AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Congresso Nazionale sul carcinoma del polmone

CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2023?

9 OTTOBRE 2023

VERONA

Hotel Leon D'Oro

Responsabile scientifico

STEFANIA GORI

Il Trattamento di prima linea della malattia EGFR mutata

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Regione Lombardia

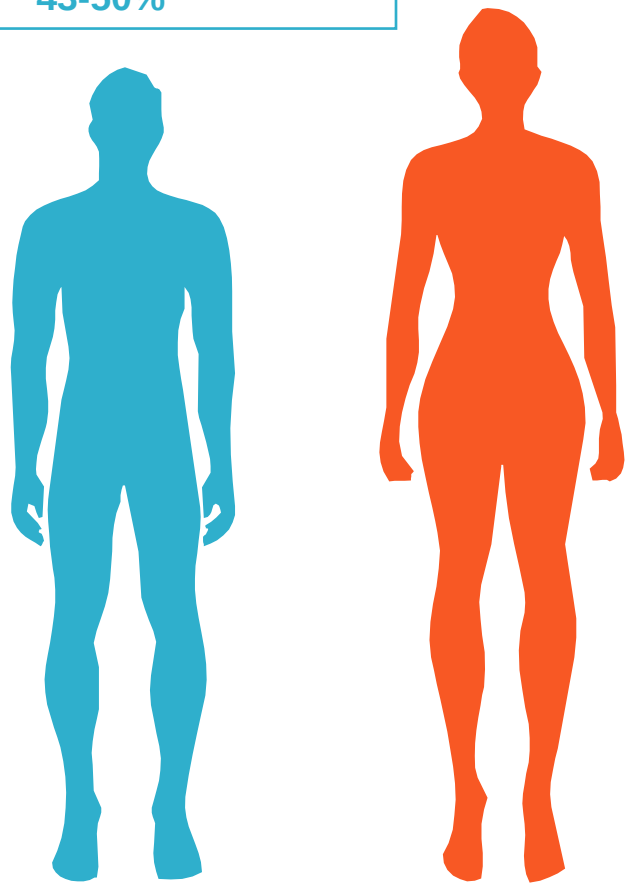
Potential conflicts of interest to declare

Type of affiliation / financial interest	Name of commercial company
Advisory Board	Astra Zeneca, Boehringer Ingelheim, MSD, Sanofi, Roche
Speaker Fees	Astra Zeneca, BMS, Novartis
Consultant	Astra Zeneca, MSD, Sanofi
Travel Grants	Pfizer, Astra Zeneca, MSD, Roche, Sanofi, BMS

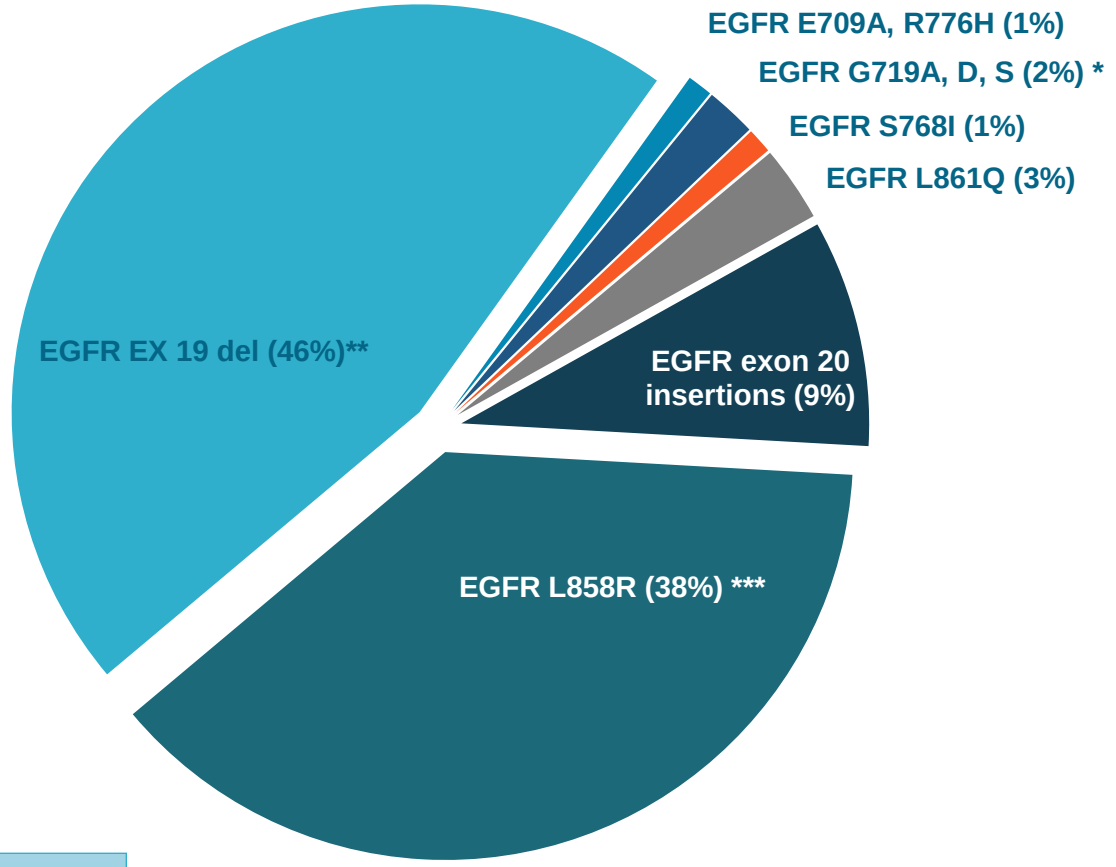
EGFR mutations

50%-67%

43-50%



EGFR-mutated cases (n=367)



EGFR: Young patients and non-smokers

Ramalingam NEJM 2019

Arcila et al. Mol Cancer Ther 2013;12:220-9

Agenda

- TKI
- Combo approaches
- Uncommon mutations

Agenda

- TKI
- Combo approaches
- Uncommon mutations

History of EGFRi use and approval

2003[1]
2004[2]

GEFITINIB

2L after CT without EGFR mut[1]
1L vs CT with EGFR mut[2]

ERLOTINIB

1L For EGFR mut

2011

2012

AFATINIB

1L in patients with EGFR mut

OSIMERTINIB

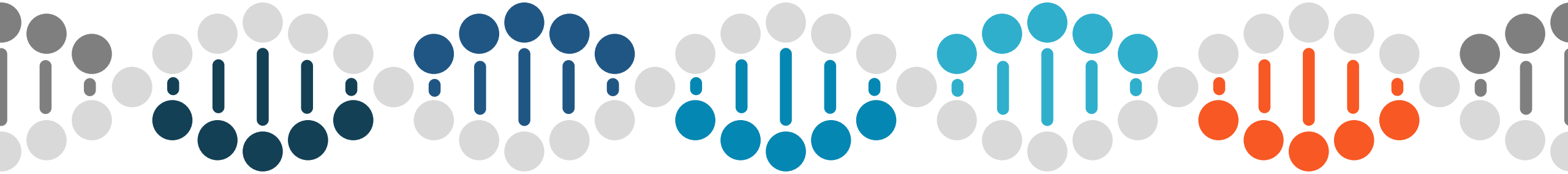
2L to overcome resistance to 1/2G TKIs

2018

2020

OSIMERTINIB

1Line standard of CARE



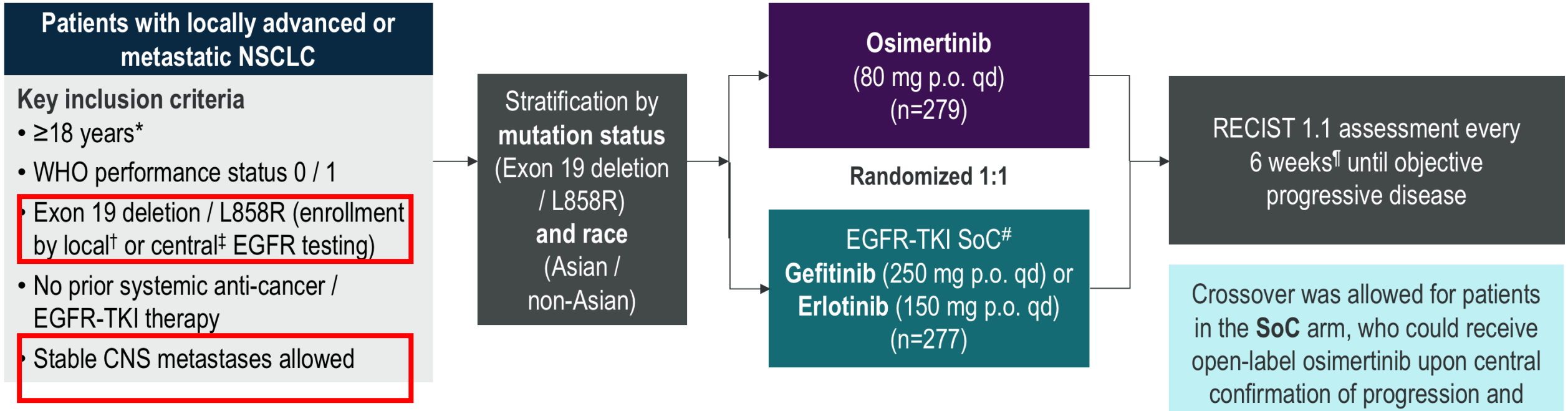
1Cohen MH, et al. *Oncologist.* 2003; 2. AstraZeneca. New Drug Application For IRESSA accepted by US Food and Drug Administration. Dec 2014. 3. Karachaliou N, et al. Transl Cancer Res. 2019; 4. Kazandjian D, et al. Oncologist. 2014; US FDA. Osimertinib. July 2017. US FDA Osimertinib feb 2021;

EGFR efficacy of 2G/3G EGFR-TKIs

EGFR-TKI	Study	ORR, % (Independently assessed)	Median PFS, months (HR [95% CI]) (Independently assessed)	Median OS, months (HR [95% CI])
EGFR-TKI vs chemotherapy				
Afatinib	LUX-Lung 3[1,2] (vs cisplatin/pemetrexed) N=345	**56** vs 23 (p=0.001)	**11.1** vs 6.9 (0.58 [0.43, 0.78]; p=0.001)	**28.2** vs 28.2 (0.88 [0.66, 1.17]; p=0.39)
	LUX-Lung 6[2,3] (vs cisplatin/gemcitabine) N=364	**66.9** vs 23.0 (p<0.0001)	**11.0** vs 5.6 (0.28 [0.20, 0.39]; p<0.0001)	**23.1** vs 23.5 (0.93 [0.72, 1.22]; p=0.61)
	LUX-Lung 3 and 6 combined[2]	Not reported	Not reported	**25.8** vs 24.5 (0.91 [0.75, 1.11]; p=0.37)
EGFR-TKI vs EGFR-TKI				
Afatinib	LUX-Lung 7[4,5] (vs gefitinib) N=319	**70** vs 56 (p=0.0083)	**11.0** vs 10.9 (0.73 [0.57, 0.95]; p=0.017)	**27.9** vs 24.5 (0.86 [0.66, 1.12]; p=0.2580)
Dacomitinib	ARCHER 1050[6,7] (vs gefitinib) N=452	**75** vs 72 (p=0.4234)	**14.7** vs 9.2 (0.59 [0.47, 0.74]; p<0.0001)	**34.1** vs 26.8 (0.760 [0.582, 0.993]; p<0.0438)
Osimertinib	FLAURA[8] (vs standard EGFR-TKIs)	**80** vs 76 (p=0.24) (Investigator-assessed)	**18.9** vs 10.2 (0.46 [0.37, 0.57]; p<0.001) (Investigator-assessed)	**38.6** vs 31.8 m HR 0.799

[1]Sequist JCO 2013; [2]Yang Lancet Oncol2015; Wu Lancet Oncol 2014; Park Lancet Oncol 2016; Paz-Arez Annals Oncol. 2017; Wu Lancet Oncol 2017; Mok JCO 2018; Soria NEJM 2018; Ramalingam NEJM 2020

FLAURA Study design, Osimertinib



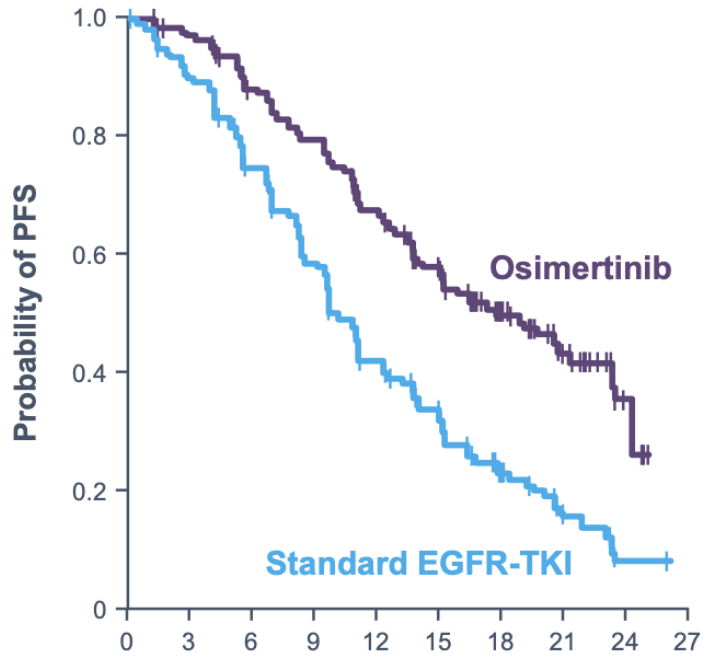
Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med, 2018

FLAURA PFS and OS Results

FULL SET analysis[1]



