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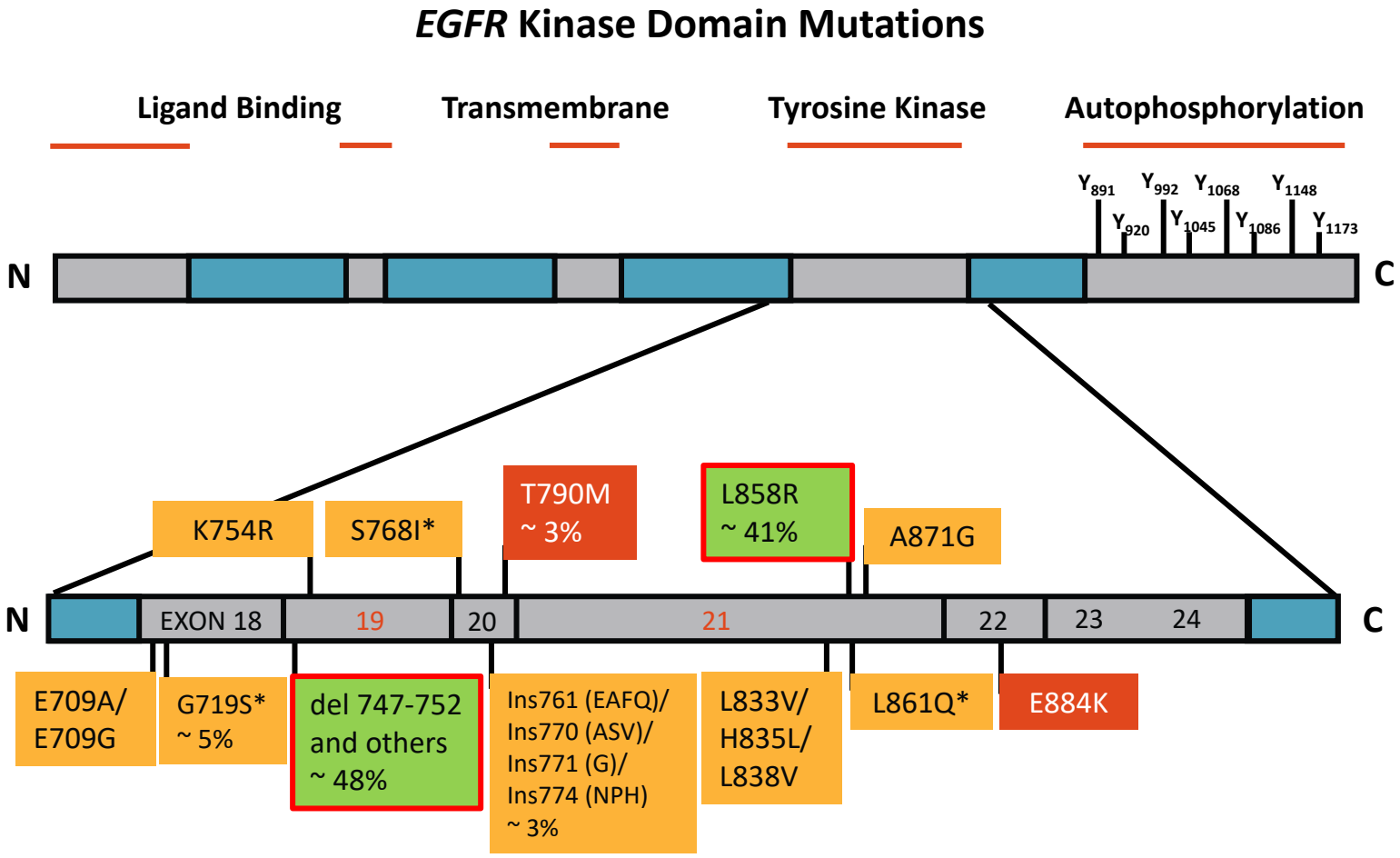
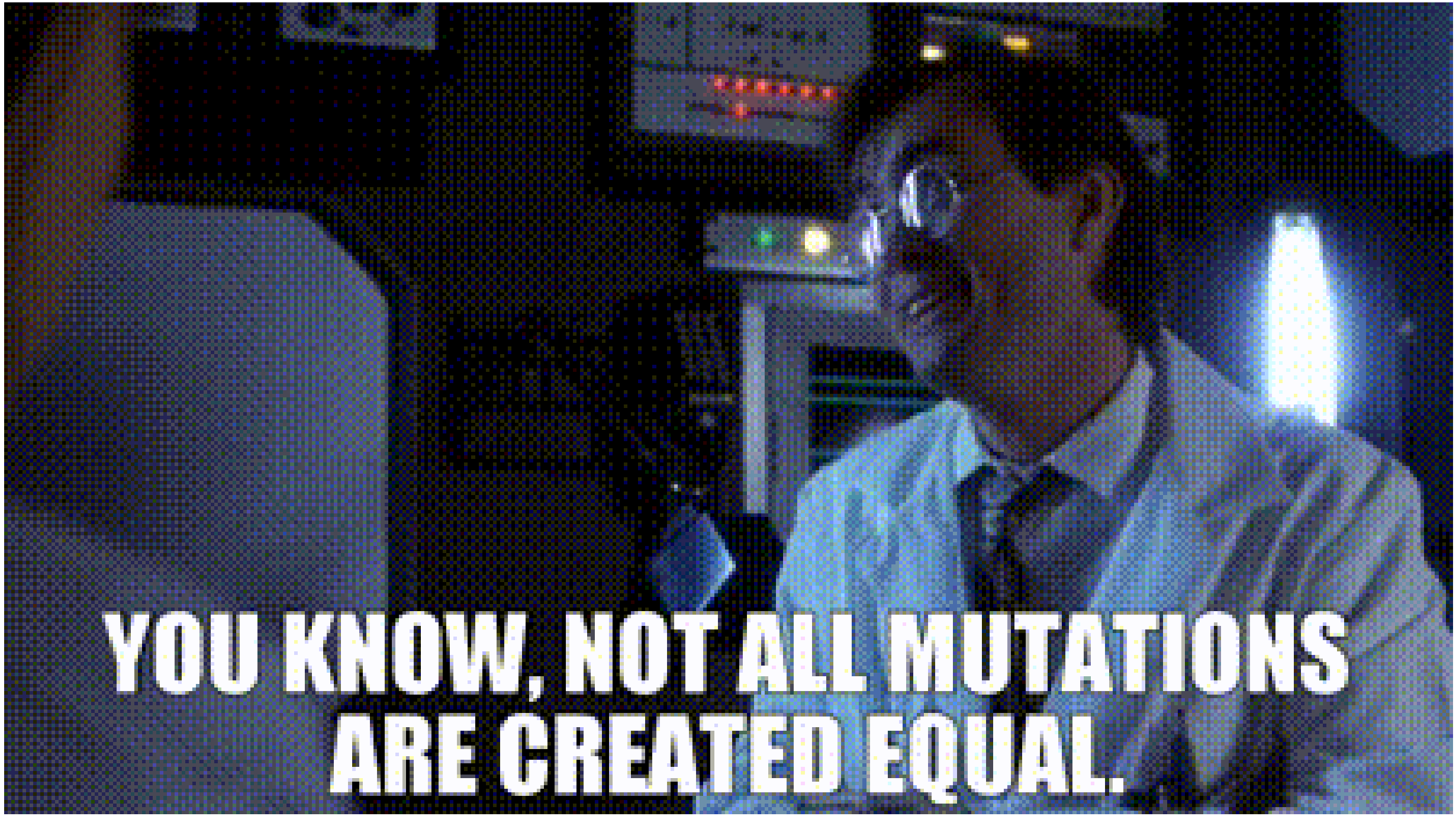
EGFR Mutational Epidemiology

- ~ 20% to 30% - NSCLC globally
- More common in never-smokers
- Adenocarcinomas, females, Asians
- Predominantly in *EGFR* exons 18-21
- Specific mutation is important:
- Sensitive mutations
- Primary resistance mutations
- De novo/acquired resistance mutations



*Noncanonical *EGFR* mutations.

Irmer. Oncogene. 2007;26:5693. Pao. JCO. 2005;23:2556. Wu. J Thorac Oncol. 2007;2:430. Zhang. Oncotarget. 2016:7:78985
Fang. Drug Des Devel Ther. 2014;8:1595. Shea. Ther Adv Respir Dis. 2016;10:113. Wang. Onco Targets Ther. 2016;9:3711
Werutsky. IASLC 7th Latin American Conference on Lung Cancer 2016. Abstr P1.08


YOU KNOW, NOT ALL MUTATIONS
ARE CREATED EQUAL.

EGFR TKIs: Properties

Parameter	Erlotinib	Gefitinib	Afatinib	Dacomitinib	Osimertinib
Generation	First	First	Second	Second	Third
EGFR mutations approved for in first-line setting	Ex19del, Ex21 L858R	Ex19del, Ex21 L858R	Ex18 G719X,* Ex19del, Ex20 S768I,* Ex21 L858R, Ex21 L861Q*	Ex19del, Ex21 L858R	Ex19del, Ex21 L858R†
EGFR binding	Reversible	Reversible	Irreversible	Irreversible	Irreversible
Half life, hr	36	48	37	59-85	48
Food effect (take on empty stomach)	Increase F from ~60% to ~100%	No change	Decrease AUC by 39%	No change	No change
CNS penetration, AUC ratio	0.03X CSF/plasma	0.01X CSF/serum	0.02X CSF/plasma	CNS activity reported	2X brain/plasma

*Uncommon nonresistant *EGFR* mutations. †Also approved for resistant mutation T790M in second-line setting and a preferred option for *EGFR* G719X, S768I, L861Q per NCCN guidelines.

Afatinib PI. Dacomitinib PI. Erlotinib PI. Gefitinib PI. Osimertinib PI. Boehrer. Cell Cycle. 2011;10:3168. Togashi. Cancer Chemother Pharmacol. 2012;70:399. Tamiya. ESMO 2016. Abstr 1241P. Engelman. Cancer Res. 2007;67:11924. Gonzalez. Mol Cancer Ther. 2008;7:1880. Jänne. Clin Cancer Res. 2011;17:1131. Ou. Drugs Des Devel Ther. 2015;9:5641. Hochmair. Target Oncol. 2018;13:269. Mizusaki. Thorac Cancer. 2021;12:114. Kudo. Intern Med. 2020;59:1739. NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022

NEJ026, Take Home Points

- **Addition of bevacizumab to erlotinib improved PFS1**
  - But NOT PFS2 or OS
  - 29% receiving bevacizumab discontinued due to toxicity*
- **How does this compare with 1st line later-gen TKIs or TKI + chemo?**
  - OS in BOTH arms outperformed FLAURA and ARCHER
    <Likely due to impact of next-line therapy>
  - OS appears similar to NEJ009 (also with 50% increase in toxicity over TKI alone)
  - Not clear if this will be better than TKI + chemo
- **No significant difference between different EGFR mutations**
- **Similar number in each arm received 2nd line osimertinib**
  - 25% is LOW compared with expected T790M rates
- **Issues: Cost, added toxicity, QOL adding IV to oral**
  - Do not support the combination outside of clinical trial

*Saito, Lancet Oncol 2019

Available Data on EGFR-VEGF Combination Therapy in *EGFR*+ Advanced NSCLC

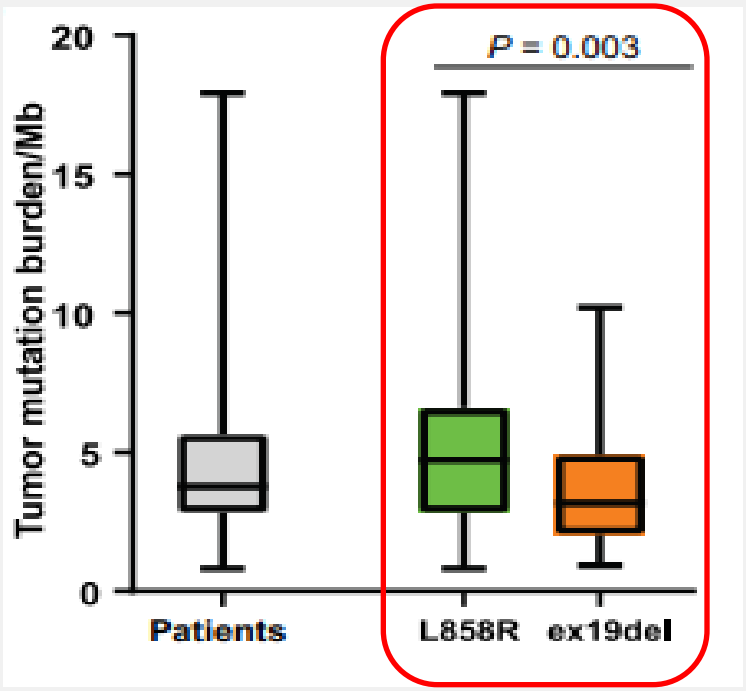
Study	Phase	N	Intervention	ORR, %	Median PFS, Mo	Median OS, Mo
BELIEF[1,2]	II	109	Erlotinib + bevacizumab	77	13.2	28.2
ACCRU[1,3]	II	88	Erlotinib + bevacizumab vs erlotinib	81 vs 83	17.9 vs 13.5 (HR: 0.81)	32.4 vs 50.6 (HR: 1.41; *P* = .33)
J025567[1,4,5]	II	154	Erlotinib + bevacizumab vs erlotinib	69 vs 64	16.0 vs 9.7 (HR: 0.54)	47.0 vs 47.4 (HR: 0.81; *P* = .33)
NEJ026[1,6,7]	III	228	Erlotinib + bevacizumab vs erlotinib	72 vs 66	16.9 vs 13.3 (HR: 0.63)	50.7 vs 46.2 (HR: 1.00; *P* = .97)
ARTemis (CTONG 1509)[1,8]	III	311	Erlotinib + bevacizumab vs erlotinib	86 vs 85	18.0 vs 11.3 (HR: 0.55)	Not reached
RELAY[1,9]	III	449	Erlotinib + ramucirumab vs erlotinib + placebo	76 vs 75	19.4 vs 12.4 (HR: 0.59)	Not reached
MSKCC[1,10]	I/II	49	Osimertinib + bevacizumab	80	19	Not reached

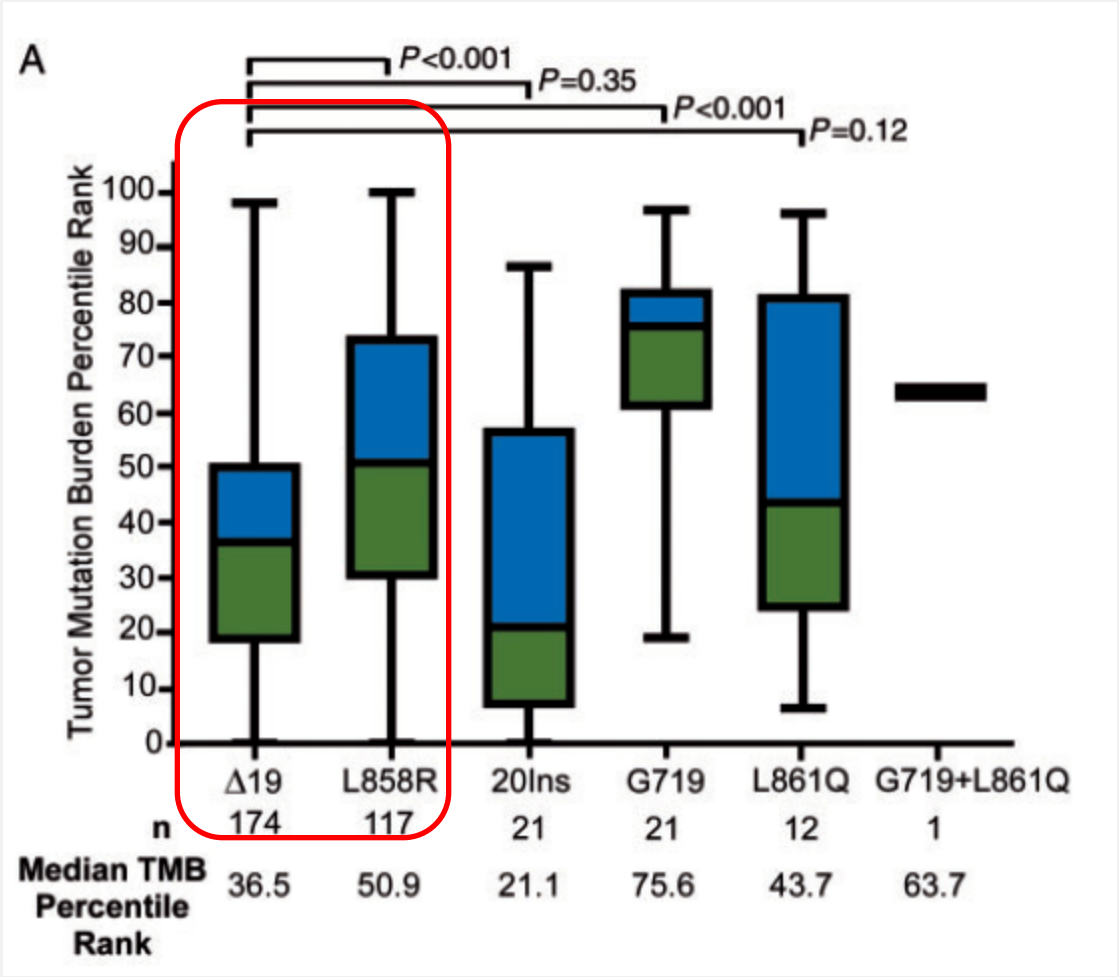
1. Le. J Thorac Oncol. 2021;16:205. 2. Rosell. Lancet Respir Med. 2017;5:435. 3. Stinchcombe. JAMA Oncol. 2019;5:1448. 4. Seto. Lancet Oncol. 2014;15:1236
5. Yamamoto. Lung Cancer. 2021;151:20. 6. Saito. Lancet Oncol. 2019;20:625. 7. Maemondo. ASCO 2022. Abstr 9506. 8. Zhou. ESMO 2019. Abstr 1480O
9. Nakagawa. Lancet Oncol. 2019;20:1655. 10. Yu. JAMA Oncol. 2020;6:1048

