AIG HOSPITALS | INSTITUTE OF ONCOLOGY
A unit of Asian Institute of Gastroenterology

OSIMERTINIB VS DACOMITINIB

Dr M Vamshi Krishna
Director, Medical oncology and Hematology
Institute of Oncology, AIG Hospitals

The key challenges in EGFR+ NSCLC

Which is the optimal treatment sequencing strategy?

Should I use a more potent new generation TKI upfront?

Should I keep the agent that is effective against resistance mutations in reserve for later-line treatment?

What are the key endpoints?
OS/PFS

OS, overall survival; PFS, progression-free survival.
Girard N. *Future Oncol* 2018;14(11):1117–32.

FLAURA Study Design

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R No prior systemic anti-cancer / EGFR-TKI therapy
- **Stable CNS metastases allowed**

Stratification Factors
- Exon 19 deletion / L858R
- **Race** (Asian / non-Asian)

Randomised 1:1

Osimertinib (80 mg p.o. qd) **(n=279)**

→ RECIST 1.1 assessment every 6 weeks¶ until objective PD

EGFR-TKI SoC#; **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) **(n=277)**

→ RECIST 1.1 assessment every 6 weeks¶ until objective PD

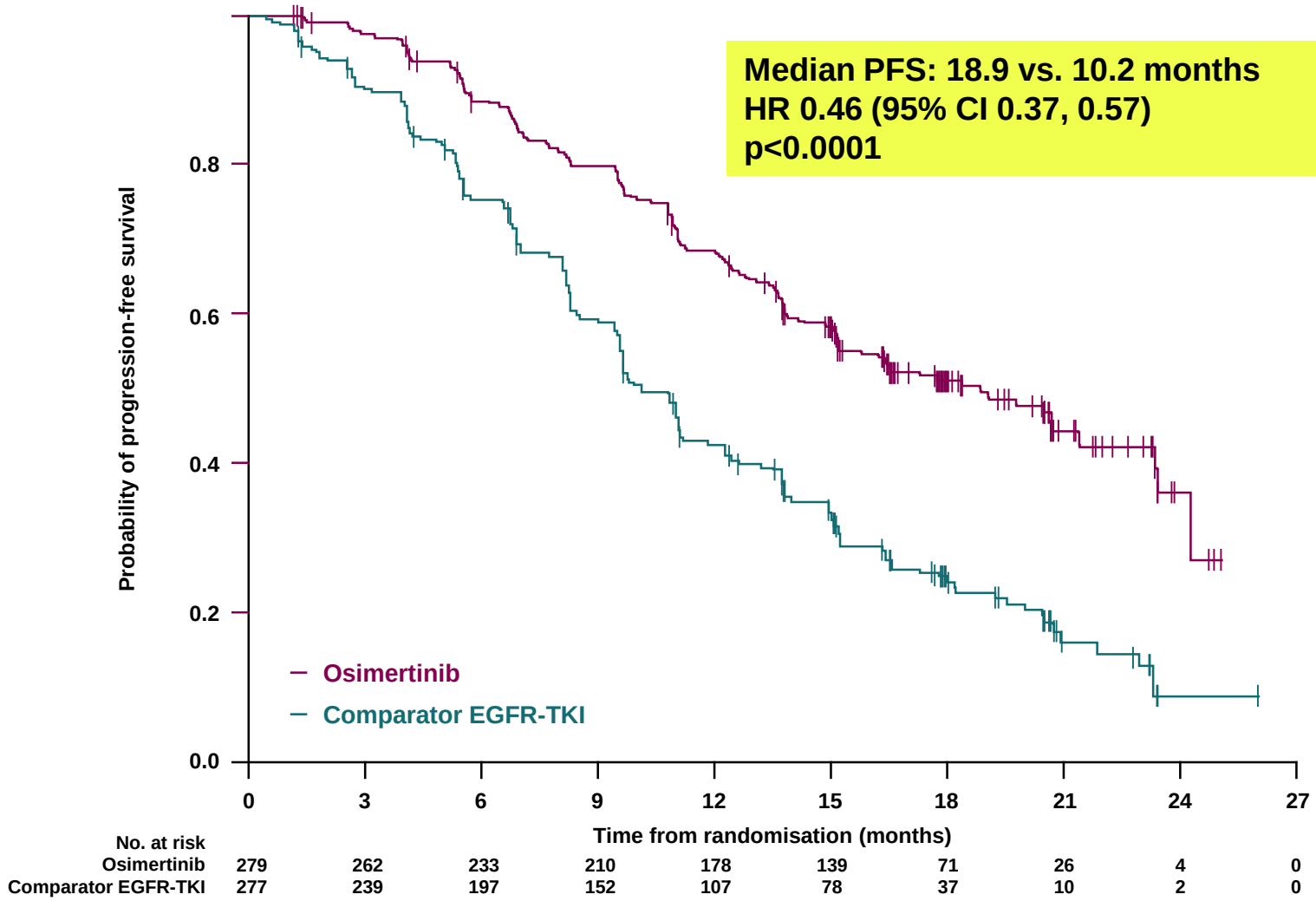
→ **CROSSOVER was allowed** Patients with confirmed PD by BICR on SoC, and T790M+, may begin post-progression open-label osimertinib

Primary endpoint	Secondary endpoints	
• **PFS based on investigator assessment according to RECIST 1.1** (90% powered to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%)	• Objective response rate • Duration of response • Disease control rate • Depth of response	• **Overall survival** • Patient reported outcomes • Safety

1. Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-of

Osimertinib demonstrated a significant improvement in PFS (primary endpoint)



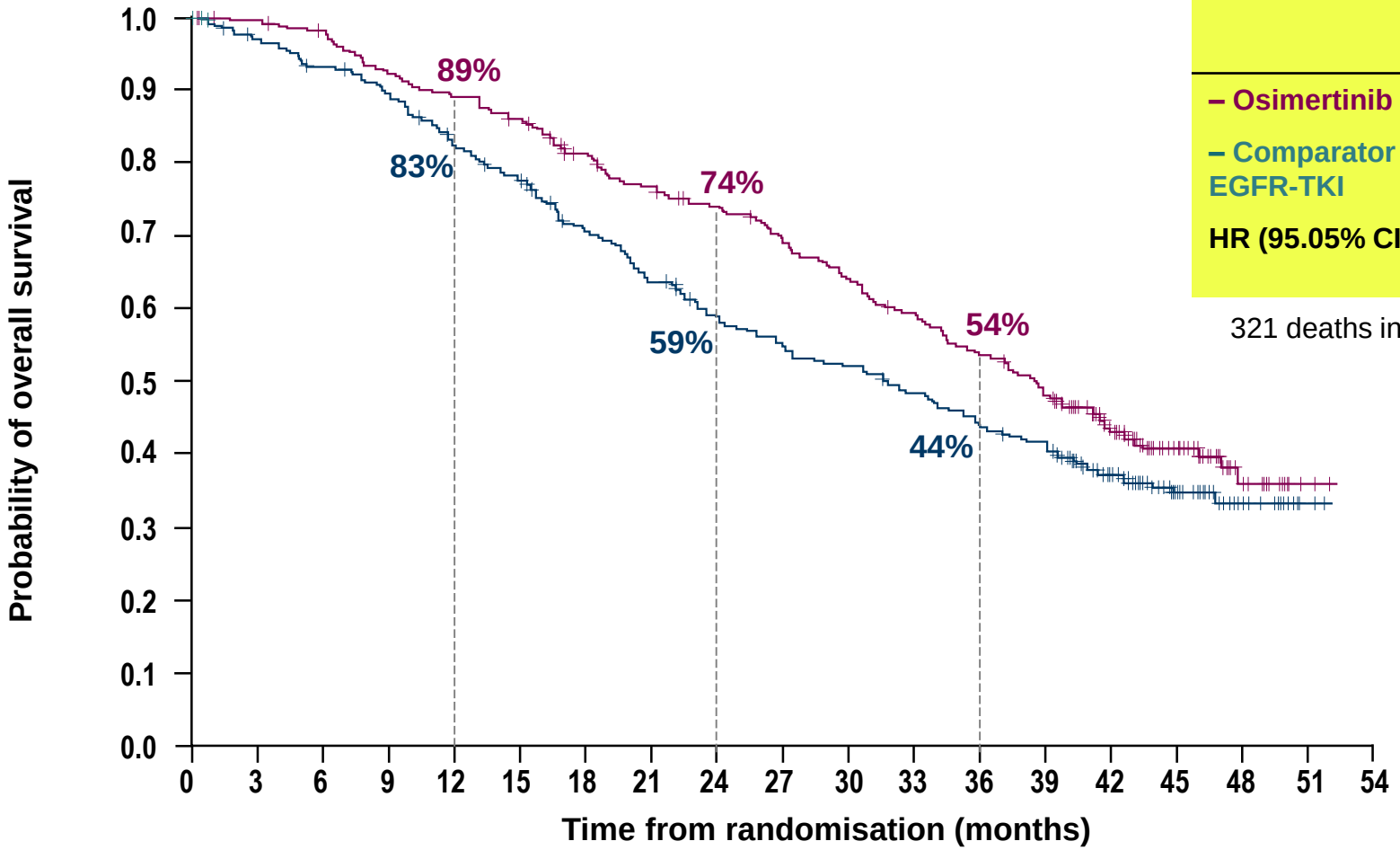
- PFS is a direct measure of the drugs benefit
- FLAURA was powered for PFS

