First Line EGFR NSCLC: Is TKI Enough?

Betteridge's law of headlines:

Any headline that ends in a question mark can be answered by the word no."

Sandip Patel MD

Professor, UCSD

Leader, Experimental Therapeutics

Deputy Director, San Diego Center for Precision Immunotherapy

Twitter: @PatelOncology

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

FLAURA Patients (N=556)

- Metastatic NSCLC
- WHO PS 0/1
- Exon 19 deletion/L858R mutation confirmed by local* or central† EGFR testing
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable, asymptomatic CNS metastases allowed

1:1 randomization

osimertinib, n=279
80 mg/day

EGFR-TKI Comparator,‡ n=277

Gefitinib (250 mg/day)
or
Erlotinib (150 mg/day)

Major Efficacy Outcome:

- Progression-free survival§

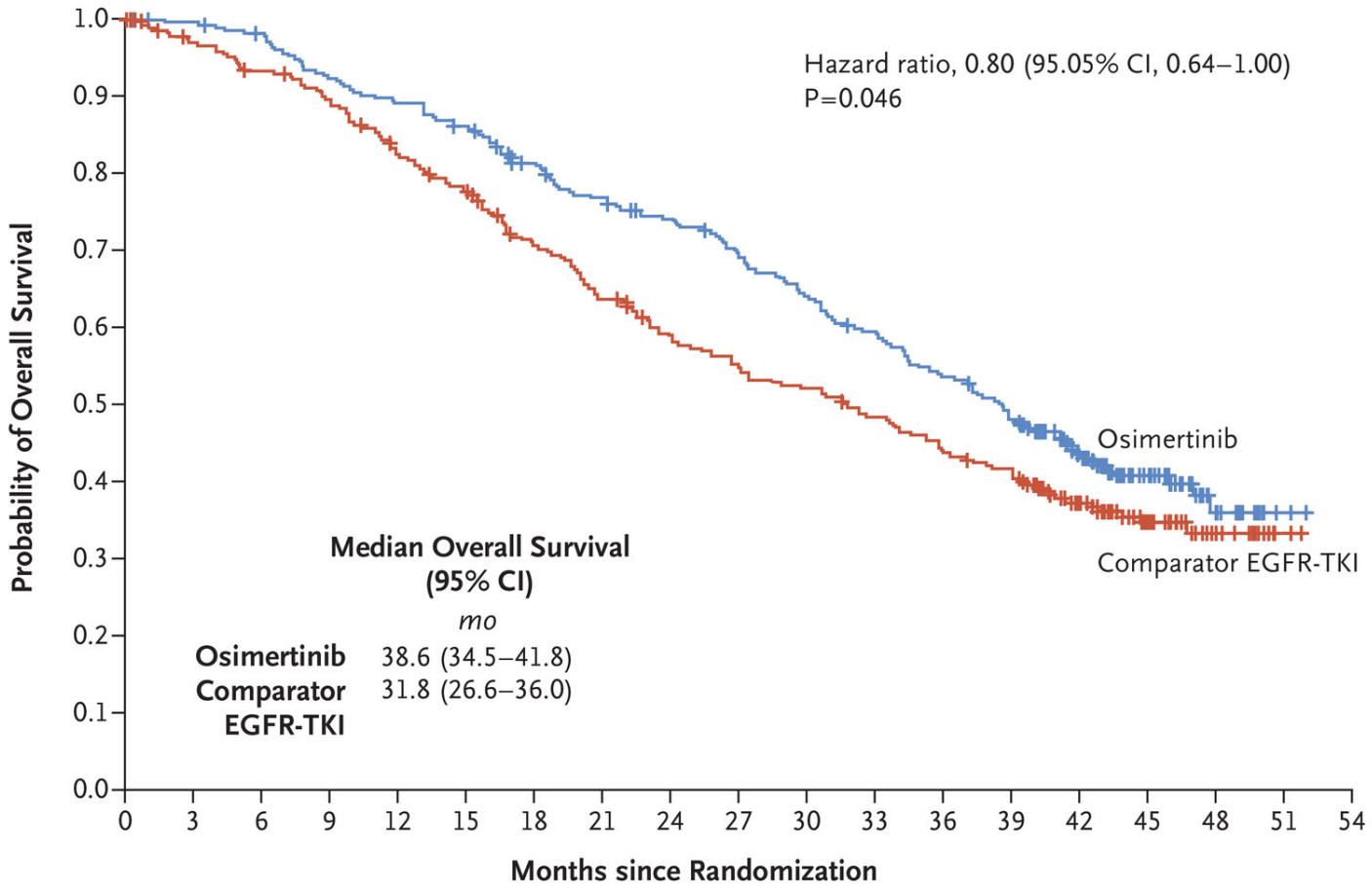
Additional Efficacy Outcomes:

- Overall response rate
- Duration of response
- CNS response
- Overall survival

Patients in the comparator arm could cross over to osimertinib if they had confirmed progression and tested positive for T790M

*No mandatory baseline CNS imaging

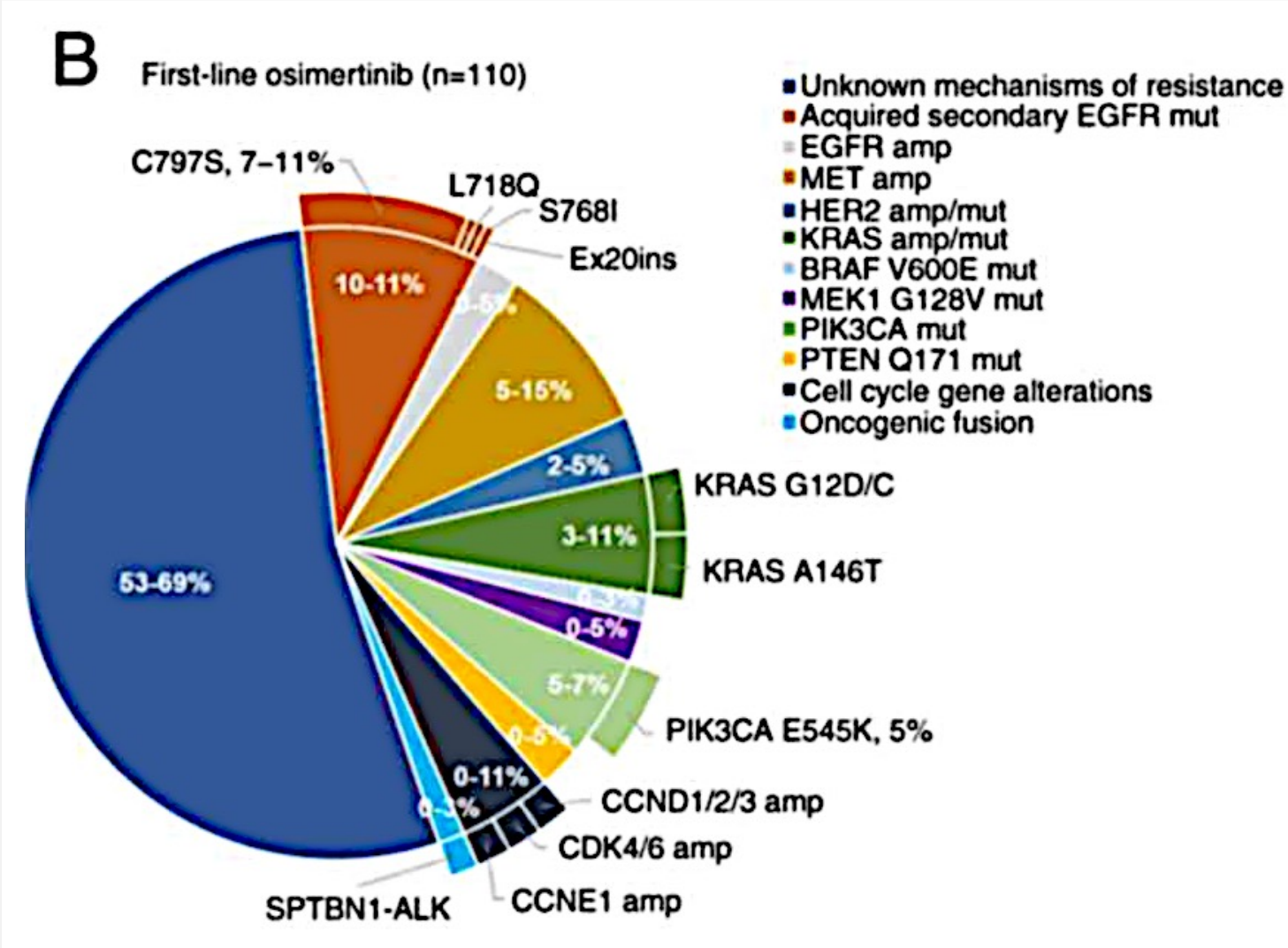
FLAURA: 1st gen EGFR TKI vs Osimertinib



No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Resistance to 1L Osimertinib (FLAURA)