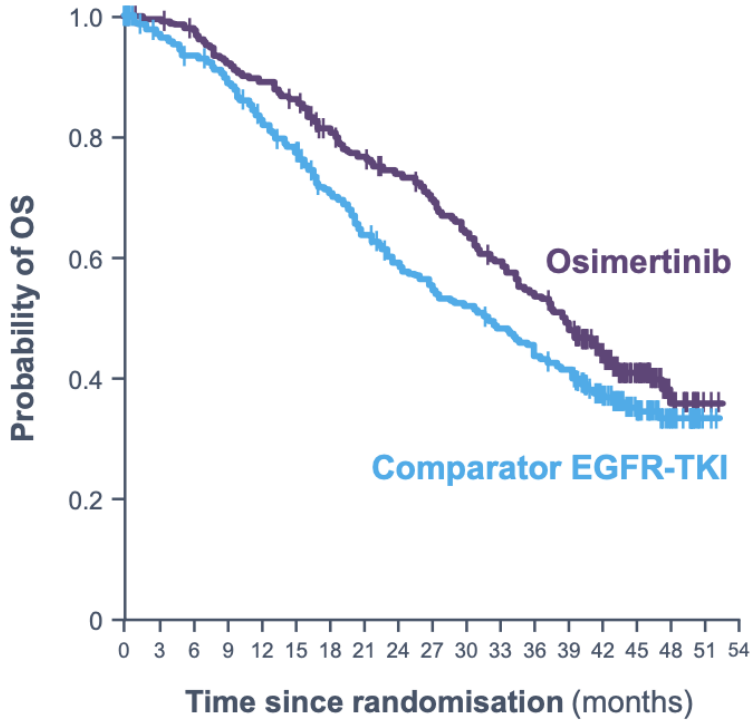
No. at risk

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

	mPFS, months (95% CI)	HR (95% CI)	P value
Osimertinib (n=279)	**18.9** (15.2–21.4)	**0.46** (0.37–0.57)	**<0.001**
EGFR TKI* (n=277)	**10.2** (9.6–11.1)		

Soria et al, N Engl J Med, 2018;

FULL SET analysis[1]



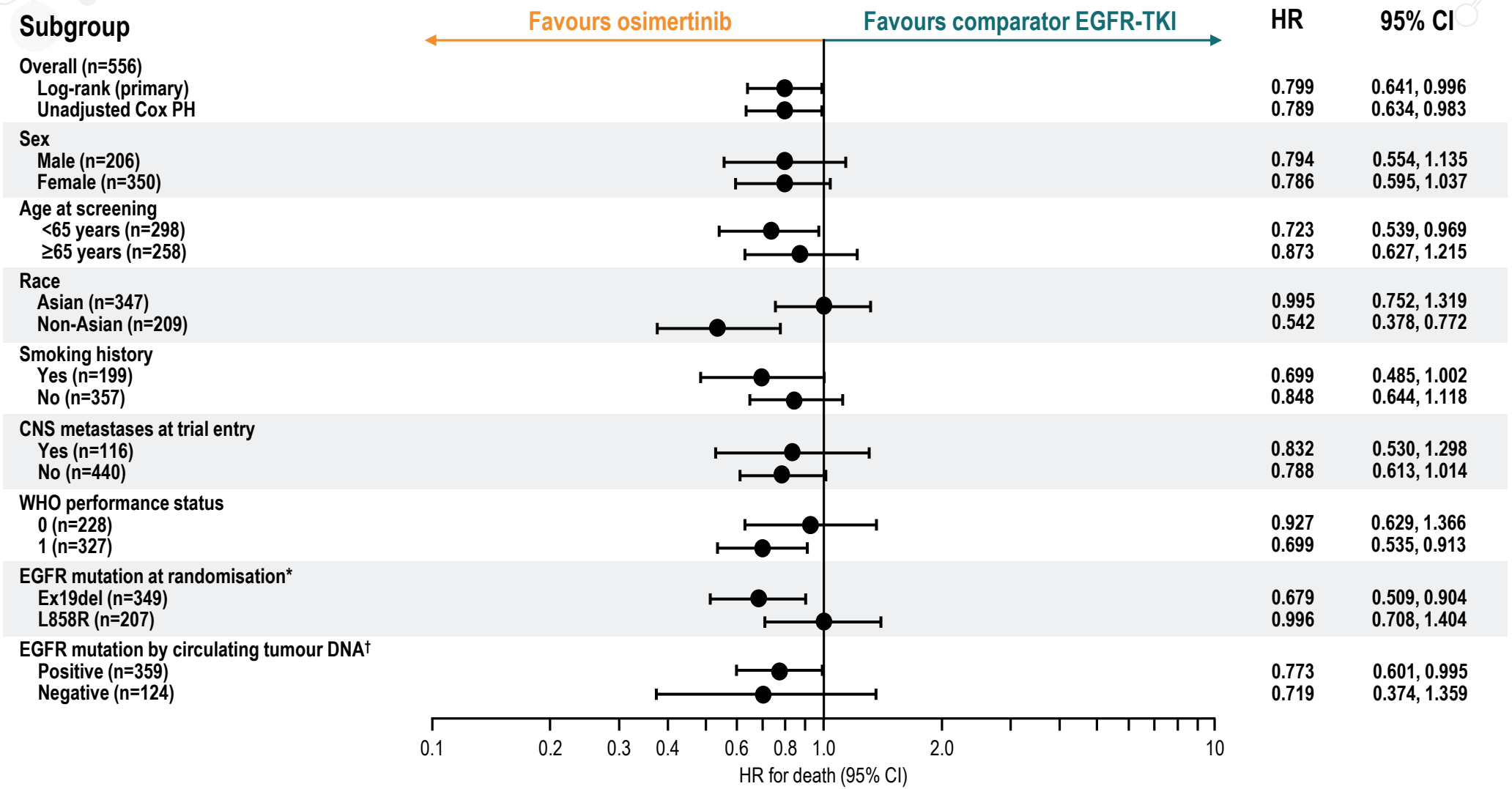
No. at risk

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

	mOS, months (95% CI)	HR (95% CI)	P value
Osimertinib (n=279)	**38.6** (34.5–41.8)	**0.80** (0.64–1.00)	**0.046**
EGFR TKI* (n=277)	**31.8** (26.6–36.0)		

Ramalingam SS, et al. NEJM. 2020;

Overall survival across subgroups



Data cut-off: 25 June 2019

Hazard ratio <1 implies a lower risk of death on osimertinib

*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

1. Ramalingam SS, et al. NEJM. 2020; 2, Ramalingam SS, et al. NEJM. appendix

Safety

AEs n (%)	Osimertinib (n=279)					SoC (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)	116 (42)	35 (13)	6 (2)	0
Dry skin	88 (32)	76 (27)	11 (4)	1 (<1)	0	90 (32)	70 (25)	17 (6)	3 (1)	0
Paronychia	81 (29)	37 (13)	43 (15)	1 (<1)	0	80 (29)	46 (17)	32 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Dermatitis acneiform	71 (25)	61 (22)	10 (4)	0	0	134 (48)	71 (26)	50 (18)	13 (5)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	51 (18)	24 (9)	22 (8)	5 (2)	0
Pruritis	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7 (3)	0	0
AST increased	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
ALT increased	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

Ramalingam SS, et al. NEJM. 2020

CNS Effects of III Generation EGFR TKI

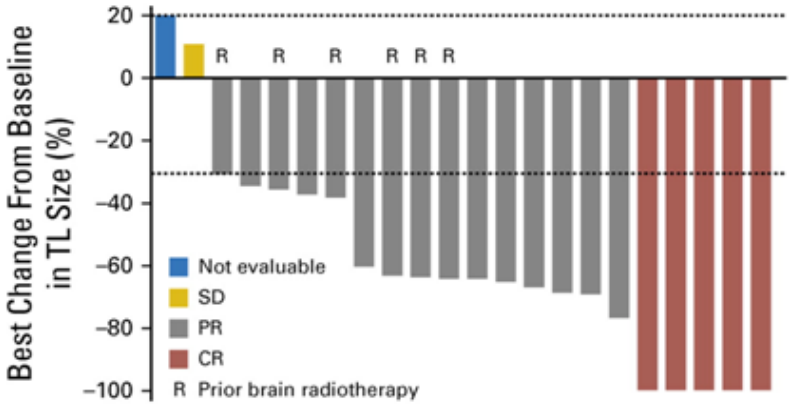
Practice Changing Data

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

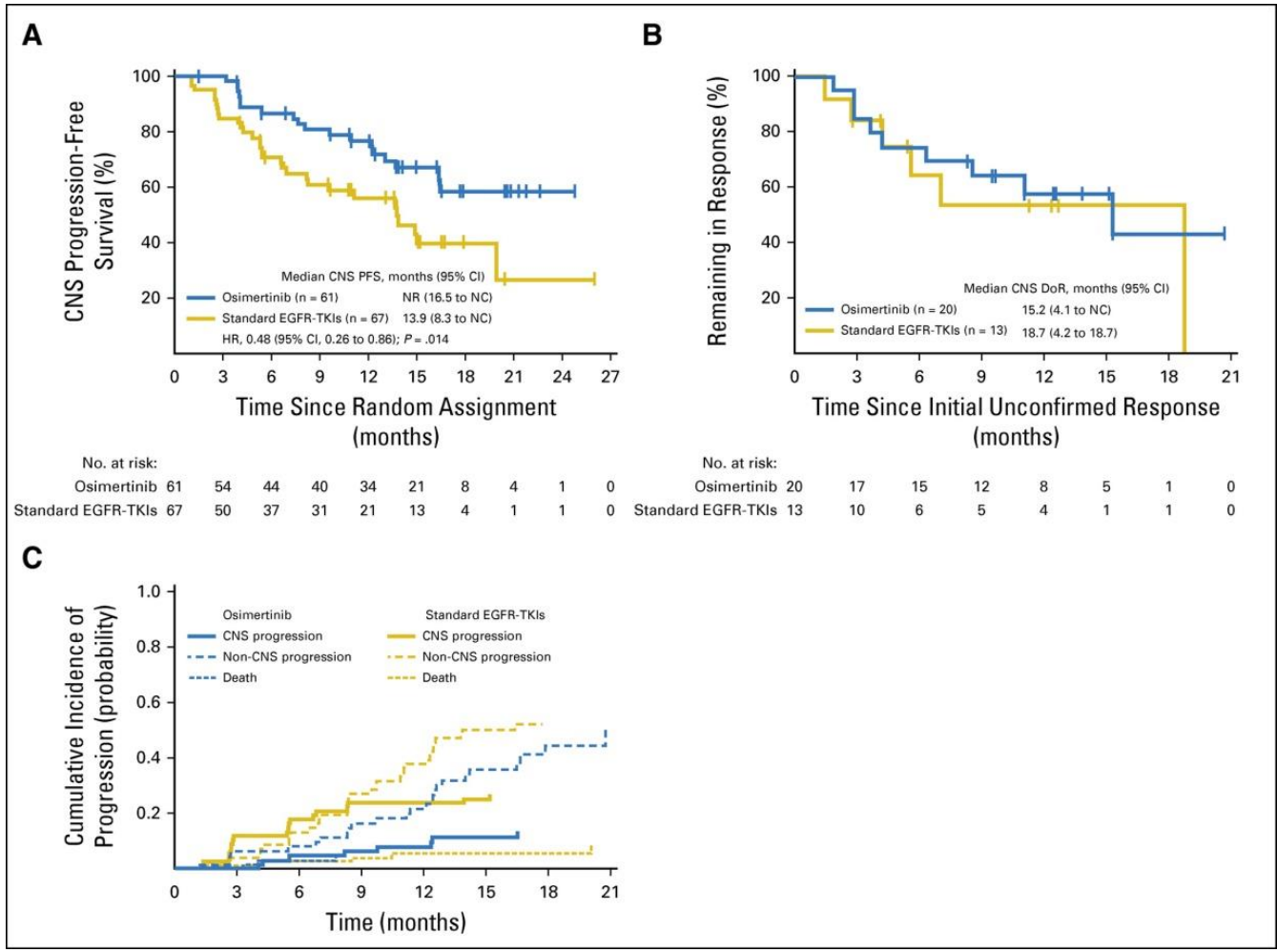
CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste



CNS evaluable for response set (n=41)	
Osimertinib (n=22)	SoC (n=19)
91% (71, 99)	68% (43, 87)

Odds Ratio 4.6 (95%CI 0.9-34.9, p=0.066)



mPFS: NR vs 13.9 months (HR 0.48, 95%CI 0.26-0.86, p=0.014)

1. What is the optimal first-line therapy for patients with common *EGFR* mutations?

STATEMENT: First-line third-generation EGFR TKIs, such as osimertinib, is considered the preferred option for patients with a tumor with common *EGFR* mutations [I,A].

2. What is the optimal management of patients with CNS disease and/or with leptomeningeal involvement?

STATEMENT: Third-generation EGFR TKIs should be prioritized for those patients with CNS metastasis, including leptomeningeal disease, as initial therapy. The benefit of radiotherapy in addition to EGFR TKIs is not supported by prospective controlled trials data. For those with intracra-

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12], F. de Marinis[1], A. M. Dingemans[13], R. Dziadziuszko[14], C. Faivre-Finn[15], J. Feldman[16], E. Felip[17], G. Curigliano[18], R. Herbst[19], P. A. Jänne[20], T. John[21], T. Mitsudomi[22], T. Mok[23], N. Normanno[24], L. Paz-Ares[25], S. Ramalingam[26], L. Sequist[27], J. Vansteenkiste[28], I. I. Wistuba[29], J. Wolf[30], Y. L. Wu[31], S. R. Yang[7], J. C. H. Yang[32], Y. Yatabe[33], G. Pentheroudakis[34] & S. Peters[35]

Passaro A, et al. Ann Oncol 2022;

What do we learn from 3rd EGFR TKIs?

Study	Region	N	Drug	RR	PFS mon (HR)	OS mon (HR)	SAE %	Dose R %
FLAURA	Global	556	Osimertinib	80% vs 76%	18.9 vs 10.2 (0.46)	38.6 vs 31.8 (0.8)	8	4
AENEAS	China	429	Aumolertinib	74% vs 72%	19.2 vs 9.9 (0.46)	NA	22	3.7
FURLONG	China	358	Furmonertinib	89% vs 84%	20.8 vs 11.1 (0.44)	NA	11	3
Betta trial	China	362	Befotertinib	76% vs 78%	22.1 vs 13.8 (0.49)	NA	20.3	31.3
LASER 301	Global	393	Lazertinib	76% vs 76%	20.6 vs 9.7 (0.45)	NA	26	21

Wu YL, WCLC 2023

What about combination strategies in first line EGFR+?

Third generation EGFR TKIs: Standard of Care since 2020

BEYOND OSIMERTINIB first line?