Data cut-off: 12 June 2017

1. Soria et al. N Engl J Med 2018;378:113-25

ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

FLAURA: overall survival (final analysis)



	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); p=0.0462**

321 deaths in 556 patients at DCO: 58% maturity

- Median OS >3 years
- Osimertinib patients were more likely to be alive at 2 and 3 year landmarks
- First time an EGFR-TKI has translated PFS to a significant OS benefit

FLAURA data cut-off: 25 June 2019
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
Ramalingam_FLAURA OS_ESMO 2019

ARCHER 1050 vs FLAURA

Study Design – Overview

ARCHER 1050

The ARCHER 1050 trial (NCT01774721) is a Phase 3, randomized, open-label study evaluating the efficacy and safety of dacomitinib versus gefitinib as first-line therapy in patients with sensitizing *EGFR* mutation–positive, advanced or metastatic NSCLC.[1]

Patients (N=452)
- Stages IIIB or IV, or recurrent NSCLC

1:1 randomization, stratified by *EGFR* mutation status (exon 19 deletion or L858R) and race (Japanese vs Chinese vs other East Asians vs non-Asian)

Dacomitinib* (n=227)
- 45 mg orally once daily

Gefitinib* (n=225)
- 250 mg orally once daily

Primary endpoint
- PFS based on masked IRC review and RECIST 1.1

Secondary endpoints
- PFS (investigator assessed)
- ORR (investigator assessed and IRC)
- DoR (investigator assessed and IRC)
- OS
- Safety
- Patient-reported outcomes

*Treatment continued until disease progression, initiation of new anticancer therapy, unacceptable adverse effects, noncompliance, withdrawal of consent, or death.

ARCHER 1050 study design and endpoints.[1]

FLAURA

The FLAURA trial (NCT02296125) is a randomized, multicenter, double-blind, active-controlled study evaluating the efficacy and safety of osimertinib versus an EGFR TKI comparator—gefitinib or erlotinib—in patients with *EGFR* exon 19 deletion or exon 21 L858R mutation-positive, metastatic NSCLC, who had not received previous systemic treatment for metastatic disease.[2]

Patients (N=556)
- Locally advanced or metastatic NSCLC

1:1 randomization, stratified by *EGFR* mutation status (exon 19 deletion or exon 21 L858R) and ethnicity (Asian or non-Asian)

Osimertinib* (n=279)
- 80 mg orally once daily

EGFR TKI comparator* (n=277)
- Gefitinib:
  - 250 mg orally once daily
- Erlotinib:
  - 150 mg orally once daily

Major efficacy outcome measure
- PFS as assessed by investigator

Additional efficacy outcome measures
- OS
- ORR

*Treatment continued until disease progression or unacceptable toxicity.

FLAURA study design and endpoints.[2]

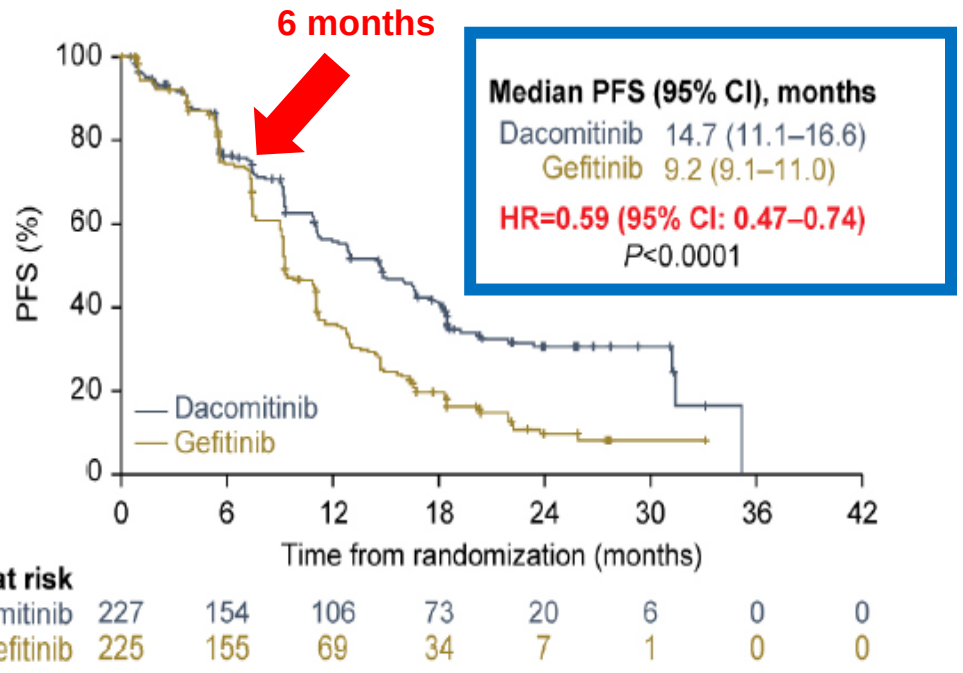
Ramalingam SS et al N Engl J Med 2019
Mok TS et al. *J Clin Oncol*. 2018; 36(22):2244-2250.

This is Cross-Trial comparison without head-to-head comparative studies

Efficacy – PFS by IRC or BICR

ARCHER 1050

Data cutoff:[1]
July 29, 2016



Median PFS (95% CI), months
Dacomitinib 14.7 (11.1–16.6)
Gefitinib 9.2 (9.1–11.0)
HR=0.59 (95% CI: 0.47–0.74)
P<0.0001

Number at risk

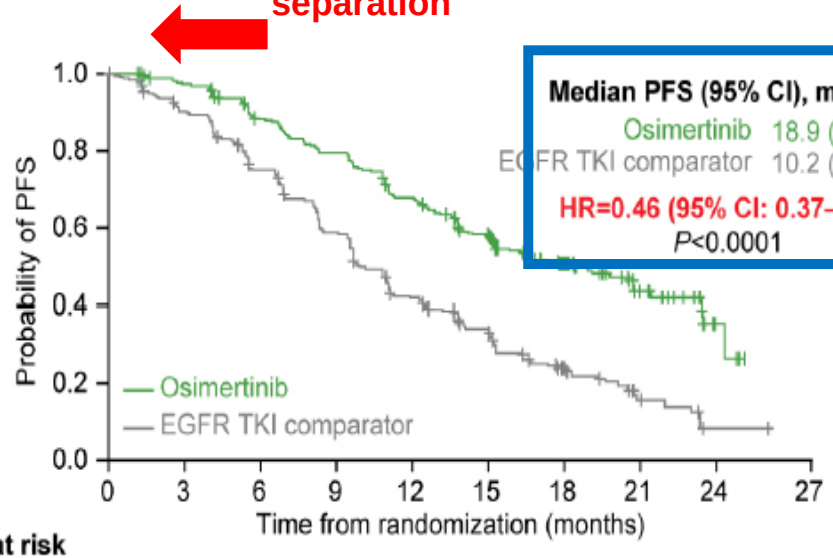
Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

IRC-reviewed PFS in the intention-to-treat population of the ARCHER 1050 trial.[1]

Efficacy – PFS by Investigator Assessment

FLAURA

Data cutoff:[4]
June 12, 2017



Median PFS (95% CI), months
Osimertinib 18.9 (15.2–21.4)
EGFR TKI comparator 10.2 (9.6–11.1)
HR=0.46 (95% CI: 0.37–0.57)
P<0.0001

Number at risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
EGFR TKI comparator	277	239	197	152	107	78	37	10	2	0

Investigator-assessed PFS in the full analysis set of the FLAURA trial.[2]

Ramalingam SS et al N Engl J Med 2019
Mok TS et al. *J Clin Oncol*. 2018; 36(22):2244-2250.