He et al. IJO 2021

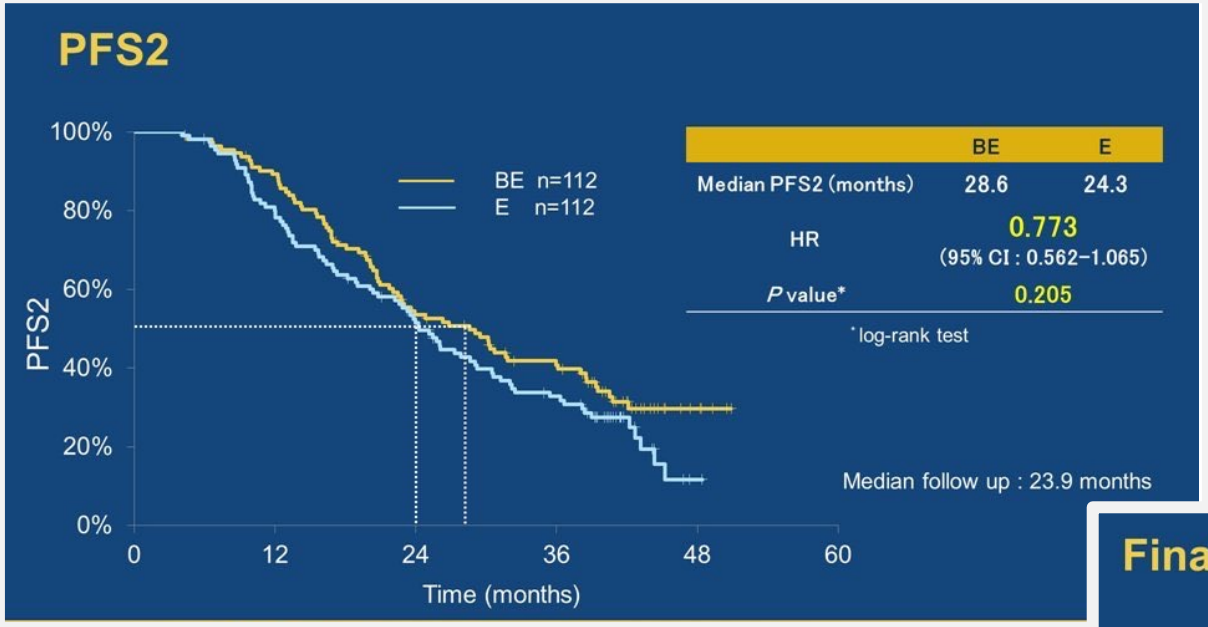
EGFRm+ NSCLC: 1L RCTs of EGFR + VEGF

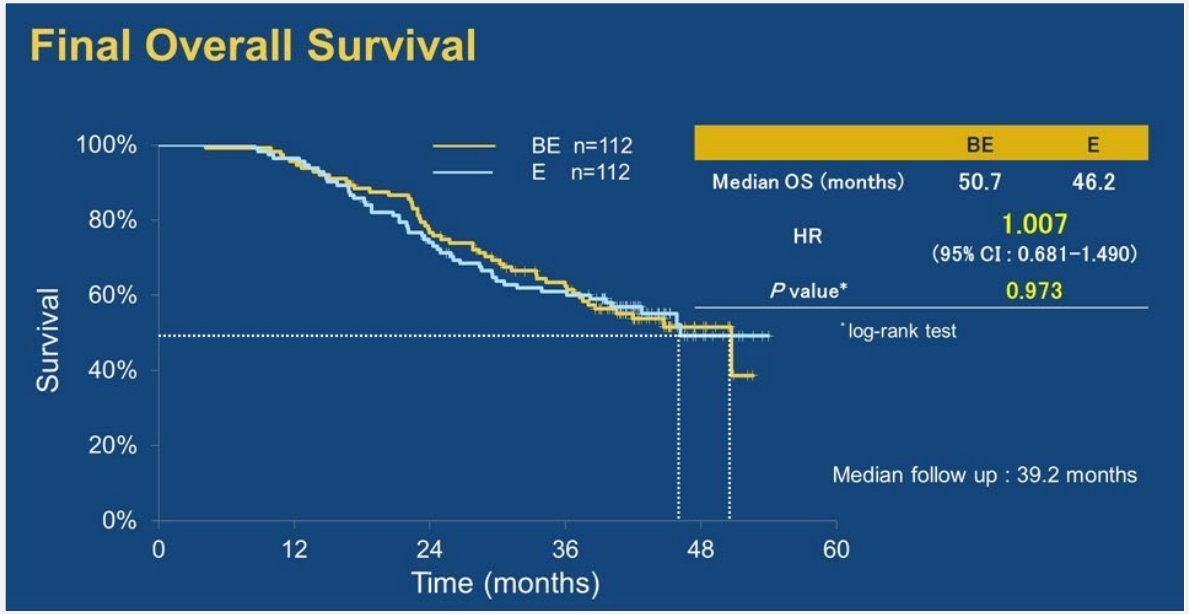
Some TKI ± VEGF studies showed improvement in PFS; no improvement in OS					
Trial	**Ph**	**N**	**Study Design**	**PFS HR (~95% CI)**	**OS HR (~95% CI)**
JO25567[1,2]	2	154	Erl +/- beva	16.4 vs 9.7 mo 0.52 (0.35-0.76); *P* = .0005	47.0 vs 47.4 mo 0.81 (0.53-1.23); *P* = .3267
NEJ026[3,4]	3	228	Erl +/- beva	16.9 vs 13.9 mo 0.61 (0.42-0.88); *P* = .016	50.7 vs 46.2 mo 1.00 (0.68-1.5); *P* = .973
ACCRU[5]	2	88	Erl +/- beva	17.9 vs 13.5 mo 0.81 (0.50-1.31); *P* = .39	32.4 vs 50.6 mo 1.41 (0.71-2.81); *P* = .33
RELAY[6]	3	449	Erl +/- rami	19.4 vs 12.4 mo 0.59 (0.46-0.76); *P*<.001	Not mature
WJOG9717L[7]	2	122	Osi +/- beva	22.1 vs 20.2 mo 0.862 (0.531-1.397); *P* = .213 (one sided)	Not reported

