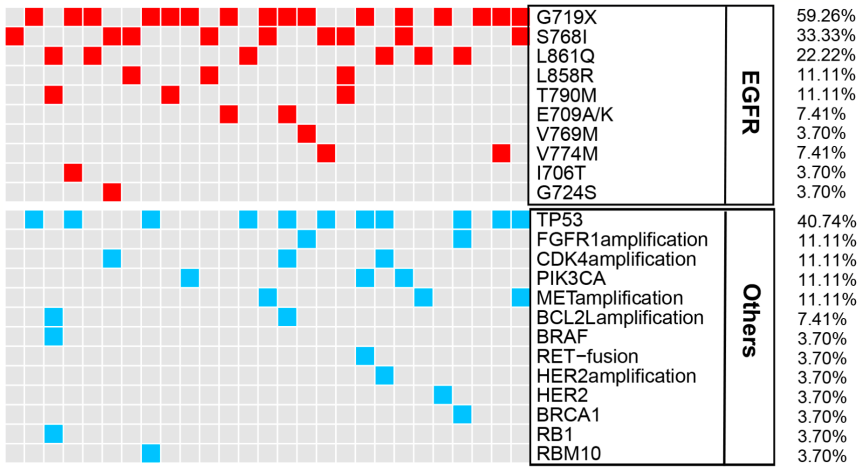


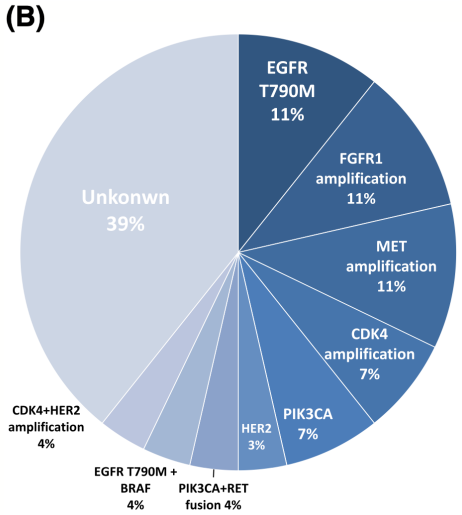
This study highlights the potential CNS efficacy of furmonertinib in NSCLC patients with uncommon EGFR mutations, suggesting furmonertinib is a promising option for the cohort.

Cun Fanf S et Yuwen X.. ELCC 2025

Resistance mechanisms in uncommon EGFR muts

AFATINIB

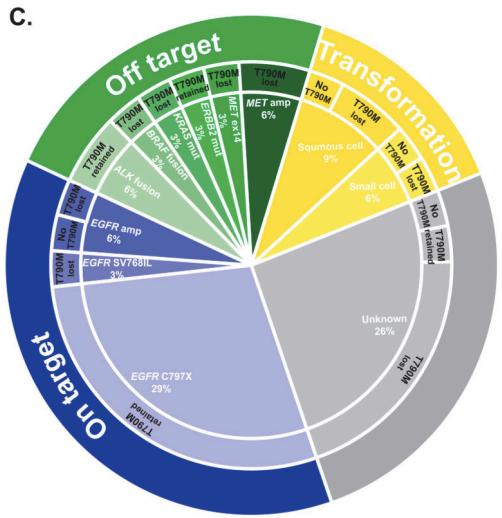




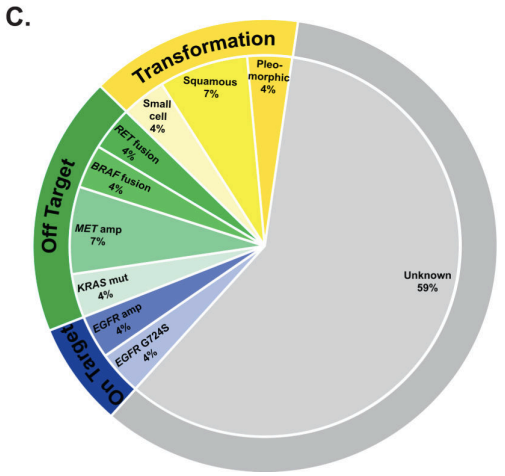
- *EGFR* T790, *FGFR1* amplification and *MET* amplification are the frequent ones
- *TP53* was the most common coexisted mutation (40.7%)
- *EGFR* T790 seems to be lower than *EGFR* classical mutations

OSIMERTINIB

Pretreated

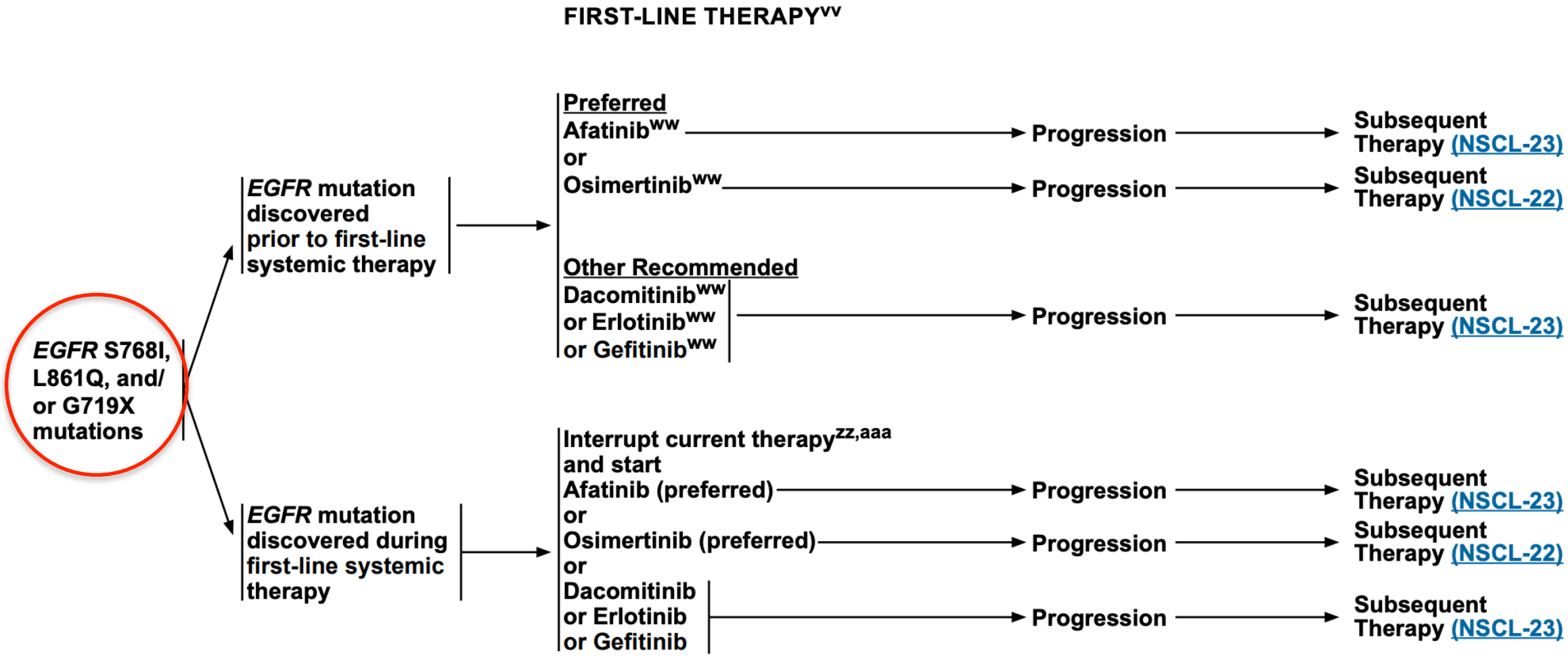


First-line



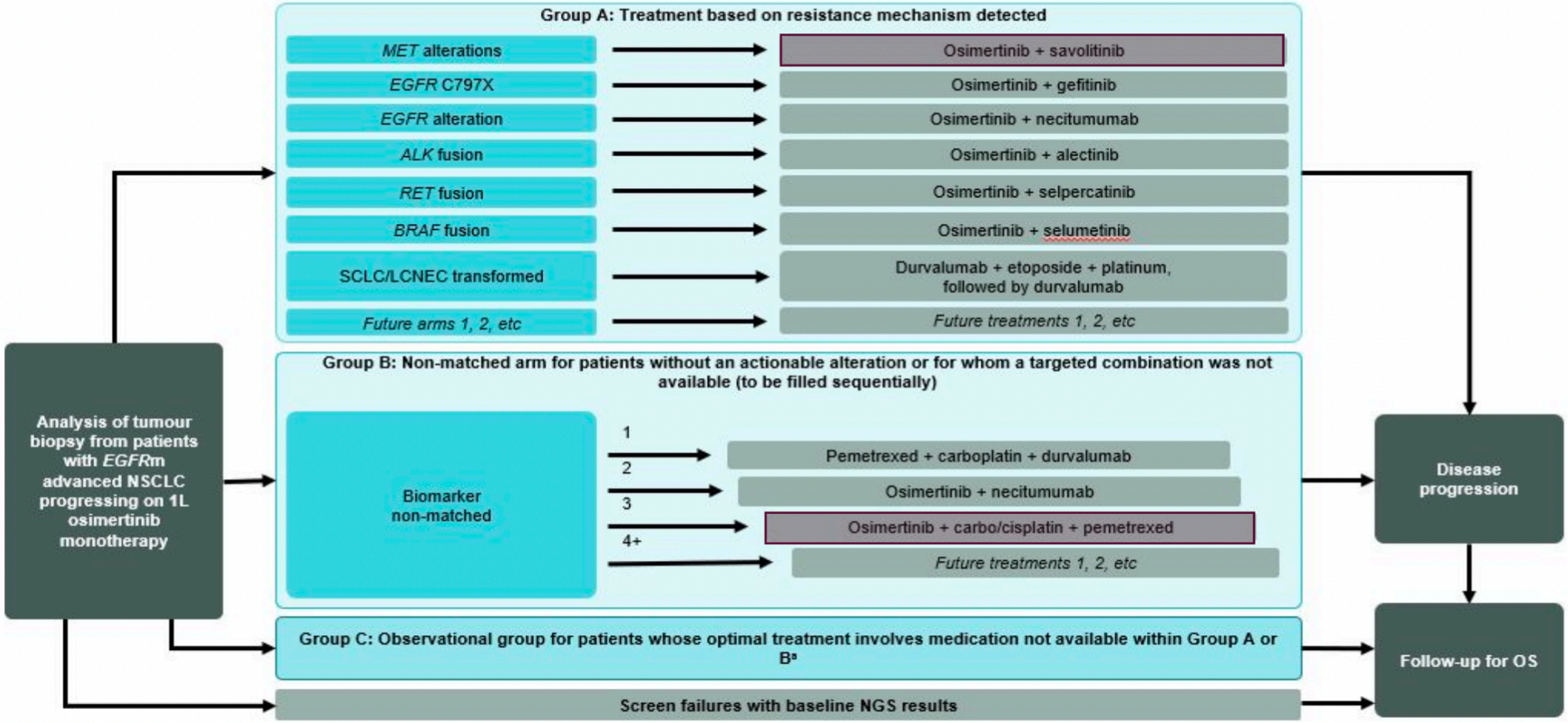
Pang L, et al. Cancer, 2022; Schoenfeld AJ, et al. Clin Cancer Res, 2020