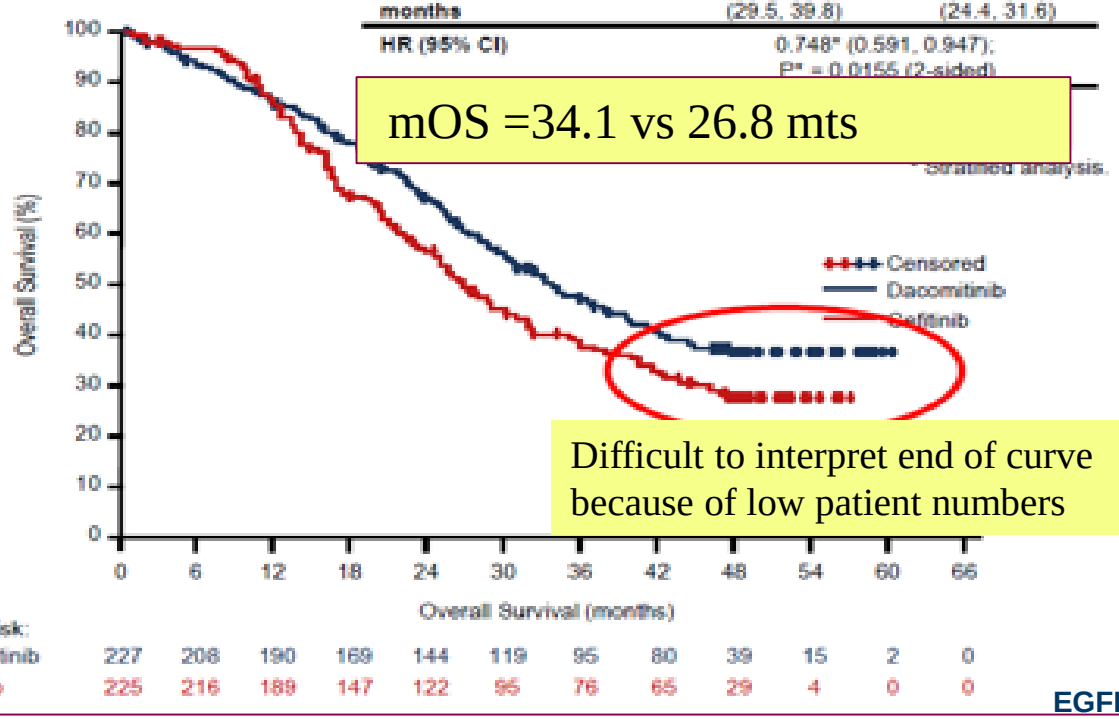
Direct comparisons between trials cannot be made due to potential differences in design and / or population

ARCHER 1050: OS not statistically significant, since the formal comparison of ORR was not statistically significant based on the study's hierarchical testing rules

Overall Survival (May 13, 2019)

	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	133	152
Median OS (95% CI), months	34.1 (29.5, 39.8)	27.0 (24.4, 31.6)
HR (95% CI)	0.748* (0.591, 0.947); P* = 0.0155 (2-sided)	

* Stratified analysis.

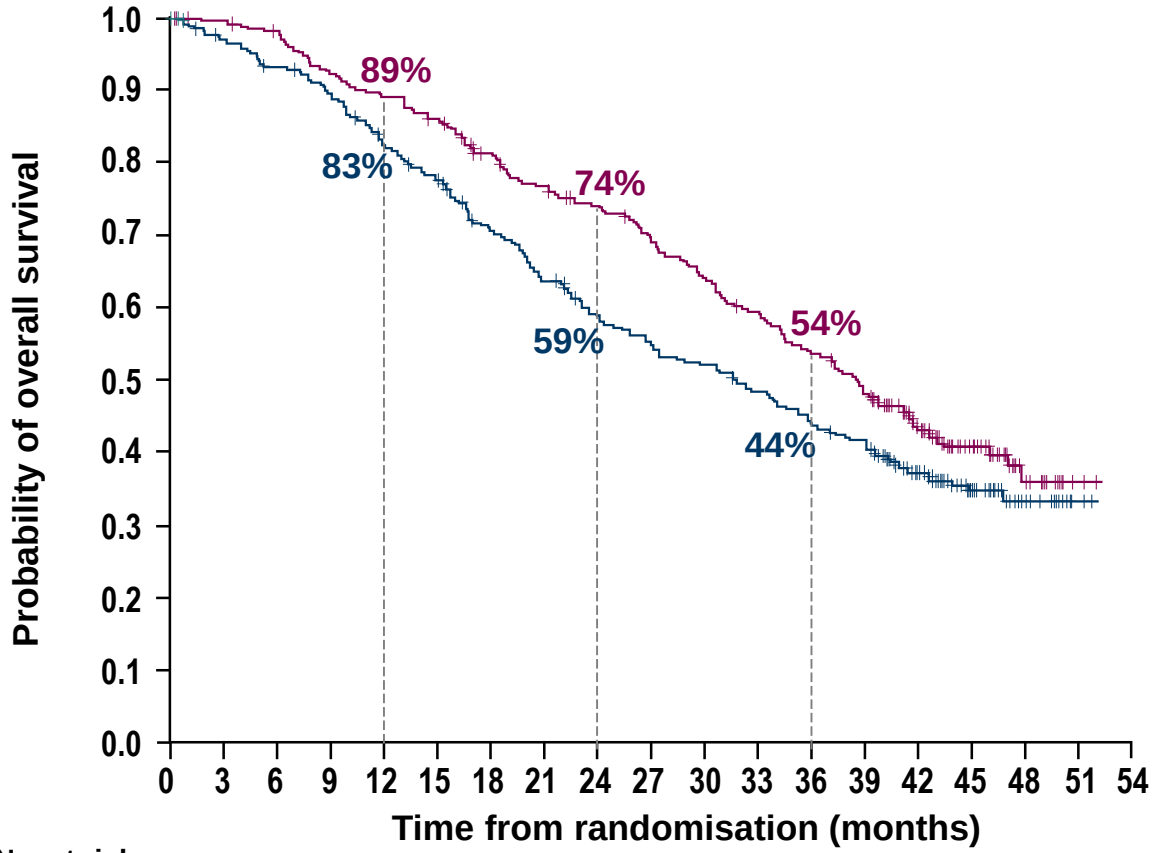


mOS =34.1 vs 26.8 mts

Difficult to interpret end of curve because of low patient numbers

No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

FLAURA: First time an EGFR-TKI has translated PFS to a significant OS benefit



No. at risk																			
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
EGFR-TKI comparator	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

8 Ramalingam SS et al N Engl J Med 2019
Mok TS et al. *J Clin Oncol*. 2018; 36(22):2244-2250.

Direct comparisons between trials cannot be made due to potential differences in design and / or population