Beva, bevacizumab; Erl, erlotinib; HR, hazard ratio; OS, overall survival; Osi, osimertinib; PFS, progression-free survival; Rami, ramucirumab.

[1]Seto T et al. *Lancet Oncol.* 2014;15(11):1236-1244. [2]Yamamoto N et al. *Lung Cancer.* 2021;151:20-24. [3]Saito H et al. *Lancet Oncol.* 2019;20(5):625-635. [4]Maemondo M et al. ASCO 2020. Abstract 9506. [5]Stinchcombe TE et al. *JAMA Oncol.* 2019;5(10):1448-1455. [6]Nakagawa K et al. *Lancet Oncol.* 2019;20(12):1655-1669. [7]Kenmotsu H et al ESMO 2021.
Courtesy: Luda Bazhenova

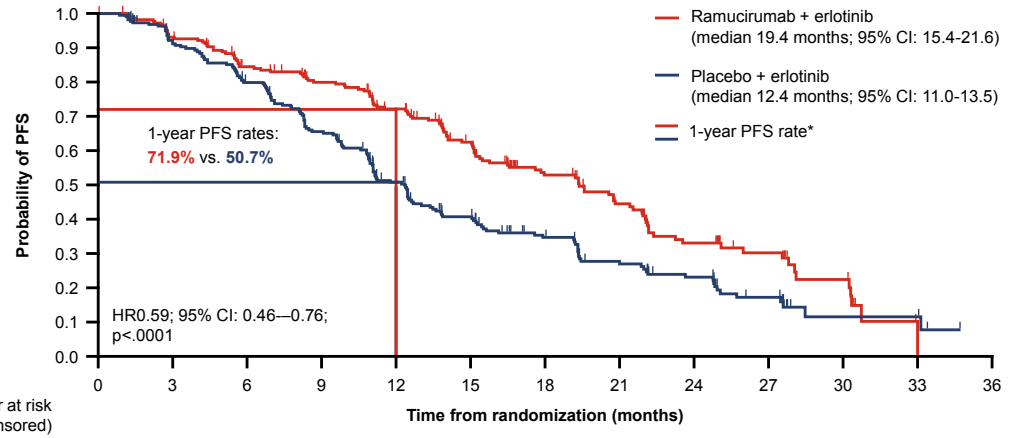
NEJ026: Phase 3 erlotinib+bevacizumab (PFS+, OS-)