Agenda

- TKI
- Combo approaches
- Uncommon mutations

EGFRi and VEGFi Combo-inhibition

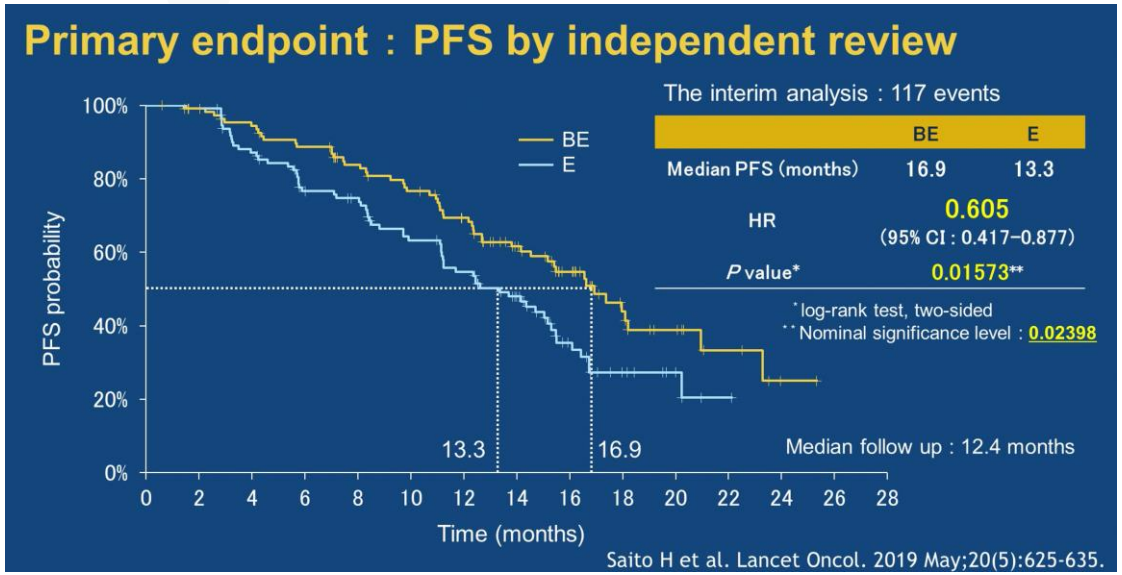
Erlotinib + Bevacizumab
NEJ026
BEVERLY

Erlotinib + Ramucirumab
RELAY

Osimertinib + Bevacizumab
WJOG9717L

Saito H, Lancet Oncol 2019, Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69.
Presented By Maria Carmela Piccirillo at 2021 ESMO Annual Meeting

NEJ026 PFS/OS: Bevacizumab + Erlotinib

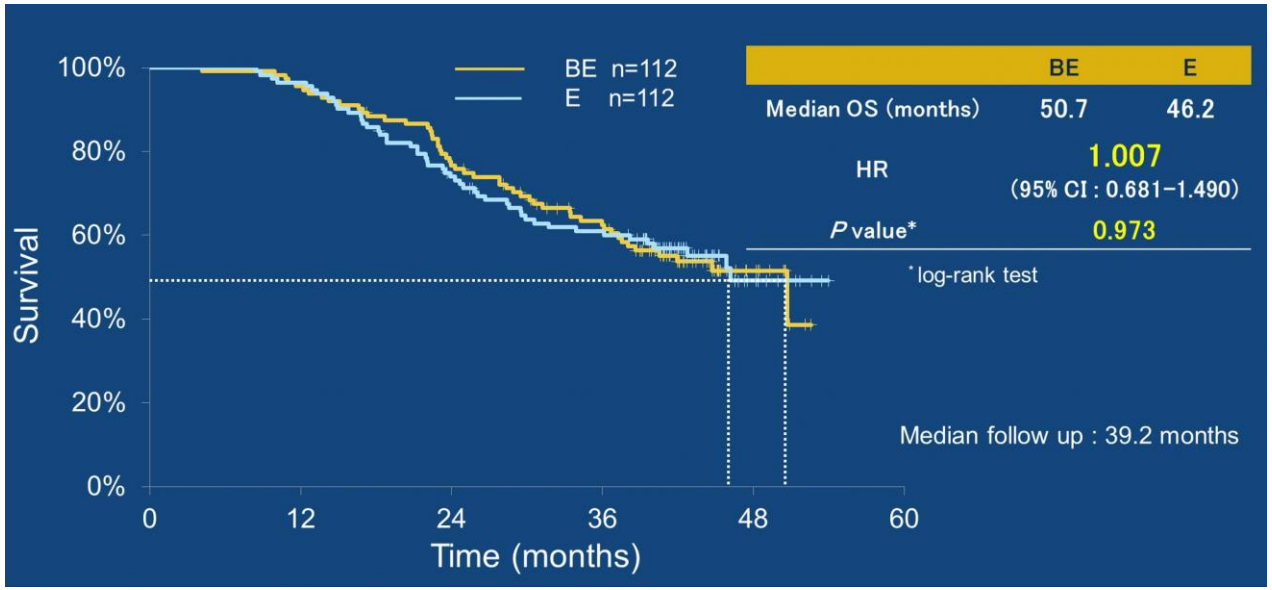


Progression Free-Survival:

16.9 mo for Bev + Erlotinib vs 13.3 mo for Erlotinib alone
HR 0.60 (95% CI, 0.41 – 0.87)

Overall Survival:

50.7 mo for Bev + Erlotinib vs 46.2 mo for Erlotinib alone
HR 1 (95%CI, 0.68 – 1.49)