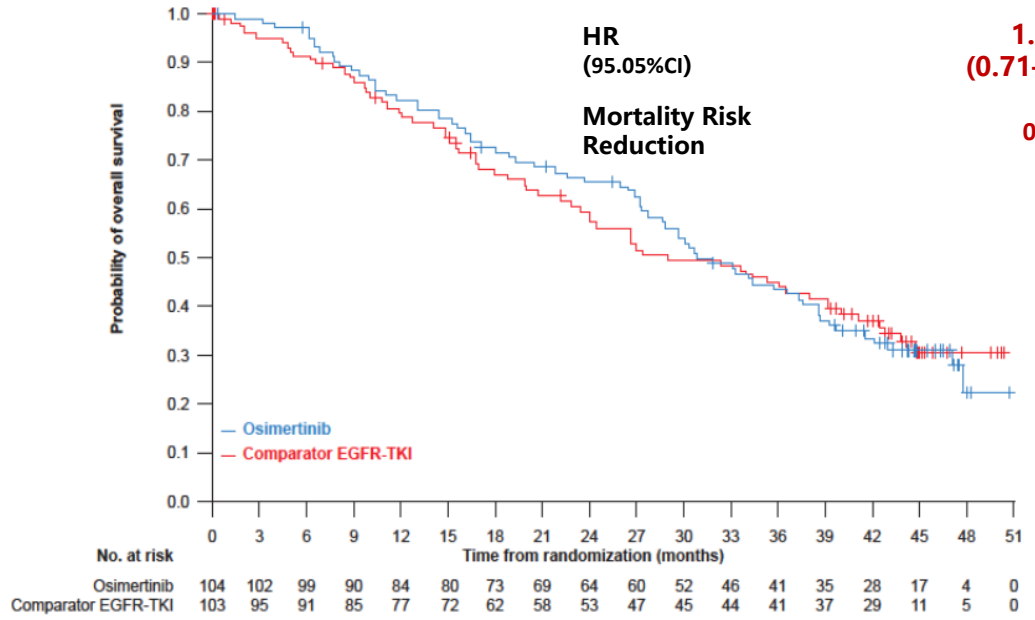
FLAURA: OS with Osimertinib in patients with L858R

OS in patients with L858R in the FLAURA trial[1-3]

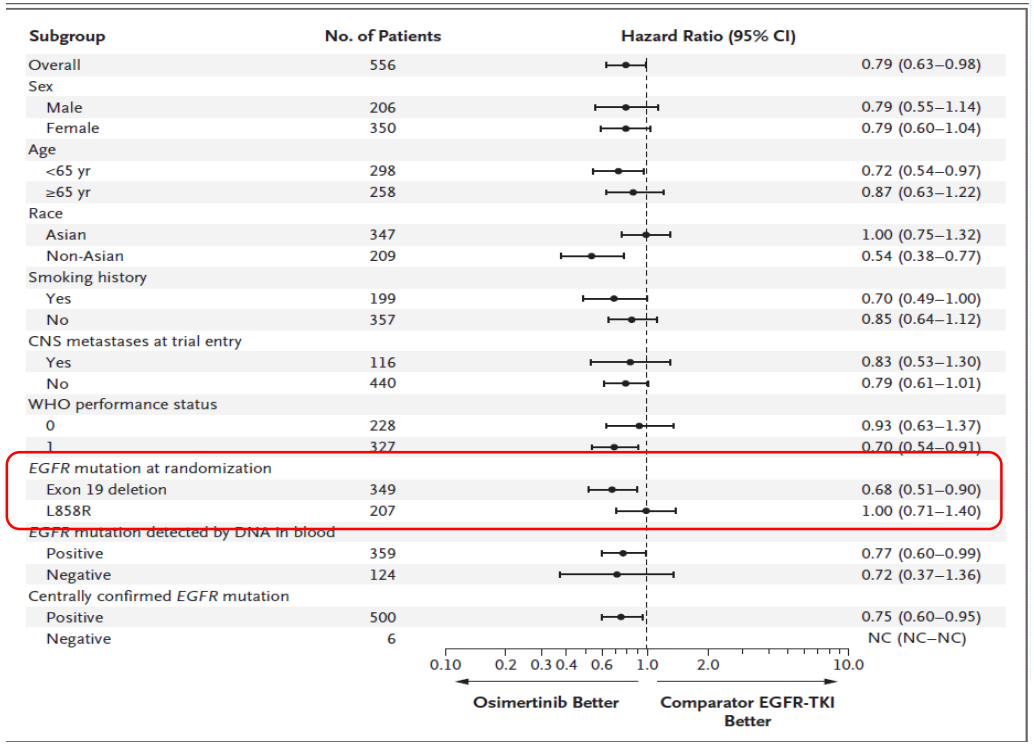
The OS HRs of 21 L858R subgroups in both the Chinese cohort and the total population were about 1.0, almost the same, validating that the 21 L858R population did not benefit from Osimertinib treatment.

21 L858R subgroup in total population

Total population	Osimertinib	EGFR-TKI control group
Median OS, months	-	-
Diff.		-
HR (95.05%CI)		1.00 (0.71–1.40)
Mortality Risk Reduction		0%



21 L858R subgroup



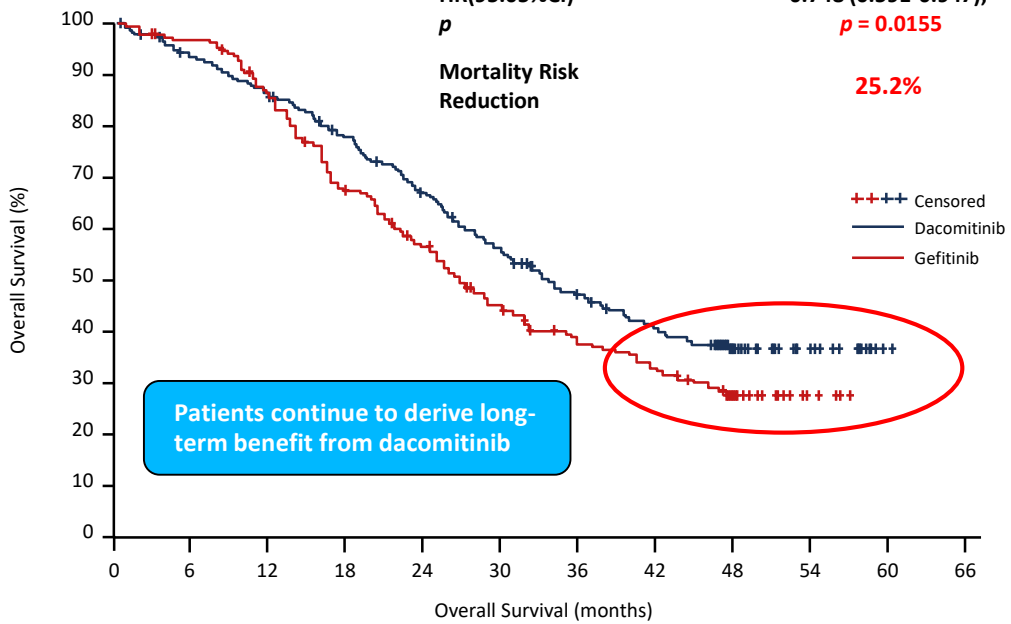
1. Ramalingam SS, et al. N Engl J Med. 2020;382(1):41–50. 2. Supplement to: Ramalingam SS, et al. N Engl J Med. 2020;382(1):41–50. 3. Cheng Y, et al. Presented at ESMO 2020. Poster No. 1295P

ARCHER 1050: OS with Dacomitinib vs Gefitinib in the L858R population

Dacomitinib has the same survival benefit in 21 L858R population and the total population

OS in overall population

Total population	Dacomitinib	Gefitinib
Median OS, months	34.1	27.0
Diff.	7.1 months	
HR(95.05%CI)	0.748 (0.591-0.947);	
p	*p* = 0.0155	
Mortality Risk Reduction	25.2%	