RELAY: 1L erlotinib + ram vs erlotinib

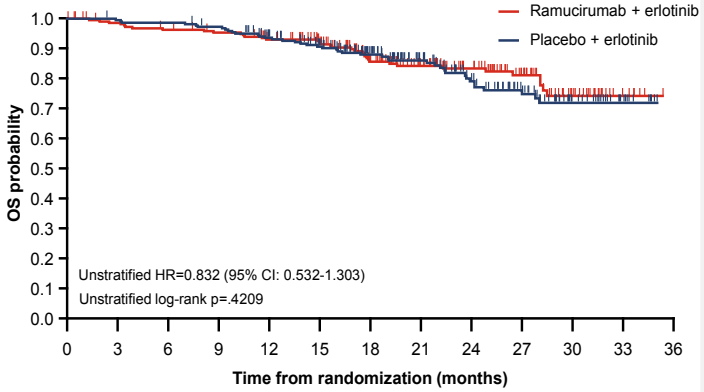
RELAY (JVCY) Primary Endpoint: Progression-free Survival (Investigator-Assessed)



Number at risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36
Ramucirumab + erlotinib	224 (0)	196 (13)	170 (21)	154 (28)	133 (34)	103 (47)	69 (66)	49 (76)	32 (81)	20 (91)	10 (97)	1 (102)	0 (102)
Placebo + erlotinib	225 (0)	196 (12)	167 (12)	136 (16)	99 (23)	72 (31)	52 (41)	37 (46)	27 (50)	15 (56)	4 (64)	4 (64)	0 (67)