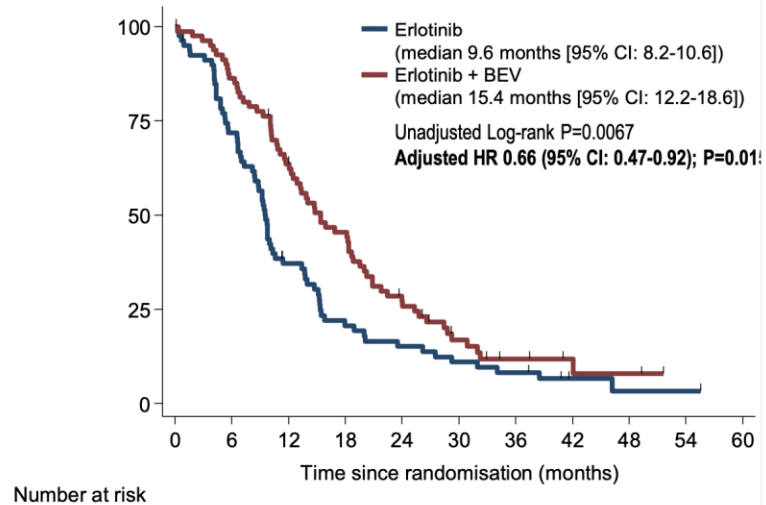


Saito H, Lancet Oncol 2019

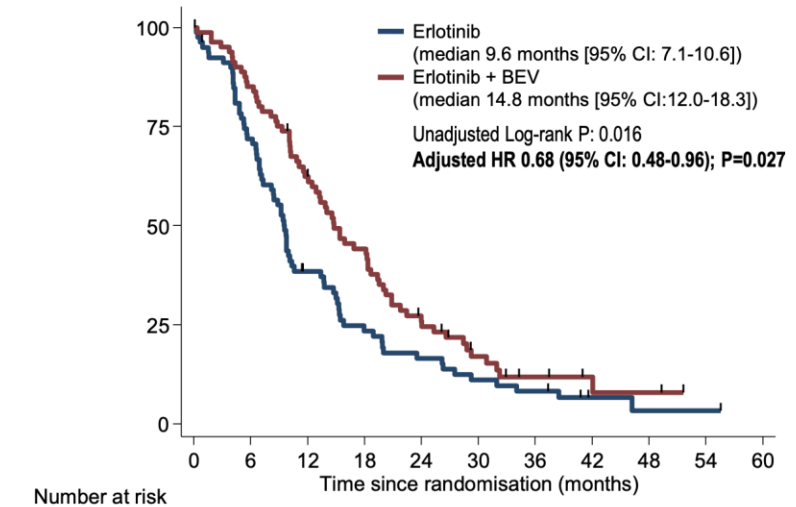
BEVERLY OS: Bevacizumab + Erlotinib

Progression-free survival

Investigator-assessed

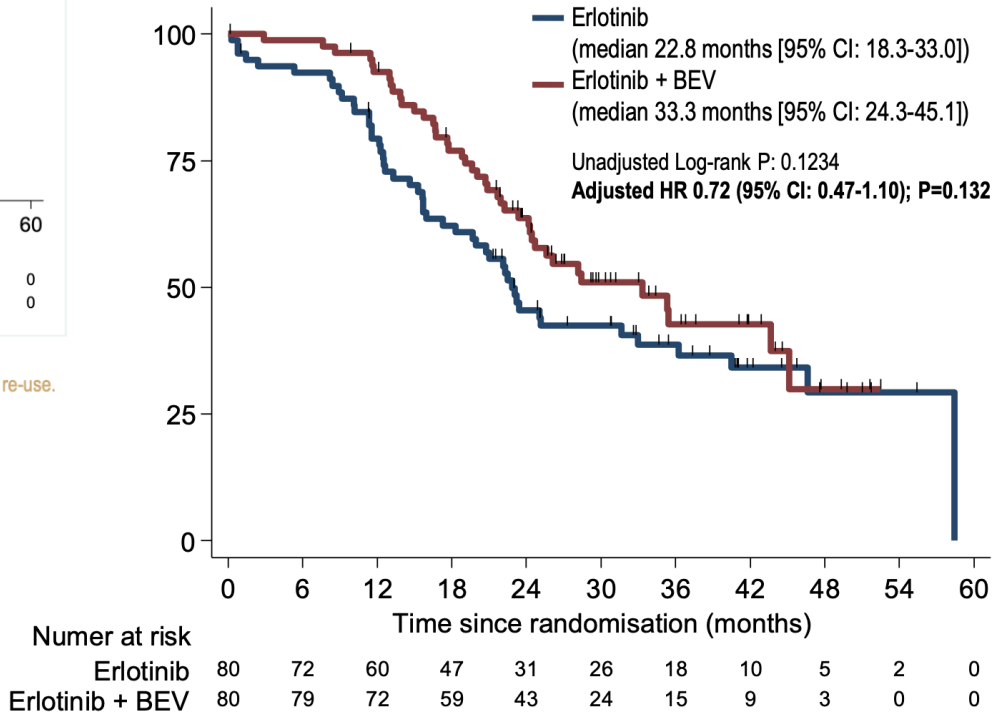


Blinded independent centrally-reviewed



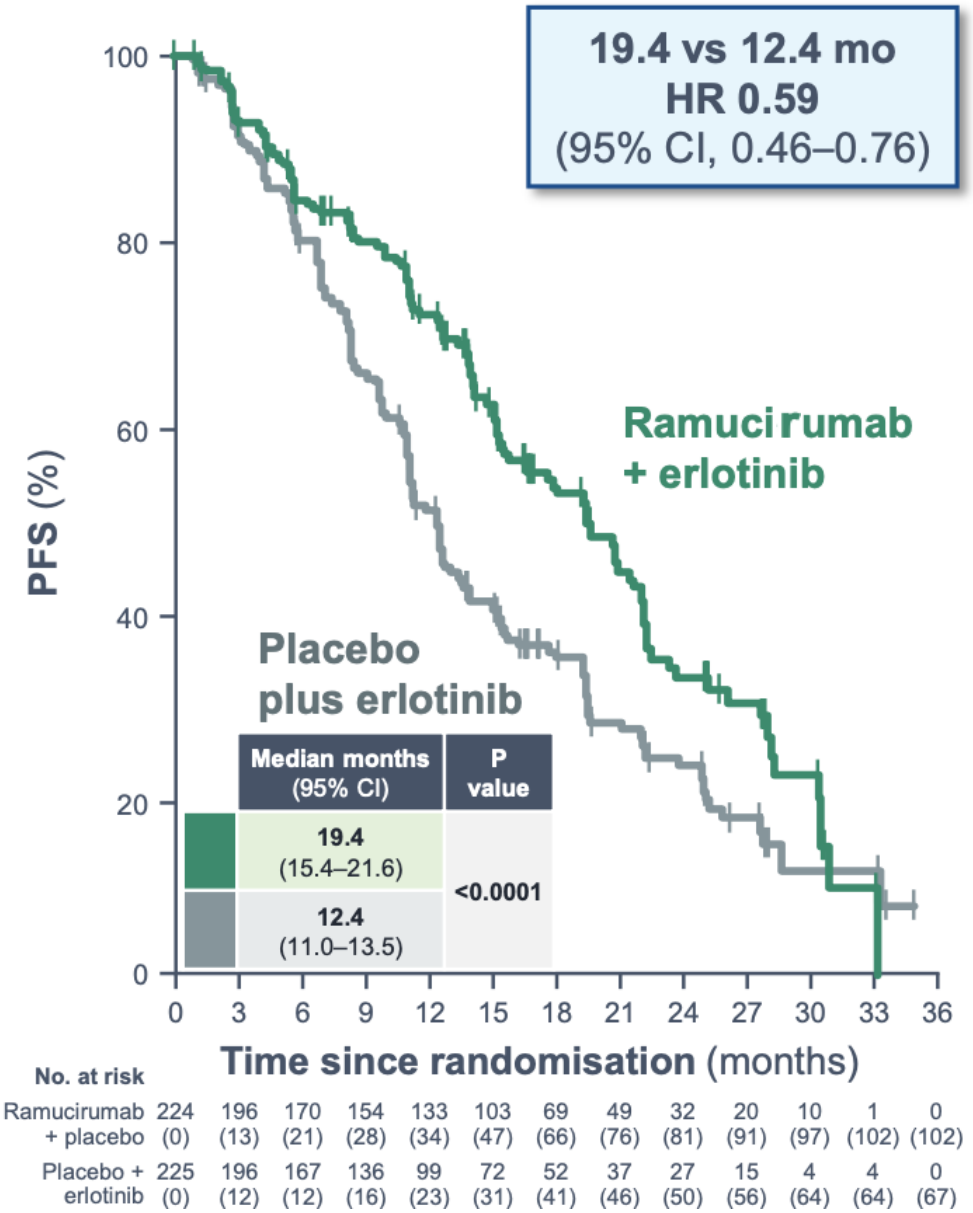
2021 ESMO congress

Overall survival



Piccirillo MC, JTO 2022

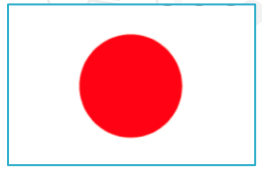
RELAY PFS: Ramucirumab + Erlotinib

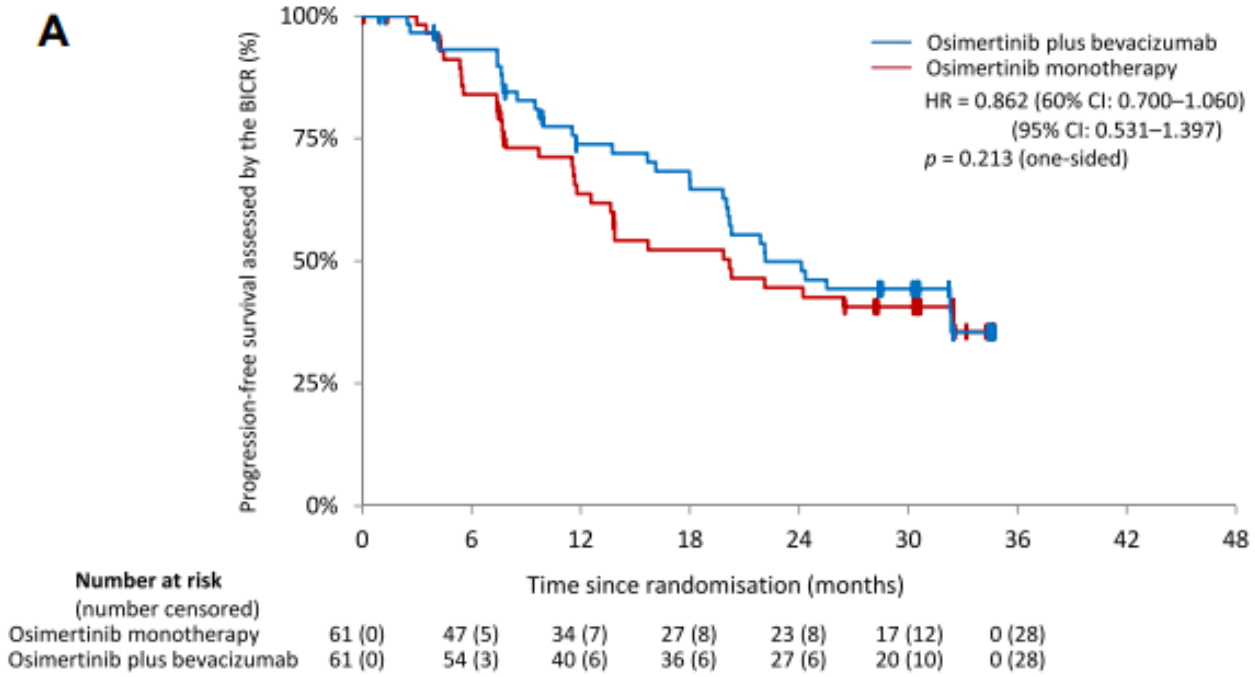


Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69.

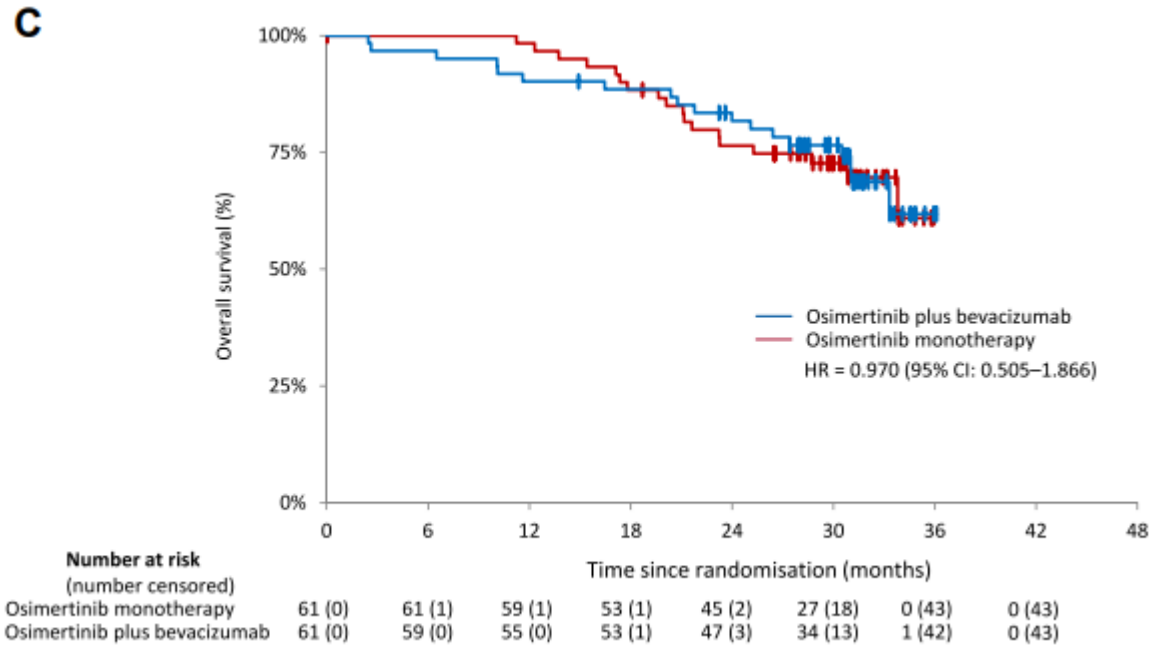
Adapted from B. Besse from ELCC 2022

WJOG9717L PFS: Osimertinib + Bevacizumab





Number at risk (number censored)							
Osimertinib monotherapy	61 (0)	47 (5)	34 (7)	27 (8)	23 (8)	17 (12)	0 (28)
Osimertinib plus bevacizumab	61 (0)	54 (3)	40 (6)	36 (6)	27 (6)	20 (10)	0 (28)



Number at risk (number censored)							
Osimertinib monotherapy	61 (0)	61 (1)	59 (1)	53 (1)	45 (2)	27 (18)	0 (43)	0 (43)
Osimertinib plus bevacizumab	61 (0)	59 (0)	55 (0)	53 (1)	47 (3)	34 (13)	1 (42)	0 (43)

Kenmotsu H, JTO 2022

EGFRi and Chemo Combo-inhibition

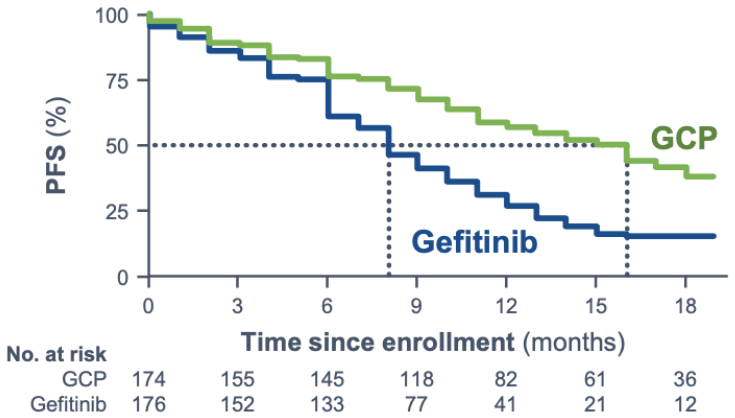
Gefitinib + Chemotherapy
TATA MEMORIAL
NEJ009

Osimertinib + Chemotherapy
FLAURA 2

Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69; 2. Hosomi Y, et al. J Clin Oncol. 2020;38:115−23. Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med. 2018

PFS, OS: Chemotherapy + Gefitinib

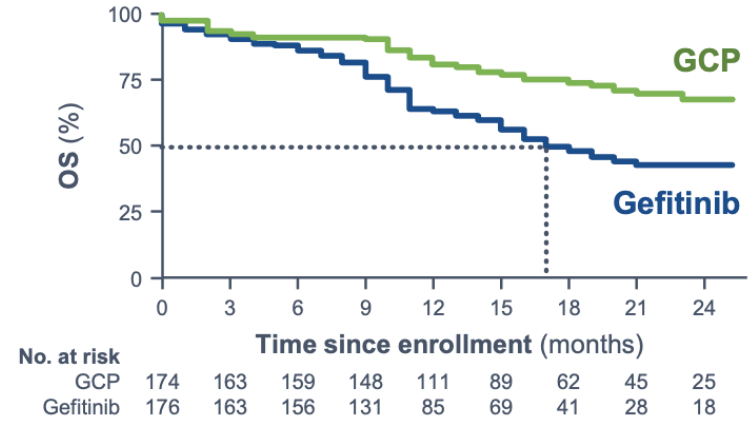
TATA MEMORIAL[1]



PFS

	HR (95% CI)	P value
GCP (n=174) / Gefitinib (n=176)	0.51 (0.39–0.66)	<0.001

16.0 vs 8.0 mo
HR 0.51
(95% CI, 0.39–0.66)



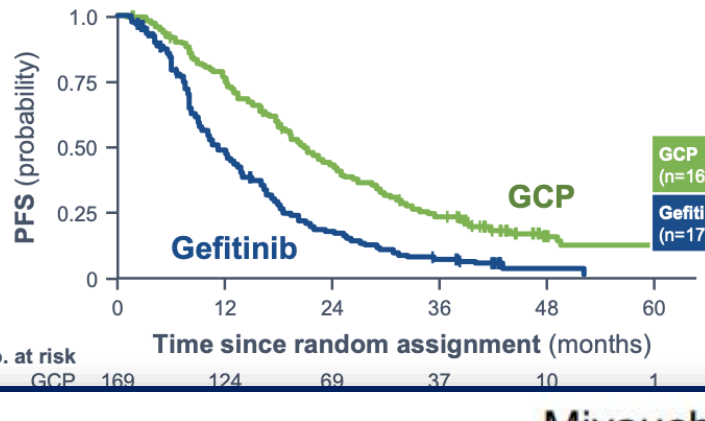
OS

	HR (95% CI)	P value
GCP (n=174) / Gefitinib (n=176)	0.45 (0.31–0.65)	<0.001

NR vs 17.0 mo
HR 0.45
(95% CI, 0.31–0.65)

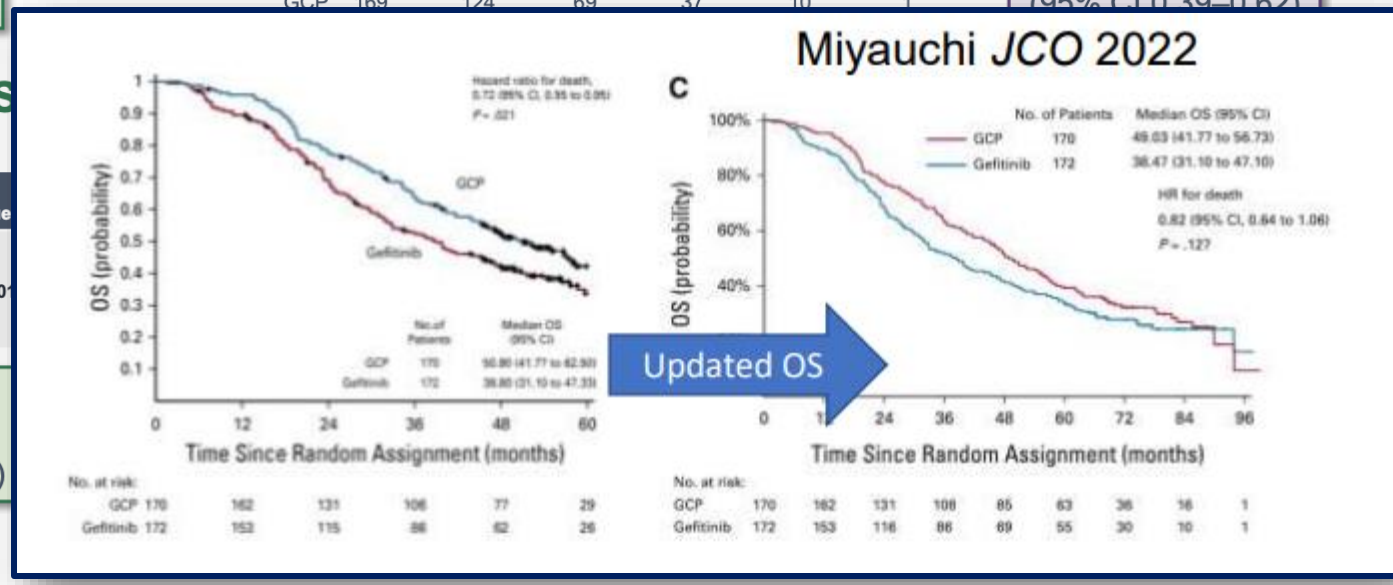
NEJ009[2]

PFS



	Median PFS (95% CI)	HR for PD or death (95% CI)	P value
GCP (n=169)	20.93 (17.94–24.20)	0.49 (0.39–0.62)	<0.001
Gefitinib (n=172)	11.17 (8.97–13.40)		

20.93 vs 11.17 mo
HR 0.49
(95% CI 0.39–0.62)



Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69; 2. Hosomi Y, et al. J Clin Oncol. 2020;38:115−23. .