Hypothesis confirmed

consider.ly

TMB was Higher in L858R Tumors Compared with Del19 Tumors

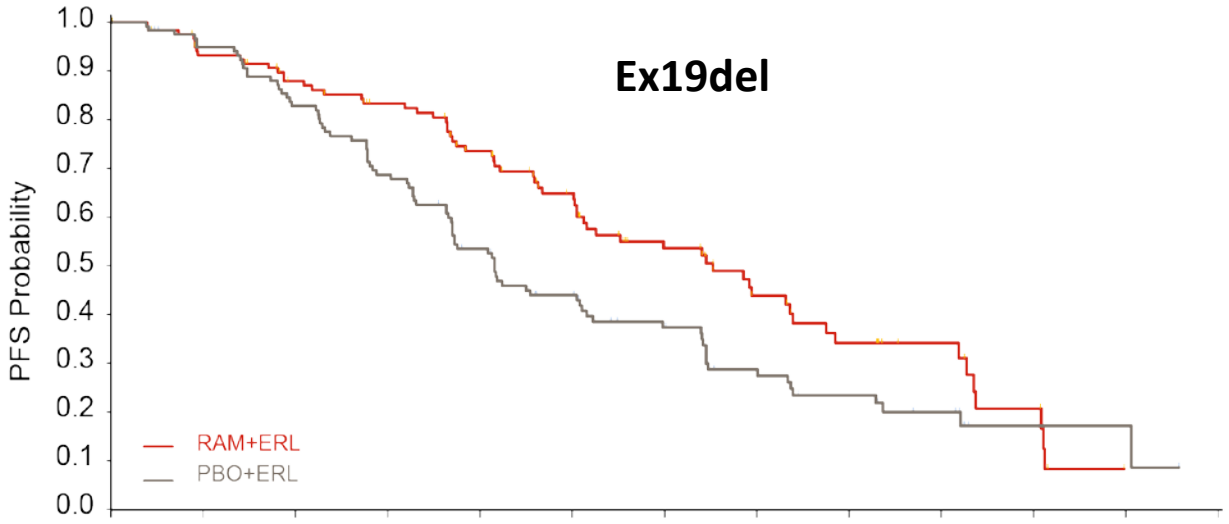


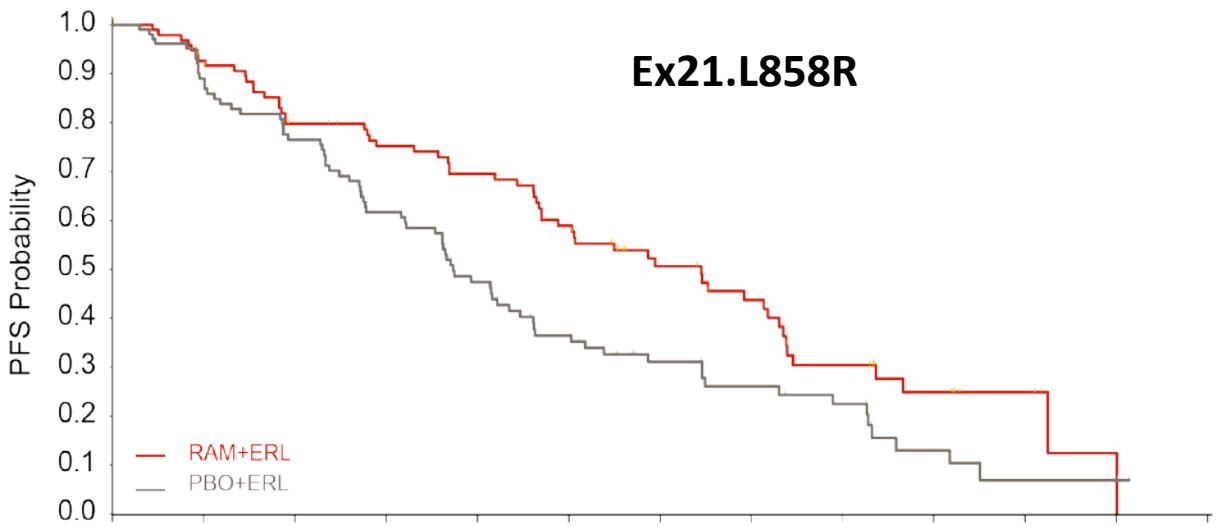


Offin M, et al. Clin Cancer Res. 2019. 2. Annals of Oncology 30: 1311–1320, 2019


You may have no choice.

RELAY: PFS by EGFR mutation type





Consistent mPFS Benefit in pre specified subgroups of both Exon 19 deletion & Exon 21 substitution mutations

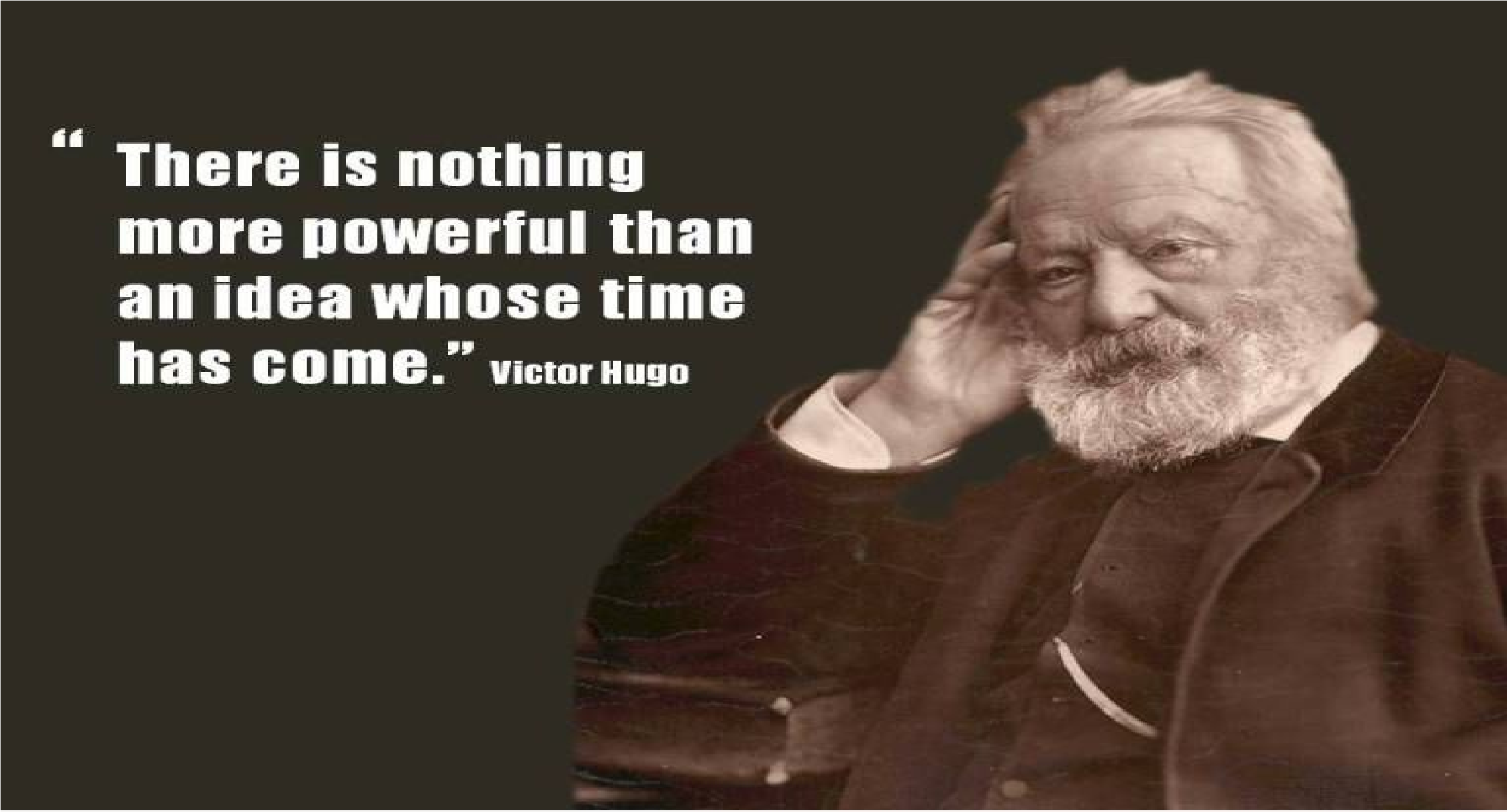
123	108	96	87	72	54	38	25	17	11	6	0	0
120	110	94	78	58	43	32	22	15	10	2	2	0

99	87	73	66	60	49	31	24	15	9	4	1	0
105	86	73	58	41	29	20	15	12	5	2	2	0

Ex19del	RAM + ERL (n = 123)	PBO + ERL (n = 120)
Events	64	84
Median, mo	**19.6**	**12.5**
(95% CI)	(15.1, 22.2)	(11.1, 15.3)
HR (95% CI); p-value	**0.651** (0.469, 0.903); 0.0098	

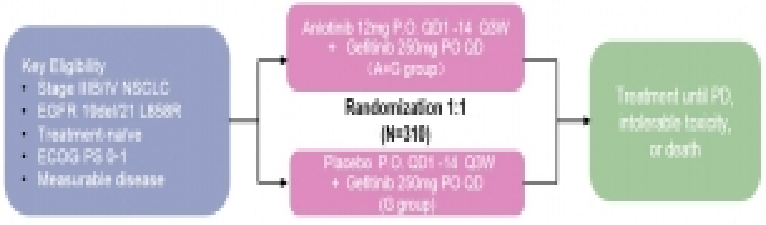
Ex21.L858R	RAM + ERL (n = 99)	PBO + ERL (n = 105)
Events	58	74
Median, mo	**19.4**	**11.2**
(95% CI)	(14.1, 21.9)	(9.6, 13.8)
HR (95% CI); p-value	**0.618** (0.437, 0.874); 0.006	

Nakagawa K et al. Lancet Oncol 2019;20:1655–9


“ There is nothing more powerful than an idea whose time has come.” Victor Hugo
GeniusQuotes.net

Study design

Phase III, randomized, Double-Blind, multicenter study in 1L EGFR+ advanced or metastatic NSCLC (NCT04028778)



Stratification factors
- EGFR status(19del vs. 21L858R)
- Gender(Male vs. Female)
- ECOG PS (0 vs. 1)
- Pathological type(Adenocarcinoma vs. other)

End points:
- Primary: PFS assessed by IRC
- Secondary: OS、ORR、DCR、DOR、CBL、Safety

Exploratory points:
- to analysis blood samples for ctDNA collected at baseline, first evaluation, and progression disease (PD) with a 329-gene panel.

cut-off date: July 31, 2022.

Baseline characteristics

		A+G group* (N=155)	G group (N=156)
Age	Median (Range)	55 (26-77)	58 (32-76)
	<65	119 (76.77)	108 (69.23)
	>=65	36 (23.23)	47 (30.32)
Gender, n (%)	Male	68 (43.87)	67 (42.23)
	Female	87 (56.13)	89 (56.77)
Smoking status, n (%)	Non-smoker	139 (89.13)	121 (78.05)
	Ex-smoker	26 (16.77)	24 (15.48)
	Smoker	10 (6.45)	9 (5.81)
	Unknown	1 (0.65)	1 (0.65)
ECOG PS, n (%)	0	19 (12.26)	16 (5.59)
	1	130 (83.87)	133 (85.69)
	Unknown	6 (3.87)	7 (4.52)
Clinical stage at screening, n (%)	IIIB	10 (6.45)	4 (2.56)
	IV	142 (91.61)	148 (95.48)
	Unknown	3 (1.94)	3 (1.94)

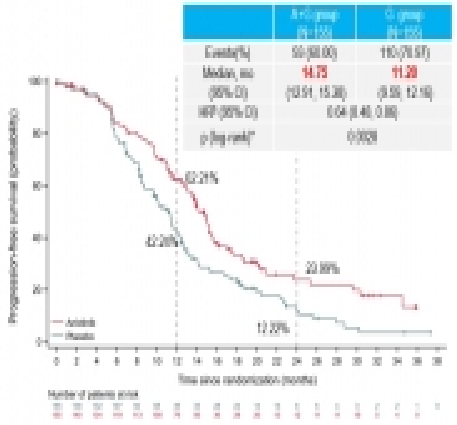
		A+G group* (N=155)	G group (N=156)
EGFR mutation type, n (%)	Exon 19 deletion	80 (51.61)	81 (52.25)
	Exon 21 L858R	75 (48.39)	74 (47.74)
Number of metastatic organs, n (%)	>2	101 (65.16)	95 (61.28)
	≤2	54 (34.84)	58 (37.42)
	Unknown	0(0.00)	3 (1.29)
Brain metastases, n (%)	No	106 (68.39)	105 (67.74)
	Yes	49 (31.61)	50 (32.26)
Liver metastases, n (%)	No	135 (87.10)	133 (85.81)
	Yes	20 (12.90)	22 (14.19)

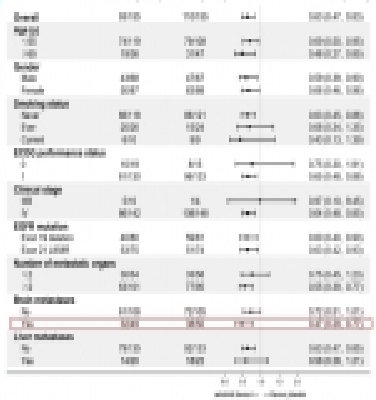
*156 patients in both groups received at least one treatment. Efficacy analysis was mainly carried out in patients receiving at least one treatment

Primary endpoint: PFS by IRC

- The median follow-up time was 17.3m in A+G group and 18.6m in G group.