NCCN Guidelines Version 1.2026 Non-Small Cell Lung Cancer



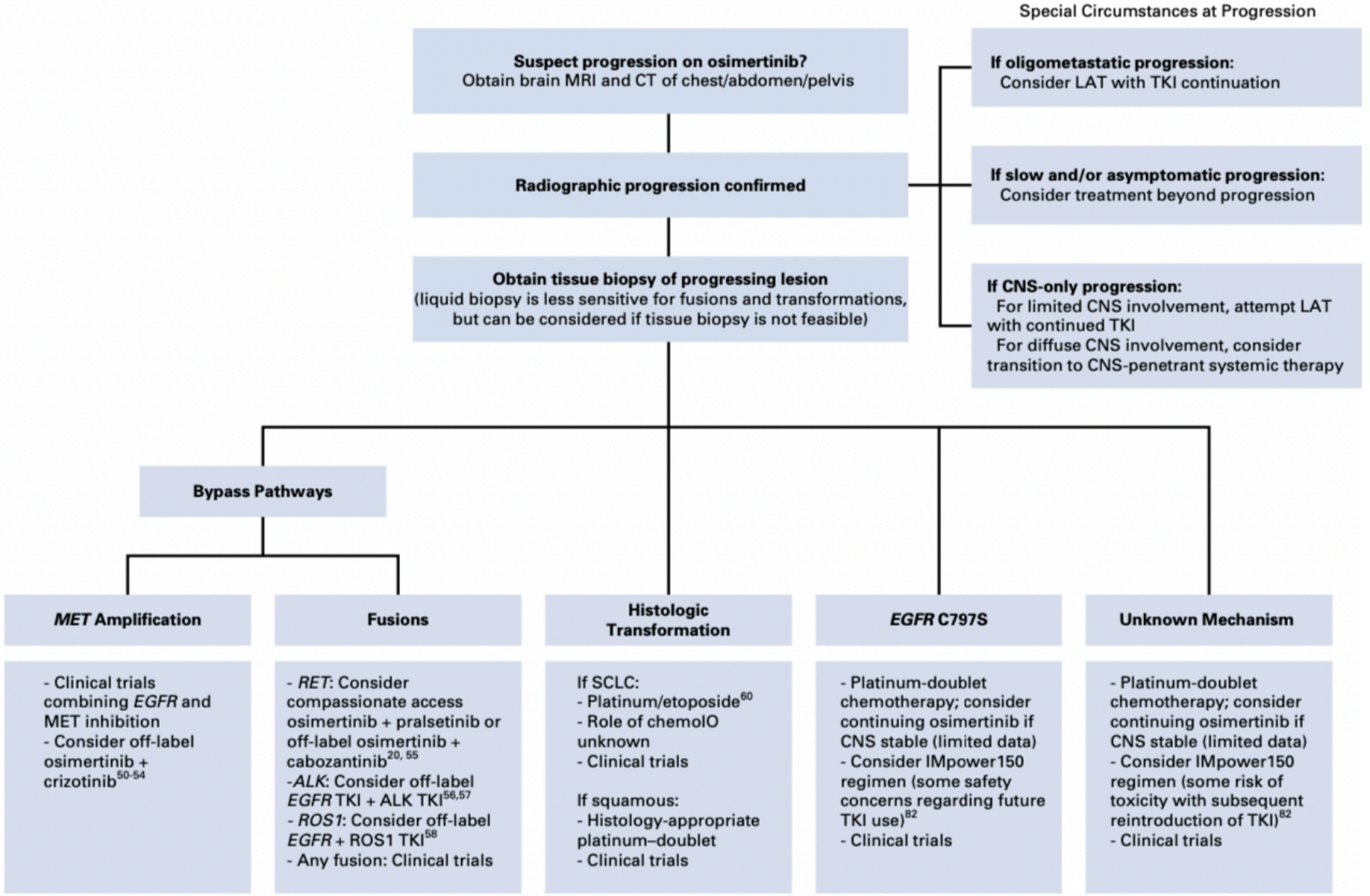
https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; accessed nov 25th, 2025

ORCHARD: Phase 2 ORCHARD Trial Designed to Understand the Resistance Mechanisms Observed After 1L Osimertinib and Explore Treatment Options[1,2,3]



NCT03944772

Treatment options when there is not a clinical trial available

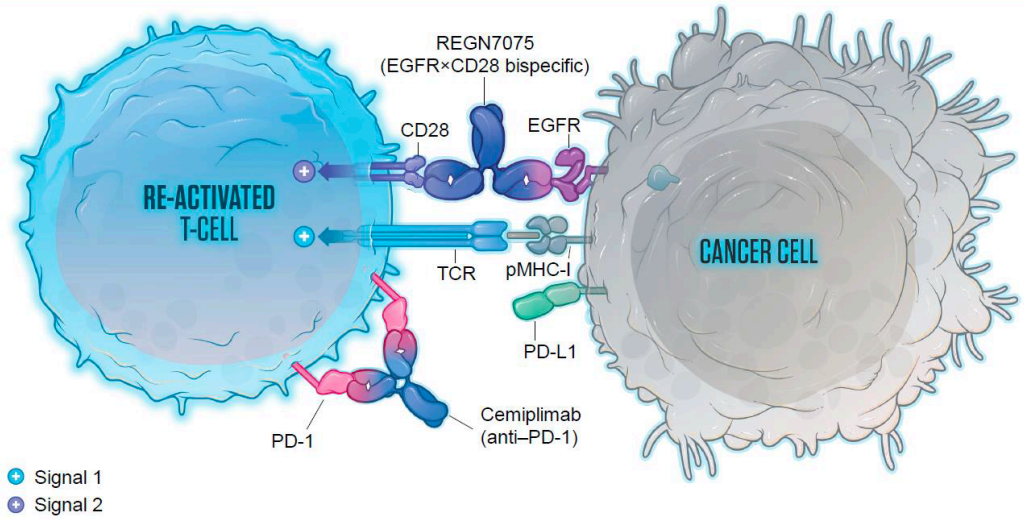


Piper-Valillo A, et al. J Clin Oncol, 2020

T-cell engagers in EGFR mutant NSCLC e.gEGFR x CD28

REGN7075, NCT04626635

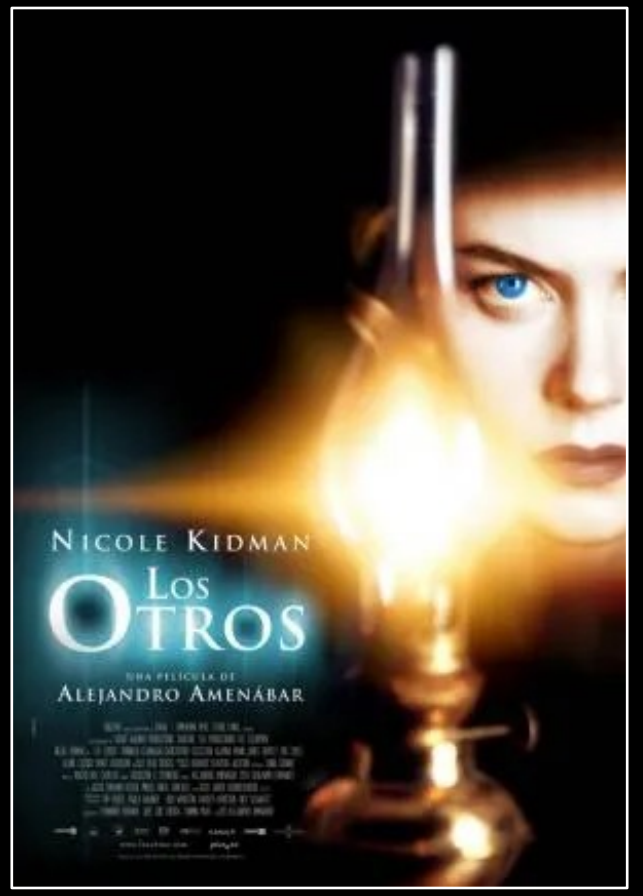
Figure 1. Mechanism of action of REGN7075 (EGFR×CD28 costimulatory bispecific antibody)



Cohort 1	Cohort 2	Cohort 3
Patients with histologically or cytologically documented locally advanced or metastatic NSCLC who:	Patients with histologically or cytologically documented locally advanced or metastatic *EGFR*-mutated non-squamous NSCLC who:	Patients with histologically or cytologically documented locally advanced or metastatic *EGFR*-mutated non-squamous NSCLC who:
• Are not candidates for curative surgery or curative radiation • Are anti–PD-1/PD-L1 naïve		
Treatment naïve with no targetable driver mutation (*ALK/ROS1/EGFR/RET*-fusion/*MET* exon 14 skipping) with any PD-L1 expression level	Have a previously documented targetable *EGFR* mutation: • NSCLC that harbors *EGFR* exon 19 deletion • NSCLC that harbors *EGFR* L858R mutation • NSCLC with activating *EGFR* exon 20 insertion • NSCLC with exon 18/21 atypical mutations Have received treatment with a third-generation TKI	
Have received no prior systemic treatment for recurrent or metastatic NSCLC (adjuvant or neoadjuvant systemic treatments will not be counted as a prior line)	Are chemotherapy naïve	Have received treatment with platinum-doublet chemotherapy