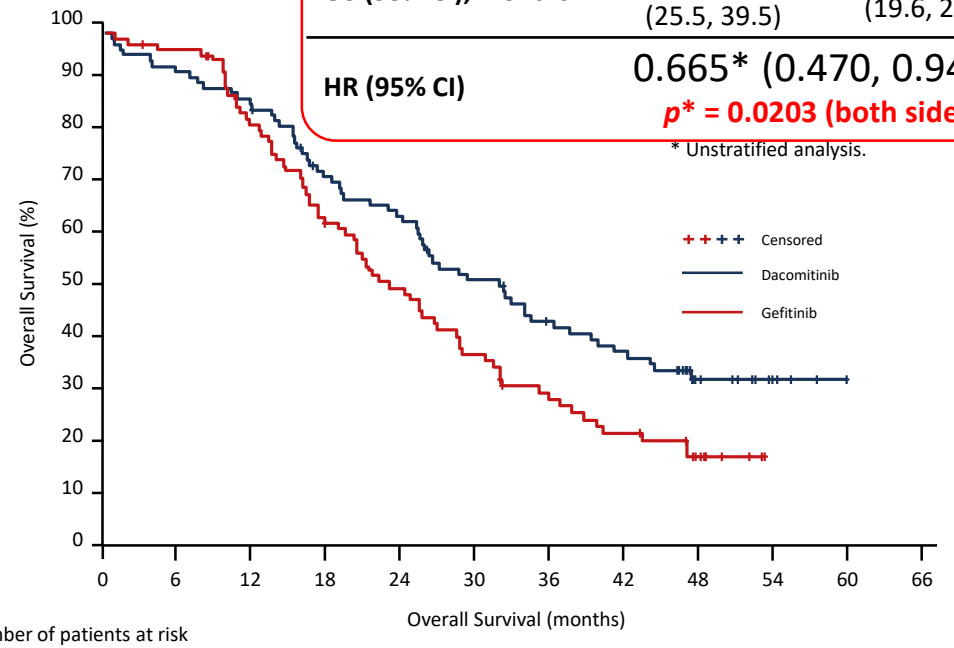
No. at risk:

Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

OS in 21 L858R mutant population

	Dacomitinib (n = 93)	Gefitinib (n = 92)
Number of Events	60	70
OS (95% CI), months	**32.5** (25.5, 39.5)	23.2 (19.6, 28.9)
HR (95% CI)	0.665* (0.470, 0.941); *p** = 0.0203 (both sides)	

* Unstratified analysis.



Number of patients at risk

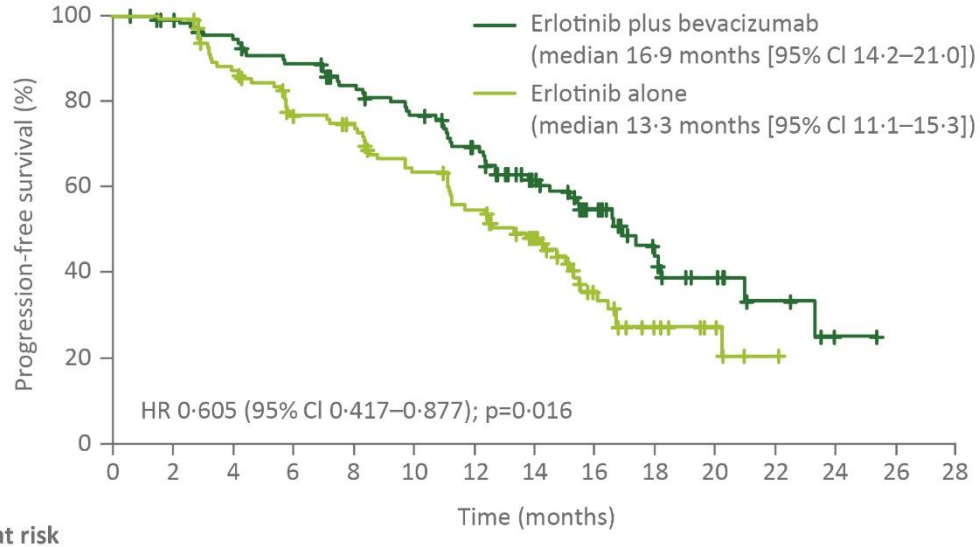
Dacomitinib	93	86	78	64	57	45	36	31	14	6	1	0
Gefitinib	92	88	72	54	43	30	22	16	8	0	0	0

Tony S. Mok, et al. 2019 ESMO Asia LBA 19

EGFR TKI + VEGF inhibitor

Prolonged PFS with addition of antibodies targeting the VEGF/ VEGFR axis

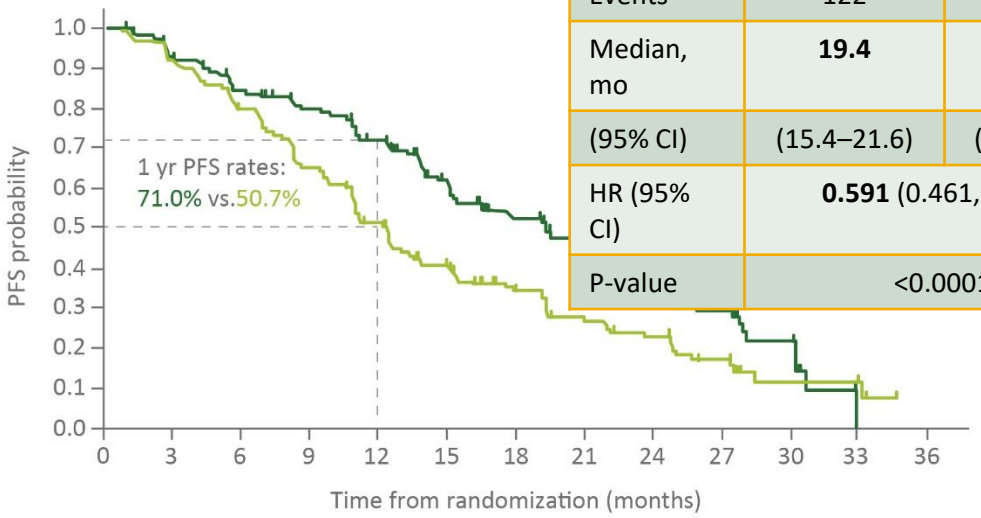
NEJ026[1–3]



Number at risk (number censored)								
Erlotinib plus bevacizumab	112 (0)	100 (6)	83 (7)	64 (17)	34 (35)	10 (52)	1 (59)	0 (60)
Erlotinib alone	112 (0)	94 (4)	73 (12)	51 (15)	18 (34)	5 (43)	0 (47)	0 (47)

RELAY[2,4,5]

	RAM+ERL n=224	PBO+ERL N=225
Events	122	158
Median, mo	**19.4**	**12.4**
(95% CI)	(15.4–21.6)	(11.0–13.5)
HR (95% CI)	**0.591** (0.461, 0.760)	
P-value	<0.0001	