	A+G group (N=155)	G group (N=155)
Event(s)(%)	59 (38.06)	110 (70.97)
Median, mo (95% CI)	16.75 (13.51, 19.38)	11.20 (9.59, 12.19)
HR* (95% CI)	0.54 (0.40, 0.73)	
p (log-rank)*	0.0002	

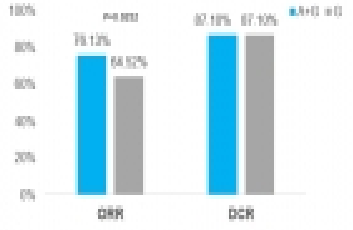


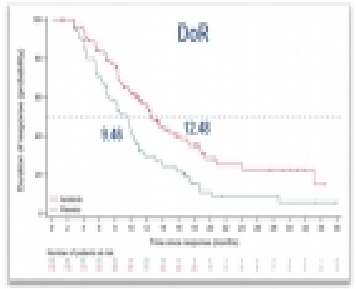


*Stratified log-rank test using random stratified factors as stratified variables. *Cox proportional hazard regression using random stratified factors as stratified variables

Secondary endpoints: ORR、DCR and DoR

Confirmed best objective response

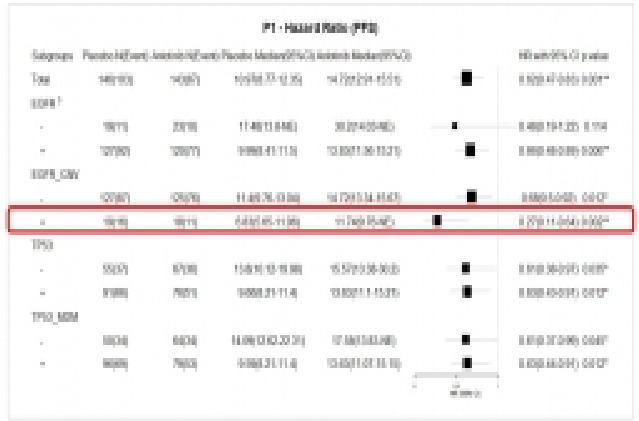




	A+G group (N=155)	G group (N=155)	p
PR	118 (76.13)	100 (64.52)	
SD	17 (10.97)	35 (22.58)	
PD	5 (3.23)	5 (3.23)	
NE	15 (9.68)	15 (9.68)	
ORR	76.13 (68.83, 82.60)	64.52 (56.44, 72.03)	0.0252
DCR	87.10 (80.79, 91.94)	87.10 (80.79, 91.94)	1.0000

	A+G group (N=155)	G group (N=155)	p
Events	70 (59.32)	77 (77.00)	
Median, mo (95% CI)	12.48 (11.07, 16.23)	9.46 (7.03, 10.26)	0.0000
HR (95% CI)	0.56 (0.40, 0.77)		0.0004

Subgroup analysis by baseline mutation status



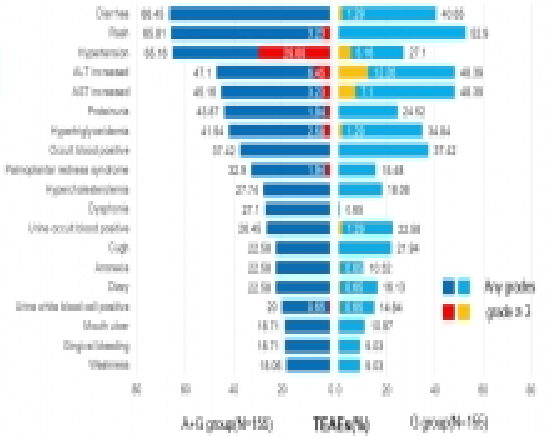
Safety analysis

Safety summary

Events(%)	A+G group (N=155)	G group (N=155)
Any TEAEs	154 (99.35)	131 (87.42)
Grade ≥ 3 TEAEs	77 (49.68)	48 (30.97)
Serious TEAEs	17 (10.97)	9 (5.81)
TEAEs leading to dose interruption, any drug	50 (32.26)	34(21.94)
TEAEs leading to dose reduction, any drug	48 (30.97)	21 (13.55)
Discontinued treatment due to TEAEs	16 (10.32)	7 (4.52)
TEAEs leading to death*	2 (1.29)	1 (0.65)

TEAEs: Treatment Emergent Adverse Events
1 A+G group: 1 patient received sudden cerebral infarction leading to death, 1 patient received ischaemic stroke leading to death
G group: 1 patient reported Pulmonary hypertension leading to death

Most common TEAEs*



Is TKI/VEGF Better Than TKI/Chemo?

	NEJ026 (Erlot/Bev)	RELAY[2] (Erlot/Ram)
OS	50.7 mo v 46.2 mo	Pending
HR OS	1.0	Interim 0.8 (NS)
PFS	16.9 mo v 13.3 mo[1]	19.4 mo v 12.4 mo
HR PFS	0.60	0.59

	Tata Memorial[3] (Carbo/ Pemetrexed/ Gefit)	NEJ009[4] (Carbo/ Pemetrexed/ Gefit)
OS	NR v 17 mo	50.9 mo v 38.8 mo
HR OS	0.45	0.72
PFS	16 mo v 8 mo	20.9 mo v 11.9 mo
HR PFS	0.51	0.49

[1]Saito, Lancet Oncol 2019; [2]Nakagawa Lancet Oncol 2019; [3]Noronha, J Clin Oncol 2019; [4]Hosomi, J Clin Oncol 2020

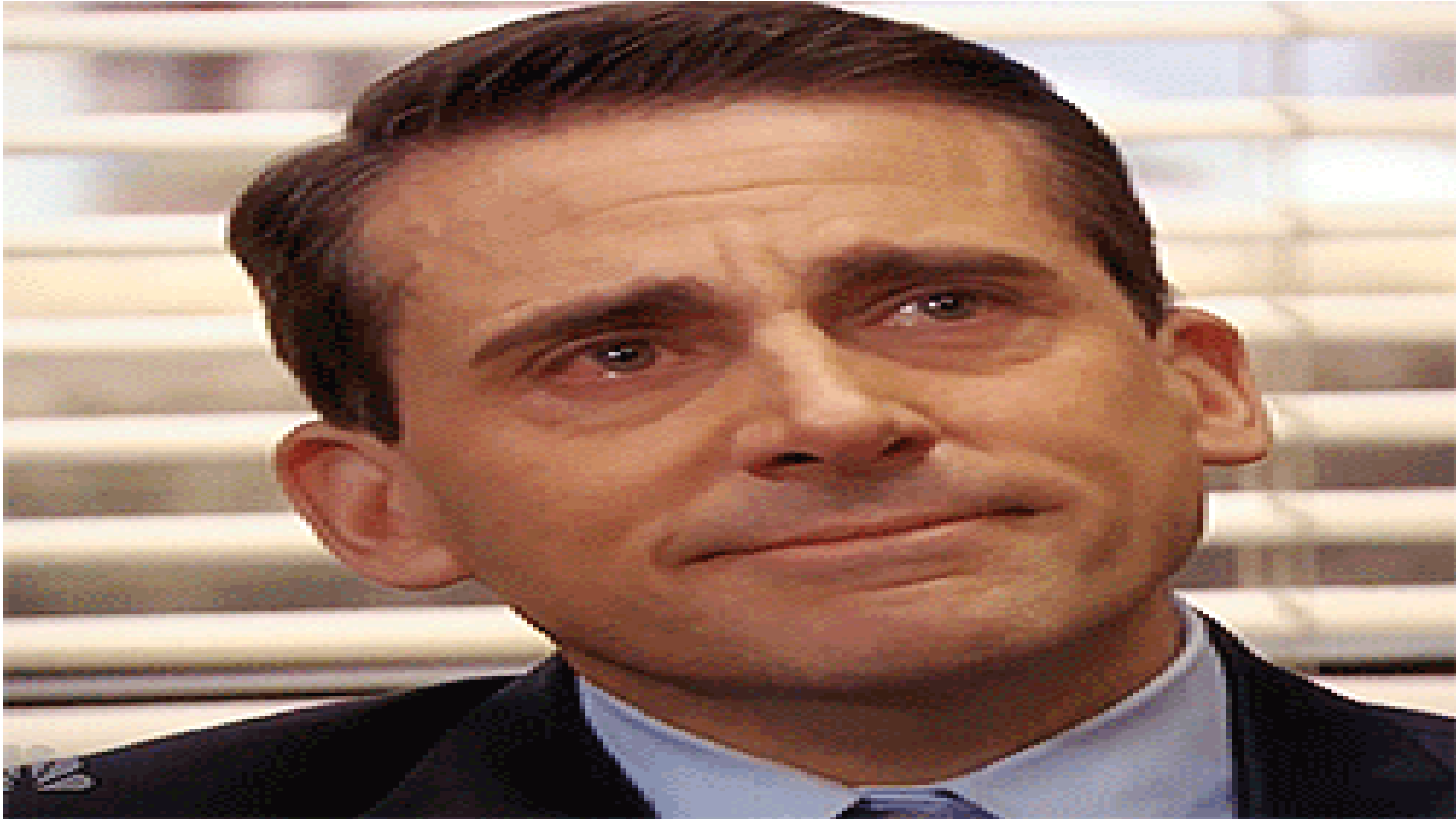

ONE SIZE DOES NOT FIT ALL.
KEEP TRYING...
AND EVENTUALLY YOU WILL FIND THE
PERFECT FIT.

Select Ongoing Studies of 3rd Gen EGFR TKI Combination Therapy

Trial	Phase	Planned N	Study Population	Treatment Arms	Primary Endpoint
WJOG9717L (UMIN000030206)	II	120	*EGFR*+ NSCLC without brain metastases	Osimertinib ± bevacizumab	PFS
NCT04181060	III	300	Metastatic *EGFR*+ NSCLC	Osimertinib ± bevacizumab	PFS
JapicCTI-184146	II	120	*EGFR*+ NSCLC	Osimertinib ± ramucirumab	PFS
RAMOSE/HCRN LUN18-335 (NCT03909334)	II	150	*EGFR*+ locally advanced or metastatic NSCLC	Osimertinib ± ramucirumab	PFS
NORTHSTAR (NCT03410043)	II	143	Stage IIIB or IV *EGFR*+ NSCLC†	Osimertinib + radiation + surgery	PFS
FLAURA2 (NCT04035486)	III	587*	*EGFR*+ NSCLC	Osimertinib ± platinum/pemetrexed	PFS
NCT03567642	I	20	*EGFR*+ metastatic NSCLC with concurrent *RB1* and *TP53* alterations	Osimertinib + platinum/etoposide	MTD
MARIPOSA (NCT04487080)	III	1000	*EGFR*+ locally advanced or metastatic NSCLC	Amivantamab + lazertinib vs osimertinib vs lazertinib	PFS

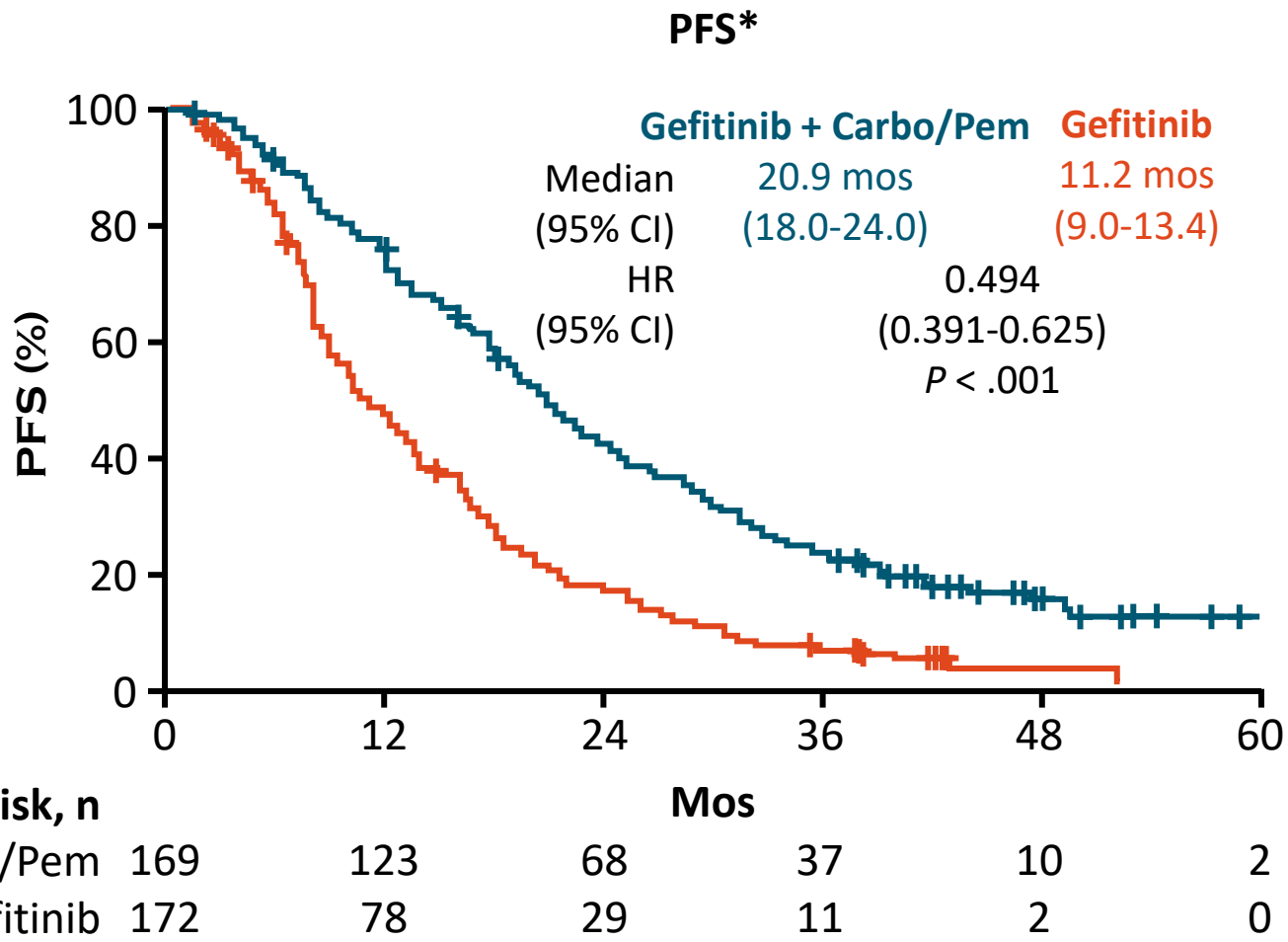
*Actual N; study active, no longer recruiting. †Patients allowed to have *EGFR* T790M+ disease following PD on early-generation EGFR TKI

Le. J Thorac Oncol. 2021;16:204



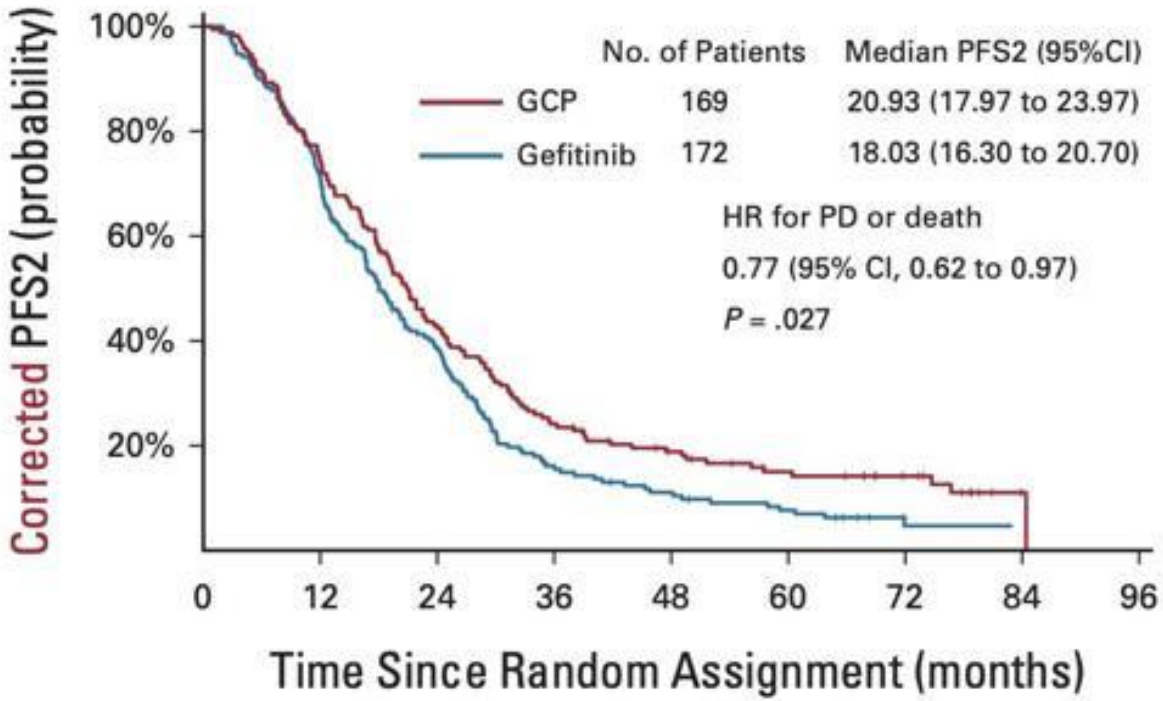
NEJ009: Response & PFS

Response, %	Gefitinib + Carbo/Pem	Gefitinib
ORR	84.0	67.4
CR	4.7	3.5
PR	79.3	64.0
SD	13.6	25.0
PD	1.2	4.7