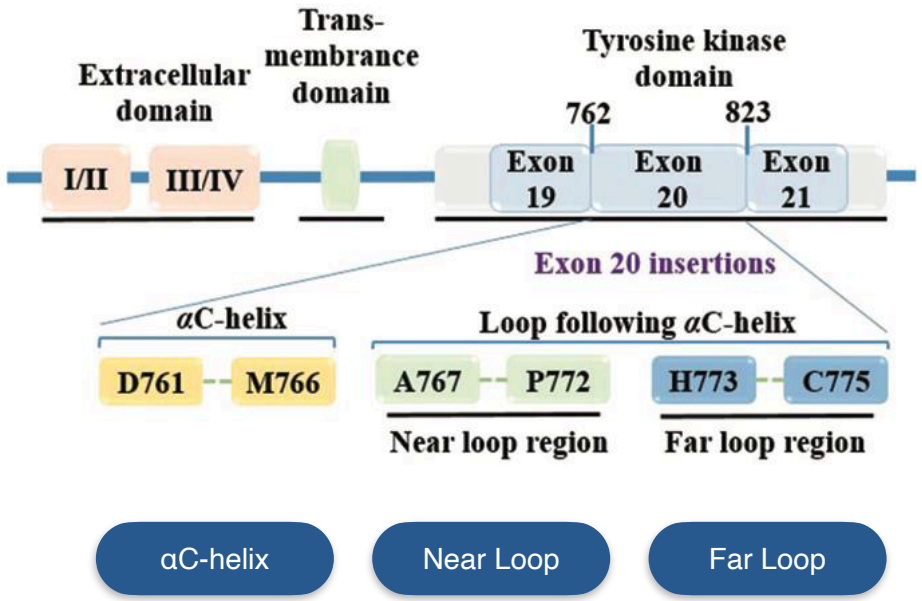
4

EGFR Ex20ins



EGFR Ex20ins is a family itself

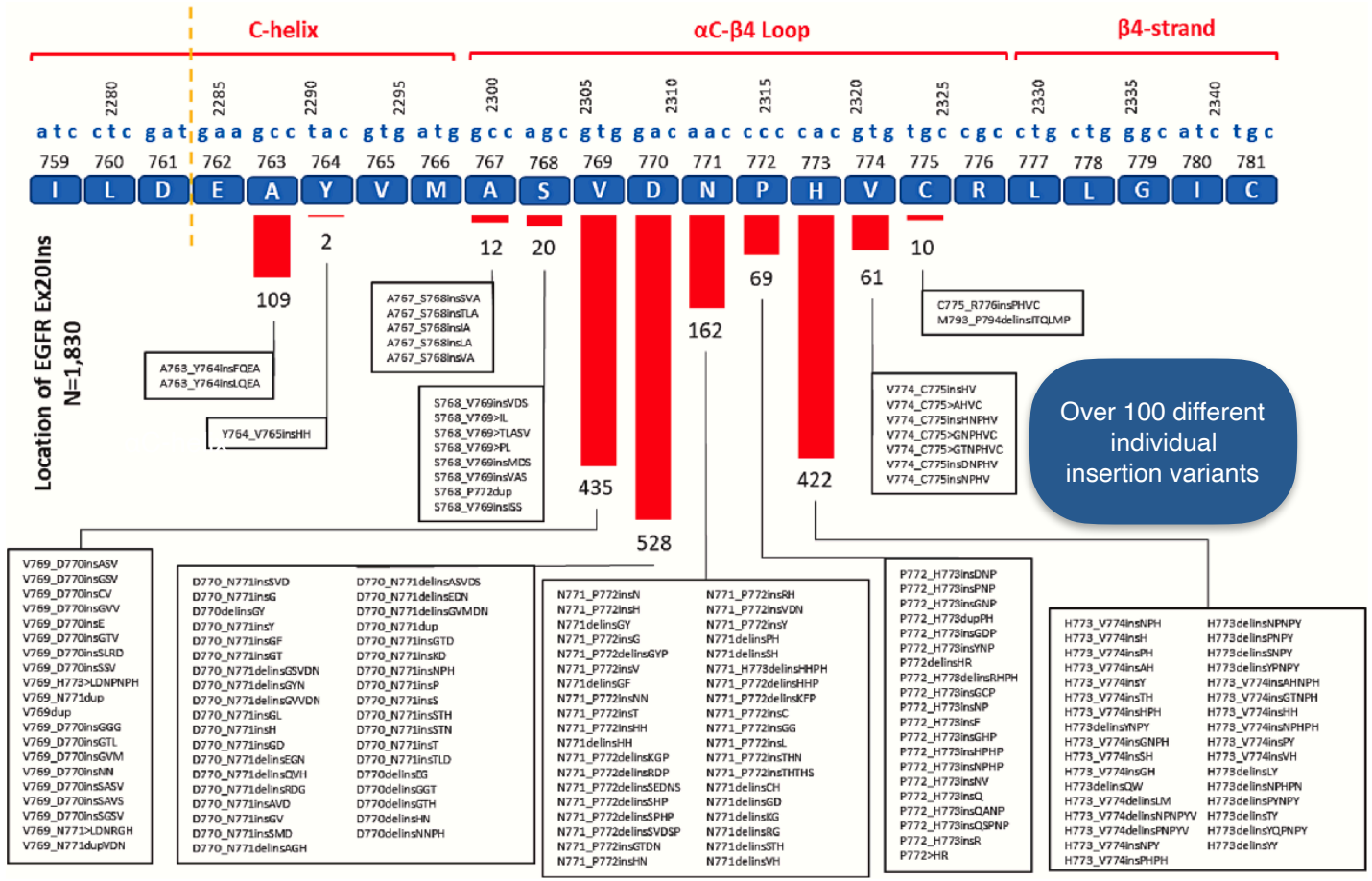
Position of insertion variants in EGFR exon 20



αC-helix | Near Loop | Far Loop

Exon 20 NSCLC: US and China

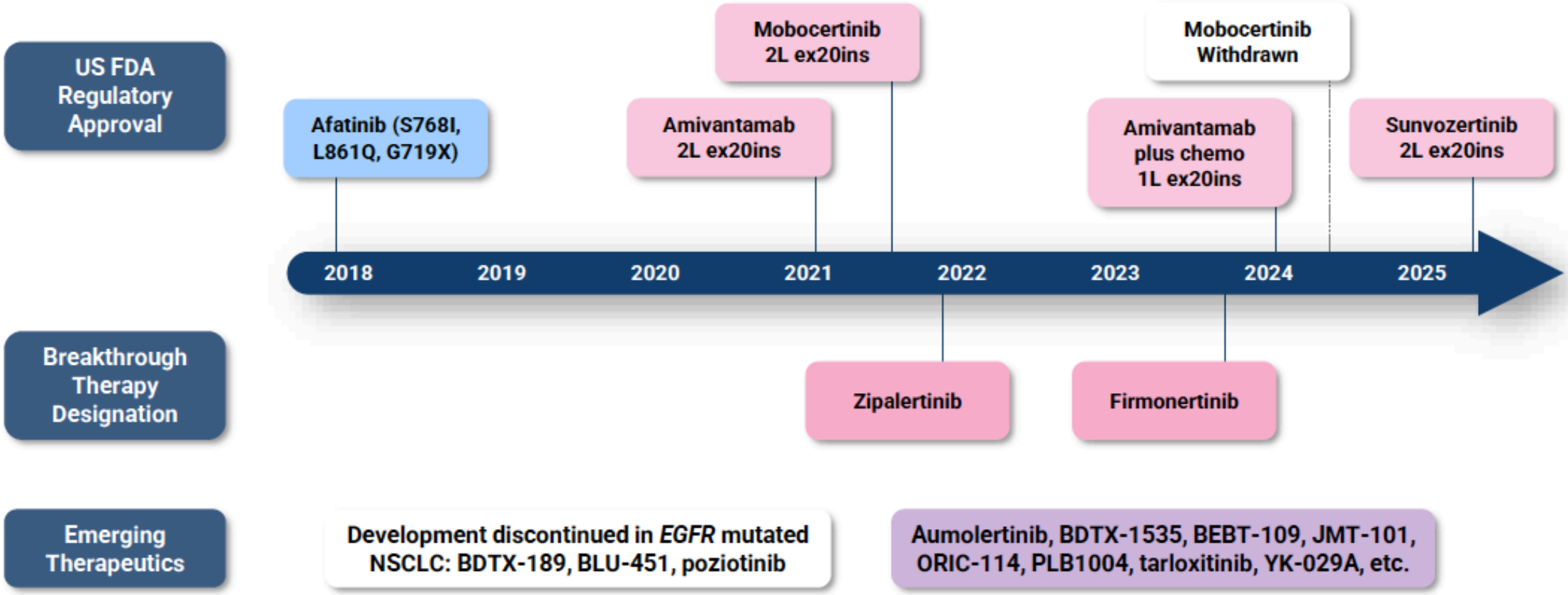
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR	2.1%	3.6%	7700
	HER2	1.5%		
China	EGFR	2.4%	6.3%	41100
	HER2	3.9%		



Prevalence of EGFR exon 20 insertion variants

Heymach J, WCLC 2018; Zhu et al, Expert Opin Ther Pat 2025; Dorta-Suárez et al, Cancer Treat Rev 2024

Treatment landscape of EGFR Ex20ins



Presented by Aaron C. Tan at IASLC WCLC 2025

EXCLAIM-2: Mobocertinib vs CT

Phase 3, randomized, open-label study (NCT04129502)

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- *EGFR* ex20ins by local testing
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS of 0 or 1
- No prior systemic anticancer treatment

N=354

Randomized 1:1

- Mobocertinib 160 mg orally qd with or without food (Arm A)
- Pemetrexed 500 mg/m² + cisplatin 75 mg/m² IV or Pemetrexed 500 mg/m² + carboplatin AUC 5 IV (Arm B)