Adapted from B. Besse from ELCC 2022

Safety: Chemotherapy + Gefitinib

Grade 3/4 AE, n (%)	Noronha et al		NEJ009	
	Gef + CBDCA+PEM	Gef	Gef + CBDCA + Pem	Gef
Liver dysfunction	8(5)	5(2)	20(11.8)	37(21.5)
Neutropenia	26(16)	0	53(31.4)	1(0.6)
Anemia	32(19)	2(1)	36(21.3)	4(2.3)
Nausea/vomiting	9(6)	3(2)	-	-
Diarrhea	23(14)	14(9)	7(4.1)	5(2.9)
Skin rash	8(5)	8(5)	7(4.1)	5(2.9)
Thrombocytopenia	8(5)	0	29(17.2)	0

Intercalated Chemo - Again Study

JCOG1404/WJOG8214L study design (original)

- NSqNSCLC
- Stage IIIB/IV or recurrence
- *EGFR* exon 19 DEL or L858R
- ECOG PS 0-1
- Age 20-74 years
- No prior systemic therapy
- Stable CNS metastases were allowed

n = 500

Randomization 1:1

Adjusted by
- institution
- clinical stage IIIB/IV or recurrence
- sex
- mutation type exon 19DEL or L858R

Gefitinib 250 mg/day day 1-PD
n = 250

Gefitinib day 1-56
n = 250

Cisplatin 75 mg/m² **Pemetrexed** 500 mg/m² (q3w, 3 courses) day 71, 92, 113

Gefitinib day 134-PD

JCOG1404/WJOG8214L study design (revised)

- NSqNSCLC
- Stage IIIB/IV or recurrence
- *EGFR* exon 19 DEL or L858R
- ECOG PS 0-1
- Age 20-74 years
- No prior systemic therapy
- Stable CNS metastases were allowed

Total: n = 500
(osimertinib: n =174)

Randomization 1:1

Adjusted by
- institution
- clinical stage IIIB/IV or recurrence
- sex
- mutation type exon 19DEL or L858R

Osimertinib 80 mg/day day 1-PD
n = 87
(total: n = 250)

Osimertinib day 1-56
n = 87
(total: n = 250)

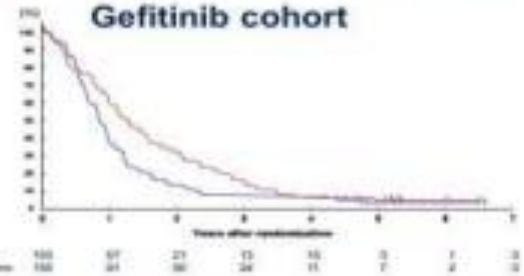
Cisplatin 75 mg/m² **Pemetrexed** 500 mg/m² (q3w, 3 courses) day 71, 92, 113

Osimertinib day 134-PD

Kanda et al. ASCO 2023

Progression-free survival by EGFR-TKI

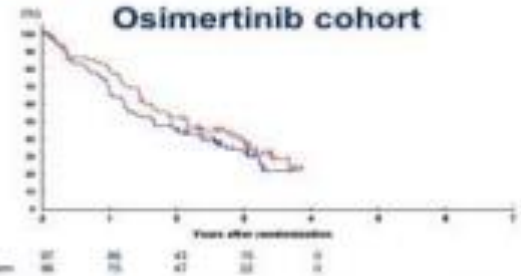
Gefitinib cohort



Median PFS (95% CI), months		
Standard arm	9.6	(9.6-12.0)
Experimental arm	14.4	(12.0-18.0)
HR (95% CI)	0.687 (0.544-0.867)	p=0.0015*

* Two-sided p-value calculated from log-rank test

Osimertinib cohort

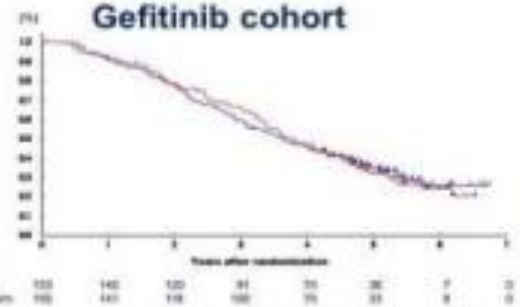


Median PFS (95% CI), months		
Standard arm	20.4	(14.4-28.8)
Experimental arm	25.2	(18.0-34.8)
HR (95% CI)	0.812 (0.572-1.155)	p=0.2475*

* Two-sided p-value calculated from log-rank test

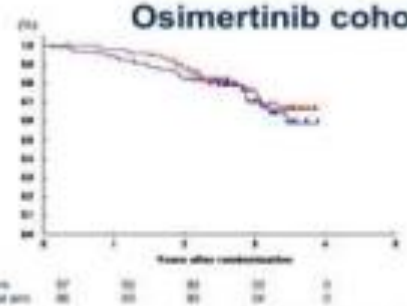
Overall survival by EGFR-TKI

Gefitinib cohort



Median OS (95% CI), months		
Standard arm	43.2	(37.2-51.6)
Experimental arm	45.6	(40.8-51.6)
HR (95% CI)	1.016 (0.774-1.332)	p=0.9124*

Osimertinib cohort



Median OS (95% CI), months		
Standard arm	NE	(40.8- NE)
Experimental arm	NE	(NE- NE)
HR (95% CI)	0.835 (0.484-1.442)	p=0.5154*

FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

1. Planchard et al. ESMO Open 2021;6:100271

*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

Pasi Janne, WCLC 2023

Baseline characteristics

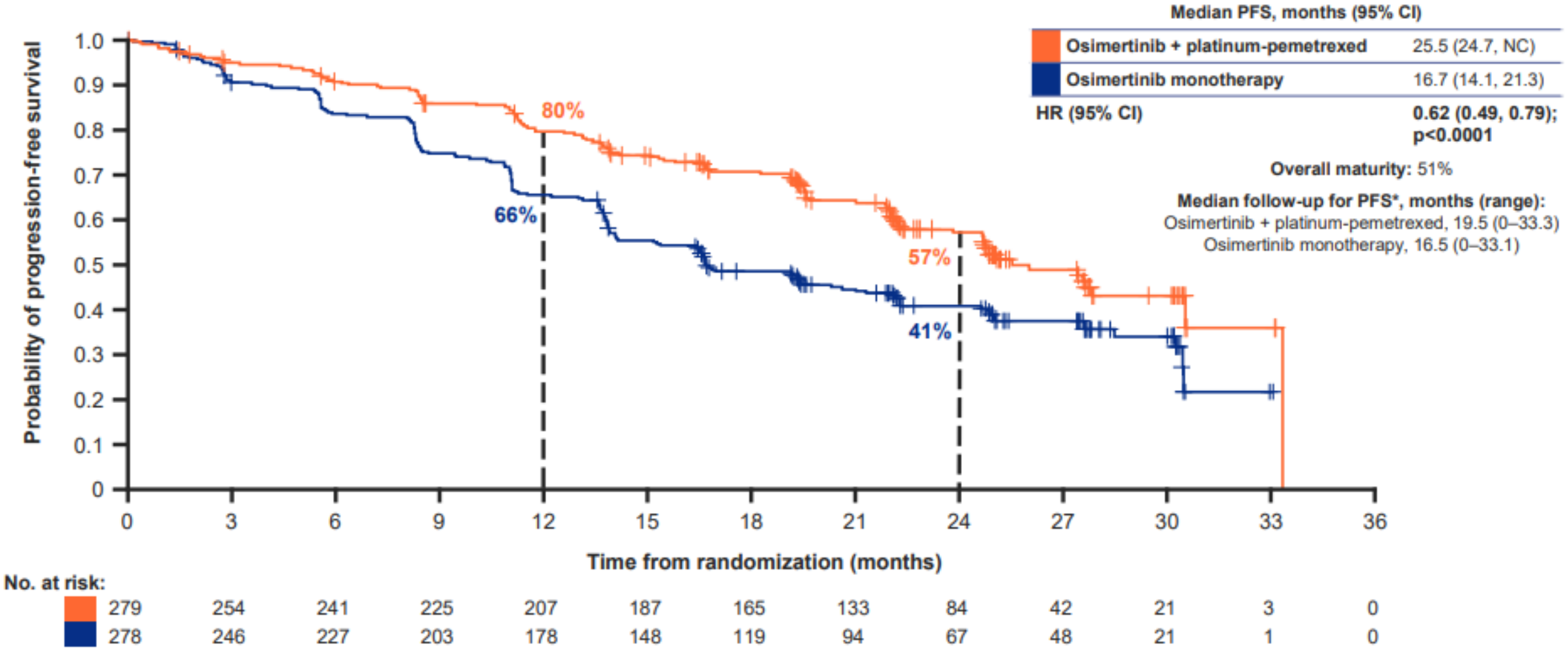
- Patient demographics / clinical characteristics were balanced between arms, and almost half of patients had CNS metastases at baseline

Characteristics, %*	Osimertinib + platinum-pemetrexed (n=279)†	Osimertinib monotherapy (n=278)†
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26–83)	62 (30–85)
Race: Chinese Asian / non-Chinese Asian / non-Asian / missing	25 / 39 / 35 / <1	25 / 38 / 36 / 1
WHO PS: 0 / 1‡	37 / 62	37 / 63
Smoking status: never / current / former	67 / 1 / 31	65 / 1 / 33
Histology: adenocarcinoma / adenosquamous / other	99 / 1 / 1	99 / 0 / 1
EGFR mutation at randomization§: Ex19del / L858R	61 / 38	60 / 38
Locally advanced / metastatic	5 / 95	3 / 97
Extra-thoracic metastases‖	53	54
CNS metastases	42	40
Baseline tumor size, mean (SD) / median (range), mm	65 (42) / 57 (10–284)	64 (39) / 57 (11–221)

Pasi Janne, WCLC 2023

Progression-free survival per investigator

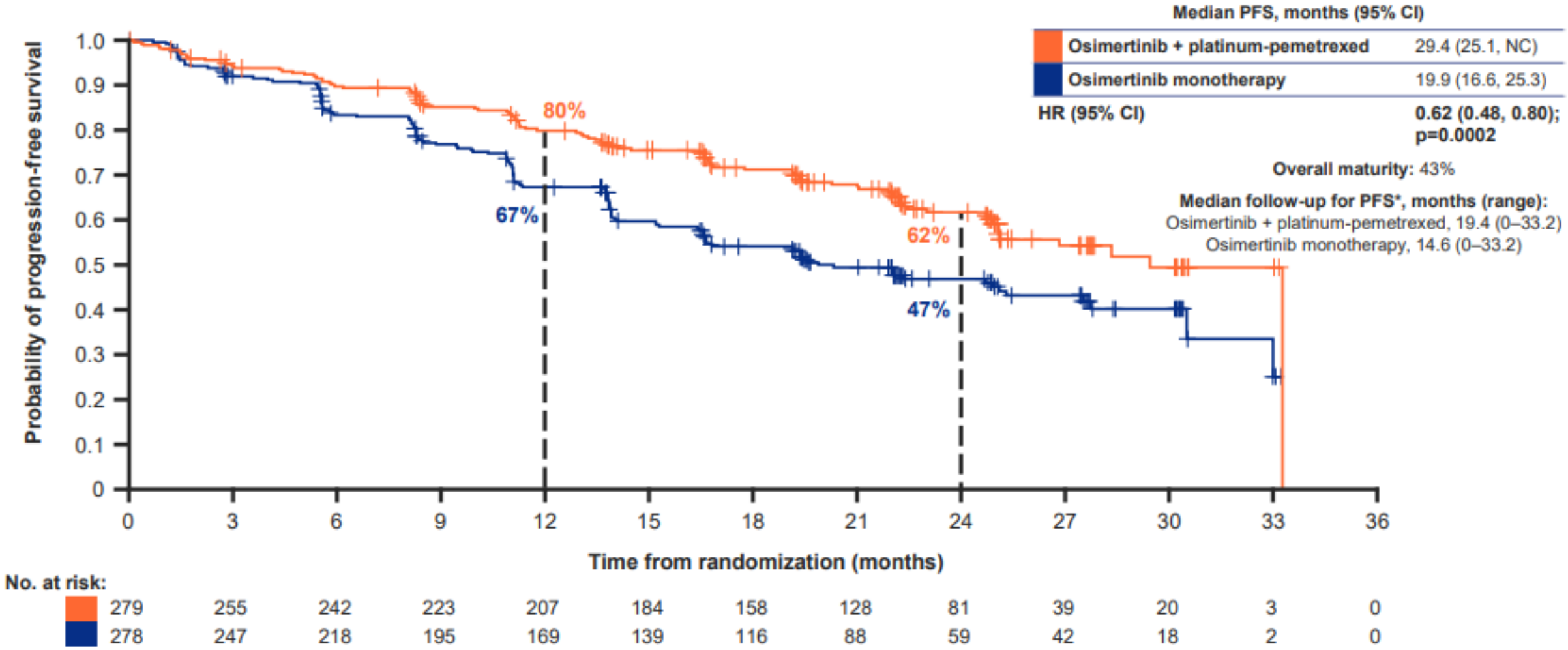
- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Pasi Janne, WCLC 2023

Progression-free survival per BICR

- Median PFS was improved by ~9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy

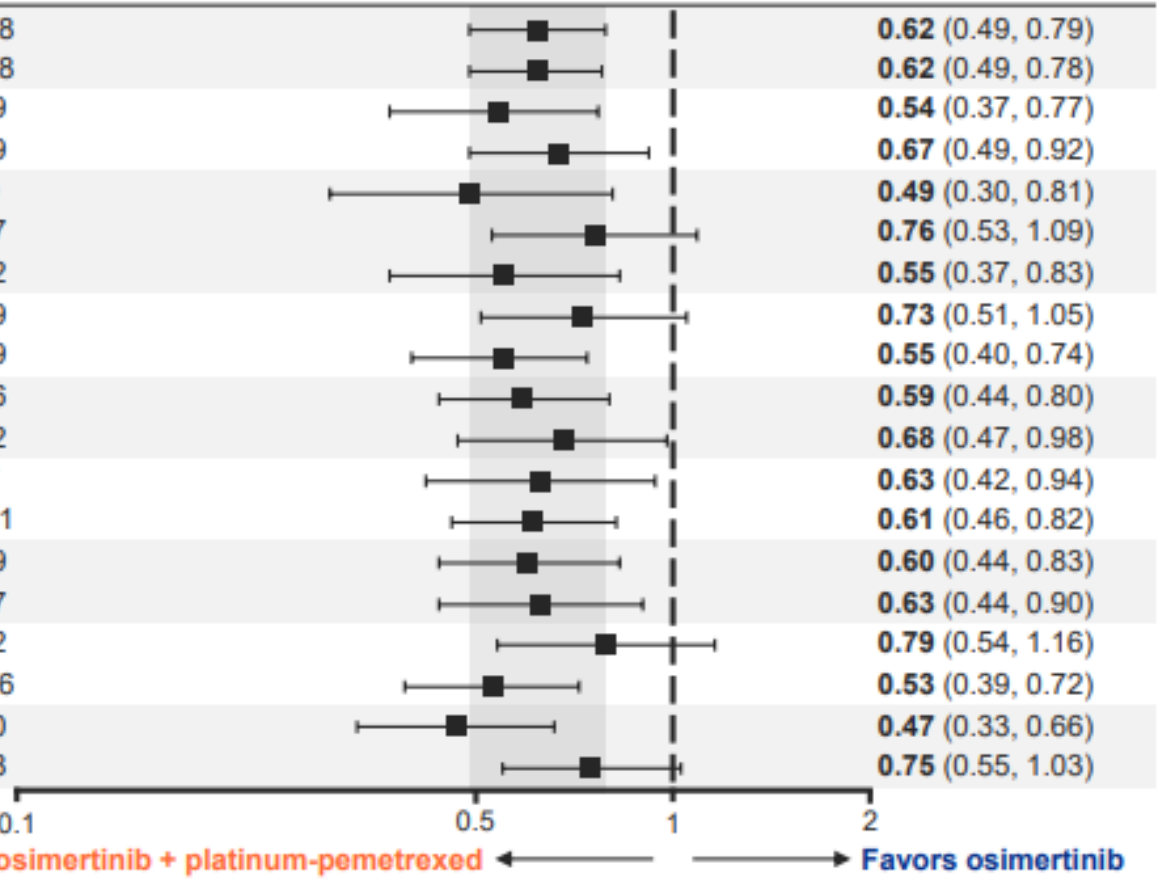


Pasi Janne, WCLC 2023

PFS per investigator across subgroups*

- PFS benefit was consistent across all pre-defined subgroups

Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type†	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)