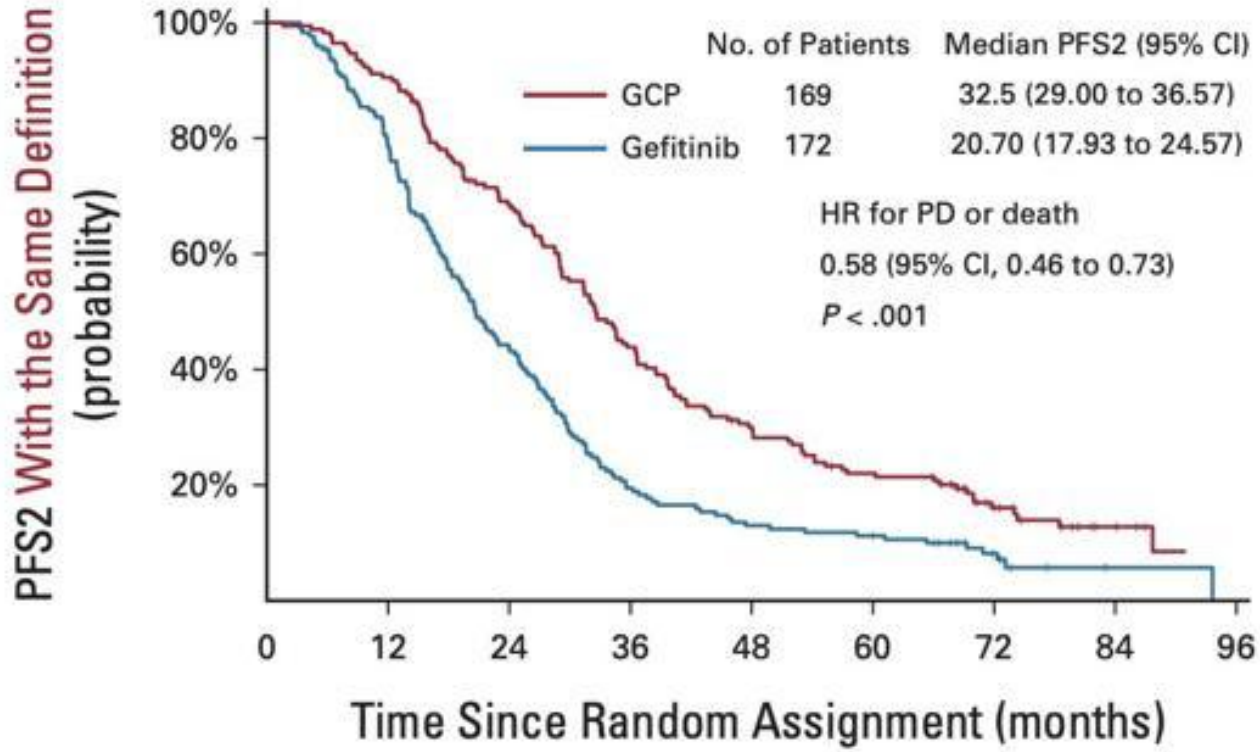
*PFS data is PFS1, which for gefitinib arm is prior to any subsequent platinum CT post progression on gefitinib

Nakamura A, et al. ASCO 2018



No. at risk:

GCP	169	124	70	39	26	18	11	1
Gefitinib	172	121	64	26	17	11	2	0



No. at risk:

GCP	169	153	114	73	49	35	18	6	0
Gefitinib	172	134	74	33	22	18	8	1	0

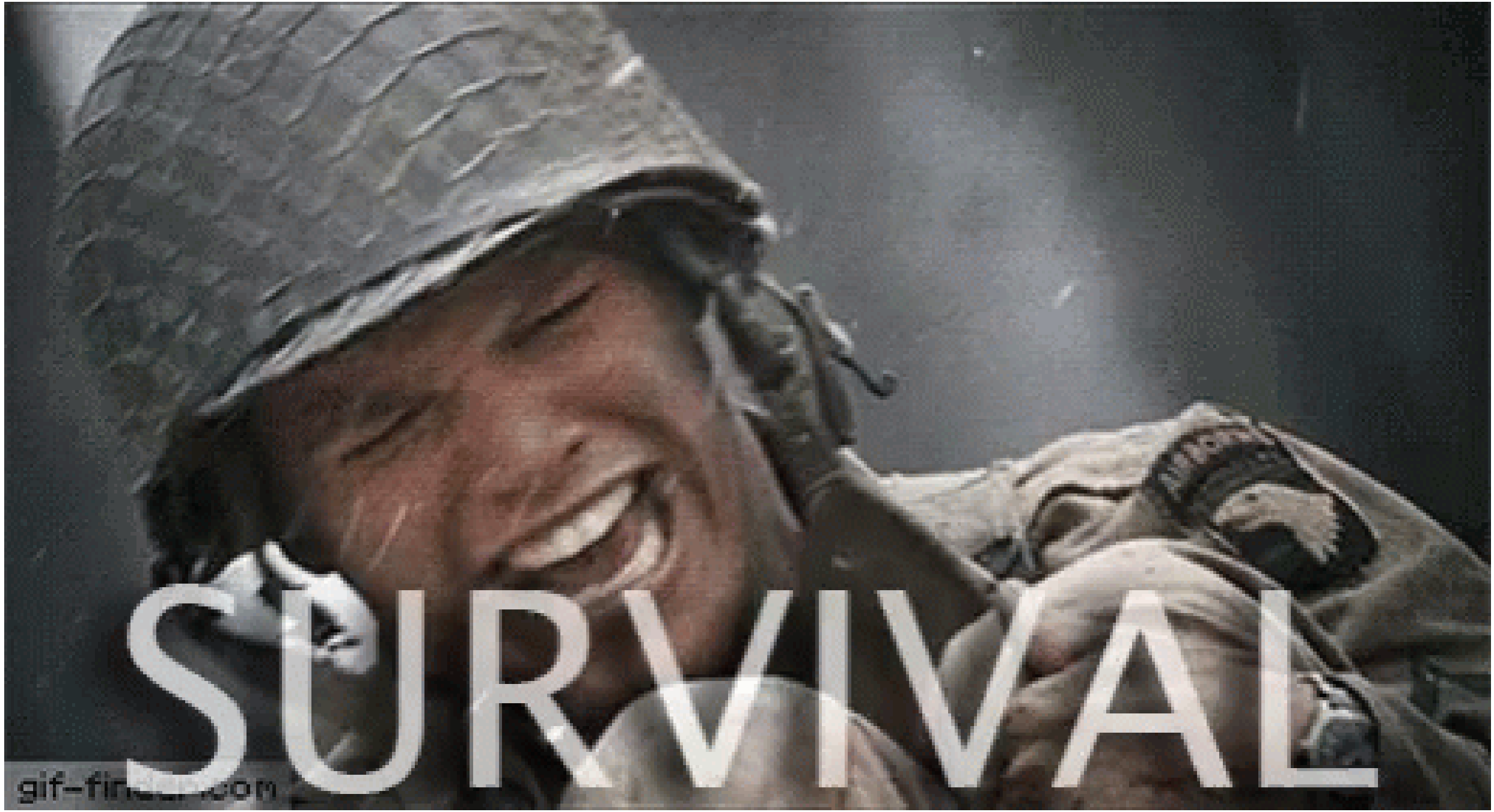

SURVIVAL

TABLE A1. Subsequent Therapy After Protocol Treatment and Tumor Response

Chemotherapy Regimen	Second-Line Therapy		Third-Line Therapy	
	Gefitinib (n = 172), No. (%)	GCP (n = 170), No. (%)	Gefitinib (n = 172), No. (%)	GCP (n = 170), No. (%)
Any treatment	153 (89.0)	125 (73.5)	114 (66.3)	88 (51.8)
Platinum-based with or without bevacizumab	102 (59.3)	16 (9.4)	18 (10.5)	6 (3.5)
Pemetrexed	0 (0.0)	0 (0.6)	6 (3.5)	2 (1.2)
Docetaxel with or without ramucirumab	4 (2.3)	37 (21.8)	26 (15.1)	13 (7.6)
Tegafur, gimeracil, and oteracil	0 (0.0)	1 (0.6)	4 (2.3)	4 (2.4)
Osimertinib	10 (5.8)	11 (6.5)	6 (3.5)	9 (5.3)
Gefitinib or erlotinib	22 (12.8)	29 (17.1)	20 (11.6)	21 (12.4)
Afatinib	3 (1.7)	15 (8.8)	15 (8.7)	19 (11.2)
Immune checkpoint inhibitors	0 (0.0)	3 (1.8)	6 (3.5)	8 (4.7)
Others	12 (7.0)	13 (7.6)	13 (7.6)	6 (3.5)
Response rate (95% CI)	34.0 (26.5 to 41.5)	20.8 (13.7 to 27.9)	16.7 (9.8 to 23.5)	19.3 (11.1 to 27.6)
Disease control rate (95% CI)	72.5 (65.5 to 79.6)	66.4 (58.1 to 74.7)	64.0 (55.2 to 72.8)	58.0 (47.6 to 68.3)

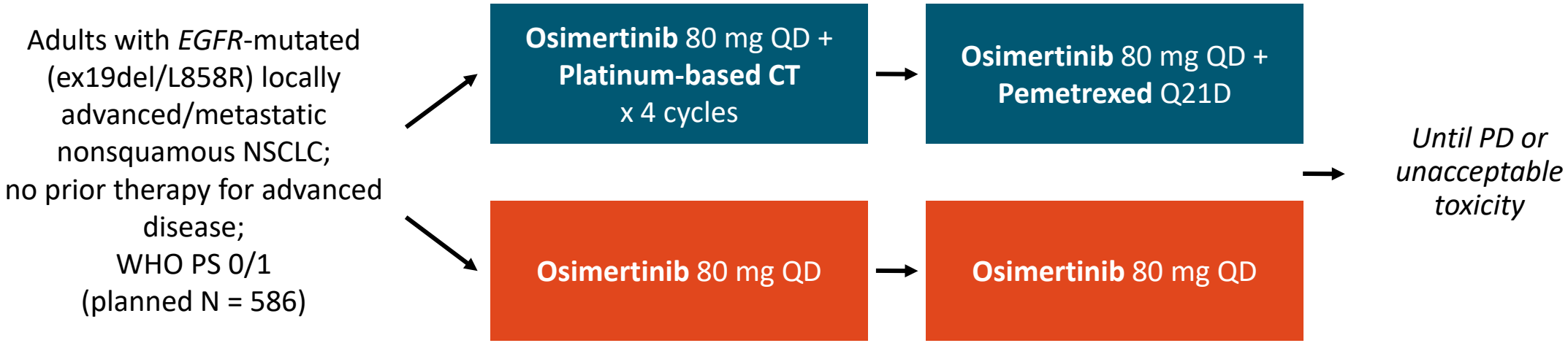
Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.

Critique of our trial

- Negatives:
  - Single institution
  - Open label design
  - Demographic pattern may vary from other countries (84% non-smokers)
  - No centralized independent radiology review
  - QOL data not analyzed yet
- Positives:
  - Use of easily available, accessible and affordable medications
  - Use of standard of care chemo (pem + platinum induction → pem maint)
  - All *EGFR* testing done in the molecular lab of medical oncology dept of TMH
  - Included PS 2 pts, brain mets, rare *EGFR* mutations: L861Q, S761I, G791X

FLAURA2: First-line Osimertinib ± Chemotherapy in Advanced or Metastatic *EGFR*-Mutated NSCLC

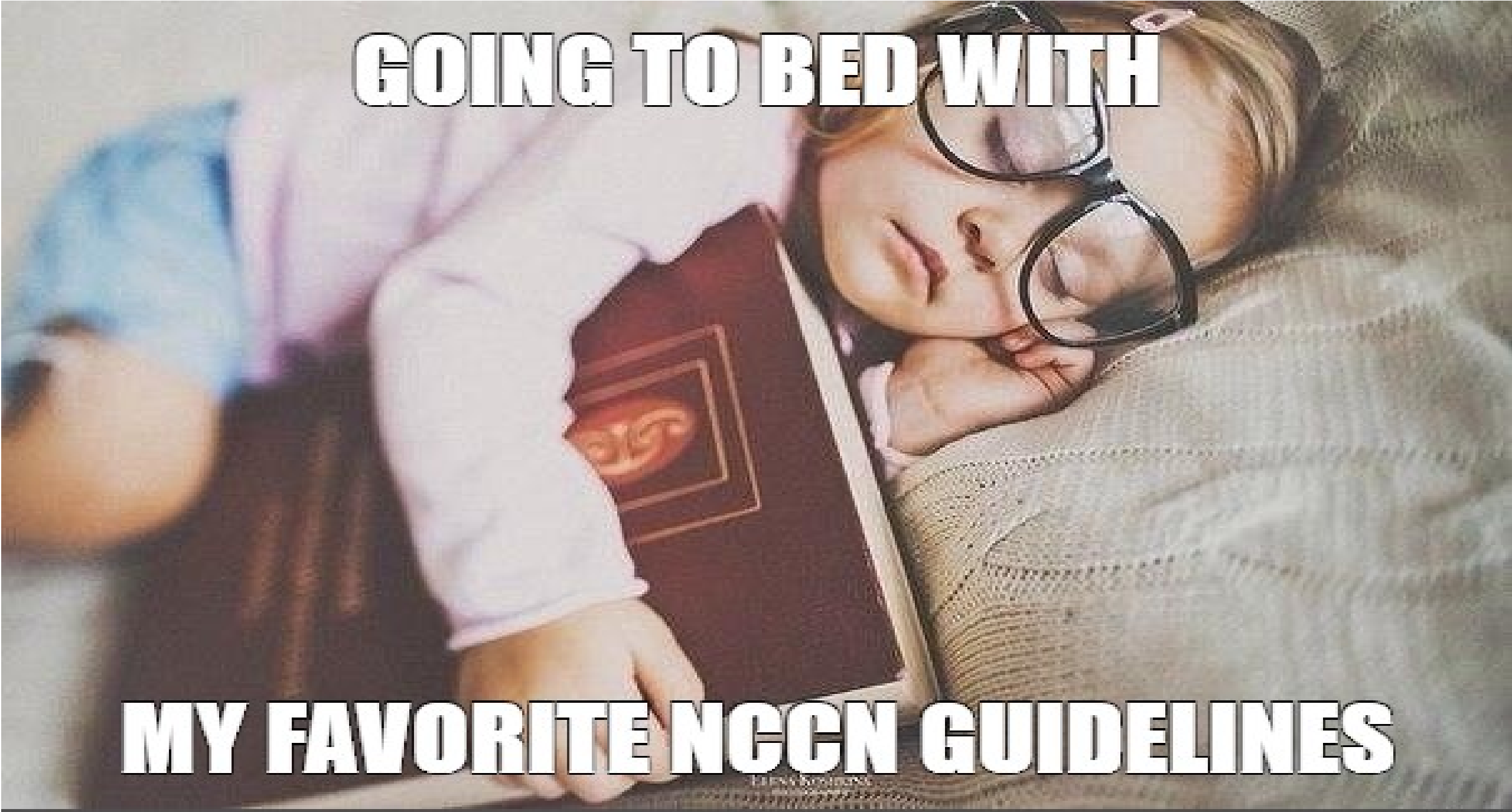
- International, randomized, open-label phase III trial