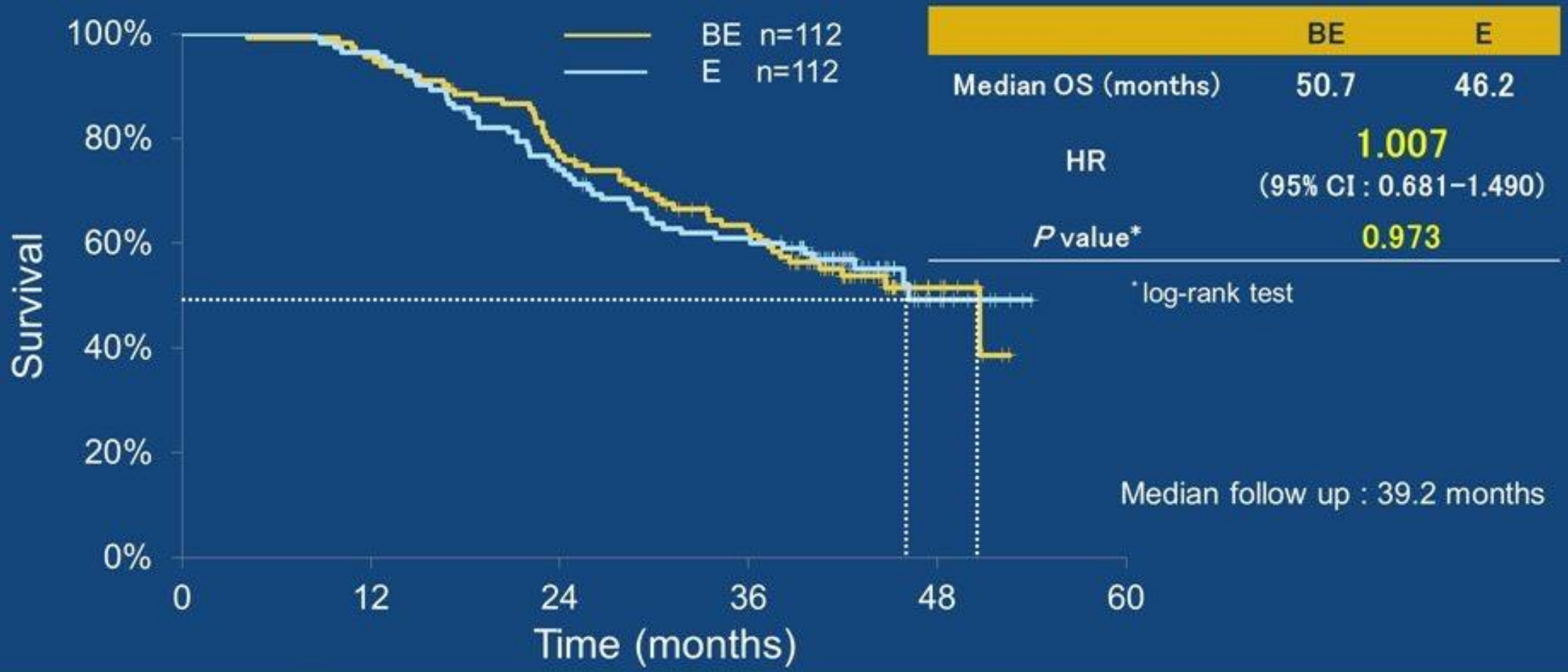
Number at risk													
RAM+ERL	224	196	170	154	133	103	69	49	32	20	10	1	0
PBO+ERL	225	196	167	136	99	72	52	37	27	15	4	4	0

Consistent PFS benefit by independent, blinded central review (HR 0.671, 95% CI 0.518–0.869; p=0.0022)

CI, confidence interval; HR, hazard ratio; m, months.

1. Saito H, et al. *Lancet Oncol* 2019;20:625–35; 2.Tarceva (erlotinib) Summary of Product Characteristics. Last updated April 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/tarceva-epar-product-information_en.pdf; 3. Avastin (bevacizumab) Summary of Product Characteristics. Last updated August 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. (All SmPCs accessed August 2019). 4. Nakagawa K, et al. Presented at ASCO 2019, Chicago, USA, 31 May–4 June; 5. Cyramza (ramucirumab) Summary of Product Characteristics. Last updated March 2016. Available at: https://www.ema.europa.eu/en/documents/overview/cyramza-epar-summary-public_en.pdf. (All SmPCs accessed August 2019).

Final Overall Survival



	BE	E
Median OS (months)	50.7	46.2
HR	1.007 (95% CI : 0.681−1.490)	
P value*	0.973	

*log-rank test

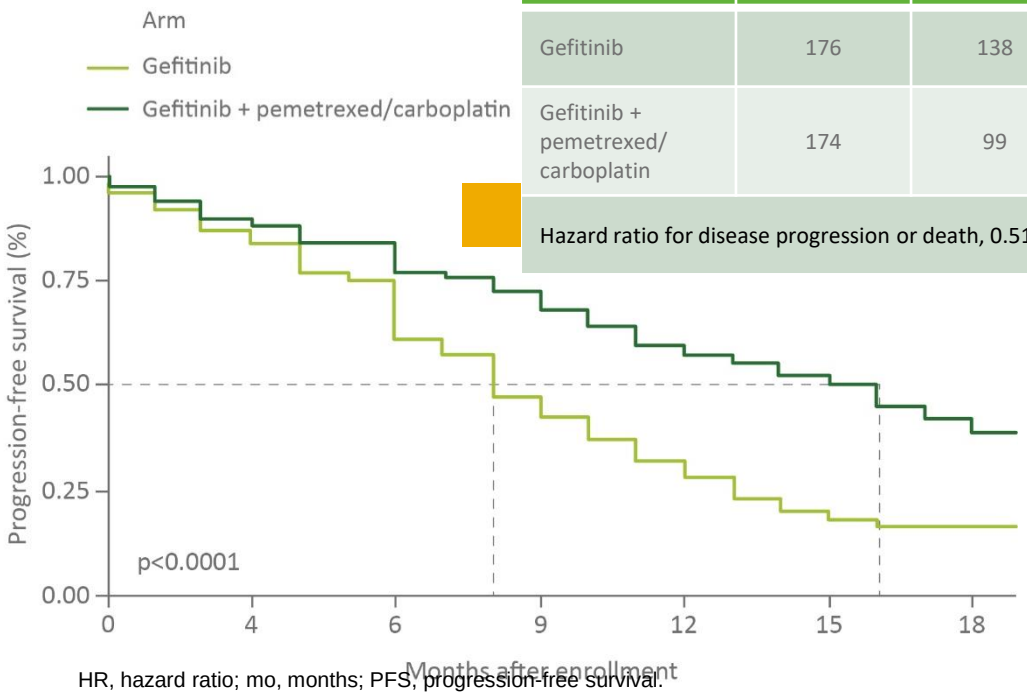
Median follow up : 39.2 months

EGFR TKI + Chemotherapy

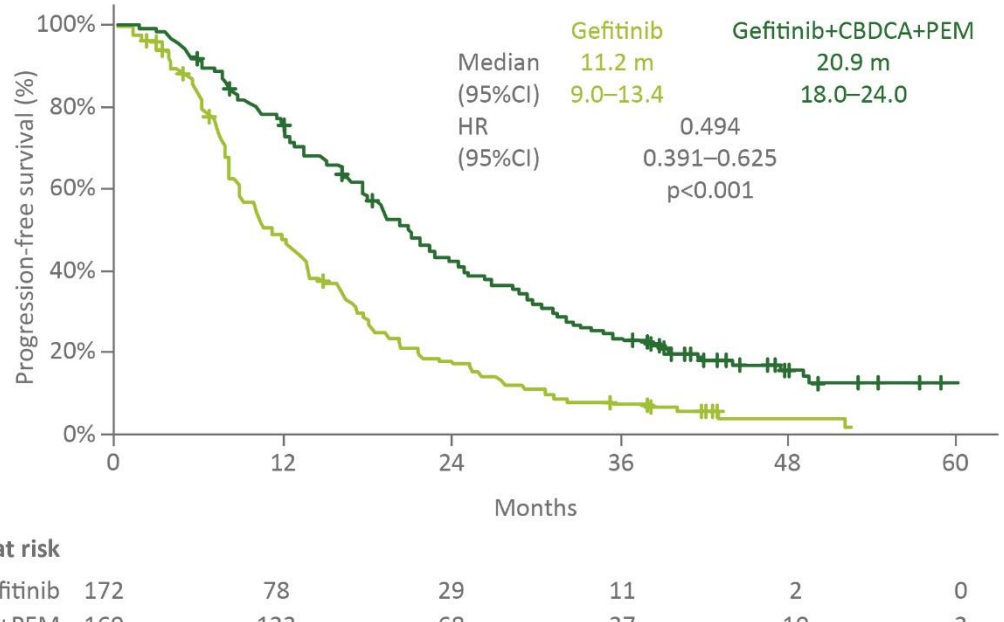
Prolonged PFS with addition of pemetrexed based chemotherapy

Chemo + gefitinib vs gefitnib[1,2]

Arm	Number of patients	Number of events	Median PFS (95% CI)
Gefitinib	176	138	8 months (7.0 to 9.0)
Gefitinib + pemetrexed/ carboplatin	174	99	16 months (13.5 to 18.5)
Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66			