Pasi Janne, WCLC 2023

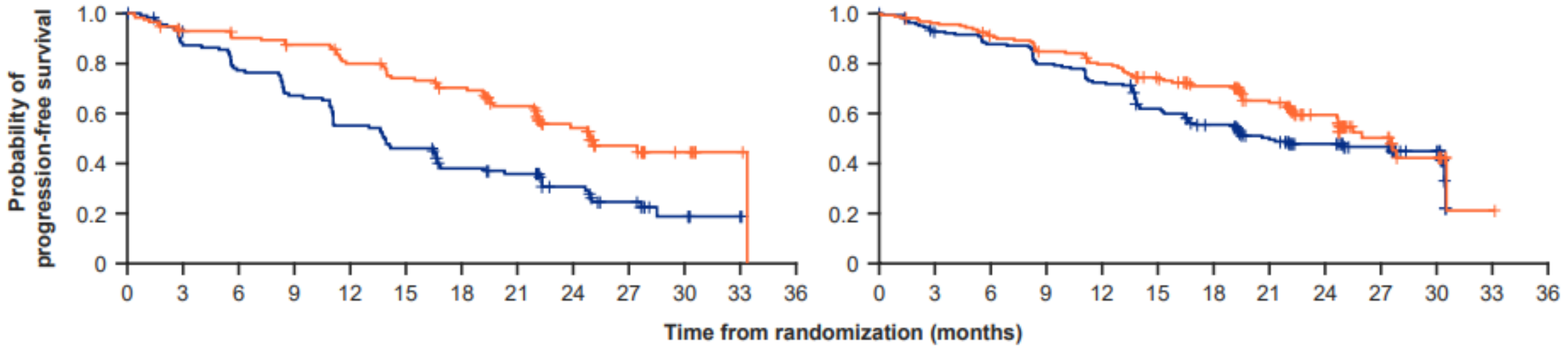
PFS per investigator in patients with / without CNS metastases at baseline*

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	**0.47 (0.33, 0.66)**

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	**0.75 (0.55, 1.03)**

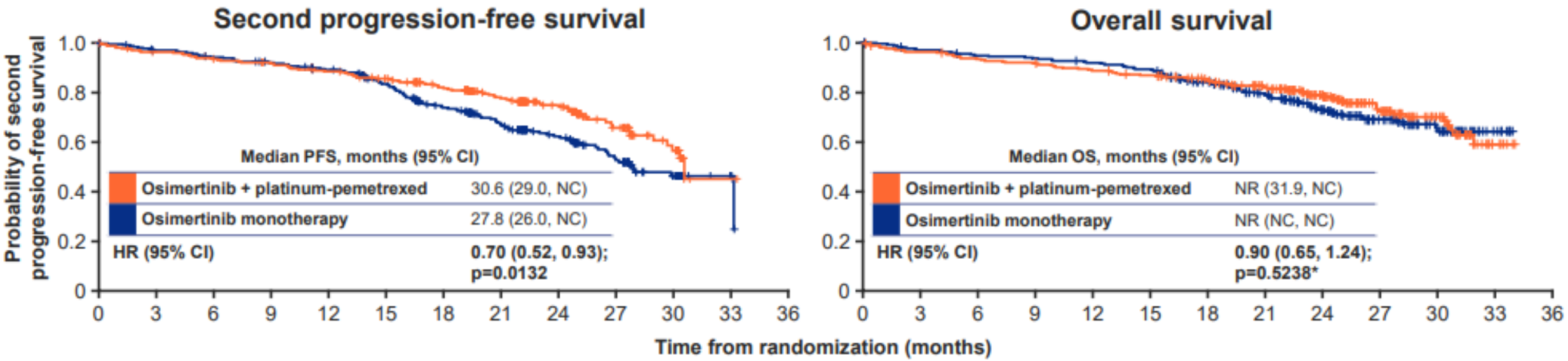


No. at risk:

	116	101	98	93	84	77	70	58	34	19	8	2	0	163	153	143	132	123	110	95	75	50	23	13	1	0
	110	95	84	73	60	50	37	32	21	13	5	1	0	168	151	143	130	118	98	82	62	46	35	16	0	0

Pasi Janne, WCLC 2023

PFS2 and interim analysis of OS



No. at risk:

	279	263	254	247	236	220	194	158	107	54	26	3	0	279	267	258	253	244	237	219	191	139	84	46	7	0
	278	265	255	246	232	206	166	130	90	58	26	3	0	278	267	260	257	251	244	214	185	133	85	46	10	0

- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

Pasi Janne, WCLC 2023

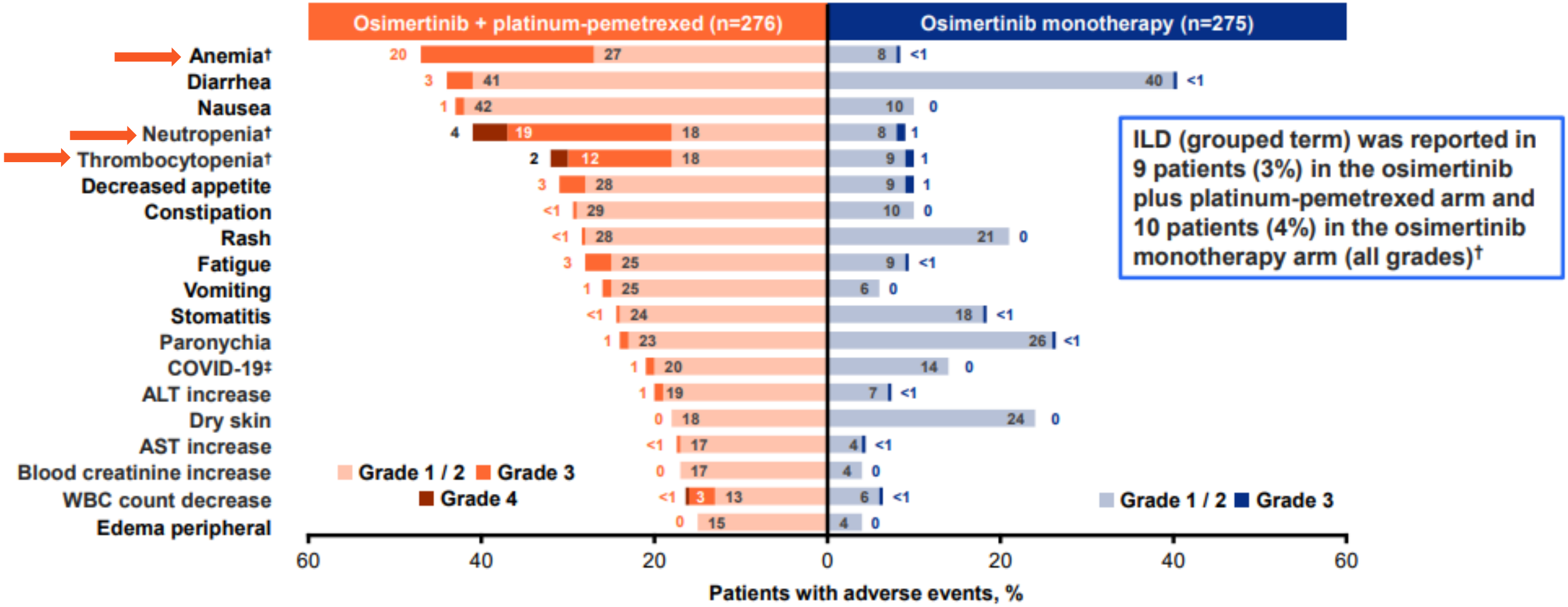
Safety summary

- Median total duration of osimertinib exposure was 22.3 months (range 0.1–33.8) in the osimertinib plus platinum-pemetrexed arm and 19.3 months (range 0.1–33.8) in the osimertinib monotherapy arm
- In the combination arm patients received a median of 12 cycles of pemetrexed (range 1–48) and 211 patients (76%) completed 4 cycles of platinum-based chemotherapy

Patients with AEs, n (%)*	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
AE possibly causally related to treatment†	**269 (97)**	**241 (88)**
Any AE Grade ≥3	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (<1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (<1) / NA / NA
Any serious AE	52 (19)	15 (5)

Pasi Janne, WCLC 2023

Common adverse events (≥15% of patients)*



ILD (grouped term) was reported in 9 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†

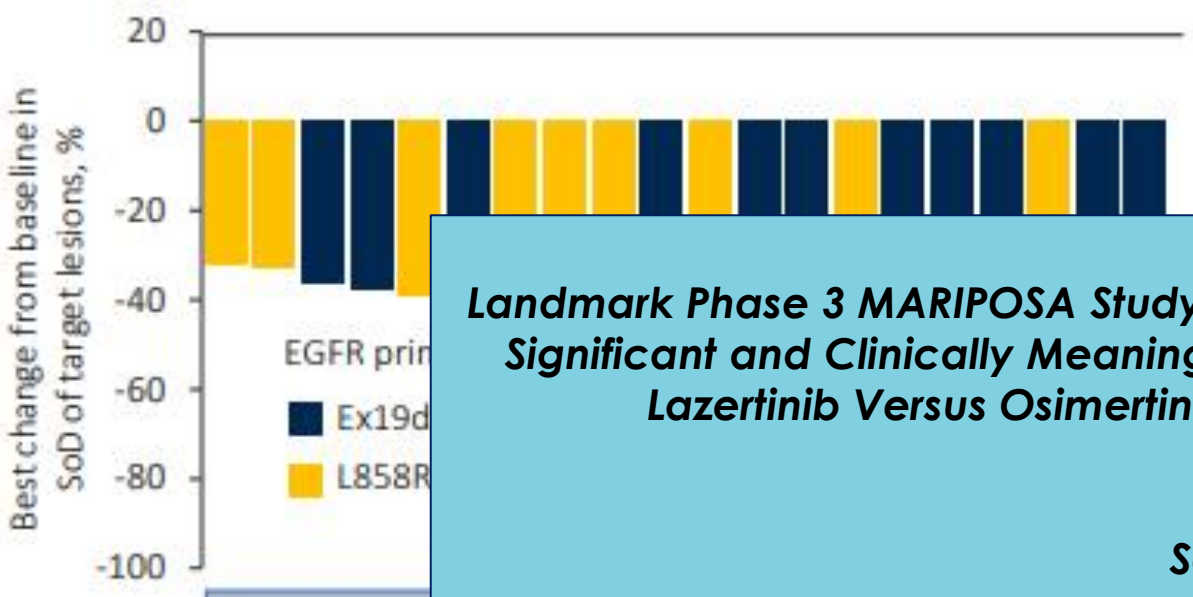
- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Pasi Janne, WCLC 2023

Should we escalate first line?

MARIPOSA trial [amivantamab + lazertinib]

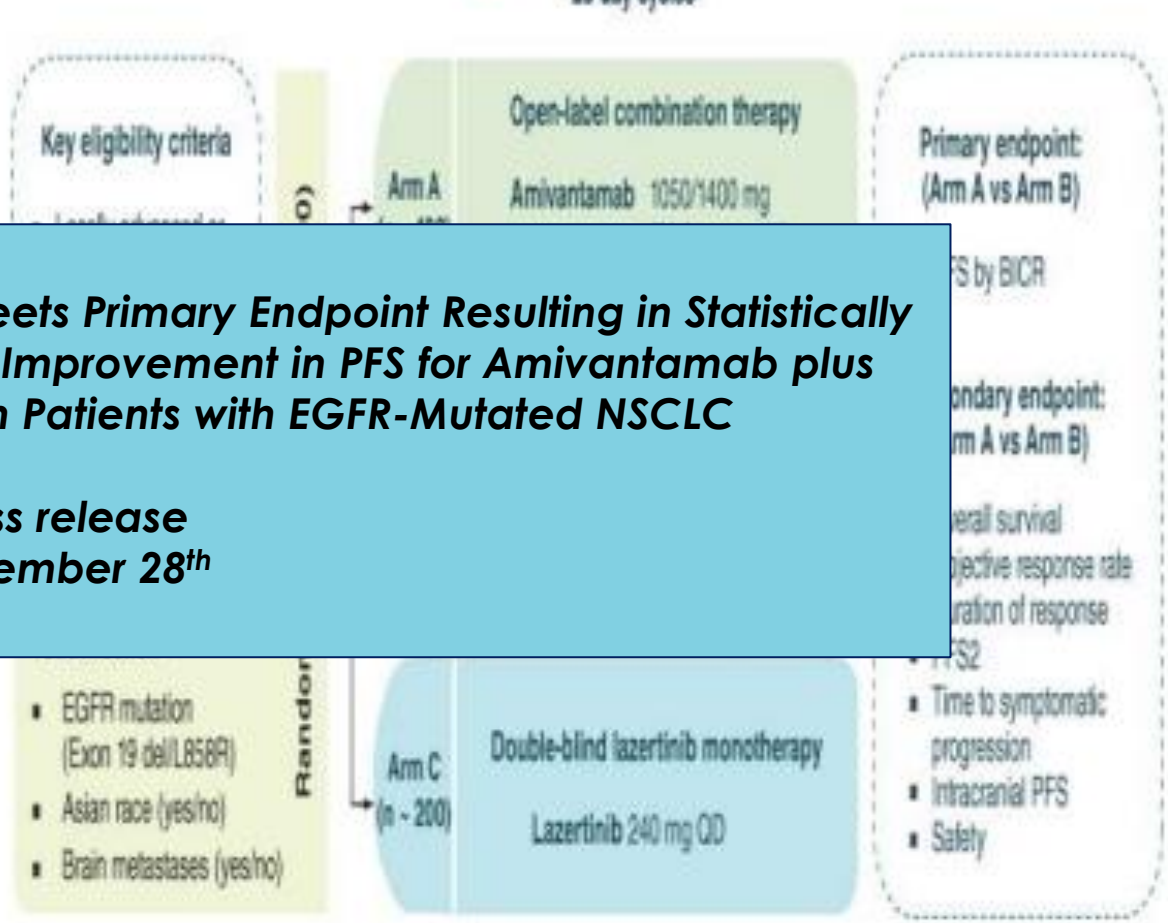
CHRYSALIS Trial:



ORR, % (95%CI) PR, n	100 (83, 100) 20
CBR, % (95%CI)	100 (83, 100)
Median follow-up, months	7 (4–10)