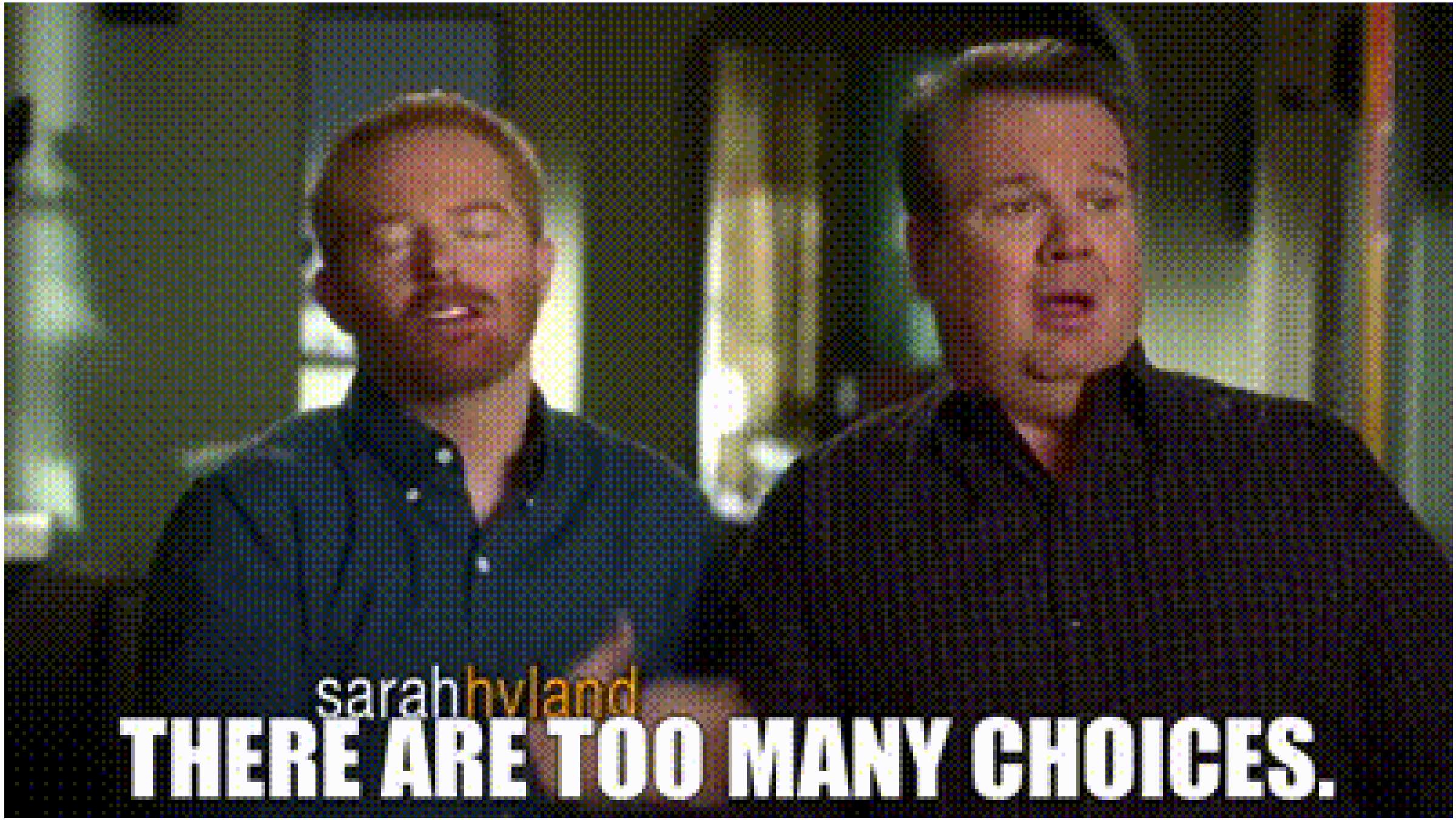


- **Primary endpoint:**
- PFS by BICR per RECIST v1.1

- **Secondary endpoints:**
- OS, ORR, DoR, DCR, PFS2, PROs, PK

NCT04035486

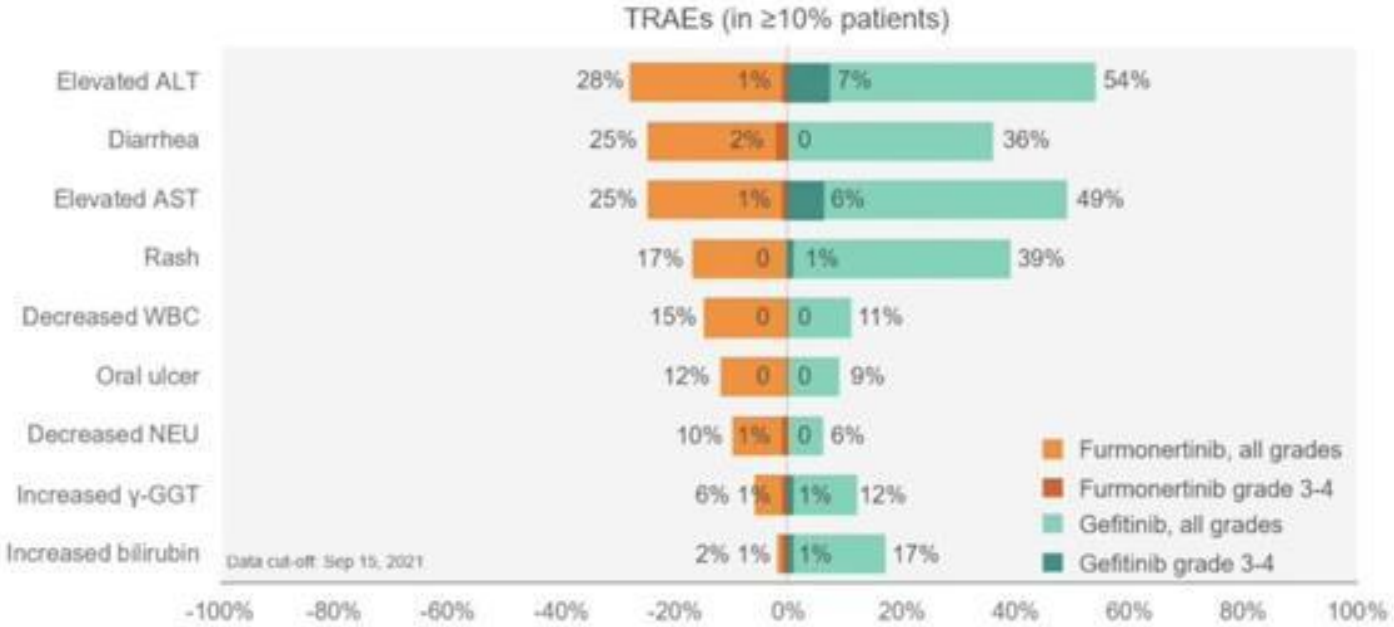



sarahhvland
THERE ARE TOO MANY CHOICES.

Yuan-Kai Shi

The most frequent treatment-related adverse events

Median duration of exposure: 18.3 months with furmonertinib and 11.2 months with gefitinib



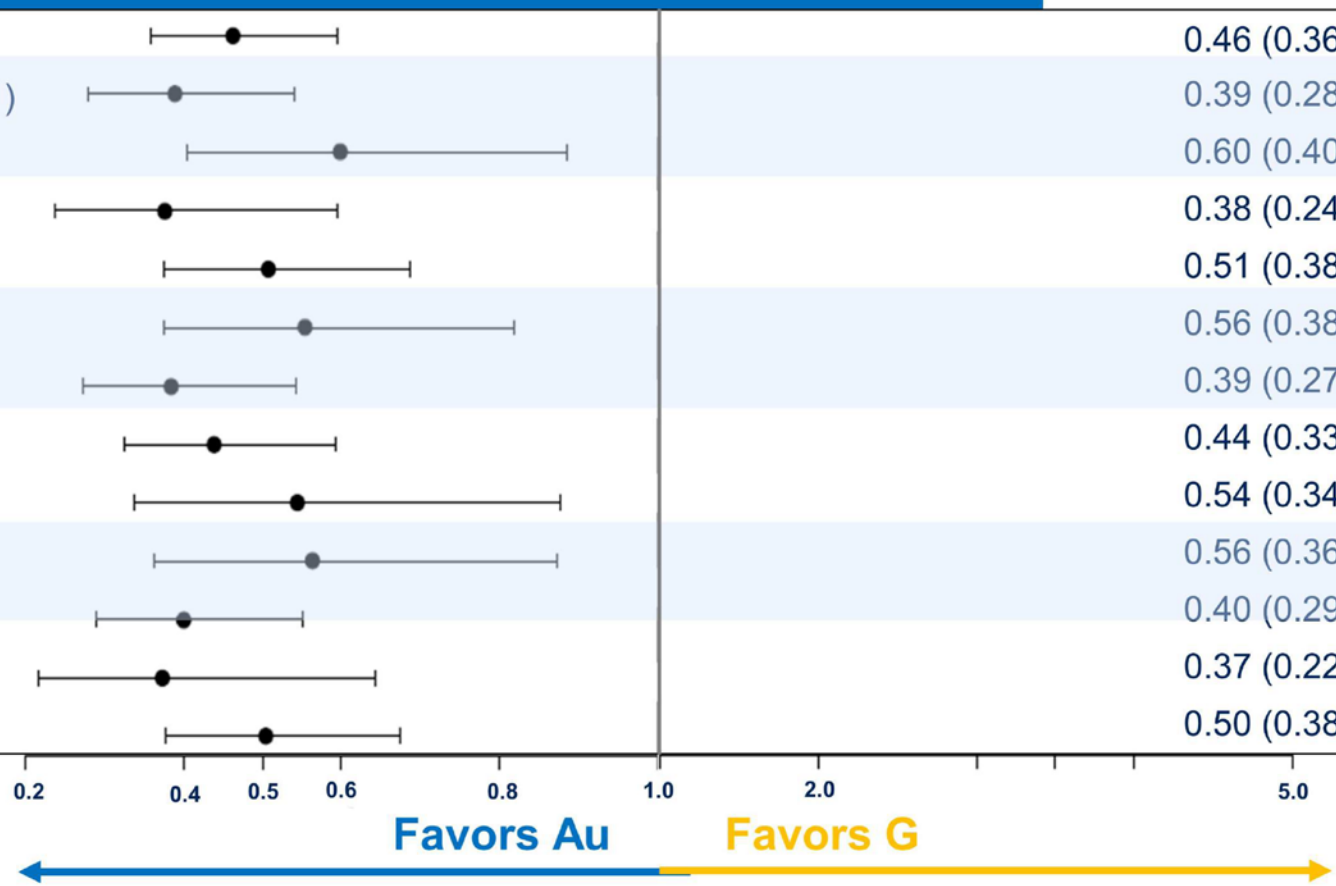
AEs of interest:

- interstitial lung disease (ILD) was recorded in 1 patient in each group (grade 1 in furmonertinib group, grade 2 in gefitinib group)
- QT prolongation was recorded in 9% and 7% patients in furmonertinib group and gefitinib group, respectively.

Treatment-related adverse events were judged by investigators. Treatment-related adverse events of ≥10% in either group are listed. ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell count; NEU: neutrophil count; GGT: glutamyltransferase. TRAE: treatment-related adverse events/.

EFFICACY: PFS ACROSS SUBGROUPS

Subgroups		HR (Aumolertinib vs. Gefitinib)	HR (95% CI)
Overall (N=429)			0.46 (0.36, 0,60)
EGFR mutation	Ex19del (n=281)		0.39 (0.28, 0.54)
	L858R (n=148)		0.60 (0.40, 0.89)
Brain metastasis	Yes (n=115)		0.38 (0.24, 0.60)
	No (n=314)		0.51 (0.38, 0.69)
Gender	M (n=160)		0.56 (0.38, 0.82)
	F (n=269)		0.39 (0.27, 0.54)
Age	<65 (n=294)		0.44 (0.33, 0.59)
	>=65 (n=135)		0.54 (0.34, 0.88)
Smoking history	Yes (n=129)		0.56 (0.36, 0.87)
	No (n=300)		0.40 (0.29, 0.55)
ECOG PS score	0 (n=105)		0.37 (0.22, 0.64)
	1 (n=319)		0.50 (0.38, 0.67)




PASSED OPTION
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MY CHOICE
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CHINA USES TIKTOK TO HACK
AND STEAL A PERSON'S DATA!
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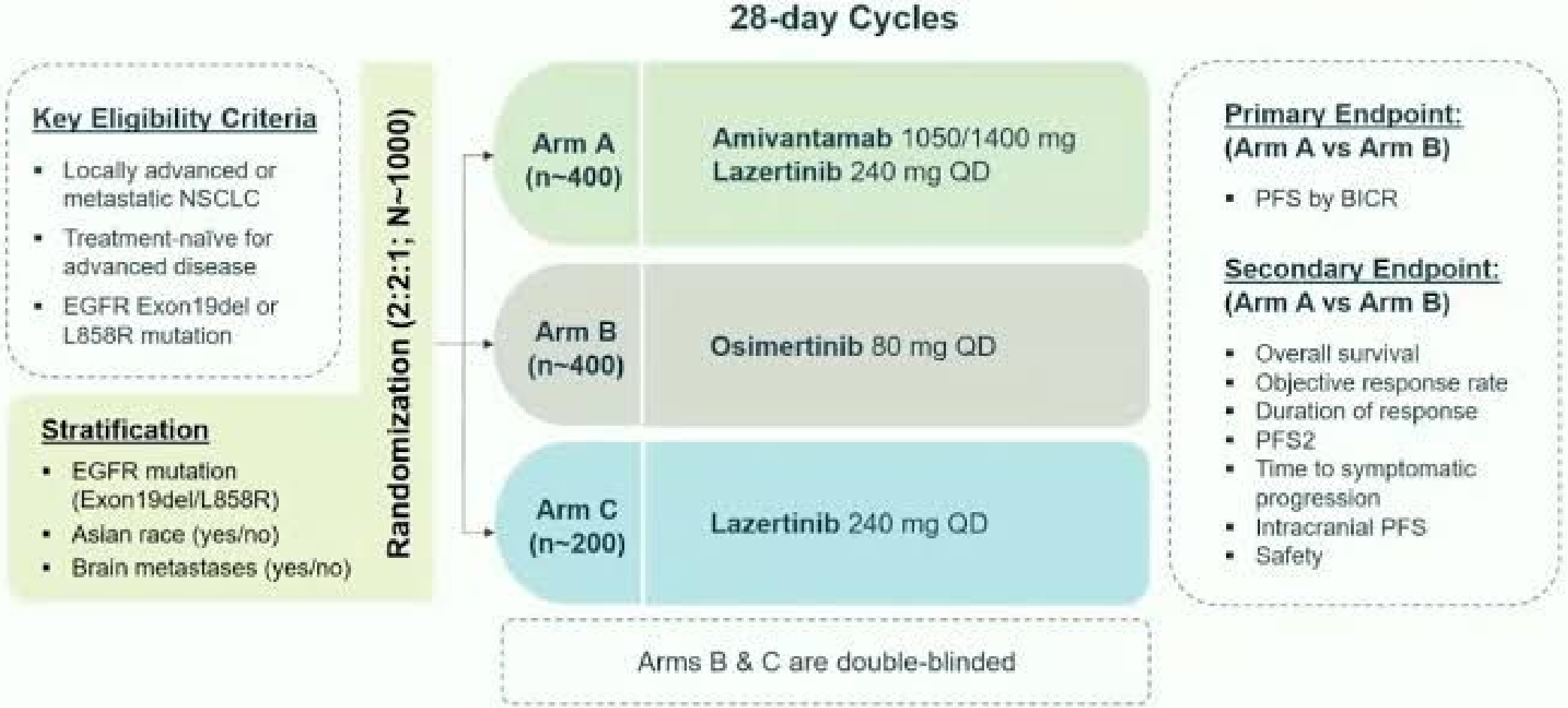
Phase 3 MARIPOSA Study (NCT04487080)

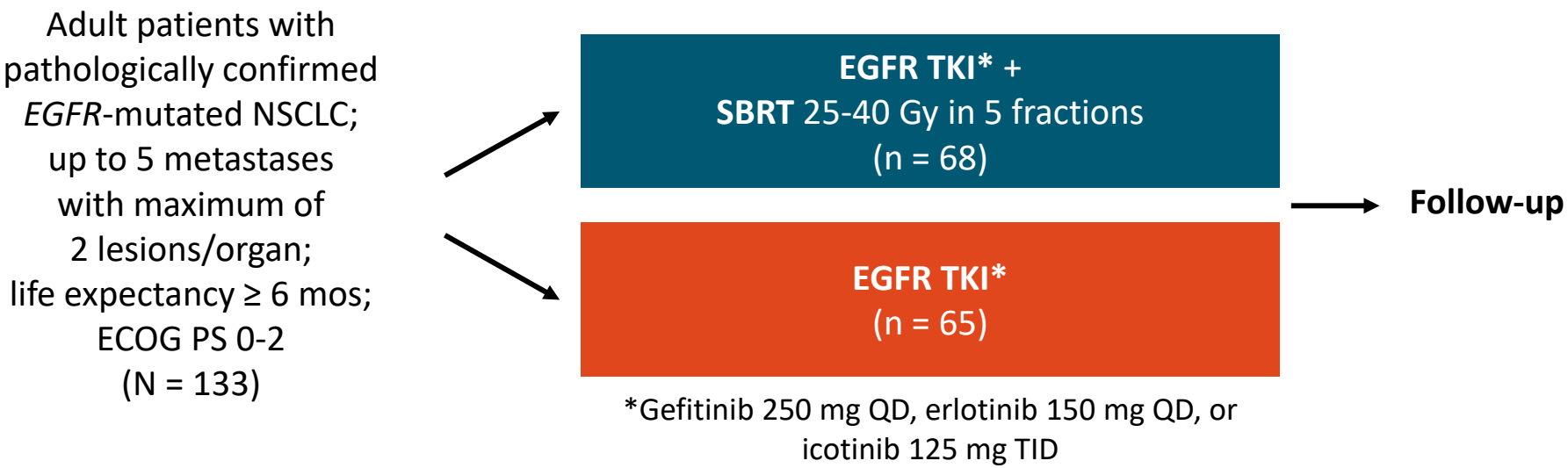


BICR, blinded independent central review; PFS, progression-free survival; PFS2, PFS after first subsequent therapy; QD, once a day