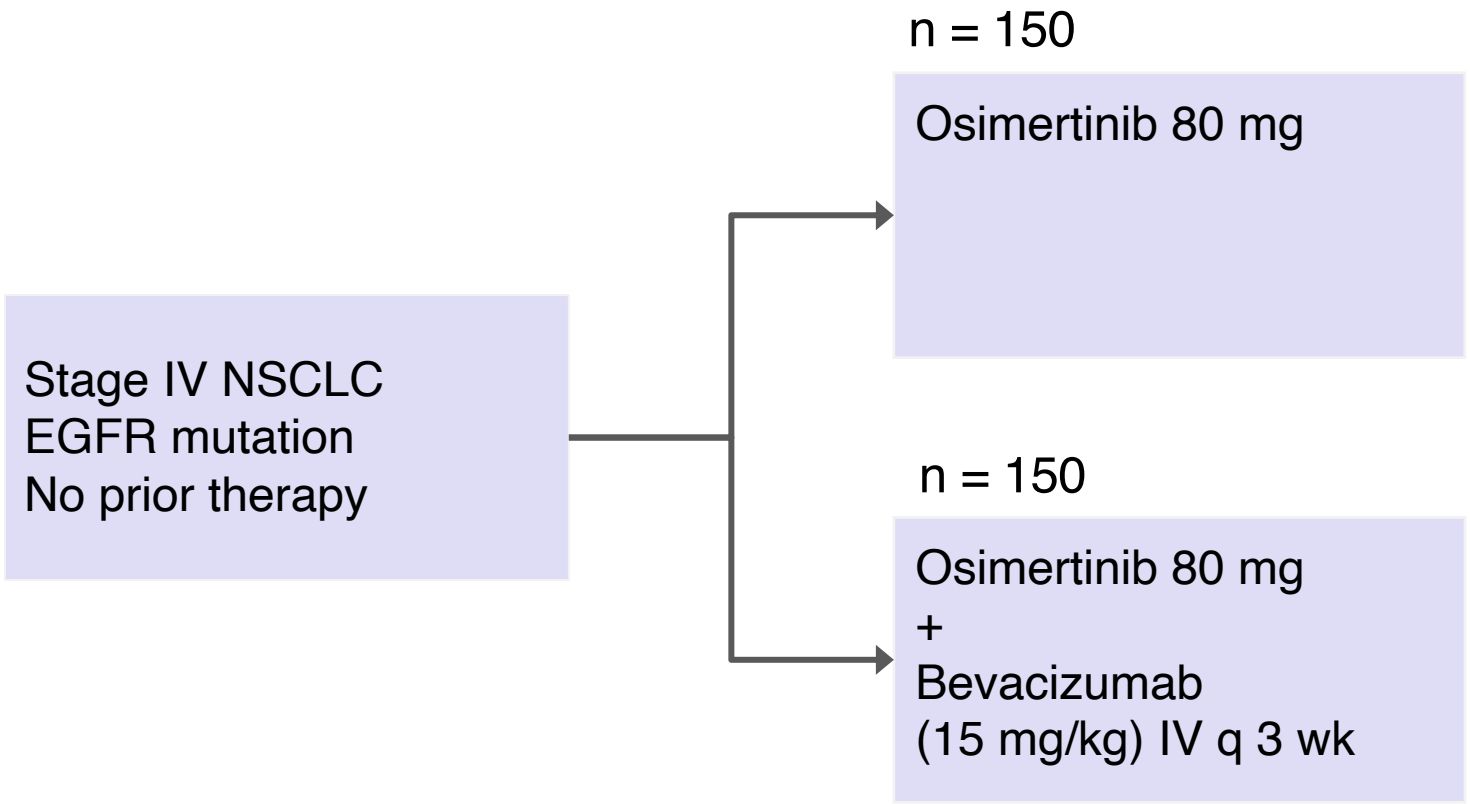
RELAY (JVCY): Interim OS

	Ramucirumab + erlotinib (N=224)	Placebo + erlotinib (N=225)
Interim overall survival analysis		
Number of events, n (%)	37 (17%)	42 (19%)
Median (95% CI), months	Not reached	Not reached
Stratified p value	…	.421
Stratified HR (95% CI)	…	0.83 (0.53-1.30)
1-year overall survival (95% CI)	93% (89-96)	94% (90-96)
2-year overall survival (95% CI)	83% (77-88)	79% (72-85)



Patients at risk (censored)	0	3	6	9	12	15	18	21	24	27	30	33	36
Ramucirumab + erlotinib	224 (0)	215 (6)	209 (10)	204 (10)	192 (17)	176 (32)	138 (58)	106 (88)	85 (108)	61 (130)	29 (158)	8 (179)	0 (187)
Placebo + erlotinib	225 (0)	223 (1)	221 (1)	216 (3)	198 (13)	178 (27)	144 (56)	111 (86)	84 (105)	59 (127)	27 (156)	11 (172)	0 (183)

EA5182: Osimertinib ± Bevacizumab



Primary endpoint: PFS
Secondary endpoints:
OS, RR, CNS PFS, mechanisms of resistance