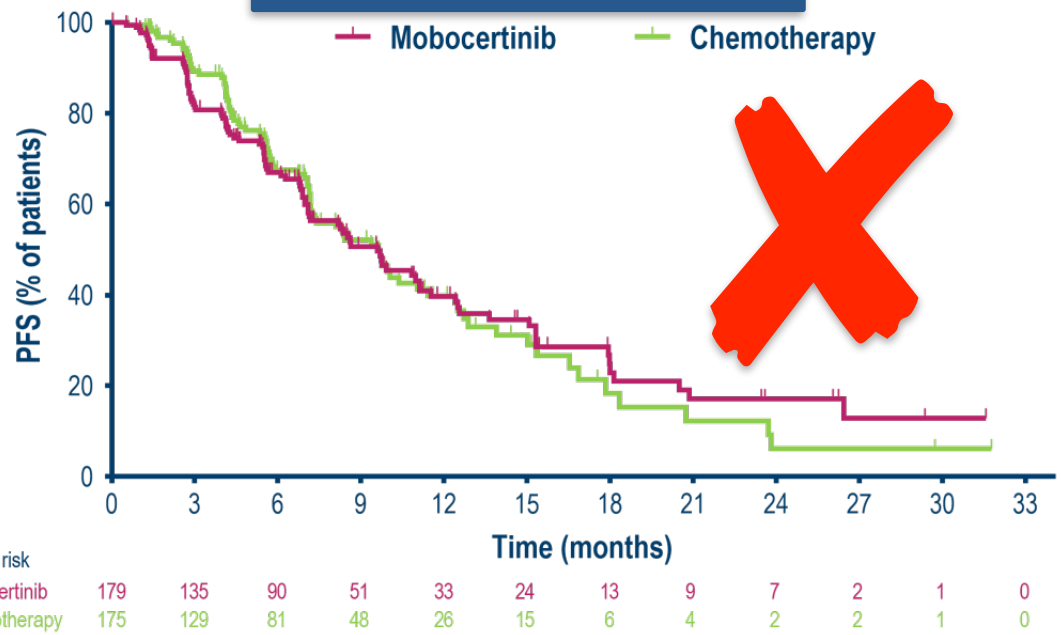
Randomization was stratified by:
- CNS metastases at baseline (y/n)
- Race (Asian/non-Asian)

Disease assessed by CT and MRI at screening and at 6-week intervals through Cycle 18 and every 12 weeks thereafter; brain MRI at baseline

Continue until:
- IRC-assessed PD
- Intolerable toxicity
- Other discontinuation criteria

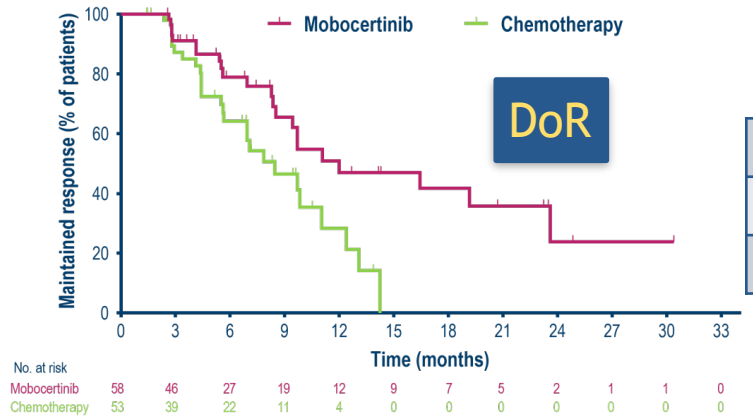
Patients in Arm B could cross over to mobocertinib after BICR-assessed PD

PFS: Primary endpoint



	Mobocertinib (n=179)	Chemotherapy (n=175)
PFS events, n (%)	98 (55)	86 (49)
Median PFS (95% CI), m	9.6 (7.1–11.1)	9.6 (7.2–11.4)
HR (95% CI)	1.04 (0.77–1.39) *P*=0.803	

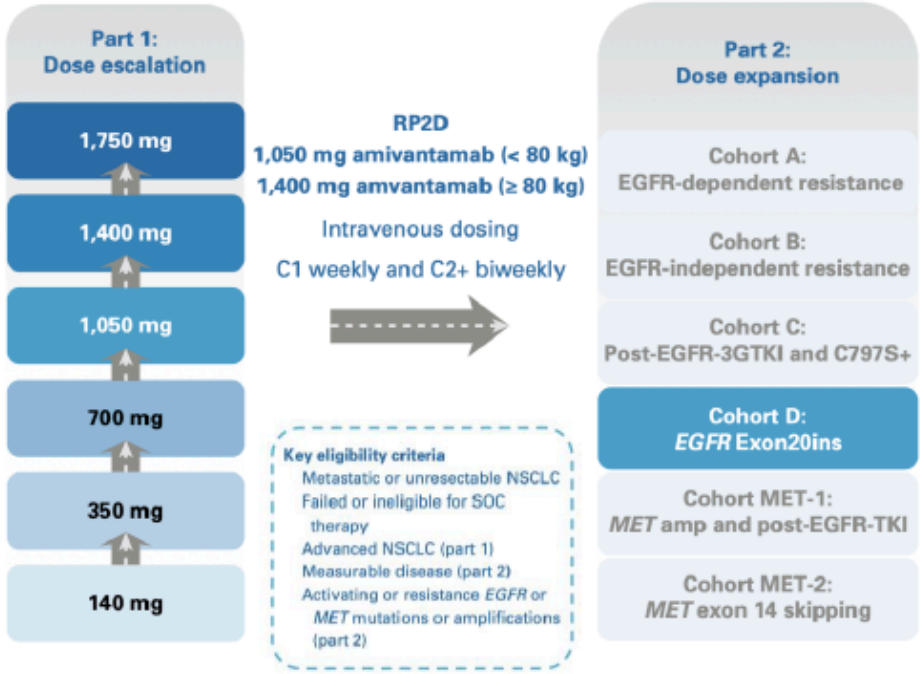
DoR



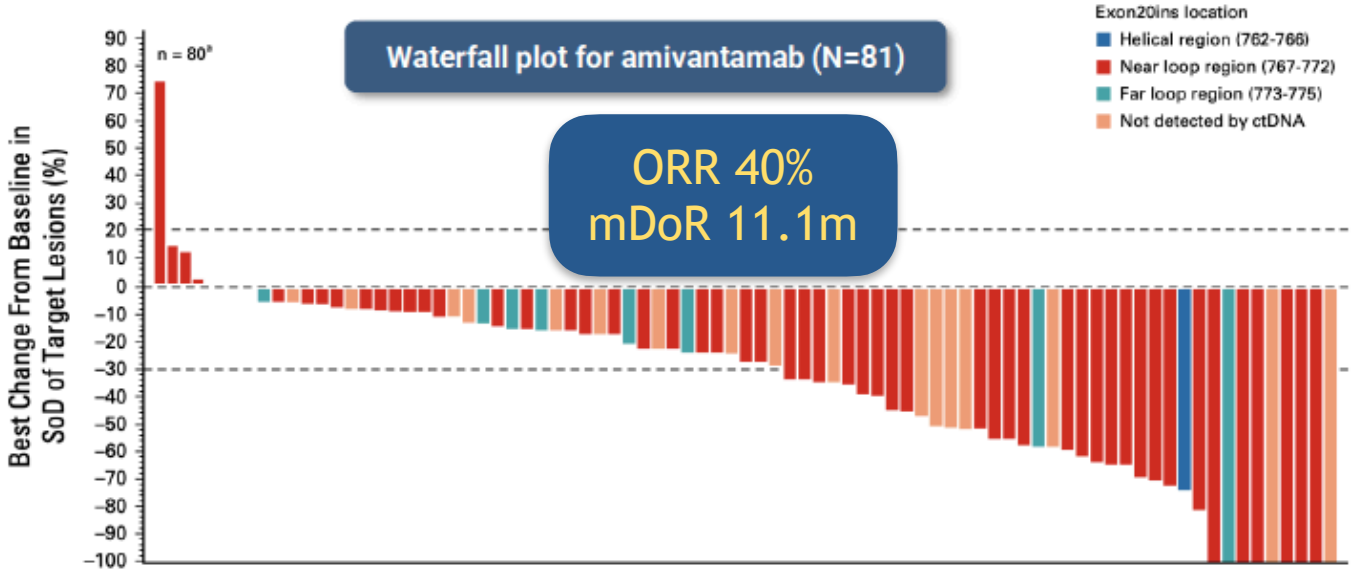
	Mobocertinib (n=58)	Chemotherapy (n=52)
Median DoR (95% CI), m	12.0 (8.5–23.6)	8.4 (5.7–11.0)
HR (95% CI)	0.48 (0.26–0.88)	

Jänne P et al. ESMO ASIA 2023

Amivantamab: CHRYSALIS phase I trial



Population Characteristics	%
Baseline brain metastases	32%
Prior EGFR TKI	26%



Efficacy (N=81): ORR 40%, mDoR 11.1 mths, mPFS 8.3 mths, mOS 23mths
Safety (all grade / ≥G3): rash (86% / 4%), infusion reaction (66% / 3%)

Park K et al, J Clin Oncol 2021

Amivantamab + CT: PAPILLON phase III trial

Key Eligibility Criteria

- Treatment-naïve,[a] locally advanced or metastatic NSCLC
- Documented *EGFR* Exon 20 insertion mutations
- ECOG PS 0 or 1

Stratification Factors

- ECOG PS
- History of brain metastases[b]
- Prior EGFR TKI use[a]

1:1 Randomization (N=308)

- **Amivantamab-Chemotherapy** (n=153)
- **Chemotherapy** (n=155)

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at week 7 (first day of cycle 3)

Chemotherapy on the first day of each cycle:

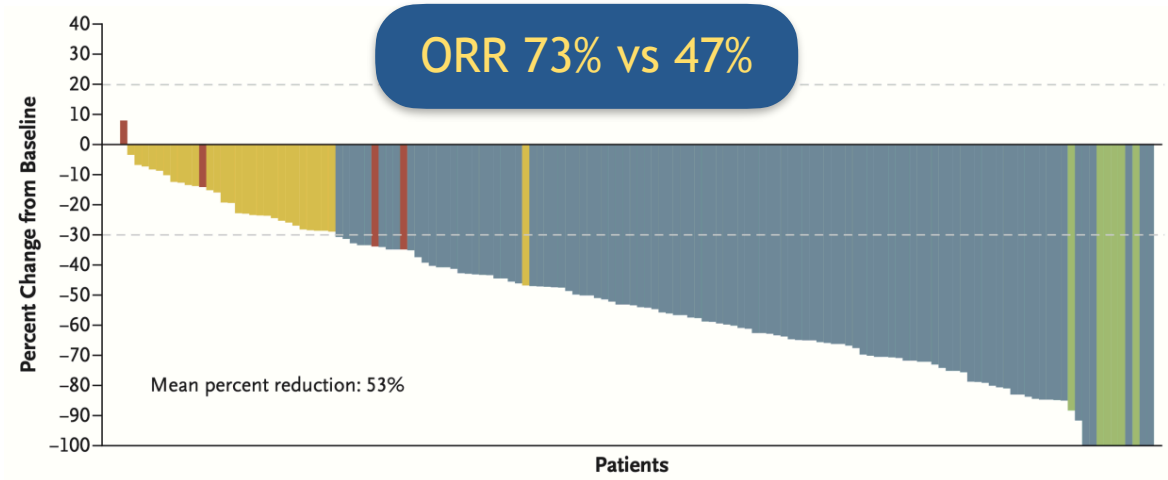
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Primary endpoint: Progression-free survival (PFS) by BICR according to RECIST v1.1[c]

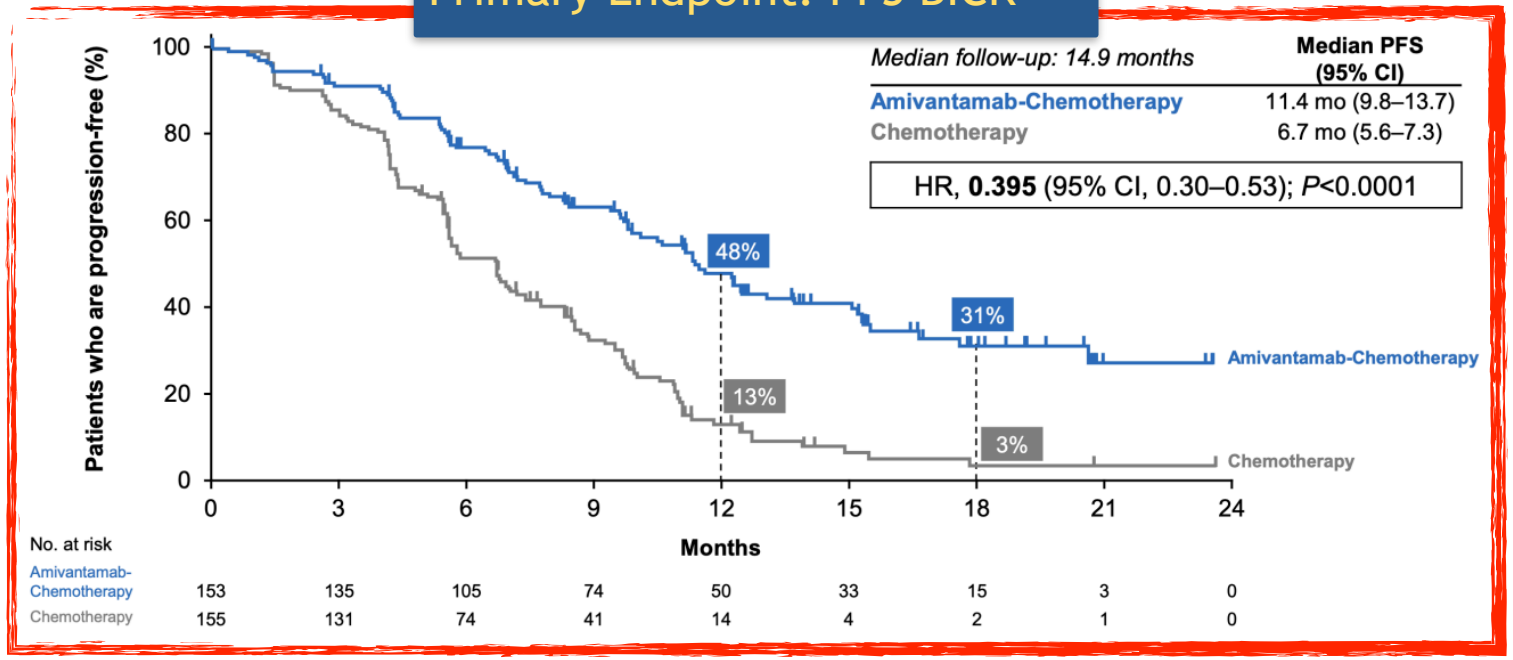
Secondary endpoints:

- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[d]
- Time to subsequent therapy[d]
- Safety

Optional crossover to 2nd-line amivantamab monotherapy[e]



Primary Endpoint: PFS BICR



Safety (ami+chemo vs chemo):

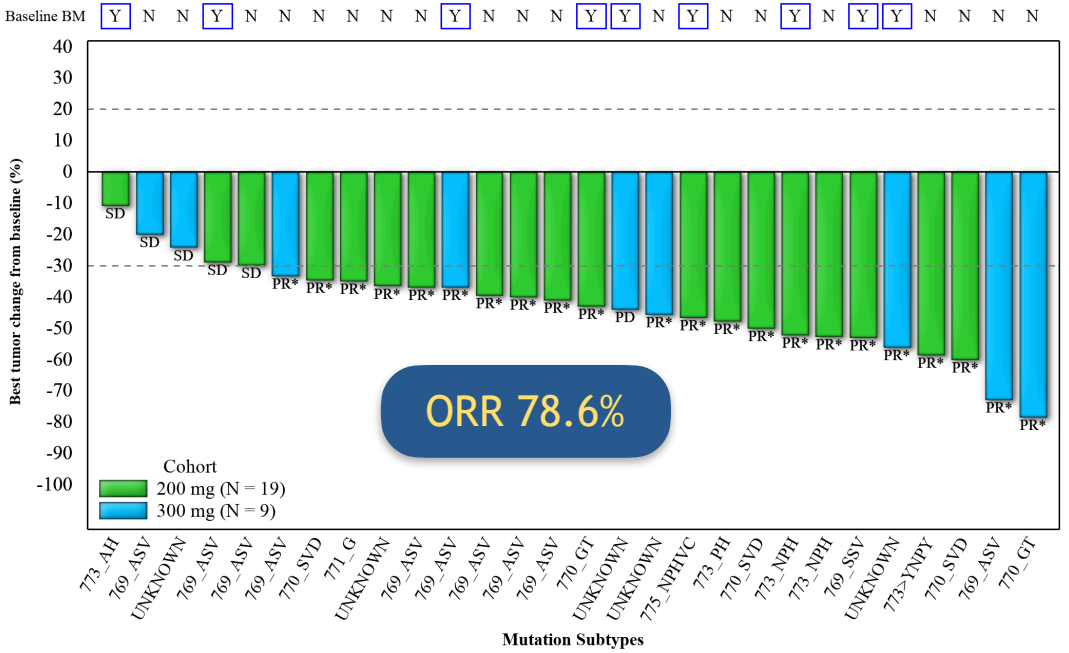
- ≥G3 75% vs 54%
- SAE 37% vs 31%
- Dose reduction 48% vs 23%
- Discontinuation 24% vs 10%

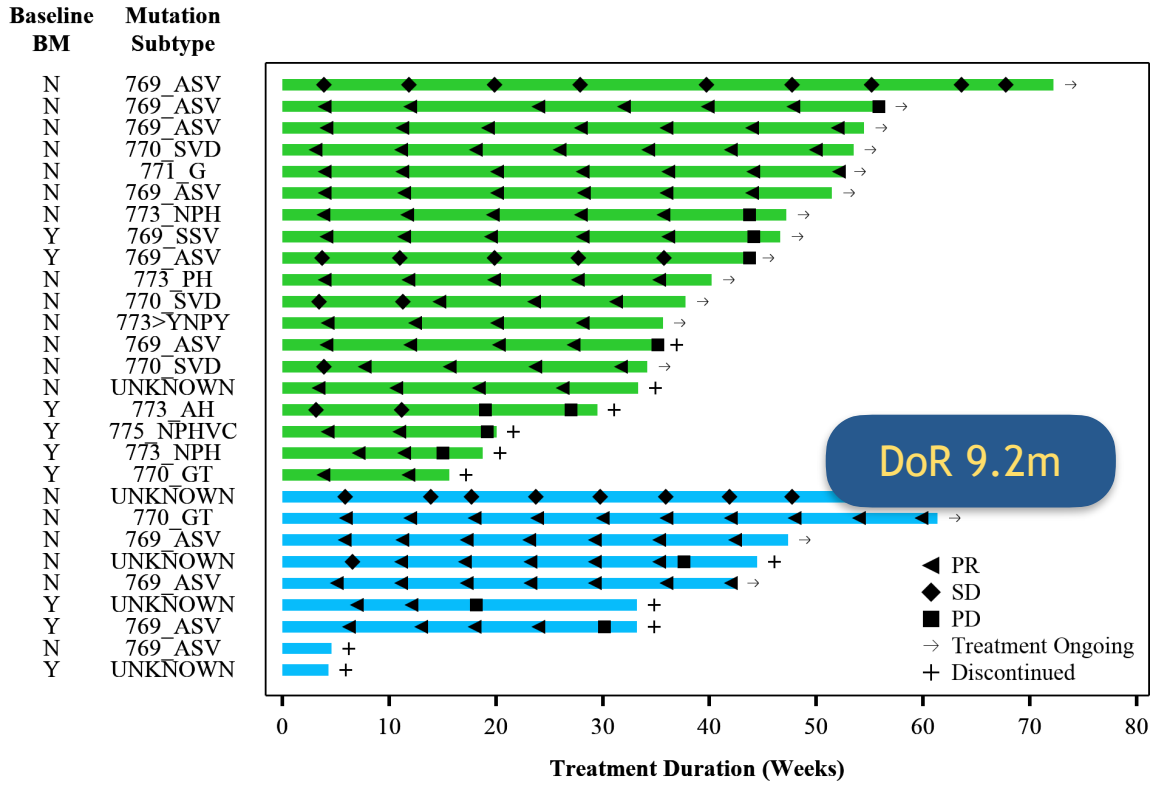
Girard N et al, ESMO 2023; Zhou C et al, N Engl J Med 2023