Cho et al. 45th ESMO Congress 2020. Abstract #2172

SINDAS Interim Analysis: Study Design

- Multicenter, open-label, randomized phase III trial in China (January 2016 - June 2019)



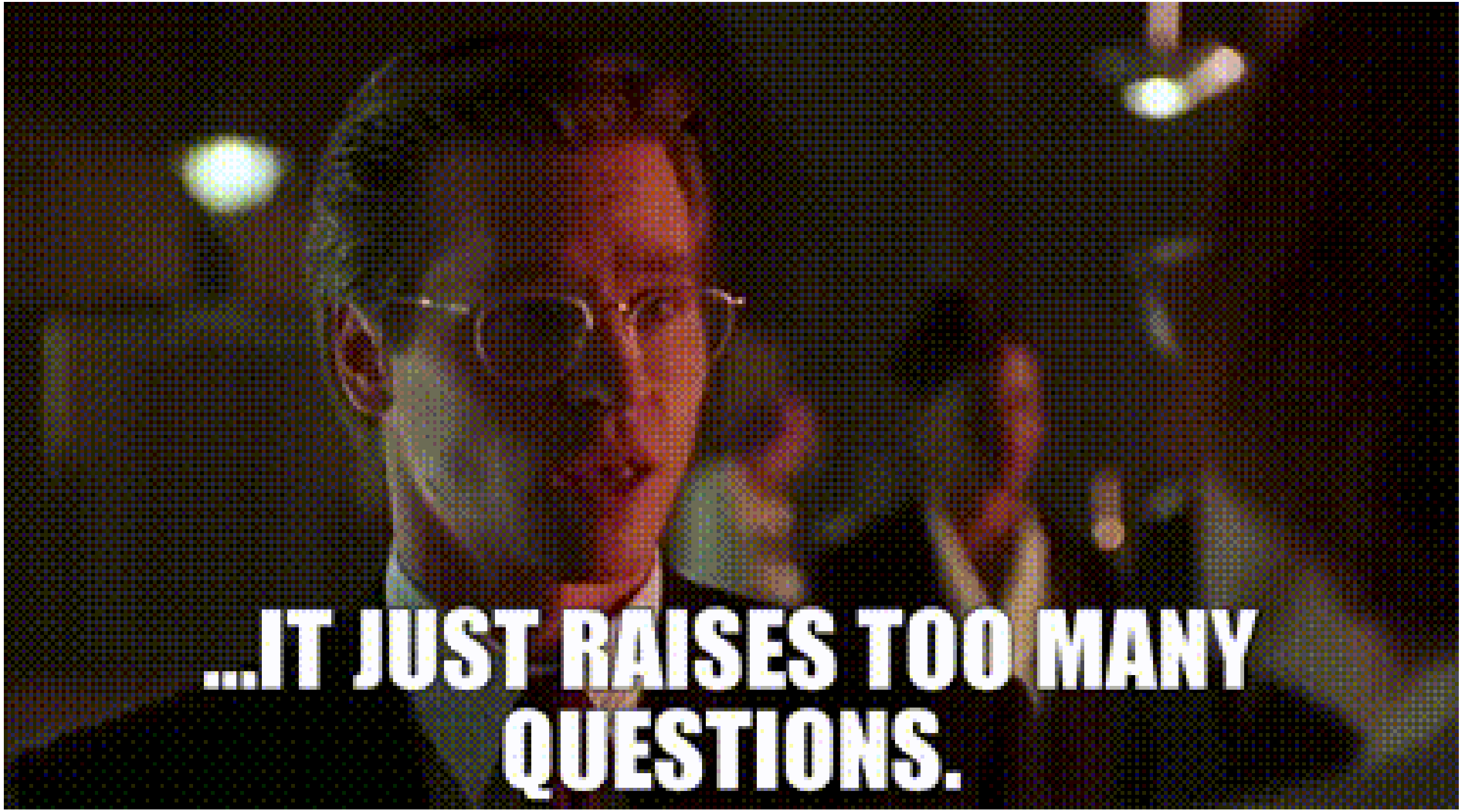
- Primary endpoint: PFS
- Secondary endpoint: OS
- Other endpoint: safety

Wang. ASCO 2020. Abstr 9508

SINDAS Interim Analysis: PFS & OS

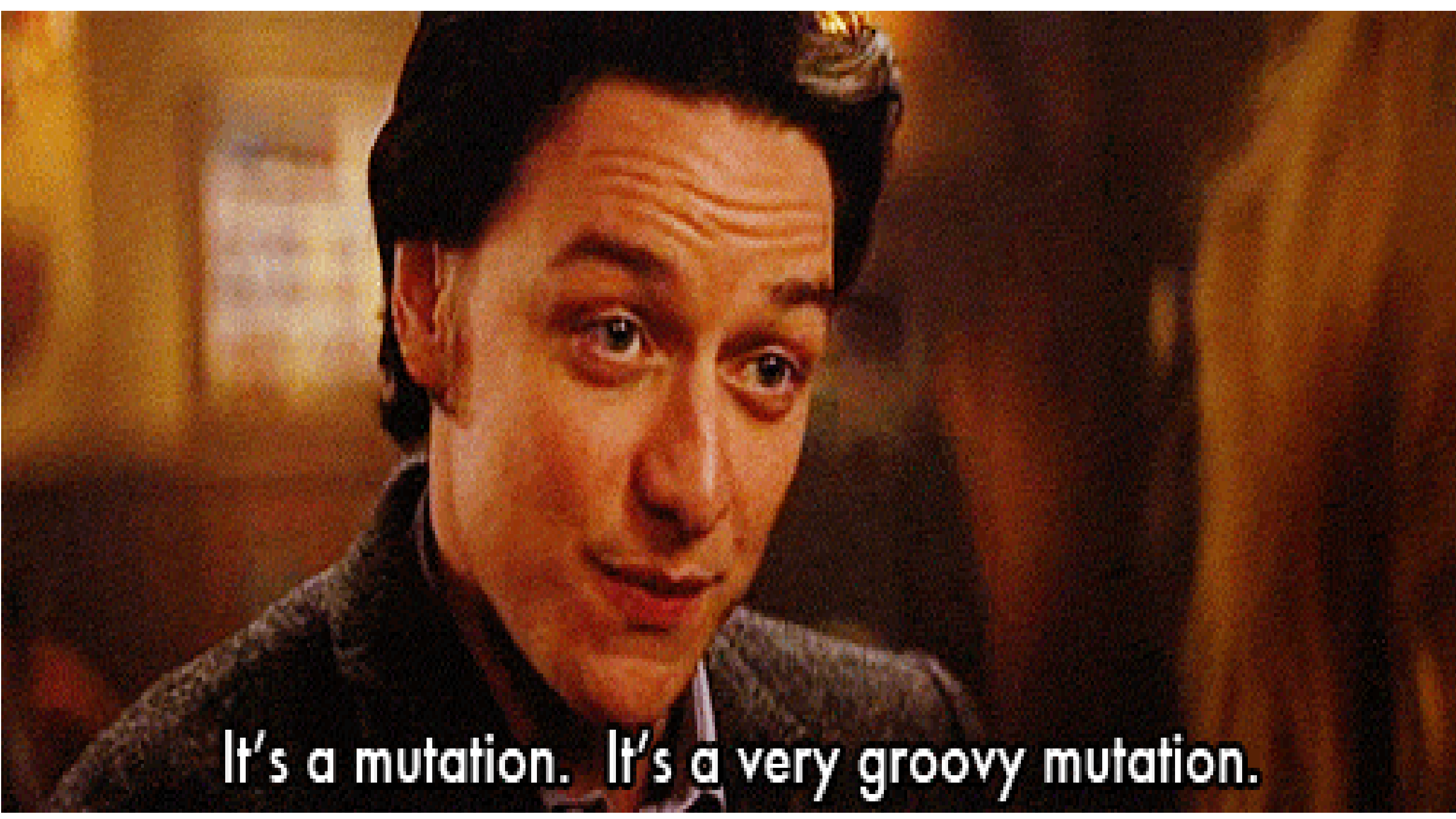
Median Outcome, Mos	EGFR TKI + SBRT (n = 68)	EGFR TKI Only (n = 65)	HR
PFS (primary endpoint)	20.2	12.5	0.618 (95% CI: 0.394-0.969; log-rank *P* < .001)
OS (secondary endpoint)	25.5	17.4	0.682 (95% CI: 0.456-1.001; log-rank *P* < .001)

- After median follow-up of 19.6 mos
- EGFR TKI + SBRT significantly prolonged PFS and OS vs EGFR TKI only


...IT JUST RAISES TOO MANY QUESTIONS.

SINDAS Trial, Take Home Points, 2

- **No significant differences in toxicity**
- **Supportive data from prior Phase II studies for combination**
- **Surgery for oligomets?**
  - SBRT less invasive
  - Better QOL expected
  - Relatively less resource utilization


It's a mutation. It's a very groovy mutation.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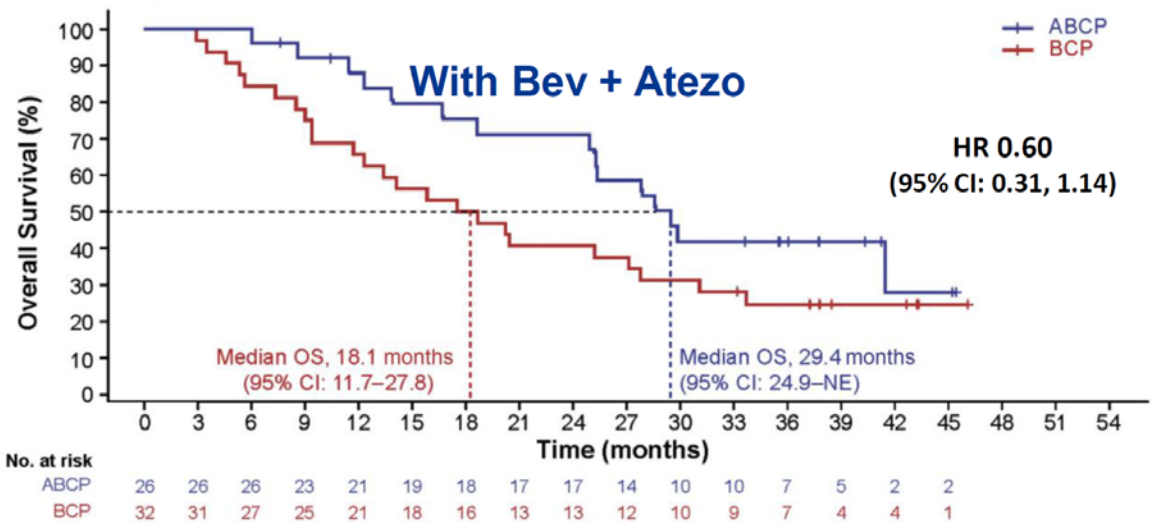
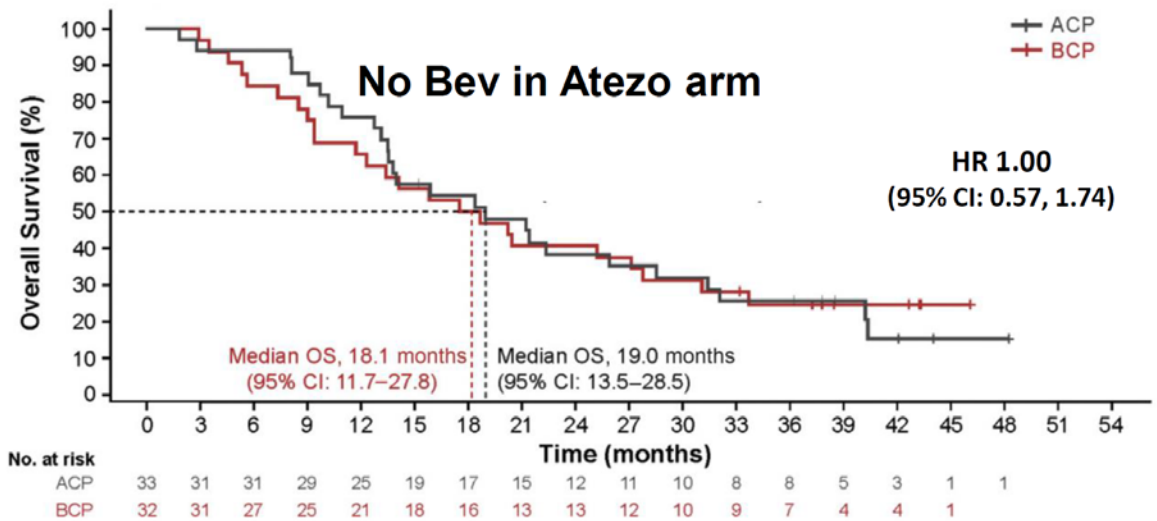
IMpower 150: IO + Chemo + VEGFi in EGFRm NSCLC

Sensitising EGFR Positive Patients (~7.6%)

ABCP vs BCP
Sensitizing *EGFR+*



ACP vs BCP
Sensitizing *EGFR+*



Nogami et.al., *JTO*, 2022

Conclusions

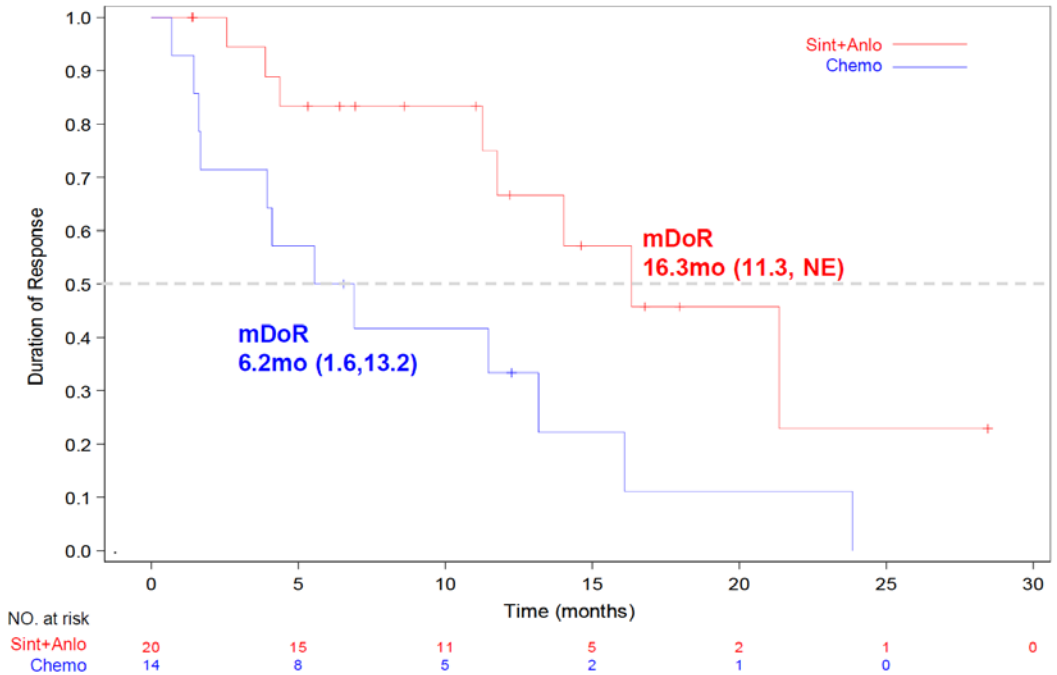
- ORIENT-31 demonstrated a significantly improved PFS with Arm B (Sintilimab + Pemetrexed + Cisplatin) versus Arm C (Pemetrexed + Cisplatin) as assessed by IRRC in patients with EGFRm nsqNSCLC who progressed after EGFR-TKIs therapy.
  - PFS HR for Arm B vs Arm C: HR 0.723 (95% CI: 0.552, 0.948), P =0.0181*
- ORR, DCR and DOR were improved in Arm B versus Arm C.
  - Confirmed ORR for Arm B vs Arm C: 34.8% vs 29.4%
- The OS was immature yet.
- The safety profile was acceptable without new unexpected safety signals.
- This is the first randomized, double-blind, placebo-controlled study that indicates significant PFS benefit with platinum-based doublet chemotherapy plus anti-PD-1 antibody with or without VEGF-inhibitor versus chemotherapy alone.