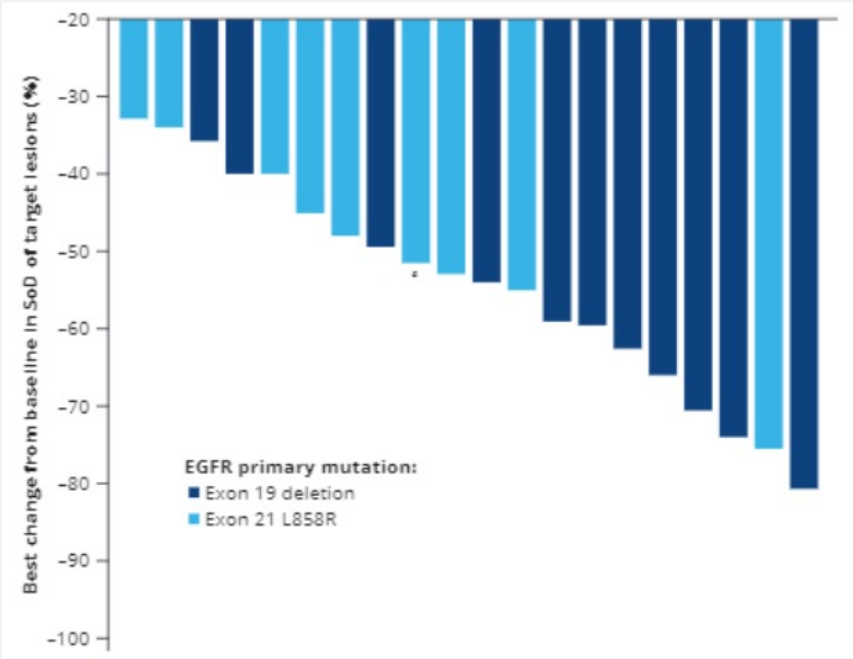
Randomized phase 2. NCT03909334

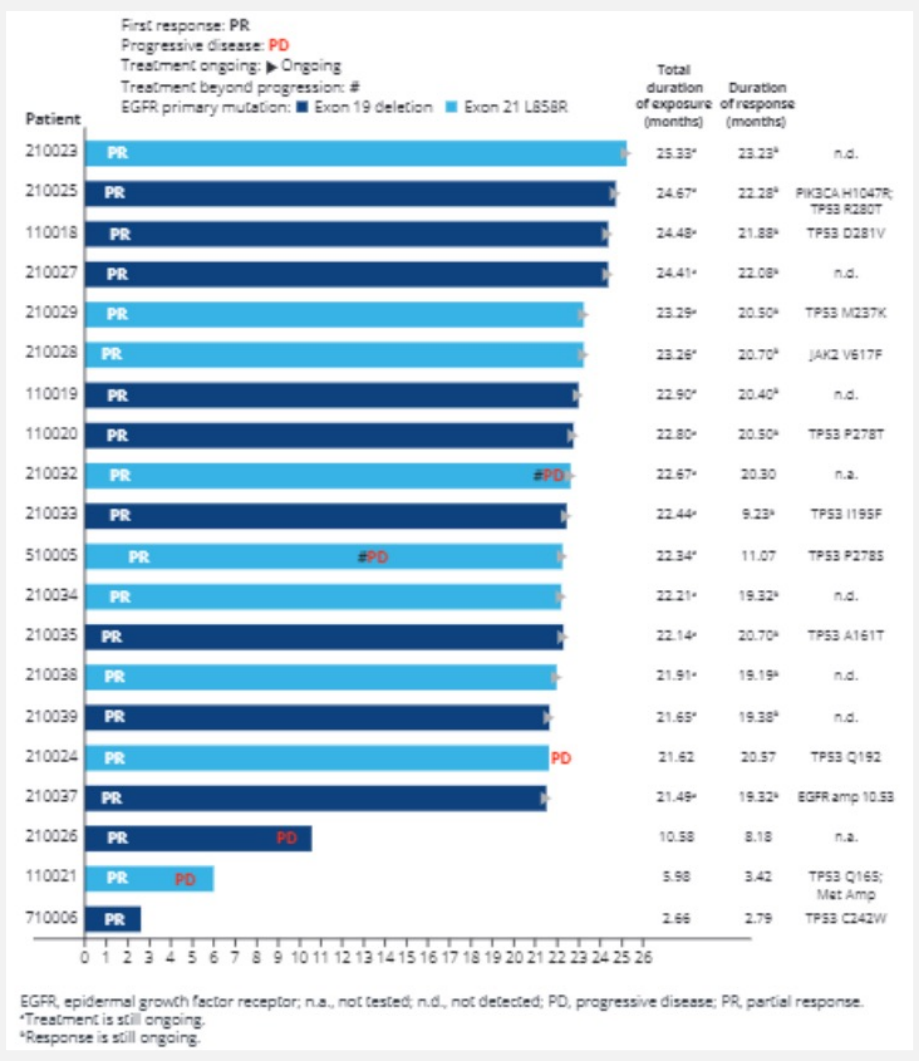
EA5182. NCT04181060. Updated May 23, 2022. Accessed May 31, 2022. https://clinicaltrials.gov/ct2/show/NCT04181060
Courtesy: Luda Bazhenova

Amivantamab and Lazertinib in 1L EGFR mutated mNSCLC

- Amivantamab is a bispecific, humanized antibody targeting EGFR and MET
- Lazertinib is a highly selective, brain penetrant, 3rd generation EGFR TKI.