Sunvozertinib monotherapy (WU-KONG1 + WU-KONG15, 1st line phase 2)

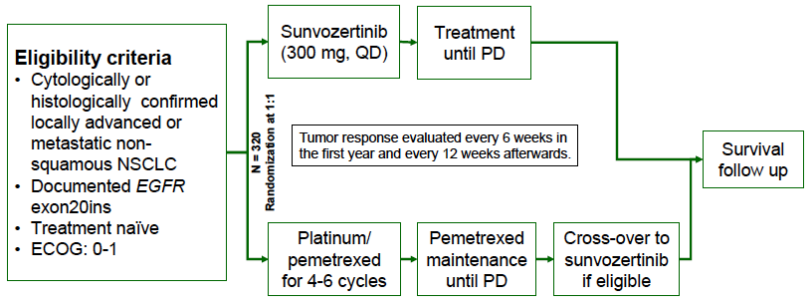
Sunvozertinib 200 or 300mg QD

Efficacy analysis set n= 28





Phase III Study Design (WU-KONG28)



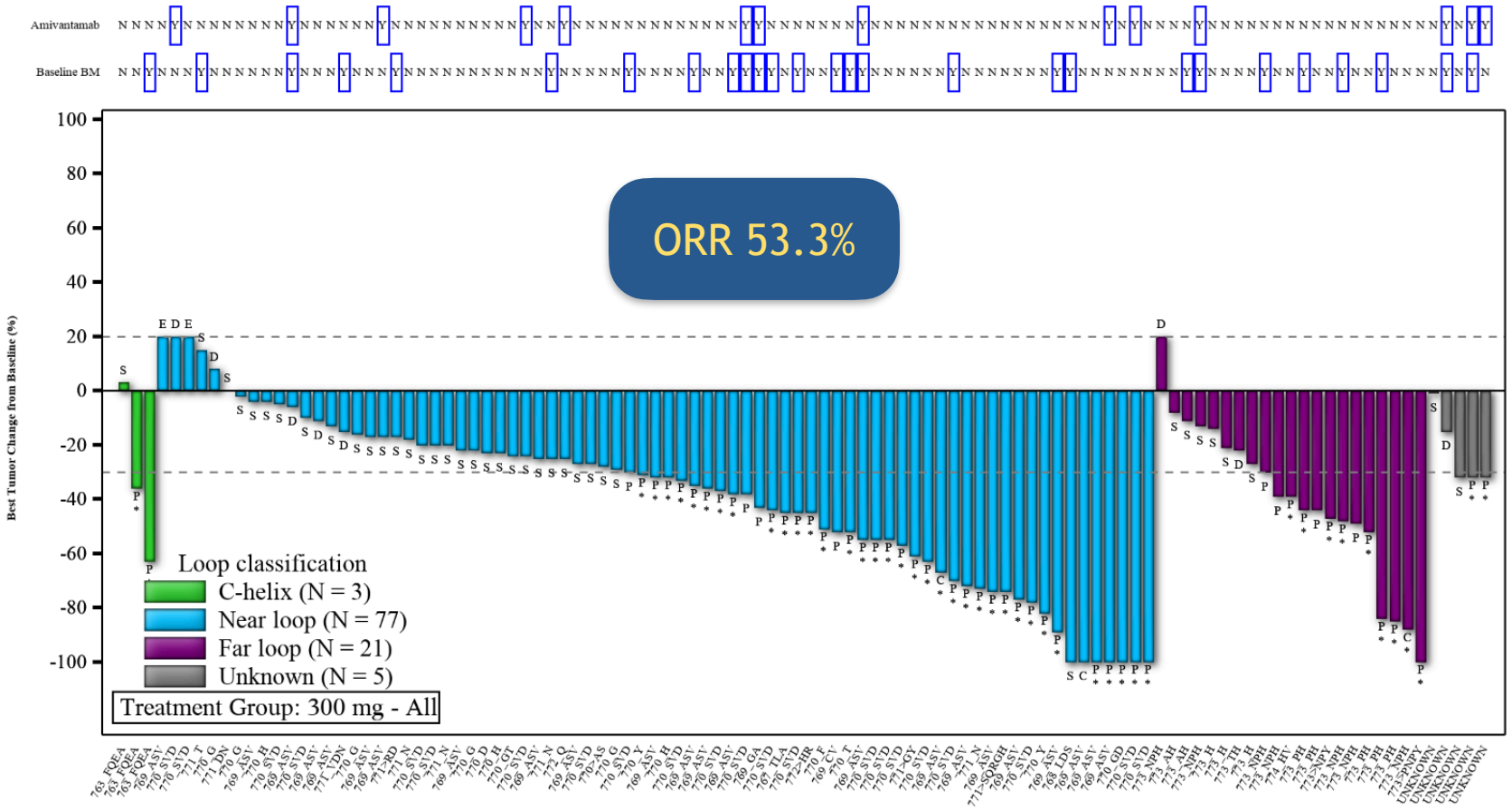
Yang JC et al. ESMO Congress 2023

Sunvozertinib monotherapy (WU-KONG1B, 2nd line phase 2)

GECP lung cancer research

Sunvozertinib 300mg QD

Characteristics	300 mg (N = 107)
Median age, y (range)	64 (37, 85)
Female, n (%)	60 (56.1)
Race (Asian/ non-Asian), n (%)	62 (57.9)/45 (42.1)
Region (Asia/ Rest of the world), n (%)	58 (54.2)/49 (45.8)
BM at baseline, n (%)	27 (25.2)
Lines of prior anti-cancer therapy(<2/ ≥ 2) , n (%)	68 (63.6)/39 (36.4)
Categories of prior anti-cancer therapy, n (%)	
Platinum-based chemotherapy, n (%)	107 (100.0)
Onco-immunotherapy, n (%)	52 (48.6)
Amivantamab, n (%)	14 (13.1)
EGFR TKI, n (%)	14 (13.1)



Doucet L et al. ESMO Congress 2024

Firmocertinib: Phase Ib trial (FAVOUR)

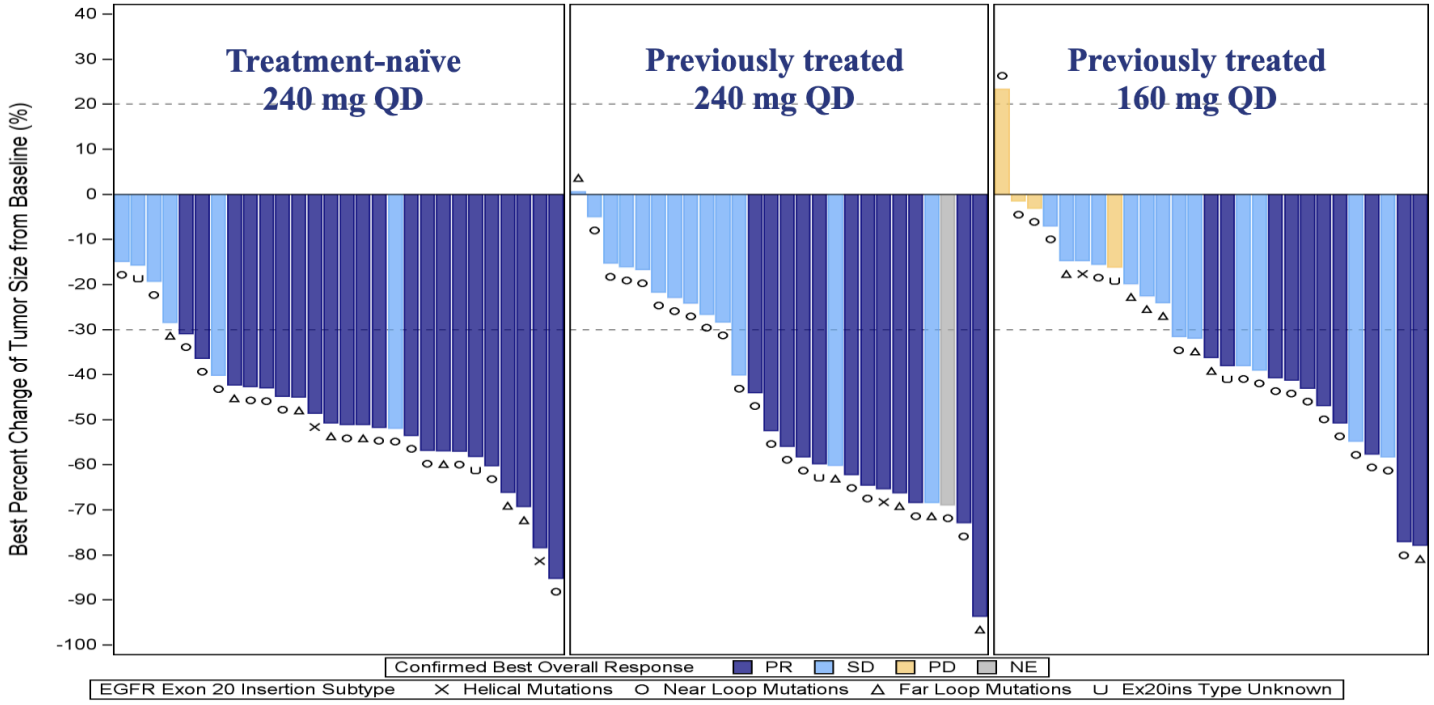
Key Inclusion Criteria:

- Age ≥ 18 years
- Locally advanced or metastatic NSCLC
- Presence of EGFR Exon 20 insertion mutation
- ECOG PS 0-1
- ≥1 measurable lesions
- Asymptomatic stable CNS metastases are allowed