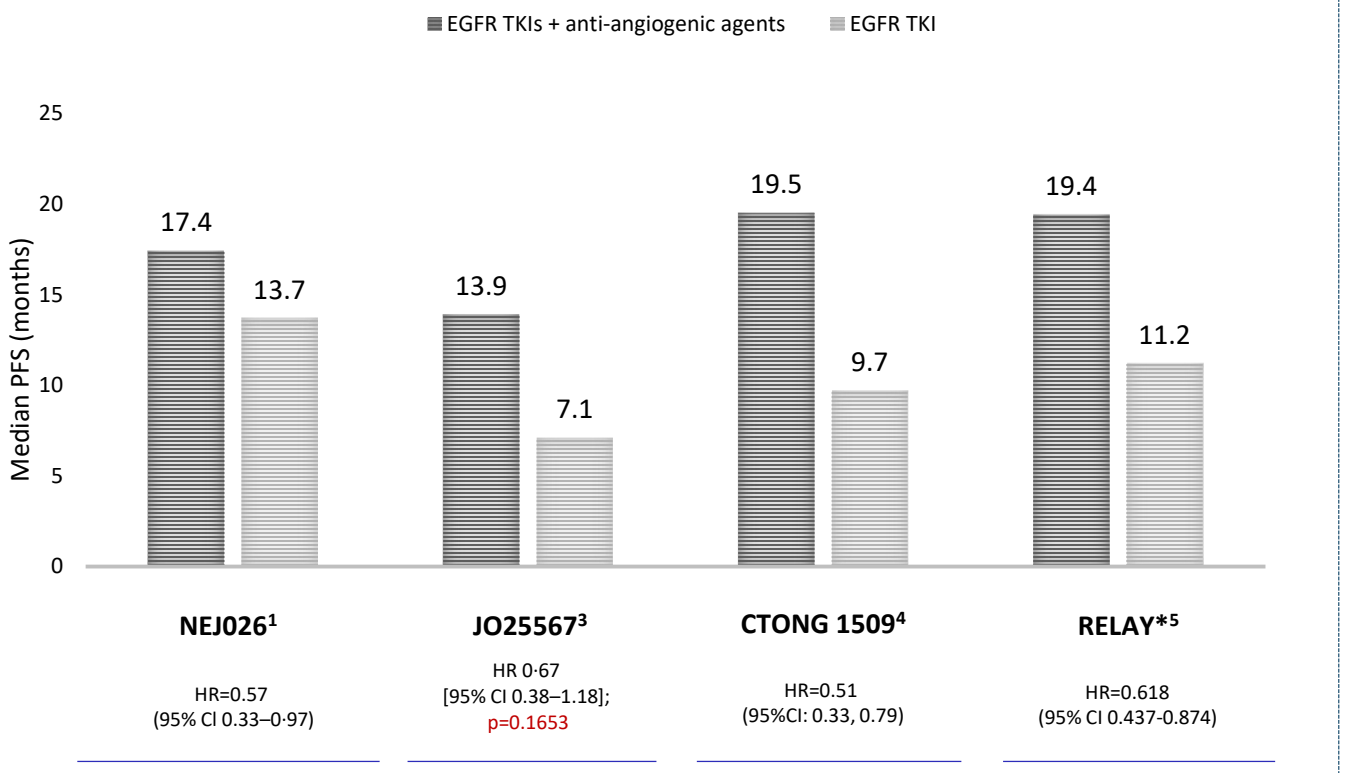
NEJ009[3,4]



HR, hazard ratio; mo, months; PFS, progression-free survival.

1. Noronha V, et al. Presented at ASCO 2019, Chicago, USA, 31 May–4 June; 2. Iressa (gefitinib) Summary of Product Characteristics. Last updated May 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf; 1. Nakamura A, et al. Presented at ASCO 2018, Chicago, USA, 1–5 June; 2. Iressa (gefitinib) Summary of Product Characteristics. Last updated May 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf; 3. Saito H, et al. *Lancet Oncol* 2019;20:625–35; 4. Tarceva (erlotinib) Summary of Product Characteristics. Last updated April 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/tarceva-epar-product-information_en.pdf; 5. Avastin (bevacizumab) Summary of Product Characteristics. Last updated August 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf. (All SmPCs accessed August 2019).

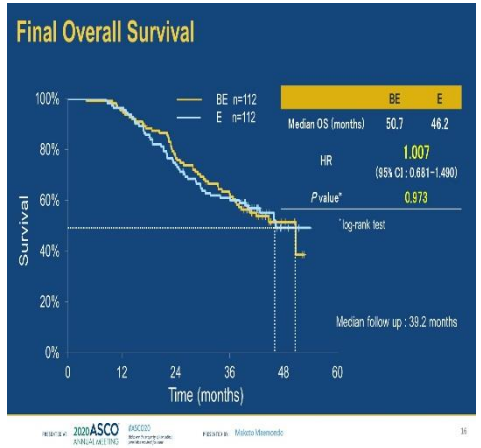
A + T prolonged PFS significantly compared with TKI monotherapy in patients with L858R mutations, but which did not translate into OS benefit

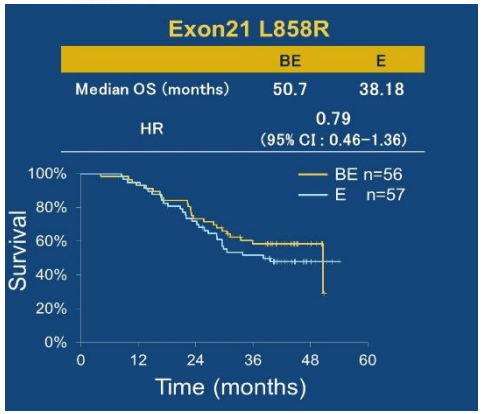


* 21 L858R Mutation subgroup is pre-defined in RELAY trial

The above research data is from various studies and should be interpreted with caution.

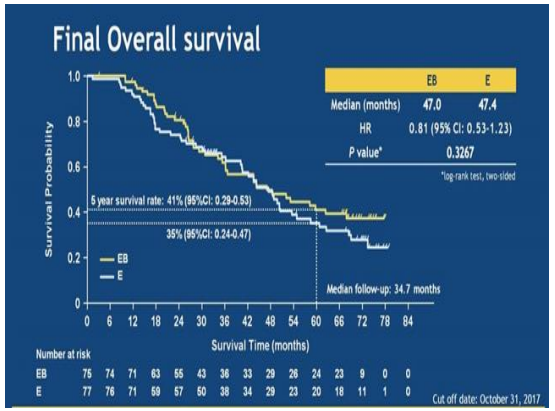
NEJ026 [1.2]

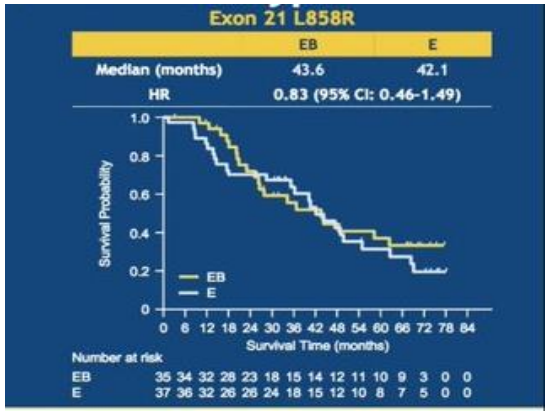




OS in 21 L858R patients

JO25567 [3]