Cho BC, et al. Ann Oncol 2020;31(suppl):Abstr 1258O

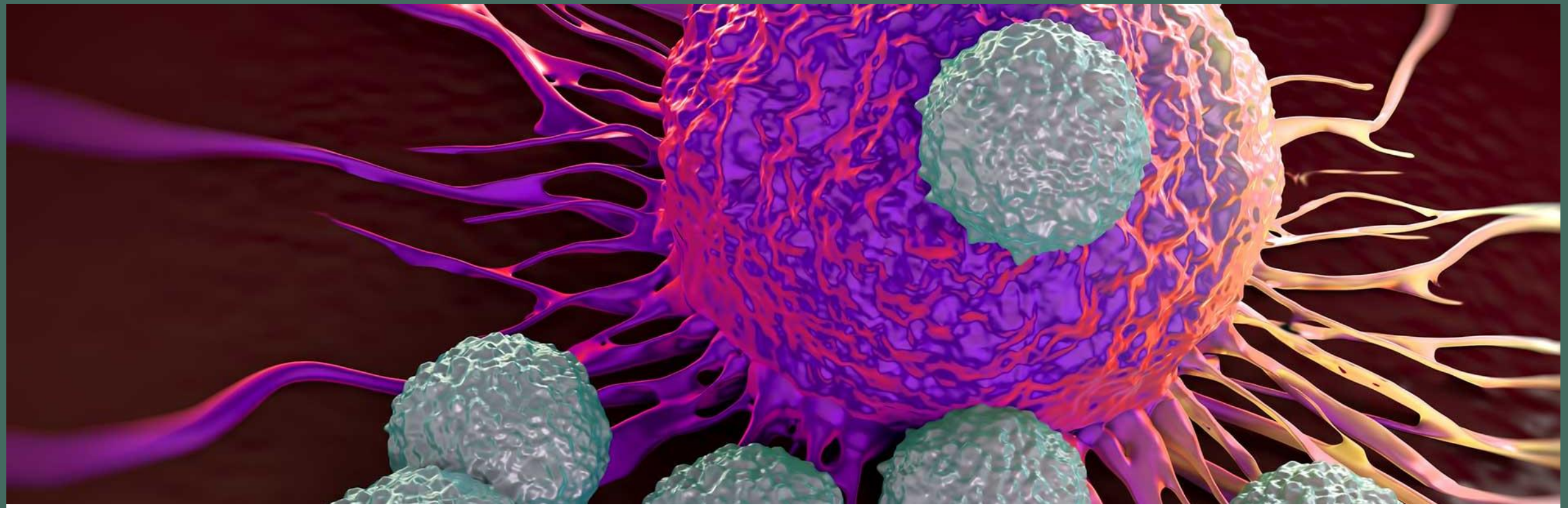
Mariposa Trial:



BC Cho et al. Future Oncol 2022

Landmark Phase 3 MARIPOSA Study Meets Primary Endpoint Resulting in Statistically Significant and Clinically Meaningful Improvement in PFS for Amivantamab plus Lazertinib Versus Osimertinib in Patients with EGFR-Mutated NSCLC

Press release
September 28th



What about immunotherapy in first line *EGFR*+ NSCLC?

ORIGINAL ARTICLE

A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

A. Lisberg, MD, A. Cummings, MD, J. W. Goldman, MD, K. Bornazyan, BS, N. Reese, MD, T. Wang, MD, P. Coluzzi, MD, B. Ledezma, MSN NP, M. Mendenhall, MSN NP, J. Hunt, BS, B. Wolf, BS, B. Jones, BS, J. Madrigal, BS, J. Horton, BS, M. Spiegel, BS, J. Carroll, BS, J. Gukasyan, BS, T. Williams, BS, L. Sauer, BS, C. Wells, BS, A. Hardy, BS, P. Linares, BS, C. Lim, BS, L. Ma, BS, C. Adame, BS, Edward B. Garon, MD, MS*

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Received 2 March 2018; accepted 25 March 2018
Available online - 1 June 2018

ABSTRACT

Background: Despite the significant antitumor activity of pembrolizumab in NSCLC, clinical benefit has been less frequently observed in patients whose tumors harbor *EGFR* mutations compared to *EGFR* wild-type patients. Our single-center experience on the KEYNOTE-001 trial suggested that pembrolizumab-treated EGFR-mutant patients, who were tyrosine kinase inhibitor (TKI) naïve, had superior clinical outcomes to those previously treated with a TKI. As TKI naïve EGFR-mutants have generally been excluded from pembrolizumab studies, data to guide treatment decisions in this patient population is lacking, particularly in patients with programmed death ligand 1 (PD-L1) expression ≥50%.

Conclusions: Pembrolizumab's lack of efficacy in TKI naïve, PD-L1+, EGFR-mutant patients with advanced NSCLC, including those with PD-L1 expression ≥50%, suggests that it is not an appropriate therapeutic choice in this setting.

Keywords: NSCLC; programmed death 1 (PD-1); *EGFR*; tumor immunology; pembrolizumab; programmed death ligand 1

Introduction

Programmed death 1 (PD-1) axis inhibition has

ORR: 0/10 evaluable pts

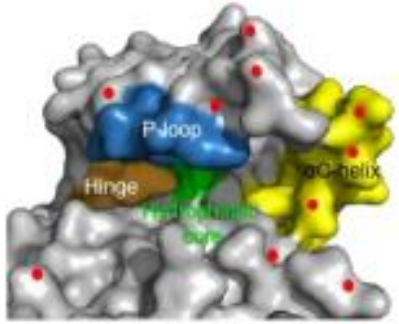
PDL-1: >50% in 7/10 pts

Agenda

- TKI
- Combo approaches
- Uncommon mutations

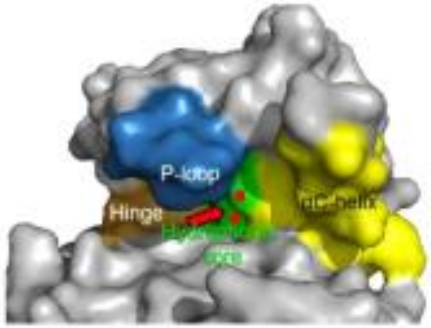
Structure/function classification EGFR mutations in NSCLC

Classical-like



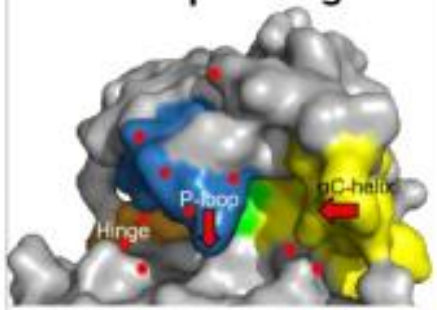
- Distal to drug binding pocket
- Modest to no impact on drug binding

T790M-like



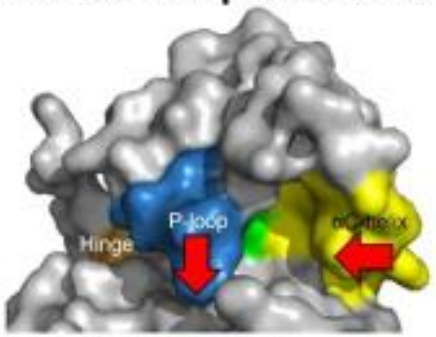
- At least one mutation in hydrophobic core
- Increased affinity for ATP compared to classical-like mutations
- Two subgroups:
  - T790M-like-3S
  - T790M-like-3R

P-loop αC-helix compressing



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

Exon 20 loop insertions



- C-terminal loop of αC-helix
- Indirect and substantial impact on drug binding (both P-loop and αC-helix)
- Two subgroups:
  - Ex20ins-near loop (light red)
  - Ex20ins- far loop (dark red)

Representative Mutations

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

Drug Sensitivity/Selectivity

Sensitive & Selective → Resistant

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

Mutation resulted structural change

⇕

Function

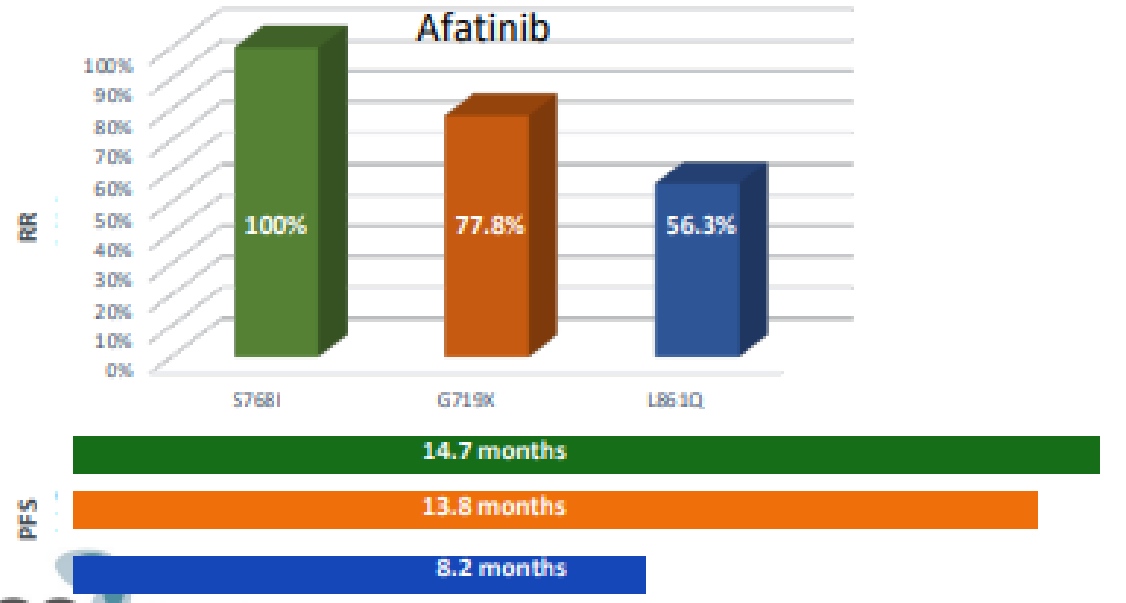
⇕

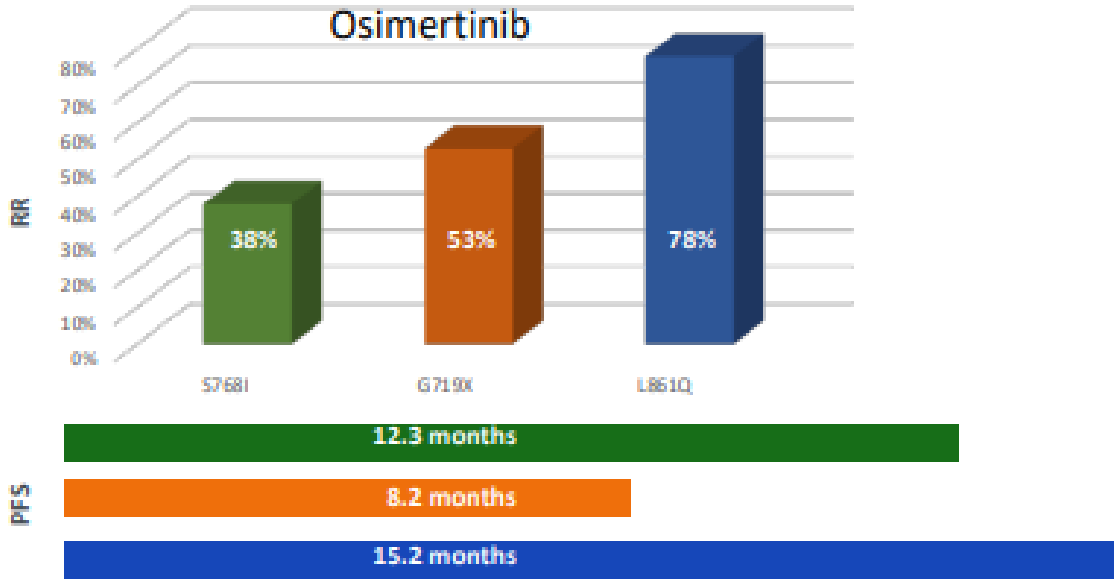
Drug sensitivity

Robichaux, Nature 2021

EGFR uncommon mutations

Overall (S768I+G719X+L861Q)	First generation EGFR TKI (gefitinib) Post-hoc NEJ002 *N*=9	Second generation EGFR TKI (afatinib) Post-hoc analysis LL 2-3-6 *N*=38	Third generation EGFR TKI (osimertinib) Phase II *N*=36
RR(%)	20	71.1	50
mPFS (months)	2.2	10.7	8.2
mOS (months)	11.9	19.4	NR





elcc European Lung Cancer Congress

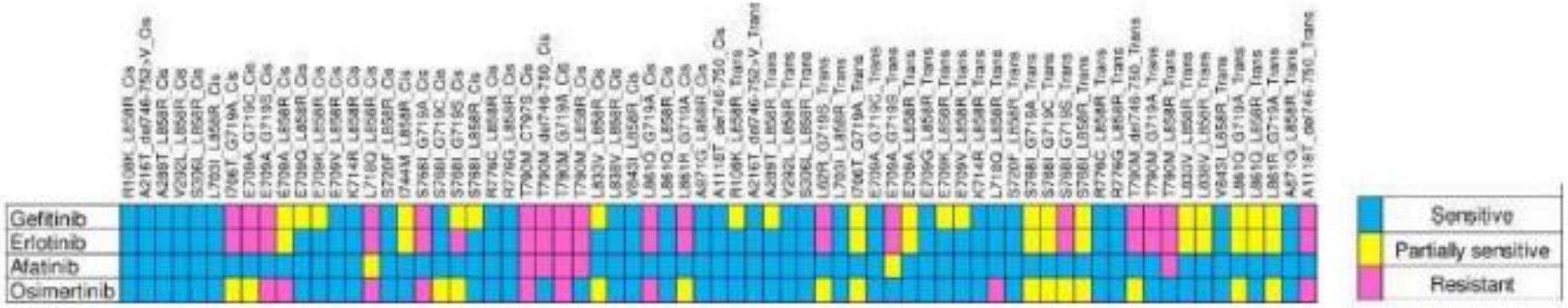
Giulia Pasello

Watanabe S, JTO 2014; Yang JCH, Lancet Oncol 2015; Cho JH, JCO 2019

Uncommon EGFR as partner of compound mutations

* *Lacking data*

Sensitivity of the co-mutation drives the overall response to different TKIs



Attili I, Curr Oncol 2022; Tam IY, Mol Cancer 2009; Kohsaka S, Sci Transl Med 2016