* For 2IA analysis, the two-sided α boundary is 0.0444.

SECONDARY ENDPOITS

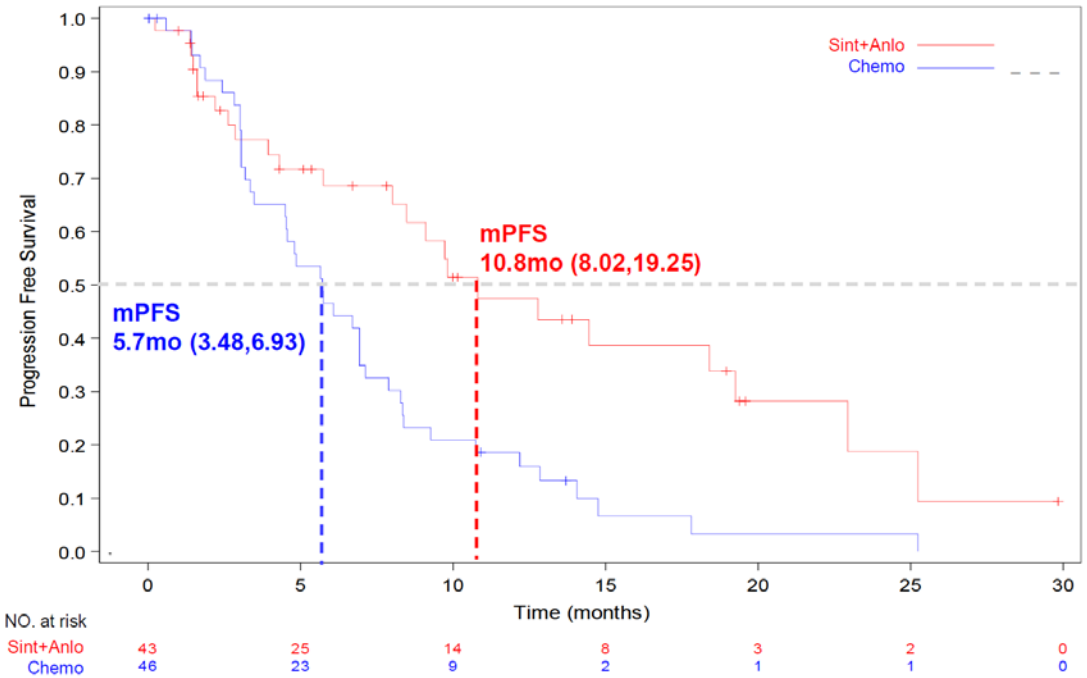
Duration of Response and Progression-Free Survival

DOR



	Patients	Events	median DOR (95%CI)
Sint+Anlo	20	8 (40.0)	16.3 (11.3, NE)
Chemo	14	12 (85.7)	6.2 (1.6,13.2)

PFS

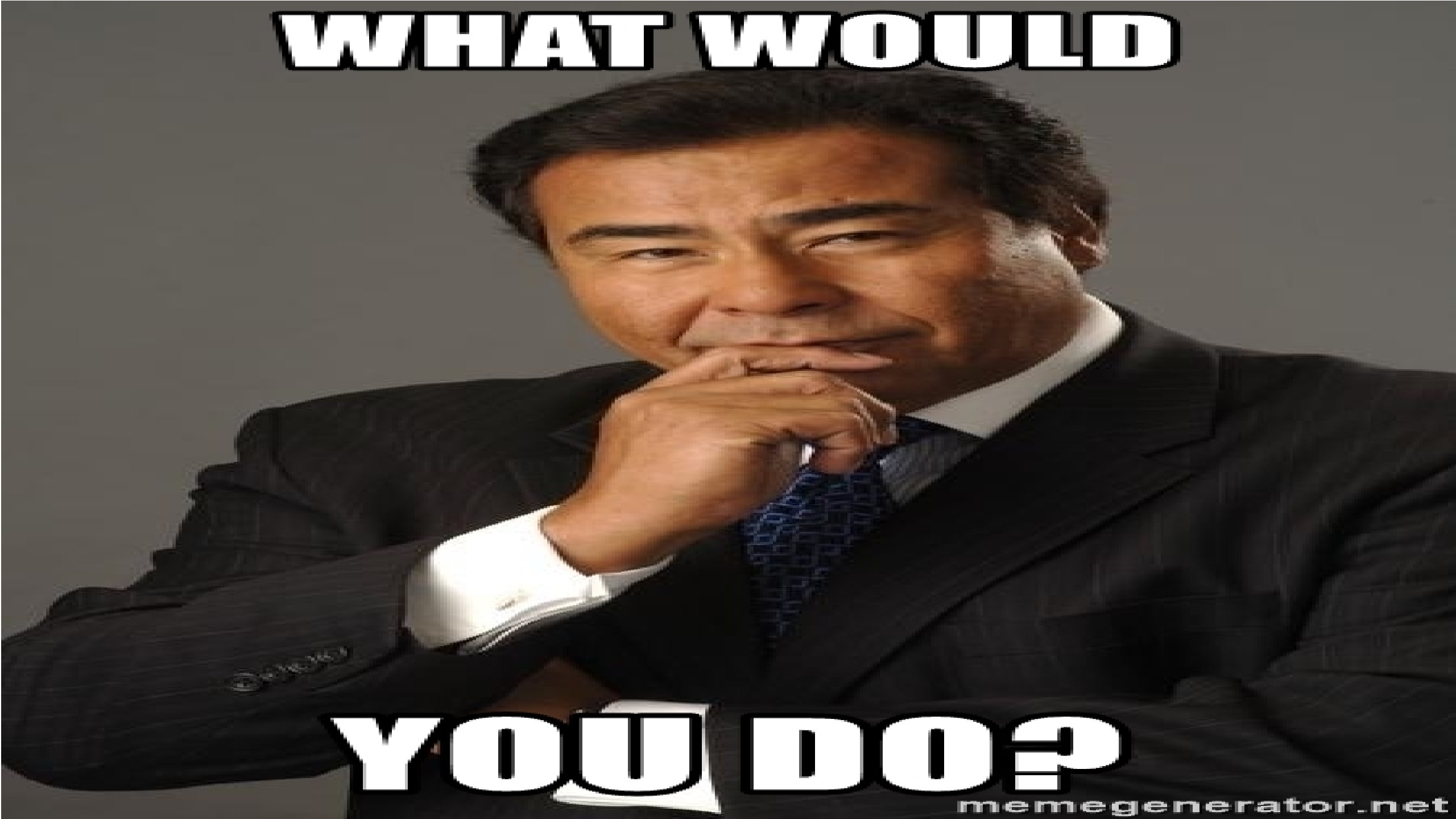


	Patients	Events	HR (95%CI)	P
Sint+Anlo	43	24 (55.8)	0.4 (0.25,0.74)	0.002
Chemo	46	41 (89.1)		

HR was calculated with stratified Cox model, and was stratified by Histology(Squamous vs non-Squamous) PD-L1 expression(≥1% vs <1%)

P value was calculated with stratified log rank test); Data cutoff : Jul. 15th 2022 ; Median follow-up 13.1 months

PRESENTED BY: Baohui Han, PhD


WHAT WOULD
YOU DO?
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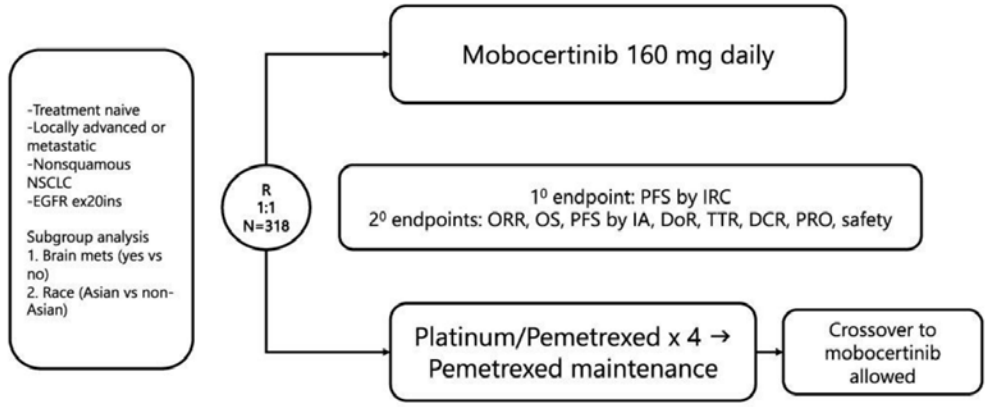
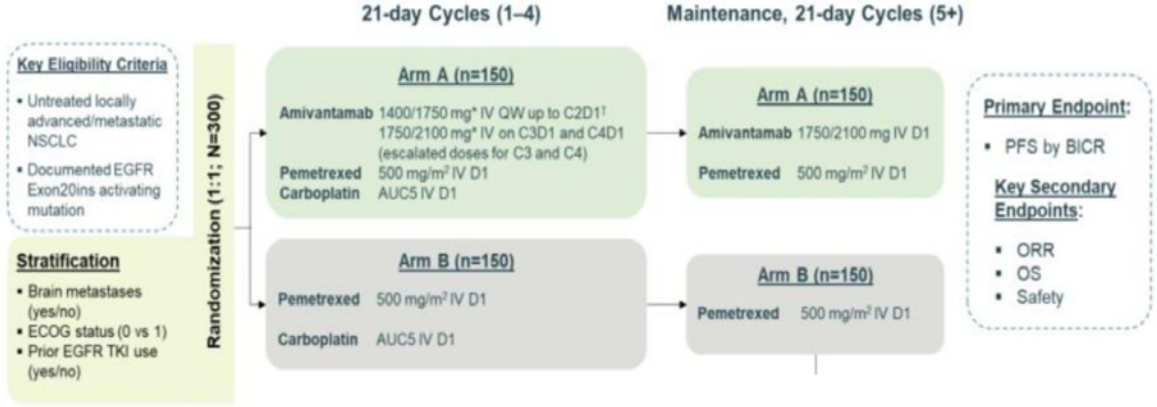
Unanswered Questions in EGFR ins20

- **Optimal First-Line Treatment Strategies**
  - PAPILLON, EXCLAIM-2 may change the standard of care
- **How should currently available therapies be sequenced?**
  - TKI -> Amivantamab | Amivantamab - > TKI | Combinations
- **Should treatment be tailored based on the location of the insertion?**
- **Management of CNS Metastases**
  - Novel agents (BLU-451, ORIC 114) may have a role
- **Overcoming acquired resistance**

EXCLAIM-2



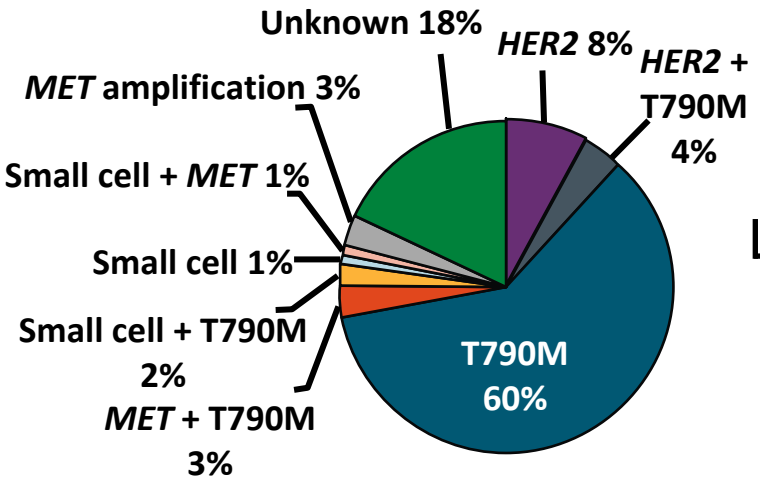
PAPILLON



Zhang SS, Zhu VW. Lung Cancer (Auckl). 2021
Agrawal T, WCLC 2020

Resistance More Challenging With Newer *EGFR* TKIs

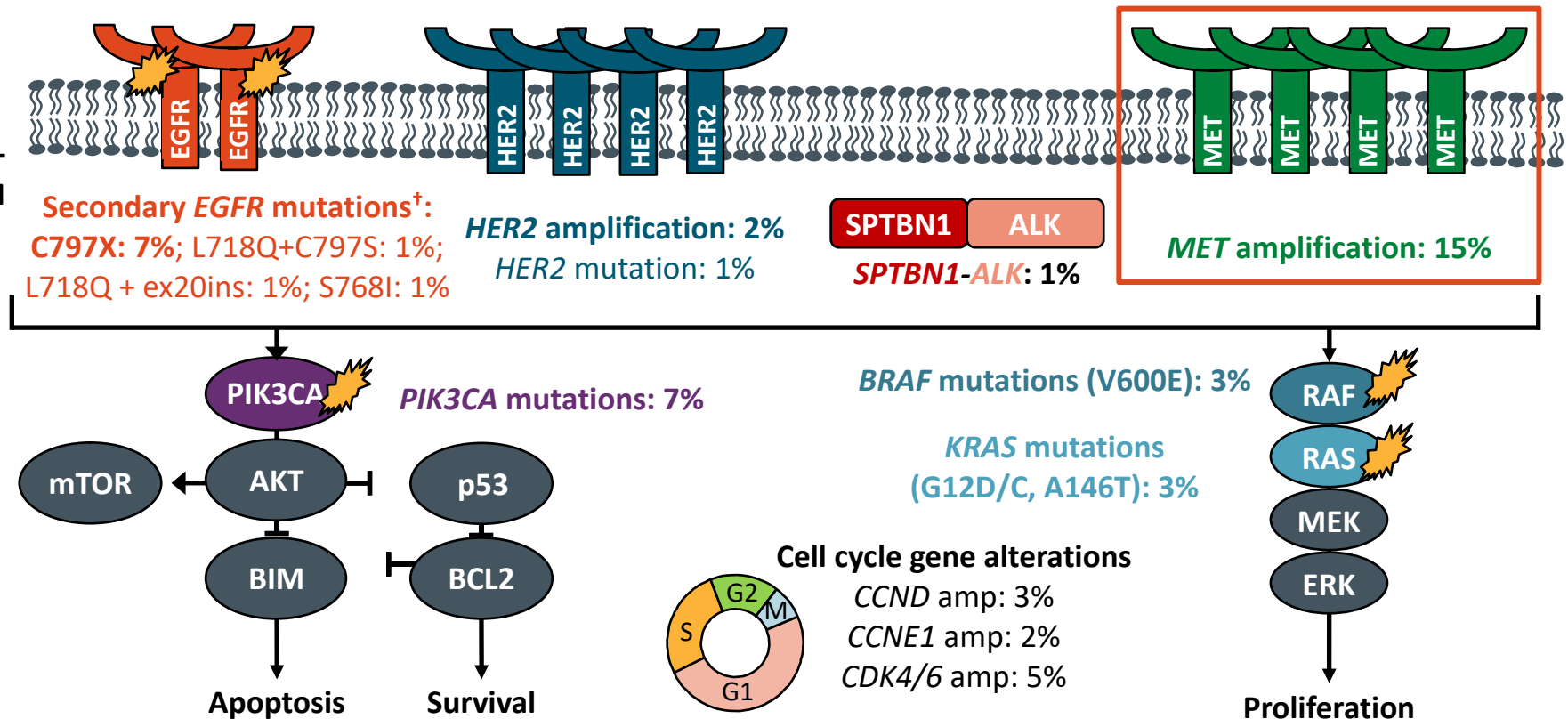
Acquired Resistance Mechanisms With Early-Gen EGFR TKIs[1]



T790M – dominant mechanism of resistance to 1st & 2nd gen EGFR TKIs‡

‡In the phase III RELAY trial, the post-progression T790M rate was 43% and 47% with ramucirumab + erlotinib vs placebo + erlotinib, respectively.[2]

Candidate Acquired Resistance Mechanisms With Osimertinib*[3]



*Overlap of reported resistance mechanism may occur. †n = 2 with de novo T790M mutations at BL; 1 acquired C797S at progression.