N=90

- Treatment naïve — Furmonertinib 240mg/day — n=30
- Previously treated — Furmonertinib 240mg/day — n=30
- Previously treated — Furmonertinib 160mg/day — n=30

Primary endpoint ORR by IRC



Population Characteristics	TxNaïve	240mg	160mg
Baseline brain metastases	17 %	29 %	39 %
Prior EGFR TKI or ex20ins	0 %	7%%	14 %

Ongoing phase III trial (FURMO-004): firmo 240mg vs firmo 160mg vs chemo

Efficacy (N=90; TxNaïve / 240mg / 160mg): ORR 79% / 46% / 39%, mDOR 15.2 / 13.1 / 9.7 mths
Safety (all grade / ≥G3, for 240mg pre-treated): diarrhoea (86% / 0%), anaemia (25% / 4%)

Han B et al, WCLC 2023

Firmocertinib after PD 1st line CT (EXCLAIM-2)

Key Inclusion Criteria

- Age ≥ 18 years
- Locally advanced or metastatic NSCLC
- Previously received platinum-based chemotherapy
- Confirmed Ex20Ins insertion mutation
- ECOG PS 0-1
- Asymptomatic stable CNS metastases are allowed

Firmonertinib

240mg, QD

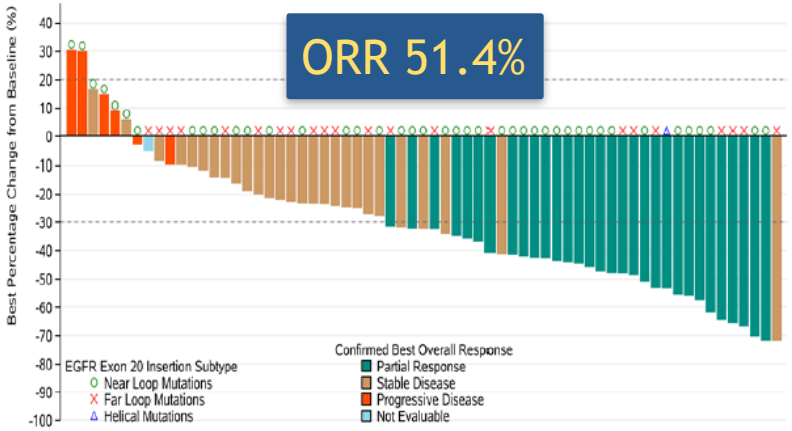
Treatment until

- Until Disease progression: every 6 weeks (±3d)
- After Disease progression or Initiation of new therapy: every 12 weeks (±7d)

Follow up

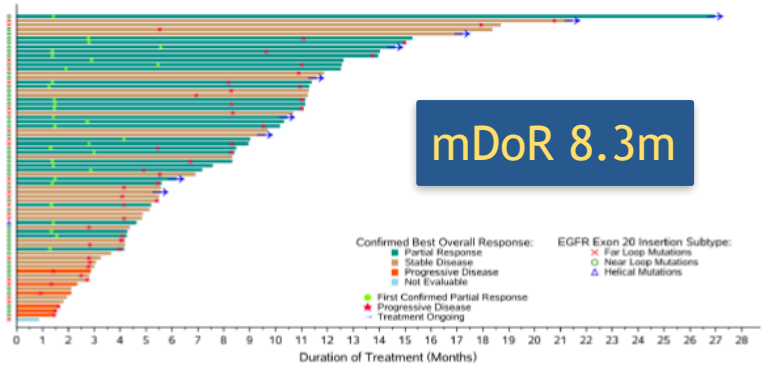
- Until Disease progression: every 6 weeks (±3d)
- After Disease progression or Initiation of new therapy: every 12 weeks (±7d)

Best tumour size change of target lesions by IRC Assessment

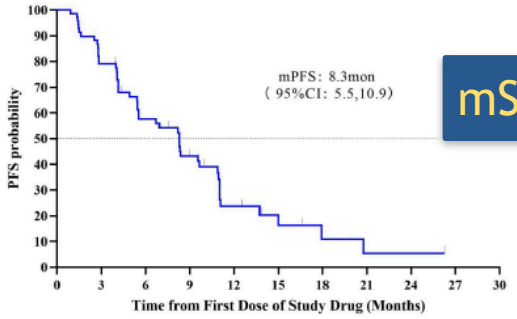


- Responses observed across near loop, far loop and helical Ex20Ins mutations
- Median maximum tumor reductions are 32.2% .

Time on Treatment and Time of Responses



- Most responses occur at the first tumor assessment for firmo treatment;
- The median Time of first response (TTR) was 1.4 months (range: 1.2–5.6).
- Longest DoR is > 24 months.



Overview of TRAEs	
TRAE all grade	95.8%
TRAE G≥3	25.4%
Treatment-related SAE	15.5%
TRAE leading to dose interruption	28.2%
TRAE leading to dose reduction	12.7%
TRAE leading to dose treatment discontinuation	5.6%
TRAE leading to fatal outcome	0
Treatment duration (median)	7.6m
Relative dose intensity (%), mean	91.1

Cheng Y et al. ESMO Congress 2025

Zipalertinib monotherapy (REZILIENT2, phase 2b)

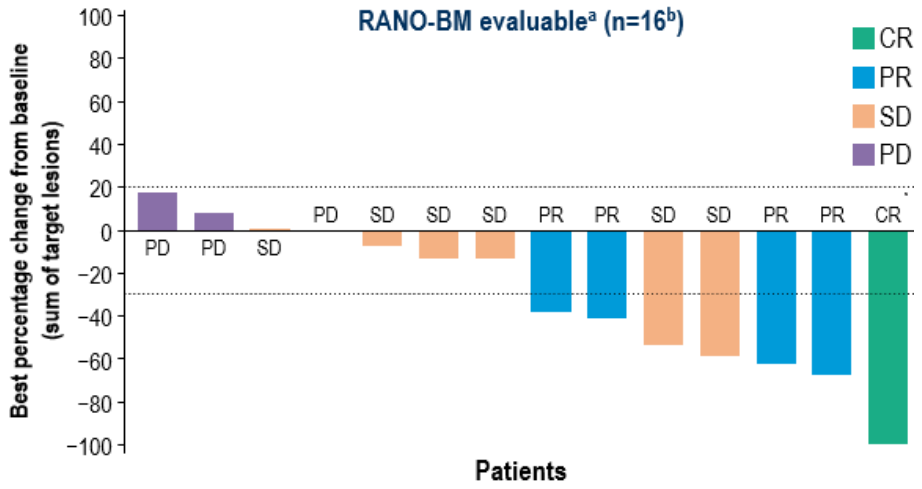
Zipalertinib 100 mg BID

Cohort A[a]	Cohort B[a]	Cohort C	Cohort D[a]
Patients with *EGFR* ex20ins mutations who have progressed on or after first-line platinum-based chemotherapy and prior therapy targeting ex20ins mutations (administered together or separately) for advanced disease	Patients with *EGFR* ex20ins mutations who have not received prior treatment for advanced disease	Patients with ex20ins, other uncommon single or compound *EGFR* mutations, and active brain metastases (including LMD) and who may or may not have received prior treatment for advanced disease	Patients harboring other, uncommon, non-ex20ins, single or compound *EGFR* mutations who have progressed on or after standard systemic therapy

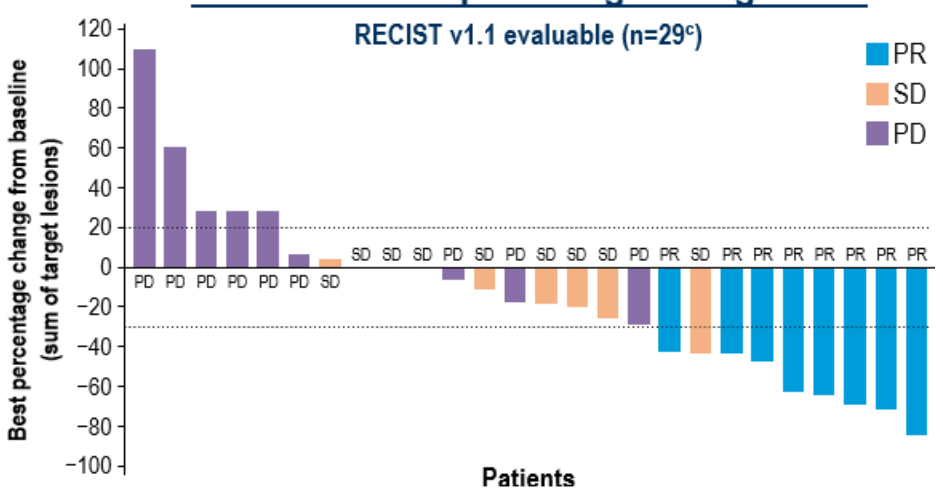
Primary	• Investigator-assessed ORR per RECIST v1.1
Secondary	• DCR, DOR, PFS • OS • Intracranial efficacy (ORR, DOR, DCR) per RANO-BM (Cohort C) • Safety and tolerability • PK
Exploratory	• Population PK parameters and association with safety and efficacy • *EGFR* mutations/biomarkers from tumor samples and ctDNA

	Any grade	Grade ≥3
Paronychia	25 %	3.1%
Dermatitis acneiform	21.9%	3.1%
Stomatitis	21.9%	0
Diarrhea	15.6%	0
Rash	15.6%	3.1%

Best RANO-BM percentage change in TL



Best RECIST1.1 percentage change in TL



Yu H et al. ASCO Annual Meeting 2024; Yu H et al. ESMO Congress 2025

New developments: Zipalertinib + CT (REZILIENT3, 1st line phase III)

Part A: Safety lead-in

Zipalertinib + pemetrexed + carboplatin *or* cisplatin

N≈6–12 patients with *EGFR* ex20ins or other common single or compound *EGFR* mutations

Dose-limiting toxicity assessment and dose selection for Part B

Part B: Randomized phase 3

Study population

1. Previously untreated,[a] locally advanced or metastatic, nonsquamous NSCLC
2. *EGFR* exon20ins mutation by local test
3. ≥1 measurable lesion per RECIST v1.1
4. ECOG PS 0 or 1
5. Stable brain metastases permitted[b]
6. Archival tumor tissue available for submission[c]