ARTICUNO

Activity of Osime**RTI**nib in Patients with NS**C**LC Harboring **UN**common EGFR Mutations: a Retrospective **O**bservational Multicenter Italian Study

Sistema Socio Sanitario

Ospedale Niguarda

Regione Lombardia

Table 1. Patients' characteristics

Characteristics	All patients N=86 (%)	Group A: common with uncommon N=13 (%)	Group B: uncommon only N=66 (%)	Group C: exon 20 insertions N=7 (%)
Median age (range) – yr	68.5 (30 – 87)	68 (42 – 80)	65.5 (30 – 87)	62 (40 – 87)
Sex				
Female	54 (63)	7 (54)	41 (62)	6 (86)
Male	32 (27)	6 (46)	25 (38)	1 (14)
ECOG PS at initiating of osimertinib				
PS 0	30 (35)	6 (46)	22 (33)	2 (29)
PS 1	43 (50)	6 (46)	29 (44)	3 (42)
PS ≥ 2	13 (15)	1 (8)	15 (23)	2 (29)
Smoking history				
Never	32 (37)	3 (23)	26 (39)	2 (29)
Former	25 (29)	5 (38)	23 (35)	1 (14)
Current	27 (31)	4 (31)	16 (24)	4 (57)
Unknown	2 (3)	1 (8)	1 (2)	0 (0)
Ethnicity				
Caucasian	81 (94)	13 (100)	62 (94)	6 (86)
Other races	5 (6)	0 (0)	4 (6)	1 (14)
Histology				
Adenocarcinoma	80 (93)	13 (100)	60 (91)	7 (100)
Other	6 (7)	0 (0)	6 (9)	0 (0)
Line of therapy				
1° line	70 (81)	11 (85)	53 (80)	6 (86)
2° line	12 (14)	2 (15)	9 (14)	1 (14)
≥ 3° line	4 (5)	0 (0)	4 (6)	0 (0)
Previous treatments for advanced disease				
TKI	10 (12)	1* (8)	8* (12)	1* (14)
Chemotherapy	8 (9)	1 (8)	7 (11)	0 (0)
Immunotherapy	3 (3)	0 (0)	2** (3)	0 (0)
Immunotherapy+Chemotherapy	1 (1)	0 (0)	1** (2)	0 (0)
TNM Stage at initiating of osimertinib				
III	3 (3)	1 (8)	2 (3)	0 (0)
IV	83 (97)	12 (92)	64 (97)	7 (100)
Sites of mets at initiating of osimertinib				
Brain	30 (35)	2 (15)	24 (36)	4 (57)
Bone	38 (44)	7 (54)	29 (44)	2 (29)
Lung	51 (59)	6 (46)	39 (59)	6 (86)
Non regional lymphnodes	31 (36)	5 (38)	22 (33)	4 (57)
Liver	16 (19)	4 (31)	10 (15)	2 (29)
Adrenal glands	7 (8)	1 (8)	5 (8)	1 (14)
Pleura	19 (22)	3 (23)	15 (23)	1 (14)
Initial EGFR mutation detected on				
Tissue biopsy	78 (91)	10 (77)	61 (93)	7 (100)
Liquid biopsy	2 (2)	1 (8)	1 (2)	0 (0)
Both	6 (7)	2 (15)	3 (5)	0 (0)
Method for EGFR analysis				
Sanger/PCR	37 (43)	4 (31)	28 (42)	2 (29)
NGS	49 (57)	9 (69)	38 (58)	5 (71)
Reasons for stopping osimertinb				
PD or death	54 (63)	3 (23)	45 (68)	6 (86)
Toxicity	1 (1)	0 (0)	1 (2)	0 (0)
Other	1 (1)	0 (0)	1 (2)	0 (0)
Treatment after osimertinib				
Immunotherapy	4	0	4^	0
Chemotherapy	26	1	23	2
Immunotherapy +Chemotherapy	1	0	1^^	0

Notes: *Previous TKI Group A: 1 afatinib; Group B: 4 afatinib, 3 erlotinib, 1 gefitinib and afatinib; Group C: 1 afatinib. ** 1 Atezolizumab, 2 Pembrolizumab. ^ 2 Atezolizumab, 2 Pembrolizumab, 1 Nivolumab. ^^ CT+pembrolizumab.

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Table 2. Activity of osimertinib in the study cohort and in uEGFR subgroups

Group of patients	N. / N. evaluable	ORR (95%CI)	DCR (95%CI)	mPFS months (95%CI)	mDOR months (95%CI)	mOS months (95%CI)	mFU months (95%CI)
All patients	86/83	42 (31-54)	77 (67-86)	8 (6-13)	13 (7- N.R)	20 (15-35)	28 (24-30)
Group A	13/13	54 (25.1-80.7)	100 (75-100)	40 (17-N.R)	20 (14-N.R)	N.R (N.R - N.R)	30 (20-N.R)
Group B	66/63	43 (30-56)	76 (64-86)	8 (6-12)	9 (6-21)	17 (12-24)	27 (21-30)
Group B: TKI-naïve	58/55	44 (30-58)	75 (61-85)	7 (5-10)	7 (5- N.R)	17 (11-N.R)	27 (21-30)

Supplementary Table 2. Intracranial response

Subgroup	N.	ORR (95%CI)	mPFS (95%CI)	mDOR (95%CI)	mOS (95%CI)	N. with measurable BM	iORR (95%CI)	iDCR (95%CI)	imPFS(95%Ci)	imDOR(95%CI)
All patients	30	40 (23-59)	6 (4-13)	9 (4-NA)	20 (9-NR)	26	58 (37-77)	96 (80-100)	9 (5-13)	7 (3-NA)
Group B	24	46 (26-67)	7 (5-20)	9 (4-NA)	20 (9-NR)	21	67 (43-85)	100 (84-100)	9 (5-13)	6.5 (3-NA)
RT-naïve	21	38 (18-62)	7 (3-13)	5.5 (3-NA)	20 (9-NR)	17	53 (28-77)	94 (71-100)	9 (5-13)	9 (6.5-NA)

Legend: BM: brain metastasis; DCR: disease control rate; i: intracranial; mDOR: median duration of response; mPFS: median progression free survival; mOS: median overall survival; ORR: overall response rate.

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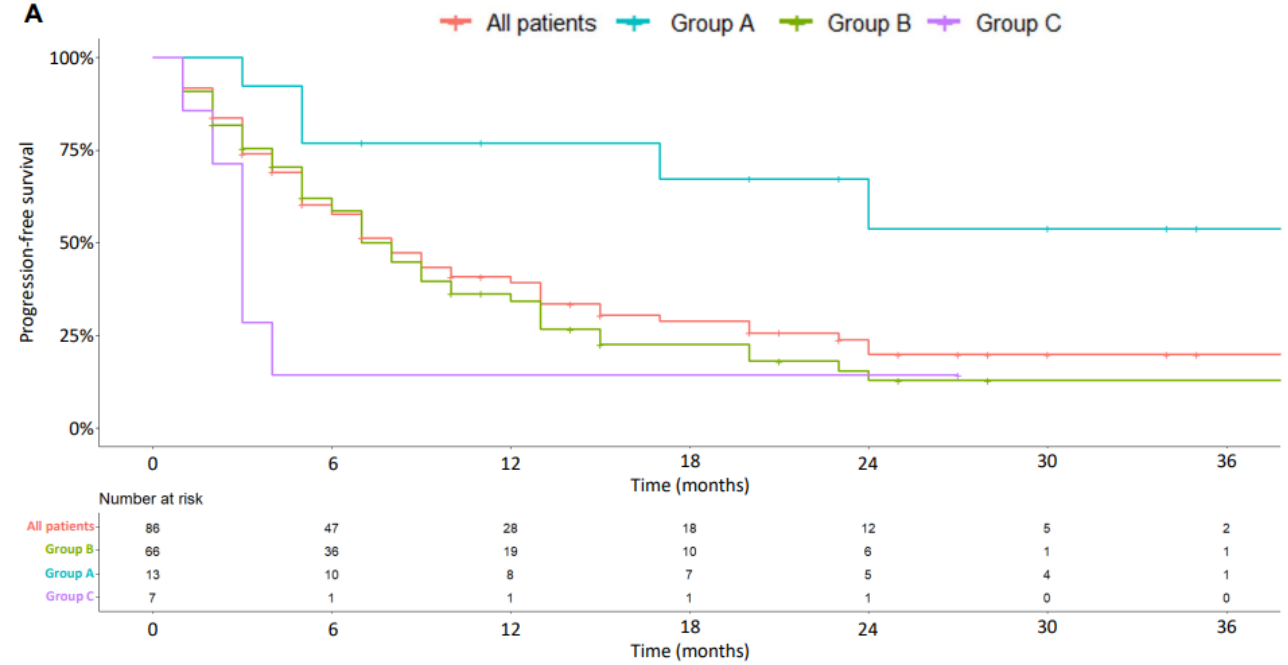

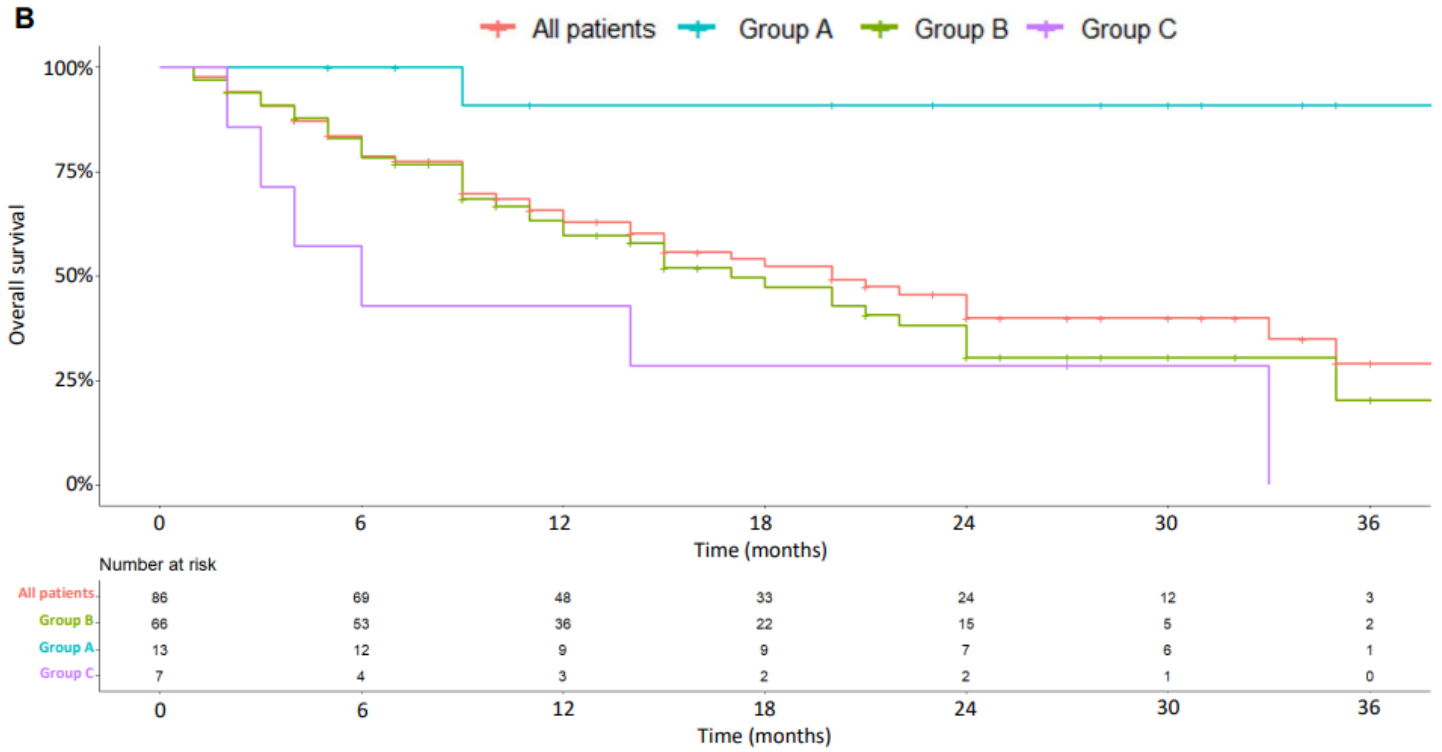

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Table 3. Summary of available studies evaluating osimertinib in patients with advanced NSCLC harboring uEGFR.

Study	N. of patients / N. evaluable (ins20 excluded)	N. TKI-naïve	N. * of major / minor / classical	ORR (95% CI)	DOR (95% CI)	DCR (95% CI)	mPFS (95% CI)	ORR in major uEGFR (95% CI)	ORR in minor uEGFR (95% CI)
ARTICUNO	79 / 76	70	51 / 28/ 13	45% (33-57)	13 mo (7-N.R.)	80% (70-89)	9 mo (7-13)	50% (36-64)	31% (14-52)
Cho et al., *JCO* 2020 (KCSG-LU15-09) [10]	35 / 35	35	32 / 3 / 0	51% (34-67)	11.2 mo (7.7-14.7)	89% (73-97)	8.2 mo (5.2-14.7) #	53% (35-71)	33% (0-90)
Bar et al., *JTO* 2022 (UNICORN) [13]	60 / 51	60	28 / 29 / 13	61% (47-73)	17.4 mo (9.1–N.R.)	92% (81-98)	9.5 mo (8.5–17.4)	57% (37-76)	68% (43-87)
Ji, et al. *JTO CRR* 2023 [34]	43 / 36	23^	26 / 18 / 0	36.1% (20.8–53.8)	N.A.	N.A.	N.A.	32.1% (15.9–52.4)	54% (25-81)
Villaruz, et al. *ESMO Open* 2023 [35]	17 / 17	17	17 / 2 / 0	47% (23-72)	8.7 mo (1.9-13.9)	94% (71-100)	10.5 mo (3.7-15.2)	47% (23-72)	0%

First line treatment in *EGFR*+ NSCLC

What's new in 2023?

- ***Osimertinib*** *is still the* ***gold standard for common mutations***
- *While waiting for FLAURA2 OS results,* ***CT + Osimertinib*** *could become an option in selected patients*
- ***Amivantamab + Lazertinib:*** *new SOC?*
- *Afatinib vs. Osimertinib for* ***uncommon mutations***


THANK YOU
Any questions?