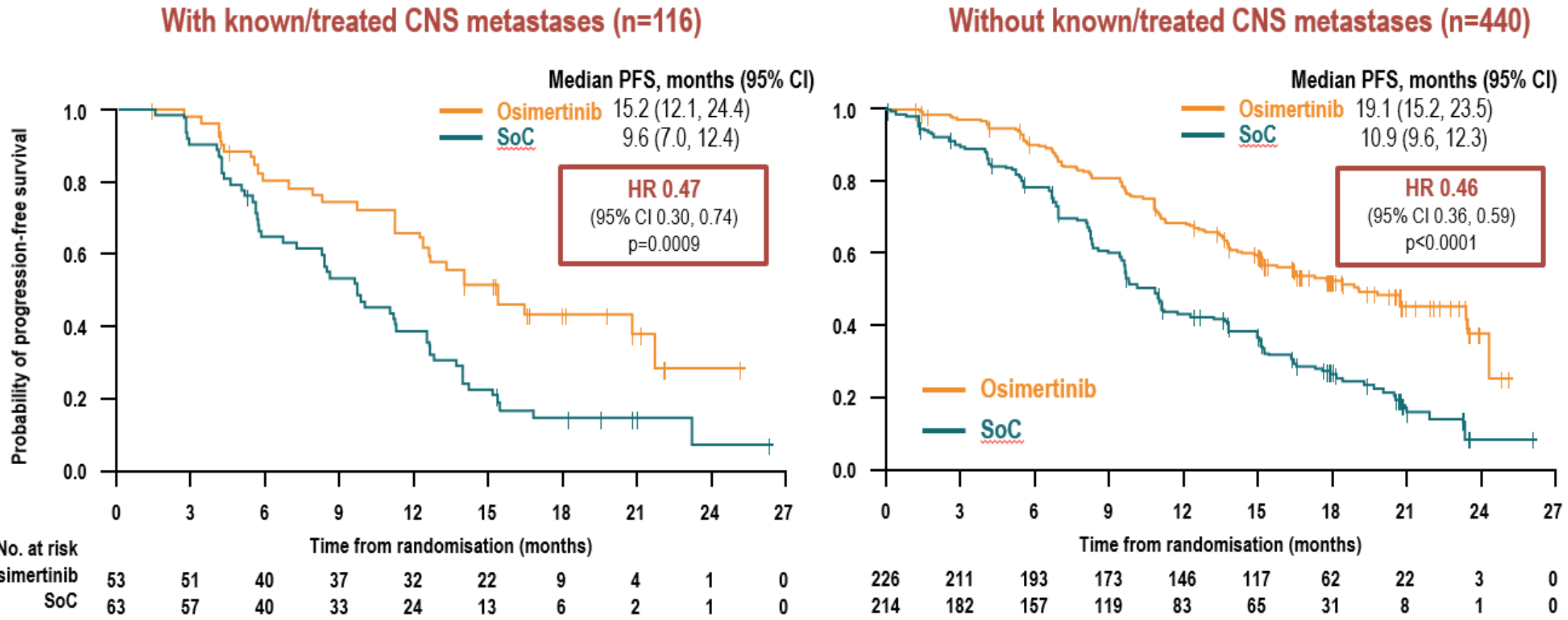


OS in 21 L858R patients

A + T: EGFR TKIs + anti-angiogenic agents

Saito H, et al. Lancet Oncol. 2019;20(5):625-635. 2. Noboru Yamamoto, et al. ASCO 2018 Slides. Presented on Monday, June 4, 2018. 3. Seto T, et al. Lancet Oncol. 2014;15(11):1236–1244. 4. Zhou Q, et al, 2019ESMO 1480O 5. Kazuhiko Nakagawa, et al. ASCO 2019. Abstract 9000

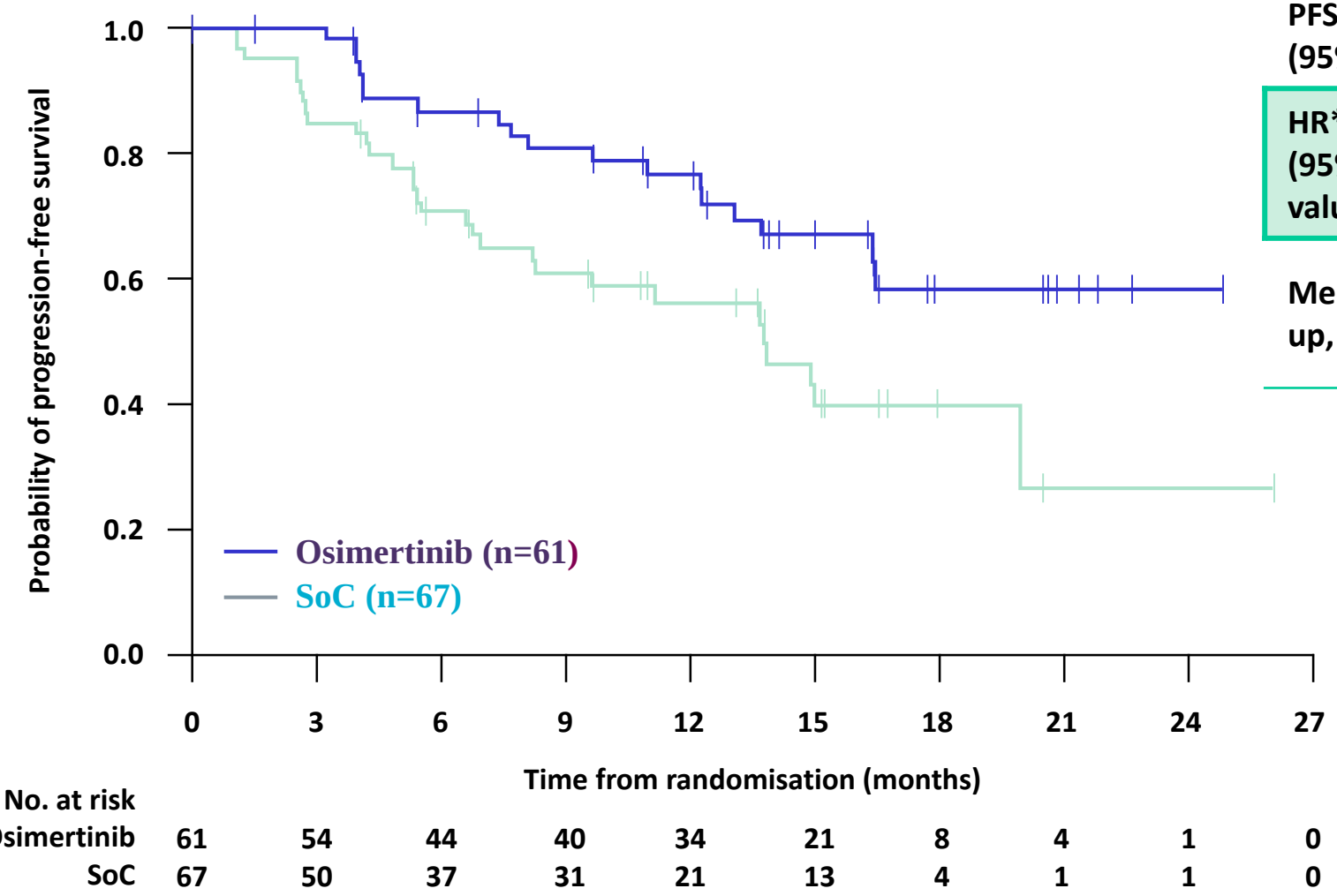
FLAURA: Osimertinib demonstrated a superior systemic PFS[a] benefit regardless of CNS disease status at study entry vs EGFR-TKI comparator[1,2]



- **CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)**

Soria J-C, Ohe Y, Vansteenkiste J, et al. N Engl J Med. 2018 Jan 11;378(2):113–25.

Intracranial (CNS) PFS: CNS Full Analysis Set



	Osimertinib (n=61)	SoC (n=67)
Median CNS PFS, months (95% CI)	NR (16.5, NC)	13.9 (8.3, NC)
HR* (95% CI); p-value	0.48 (0.26, 0.86); p=0.014	
Median follow up, months	12.4	7.0

- CNS PFS was statistically significant with Osimertinib vs comparator

FLAURA data cut-off: 12 June 2017
*HR was calculated from a Cox proportional hazards model with a factor for treatment; CI was calculated using profile likelihood. HR <1 favours osimertinib.
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NC, not calculable; NR, not reached; NS, not significant; OS, overall survival; PFS, progression-free survival; SoC, standard-of-care
Vansteenkiste ESMO Asia 2017 Abs LBA6

EGFR POSITIVE

Ex 19 del

NO CNS mets

- Osimertinib
- Erlo Bev ?
- Chemo Gefitinib

CNS METS

Osimertinib

? Erlo Bev

Ex 20 ins

L585R

NO CNS METS

Dacomitiinib

Erlo Ramu ?

Erlo Bev ?

Osimertinib ?

CNS METS

Osimertinib

Rare mutations

- TILL FURTHER EVIDENCE ....

OSIMERTINIB

AIG HOSPITALS | INSTITUTE OF ONCOLOGY
A unit of Asian Institute of Gastroenterology

THANK YOU