R 1:1

- **Pemetrexed + carboplatin *or* cisplatin** → **Optional crossover to zipalertinib monotherapy**
- **Zipalertinib + pemetrexed + carboplatin *or* cisplatin**

After BICR confirms disease progression

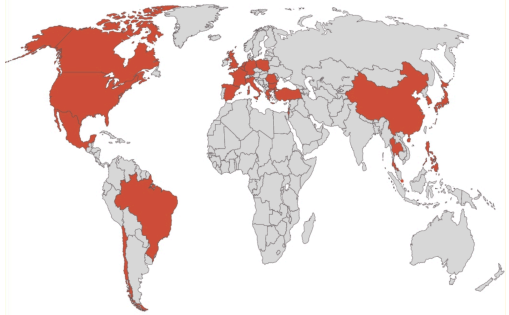
Stratification factors

1. ECOG PS (0 vs 1)
2. Brain metastases (yes vs no)
3. Geography (Asia vs other)

N≈260

Primary endpoint: PFS by BICR
Secondary endpoints: PFS by investigator assessment, ORR, DCR, DOR, OS, safety, PK, PROs

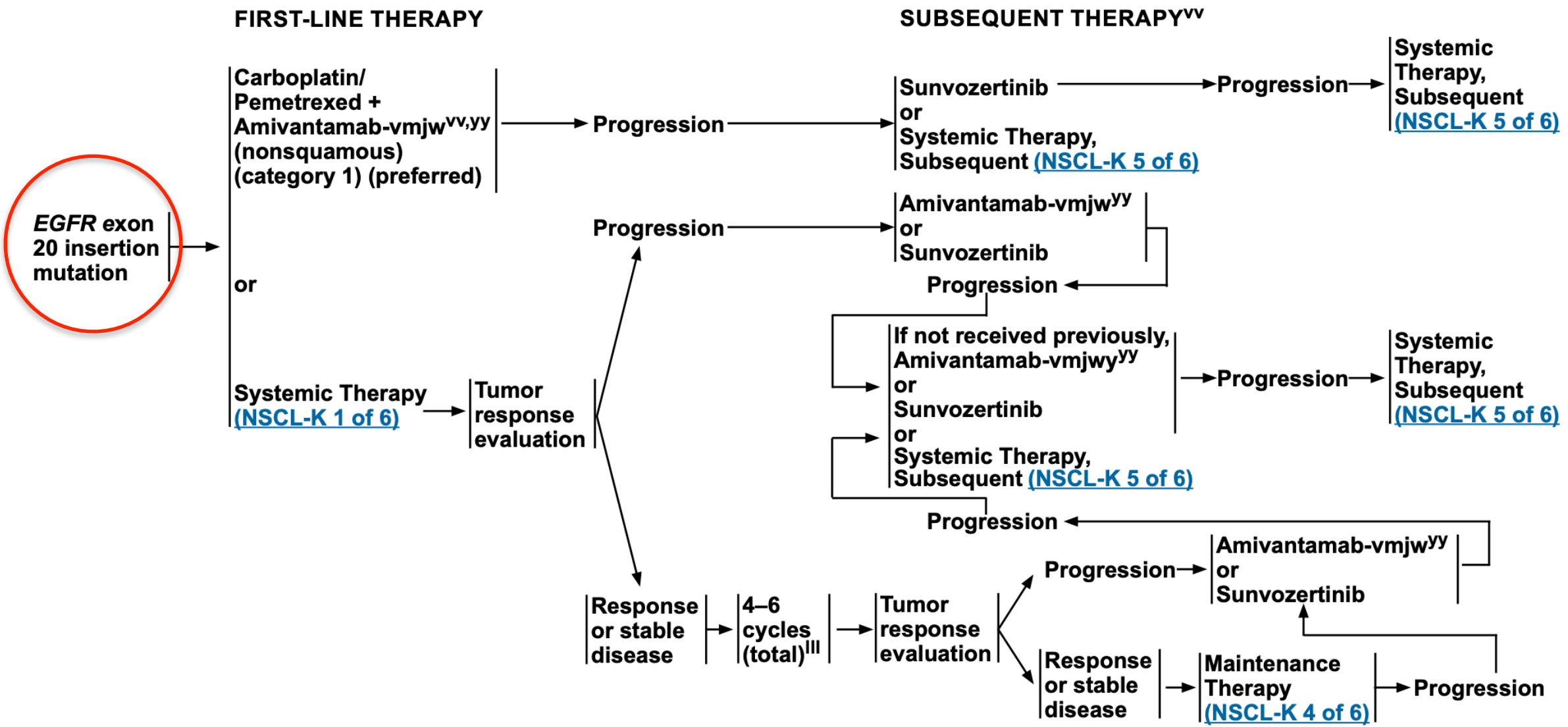
https://clinicaltrials.gov/study/NCT05973773



- **Study start date:** June 30, 2023
- **Estimated study completion date:** August 24, 2026

Yu H et al. ASCO Annual Meeting 2024

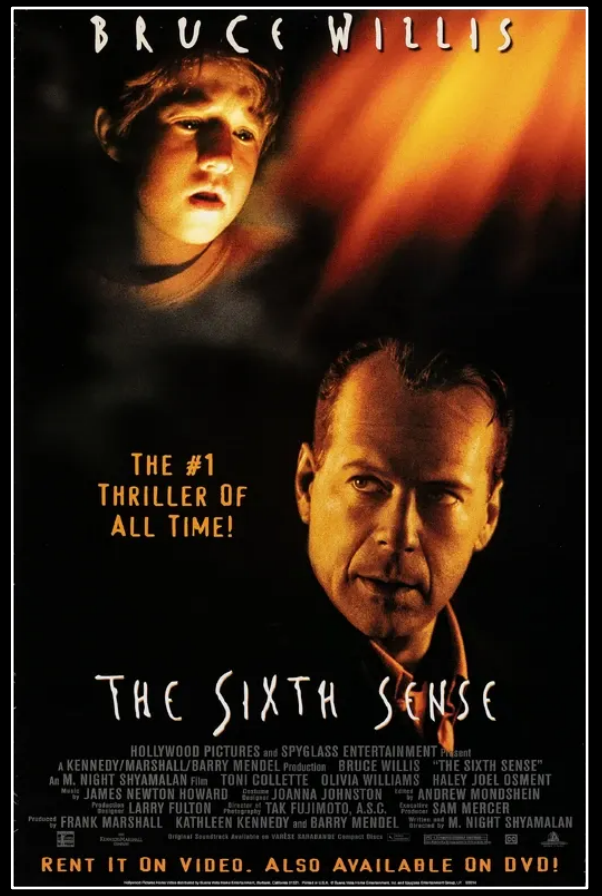
NCCN Guidelines Version 1.2026 Non-Small Cell Lung Cancer



https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; accessed nov 25th, 2025

5

The end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ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer (2022)

What is the optimal management for patients with uncommon sensitizing EGFR mutations?

STATEMENT: Afatinib and osimertinib should be considered as monotherapy, based on a tailored approach including all emerging data, for the treatment of patients with major uncommon sensitizing EGFR mutations (p.G719X, p.L861Q, p.S768I) or compound mutations. The use of chemotherapy could be considered where a strength of recommendation in favor of TKI is limited or missing [II,B]

What is the optimal management for patients with EGFR exon 20 insertions mutant lung cancer?

STATEMENT: Platinum-based chemotherapy should be offered as first-line therapy, preferably without checkpoint ICIs due to the potential risk of toxicity with later lines of targeted therapy. After platinum failure, targeted agents such as amivantamab or mobocertinib, should be considered as second-line therapy [II,B]

Passaro A et al. Ann Oncol. 2022 May; 33(5):466-487

Uncommon EGFR muts: Real access in Spain (27nov25)

	Indicación autorizada	Situación expediente indicación	Resolución expediente de **financiación** indicación
Uncommon	**TAGRISSO** está indicado en monoterapia para el tratamiento de primera línea de pacientes adultos con cáncer de pulmón no microcítico (CPNM) localmente avanzado o metastásico con ***mutaciones activadoras*** del receptor del factor de crecimiento epidérmico (EGFR).	**Resuelto**	**Sí, financiada indicación autorizada**
	GIOTRIF en monoterapia está indicado para el tratamiento de pacientes adultos naïve (sin tratamiento previo) a inhibidores de la tirosin quinasa (TKI) del Receptor del Factor de Crecimiento Epidérmico (EGFR) con cáncer de pulmón no microcítico (CPNM) localmente avanzado o metastásico con ***mutaciones activadoras*** del EGFR	**Resuelto**	**Sí, financiada indicación autorizada**
Ex20ins	**Rybrevant** está indicado en combinación con carboplatino y pemetrexed para el tratamiento en primera línea de pacientes adultos con cáncer de pulmón no microcítico (CPNM) avanzado con ***mutaciones activadoras de inserción en el exón 20 del EGFR***	**Resuelto**	**No incluida**
	Rybrevant en monoterapia está indicado para el tratamiento de pacientes adultos con cáncer de pulmón no microcítico (CPNM) avanzado con ***mutaciones activadoras de inserción en el exón 20*** del receptor del factor de crecimiento epidérmico (EGFR), tras el fracaso de un tratamiento de terapia basada en platino.	**Resuelto**	**No incluida**

Fuente: BIFIMED (acceso nov'25)

Wrap-up

Treatment decisions in unfrequent mutations

The uncommon as all we know them

- Infrequent EGFR mutations comprise a very heterogeneous and relatively numerous group of alterations
- The three major uncommon EGFR mutations are: Exon 18 G719X, Exon 20 S768I, Exon 21 L861Q
- EGFR uncommon mutations are associated with more sensitivity to afatinib or osimertinib; compound mutations seem to obtain better benefit from osimertinib

The special group

- EGFR exon 20 insertions are a subgroup in themselves with good specific targeted options based on Amivantamab and TK inhibitors, with a prominent field of development

Questions?


Savage Chickens
by Doug Savage
I WISH WE DIDN'T ARGUE SO MUCH...
MAYBE YOU SHOULD TRY NOT BEING WRONG ABOUT EVERYTHING?
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