Treatment naïve cohort of CRYSALIS
N=20
55% del 19, 45% L858R

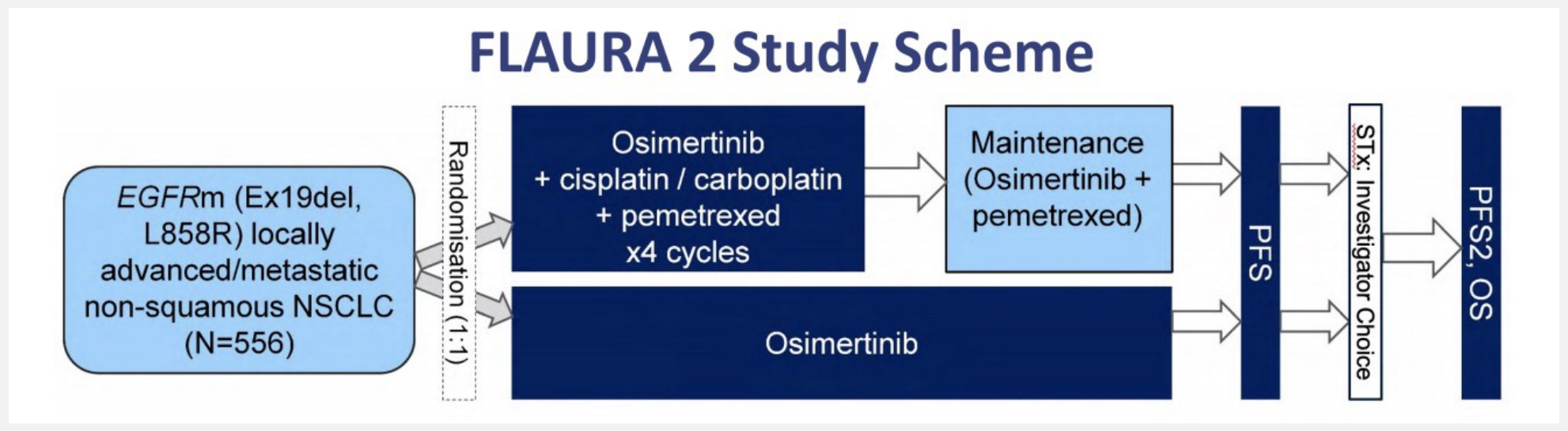




Cho et al, WCLC 2022
Courtesy: Luda Bazhenova

Chemotherapy Combinations

	Study Design	mPFS	mOS
NEJ009[1, 2]	Gef ± plat doublet	11.9 vs 20.9 mo HR 0.49 (0.39-0.62); P = .001	39 vs 51 mo HR 0.72 (0.55-0.95); P = .021
Tata Memorial[3]	Gef ± plat doublet	8 vs 16 mo HR 0.51 (0.39-0.66); P <.001	17 vs NR HR 0.45 (0.31-0.65); P <.001



At this point TKI chemotherapy combinations are not my standard of care

[1]Hosomi Y et al. *J Clin Oncol*. 2020;38(2):115-123. [1]**Miaychi et al, JCO 2022,** 40:3587-3592 [1]Noronha V et al. *J Clin Oncol.* 2020;38(2):124-136.
Courtesy: Luda Bazhenova

NEJ009: chemotherapy + 1L EGFR TKI

Previously untreated Advanced non-sq NSCLC

Up to 75 years old

PS 0-1

EGFR mutant

1:1

Gefitinib 250 mg/day Carboplatin + pemetrexed Q 21 for 4-6 cycles

Maintenance Gefitinib + Pemetrexed

Gefitinib 250 mg OD

Primary endpoints: PFS, PFS2, and OS

Hosomi et al, JCO 2020

Gefitinib +/- Carbo/Pemetrexed: Preferred option if Osimertinib not available

Study	Arm	PFS (mos)	HR, p	OS (mos)	HR, p
NEJ009	Gefitinib	11.9	0.49 P<0.001	38.8	0.72 P=0.021
	Carbo/Pem + G	**20.9**		**50.9**	
Noronha, et al	Gefitinib	8	0.51 P<0.001	17	0.45 P<0.001
	Carbo/Pem + G	**16**		**NR**	

FLAURA2

Phase III, open-label, randomized trial[1,2]

Osimertinib
(EGFR)

Patients with locally advanced or metastatic EGFR mutation-positive,[a] nonsquamous NSCLC who have had no therapy for advanced disease[1,2]

N=587[1]

R 1:1

Safety run-in (n=30)[2]

Osimertinib + CT (cisplatin or carboplatin + pemetrexed)[b] → **Osimertinib + pemetrexed (maintenance)[c]**

Primary endpoint[2]
- Safety

Phase III (n=556)[2]

Osimertinib + CT (cisplatin or carboplatin + pemetrexed)[b] → **Osimertinib + pemetrexed (maintenance)[c]**

Osimertinib[d]

Primary endpoint[2]
- PFS

Key secondary endpoints[2]
- ORR, DoR, DCR, OS
- PFS2, TFST, TSST
- QoL

Future Directions

- Use of EGFR combination therapy may be (If?):
  - Upfront clinical decision: For patients with symptomatic or large volume disease
    - Similar to PD-L1 >50% decision-making chemoIO or anti-PD-1 alone
  - Upfront biomarker decision: For patients with high risk molecular features (p53, Rb)
    - Similar to how some consider STK11/KEAP1 for IO decisionmaking for including aCTLA4
  - Dynamic clinical decision: Add chemotherapy or 2nd agent for patients with suboptimal radiographic response
    - Radiomics?
  - Dynamic biomarker decision: Add chemotherapy or 2nd agent for patients with suboptimal cfDNA response (+MRD)
    - Tumor informed personalized assay (tissue + cfDNA) vs cfDNA panel only?

Future Directions

- Identifying best combinatorial partner to EGFR TKI (What?)
  - Driven by molecular biology
    - MET amplification may benefit from bispecific MET/EGFR
  - Targeted angiogenesis
    - Which biomarker or population?
  - Cytotoxic chemotherapy combination
    - Use of chemotherapy in high-risk cases
- More questions than answers, important clinical trials ongoing
- My current practice is osimertinib alone if clinical trial of EGFR combination therapy unavailable

Thanks

Sandip Patel, MD

Email: patel@ucsd.edu

Twitter: @PatelOncology