No dominant and more heterogeneous mechanisms of resistance to 3rd-gen EGFR TKI osimertinib

1. Yu. Clin Cancer Res. 2013;19:2240. 2. Nakagawa. ASCO 2019. Abstr 9000. 3. Ramalingam. ESMO 2018. Abstr LBA50

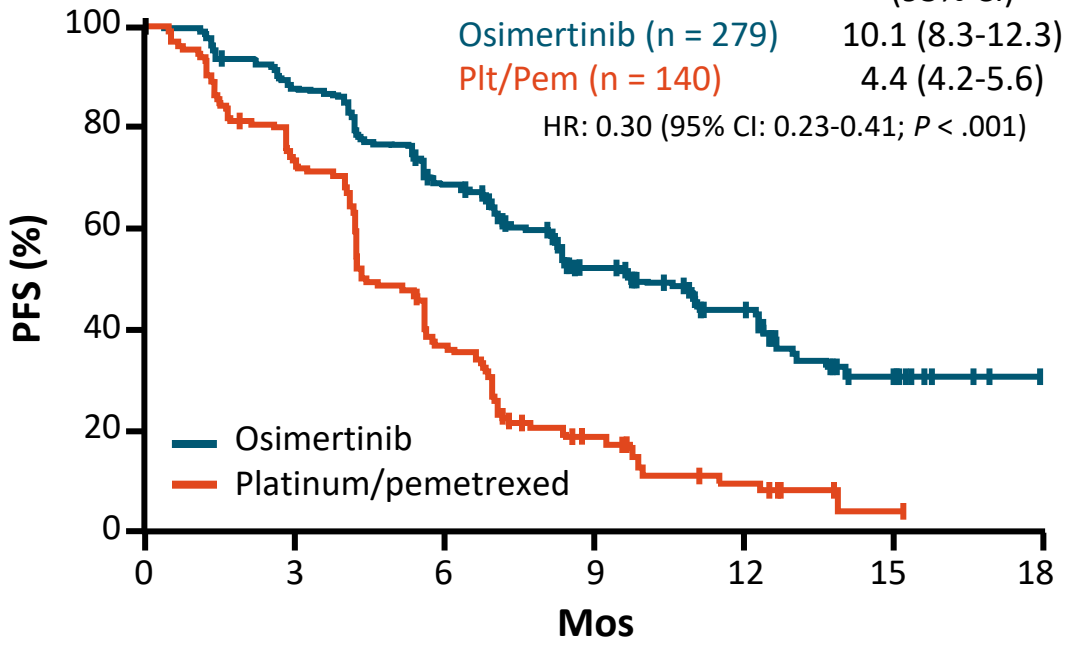

#CRAZYRICHASIANS
THIS... IS GOLD STANDARD

AURA3: Osimertinib vs CT in NSCLC With EGFR T790M Mutation–Positive Acquired Resistance

PFS (ITT)[1]

	Median PFS, Mos (95% CI)
Osimertinib (n = 279)	10.1 (8.3-12.3)
Plt/Pem (n = 140)	4.4 (4.2-5.6)

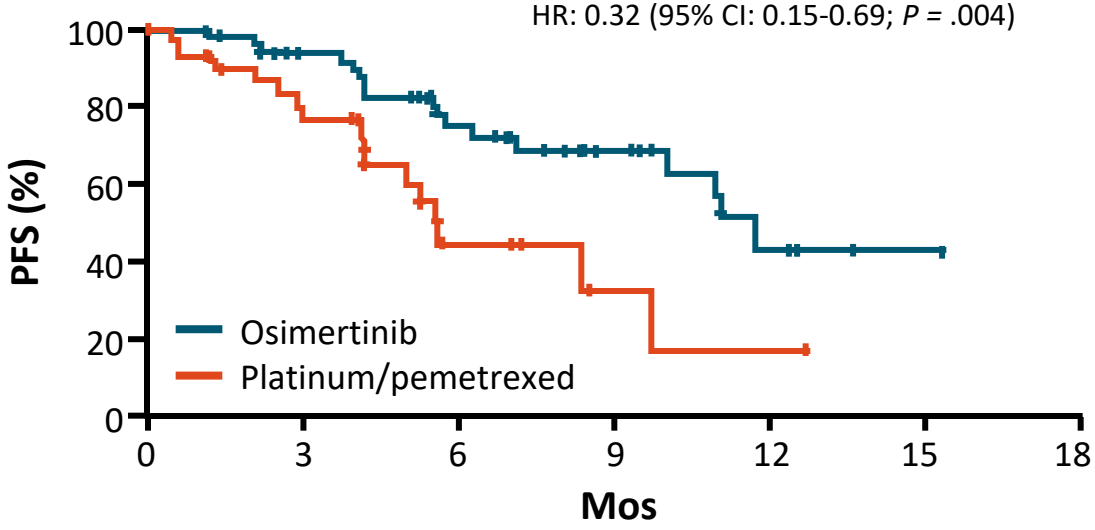
HR: 0.30 (95% CI: 0.23-0.41; *P* < .001)



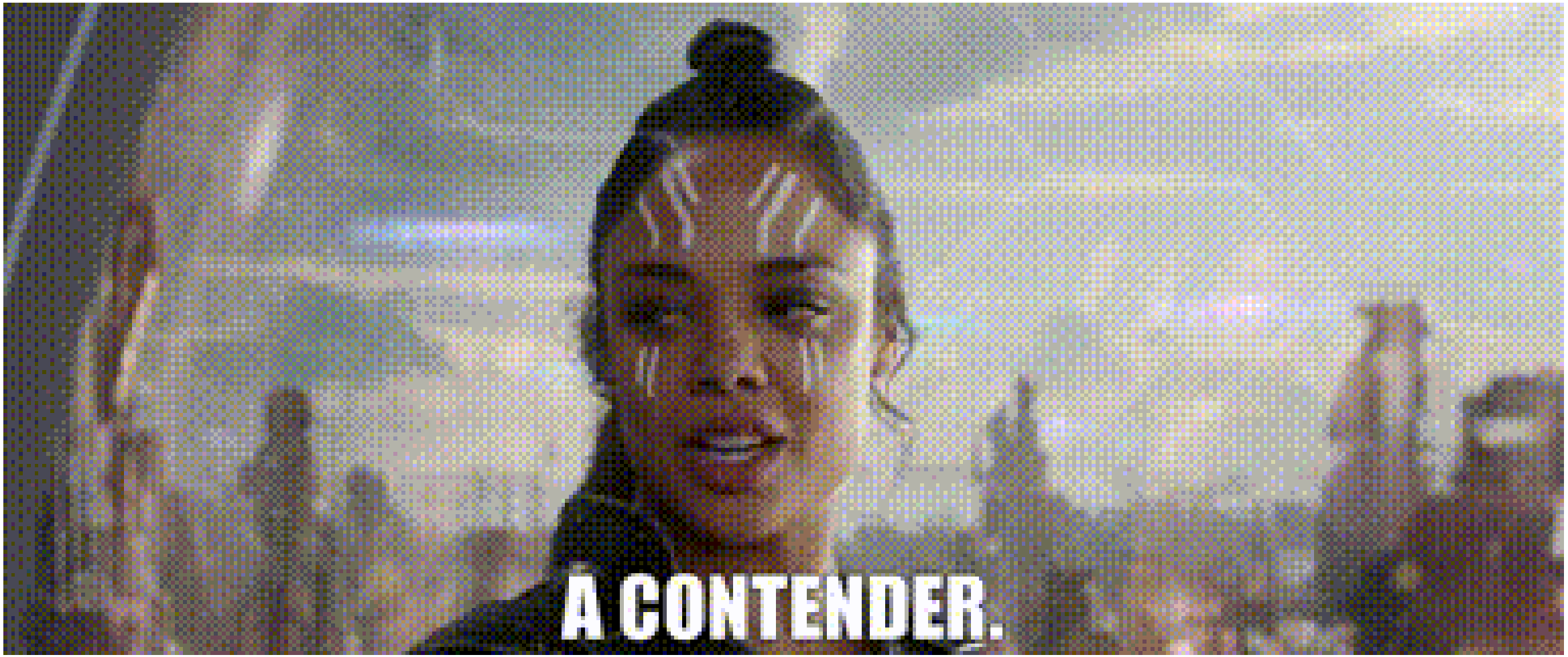
CNS PFS[2]

	Median CNS PFS, Mos
Osimertinib (n = 75)	11.7
Plt/Pem (n = 41)	5.6

HR: 0.32 (95% CI: 0.15-0.69; *P* = .004)



1. Mok T, et al. N Engl J Med. 2017;376:1993-1994


A CONTENDER.

Endpoints	BICR	Investigator
ORR %, n (95% CI)	57.6% (44.1, 70.4)	54.2% (40.8, 67.3)
CR, n (%)	0	1 (1.7%)
PR, n (%)	34 (57.6%)	31 (52.5%)
DCR %, n (95% CI)	98.3% (90.9, 99.9)	96.6%(88.3, 99.6)
Median PFS, months (95% CI)	12.4 (8.3, NA)	11.7 (8.2, 16.8)
Median DOR, months (95% CI)	15.2 (8.3, NA)	11.1(7.2, NA)
Median OS, months (95% CI)	Not Reached	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WE HAVE A WINNER!
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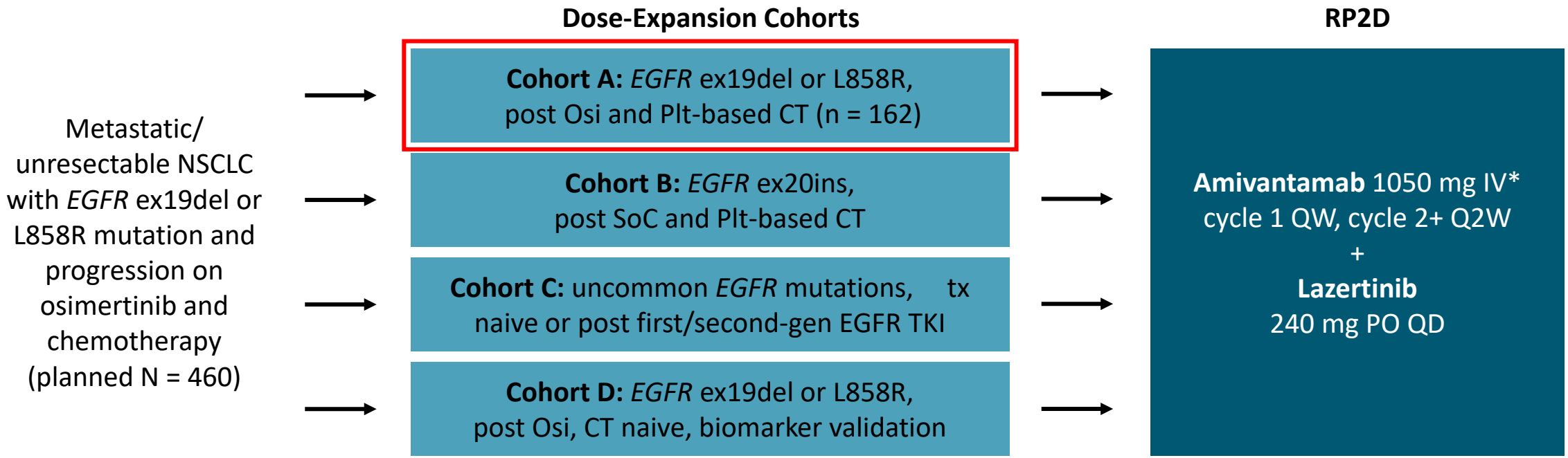
CHRYSALIS-2: Amivantamab + Lazertinib in *EGFR*-Mutated NSCLC

- Multicohort dose-escalation and dose-expansion phase I study
  - **Current report focused on cohort A**



*1050 mg if <80 kg and 1400 mg if ≥80 kg

- **Primary endpoint:** ORR
- **Key secondary endpoints:** DoR, CBR, PFS, OS, safety

Shu. ASCO 2022. Abstr 9006. Bauml. ASCO 2021. Abstr 9006. NCT04077463


THE REAL DEAL!

Select Ongoing Studies of Amivantamab Combination Regimens in *EGFR*-Mutated Advanced NSCLC

Trial	Phase	Planned N	Study Population	Treatment	Primary Endpoint(s)
CHRYSALIS-2 (NCT04077463)	I	460	*EGFR*-mutated advanced NSCLC with PD on or after EGFR TKI and plt-based CT	Amivantamab + lazertinib	ORR
NCT04965090	II	40	*EGFR*-mutated advanced NSCLC with CNS metastases or LM	Amivantamab + lazertinib	CNS ORR
MARIPOSA (NCT04487080)	III	1074*	*EGFR*-mutated advanced NSCLC	Amivantamab + lazertinib vs osimertinib	PFS
MARIPOSA-2 (NCT04988295)	III	600	*EGFR*-mutated advanced NSCLC with PD on or after EGFR TKI and plt-based CT	Amivantamab + lazertinib + plt-based CT vs amivantamab + plt-based CT vs plt-based CT	PFS
NCT05388669	III	640	*EGFR*-mutated advanced NSCLC after progression on osimertinib and plt-based CT	Lazertinib + SC amivantamab (manual injection) vs IV amivantamab vs SC amivantamab (on-body delivery)	C_{trough}, AUC, C_{max}

*Actual N; study active, no longer recruiting

Patritumab Deruxtecan in *EGFR*-Mutated NSCLC: Study Design

- Multicenter, open-label, multicohort phase I trial; current report focused on cohort of patients with *EGFR*m NSCLC adenocarcinoma after failure of EGFR TKI therapy

Patients with locally advanced or metastatic NSCLC with *EGFR* mutations and progression on previous EGFR TKI; stable brain metastases allowed; tumor biopsy required, but selection not based on HER3 expression (planned N = 264)

Dose Escalation

HER3-DXd
6.4 mg/kg IV Q3W
(n = 5)

HER3-DXd
5.6 mg/kg IV Q3W*
(n = 12)

HER3-DXd
4.8 mg/kg IV Q3W
(n = 15)

HER3-DXd
3.2 mg/kg IV Q3W
(n = 4)

Dose Expansion†

HER3-DXd
5.6 mg/kg IV Q3W*
(n = 45)

Patritumab deruxtecan given in 21-day cycles.
* Recommended patritumab deruxtecan dose for dose expansion.
† Patients in dose-expansion phase required to have received 1 platinum-based CT regimen. Other cohorts included in dose-expansion phase not reported in this analysis.

- Efficacy evaluation: antitumor activity in patients receiving 5.6 mg/kg dose (n = 57)
- Safety evaluation: safety and tolerability in all patients in dose escalation and expansion (n = 81)

Jänne. ASCO 2021. Abstr 9007. Jänne. Cancer Discovery. 2022;12:74. NCT03260491


WOULD YOU LIKE TO KNOW
YOUR FUTURE?

Select Ongoing Studies of Patritumab Deruxtecan in *EGFR*-Mutated Advanced NSCLC

Trial	Phase	Planned N	Study Population	Treatment	Primary Endpoint(s)
NCT03260491*	I	264	*EGFR*-mutated advanced NSCLC with PD on or after EGFR TKI	HER3-DXd	▪ DLT, AEs (dose escalation) ▪ ORR (dose expansion)
NCT04676477	I	252	*EGFR*-mutated advanced NSCLC: ▪ Newly diagnosed (1L dose expansion) ▪ With PD following osimertinib (dose escalation, 2L dose expansion)	HER3-DXd + osimertinib	▪ DLT, AEs (dose escalation) ▪ ORR (2L dose expansion) ▪ AEs (1L dose expansion)
HERTHENA-Lung 01 (NCT04619004)	II	420	*EGFR*-mutated advanced NSCLC with PD on or after ≥1 EGFR TKI and plt-based CT	HER3-DXd	ORR
HERTHENA-Lung 02 (NCT05338970)	III	560	*EGFR*-mutated advanced NSCLC with PD on or after 1-2 EGFR TKIs, which must include a 3rd-gen EGFR TKI	HER3-DXd + plt-based CT	PFS


THANK YOU!